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REVIEW ARTICLE

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Early compensatory responses against neuronal injury: A new therapeutic window of opportunity for Alzheimer's Disease?

Sara Merlo | Simona Federica Spampinato | Maria Angela Sortino

Department of Biomedical and Biotechnological Sciences, Section of Pharmacology, University of Catania, Catania, Italy

Correspondence: Maria Angela Sortino, Department of Biomedical and Biotechnological Sciences, Section of Pharmacology, University of Catania, Via S. Sofia 97, 95125 Catania, Italy (msortino@unict.it).

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Summary

Alzheimer's disease (AD) is characterized by extensive neurodegeneration and inflammation in selective brain areas, linked to severely disabling cognitive deficits. Before full manifestation, different stages appear with progressively increased brain pathology and cognitive impairment. This significantly extends the time lag between initial molecular triggers and appearance of detectable symptoms. Notably, a number of studies in the last decade have revealed that in the early stage of mild cognitive impairment, events that appear in contrast with neuronal distress may occur. These have been reproduced in vitro and in animal models and include increase in synaptic elements, increase in synaptic and metabolic activity, enhancement of neurotrophic milieu and changes in glial cell reactivity and inflammation. They have been interpreted as compensatory responses that could either delay disease progression or, in the long run, result detrimental. For this reason, these mechanisms define a new and previously undervalued window of opportunity for intervention. Their importance resides especially in their early appearance. Directing efforts to better characterize this stage, in order to identify new pharmacological targets, is an exciting new avenue to future advances in AD research.

KEYWORDS

beta-amyloid, cognitive impairment, compensation, glial reactivity, neurodegeneration

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative condition characterized by extensive neuronal damage and death, with consequent progressive decline in cognition, up to the total loss of self-sufficiency in all basic skills. AD includes rare familial forms with an early onset and a more common sporadic form that primarily affects the elderly. The increased average age of the world's population, makes it a major emergency for modern society. From a molecular point of view, two main factors play a major role in the pathophysiology of AD, beta amyloid peptide (Aβ) accumulation and hyper-phosphorylation of tau protein. Although the latter is receiving increasing attention, Aβ has been assigned a leading role in triggering the sequence of events that result in the serial stages of AD development.[1–3] Aβ is prone to aggregation into species of progressively higher molecular weight, ranging from oligomeric (oAβ) to protofibrillar and fibrillar, with different relevance as pathological effectors. To date, oAβ is acknowledged as the most synaptotoxic aggregate.[4,5] oAβ specifically interacts with a variety of receptors on the surface of both neuronal and glial cells, evoking signaling cascades that in turn modify the cellular profile of gene transcription/protein expression.[6–9] In general, research on Aβ toxicity has focused mainly on its detrimental effects, culminating with significant declines in synaptic activity, neuronal metabolism, neurotrophic factors, as well as increased glial activation/inflammation. However, a more attentive look at the literature of the last two decades, points out the existence of a biphasic trend where all these reductions are preceded by transient paradoxical rises.[10,11] These were described in AD patients and replicated in animal and in vitro models and were interpreted as compensatory responses to initial damage. Compensation likely contributes to central nervous system (CNS) resilience, conferring the ability to "tolerate" greater amounts of Aβ and delay appearance

of symptoms. This would be in agreement with the lack of a constant correlation between levels of Aβ pathology and actual degree of cognitive impairment.[12]

Thus, since the strategies that focused on late interventions on AD were all unsuccessful, focusing on the early compensatory mechanisms represent an alternative therapeutic strategy that deserves more attention for future research in the field. We will here present an up-to-date summary on paradoxical compensatory responses in AD, individually reviewing the main biological processes involved.

2 | SYNAPTIC ELEMENTS

In a modern perspective, with increased knowledge of underlying molecular mechanisms, AD can be described as a "synaptic failure".[13,14] Synapses are in fact key elements in AD, and there is a clear correlation between their dysfunction or loss and onset of dementia.[14–17] Focusing specifically on changes in synaptic structure and function during disease progression is thus of paramount importance for therapeutic developments. The first observations of a biphasic trend of expression for synaptic components, with an early but transient increase, followed by reduction as neurodegeneration progresses, date a couple of decades back. A number of studies, carried out on human subjects and transgenic animal models, started to report what was then described as an "unexpected" or "paradoxical" increase in glutamatergic, cholinergic, and GABAergic presynaptic bouton density.[18–22] This always appeared upstream of extensive neurodegeneration and before appearance of important cognitive deficits. Furthermore, a compensatory upregulation of hippocampal 5-HT1A receptor density was shown in the early stage of MCI, whereas a dramatic decline was found at later stages of AD.[23] Such compensatory increase in receptor density, evaluated by positron emission tomography (PET), was observed in the hippocampus (HC) of an experimental rat model, as a consequence of induced reduction in serotonin levels.[24]

