PERSPECTIVE OPEN

Neuroglia in cognitive reserve

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The concept of cognitive reserve was born to account for the disjunction between the objective extent of brain damage in pathology and its clinical and intellectual outcome. The cognitive reserve comprises structural (brain reserve) and functional (brain maintenance, resilience, compensation) aspects of the nervous tissue reflecting exposome-driven life-long plasticity, which defines the ability of the brain to withstand aging and pathology. The mechanistic background of this concept was primarily focused on adaptive changes in neurones and neuronal networks. We present arguments favoring the more inclusive view, positing that neuroglia are fundamental for defining the cognitive reserve through homeostatic, neuroprotective, and neurodegenerative mechanisms. Neuroglia are critical for the life-long shaping of synaptically connected neuronal circuits as well as the brain connectome thus defining cognitive reserve. Neuroglial homeostatic and protective physiological responses define brain maintenance and resilience, while neuroglia regenerative capabilities are critical for brain compensation in pathology. Targeting neuroglia may represent an untrodden path for prolonging cognitive longevity.

Molecular Psychiatry (2024) 29:3962–3967; https://doi.org/10.1038/s41380-024-02644-z

THE CONCEPT OF COGNITIVE RESERVE

It is a truth universally acknowledged, that the functional consequences of brain damage are highly individual and are out of joint with the degree of the injury. The very same structural damage to the brain leads to widely different neurological and cognitive outcomes in different patients. This applies to all diseases of the central nervous system (CNS), including trauma (mechanical, toxic, or autoimmune), infection (local or systemic), or ischaemia/stroke. Similarly, individuals display widely different susceptibility to chronic diseases, as in stress-induced psychiatric disorders and in age-dependent neurodegeneration. It is the disjunction between structural brain damage and its clinical outcome, both cognitive and neurological, that lies behind the concept of cognitive reserve formalised by Yaakov Stern at the beginning of the third millennium [1–5].

Clinical and cognitive manifestations of Alzheimer's disease (AD), the most commonly diagnosed form of dementia, highlight substantial individual differences. It is undeniable that AD stems from a complex of specific genetic and molecular factors, while accumulated environment-induced alterations significantly contribute to the disease progression and cognitive deficit [6, 7]. Although early studies established a degree of correlation between mean plaque count, a hallmark of neurodegeneration, in the post-mortem brains of patients and their cognitive impairment determined antemortem, the same studies revealed individual cases with high plaque loads but preserved memory and intelligence [8]. Similarly, a study of elderly (aged 70–103 years) population found that around one-third of aged people whose neuropsychological score prior to death was unimpaired met full pathohistological post-mortem criteria for AD [9]. These findings emphasised individual differences in the capability of the brain to withstand insults and provide for functional compensation. Thus the brains were deemed different, reflecting that brain development is determined by both genetic and acquired influences; with functional training, education, intellectual and sociocultural engagement improving, through neural plasticity and systemic factors, brain resilience to aging and neuropathology [10–12]. At the same time, diseases and stresses experienced by the individual during life span lead to an accumulation of pathological burden, increasing brain vulnerability to incoming insults. Thus life experience may have both beneficial and adverse effects on the ability of the brain to withstand pathology through positively or negatively modulating the cognitive reserve.

THE COMPLEXITY OF THE COGNITIVE RESERVE

Conceptually, cognitive reserve defines an individual property of the brain to maintain cognitive performance above expected age- or disease-inflicted damage. Fundamentally, cognitive reserve is the result of the history of the interaction of every given brain with life-long exposure to environmental factors (commonly known as exposome) leading to beneficial (life-long learning, plasticity) or detrimental (accumulation of pathological changes) modifications. These interactions also depend on the genes, which encode individual brains. These modifications are specific to the nervous tissue as well as systemic, both being in the most intimate interrelation.

The cognitive reserve as it is currently considered [4] includes (i) the brain reserve, (ii) the brain maintenance, (iii) the brain resilience (this concept was initially developed in psychiatry as a

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Received: 9 March 2024 Revised: 18 June 2024 Accepted: 21 June 2024
Published online: 2 July 2024

measure of ability to tolerate environmental stress without pathological changes [13, 14]) and (iv) the brain compensation reflecting the regenerative capacity of the brain, which defines the postlesional neurological, structural, and functional recovery.

