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Trajectories and contributing factors of neural compensation in healthy and pathological aging

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ABSTRACT

Neural degeneration is a hallmark of healthy aging and can be associated with specific cognitive impairments. However, neural degeneration per se is not matched by unremitting declines in cognitive abilities. Instead, middle-aged and older adults typically maintain surprisingly high levels of cognitive functioning, suggesting that the human brain can adapt to structural degeneration by neural compensation. Here, we summarize prevailing theories and recent empirical studies on neural compensation with a focus on often neglected contributing factors, such as lifestyle, metabolism and neural plasticity. We suggest that these factors moderate the relationship between structural integrity and neural compensation, maintaining psychological well-being and behavioral functioning. Finally, we discuss that a breakdown in neural compensation may pose a tipping point that distinguishes the trajectories of healthy vs pathological aging, but conjoint support from psychology and cognitive neuroscience for this alluring view is still scarce. Therefore, future experiments that target the concomitant processes of neural compensation and associated behavior will foster a comprehensive understanding of both healthy and pathological aging.

1. Introduction

When neural tissue or circuitry in the human brain degenerates with age, this becomes more or less obviously detectable by using macroscopic neuroimaging methods or by studying subtle markers in the serum or liquor. However, it is striking to note that such signs of neural degeneration hold only very limited value in inferring an individual's cognitive state or behavioral abilities. For instance, while manifest dementia or cognitive impairment can typically be traced back to neural degeneration, the reverse is not always true. This indicates that the human brain can counteract structural degeneration to a degree that psychological functions (perception, cognition, behavior) are only minimally or partly compromised. While this so-called neural compensation has previously been discussed (Cabeza et al., 2018; Raz, 2009), the mechanistic details and its predictive value in distinguishing healthy brain aging from its pathological or more malign variants still remain unclear. Delineating this gap in our current understanding is a key goal of this review.

One of the most prominent theoretical frameworks on neural compensation is the "Scaffolding Theory of Aging and Cognition" (STAC) (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014). It suggests that healthy aging is associated with "neural challenges", including white and grey matter degeneration, and "functional deterioration", including dedifferentiation or reduced cortical activity, as shown in several studies (Biel et al., 2021; Bunzeck et al., 2007; Steiger et al., 2016). These processes are being ameliorated by "compensatory scaffolding", including bilateral or enhanced recruitment of secondary brain regions, distributed processing and enhanced connectivity, to uphold cognitive and behavioral functioning. For example, older adults typically show lower memory scores and lower functional activity within the medial temporal lobe (MTL) (Cabeza et al., 2004) as well as changes in the default mode network (Raichle et al., 2001; Reuter-Lorenz and Park, 2010). Importantly, high performing-older adults showed bilateral, instead of unilateral, prefrontal cortex (PFC)

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activity in a memory retrieval task suggesting neural compensation through the recruitment of a more distributed neural network to maintain behavioral functioning (Cabeza, 2002; Cabeza et al., 2002). Several more recent studies, not only including fMRI but also EEG, are compatible with such a view (Guran et al., 2022; Steiger et al., 2022).

A second prominent framework is the "Compensation-Related Utilization of Neural Circuits Hypothesis" (CRUNCH) (Reuter-Lorenz and Cappell, 2008). It is based on the observation that neural activity typically scales with task demands in a quadratic fashion, as evident in prefrontal theta (4–8 Hz) and alpha (8–13 Hz) oscillations (Eckart et al., 2016, 2014). Importantly, the underlying quadratic function is assumed to be shifted to the left (i.e., towards lower levels of demand) in older individuals, possibly due to lower neural resources. Therefore, age-related differences in the link between brain activity and behavior strongly depend on task demands. Evidence for CRUNCH is mainly based on working memory studies showing that age-related neural activity (Cappell et al., 2010; Proskovec et al., 2016; Schneider-Garces et al., 2010) and connectivity (Heinzel et al., 2017) patterns in the PFC depend on memory load. Therefore, a parametric modulation of task demands can be important to understand and fully interpret age-related differences in brain activity and their link to behavior.

Taken together, STAC and CRUNCH are fundamental models in cognitive aging research. They are complementary in several ways, and they offer an important framework for future investigations on the notion that overactivations in older adults reflect neural compensation promoting cognition and behavior. Most importantly, despite initial evidence, most studies (see below) do not report a direct relationship between structural degeneration, overactivation (i.e., neural compensation) and behavior. Therefore, these core elements of STAC and CRUNCH remain indirect and should be addressed in future work.