The same biphasic pattern of expression was later shown for a number of synaptic components, for which reduction is a late-stage event in different regions of postmortem AD or demented elderly brains. Some examples are presynaptic proteins synaptophysin (SYP), synaptopbrevin, SNAP-25, rab 3A, and postsynaptic proteins such as syntaxin, drebrin, and PSD-95.[25–29] This observation was reproduced in AD animal models[30–32] and in vitro models.[33–35] In early stages, again coincident with mild cognitive symptoms, many of these were found to be transiently increased.[26,29,36] Among others, synaptic vesicle component SYP has been a distinctive marker for evaluating synaptic conditions. In general, SYP increase is associated with improved synaptic function. Higher levels of SYP correlated with yet normal cognition in older people displaying extensive A brain pathology, compared to cognitively impaired AD patients.[29] In addition, in 3xTg-AD animal brains, SYP region- and time-selective upregulation appeared even after an initial loss of synaptic components.[37] This compensatory rise was related to partial recovery of cognitive functions, followed by SYP loss as symptoms worsened. In our own recent studies, in a model of slow-developing neuronal damage, obtained by exposing rat organotypic hippocampal slices to sub-lethal concentrations of oAβ42, we showed an initial compensatory increase in SYP levels and vesicle recycling.[35] A similar trend was evident for postsynaptic density protein PSD-95.

Altogether, these results confirm the existence of a combined attempt to compensate for reduction in synaptic connections with an overexpression of the main players involved, as here discussed.

3 | NEURAL ACTIVATION

The compensatory structural changes induced by Aβ toxicity in synapses, find a correlate in intensification of neural activity, as seen by functional magnetic resonance imaging (fMRI) studies.[38] In particular, hyperactivation appeared in selective brain areas and exclusively where Aβ accumulation was detected, as shown by fMRI studies comparing MCI patients and normal subjects with or without Aβ deposits.[39–43] In the presence of neuronal hyperactivity, cognition was transiently ameliorated, although this effect was only evident below a threshold degree of neuronal damage. In agreement, in MCI patients, hyperactivation shifted among different brain areas as disease progressed, coming into play to selectively compensate specific compromised functions depending on disease severity.[44] The compensatory and beneficial nature of neural hyperactivation finds support in the observation that nondemented older individuals, carrying the ApoE 4 allele, achieved memory, and learning performances comparable to their matched 3 counterparts by activating compensatory mechanisms.[45]

Also in animal models of AD, neuronal hyperactivity occurs early during disease development, even before plaque appearance.[46,47] Based on animal and in vitro studies using sub-lethal concentrations of Aβ for slow development of neuronal damage, early improvements in synaptic plasticity and memory were proposed to be mediated by an increased rate of neurotransmitter release. With time, however, this would be responsible for excitotoxic damage and decline of these functions.[48]

Unexpectedly, several molecules not exclusively linked to neuronal activation, also show a biphasic pattern of expression during disease progression. For example, in presymptomatic AD mouse models, a compensatory mechanism acts through upregulation of nitric oxide (NO) synthase and recruitment of NO. In turn, NO signaling would increase calcium responses and rescue synaptic plasticity. This phenomenon once again appears transient and counteracts maladaptive synaptic depression that takes places later on as AD progresses.[49] Similarly, Chol-1α gangliosides, selectively expressed in cholinergic neurons, are increased in the frontal lobes of AD patients as a compensatory event aimed at preserving cholinergic transmission.[50]

The real significance of compensatory mechanisms involving neural activation as a protective strategy in AD is still a rather controversial issue. While on the one hand improved neural activity is indicative of a rescued function, hyperactivation can in the long run lead to excitotoxicity, potentially exacerbating neuronal damage.

