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REVIEW

Clear-headed into old age: Resilience and resistance against brain aging—A PET imaging perspective

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Abstract

With the advances in modern medicine and the adaptation towards healthier lifestyles, the average life expectancy has doubled since the 1930s, with individuals born in the millennium years now carrying an estimated life expectancy of around 100 years. And even though many individuals around the globe manage to age successfully, the prevalence of aging-associated neurodegenerative diseases such as sporadic Alzheimer's disease has never been as high as nowadays. The prevalence of Alzheimer's disease is anticipated to triple by 2050, increasing the societal and economic burden tremendously. Despite all efforts, there is still no available treatment defeating the accelerated aging process as seen in this disease. Yet, given the advances in neuroimaging techniques that are discussed in the current Review article, such as in positron emission tomography (PET) or magnetic resonance imaging (MRI), pivotal insights into the heterogenous effects of aging-associated processes and the contribution of distinct lifestyle and risk factors already have and are still being gathered. In particular, the concepts of resilience (i.e. coping with brain pathology) and resistance (i.e. avoiding brain pathology) have more recently been discussed as they relate to mechanisms that are associated with the prolongation and/or even stop of the progressive brain aging process. Better understanding of the underlying mechanisms of resilience and resistance may one day, hopefully, support the identification of defeating mechanism against accelerating aging.

KEYWORDS
aging, Alzheimer's disease, PET, resilience, resistance

> There is a fountain of youth: it is your mind, your talents, the creativity you bring to your life, and the lives of people you love. When you learn to tap this source, you will truly have defeated age.
>
> Sophia Loren

With the advances in modern medicine and the adaptation toward healthier lifestyles, the average life expectancy has doubled since the 1930s, with individuals born in the millennium years now carrying an estimated life expectancy of around 100 years. And even though many individuals around the globe manage to age

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid β; CSF, cerebrospinal fluid; [^{11}C]-PiB, [^{11}C]-Pittsburgh Compound B; [^{18}F]-FDG, [^{18}F]-Fluorodeoxyglucose; (f)MRI, (functional) magnetic resonance imaging; NFT, neurofibrillary tangles; PART, primary age-related tauopathy; PET, positron emission tomography.

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successfully, the prevalence of aging-associated neurodegenerative diseases such as sporadic Alzheimer's disease has never been as high as nowadays. The prevalence of Alzheimer's disease is anticipated to triple by 2050, increasing the societal and economic burden tremendously. Despite all efforts, there is still no available treatment defeating the accelerated aging process as seen in this disease. Yet, given the advances in neuroimaging techniques, such as in positron emission tomography (PET) or magnetic resonance imaging (MRI), pivotal insights into the heterogenous effects of aging-associated processes and the contribution of distinct lifestyle and risk factors already have and are still being gathered. In particular, the concepts of resilience (i.e., coping with brain pathology) and resistance (i.e., avoiding brain pathology) have more recently been discussed as they relate to mechanisms that are associated with the prolongation and/or even stop of the progressive brain aging process. A better understanding of the underlying mechanisms of resilience and resistance may one day, hopefully, support the xml:identification of defeating mechanisms against accelerating aging.

1 | THE TWO EXTREMES OF THE AGING PROCESS

While we use "aging" as a simple term in our daily life, the word actually comprises a highly complex degenerative and multi-factorial process resulting from the accumulation of molecular and cellular damage that eventually leads to cell and tissue dysfunction. According to the current theories of aging, age linearly correlates with the aggregation of reactive oxygen species, DNA damage, mitochondrial dysfunction, and telomere shortening (Wagner et al., 2018). However, regarding aging-related processes of the brain, high interindividual variance has been observed (Arenaza-Urquijo and Vemuri 2018). In this regard, one extreme of the brain aging process represents sporadic Alzheimer's disease, the most frequent form of neurodegeneration. This sporadic disease shows a strong age-dependency with an exponential increase in incidence at higher age (>40% of persons > 90 years) (Corrada et al., 2010). The characteristic neuropathological hallmarks of Alzheimer's disease, namely amyloid ß (Aß) plaques and neurofibrillary tau tangle (NFT) aggregation, are closely linked to DNA damage (Petr et al., 2020) and mitochondrial dysfunction (Mammucari & Rizzuto, 2010). While both, DNA-damage and mitochondrial dysfunction, are linearly associated with increasing aging, their detrimental effects exponentially increase in Alzheimer's disease. Therefore, sporadic Alzheimer's disease has often been considered to represent a form of precocious or accelerated aging of the brain (Guerreiro & Bras, 2015). However, with the recent developments in neuroimaging techniques, such as in positron emission tomography (PET), it has become apparent that brain aging can occur in an accelerated fashion such as seen in Alzheimer's disease, but also in a more resistant fashion without the accumulation of Alzheimer's disease proteinopathies or severe consequences of this aggregation on cognitive function. In this regard, successful aging has been suggested to be fostered by resilience (i.e., coping with brain pathology) or resistance (i.e., avoiding brain pathology) mechanisms that overall prolong or even halt the progressive cognitive aging process. While the majority of studies have so far focussed on resilience mechanisms, recent interest has shifted toward the other extreme of aging, namely successful aging without the aggregation of Alzheimer's disease-related pathology. This extreme of brain aging may be represented by the phenomenon of so-called "super-aging." This term refers to the maintenance of far above-average cognitive performance in elderly individuals, sometimes comparable to levels found in subjects being 20–30 years of age (Harrison et al., 2012).

These two extremes, super-aging and unhealthy aging such as Alzheimer's disease, suggest that the aging process is modifiable and influenced by environmental, molecular, and (epi-)genetic factors either de- or accelerating the association between age and degeneration. Yet, it is not clear if super-aging is supported by a general deceleration of brain aging effects, thus greater resistance against the build-up of neurodegenerative pathologies and/or by greater resilience, i.e., reserve mechanisms allowing to compensate ongoing aging and neurodegenerative processes. Recent studies on the molecular underpinnings in super-aging have revealed lower DNA damage, high genomic stability, and telomere maintenance in blood samples of super-agers (Franzke et al., 2015; Halaschek-Wiener et al., 2008; Wagner et al., 2000). Also, the absence or presence of certain genes has been related to the phenomenon of super-aging (Huentelman et al., 2018; Rogalski et al., 2013).

Importantly, while the determination of these molecular differences in super-agers and unhealthy agers such as Alzheimer's disease is important, no inferences can be drawn on how these differences relate to the neurophysiological mechanisms seen on the aging spectrum. With the advances in the field of neuroimaging, age-related changes on the structural and functional level can be detected in vivo by means of magnetic resonance imaging (MRI) as well as age-related intracerebral molecular changes by means of PET. The combination of both modalities thereby yields unique information on the age-related and pathophysiological mechanisms influencing the functional and structural integrity of the brain (Cabeza et al., 2016). In particular, the use of PET ligands for the visualization of cellular, molecular changes, and protein aggregations has led to major breakthroughs in recent years, as will be elucidated in the following.

2 | ILLUMINATING THE PATHOPHYSIOLOGY OF AGING IN VIVO USING POSITRON EMISSION TOMOGRAPHY

PET is an imaging technique permitting the visualization of molecular changes and protein aggregations in vivo by injection of radioactively labeled tracers into the blood, which binds to the biomolecules of interest. Briefly, it is based on the following technique: The radioactively labeled tracers contain short-lived positron-emitting radionuclides such as fluorine-18 (^{18}F) or carbon-11 (^{11}C). The beta decay

of these radionuclides (e.g., ^{18}F) attached to the target biomolecule (e.g., glucose) results in the emission of a positron which annihilates with an electron after traveling less than 1 mm in the tissue. The annihilation process results in two gamma-photons being emitted in opposite directions. These gamma-rays are then detected by scintillation detectors, which register the annihilation photons in coincidence and store the events. Finally, using computer analysis, the PET activity distributions are reconstructed as three-dimensional images based on the coincidence events. The final images are then used for diagnostic or research purposes (Hönig, 2020).

Up to now, several PET tracers have been developed, which can cross the blood–brain barrier and visualize aging-associated protein aggregations like the extracellular deposition of amyloid-beta (Aβ) in senile plaques and the intracellular aggregation of neurofibrillary tangles (NFTs)—the characteristic hallmarks of Alzheimer's disease.