2. Types of neural compensation

In an elegant attempt to more systematically pinpoint the concept of neural compensation, Cabeza et al. (2018) differentiated three types of compensation: compensation by *upregulation*, compensation by *selection*, and compensation by *reorganization* (Fig. 1). While these differ in several ways, their common element is that neural compensation is a change in neural activity (or connectivity) due to structural degeneration to promote behavior and cognition.

Upregulation describes a *quantitative* difference in neural activity between young and older adults to reach an adequate level of performance. In other words, the same underlying brain regions are involved in a given task, but with significantly more activity in older adults. Ideally, this also includes a systematic relationship with behavior to exclude inefficient processing or dedifferentiation (Cabeza et al., 2018; Knights et al., 2021; Reuter-Lorenz and Park, 2010). Upregulation appears to be well documented and includes several domains, such as perception, memory encoding and retrieval as well as executive functioning (Spreng et al., 2010). Yet, how exactly increases in neural activity (including network measures such as functional connectivity) relate to changes in behavior and structural degeneration, remains unclear.

Selection describes *shifts* in the involvement of underlying brain

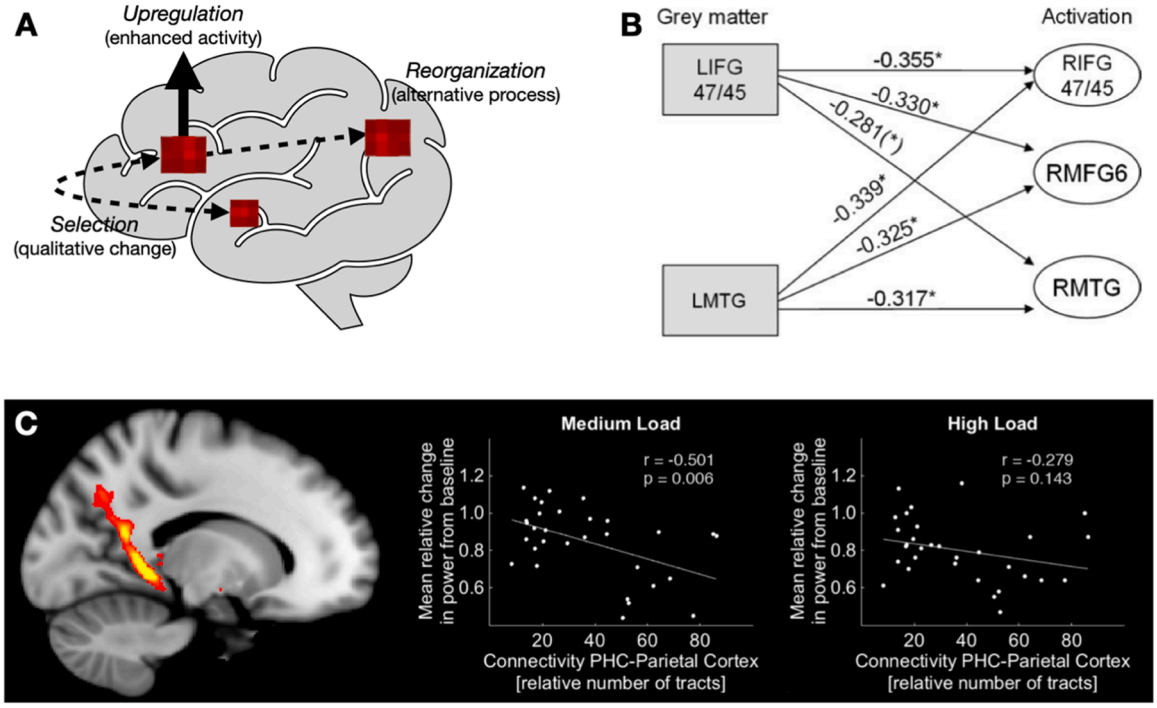

Fig. 1. **A** Schematic depiction of three possible types of neural compensation, as suggested by Cabeza et al. (2018). In older adults, structural degeneration may be compensated through ***upregulation*** (i.e., enhanced neural activation), ***selection*** (i.e., a qualitative change in neural activation), or ***reorganization*** (i.e., the use of an alternative neural process) to achieve an optimal level of behavior. See text for further explanation. **B** In a language processing tasks, preserved syntax in healthy middle-aged and older adults (49–86 years) was associated with increased activation in the fronto-temporal cortex (including right inferior frontal gyrus, RIFG, right middle frontal gyrus, RMFG, and right middle temporal gyrus, RMTG), which negatively correlated with grey matter in the left fronto-temporal cortex (including left inferior frontal gyrus, LIFG, and left middle temporal gyrus, LMTG). This is compatible with neural compensation by upregulation. (*) $p < 0.1$; * $p < 0.05$. **C** In a working memory study with healthy middle-aged and older adults (56–78 years), tract strength between the parahippocampal cortex (PHC) and parietal cortex, as measured with DTI (here shown for one single subject, thresholded at 25% connectivity for display purposes), correlated with load-specific power change in the theta-alpha band (5–12 Hz) as derived from EEG. This multimodal investigation of a structure-function relationship is compatible with STAC and CRUNCH, and may serve as a blueprint for future work.
(b) Adapted from Tyler et al. (2010), published under a Creative Commons Attribution Non-Commercial License. (c) Adapted from Steiger et al. (2019), published under a Creative Commons Attribution 4.0 International License.

regions and associated behavior in older adults while performing the same task. In a long-term memory task, younger adults typically show higher recollection scores (i.e., recognition associated with recollective experiences of the encoding episode) and hippocampal activation; older adults, on the other hand, show higher familiarity scores (i.e., recognition without recollective experiences) and activity in the parahippocampal region (Daselaar et al., 2006). Thus, while overall recognition memory may not differ between younger and older adults, which we have also previously observed (Guran et al., 2022; Packard et al., 2020; Yousuf et al., 2021), the *quality* of memory and associated neural processes can change. However, neurophysiological evidence of age-related compensation by selection in favor of a different cognitive domain, is scarce.