Brain reserve: a passive principle

Brain reserve (defined initially as neural or functional reserve [15]), was considered from purely anatomical view as a resource determined by the size and/or structural properties of every given brain at the time of the insult. Initially, the brain reserve was linked to the brain size (incidentally, people with larger brains have lesser prevalence of dementia [16, 17]) or the number of neurones and synapses; the larger are these numbers and the total brain size the more damage can the individual brain absorb, exhibiting higher reserve [15, 18]. The brain reserve therefore is a 'passive' principle which defines the 'threshold' of the neuroanatomical structure which has to be reached for cognitive impairments to become clinically apparent. At the same time, the anatomical architecture of the brain and neuronal connectivity are sculpted by life-long plasticity.

Cognitive reserve: an active principle

The cognitive reserve represents a more active principle, reflecting adaptations attained in the course of life. Accordingly, the brain structure is being continually remodelled through learning and memory as well as in response to insults encountered through life. Thus, cognitive reserve is a property of every individual; it reflects the life-long interaction of genetic factors with the environment, accumulated plastic (morphological and functional) changes of the nervous tissue as well as pathological damages accrued throughout life. At the moment of injury, the life-long plastic experience, which sculpts the brain structure, as well as the functional state of defensive and homeostatic systems, determines the susceptibility to the disease as well as the level of cognitive decline and/or recovery. These factors also define brain resilience which is the capacity of the brain to withstand the insult without developing the pathology.

Cognitive reserve includes other components defining the overall capacity of reserve and resilience, represented by brain maintenance and brain compensation. The brain maintenance in particular determines physiological brain ageing and cognitive longevity by employing various mechanisms preserving the brain physiology. Finally, brain compensation refers to multiple protective mechanisms aimed at the repair and regeneration of damaged neuronal circuits or damaged nervous tissue to restore brain health and cognitive capacity.

CELLULAR MECHANISMS OF THE COGNITIVE RESERVE: THE ROLE FOR NEUROGLIA

For almost a century the understanding of how the nervous system functions in health and disease focused on neurones. Therefore, it is not surprising that the neuronocentric view in neurophysiology, neurology, psychology, and psychiatry also earmarked neurones as the site of the cognitive reserve [4, 5]. The nervous tissue however is made not only of neurones, it includes non-neuronal elements, represented by neuroglia and cells of brain vessels [19]. Evolution of the nervous system progressed through the division of functions, segregating neurones, responsible for rapid information processing and transfer, and neuroglia, responsible for homeostasis and defence of the nervous tissue [20]. All cellular elements of the nervous tissue (neurones, neuroglia, and cells of vasculature) operate in the closest concert, being highly interdependent and forming the active milieu of the brain, characterised by elaborated feedback signalling [21]. Contributions of different cell types are nonetheless different being determined by specific sets of genes defining cellular functions executed in distinct time domains [22]. The role for neuronal plasticity which shapes, through learning, synaptic contacts, and connectome in defining the cognitive reserve is universally acknowledged [23]. The maintenance of massive brain vascularisation (the total length of human brain blood vessels is around 600 km [24]) is similarly critical for cognitive reserve. Both endothelial cells (the human brain contains 5–10 billions of them) and pericytes undergo complex alterations in the course of life and contribute to the age-dependent remodelling of the brain vasculature which defines blood supply and hence metabolic wellbeing of the nervous tissue. In particular, pericytes are coming to the spotlight because of their roles in brain compensation and repair [25]. In this perspective, however, we focus on the role of neuroglia, the homeostatic and defensive cells of the nervous system, which are fundamental for life-long adaptation of the nervous tissue.

Neuroglial cells (which, in the CNS are represented by astroglia, oligodendroglia, and microglia) are endowed with intricate molecular cascades controlling the nervous tissue environment in health and responding to the disease conditions through mounting defensive responses. Thus neuroglia support physiological neuroplasticity at multiple levels; neuroglial cells also define the progression and outcome of all neurological diseases [19, 26–28]. Similarly, neuroglia, acting through the cell-specific mechanisms [29], contribute and, to a large extent, define cognitive reserve (Fig. 1).

Neuroglia and the brain reserve

As mentioned before, the brain reserve is defined by a number of neurones and interneuronal connections formed by axonal projections (the connectome) and synapses. All these are regulated by neuroglia. Embryonic neurogenesis is the function of radial glia, whereas adult neurogenesis is supported by radial stem astrocytes (also known as neural stem cells, but exhibiting all major properties of astroglia [30–32]). Synaptic connectivity is regulated by astrocytes, which secrete numerous factors regulating synaptogenesis, synaptic maturation, and synaptic extinction [33–38], as well as by microglia, which remove redundant, silent or malfunctional synapses through synaptic pruning, thus shaping neuronal ensembles [39–42]. Brain-wide connectome is supported by oligodendroglia [19, 43], which is also responsible for activity-dependent myelination [44, 45]. White matter occupies ~50% of the adult human brain, in comparison with ~10% in rodents, and is one of the main determinants of the human brain computing power and cognitive abilities [19].