2.1 | Amyloid PET imaging

In the mid-1980s of the last century, the extracellular accumulation of Aß peptides was first discovered as the main constituents of senile plaques in Alzheimer's disease and Down's Syndrome (Glenner & Wong, 1984; Masters, Multhaup, et al., 1985; Masters, Simms, et al., 1985; Cohen et al., 2012). Given the ground-breaking introduction of a specific Aβ-plaque PET tracer by Chet Mathis and William Clunk in 2002, almost two decades after the initial discovery of Aβ deposits, a novel perspective was introduced permitting to study the dynamic accumulation process of Aβ in the normal vs. unhealthy aging process. The developed tracer, the so-called [^{11}C]-Pittsburgh Compound B ([^{11}C]-PiB) shows high affinity and selectivity to fibrillar amyloid in senile plaques (Mathis et al., 2002; Cohen et al., 2012) and has ever since widely been used in Alzheimer's disease research (for more information see Bischof & Jacobs, 2019). Yet, given the short half-life of [^{11}C]-PiB of only 20 min, its use is limited to centers that have a cyclotron and a department of radiochemistry on-site. As a result of this limitation, Flourine-18-(^{18}F)-labeled tracers with similar affinity profiles, but a half-life of around 120 min, were developed, among them: [^{18}F]Florbetaben (Rowe et al., 2008), [^{18}F]Florbetapir (Wong et al., 2010), and [^{18}F]Flutemetamol (Rinne et al., 2012).

Ever since these amyloid tracers have been available, a large body of evidence has been gathered supporting the utility of these tracers as diagnostic tools for dementia because of Alzheimer's disease (Cotta Ramusino et al., 2021) as well as for patient selection (Fantoni et al., 2018) and the evaluation of drug efficacy in clinical trials (Cummings et al., 2021). Based on these studies, recent recommendations have been provided concerning the use of amyloid PET in diagnostic investigations of Alzheimer's disease (Chételat et al., 2020).

Aside from its clinical application, these tracers have successfully been utilized to study the spatial distribution of this protein in healthy and unhealthy aging. A plethora of studies demonstrated that Aß deposition is a key component of Alzheimer's disease, but it is also present in at least 20% of cognitively unimpaired individuals from the age of 50 years (Jansen et al., 2015) and up to 30% in those aged over 80 years (Fleisher et al., 2011). Moreover, it was suggested that Aß burden in the 50s might be an early predictor of accelerated cognitive decline (Vemuri et al., 2019). Complementing this finding, it was further shown that regional amyloid in particular in the posterior cingulate cortex, precuneus, and lateral parietal were associated with longitudinal cognitive decline in amyloid-negative cognitively normal elderly (Gao et al., 2018; Farrell et al., 2018). Yet, the majority of these studies have largely been carried out in groups older than 60 years (Aizenstein et al., 2008; Mormino et al., 2009; Pike et al., 2007; Villemagne et al., 2008), thus limiting our knowledge on Aβ aggregation in mid-life. Interestingly, recent efforts extending their investigation to middle-aged individuals have provided evidence for Aβ accumulation being present already in this lifespan. It was thereby shown that Aβ was a significant factor of memory decline even in midlife (Farrell et al., 2017). However, it still remains unclear whether subtle increases in Aβ during midlife are actually predictive of a higher risk of Alzheimer's disease later in life or whether these increases are associated with normal aging processes. Moreover, given that a large proportion of individuals with pathological amyloid burden late in life (i.e., amyloid positive individuals) do not develop cognitive symptoms (Roberts et al., 2018), the short-term prognostic utility of Aβ PET is still under debate (Iaccarino et al., 2017). Recent accounts report that regional levels of Aβ need to be considered as a prognostic biomarker of Alzheimer's disease rather than global levels (Grothe, Barthel et al., 2017; Jelistratova et al., 2020; Pfeil et al., 2021).

While a large body of in vivo evidence has been gathered in the past two decades on the role of Aβ aggregation in the aging process, a current drawback of the available tracers is that they only bind to insoluble plaques and not to the more toxic and soluble forms of Aβ (Haass and Selkoe, 2007). These forms, given their solubility, can spread throughout the brain (Chen et al., 2017), disrupt synaptic function, and trigger downstream toxic pathways (Mucke & Selkoe, 2012), whereas the insoluble plaques are believed to represent the final product of the aging-associated process that commences decades before overt clinical symptoms. Moreover, albeit its major role in defining Alzheimer's disease, amyloid PET imaging presents a relatively low correlation with clinical and cognitive parameters (Brier et al., 2016). This may be because of a plateau effect at the point of clinical diagnosis. Given the low correlation with clinical measures, this PET modality is less well-suited for the staging of the disease. Thus, for better information regarding the progression and staging of the disease as well as cognitive aging, more recently tau PET compounds have been introduced.

2.2 | Tau PET imaging

Aside from Aβ deposits, NFTs represent the second neuropathological hallmark of Alzheimer's disease, but also other neurodegenerative diseases known as tauopathies. NFTs are aggregates of the hyperphosphorylated microtubule-associated tau protein

(Grundke-Iqbal et al., 1986; Weingarten et al., 1975). In the adult human brain, six isoforms of the tau protein are present, which can further be separated based on the length of their repeat binding domains, namely three or four carboxy repeat domains (3R and 4R). In the adult human brain, the 3R and 4R forms of tau are equally expressed, but this ratio changes in neurodegenerative diseases (Gao et al., 2018). In Alzheimer's disease, both 3R and 4R forms of tau undergo hyperphosphorylation (Iqbal et al., 2005). Importantly, in cognitively unimpaired individuals the misfolded tau protein (3R/4R) has consistently been found in medial temporal regions with higher age, with minimal to absent Aß pathology (Josephs et al., 2017; Josephs et al., 2020). This neuropathological designation has been termed *primary age-related tauopathy* (PART; (Crary et al., 2014)). Notably, discussions pertain arguing that PART may actually represent an early form of Alzheimer's disease (Duyckaerts et al., 2015). This argument also complies with the dual pathway hypothesis which suggests that tau pathology and Aß may represent independent pathophysiological processes sharing an upstream causative factor (Small & Duff, 2008). xml:identification of the exact mechanisms leading to the hyperphosphorylation of tau in these neuropathological designations and cognitively normal aging are required to prove or refute these assumptions.

Importantly, with the recent introduction of tau PET compounds, the dynamic interplay between Aß plaques and NFTs can be assessed in vivo. The heterogenous isoforms of the tau protein and its intracellular location have been major challenges in the development of selective tau PET tracers. Overcoming these challenges, several radioactive substances have been developed. The most widely studied are: [^{18}F]-AV-1451 (Flortaucipir) (Chien et al., 2014), [^{18}F]-THK5117 (Harada et al., 2015), [^{18}F]-THK5351 (Harada et al., 2016), and [^{11}C]-PBB3 (Maruyama et al., 2013). Before the introduction of these compounds, solely cerebrospinal fluid (CSF) measures could provide information on abnormalities in tau phosphorylation in the central nervous system, but no information on the regional distribution of tau pathology could be obtained. The introduction of tau PET tracers has, therefore, led to new possibilities for diagnostic and research-oriented considerations (Leuzy et al., 2019; Saint-Aubert et al., 2017).

Indeed, a progressively accumulating body of evidence suggests that tau PET is a suitable progression and staging marker, as it is more closely associated with neurodegeneration and cognitive decline than amyloid PET (Bischof et al., 2016; Brier et al., 2016; Bucci et al., 2021; Chen et al., 2021; La Joie et al., 2018; Ossenkoppele et al., 2016; Pontecorvo et al., 2017; Scholl et al., 2016;). Additionally, recent longitudinal tau PET studies have provided the first insights into the pathogenic cascade of Alzheimer's disease (Chiotis et al., 2018; Jack et al., 2018; Southekal et al., 2018, Leuzy et al., 2022) and its mechanistic pathways (Hoenig et al., 2018; Schäfer et al., 2020). Moreover, potential evidence in support of PART was recently observed in vivo. By means of tau PET imaging in cognitively normal older adults, it was shown that the signal was largely restricted to medial temporal lobe regions in absence of Aβ accumulation, which aligns with findings from postmortem studies on age-related accumulation of tau deposits (Leuzy et al., 2022; Yoon, et al., 2022).

