

# Resistance vs resilience to Alzheimer disease

## Clarifying terminology for preclinical studies

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### Abstract

Preventing or delaying Alzheimer disease (AD) through lifestyle interventions will come from a better understanding of the mechanistic underpinnings of (1) why a significant proportion of elderly remain cognitively normal with AD pathologies (ADP), i.e., amyloid or tau; and (2) why some elderly individuals do not have significant ADP. In the last decades, concepts such as brain reserve, cognitive reserve, and more recently brain maintenance have been proposed along with more general notions such as (neuro)protection and compensation. It is currently unclear how to effectively apply these concepts in the new field of preclinical AD specifically separating the 2 distinct mechanisms of coping with pathology vs avoiding pathology. We propose a simplistic conceptual framework that builds on existing concepts using the nomenclature of resistance in the context of avoiding pathology, i.e., remaining cognitively normal without significant ADP, and resilience in the context of coping with pathology, i.e., remaining cognitively normal despite significant ADP. In the context of preclinical AD studies, we (1) define these concepts and provide recommendations (and common scenarios) for their use; (2) discuss how to employ this terminology in the context of investigating mechanisms and factors; (3) highlight the complementarity and clarity they provide to existing concepts; and (4) discuss different study designs and methodologies. The application of the proposed framework for framing hypotheses, study design, and interpretation of results and mechanisms can provide a consistent framework and nomenclature for researchers to reach consensus on identifying factors that may prevent ADP or delay the onset of cognitive impairment.

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## Glossary

A $\beta$  =  $\beta$ -amyloid; AD = Alzheimer disease; ADP = Alzheimer disease pathology.

Alzheimer disease (AD) is associated with the deposition of  $\beta$ -amyloid (A $\beta$ ) into plaques and hyperphosphorylated tau as neurofibrillary tangles. These 2 AD pathology (ADP)-related changes are the drivers of neuronal dysfunction (hypo-metabolism and brain atrophy) and subsequent cognitive impairment seen with AD. The recent availability of imaging and CSF biomarkers to assess ADP and neuronal dysfunction has brought us closer to understanding the mechanistic underpinnings of AD. Biomarkers have been proposed for staging of individuals in preclinical stages of AD for research studies, i.e., in cognitively normal individuals with AD-related changes.<sup>1-3</sup> These research developments allow for classification of individuals as positive or negative for significant levels of ADP, i.e., presence/absence or abnormal/normal levels of A $\beta$  (A+/A-) or tau (T+/T-). These new frameworks for preclinical disease have accelerated the development of therapeutics<sup>4,5</sup> and have also brought substantial research interest to the field of reserve, resilience, and protective factors.

### Why are some individuals with AD pathologies cognitively normal?

Since the initial observations of the disconnect between the degree of pathology and cognition,<sup>6-9</sup> there has been tremendous interest in understanding the mechanisms underlying resilience. Furthermore, studies have shown that lifestyle, genetic, and brain factors play an important role in delaying or slowing cognitive decline.<sup>10-18</sup> In this context, the reserve hypothesis has been the most widely used approach to resilience, including its active<sup>10,11</sup> and passive forms.<sup>6,19</sup> Other notions such as brain maintenance<sup>20</sup> may also be useful in capturing some aspects of resilience.

### Why do some individuals have lower burden of AD pathologies?

There is emerging evidence that some lifestyle and behavioral factors may slow or halt the progression of ADP.<sup>21-30</sup> This concept is distinct from the concept of pathology and cognition disconnect and not acknowledged in the concept of reserve. It fundamentally aims to explain how some individuals are able to slow ADP progression. For example, recent evidence supports the idea that certain individuals, referred to as exceptional agers, do not have significant ADP even at advanced ages due to better lifestyles.<sup>31</sup>

While there have been varied terminologies to investigate the above mentioned ideas, including cognitive<sup>10,19</sup> and brain reserve,<sup>6,32</sup> brain maintenance,<sup>20</sup> or general notions such as (neuro)protection and compensation, the use of varied concepts and terminologies across publications has led to a lack of

consensus across studies. It has importantly led to a lack of common ground for interpreting study results and for conveying hypotheses/ideas, which is more apparent in preclinical AD biomarker studies. With this in mind, our primary goal was to propose a simplistic conceptual framework for preclinical studies in AD that can aid with framing of hypotheses, understanding mechanisms, and interpreting results, especially in AD biomarker studies. We do not aim to propose new concepts but rather propose a framework that highlights the complementarity and clarity of existing concepts. The simplistic framework proposed here can aid with both conveying the results and moving the field toward a common goal using consistent nomenclature. The secondary aim was to discuss different study designs and methodologies that can be employed to investigate these ideas and illustrate their application in the literature.