Neuroglia and the brain maintenance

The brain maintenance keeps all in optimal near-equilibrium steady state, defined by Claude Bernard as a stability of the *milieu interior* [46] and by Walter Cannon as homeostasis [47]. Homeostasis of the CNS (as well as in all other tissues, organs, and indeed the whole organism) is not static or fixed, but is achieved through constant adjustments to environmental challenges, termed adaptive homeostasis [48], or allostasis (*αλλο* – variable and *στασισ* - standing still - that is 'remaining stable by being variable' or 'maintaining homeostasis through change' [49]). Astroglia, the main homeostatic cells of the CNS, play the dominant role in brain maintenance. Astrocytes are central for the dynamic regulation of the ionic composition of the CNS interstitium, the ionostasis, through a wide array of dedicated pumps and transporters; astrocytes control all major biological ions (Na^+, Ca^{2+}, K^+, and Cl^- [50–52]) and trace metals indispensable for CNS function [53]. Astrocytes are key elements of neurotransmission, through neurotransmitter clearance (astrocytes express transporters removing glutamate, GABA, catecholamines, and adenosine), neurotransmitter catabolism (astrocytes convert glutamate to glutamine and degrade catecholamines and adenosine), and they supply neurones with obligatory neurotransmitter precursors such as glutamine or L-serine [19]. Astrocytes mediate neuroprotection through multiple pathways; in particular, astrocytes represent the main anti-oxidant system of