Finally, reorganization refers to the use of an *alternative* neural process or network in older adults due to neural degeneration. Importantly, these neural processes are not available to younger adults, which is a main difference to selection. The most prominent example in this context has already been mentioned above: in younger adults, the successful retrieval of information from long-term memory typically includes the left PFC, but in high-performing older adults, it is associated with bilateral PFC activity indicating functional reorganization to promote behavior (Cabeza et al., 2002). Despite the popularity of this example, there is only limited evidence from other cognitive domains and, importantly, for a direct relationship with structural degeneration in healthy older adults.

In sum, age-related neural degeneration may be compensated by upregulation, selection and reorganization to achieve an optimal level of cognition and behavior. While these concepts greatly help to systematically characterize neural and behavioral changes during healthy and pathological aging, it is also clear that direct empirical evidence for this tripartite organization of neural compensation is limited.

Along these lines, a sharp distinction from alternative explanations, such as inefficient processing or dedifferentiation (Knights et al., 2021), requires clear-cut evidence in favor of specific relationships between neurodegeneration, function and behavior. Such evidence can be obtained through state-of-the art methods and analysis tools, including multivariate pattern analysis (MVPA), neural variability measures or resting-state (rs)fMRI and rsEEG. Finally, upregulation, selection and reorganization are not necessarily mutually exclusive (Cabeza et al., 2018), but they could, in principle, jointly counteract structural degeneration. Therefore, future studies will need to address how different types of neural compensation are implemented in the human brain to allow for adaptation to environmental needs. Further, age-related structural degeneration is a rather slow process, which can take years or even decades (Coupé et al., 2017; Planche et al., 2022), but the timescales of neural compensation, especially reorganization, can be much faster (e.g., after recovery from lesions). This issue will be best addressed by longitudinal designs and by investigating participants with different age-related diseases (see below) in combination with different imaging modalities.

3. Compensation of structural degeneration: the need for multimodal imaging

First hints for a direct link between structural integrity, functional compensation and behavior, were identified by Tyler et al. (2010) who focused on language abilities in a study combining behavioral measures (word-monitoring task), fMRI and structural MRI. They showed that preserved syntax in middle-aged and older humans (49–86 years) is associated with increased activation in the right fronto-temporal cortex, which in turn was negatively correlated with structural integrity in the left fronto-temporal cortex (which typically serves language processing, Fig. 1**B**). This result, together with a similar finding on language processing using graph theoretical approaches (Meunier et al., 2014), and a study on long-term memory using multivariate behavior partial-least-squares analysis (Snytte et al., 2022), strongly argues in favor of a behaviorally relevant link between neural compensation and neural degeneration. Therefore, these studies, which employed a combination of functional and structural measures in healthy young and older humans, could serve as a blueprint for further investigations (see also Daselaar et al., 2015). To this end, a focus on a wider range of cognitive domains, such as sensation, perception, working memory, long-term memory, or cognitive control, in combination with additional methods, such as EEG and TMS, will provide further insights into the underlying neurobiology and causal relationships.