## Terminology

### Resistance vs resilience to AD: Avoiding vs coping

A substantial proportion of people remain cognitively normal throughout their lifetime, some with ADP at autopsy or in vivo imaging (~30%) and some without ADP as outlined in the Introduction.<sup>33-37</sup> Here, we propose a simplistic framework of resistance and resilience that provides a conceptual distinction between these 2 aspects. We refer to resistance in the context of avoiding pathology, i.e., remaining cognitively normal with low ADP. We refer to resilience in the context of coping with pathology, i.e., remaining cognitively normal despite substantial ADP. This distinction of nomenclature will help advance our understanding of the genetic, behavioral, and brain mechanisms underlying the maintenance of normal cognition in the context of preclinical AD.

### Definitions and common scenarios

Resilience denotes the ability to cope in the face of adversity. Resilience to AD thus may represent an individual's ability to sustain a better-than-expected cognitive performance in relation to the degree of ADP (see, for example, reference 16). The mechanisms underlying resilience may explain higher than expected cognitive performance. Note that we are considering resilience in the context of AD pathway and therefore require the elevation of A $\beta$  or A+.

Resistance denotes "the act of resisting, opposing, or withstanding." Resistance to AD will thus imply avoiding the appearance of ADP. In preclinical AD studies, resistance could be translated as individuals with absence or lower than expected levels of ADP. Therefore, the mechanisms underlying resistance may explain lower than expected ADP levels.

It is important to note that both terms are used in the context of AD including when we are discussing populations at risk. While this is implicit in the definition of resilience (the presence of ADP would be required), this should be more carefully considered in the definition of resistance to ADP. For example, being A $\beta$ -negative alone does not imply resistance to ADP; however, being APOE4-positive with lower than expected A $\beta$  levels implies resistance. Similarly, being older than 85 years with low/no A $\beta$  or tau implies resistance. In other words, studies assessing resistance to AD should include either individuals at risk or methods that can indicate lower than expected ADP levels. Thus, the study of resistance would rely on known effects of risk factors on pathologic processes (e.g., APOE4 and age). While the present article focuses on preclinical AD, the concepts of resistance and resilience may be extended from aging to dementia, which will help characterize the underlying mechanisms.

In table 1, we present the broad definitions of resistance and resilience. These definitions clarify and differentiate the 2 concepts, make them testable using AD biomarkers, and facilitate their use in both cross-sectional and longitudinal studies. Note that, especially in the case of resilience, the terminology used to describe the data and study should not be confounded with the method used to approach the concept. The choice of methodology would be made to optimally test the researchers' proposed hypothesis. For example, a longitudinal approach rather than a cross-sectional approach might help distinguish an individual who is early in disease process from an individual who is truly coping with pathology (i.e., resilient). However, in most cases, the results may drive how the data would be presented and described. In such cases, the 2 frameworks would help convey if individuals were truly coping with pathology, i.e., resilience, or if there were differences in the ADP progression between individuals, i.e., resistance. Some approaches are discussed in the Study design and methodologies section.

Given the existing terminology to explain mechanisms, one may argue against the need for new terminology. However, the varied terminology as discussed below and also classification of the existing terminologies into one of the 2 bins of

resistance and resilience make the use of these terms appealing. These broader terms are particularly helpful while studying each specific process along the preclinical AD trajectories and relevant for AD prevention.

To disambiguate the terms of resistance and resilience, extensively used in other fields such as psychology, it will be useful to refer to resistance to AD and resilience to AD in preclinical AD studies. These terms can be further refined depending on primary outcomes of interest; for example, resistance or resilience to A $\beta$  when studying A $\beta$  markers or cognitive resilience when cognition is the primary outcome (tables 2 and 3). The term protective can be used when discussing factors and mechanisms contributing to resilience and resistance; for example, protective genes when discussing genes that confer protection against A $\beta$  deposition. In the context of mechanisms, we propose the terms brain resistance and brain resilience to AD, which are discussed below. In table 2, we present common scenarios seen typically in studies to make a clear distinction between the uses of the 2 terminologies.