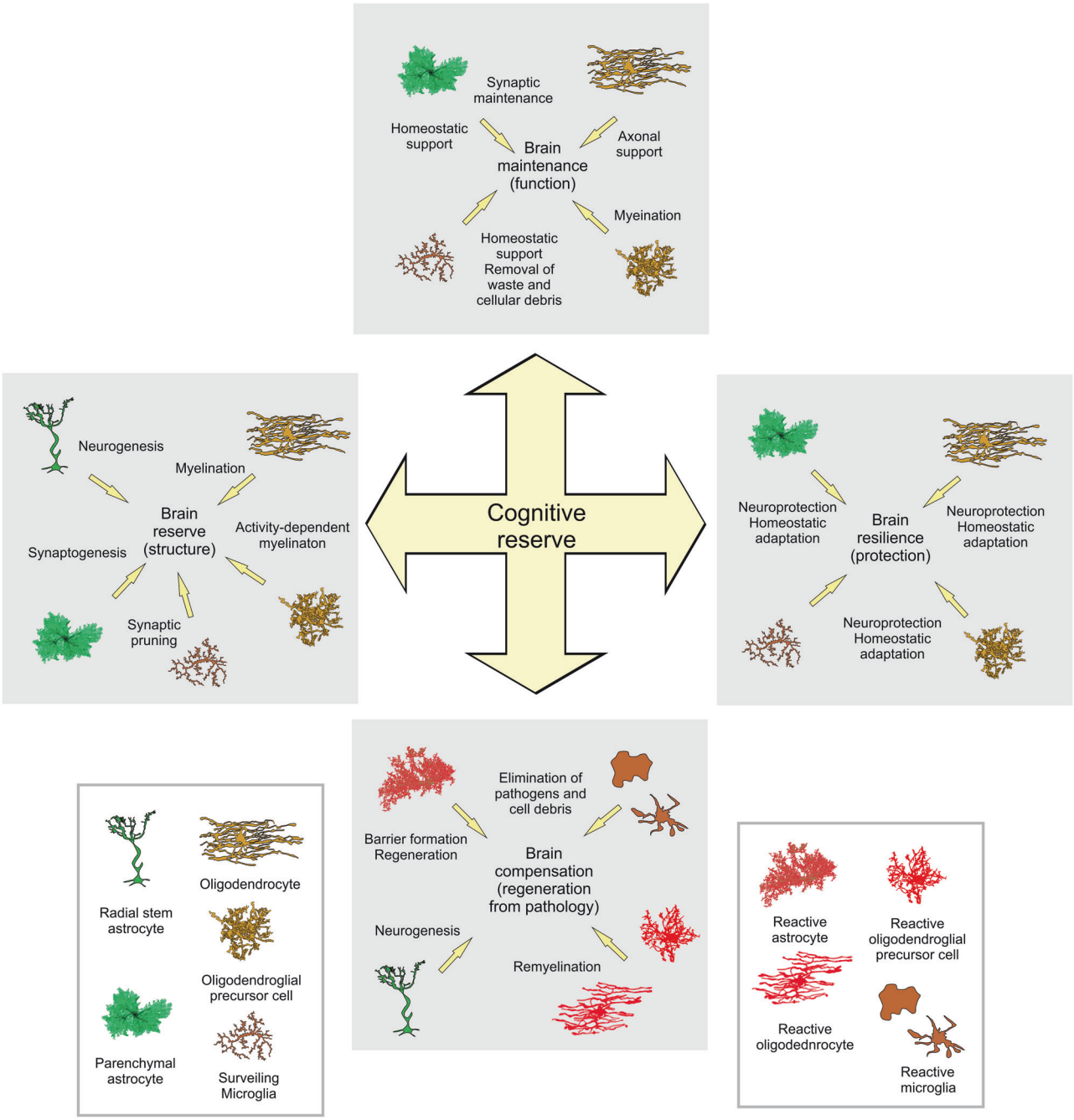

Fig. 1 Neuroglia contribution to the cognitive reserve. Neuroglial cells are fundamental for all aspects of cognitive reserve. *Brain reserve*. Neuroglia working in concert with neurones define the brain structure and shapes its cytoarchitecture. Radial glia (prenatally) and stem radial astrocytes (postnatally) provide for neurogenesis. Astrocytes, through secretion of multiple factors such as trombospondins, hevins, glypicans, and cholesterol stimulate synaptogenesis, control synaptic maturation, and provide material for the adaptive remodelling of neuronal membranes. Microglia thorough synaptic pruning and trogocytosis shape synaptically connected neuronal ensembles, while oligodendroglial cells support connectome and provide for activity-dependent life-long myelination. *Brain maintenance and brain resilience*. Neuroglial cells through multiple molecular cascades support CNS homeostasis and define brain resilience through numerous protective pathways. *Brain compensation*. Neuroglia are central element of brain defense and regeneration; reactive glial cells erect perilesional barriers, remove pathogens and cellular debris, and orchestrate regeneration.

the CNS [54–56]. Astrocytes contain glycogen and glycogenolysis results in the production of L-lactate, which can be used as fuel by neurones [57–59]. Similarly, oligodendrocytes support axons [60], while oligodendroglial precursor cells (OPCs) provide for life-long remyelination and de novo activity-dependent myelination as well as contribute to overall CNS homeostasis [61]. Finally, microglia are involved in debris removal, ongoing repairs, and maintenance of the immunological homeostasis of the nervous tissue [62].

Neuroglia and the brain resilience

The brain resilience to insults depends on the ability of the nervous tissue to absorb certain amount of damage without developing pathology. The mechanisms of resilience are obscure, although the role of neuroglia is supposedly substantial. Every insult disturbs homeostasis and these are the neuroglia that by mounting homeostatic response counteract environmental challenges. When such response is compromised the pathology

ensues. In chronic stress, for example, astrocytes demonstrate prominent atrophy, which arguably underlies loss of function and aberrant neurotransmission leading to depressive behaviours [63, 64]. At the same time in some animals subjected to the same stress astrocytes remain unperturbed, which correlates with resilience to depression (own unpublished observations).

Neuroglia and the brain compensation

Neuroglia represent the principal defensive system of the CNS. Neuroglial cells actively respond to pathology by mounting reactive gliosis, an evolutionary conserved program of glial defence [26, 28, 65]. Reactive gliosis is complex, context-, and disease-specific. Brain trauma (mechanical, infectious, ischaemic or autoimmune) triggers proliferative anysomorphic gliosis, characterised by the proliferation and accumulation of astrocytes, microglia, and OPCs close to the lesion to form the protective glial barrier. In addition, glial cells undergo substantial biochemical and morphological remodelling (some microglia turn into phagocyting macrophage-like cells clearing the debris inside the lesion core; astrocytes lose their complex arborisations and become barrier-reactive astrocytes [19, 28, 65, 66]). Glial barriers effectively protect surrounding nervous tissue, assist wound closure, and are indispensable for postlesional regeneration [67, 68]. Regeneration of the brain is also supported by neurogenesis which is provided by radial stem astrocytes [69, 70]. In chronic pathologies, including AD, astrocytes undergo isomorphic, non-proliferative gliosis; in AD reactive astrocytes together with reactive microglia surround senile plaques thus limiting neuronal damage [71–73]. This protective effect is diminishing with age and AD progression; glial paralysis at the advanced stages of the disease facilities neuronal death that translates into clinical dementia [74]. Finally, OPCs in various forms of pathologies act as a source for regenerative remyelination [61]. All in all, neuroglial cells are central for brain compensation.