Age-related structural degeneration has often been investigated using T1-weighted structural MRI images. However, recent advances, especially MRI based multi-parameter mapping (MPM) and more commonly, diffusion tensor imaging (DTI), allow us to estimate tissue microstructure properties, including iron levels and demyelination, that could serve as more detailed biomarkers (Tabelow et al., 2019; Weiskopf and Helms, 2008). For instance, iron levels and myelin content in the ventral striatum predicted memory performance in the healthy aging brain (Biel et al., 2021; Steiger et al., 2016); and working memory performance in older humans related to theta-alpha oscillations (5–12 Hz), which correlated with tract strength between the parahippocampal and parietal cortex (Fig. 1C, Steiger et al., 2019). Moreover, in patients with Parkinson's disease (PD), iron load within the basal ganglia was closely related to motor phenotype, which is a key indicator of disease progression (Bunzeck et al., 2013).

Despite advantageous methodological developments, several caveats need to be considered in future research. First, changes or group differences in univariate fMRI activity need to be interpreted with caution since they do not necessarily reflect changes in "efficient" neural processing. Therefore, future studies should be based on multimodal imaging, including structural MRI in combination with pattern classification (Haxby, 2012; Kriegeskorte et al., 2008) and network analyses (Bullmore and Sporns, 2009; Lee et al., 2013; Zang et al., 2004) of both EEG and fMRI data. Further, behavioral paradigms should include a parametric variation of task demands to better interpret group differences (Reuter-Lorenz and Cappell, 2008). This is particularly relevant in light of the CRUNCH model, suggesting that overactivation in older adults can break down with increasing task demands.

Taken together, multimodal imaging approaches, including functional and anatomical measures, in combination with state-of-the-art analysis tools and thoughtful behavioral paradigms across a wide range of cognitive domains are necessary to understand how age-related structural degeneration drives neural compensation to promote cognition and behavior (Reuter-Lorenz and Park, 2014).

4. Causal factors in neural compensation

Our rationale of neural compensation in the context of age-related structural degeneration (Fig. 2) is based on principles from lifespan development (Berk, 2017; Lindenberger, 2014). Accordingly, development is multidimensional (i.e., it depends on biological, psychological and social factors), multidirectional (i.e., it includes growth and decline) and characterized by plasticity (i.e., potential for change). Therefore, cognitive abilities differentially unfold over the lifespan with marked interindividual variability (Hartshorne and Germine, 2015; Hedden and Gabrieli, 2004; Lövdén et al., 2005), and the potential for individual change, for instance, through cognitive trainings (Anguera et al., 2013; Heinzel et al., 2016; Richmond et al., 2011).

Therefore, a positive effect of lifestyle factors on the trajectories of cognitive development resonates well with the notion of development as a process influenced by an individual's interaction with their environments. This implies that healthy aging and development can be promoted by specific factors, including – but not limited to – physical fitness (Duzel et al., 2016), cognitive fitness (Fratiglioni et al., 2004), nutrition (Roberts et al., 2021), sleep habits (Mander et al., 2017), and social integration (Fratiglioni et al., 2004).

Cardiovascular fitness has been linked to MTL integrity and

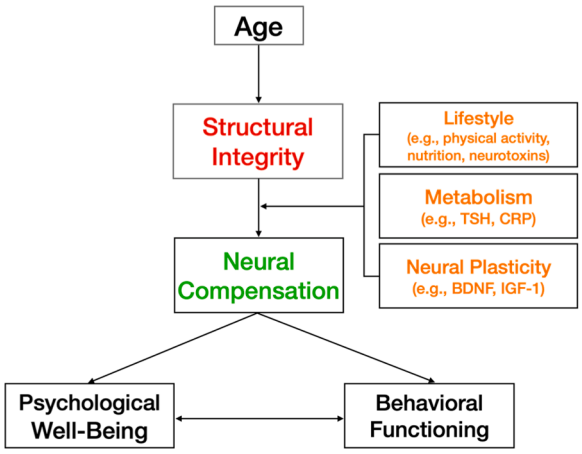

Fig. 2. Model of a relationship between structural brain integrity and neural compensation during aging. Based on previous work, we suggest that older adults' chronological age directly relates to structural brain integrity; this is hypothesized to trigger neural compensation that is moderated by lifestyle (e.g., physical activity, nutrition and neurotoxins), metabolism (e.g. TSH, CRP) and neural plasticity (e.g. BDNF, IGF-1), which all closely interact. Neural compensation, on the other hand, promotes psychological well-being and behavioral functioning, which is characterized by an optimal level of cognitive performance despite neural degeneration. A breakdown of neural compensation, as a precursor to declines in behavioral functioning and psychological well-being, is thought of as a hallmark of pathological aging (see Fig. 3).