4 | BRAIN METABOLIC ACTIVITY

According to recent research, transient compensatory responses in early AD include increased brain glucose metabolism, as determined by [18F]-fluoro-deoxyglucose PET (FDG-PET) scans.[51–54] However, discrepancies emerged regarding the real correlation between rate of glucose consumption and the degree of Aβ deposition. FDG-PET analysis in a group of MCI subjects with different levels of Aβ pathology, revealed that increased metabolic rate in selective cortical areas was limited to subjects with lower Aβ levels. Therefore compensation is an early event followed by a decline in brain metabolism as Aβ load worsens.[51] In a different study, brain metabolism was correlated directly to Aβ load in MCI, but inversely in AD.[54] Despite apparently discordant results on the correlation with levels of brain pathology, both studies showed that metabolic compensation was protective and delayed MCI to AD conversion. A biphasic pattern of glucose metabolism was also reported in Down syndrome patients, wherein a stage preceding dementia was characterized by hypermetabolism that decreased progressively as disease developed.[55] In contrast, such positive correlation was not confirmed in a recent study enrolling a heterogeneous population of cognitively impaired patients. In this case, hippocampal hypermetabolism was interpreted as a maladaptive, detrimental event, rather than a beneficial compensatory response.[56] Results obtained in animal models appear in line with clinical data, as a peak in brain metabolic rate was described in Tg2576 AD mice at 7 months of age, progressively decreasing to reach wild type levels by 19 months of age.[57] Curiously, authors negatively interpreted these data as a limitation to translatability of the animal model, although actually in line with the compensatory response observed in patients.

Hypermetabolism in MCI was also associated with insulin resistance (IR), an established risk factor for AD,[58] in a study relating IR with FDG metabolism in AD-vulnerable brain areas.[59] IR was associated, in a region-specific fashion, with hypermetabolism in MCI-progressors to AD as opposed to MCI-stable subjects, and with hypometabolism in AD. Although the role of IR is currently unclear, such biphasic trend observed selectively in MCI progressors is suggestive of a transient compensatory effect induced by IR during AD pathogenesis.

Quite interestingly, glucose hypermetabolism was also shown to underlie the impact of education on the degree of tolerance to Aβ before appearance of cognitive symptoms.[52] In fact, intellectual enrichment delayed the rate of cognitive decline in AD patients, compared to lower degree of education.[60] As the level of education is not always taken into account, this finding could be relevant to explain discrepancies among studies.

5 | NEUROTROPHIC MILIEU

Neurotrophins are a family of small peptides comprising brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophins-(NT) 3 and 4/5, each acting through selective receptors. Neurotrophins impact CNS development and homeostasis, as well as synaptic modeling and function,[61] so that any imbalance in the neurotrophic environment will inevitably take a toll on neuronal function and survival. A plethora of studies have explored BDNF expression in brain and plasma from patients at different disease stages, from MCI to early and advanced AD, as well as in animal models and in vitro studies, yielding extremely variable results (extensively reviewed in [62,63]). As mentioned before, variability likely derives from the stages of progression of disease, which may be difficult to compare considered the now well-acknowledged lack of correspondence between degree of pathology and degree of cognitive symptoms in AD. In particular, the transient nature of compensatory responses makes them potentially difficult to identify. Nevertheless, it is again possible to discern a trend of biphasic expression of BDNF, where a compensatory increase appears early and is followed by a drop in advanced AD.[62] Increased serum levels of BDNF correlated with slower worsening of cognitive symptoms in a study comparing slow vs fast declining AD patients.[64] Intriguingly, early administration of the orally bioavailable neurotrophic compound P021, able to induce BDNF expression, rescued cognitive impairment in different animal models of aging and AD.[65] This is a promising result that identifies the support of the neurotrophic milieu during compensatory phases as a potential new strategy.

Increased expression was described for NGF and its pro-form. However, this was a late event in advanced AD, when BDNF levels were already declined.[66–70] Thus, it implicates mechanisms other than a compensatory survival attempt.