Importantly, in contrast to amyloid PET, tau PET further permits the differentiation between typical and atypical phenotypes of Alzheimer's disease, and Alzheimer's disease from other tauopathies (Xia et al., 2017, Phillips et al., 2018, Kikuchi et al., 2016; Ossenkoppele et al., 2016; Dronse et al., 2017; Hammes et al., 2017; Passamonti et al., 2017; Whitwell et al., 2017; Whitwell et al., 2018, Brendel et al., 2020), thereby providing a meaningful biomarker for differential diagnosis.

Despite the current advances of tau PET imaging, an unresolved issue of the first-generation tau PET tracers remains the off-target binding to subcortical structures (Marquié et al., 2015; Lowe et al., 2016; Ng et al., 2017) and the lower affinity to different tau isoforms (Smith et al., 2017). Therefore, second-generation tracers have been developed with improved binding properties and lower off-target signal, among them [^{18}F]-MK-6240 (Walji et al., 2016), [^{18}F]-PI-2620 (Mueller et al., 2017), and [^{18}F]RO-948 (Kuwabara et al., 2018). Studies using these second-generation tracers revealed similar regional binding behavior as the first-generation tracer, but lower off-target binding (Betthauser et al., 2019; Gogola et al., 2022; Pascoal et al., 2021; Wong et al., 2018). Moreover, direct head-to-head comparison of a first-generation ([^{18}F]-AV-1451) against a second-generation tracer ([^{18}F]-MK-6240) (Gogola et al., 2022) or [^{18}F]RO-948 (Smith et al., 2020) yielded a greater dynamic range in signal strength in regions typically affected by tau pathology indicating that this tracer may better be able to detect early tau pathology aggregation as well as subtle longitudinal changes. Importantly, more recent studies utilizing the second-generation tau PET tracer in combination with blood-based biomarkers of tau pathology (p-tau181 and p-tau231) suggested that plasma biomarkers and tau PET appear to reflect different stages of tau progression (Tissot et al., 2022). This is in line with another recent study indicating that plasma p-tau217 was more relevant in preclinical Alzheimer's disease, while tau PET becomes crucial in prodromal Alzheimer's disease (Leuzy et al., 2022). Collectively, these tracers are currently still under investigation for their clinical and research utility (Hostetler et al., 2016; Villemagne et al., 2018). Recent consensus is that the validation of the second-generation tracers has proven superiority over first-generation tracers in terms of off-target binding potential and analytical validity, but their clinical validation is still lacking (Bischof et al., 2021).

Since tau PET imaging has only been available for less than a decade, longitudinal lifespan studies are still pending. Yet, recent evidence from a longitudinal study suggests that the rise in Aβ was associated with subsequent changes in tau burden (Hanseeuw et al., 2019). Additionally, it was shown that Aβ caused changes in soluble tau release and phosphorylation (based on fluid biomarkers), which were subsequently followed by tau aggregation (based on tau PET) several years later (Mattsson-Carlgren et al., 2020). Aside from that, Klotho-VS heterozygosity, a gene associated with longevity, was recently found to carry a protective effect concerning amyloid-related tau pathology and tau increases in Alzheimer's disease

patients and cognitively normal subjects (Neitzel et al., 2021). Nonetheless, current longitudinal studies are limited to follow-up periods of up to seven years and have been conducted in the elderly population and mostly in Alzheimer's disease patients. Future investigations in younger cohorts will thus be pivotal in assessing the temporal and spatial evolution and synergistic effects of Aß and NFTs in successful and unhealthy aging.

2.3 | Additional PET compounds to measure aging-associated processes

Given the complexity of the aging process and neurodegenerative diseases such as Alzheimer's disease, other factors besides these two proteinopathies also deserve consideration. Importantly, by means of additional PET compounds, both, down- and upstream effects of these proteinopathies, can be examined.

In terms of downstream effects, [^{18}F]-fluorodeoxyglucose ([^{18}F]FDG) PET, the most established PET tracer for brain imaging, can be used to study changes in glucose metabolism. It has been postulated that FDG PET measures synaptic function rather than overall neuronal function (Harris et al., 2012). Thus, a decrease in FDG PET signal (i.e., hypometabolism) reflects an index of synaptic failure (Iaccarino et al., 2017). Over the past two decades, FDG PET has been demonstrated to provide high diagnostic accuracy (Chételat et al., 2020). Distinct regional patterns of hypometabolism have been observed for the clinical phenotypes of Alzheimer's disease (Dronse et al., 2017; Ossenkoppele et al., 2016). Moreover, a close spatial relationship between the tau PET signal and the FDG PET signal has been reported by several studies (Bischof et al., 2016; Brier et al., 2016; Ossenkoppele et al., 2016). Importantly, the recent introduction of synaptic density PET (e.g. [^{11}C]-UCB-J) has opened another avenue to study the effects of protein aggregation on synaptic integrity at an even more direct level than FDG PET. Indeed, recent accounts showed that in vivo tau pathology was closely associated with synaptic density loss and function (Coomans et al., 2021).

Aside from that, PET can also be employed to study whether the accumulation of amyloid and tau pathology is preceded by other factors. It was recently suggested that neuroinflammatory processes may precede tau seeding and overt tau pathology (Wang & Mandelkow, 2016). Concordantly, also PET imaging studies proposed that neuroinflammatory processes, which can be quantified by for example TSPO ligands (e.g., [^{11}C]-PBR28), may peak early in the temporal evolution of Alzheimer's disease-related pathophysiological processes (Rodriguez-Vieitez et al., 2016). Furthermore, a close relationship between microglia activation and tau aggregation patterns has been observed in disease and aging (Dani et al., 2018; Ismail et al., 2020; Su et al., 2021; Terada et al., 2019). Moreover, other neuroinflammatory processes such as reactive astrogliosis may be visualized by BU99008, which has recently been suggested as a clinical astrocytic PET tracer (Kumar et al., 2021).

Another exciting avenue in the field of PET imaging of brain aging processes was recently provided by the introduction of mitochondrial PET (Terada et al., 2020; Terada et al., 2021). Mitochondria regulate a number of key aspects of aging and mitochondrial dysfunction has been consistently found in neurodegenerative disease (Mammucari & Rizzuto, 2010). By means of this compound, the first evidence was provided demonstrating mitochondrial dysfunction in the parahippocampus in early-stage Alzheimer's disease (Terada et al., 2020; Terada et al., 2021). Potentially, this tracer can be used to detect early changes in mitochondrial dysfunction before measurable brain pathology, thereby providing prognostic utility.

Collectively, the use of these different PET tracers provides unique information on the evolution of the molecular characteristics of healthy and unhealthy brain aging (Figure 1). Moreover, the great advantage over the blood or CSF measurements is that this technique provides spatial information on the underlying neurodegenerative processes rendering this technique well-suited for differential diagnosis. Moreover, combining these PET tracer with neuroimaging techniques such as diffusion tensor imaging or functional MRI (fMRI) allows the in vivo investigation of spreading mechanisms across structural and functional pathways, which will support a better understanding of disease- or general age-related processes (Bischof et al., 2019), as will be discussed in the following.

3 | TEMPORO-SPATIAL DISTRIBUTION OF AGING- AND DISEASE-ASSOCIATED PROTEINOPATHIES—A NETWORK PROBLEM?

Both, histopathological studies and in vivo studies have reported a spatial and temporal lag of Aß and NFTs. An ever-increasing body of evidence suggests that the two neuropathological hallmarks of Alzheimer's disease appear to evolve in temporo-spatial order with a long preclinical phase (Braak et al., 2011), as summarized by the model of biomarker evolution in Alzheimer's disease (Jack Jr et al., 2013; Jack Jr & Holtzman, 2013). Aside from the temporal lag of this dual proteinopathy, autopsy studies consistently demonstrated that both proteinopathies commence in distinct regions from each other. The stereotypical distribution patterns have been summarized for amyloid pathology by the Thal phases (Thal et al., 2002) and tau pathology by the Braak stages (Braak et al., 2006; Braak & Braak, 1991). Interestingly, studies comparing autopsy data and in vivo imaging revealed that the earliest Thal phases cannot be visualized using amyloid PET (Murray et al., 2015; Thal et al., 2015). More recently, distinct in vivo regional patterns of amyloid pathology have been associated with early and late disease stages (Grothe, Barthel et al., 2017). In contrast, tau PET imaging studies consistently demonstrated that tau pathology in vivo follows the neuropathologically defined Braak stages (Hoenig et al., 2017; Pascoal et al., 2021; Scholl et al., 2016; Schwarz et al., 2016; Seemiller et al., 2021).