associated memory abilities in older adults (Duzel et al., 2016; Kern et al., 2021), possibly via reduced neuroinflammation (Pinto and van Praag, 2022) as suggested in humans (Papenberg et al., 2016) and animal work (De Miguel et al., 2021). Further, low cardiovascular fitness and low cognitive abilities at the age of 18 were associated with an increased risk for early-onset dementia and early-onset mild cognitive impairment (MCI), respectively (Nyberg et al., 2014). This is in line with the observation that cognitive abilities during childhood accounted for the association between cognitive abilities and cortical thickness in older adults (Karama et al., 2014), which underlines the need for a lifespan perspective. On a practical level, this could be achieved by quantifying past and current lifestyle measures, including the highest degree of education and retrospective questionnaires on physical activities during childhood and adolescents. Taken together, a healthy, active, and socially integrated lifestyle reduces the risk for cognitive decline with increasing age.

Whether lifestyle factors shape the relationship between structural degeneration and neural compensation (Fig. 2) remains unclear. From a theoretical point of view, they could act as "neural resource enrichment" or conversely, as "neural resource depletion" (Reuter-Lorenz and Park, 2014). While the former may include intellectual engagement, nutrition, physical fitness or sleep (Agbangla et al., 2019), the latter relates to stress, and exogenous neurotoxins such as alcohol or nicotine (Cherbuin et al., 2009). While one line of future research may focus on possible moderating effects between structural degeneration and neural compensation and therefore psychological well-being and behavior (Fig. 2), others might investigate how these factors stop or even reverse age-related neural degeneration. In any case, a quantification should be based on appropriate questionnaires or other methods such as wearables or physiological measures.

From a more mechanistic point of view, the interplay between structural degeneration, neural compensation and lifestyle may further depend on a brain's physiological capacity for neural plasticity. Such plasticity-related variables include brain-derived neurotrophic factor (BDNF), insulin-like growth factor type 1 (IGF-1), and vascular endothelial growth factor (VEGF). All three have been linked to physical exercise and brain plasticity in older humans (Maass et al., 2016; Voss et al., 2013a), as well as cognitive stimulation and enriched environments (Duzel et al., 2016; Voss et al., 2013b), which is compatible with work on novelty exploration, dopaminergic neuromodulation and learning (Düzel et al., 2010; Steiger et al., 2022).

Further, metabolic markers could serve as indicators of physical health, including C-reactive protein (CRP, inflammatory mediator) and thyroid-stimulating hormone (TSH) (Babayan et al., 2019). Additionally, grip force of the hand (i.e., grip strength) has been suggested as reliable indicator of age-related physical, cognitive, and cardio-vascular functioning (Leong et al., 2015; Rijk et al., 2016; Wang et al., 2019), which might complement metabolic markers.

Finally, amyloid-β and pTau are important markers of Alzheimer's disease (AD), including preclinical AD and MCI (Ashton et al., 2023; Blennow, 2021; Milà-Alomà et al., 2022), that can be quantified via blood samples. In fact, changes in plasma p-tau231 and p-tau217 can be observed even in preclinical AD (Milà-Alomà et al., 2022). Therefore, state-of-the-art blood-based biomarkers of proteinopathology could be used in combination with well-established neuropsychological means to correctly classify participating subjects and, importantly, to investigate their possible role in neural compensation.

5. Is a breakdown of neural compensation characteristic for pathological aging?

5.1. Empirical evidence

Healthy aging is a developmental process in the absence of severe health issues and characterized by successful adaptation to changing environmental needs despite typical neurodegeneration. This implies that a breakdown of neural compensation may be a fundamental tipping point that distinguishes healthy vs. pathological aging. Indeed, the STAC model already suggested that preserved cognition in older adults is being achieved "by means of preserved neurobiology, compensatory processes, or a combination of these factors" (Reuter-Lorenz and Park, 2014). Therefore, when neural degeneration exceeds a tipping point, neural compensation may break down (Fig. 3A) leading to a severe decline in cognitive functioning and psychological well-being – see also (Cabeza et al., 2018) for similar conclusions. However, empirical evidence is still scares, probably since pathological aging is no coherent concept, including severe, often widespread, neural degeneration and cognitive or behavioral decline (Berchtold and Cotman, 2009; Jagust, 2018; Risacher and Saykin, 2019). In this section, we will further develop these thoughts by focusing on rather apparent age-related disorders, such as PD and AD, but also late life depression (LLD) and chronic pain, which are both highly prevalent in older humans.