6 | OXIDATIVE STRESS RESPONSES

Oxidative stress, deriving from imbalance between production and removal of reactive oxygen species (ROS), is an early event in AD.[71,72] Due to its high oxygen consumption, the brain is exposed to particularly high ROS concentrations. With ageing, alterations in the ability to counteract oxidative stress make the brain even more prone to accumulate ROS, which promote neuronal damage and death.[73] In agreement, levels of expression/activity of antioxidant enzymes, such as Cu/Zn- and Mn-superoxide dismutase (SOD), were reported to be decreased in AD brains compared to control subjects.[74–76] Interestingly, a compensatory increase in the expression of Mn-SOD and glutathione reductase (GSSG-R) proteins was described in MCI.[77] Even in AD patients, protein and mRNA levels of glutathione peroxidase, GSSG-R and catalase were increased, compared to control subjects, in selective areas also characterized by increased lipid peroxidation.[78–80] Altogether these results are suggestive of a compensatory local rise in response to increased ROS levels, which may even persist through AD and precede loss of antioxidant function. Accordingly, expression of the anti-oxidant heme oxygenase-1 was increased in temporal cortex and HC in MCI as well as AD and this negatively correlated with cognitive performances.[81] Once again, this implies attempts to realize compensatory mechanisms against oxidative stress. Evidence that a generalized compensatory response

is able to actually contrast oxidative stress comes from studies on AD patients. Evaluation at different stages of pathology showed that oxidative damage was highest at early stages but decreased with progressive A deposition and concurrent disease progression. Of note, this correlation appeared more significant in ApoE 4 carriers.[82]

An additional source of oxidative damage in AD is the presence and redox state of copper and iron.[83] Accordingly, the copper-binding protein ceruloplasmin, responsible for copper entry in the brain and for the redox state of iron, was increased in selective AD-vulnerable brain areas, suggesting a compensatory response to locally increased oxidative stress.[84]

Finally, lysosomal activation and autophagy emerged as antioxidant protective mechanisms that also undergo a compensatory induction early in AD.[85,86] However, later in disease progression as the load exceeds lysosomal clearance capability, they become unsuccessful.[87]

7 | NEUROGENESIS

Adult neurogenesis continues throughout adult life in the dentate gyrus (DG) of the HC and in the subventricular zone (SVZ) of the mammalian brain. Here, newly generated neurons are integrated into local circuitries, where they play a role in plasticity of the HC and olfactory system.[88,89] Ageing and disease modify the neurogenic potential of the brain, with a general trend toward its decline.[90] Impairment in neurogenesis is counteracted by a compensatory increase as observed in patients and in AD animal models. Likewise, in the ageing brain, declining neuronal functions are compensated in individuals with preserved neurogenesis.[91]

Postmortem brain studies of AD patients showed increased hippocampal neurogenesis in DG and CA1.[92] A more detailed study further showed that alterations in neurogenesis vary differently during specific phases of the neurogenic process and in selective neurogenic niches, depending also on the stage of progression of AD. In particular, progenitor stem cells in the DG decreased in early AD stages, an effect contrasted by a compensatory increase of transit-amplifying cells.[93] Accordingly, increased neurogenesis appeared consistently during AD progression in animal models although at variable stages of disease. Enhanced proliferation and increased expression of immature neuronal markers were shown in both the DG and SVZ of APPswe/PS1dE9 mice at 3 months of age. These changes preceded amyloid deposition and neuronal loss, indicative of early compensatory responses likely triggered by early neuronal dysfunction.[94] More studies on different genetic mice models of AD confirmed a compensatory increase of neurogenesis in younger animals, followed by decreased hippocampal adult neurogenesis at older ages.[95–97] In contrast, a similar increase was also reported in older animals, already affected by memory impairment and Aβ deposits.[98] It is interesting to note that increased proliferation of progenitors was not always followed by an actual development of new cells into mature and functional network-integrated neurons.[93,99] On the whole, these data show that despite the lack of a uniform time/regional pattern of activation of compensatory neurogenesis, its promotion may represent an important defense mechanism against disease progression. Accordingly, drugs and hormones that are known to upregulate neurogenesis, such as the acethylcholinesterase inhibitor galantamine, the NMDA antagonist memantine, estrogen and allopregnenolone or the dopamine D2/3 receptor agonist pramipexole, have a great anti-neurodegenerative potential as from in vitro and in vivo studies.[100–104]

Of note, as evidenced for other responses, the contribution of environmental enrichment in potentiating compensation was demonstrated also for neurogenesis, where it rescued reduced survival and maturation of newly generated neurons.[105]

8 | GLIAL CELLS

It has long been established that glial cells not only provide structural support to neurons, but also hold an active role in neuronal development and function. At the synaptic level, neuronal and glial cells closely interact, with glia directly modulating synaptic transmission.[106,107]