To date, several factors and hypotheses have been considered concerning the stereotypical spread of these neuropathologies, such as susceptibility of distinct neuron groups (Fu et al., 2019;

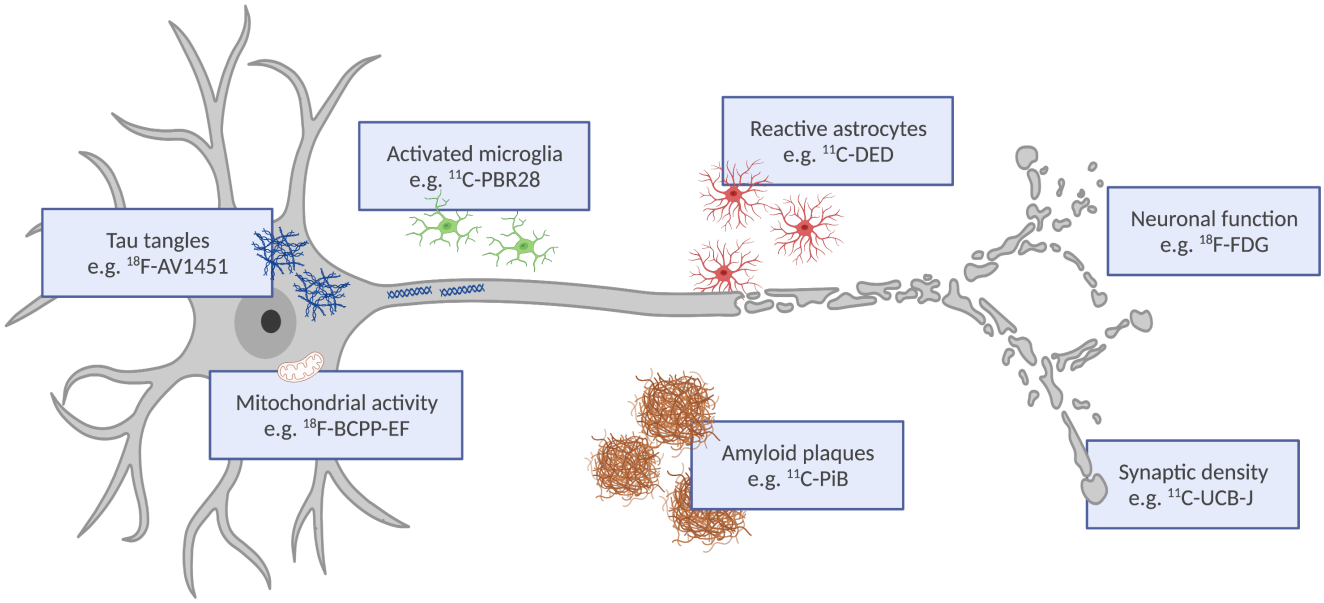

FIGURE 1 Overview of PET compounds used to visualize the neurophysiological processes of aging. Examples of major PET compounds and their target sites are provided. ^{18}F-AV-1451 is used to visualize paired helical filaments and neurofibrillary tangles in the neuron. ^{11}C-PiB binds to amyloid β plaques in the extracellular space and ^{18}F-FDG is a marker of metabolic consumption mainly at the synapse. Moreover, ^{11}C-UCB-J is a PET compound that provides a proxy of synaptic density. Mitochondrial function can be quantified by ^{18}F-BCPP-EF, whereas inflammatory processes can be quantified by ^{11}C-PBR28 (activated microglia) and ^{11}C-DED (reactive astrocytes). Created by the authors with BioRender www.biorender.com

Shen et al., 2016), gene expression patterns (Grothe, Sepulcre et al., 2018; Sepulcre et al., 2018), and cell-to-cell transmission processes (Clavaguera et al., 2009; De Calignon et al., 2012). Furthermore, multimodal imaging studies consistently reported that the topographies of neurodegenerative disease pathologies overlap with large-scale neuronal networks (Drzezga, 2018). This suggests that functional and structural connectivity between regions promotes the distribution of these pathologies across neuronal networks, an observation that is summarized by the network degeneration hypothesis (Palop et al., 2006; Seeley et al., 2009). Importantly, although some studies have pointed at a susceptibility of Aß aggregation in hub regions of functional networks (Buckner et al., 2005; Buckner et al., 2009; Greicius et al., 2004; Jones et al., 2015), network degeneration appears to rather depend on global levels of Aß than local levels (Drzezga et al., 2011; Iaccarino et al., 2018). This may be as a result of the location of Aß, which distributes diffusely in the extracellular space throughout the brain (Hönig, 2020). Therefore, it was recently suggested that tau pathology because of its intracellular location, its trans-synaptic spreading potential, and its close relationship to neurodegeneration, better relates to network dysfunction and degeneration in Alzheimer's disease. Indeed, first in vivo studies have documented a close relationship between large-scale networks, functional connectivity, and tau pathology distribution patterns in typical Alzheimer's disease, but also cognitively normal subjects (Franzmeier et al., 2019; Hansson et al., 2017; Hoenig et al., 2018; Jones et al., 2017; Vogel et al., 2020). Moreover, it was recently suggested that tau pathology carries a role in disconnecting the hippocampus from functional networks involved in memory systems, eventually resulting in memory decline (Harrison et al., 2019; Marks et al., 2017). Aside from that, it was found that the spread of tau pathology and tau burden of affected cortical regions depends on the overall functional in-/output (functional weights) rather than the metabolic rate of a region (Weller, Bischof et al., 2019, Cope et al., 2018). Also, in animal models, exacerbated pathological tau aggregation in vivo was found upon an increased neuronal activity (Wu et al., 2016) and normal tau was released in an activity-dependent manner (Pooler et al., 2013). In line with this, it was proposed that regional hyperconnectivity may render network hubs most vulnerable to brain pathology because of constant elevated metabolic stress (Foster et al., 2018; Hillary & Grafman, 2017).

Aside from the functional contribution to pathology dissemination, human studies recently demonstrated that tau tangles distribute via axonal pathways in amyloid positive individuals (Jacobs et al., 2018; Strain et al., 2018) pointing toward a prion-like seeding behavior. Repetition of this seeding process potentially results in the infestation of synaptically linked networks (Mudher et al., 2017; Schäfer et al., 2020).

While the aforementioned studies provide mechanistic pathways for the distribution of these proteinopathies, it still remains unclear why these proteinopathies commence in specific regions and infiltrate distinct networks. Potentially, a combination of cellular, molecular, and genetic mechanisms causes this distribution pattern. Importantly, even though these mechanisms may be similar across individuals, their consequences on cognitive function may nonetheless differ. For instance, it was recently shown that modulation in the efficacy of affected networks supports the maintenance of

cognitive performance in the phase of Alzheimer's disease-related brain pathology (Weiler et al., 2018). Some individuals are thus capable of coping with network dysfunction or degeneration better than others. Aside from that, some individuals even appear to be resistant toward the aggregation of these proteinopathies (Hoenig et al., 2020), which likely supports the functional preservation of these neuronal networks even at an advanced age. Hence, while the risk for neurodegenerative disease such as Alzheimer's disease increases with higher age, chronological age alone does not explain age- and disease-related functional changes.

4 | RESISTANCE AND RESILIENCE TO AGING-ASSOCIATED PROCESSES—FROM THEORETICAL CONSTRUCTS TO NEUROBIOLOGICAL EVIDENCE

The above-mentioned studies collectively provide insights into the role of protein aggregation in physiological aging and disease-related processes. Yet, the consequences of these processes, in terms of behavior and cognition, may nevertheless individually differ. Thus, there is a difference between cognitive aging and brain aging, which has already been noted by Katzman and colleagues in 1980 reporting a disparity between the neuropathological burden and the individual cognitive profile (Katzman et al., 1988). Over the past decades, it was consistently shown that the rate of cognitive decline given a certain level of pathological burden is highly variable between individuals. While the majority of elderly individuals experience a deterioration of cognitive function with increasing age, others present preservation or even increase in cognitive performance despite advanced age (Jazwinski & Kim, 2017). The different trajectories of cognitive decline observed in the elderly population (Park & Bischof, 2011) suggest that the aging process, including aging-associated accumulation of proteinopathies in the brain, is heterogenous.