The dopaminergic mesolimbic system, including the substantia nigra, ventral striatum, MTL and interconnected PFC, has long been associated with working memory abilities (Brozoski et al., 1979; Cools et al., 2008; Eckart et al., 2014). Typical age-related declines of this network in healthy older adults are even more pronounced in patients with PD (Humphries et al., 2018; Siegert et al., 2008), which is characterized by an extensive loss of dopaminergic neurons in the basal ganglia, including the substantia nigra. However, by using enlarged and more distributed neural substrates, cognitively normal PD patients are able to efficiently perform WM tasks (Trujillo et al., 2015), which may reflect neural compensation to account for dopamine deficiency (Hattori et al., 2022; Poston et al., 2016). While direct neurotransmitter imaging, such as PET, may not always be available, more indirect measures could also be fruitful. Specifically, iron loads within the basal ganglia (Bunzeck et al., 2013), and neuromelanin in the substantia nigra (Prasuhn et al., 2021) – both measured with MRI – make important contributions to the motor phenotype in PD. Locus coeruleus pathology, on the other hand, was related to cognitive impairment (Prasuhn et al., 2021).

Apart from working memory, other prominent non-motor deficits in PD include cognitive control and response inhibition (Manza et al., 2017). Specifically, PD patients showed reduced stopping speed

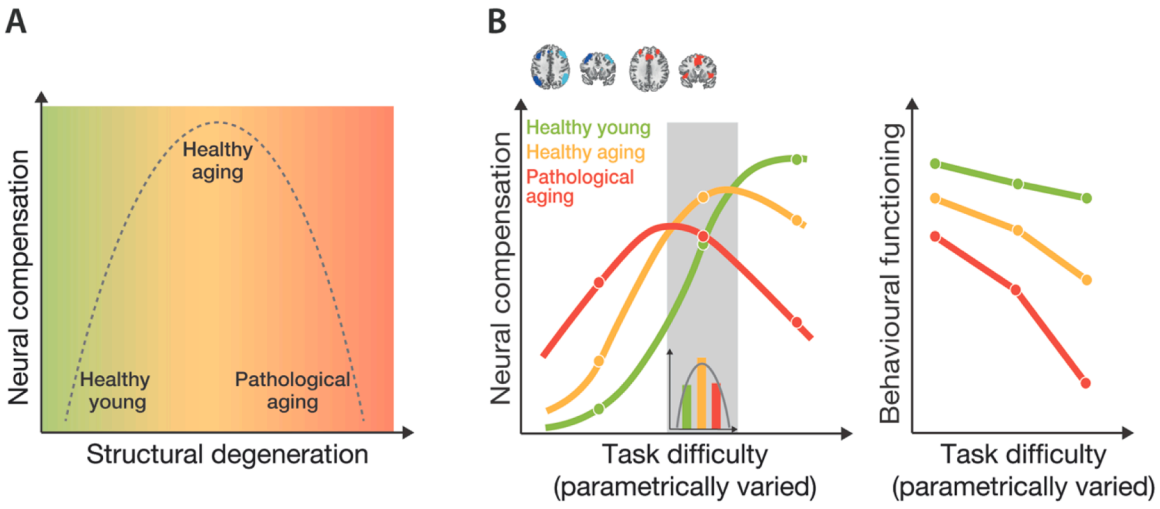

Fig. 3. A Hypothesized relationship between structural degeneration and neural compensation across the adult lifespan. In healthy young adults, structural degeneration is low, therefore, no neural compensation is required. With increasing age, structural degeneration increases, triggering functional compensation to uphold an appropriate level of behavior. During pathological aging, structural degeneration is much more pronounced, and therefore, neural compensation and associated behavior breaks down. **B** Hypothesized pattern of neural and behavioral results that would support the proposed relationship. Differences in neural compensation as a function of structural degeneration are best studied using behavioral tasks of parametrically varied difficulty. The hypothesized inverted u-shaped relationship depicted in the inset should be most evident at intermediate levels of difficulty (shaded in grey).

together with right inferior frontal gyrus (rIFG) hypoactivation during stopping (Ye et al., 2015, 2014) and functional reorganization in the cortico-basal ganglia inhibition network (Harrington et al., 2018). The specific effects of PD on reactive as compared to proactive inhibition seem more heterogeneous, but even early-stage PD patients showed impaired reactive inhibition (Di Caprio et al., 2020), whereas PD patients at later stages showed a general deficit in proactive and reactive inhibition (Mirabella et al., 2017). Together with an age-related hyperactivation in prefrontal and parietal nodes of the inhibition network (Hu et al., 2019; Kleerekooper et al., 2016) and associated structural decline in subthalamic nucleus (STN) projections (Coxon et al., 2016, 2012), this also points towards the proposed inverted u-shaped relationship (Fig. 3A).

