● PERSPECTIVE

What good is the reserve? A translational perspective for the managing of cognitive decline

The concept of reserve appears in the neurological literature in the 1940s arising from the observation that there is no linear relationship between neurological damage and severity of the clinical symptoms. Basically, this concept sustains that the experiences pursued during life-span enrich the brain by making it more resilient to neuronal damage. However, in the last three decades the reserve concept has become very popular in the scientific field, mainly associated with the pathophysiological mechanisms underlying the Alzheimer's Disease (AD) (Serra et al., 2018; Stern et al., 2018). In this time period the concept has been substantially modified (Serra et al., 2018; Stern et al., 2018), passing from a structural concept–the brain reserve (BR)–to a more functional concept–the neural reserve (NR)–by way of a cognitive concept-the cognitive reserve (CR). The BR is related to the brain structure in terms of number of neurons, synapses, and dendrites, and postulates that individuals with larger brain cope better with the neurological damage than subjects with smaller brains (Serra et al., 2018; Stern et al., 2018). The concept of CR is related to the efficiency of cognitive functioning, and postulates that subjects with higher level of CR use more efficiently the pre-existent cognitive processes or are able to enlist alternative cognitive functions to cope better with brain damages (Serra et al., 2018; Stern et al., 2018). The NR is a sort of summa of the previous concepts. Indeed, NR is related to the efficiency of brain networks, namely subjects with higher NR are able to engage more efficiently different brain routes to use more effectively the cognitive functions withstanding the cerebral damage (Serra et al., 2017b). Moreover, Stern (2017) introduced the concept of brain maintenance that postulates that life experiences (including cognitive, social and physical activities) reshape the brain, such increasing the ability to maintain the cognitive integrity. It is well known that several factors that may be associated with genetic background and also with environmental factors impact positively or negatively on brain resilience making subjects able or not to counteract the damages (Serra et al., 2018). An important part of the research on the reserves is dedicated to identify the better proxy measure to capture brain changes due to reserves' mechanisms (BR, CR, NR).

To evaluate the BR and NR *in vivo*, in the human being the best indicators derive from neuroimaging techniques. Indeed, several studies that use magnetic resonance imaging reported brain structural and functional changes related to reserves in patients with AD at different clinical stages (Serra et al., 2017b, 2018; Stern et al., 2018). On the same slipstream CR has been evaluated using two kinds of indicators. The first to be studied and the most common indicators are the level of education, the type of occupation and the quantity and quality of leisure activities. These indicators are defined as static measures of reserve because are not directly related to cognitive functioning and are relatively stable during life (Serra et al., 2018). More recently, the dynamic CR measures have been introduced in the literature (Reed et al., 2010; Serra et al., 2017a). These measures are directly linked to cognitive changes and they express the amount of cognitive functioning residual after removing the effect of brain damage. Actually, in the studies on human beings the indicators of BR, NR, and dynamic (but not static) CR can be indifferently used as proxy measures of reserve or as measures of the effects of reserve. Although from a methodological point of view both these strategies are equally correct, this ambiguity affects the strength and the clinical value of such heterogeneous studies. This topic remains very intriguing and, in our opinion, deserves of further studies specifically finalized to disentangle and compare the "two faces" of the reserve measures.

In animals, the effects of the experience on cognitive functions are investigated by using the model of environmental enrichment. This model is realized by exposing the animals– usually, rodents-to a complex of multifarious stimulations (such as rearing in large cages and numerous groups, with the access to running wheels and ever-changing objects) (Rosenzweig et al., 1978; Petrosini et al., 2009). Thus, the "reserve-builders" that are considered in humans are paralleled in the controlled manipulation of some variables, such as social interactions (human factor), complex and ever-changing environment (cognitive factor), and physical activity and exploration (physical factor). In this model, the researcher is able to fix the beginning and the duration of the exposure to the enriching factors, and also to choose a unimodal or multimodal sensory stimulation (Gelfo et al., 2018). In this way, the environmental enrichment model overcomes some issues that are present in the human studies. Indeed, it allows comparing individuals to verify the effects of well-defined factors, by ensuring comparable background and by making possible the analysis of a great number of cellular and molecular brain indexes (Serra et al., 2018).

In animal studies two reserve measures are principally considered, such as BR and CR. To investigate BR, molecular and supra-molecular biological indices are considered (Gelfo et al., 2018). To investigate CR, the performances in behavioral tests are taken into account (Petrosini et al., 2009). Also, evidence on NR may be inferred from some brain structural adjustments, such as neurogenesis, gliogenesis, angiogenesis, synaptogenesis, etc. (Gelfo et al., 2018). In contrast to human studies (in which static indexes of reserve are not experimentally manipulable but only observable), the high-level control of the "reserve-builders" allowed by animal models permits the direct manipulation of all factors involved in the experimental design. As a consequence, the indicators of BR, CR, and NR are generally analyzed as dependent variables that indicate the effects of the reserve (Serra et al., 2018). Anyway, also in animal models these reserve measures could be analyzed as causal factors.