Several concepts have been introduced to explain the increased variability of cognitive function in aging, such as the concept of cognitive and brain reserve (Stern, 2002; Stern, 2002) and the concept of brain maintenance (Nyberg et al., 2012). The reserve concepts introduced by Yaakov Stern account for compensatory and reserve strategies ameliorating the impact of neuropathological age-related alterations on cognitive function and brain morphology. Cognitive reserve thereby reflects a more dynamic process, thus the software of the brain, which is associated with the adaptability of cognitive processes to maintain functionality. Brain reserve, in a more passive form, accounts for differences in brain integrity and thereby reflects the hardware of the brain. In contrast, the concept of brain maintenance relates to the preservation of cognitive function because of the resistance toward the build-up of pathophysiological burden. While cognitive and brain reserve present *resilience* mechanisms, brain maintenance is associated with *resistance* toward the aging process (Arenaza-Urquijo and Vemuri 2018, Arenaza-Urquijo & Vemuri, 2020).

Importantly, these concepts are not mutually exclusive but interconnected. Brain maintenance and brain reserve are both based on the neurobiological underpinnings of the brain such as the integrity of grey matter volume or synaptic density. Yet, brain maintenance mechanisms can only be examined in longitudinal approaches as the term already implies that brain integrity is maintained over time. Mechanisms associated with this concept can be assessed employing brain imaging techniques such as structural MRI for the quantification of brain morphology or PET imaging measuring the pathological burden. Brain reserve, in contrast, represents a snapshot of brain integrity at a single point in time, which can be assessed in cross-sectional study designs by means of structural MRI or PET imaging of synaptic density ([^{11}C]-UCB-J) or function ([^{18}F]-FDG). Complementing these two concepts, cognitive reserve requires a biological foundation, hence a relatively preserved brain integrity, which permits network-related adaptations. Research questions related to cognitive reserve can be addressed cross-sectionally, but also in longitudinal designs. The neuroimaging methods probably best capture cognitive reserve-related changes are fMRI or diffusion tensor imaging. Given that brain maintenance and brain reserve are both associated with brain integrity (longitudinally or cross-sectionally) and cognitive reserve requires a biological foundation, these three concepts are closely interconnected and carefully chosen study designs are necessary to distinguish between mechanisms associated with either one of them. Importantly, these concepts appear to be supported by modifiable (i.e., lifestyle, vascular risk) and non-modifiable factors (i.e., genetics, IQ), which mitigate and modulate the association between pathology, neuronal dysfunction, and subsequent functional impairment (see Figure 2 for summary).

To investigate mechanisms underlying resilience or resistance, the two extremes of the aging process; hence, super-aging and Alzheimer's disease may provide valuable information on influential factors contributing to decelerating or ameliorating the effects involved in the brain aging process.

4.1 | Resisting the aging process—The phenomenon of super-aging

Despite the exponential increase of individuals with Alzheimer's disease with advancing age, there is a small proportion of cognitively normal elderly over 80 years (<5% in a screened population of over 1000 cognitively normal individuals above 80 years), who demonstrate exceptional cognitive performance, similar to 50–60-year-old individuals or even similar to younger adults (Rogalski et al., 2013). Several terms have been used to describe these individuals, who appear to resist the aging process. These individuals are commonly referred to as *super-agers*, *super-normals*, *nonagenarians*, or *escapers* and may represent individuals with high brain maintenance mechanisms.

Arguably, super-aging can be supported through increased resilience mechanisms such as greater metabolic activity in certain brain regions (Arenaza-Urquijo et al., 2019), but also by the

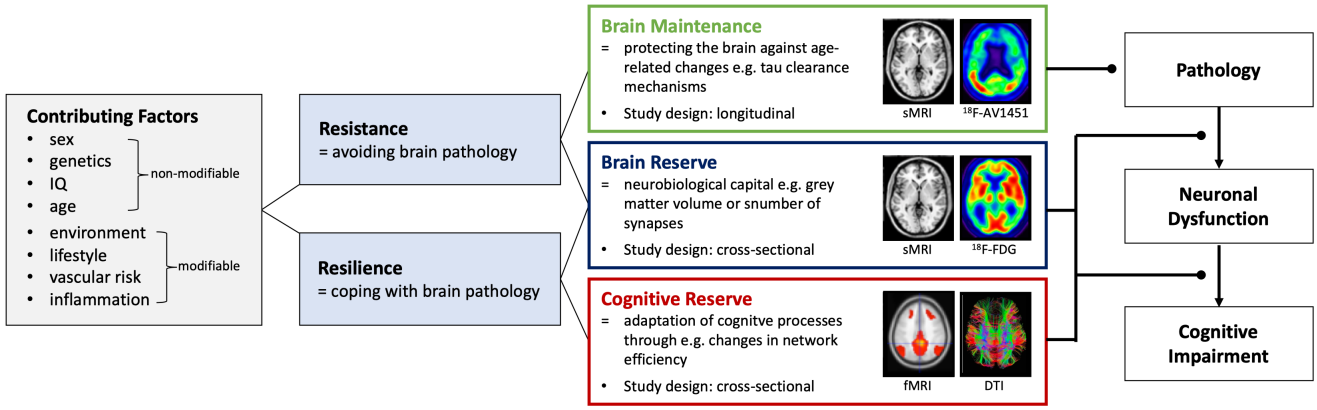

FIGURE 2 Summary of resistance and resilience concepts. Contributing factors that support resistance and resilience mechanisms are for example lifestyle factors (modifiable) or distinct genes (non-modifiable). Resistance is associated with brain maintenance, whereas resilience is closely associated with brain reserve and cognitive reserve. These concepts can be assessed by means of neuroimaging techniques. While brain maintenance can only be studied in longitudinal study designs by means of for example structural MRI or protein pathology PET, brain reserve can be assessed in cross-sectional designs by structural MRI or PET measures of synaptic function and density. Lastly, cognitive reserve is best captured by functional MRI or DTI as these measures provide information on network changes. Importantly, the three concepts modulate the relationship between pathology build-up, neuronal dysfunction, and cognition. Modified from (Arenaza-Urquijo and Vemuri 2018)

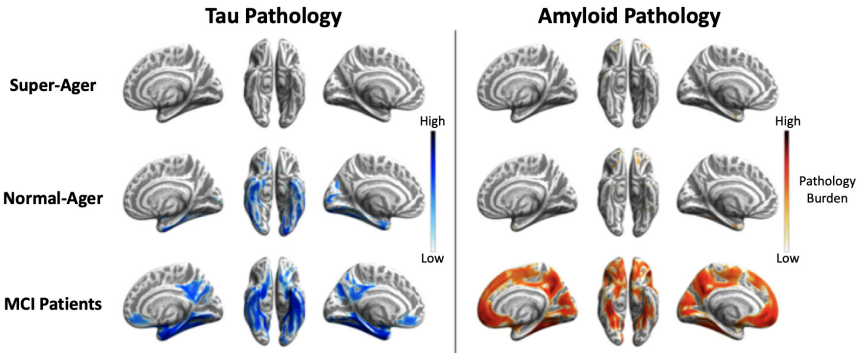

FIGURE 3 The Extremes of the Brain Aging Process. Tau and amyloid distribution patterns are depicted for the heterogeneous aging process (i.e., super-aging, normal aging, and mild cognitive impairment because of Alzheimer's disease). All brain projections represent the contrast of the respective group against a younger healthy cognitively normal group. Copyright pertains to JAMA Network Open. Reference: Hoenig et al., 2019

resistance against the accumulation of aging-proteinopathies and aging-associated diseases (Evert et al., 2003). While the former explanation relates to resilience, the latter appears of particular interest as it supposes that certain factors exist that provide resistance against the aging process. Indeed, recent neuroimaging and histopathology studies confirmed a relative absence or lower frequency of tau and amyloid pathology in super-agers (Gefen et al., 2015; Hoenig, et al., 2020; Rogalski et al., 2019; Snitz et al., 2020). It was thereby shown that individuals with above-average cognitive performance at an advanced age (80 years plus) show no difference in tau and amyloid burden when compared to a younger cognitively normal control group in their mid-60s (Hoenig, et al., 2020). This is in line with a recent histopathological study, which reported a lower frequency of neurofibrillary tangles and Aß plaques in super-agers when compared to age-matched counterparts (Gefen et al., 2015). Interestingly, another histopathological study reported an absence of NFT-induced neurodegeneration in super-agers, pointing toward brain maintenance factors against the neurotoxic effects of tau pathology in this group of individuals (Rogalski et al., 2019).