In AD, several studies demonstrated enhanced neural activation before the onset of clinical symptoms, indicative of neural compensation accompanying disease progression. For example, hippocampal activity was increased during a memory task in amyloid-β positive patients with mild MCI, despite smaller hippocampi, as compared to amyloid-β negative MCI patients (Huijbers et al., 2015). A similar pattern was reported in non-demented MCI patients, were MTL activity positively correlated with memory performance (Dickerson et al., 2004). With regard to AD progression, recent work suggests the basal forebrain's Nucleus basalis of Meynert (NbM) as an early origin of structural degeneration, followed by the entorhinal cortex and other cortical brain regions (Fernández-Cabello et al., 2020; Schmitz and Spreng, 2016). In line with such a view, resting-state activity in the basal forebrain predicted functional degeneration in the entorhinal cortex and decreased with AD progression (Mieling et al., 2023a). Therefore, previously described anatomical brain changes in AD (Fernández-Cabello et al., 2020; Schmitz and Spreng, 2016) and work on functional activity (Mieling et al., 2023a) is also partially compatible with the proposed inverted u-shape relationship between neural compensation and structural degeneration (Fig. 3A) but more direct evidence, including healthy young adults, is missing.

LLD is associated with severe cognitive decline and poor quality of life. Indicators of the underlying pathophysiology include reduced grey matter volume, increased white matter hyperintensities (WMH) due to ischemic lesions, and damage to white matter microstructure all particularly affecting executive control networks in prefrontal cortex (PFC) (Kim and Han, 2021). However, systematic investigations into the neural compensatory mechanisms linking observed structural and cognitive deterioration in LLD, and that might explain changes from healthy to pathological aging are still missing. To this end, speech processing – that typically remains stable across age (Shafto and Tyler, 2014) – might be a promising domain, especially since the breakdown of successful comprehension poses a crucial risk factor of LLD (Rutherford et al., 2018). Along these lines, mild afferent hearing loss (HL) covaries with an increased risk of subsequently developing forms of dementia in the next five years (Lin et al., 2011; Livingston et al., 2020). The pathways from such sensory impairment beginning in middle adult life to an increased risk of subsequently developing dementia are unclear, but they could also follow an inverted u-shaped relationship (Fig. 3B). More specifically, sensory decline might causally contribute to pathological aging via altered neural communication between auditory and medial temporal areas in sensorineural hearing loss (Griffiths et al., 2020).

Finally, pain perception – a biologically important mechanism – is largely maintained during healthy aging (El Tumi et al., 2017). In contrast, tactile acuity for non-noxious stimuli, measured in a two-point discrimination task, deteriorates with age (Kalisch et al., 2009), as do decreases in perception thresholds, which are correlated with structural brain degeneration (Johnson et al., 2021). This suggests that age-related structural brain changes within the salience detection network (SDN) (Legrain et al., 2011), are functionally compensated to maintain intact perception of noxious (but not non-noxious) stimuli (Lautenbacher et al., 2005), and this compensation might break down in patients with chronic pain, in which the processing (Kregel et al., 2015) and perception (Amiri et al., 2021) of noxious stimuli are altered. Such alterations may include increased cortical representations of body parts within the somatosensory cortex, increased functional connectivity of key regions, such as SI and SII, and decreased connectivity of the pain inhibitory network, potentially explained by reduced intracortical inhibition (Lenz et al., 2012).

Taken together, apart from AD (Knopman et al., 2021), its precursor MCI, and PD (Poewe et al., 2017), there are other prominent aspects, such as chronic pain (Cruz-Almeida and Cole, 2020) and LLD (Kim and Han, 2021), that are associated with pathological aging. Therefore, several different age-related diseases could serve as models to further investigate the hypothesis that a breakdown of neural compensation is a distinct feature for pathological aging.

5.2. Conceptual evidence

From a more conceptual point of view, neural compensation is expected to break down in pathological aging for several reasons. First, age-related neurodegenerative disorders are not only characterized by structural brain changes but also by reduced neuroplasticity (Toricelli et al., 2020). Especially in AD, it has been argued that not a single feature, such as amyloid plaques, neurofibrillary tangles or cholinergic depletion can explain the divers clinical and neuropathological characteristics; instead a failure in neuroplasticity, i.e. the brain's ability to change its organization and activation, may represent the core characteristic (Mesulam, 1999). In other words, progressing neuropathology, including a loss of neurons, should go hand in hand with the inability to functionally compensate for it.