### Mechanisms and factors associated with the development vs the clinical expression of ADP

The figure summarizes the definitions of resilience and resistance and the contributing factors. It also illustrates previous theories within the framework of resistance and resilience, highlighting common and specific mechanisms. The present framework attempts to guide research into 2 sets of factors/mechanisms: (1) those associated with ADP processes and (2) those associated with the clinical expression of ADP. The first set of factors/mechanisms are associated with resistance to AD, should explain lower than expected ADP, and include amyloid and tau clearance mechanisms as well as structural and functional brain characteristics that may result in diminished ADP. The second set of factors/mechanisms underlie resilience to AD, should explain better than expected cognition in the face of ADP, and include structural and functional brain characteristics that may enable coping with ADP either through response mechanisms or through inherent brain efficiency/characteristics. Novel evidence supports this framework, suggesting that these 2 concepts may be

**Table 1** Theoretical differentiation between resistance and resilience to Alzheimer disease

	Resistance	Resilience
<b>Cognition</b>		Better than expected <sup>a</sup>
<b>Alzheimer disease pathologies</b>		
<b>Amyloid</b>	Negative or lower than expected	Positive or higher than expected <sup>b</sup>
<b>Tau</b>	Negative or lower than expected	Positive or higher than expected <sup>b</sup>
<b>Mechanisms</b>	Mechanisms that explain negative or lower than expected ADP levels	Mechanisms that explain better than expected cognition

Abbreviation: ADP = Alzheimer disease pathology.

Resistance implies absence or lower than expected ADP.

<sup>a</sup> Resilience can be defined as performing better than expected relatively to the amount of ADP.

<sup>b</sup> Resilience can also be defined as higher than expected ADP for a given level of cognitive performance.

**Table 2** Common scenarios and recommendations to use the terms resistance and resilience

Categorization	Primary Outcome	Evaluation of protective mechanisms/factors that explain	Specific Terminology
<b>Resilience</b>	Brain structure/function in those with abnormal or high levels of amyloid and/or tau	Higher than expected brain structure/function	Brain Resilience to ADP
		Increased brain function as a function of A $\beta$	Brain Resilience to A $\beta$
		Increased brain function as a function of tau	Brain Resilience to tau
	Brain structure/function	Higher than expected brain structure/function as a function of a protective factor	Brain Resilience
	Cognition in those with abnormal or high levels of amyloid and/or tau	Higher than expected cognitive performance	Cognitive Resilience to ADP
	Cognition	Higher than expected cognition as a function of a protective factor	Cognitive Resilience
	Amyloid and/or tau	Higher than expected A $\beta$ and tau at similar cognitive performance	Resilience to ADP
		Higher than expected A $\beta$ at similar cognitive performance	Resilience to A $\beta$
		Higher than expected tau at similar cognitive performance	Resilience to tau
<b>Resistance</b>	Amyloid and/or tau	Lower than expected A $\beta$ associated with a potential explanatory mechanism	Brain Resistance to A $\beta$
		Lower than expected tau associated with a potential explanatory mechanism	Brain Resistance to tau
		Lower than expected A $\beta$ and tau	Resistance to ADP
		Lower than expected A $\beta$	Resistance to A $\beta$
		Lower than expected tau	Resistance to tau

Abbreviations: A $\beta$  =  $\beta$ -amyloid; ADP = Alzheimer disease pathology.

underlain by distinct phenotypic traits. For example, resilience might be linked to the preservation of neuronal, synaptic elements and spine plasticity<sup>38,39</sup> and resistance might be linked to enhanced A $\beta$  clearance.<sup>40</sup> Previous studies suggest that resistance and resilience may be promoted by genetic and lifestyle variables, including sex, *APOE*, vascular risk, current and lifelong cognitive and physical engagement, and sleep.<sup>17,37,38,41–46</sup> For example, sleep acts possibly as

a resistance mechanism (for a review, see reference 46) through amyloid clearance vs intellectual enrichment, which may act primarily as a resilience mechanism (see for example reference 47) with possible associations with lower ADP (for a review, see reference 48). Examples from the literature considering other factors and potential mechanisms are provided in table 4. There needs to be further research in clarifying the extent to which several important factors promote resistance vs resilience.