Microglia show two phases of activation that occur early and late in disease progression. Longitudinal PET studies on MCI vs AD patients over a 14-month follow-up, showed in fact in MCI the appearance of an early peak of an anti-inflammatory, protective microglial phenotype. However, as amyloid load increases and probably exceeds its clearance capacity, a secondary activation begins that switches microglia to a pro-inflammatory phenotype.[108] It is known that overexpression of the transmembrane triggering receptor expressed on myeloid cells 2 (TREM2) favors an anti-inflammatory phenotype in primary microglia exposed to increasing amyloid concentrations. Accordingly, a compensatory upregulation of TREM2 occurs during disease progression in a transgenic AD mouse, and this correlates with improved pathology and cognition.[109] Of note, TREM-2 overexpression, at further disease stages, failed to provide neuroprotection and did not correlate with improvement of neuropathology or cognitive impairment,[110] suggesting that TREM-2-mediated protection yields significance only at a particular disease phase, likely depending on microglial functional condition.

What happens in microglia is sometimes recapitulated in astrocytes and both cell types ameliorate neurotrophic environment in models of AD. For instance, astrocytic and microglial production of BDNF is significantly increased around plaques in transgenic mice[111] and selectively in rat primary microglial cells exposed to sub-lethal concentrations of oligomeric Aβ42.[112]

With regard to astrocytes, several controversies still exist on the real function of their reactivity in AD pathogenesis.[10] The appearance of a reactive astrocytic phenotype is a relatively early event occurring before the appearance of Aβ deposits both in AD mouse models[113] and in AD patients.[114] Such astrogliosis represents a compensatory event and in fact dampening of this activation increased the number of dystrophic neurites[115] and accelerated plaque formation in APP/PS1 mice.[116]

In contrast, others described the appearance of hypertrophic astrocytes with increased GFAP levels only as a consequence of Aβ deposition and only surrounding plaques at late disease stages in transgenic mice.[117,118] Interestingly, these divergent responses appeared to be region specific. The same group reported in fact the coexistence of hyper/hypotrophic astrocytes in the HC, but not in the entorhinal cortex (EC) where only the hypotrophic phenotype was detected at all disease stages.[117,119,120] According to the Authors, the hypotrophy observed in EC may contribute to the higher vulnerability of this area to AD pathology,[120] confirming that the lack of reactive gliosis correlates with a negative outcome. Another study analyzed astroglial reactivity in the post mortem EC region of subjects with AD pathology associated (AD-D) or not (AD-N) with dementia.[121] Both were characterized by an increased number of GFAP+astrocytes in layer I/II compared to normal brain. However, in AD-N subjects, these displayed thicker and longer processes, indicative of glial reactivity, together with enhanced glutamate transporter-1 (GLT-1) expression. As these astrocytes play an important role in preservation of synaptic transmission to CA1, their selective reactivity in the AD-N group was suggested as a compensatory mechanism in response to synaptic damage.[121]

Of note, astrocytic compensation in old 3xTg-AD mice and AD patients also involves membrane Kir6.2 channels, whose function results in enhanced glutamate uptake.[122]

Finally, in line with the hypothesis of astrogliosis coming into play after Aβ deposition/later into disease development, exposure to Aβ in vitro, or the presence of Aβ deposits in TgCNRD8 AD animals, modified astrocytic bioenergetics through upregulation of the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB3). This increases neuronal supply of lactate as an alternative energy source, under conditions of impaired oxidative phosphorylation processes. Notably, inhibition of PFKFB3 made astrocytes vulnerable to Aβ toxicity.[118]

9 | CONCLUSIONS

Compensatory mechanisms in AD have been well documented over the years. They appear early, transiently, and selectively in brain areas affected by the disease, comprising a wide spectrum of biological processes involved in brain function and homeostasis. These are all somehow linked to one another and give life to a concerted series of actions: strengthening of synaptic structure is linked to upregulation of synaptic activity, also contributed to by neurogenesis, with delivery of new neurons into the disrupted network. Concurrently, brain metabolism increases and protective antioxidant activity is potentiated. All the while, glial cells are activated to contribute putting into place all these responses. Although most likely originating as an attempt to contrast conditions harmful to neurons, it is not yet clear whether the final outcome of compensation can indeed be a positive one. On the one hand, data seem to suggest that compensatory responses