Importantly, while the accumulation of tau pathology appears to be part of the normal aging process (Josephs et al., 2020), which eventually results in memory loss in aging (Ikeda et al., 1999; Nelson et al., 2009; Pontecorvo et al., 2019; Scholl et al., 2016), the absence of Aß seems particularly pivotal to avoid accelerated aging as seen in Alzheimer's disease (Kawas & Corrada, 2020). Considering the cognitive aging spectrum, it appears that super-agers may be able to resist PART, but normal-agers may not and are thus exposed to inevitable cognitive decline because of the accumulation of neurotoxic tau tangles and the advancing aging process (Figure 3). Moving further to the other extreme of aging, namely Alzheimer's disease, the synergistic effect of amyloid and tau burden likely accelerates the unsuccessful aging (Figure 3).

Thus, the heterogenous cognitive trajectories may potentially be regarded on a spectrum whereby resistance toward Alzheimer-typical proteinopathies like amyloid and tau represents one side of the spectrum, which is supported by high brain maintenance. In contrast, the continuous accumulation of these toxic molecules leads to a shift to the opposite side of the spectrum, which is likely because of a failure of brain maintenance mechanisms and an increased predisposed risk of developing Alzheimer's disease. Yet, even in the phase of Alzheimer's disease pathology, some individuals appear to be able to compensate the neurotoxic effects at least to a certain degree (i.e. resilience), partly explaining the clinical heterogeneity seen in this disease.

To date, the exact mechanisms associated with the phenomenon of super-aging have not yet been deciphered, given that they are most probably not driven by a single factor, but by a multifold combination of inter-related molecular, cellular, and genetic mechanisms. Nevertheless, several studies have already xml:identified potential factors contributing to successful brain aging. Investigations of the genetic imprints of super-aging thereby yielded a lower frequency of the ApoE4 allele, a gene variant that represents the greatest known genetic risk factor for Alzheimer's disease (Rogalski et al., 2013). Aside from that, it was recently shown that polymorphisms of the Mitogen-Activated Protein Kinase 3 *(MAP2K3)* gene were associated with superior memory performance (Huentelman et al., 2018). This gene is involved in the Aß-mediated apoptosis and enriched in microglia (Huentelman et al., 2018). Also, genotypes such as the ApoE2 carriership appear to be associated with lower Aß aggregation, preserved cognition, and brain maintenance in cognitively normal older adults (Grothe, Villeneuve et al., 2017). Complementing this finding, it was recently shown that ApoE2 carriership and lower pulse pressure were related to the resistance against Aβ pathology (Snitz et al., 2020). Moreover, the Klotho gene, which is primarily expressed in the kidney and brain, has consistently been implicated as a longevity factor and with preserved brain health in aging (for review see (Kuro-o, 2019)). It was found to be associated with increased synaptic plasticity and enhanced cognition in the elderly (Dubal et al., 2014). Moreover, Klotho-VS heterozygosity has recently been associated with lower tau pathology aggregation (Neitzel et al., 2021). This gene is particularly involved in the aging process as it regulates phosphate homeostasis and is involved in insulin signaling (Kuro-o, 2019). Given that these genes have been associated with a lower prevalence of pathological protein aggregation, they represent non-modifiable imprints supporting brain maintenance across time. Moreover, these genetic imprints suggest that the phenomenon of super-aging and hence successful aging is one hand potentially supported by a lower prevalence of risk loci associated with neurodegenerative diseases and on the other hand facilitated by distinct genetic polymorphisms.

Importantly, despite these inherited imprints, also epigenetic, metabolomic, environmental, and lifestyle factors have also been related to enhanced resistance toward brain aging processes and subsequently brain maintenance. For instance, super-aging was associated with a distinct metabolomic signature that involved pathways regulating oxidative stress and inflammation (Mapstone, Lin et al., 2017). Additionally, also cellular and structural differences were observed in the brains of super-agers when compared to age-matched or younger counterparts. Individuals performing superior for their age presented three to fivefold higher number of Economo neurons in the cingulate cortex when compared to their age-matched and younger counterparts (Gefen et al., 2015). Moreover, neuroimaging studies observed greater hippocampal volumes (Harrison et al., 2012), and thicker cerebral cortices, in particular, in the anterior cingulate cortex (Lin et al., 2017). These neurobiological underpinnings are likely influenced by environmental and lifestyle factors. Being an individual of the oldest old was associated with an active social environment, regular exercise, modest alcohol consumption (a glass of wine/day), and modest caffeine intake (Kawas & Corrada, 2020). However, only physical exercise was related to preserved cognition in this study (Kawas & Corrada, 2020). In support of this finding, a recent histopathological study demonstrated that regular late-life physical exercise was linked to preserved synaptic integrity, hence supporting the notion of brain maintenance (Casaletto et al., 2022).

Notably, to date, there are only a few studies reporting on the neurophysiological underpinnings associated with the phenomenon of super-aging (for review see (Borelli et al., 2018)) and the focus has been mostly laid on Alzheimer's disease-related brain pathology. Presumably, super-agers may also be able to resist brain pathology associated with other neurodegenerative diseases such α-synuclein or TDP43. As there are no selective PET tracers currently available for these proteinopathies, this assumption cannot yet be tested in vivo. Nevertheless, super-agers likely obtain certain genetic imprints or distinct clearance/degradation mechanisms allowing them to counteract the accumulation of neurotoxic proteins and thereby maintaining their brains' function and thus cognitive performance even at high age. Given the multitude of factors involved in the aging process, it will be challenging to develop therapeutics tackling distinct factors of the successful aging process. Nonetheless, potential pathways can be xml:identified that promote successful aging by characterizing individuals who are resistant to tau and amyloid pathology using PET imaging (Hoenig, et al., 2020). Importantly, the determination of these cellular and molecular differences will offer novel treatment targets that may not only be relevant for Alzheimer's disease but other aging-associated diseases such as vascular disease or other forms of dementia (Hoenig, et al., 2020).

4.2 | The important contribution of modifiable factors to healthy brain aging

While the phenomenon of super-aging may represent one exciting avenue to study resistance mechanisms, assessing the contribution of modifiable factors to brain maintenance supports the development of interventions focussing on lifestyle adaptations. In this regard, it was recently suggested that modifying 12 particular risk

factors may actually prevent or delay up to 40% of all dementia cases (Livingston et al., 2020). The comprehensive review provided valuable evidence indicating that for instance treating hypertension, preventing head injury, reducing exposure to air pollution, higher education, and maintaining frequent physical exercise can reduce the neuropathological burden and preserve cognitive function in the aging process (Livingston et al., 2020).

Particularly, it was shown that greater exposure to air pollution contributed to increased pathological burden (Iaccarino et al., 2021), whereas adherence to a Mediterranean-style diet was associated with a slower progressive Alzheimer's disease biomarker change (Berti et al., 2018). A physically active lifestyle in mid-life was further related to an attenuation of the negative contribution of age on amyloid pathology and neurodegeneration in an elderly cohort (Jeon et al., 2020). Also, early-life cognitive enrichment was related to later cognitive performance partly mediated through fewer Alzheimer's disease-related biomarker changes (Oveisgharan et al., 2020). Moreover, recent imaging studies reported a relationship between lifestyle factors, BDNF, vascular and insulin growth factor levels, better cognition, and greater brain volume in humans (Coelho et al., 2014; Hohman et al., 2015; Westwood et al., 2014). Besides this, the notion of sleep being an important modulator in the build-up of neuropathology has recently received increased attention. High sleep quality across a lifetime was thereby associated with lower amyloid and tau pathology in a group of elderly subjects (Winer et al. 2019).