**Table 3** Previous theories/concepts as defined in original articles under the umbrella terms of brain resistance and brain resilience

Brain resistance	Brain resilience
(Neuro)protection	Compensation
Brain maintenance	Metabolism maintenance <sup>a</sup>
	Structure maintenance <sup>a</sup>
Neural efficiency	Brain reserve (threshold model)
Cognitive reserve (neural reserve)	Cognitive reserve (neural compensation)

<sup>a</sup> Aspects related to brain maintenance that have been shown to be useful in preclinical Alzheimer disease research, considering the maintenance of brain structure and metabolism in the setting of Alzheimer disease pathology, instead of maintenance in an absolute way, as considered in the original article.

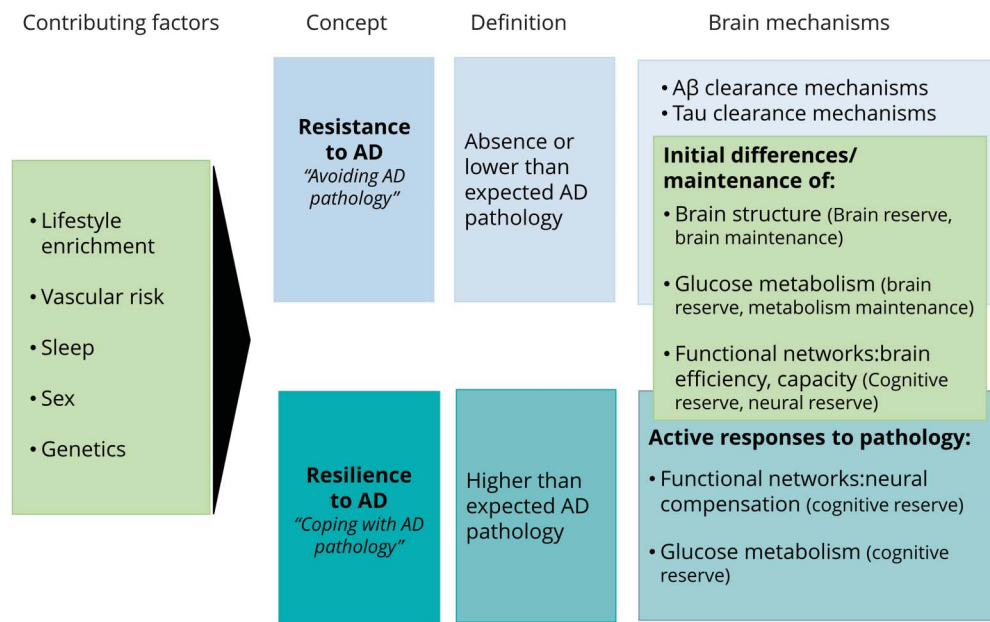
### Brain resistance and brain resilience to explain brain mechanisms

The concepts of resilience and resistance can also be used to explain brain mechanisms. Brain resistance and brain resilience to AD refer to the brain processes underlying the ability to better resist or cope with pathology. From a theoretical perspective, existing concepts may fall in 1 of 2 categories (resistance or resilience). For instance, while the reserve concept stresses the way of coping with pathology (resilience), the brain maintenance concept focuses on the relative lack or postponement of brain changes as the key to preserving cognition in elderly (resistance) (adapted from Nyberg et al.<sup>50</sup>).

### Existing concepts/theories that explain brain resistance

Brain resistance refers to the brain processes underlying the ability to better resist pathology. There have been a few existing

**Figure** Relation between the concepts of resistance and resilience, brain mechanisms, and contributing factors



Lifestyle factors, vascular risk, sleep, sex, and genetics are contributors to resistance and resilience. Mechanisms specific to resistance include those related to (A $\beta$ ) and tau clearance. Common mechanisms comprise initial differences in brain structure (brain reserve) and function (neural reserve-cognitive reserve) and brain maintenance processes, including the preservation of brain structure, glucose metabolism, and functional networks. Specific brain mechanisms of resilience include those that appear as an active response to pathology including neural compensation and compensatory glucose metabolism increases. Light blue indicates the concept, definition, and brain mechanisms associated with resistance to Alzheimer disease (AD). Dark blue indicates the concept, definition, and brain mechanisms associated with resilience to AD. Green indicates factors and mechanisms associated with both concepts. A $\beta$  =  $\beta$ -amyloid.