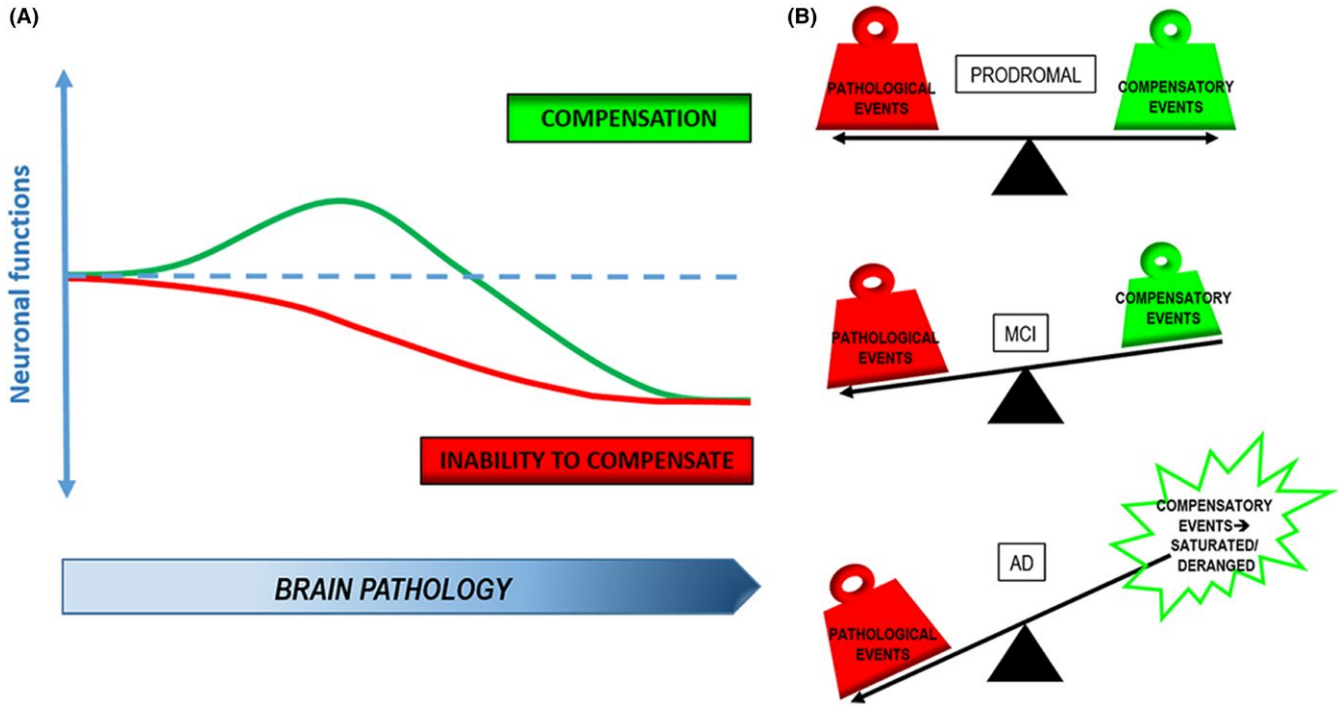

FIGURE 1 Compensation as a neuroprotective strategy in AD. A, As Aβ/tau brain pathology increases, compensatory events come into play to counteract the decline in neuronal functions and confer increased tolerance to brain pathology. Inability to adopt compensatory responses results in an earlier decline. B, Compensatory events evenly balance pathological ones in early prodromal stages of disease, but they begin to fail due to overload of pathology in MCI until they are no longer able to efficiently contrast pathology, or even become detrimental, in severe AD

succeed in promoting resilience to pathology progression. On the other hand, paradoxical increases in processes like neural activity or autophagy may also lead to exacerbation of neuronal damage. The existence of different thresholds of neuronal resistance to insults has been described as *cognitive reserve*.[123] This has a primary role in determining an individual's ability to activate compensation against incipient brain decline in AD (Figure 1). So, in our hands, it seems logical to infer that enhancement of compensatory events will most likely be an effective strategy, making it mandatory to shift attention to the cellular mechanisms at the heart of the axis *cognitive reserve-compensation-resilience*. In perspective, exploiting the beneficial fallouts of compensation, while containing the negative, will offer new grounds for disease modifying or even preventive approaches in AD.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Sara Merlo http://orcid.org/0000-0002-6558-9800

Simona Federica Spampinato http://orcid.org/0000-0001-7564-1986

Maria Angela Sortino http://orcid.org/0000-0002-2734-1521

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