Importantly, these environmental and lifestyle variables have been associated with a decreased risk of developing an aging-associated disease such as Alzheimer's disease (for review see (Livingston et al., 2020)). But they have also been found to be linked to neurobiological underpinnings that mitigate the association between Alzheimer's disease pathology and cognitive impairment.

4.3 | Resilience mechanisms against aging-associated processes

The notion that 50% of adults over 80 years present relatively preserved cognition despite Alzheimer's disease pathology (Arenaza-Urquijo et al., 2019, Crystal et al., 1988; Katzman et al., 1988; Price et al., 2009) and given the clinical heterogeneity seen in Alzheimer's disease, the varying cognitive trajectories in the phase of Alzheimer's disease pathology may partly be explained by differences in individual resilience capacity, thus the ability to cope with the underlying brain pathology.

The most commonly used proxy in resilience research has been educational attainment given its relatively simple recording in clinical and research settings. Furthermore, education is a variable, which is an early lifetime factor occurring when the brain is still developing and most plastic and it is closely related with beneficial mid- and late-life factors (Jefferson et al., 2011). In line with this, it was recently reported that early lifetime factors are positively associated with age-related structural brain trajectories and cognitive function late in life (Walhovd et al., 2016). This indicates that these factors contribute to the build-up of resilience mechanisms crucial for late-life cognition and complies with the findings from environmental enrichment studies in animal models (Bloss et al., 2011; Wagner et al., 2000).

Additionally, PET imaging studies have consistently shown that higher education was associated with greater neuropathological burden despite relative preservation of cognitive function. These studies demonstrated that individuals with higher levels of education can maintain higher cognitive function at similar levels of an amyloid burden than lower educated individuals (Roe et al., 2008). Likewise, individuals with higher education can tolerate more amyloid pathology (Kemppainen et al., 2008), hippocampal atrophy (Vuoksimaa et al., 2013), and hypometabolism in temporo-parietal areas than lower educated individuals with similar clinical impairment (Ewers, et al., 2013; Kemppainen et al., 2008; Morbelli et al., 2013). Information regarding tau pathology load in vivo and educational attainment level is still relatively limited because of the only recent availability of tau PET compounds. Nonetheless, recent tau PET studies demonstrated that higher education was associated with greater tau pathology compared to lower education in aging and Alzheimer's disease (Hoenig et al., 2017; Rentz et al., 2017; Shimada et al., 2017). In particular, highly educated individuals with Alzheimer's disease demonstrated tau pathology burden in advanced Braak stages, but only mild cognitive impairment at the point of clinical diagnosis (Hoenig et al., 2017) (see Figure 4A). Moreover, higher education and global cortical thickness were related to the relative preservation of cognitive function in the presence of tau pathology in individuals with MCI because of Alzheimer's disease or Alzheimer's dementia (Ossenkoppele et al., 2020). Aside from education, also physical activity, as well as distinct personality traits, have recently been associated with varying neuropathological burden and their consequences for cognitive impairment (Binette et al., 2021). While it is undisputed that these lifetime factors support the build-up of resilience against aging-associated processes, the exact mechanisms through which these factors mitigate the neurotoxic effects of these aging-associated proteinopathies remain sparsely defined, but first indications on structural (i.e., brain reserve) and functional (i.e., cognitive reserve) underpinnings have been provided.

4.4 | Brain reserve

In line with the concept of brain reserve, which refers to the neurobiological capital, morphological differences have been associated with resilience toward aging-associated diseases such as Alzheimer's disease. According to the brain reserve hypothesis, there is more neurobiological capital that can be lost before clinical symptoms or cognitive decline become apparent (Stern 2002). This is because an individual with a high brain reserve obtains enough neuronal substrate to compensate for the brain damage or pathology. Several

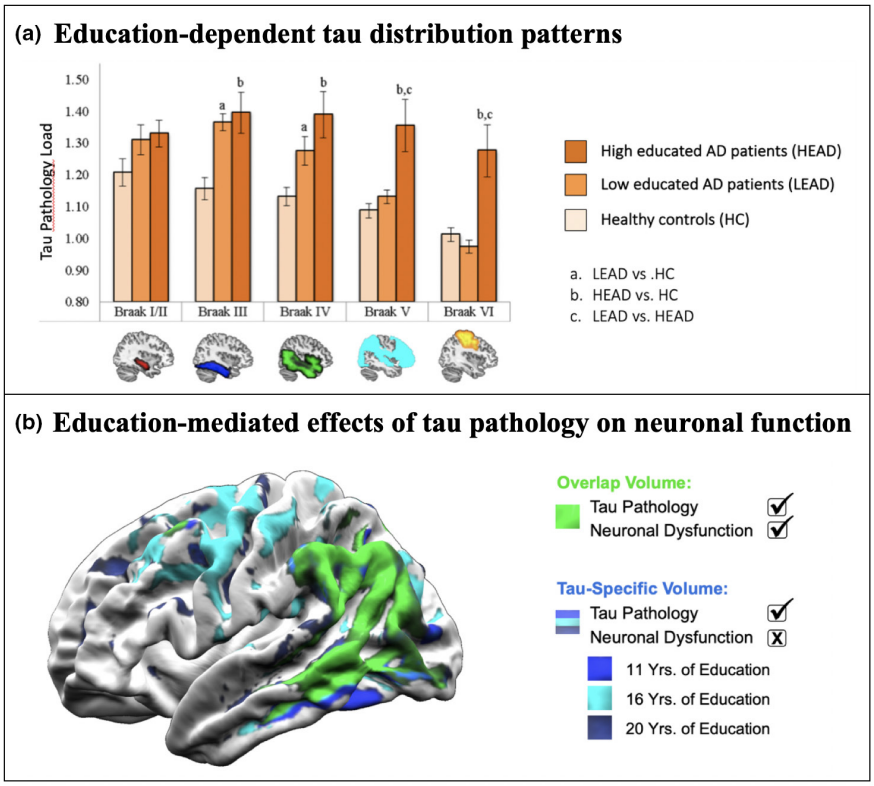

FIGURE 4 Resilience-associated effects of educational attainment on tau pathology in Alzheimer's disease. (a) Higher educated patients with Alzheimer's disease present tau pathology burden in regions that are typically affected in advanced stages of the disease. Moreover, higher educated patients show greater tau burden than lower educated patients with similar cognitive impairment pointing toward resilience-associated mechanisms in the higher educated group. Copyright of the figure pertains to Neurobiology of Aging, Hoenig et al., 2017. (b) A close spatial relationship has consistently been reported for tau pathology and neuronal dysfunction. This relationship appears to be mitigated by the level of education. Higher education is associated with greater tau-specific volume (in blue), thus regions that are affected by tau pathology, but do not show neuronal dysfunction. This indicates that the neurotoxic effects of tau pathology are potentially mitigated through resilience mechanisms supported by higher education. The overlap volume (in green) represents the overlap between significant tau pathology and neuronal dysfunction in patients with typical AD. Copyright of the figure pertains to EJNMMI, Hoenig et al., 2019

structural MRI studies provided support for the concept of brain reserve, using grey matter volume, intracranial volume, cortical thickness but also head circumference as brain reserve proxies. These studies indicated that higher education was associated with better brain integrity (Chang et al., 2016; Groot et al., 2018; Ossenkoppele et al., 2020; Perneczky et al., 2010; Schofield et al., 1997). The greater neurobiological substrate may explain, why the effects of toxic proteins may be less harmful to overall neuronal function, as can be assessed by means of FDG PET. Indeed, it was found that a greater tau burden was required to induce neuronal dysfunction at higher levels of education, which was used as a proxy of resilience capacity (Hoenig, Bischof et al., 2019). Moreover, higher levels of education appeared to mitigate the detrimental effects of tau pathology on neuronal function (Figure 4B; (Hoenig, Bischof et al., 2019).