Neuroglia, ageing and age-associated cognitive decline

Ageing is associated with cognitive decline and ageing is the main risk factor for neurodegenerative disorders. Physiological ageing is characterised by relative preservation of neuronal numbers [75], and a significant loss of white matter [76] associated with a decrease in number of oligodendrocytes and proliferative arrest of OPCs [61]. Both astrocytes and microglia demonstrate significant atrophy in the aged brain, which translates into decreased homeostatic support and defensive capacity [77, 78]. Ageing is also associated with tau astrogliopathy, which underlies several neurodegenerative pathologies linked to cognitive deficits [79, 80]. In particular, age-dependent tau astrogliopathy was consistently observed in the brains of 'super-centenarians' aged more than 110 years [81]. Thus age-dependent cognitive decline is, at least in part, linked to neuroglial decline and paralysis.

GLIA-BASED ENHANCEMENT OF COGNITIVE RESERVE: THE ROLE OF THE NORADRENERGIC SYSTEM

Lifestyle

Lifestyle, which includes dieting, exercise, sociocultural and intellectual engagement, is known to be a powerful factor modifying cognitive reserve and cognitive longevity [82, 83]. Experiments on various animal models and on aged animals demonstrated that, at least in part, cognition-enhancing effects of environmental stimulation and physical exercise are mediated through an increase in neuroglial morphology and homeostatic support. Brain ageing as well as chronic brain diseases are often associated with atrophy and asthenia of astrocytes and microglia; these atrophic changes can be reversed by various forms of environmental stimulation and dieting [78, 84–88]. Incidentally, replacing old atrophic astrocytes and microglia with young ones rescues cognitive deficits in aged mice [89, 90]. Exposure to enriched environment and physical exercise also improves neurogenesis in AD mice [91]; similar effect is achieved through dietary supplementation with polyunsaturated fatty acid 2-hydroxy-docosahexaenoic acid [92]. Caloric restriction induces the growth of astroglial perisynaptic leaflets; consequent increase in synaptic coverage improves glutamate clearance, K^+ buffering and translates into increased synaptic plasticity [93].

Noradrenergic innervation

At the neurochemical level, effects of environmental stimulation and lifestyle on the brain are mediated, at least partially, through the noradrenergic pan-brain innervation mainly provided by neurones of the *Locus coeruleus* (LC), a small nucleus located at the fourth ventricle; LC is the main source (~70%) of noradrenaline (NA) in the CNS [94–96]. In ageing and chronic age-dependent pathologies LC neurones degenerate thus limiting noradrenergic bioavailability [97, 98], it was even suggested that the demise of the noradrenergic system may be a possible causative factor in AD [99, 100].

Astrocytes are primary cellular targets for NA through an abundant expression of α- and β-adrenoceptors [101]. Additionally, astrocytes are the sole possessors of MAO-B, the central enzyme of catecholaminergic catabolism. Expression of MAO-B is known to increase in ageing and neurodegeneration, which may further limit noradrenergic innervation [102]. Indeed, aberrant astrocytic Ca^{2+} signals due to the reduced levels of noradrenaline were found in mouse AD model [103]. Usage of MAO-B inhibitors, reversible and irreversible, may be a valid strategy to increase cognitive reserve [102]. Transcranial direct current stimulation (tDCS), known to improve memory, facilitate motor rehabilitation, alleviate depression, and slow down the progression of cognitive impairments in AD patients [104] acts through astrocytes and their adrenoceptors. Exposure to tDCS triggers massive astrocytic Ca^{2+} signals that are inhibited by the ablation of noradrenergic neurones or by pharmacological inhibition of α_1-adrenoceptors [105, 106].

SUMMARY

Cognitive reserve reflects the life-long adaptation to the exposome that dynamically shapes the brain structure through functional use of the brain and contributes to the brain capacity to withstand the damage. Neuroglia, the principle homeostatic and defensive element of the CNS, play leading role in defining the cognitive reserve. Targeting neuroglia, both pharmacological and holistic, represents the novel strategy for improving the cognitive reserve and prolonging cognitive longevity.

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AUTHOR CONTRIBUTIONS

The authors contributed equally.

FUNDING

This work was supported by the Slovenian Research Agency grant P3 310 (Cell Physiology), I0-0048 (CipKeBip), I0-0022 (MRIC Center for Confocal Microscopy C. Zeiss), J3-2523and EU Interreg Italia-Slovenia Immunocluster-2 grants, and EU COST actions CA18133 (ERNEST) and CA18240 (Adher'n Rise).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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