concepts that focus on how some older adults have low or no pathology or age-related changes. The notion of neuroprotection refers to the maintenance of neuronal integrity against internal or external insults.<sup>49</sup> In line with this idea, Nyberg et al.<sup>20</sup> proposed the theory of brain maintenance, which considers the idea of preservation of brain structure (neuroprotection), preservation of task-related networks, along with the absence of significant pathologies as the best predictors of successful cognition. However, it has been shown that the use of maintenance to make reference to the preservation of some aspects of brain structure and function (instead of in an absolute way) might be useful in the context of resilience to AD (for example, metabolism maintenance).<sup>50</sup> The concept of neural reserve<sup>19</sup> also emphasizes strategies used when coping with task demands that can be identified in the absence of pathologic changes.

### Existing concepts/theories that explain brain resilience

Brain resilience refers to the brain processes through which positive outcomes are achieved in the context of pathologic changes (adapted from Masten<sup>51</sup>) and it may include passive or active processes. For example, the theory of cognitive reserve is mechanistically explained by the ability to cope with pathology. The notion of compensation is used to refer to strategies used to compensate for cognitive decline and thus counteract the changes that occur during aging<sup>52,53</sup> or pathology.<sup>19</sup> The theory of cognitive reserve includes the notion

of neural compensation to refer to an active response implying the use of new or alternate brain networks after pathology has affected those networks typically utilized.<sup>19</sup> Passive processes, such as starting with a greater brain structure, may also play an important role in brain resilience. For example, the threshold models of brain reserve<sup>54</sup> posit that there is a specific cutoff that sets the amount of brain damage that can be sustained before reaching a threshold for clinical symptoms, e.g., individuals with greater brain volumes may tolerate higher levels of A $\beta$  deposition.

### Potential common mechanisms

Common mechanisms include preexisting or better preserved/maintained brain characteristics that may be associated with diminished ADP or enhanced capacity to cope with ADP. For example, preexisting functional differences may result in greater lifelong neural efficiency, which may be associated with lower A $\beta$ .<sup>55</sup> On the other hand, these preexisting differences in neural efficiency may also help tolerate greater ADP. See figure 1 for further details.

## Study design and methodologies

We provide examples of study designs that could use the present framework along with some specific examples and new approaches from the literature with specific focus on biomarker studies. (detailed information in table 4).

**Table 4** Examples of observational studies using different study designs and methodologies

Concept	Specific terminology	Main outcome	Study type	Subtype	Example of finding	Examples of studies	Related concepts
<b>Resistance</b>	Resistance to A $\beta$	Amyloid pathology	Cross-sectional	Correlational	Lower A $\beta$ associated with cognitive and physical engagement or sleep quality	22,23,26,28,30,e9 (links.lww.com/WNL/A347)	Brain maintenance
				Risk modification	Lifestyle factors moderate the effects of APOE4 on A $\beta$	24,25,29	
				Genetics	Specific genes are related to lower A $\beta$	44	
			Longitudinal	Cohort study	Education relates to slower rates of A $\beta$	27	
	Resistance to tau	Tau pathology	Cross-sectional	Correlational	Education relates to lower tau pathology	e10	
	Resistance to A $\beta$ /brain resistance	Amyloid pathology, brain structure	Cross-sectional	Case-control	Greater brain structure and lower AD pathology in very old individuals with high cognitive abilities	e3,e4	Brain maintenance
		Longitudinal	Correlational	Cognitive lifestyle is associated with slower atrophy trajectories	e6		
<b>Resilience</b>	Resilience to A $\beta$ or tau	Amyloid or tau pathology	Cross-sectional	Correlational	Higher than expected A $\beta$ /tau for a given level of cognition	56,57	Brain maintenance
	Brain resilience	Brain structure/function	Cross-sectional	Case-control	Higher gray matter volume and metabolism in A $\beta$ -positive normal elders	e2,e11	Brain reserve
			Cross-sectional	Correlational	Protective factors are associated with higher structure or function in at risk or cognitively impaired individuals	27,28,e1,e12	Brain maintenance Neuroprotection
	Brain resilience to A $\beta$ (and neurodegeneration)	Brain function	Cross-sectional (fMRI)		Amyloid pathology or hypometabolism are associated with higher fMRI activations or connectivity	58,59,e13	Cognitive reserve, compensation
	Cognitive resilience	Cognition	Cross-sectional	Effect modification	Education moderates the effects of A $\beta$ on cognition	60,e14	Cognitive reserve
			Cross-sectional and longitudinal	Correlational	Positive effects of lifestyle factors on baseline cognition or longitudinal trajectories	14,17,e15,e16	Cognitive reserve
<b>Factors contributing to resistance/resilience</b>		Protective/risk factors	Cohort study	Case-control	Better lifestyles and higher intracranial volume in participants a priori classified as resilient/resistant	12,31,e4,15,16	—