The effects of the exposure to environmental enrichment are investigated in a large number of disease models characterized by cognitive decline (such as models of physiological or pathological aging). Strong evidence is provided by research on animals about the BR and CR by which the exposure to the environmental enrichment equips the animals. Several studies documented that enriched animals show superior cognitive performance in behavioral tasks (that allow to evaluate a number of cognitive functions), in healthy conditions and also in the presence of neurological damage (Mandolesi et al., 2008; Petrosini et al., 2009; Serra et al., 2018). Moreover, the exposure to environmental enrichment provokes a large range of molecular and supra-molecular plastic changes (such as neurogenesis, gliogenesis, angiogenesis, synaptogenesis, modifications in neurotransmitter and neurotrophic factor systems, *etc.*) that support the amelioration in behavioral performance (Gelfo et al., 2009, 2018; Petrosini et al., 2009).

Overall, a plethora of human and animal studies supports the existence of reserve mechanisms. However, a majority of these studies are focalized on the conceptual framework of reserves, but disregards the real impact and potential usefulness of reserves in the clinical setting. Indeed, although it is mandatory to deepen the knowledge of the different aspects of reserves, nevertheless we retain that the time is ripe to push down these theoretical concept to the real clinical practice in the physician room. A better usability of the reserve concepts could aid the physician to obtain a more "on the patient-tailored" medical decision-making finalised to increase the awareness in designing therapeutic pathways.

To realize this point of view, it is important to outline some fundamental hot-points on which the future studies should be focused.

First of all, a more accurate definition of the variables considered in the operationalization process of the proxy measures of reserve is required. This is an exigency regarding both human and animal research. Animal models permit a better control of the experimental setting with a more precise definition of the variables involved in the design. This is an advantage and it should be exploited to directly investigate the peculiar and different levels of the factors that regard the human being. As stated above, the disentangling of the "two faces" of reserve measures should be closely pursued in the studies.

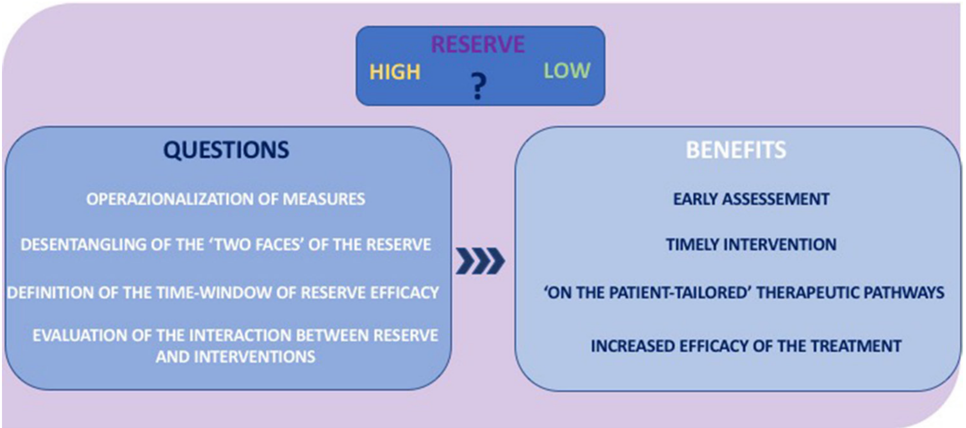

Figure 1 Panel representing the main topics that are addressed in the perspective.
On the left, the key issues on the reserves that should be investigated and clarified are listed. On the right, the principal benefits that could be gained by clarifying the listed issues are in turn listed.

In addition, it is not completely clear the time-window of action of the reserves' mechanisms. Indeed, some studies report that reserves have a modulatory effect in aging, in pre-clinical and even severe stages of AD. However, by now this point is still under debate, since some studies find reserve effects only in one of these stages. A more precise definition of the time-window of action of the reserves is needed, because it could consent a more tailored therapeutic intervention (Serra et al., 2018). We are not able to directly manipulate the timing of the reserve in the humans. Conversely, the animal model represent the ideal experimental setting to investigate this issue by direct manipulating the duration of the exposure to environmental enrichment.

Another critical point that currently is not still adequately addressed is the interaction between different levels of reserve and therapeutic interventions. Namely, a fundamental question regards the eventual variability in the efficacy of pharmaceutical/not-pharmaceutical treatments in the presence of different levels of reserve. By now, this relationship appears scarcely investigated in the literature, since the research spotlight omitted the importance of clinical application of reserve mechanisms. Therefore, specific studies that investigate the reserve/intervention relationship are currently lacking. This limitation has important repercussions in the clinical practice. According to the classical Stern model, patients with higher reserve accumulate more neuropathological damage and they arrive later to diagnosis. In this picture, it is conceivable that an intervention following the late diagnosis may be partially or completely inefficacious. If evidence is provided that high-level reserve patients could obtain more benefit from interventions in comparison to the low-level reserve ones, then it could be desirable to early assess the reserve level together with the risk to develop dementia (by using different biomarkers), in order to offer precocious treatments that maximize the advantages (**Figure 1**).

In conclusion, we have to remember that the world population is in ever-increasing aging with an exponential augment of the risk of developing neurodegenerative disorders. It is by now established that life-style shapes brain resilience. Thus, the promotion of a precocious attention to the care of the individual brain maintenance is fundamental. Also, it has to be beneficially inserted in the active clinical managing of the risk to develop cognitive decline.

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