While the quantification of neuronal function and brain integrity by means of FDG-PET or structural MRI only represents an indirect measure of brain reserve level or neurobiological capital, the newly introduced PET imaging technique for the visualization of synaptic density, such as the [^{11}C]-UCB-J PET tracer (Chen et al., 2018; Finnema et al., 2018), has opened a new avenue to directly study the compensatory effects of brain reserve. Using this technique, quantification of the underlying synaptic density is now feasible and the effects of neuropathological burden on neuronal and cognitive function in groups with high and low synaptic density can directly be assessed. Moreover, in vivo measures of synaptic density can further be associated with modifiable risk factors providing insights into their direct contribution to resilience, but also resistance mechanisms.

4.5 | Cognitive reserve

Aside from resilience-related morphological underpinnings, several studies have further shown that the adaptation of network efficacy and recruitment of additional brain areas may, in turn, provide coping mechanisms for increased pathological burden (Morbelli et al., 2013, Yoo et al., 2015, Franzmeier, Duering et al., 2017, Franzmeier, Hartmann, et al., 2017, Stern et al., 2018, Weiler et al., 2018, Lee, Lee et al., 2019). This is in line with the cognitive reserve hypothesis, which assumes cognitive preservation through functional

adaptations of large-scale networks. In particular, these studies showed that network adaptations and compensation are associated with higher levels of educational attainment (Morbelli et al., 2013, Yoo et al., 2015, Franzmeier, Duering et al., 2017, Franzmeier, Hartmann, et al., 2017, Stern et al., 2018, Weiler et al., 2018, Lee, et al. 2019). More specifically, it was recently demonstrated that left frontal connectivity mitigated the deleterious effects of tau pathology on cognitive function in non-demented elderly and MCI patients (Neitzel, et al., 2019). This region has also been demonstrated to provide compensation in the phase of emerging neuronal dysfunction (Franzmeier, Hartmann, et al., 2017). Moreover, in amyloid-positive individuals over 80 years, increased metabolic activity in the anterior cingulate cortex and the temporal pole was associated with better baseline cognition and longitudinal cognitive change (Arenaza-Urquijo et al., 2019). Interestingly, while cognitive reserve mechanisms appear to support cognitive maintenance in prodromal phases of Alzheimer's disease in individuals with higher reserve, cognitive function declines more rapidly in these subjects with onset of clinically manifest disease, likely because a certain threshold is reached at which resilience effects no longer work (van Loenhoud, et al., 2019)

Collectively, it appears that the abovementioned resilience mechanisms are mediated through morphological and structural differences, metabolic and functional adaptations. But also genetic heterogeneity has recently been suggested to explain the intra-individual difference in resilience to Alzheimer's disease-related pathology (Ramanan et al., 2021). Genes associated with synaptic plasticity (CNOT 7, (Ramanan et al., 2021)) and the brain-derived neurotrophic factor (Val66Metased risk of Alzheimer's disease) were thereby linked to preserved cognitive performance in the phase of Alzheimer's disease-related pathology. Also, the recent discovery of the ApoE3 Christchurch mutation as a protective factor in the presence of amyloid positivity and mutation of the PSEN1 gene further points toward inherited imprints providing resilience toward the effects of Alzheimer's disease-related pathology (Zalocusky et al., 2019).

5 | OUTLOOK

Overall, a better understanding of the mechanisms underlying resilience and their association with brain and cognitive aging carries important implications for the diagnosis and prognosis of aging-associated diseases as disease trajectories vary depending on the level of resilience. Consistent evidence signifies that individuals with high education present initial clinical symptoms at advanced pathological stages. Hence, it will be important to develop sensitive diagnostic tools for the early xml:identification of individuals with high levels of resilience (Hönig, 2020). Moreover, resilience-related influences need to be considered in the general conception of aging-associated diseases since the temporal and spatial evolution of Alzheimer's disease biomarkers is not uniform across patients (Brown et al., 2013; Landau et al., 2012; Wirth et al., 2014). This is particularly crucial with regard to the assessment of pharmacological strategies. Resilience capacity may potentially change the responsiveness to the treatment (Gallucci et al., 2016), but may also lead to an observation of effects that may not be as a result of the drug itself, but resilience capacity interfering with pathophysiological processes (Hönig, 2020). Finally, better knowledge on factors supporting resilience may support the design of non-pharmacological prevention trials, which are urgently needed given the increasing prevalence of Alzheimer's disease as a result of the demographic change in Western societies.

Currently, there are a number of studies on non-pharmacological resilience boosting therapies including physical exercise or cognitive training (for review see (Wang et al., 2020)). One of the largest and currently still ongoing randomized control trial is the worldwide Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (WW-FINGERs) trial, which involves a multidomain lifestyle intervention program among older at-risk individuals (www.alz.org/wwfingers). Evidence from this randomized control trial indicated that the multidomain FINGER intervention was able to improve cognitive performance in at-risk elderly people (Ngandu et al., 2015). Importantly, this intervention did not only prove to be effective in terms of enhancing or maintaining cognitive performance but also in preventing cerebrovascular events (Lehtisalo et al., 2022). These insights demonstrate that resilience boosting therapies may not only be relevant for Alzheimer's disease but other aging-associated diseases.

To xml:identify at-risk individuals and thus those, who potentially profit the most from such interventions, screening tools are necessary that are widely available and come at low cost. And even though PET imaging provides unique information about the underlying spatial and temporal distribution of neuropathology, this technique comes at high costs, is invasive, and offers only limited accessibility, limiting its utility in the screening of at-risk populations as well as monitoring of treatment efficacy in larger cohorts. The recent development in blood-based biomarkers may thereby provide a novel avenue in studying the aging process because of its wide accessibility. Even though these biomarkers are currently not as accurate as PET or CSF biomarkers, they are anticipated to soon be available for clinical diagnostic and prognostic purposes (Teunissen et al., 2022). Moreover, a consensus has reached that these fluid biomarkers facilitate screening of large populations, xml:identification of individuals at-risk of developing Alzheimer's disease, and subsequent selection of individuals, who may profit from a more detailed clinical assessment including PET imaging. This is particularly important in light of the recent approval of an anti-amyloid therapy, *aducanuma*b, which was based on amyloid PET results. Importantly, while blood-based markers may support screening and xml:identification of at-risk individuals already in preclinical stages of the disease (Teunissen et al., 2022), PET imaging is recommendable to be used for quantification and monitoring of therapy effects. This does not only account for pharmacological but also non-pharmacological lifestyle interventions, boosting resilience and resistance levels. Notably, even short delays and prolongation in disease progression may reduce the number of individuals with

Alzheimer's disease. Studies have argued that postponing symptom onset by two years would result in a significant decrease of around 16% of cases with overt Alzheimer's disease in 2040 (Brookmeyer et al., 2007), which will be pivotal in the future reduction of the economic and societal burden associated with aging-associated diseases such as Alzheimer's disease.

6 | CONCLUSION

The above-mentioned studies overall document that non-modifiable and modifiable factors together equip the brain with means to protect it against or to cope with aging-related neuropathologies. Importantly, these factors can alter brain structure and function through mechanisms associated with resilience. Additionally, these factors support the maintenance of the neuronal substrate over life, thereby, on the one hand, decreasing the risk of developing dementia (Dekhtyar et al., 2016; Stern et al., 1994; Wang et al., 2017) and on the other hand slowing the accumulation of brain pathology (Brown et al., 2013; Landau et al., 2012; Wirth et al., 2014). While it is certainly important to understand the pathophysiological mechanisms and risk factors of a given disease, xml:identifying mechanisms that protect against the detrimental effects of neuropathology may offer another pathway for novel treatment strategies. In this regard, the use of neuroimaging techniques in combination with blood-based biomarkers will be crucial to study the in vivo characteristics of aging-associated processes and factors that protect against neurodegenerative diseases such as Alzheimer's disease, but also Parkinson's disease or frontotemporal dementia. Hopefully, these efforts will further contribute to the development of strategies to delay pathological brain aging or even to cure aging-associated neurodegenerative diseases.

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https://kups.ub.uni-koeln.de/10699/1/Doktorarbeit_Merle Hoenig_PrintVersion.pdf. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

MH reports no conflict of interest. AD reports having received consulting and speaker honoraria as well as research support from Siemens Healthcare, AVID Radiopharmaceuticals, Lilly, Life Molecular Imaging, Sofie, and GE Healthcare.

AUTHOR CONTRIBUTION

MH and AD were responsible for the content and the writing of the manuscript.

DATA AVAILABILITY STATEMENT

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