Second, the progression of age-related neurodegenerative disorders is often region- and disease-specific. For instance, neurodegeneration in the MTL in AD is preceded by structural degeneration and accumulation of beta-amyloids within the basal forebrain and followed by other cortical areas (Fernández-Cabello et al., 2020; Mieling et al., 2023b; Schmitz and Spreng, 2016). In PD, on the other hand, neurodegeneration typically affects the nigrostriatal pathway, including dopamine neurons in the substantia nigra and their projection terminals in the striatum (Aarsland et al., 2021). At the same time, PD is characterized by widespread accumulations of intracellular proteins (α-synuclein) that differ from AD pathology (Poewe et al., 2017). Therefore, a disease-specific spread of neuropathologies and associated cumulative neurodegeneration should lead to specific patterns of impaired compensation. Along these lines, when neurodegeneration includes highly vulnerable brain regions, such as the entorhinal cortex, which is considered a critical relay for the communication between the neocortex and hippocampus (Mišić et al., 2014; Moscovitch et al., 2016; Schultz et al., 2015), this may accelerate the failure of compensatory mechanisms.

Third, age-related neurodegenerative diseases are often associated with synaptic dysfunction (also known as synaptopathies), impairing the communication between neurons, which can lead to specific cognitive and behavioral impairments (Taoufik et al., 2018; Wilson et al., 2023). Since neural plasticity largely depends on forming new connections or strengthening existing ones, synaptic dysfunction due to disease progression may also diminish the brain's ability to compensate.

Fourth, age-related neurodegenerative diseases often trigger neuroinflammatory responses, which can exacerbate neural damage (Wilson et al., 2023). Therefore, chronic inflammation could interfere with neural compensation and further disrupt the brain's ability to adapt to structural degeneration. In fact, this later point makes the aging brain (together with the developing brain) strongly susceptible to environmental neurotoxins that also act through neuroinflammatory processes (Han et al., 2021; Pang et al., 2019).

Taken together, there is not only initial empirical evidence that argues in favor of a breakdown of neural compensation at the tipping point of healthy vs pathological aging. Additionally and importantly, conceptual considerations of limited neural plasticity, disease specific progression of cumulative neurodegeneration, synaptopathies, and neuroinflammation will allow to build a more mechanistic account of this hypothesized role of neural compensation.

6. Fostering new insights into neural compensation: embracing collaboration, open data, and diverse analytical approaches

Future studies on neural compensation would greatly benefit from quantifying structural brain integrity, the level of neural compensation, cognitive and behavioral abilities, as well as lifestyle factors and markers of metabolism and neural plasticity (Fig. 2). In combination with open science strategies, including open code, open data and open access, this would allow joint data analyses using e.g., structural equation modeling, advanced regression modelling, and explainable artificial intelligence (AI) methods (Vilone and Longo, 2020). Other approaches, such as the D50 model, could be used to estimate individual development on the basis of cross-sectional data, as previously shown for Amyotrophic Lateral Sclerosis (ALS) (Dreger et al., 2021; Steinbach et al., 2021, 2020; Westeneng et al., 2018). While cross-sectional approaches have clear advantages (no training effects, low dropout rate, fast and efficient), longitudinal designs have a greater potential to characterize individual development. At the same time, they help to better control for pre-existing conditions or cohort effects (e.g. differences in education or nutrition).

7. Summary and conclusion

Neural compensation has long been suggested as a pivotal mechanism to uphold cognition and behavior when structural degeneration progresses with age. Empirical evidence, however, has remained limited. Therefore, future research should:

(1) establish the psychological and neurobiological principles that constitute neural compensation;
(2) elucidate how lifestyle parameters, metabolic markers, and markers of neural plasticity contribute to healthy aging and preserved behavioral functioning via neural compensation; and
(3) provide causal evidence that a breakdown of neural compensation distinguishes healthy from pathological aging.

To achieve these goals, future work requires multi-modal imaging approaches and sophisticated analyses tools, and as such will require transdisciplinary expertise emerging at the borders of psychology, cognitive neuroscience, medicine as well as computer and health sciences. This new line of research would not only have direct implications for our scientific understanding of the developmental trajectories of healthy and pathological aging, but it may also offer strategies for novel interventions to promote health across the lifespan. These are most relevant given the demographic change in Western societies and the associated age-related impairments and health care costs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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