Abbreviations: A $\beta$  =  $\beta$ -amyloid; AD = Alzheimer disease.  
 These studies illustrate how the resistance and resilience framework can be applied for research.

## Study designs

Several approaches described here can be used to investigate protective factors/mechanisms that contribute to maintenance of normal cognition in the context of resistance vs resilience. However, both the recruitment mechanism and study design need to be carefully considered while interpreting the generalizability of the results. We present studies that include 3 sets of variables. (1) Protective factors or measures contributing to resilience and resistance: (1a) behavioral/lifestyle; (1b) genetic; (1c) cerebral (brain structure and function). While protective and conversely risk factors are numerous, here we focus on the 3 common categories of factors. We have included cerebral measurements as they can possibly reflect protective mechanisms. (2) Biomarkers or surrogates of ADP: CSF, imaging, or plasma biomarkers. These are key variables to define resistance and resilience to AD and may not be needed for studying cognitive resilience in individuals at risk. (3) Cognitive measurements are necessary to determine if the study participants are performing better than expected for studying resilience. Most study designs also use cognition to ensure that study participants are performing within a given range (in the context of resistance).

### Cross-sectional study designs

Cross-sectional study designs can be used to assess the associations between hypothesized factors contributing to resistance or resilience (1), ADP (2), or cognition (3). A limitation of these studies is that they do not address causal relationships or change over time. A cross-sectional study design addressing the resistance hypothesis could test the relationship between early intellectual enrichment (1a) or *APOE2* carriage (1b) and  $A\beta$  deposition (2). Findings in line with the resistance hypothesis may include associations between greater intellectual enrichment/*APOE2* carriage and lower  $A\beta$  deposition.<sup>22,44</sup> A cross-sectional study design showing participants with higher than expected ADP for a given level of cognition provides evidence consistent with the resilience hypothesis.<sup>56,57</sup> Evidence of brain resilience, and notably of neural compensation, may come from studies evaluating changes in brain function as a function of ADP/neurodegeneration; for example, increased brain activations or brain connectivity at rest or during a cognitive task.<sup>58,59</sup> Cross-sectional studies may also test the modification effect of factors contributing to resilience/resistance on the association of ADP with cognition. For example, the effects of  $A\beta$  deposition on cognitive performance might be minimized with higher education,<sup>60</sup> and the effects of *APOE4* on  $A\beta$  might be modified by intellectual enrichment variables or physical activity (for example, reference 29). Finally, cross-sectional studies that do not include AD biomarkers information may assess the relationship between lifestyle factors (1a) and brain structure or function (1c), thus investigating brain resilience. In the absence of AD biomarkers, the study framework and the interpretation of the results will determine the evidence of resistance or resilience (for example,<sup>e1</sup> [links.lww.com/WNL/A347](https://links.lww.com/WNL/A347)).

### Case-control study designs

Case-control study designs are convenient for identifying factors contributing to resistance or resilience by studying individuals who do not show an expected negative outcome in the setting of a given exposure, as compared to a control group. For example, while normal cognition (3) in the setting of  $A\beta$  deposition (2) implies resilience, absence of ADP/neurodegeneration (2) at very old age implies resistance. Usually, individuals are retrospectively assigned to a group (for example, reference 12). Several studies have mimicked such a study design by assigning groups cross-sectionally. Findings in line with the resilience hypothesis may include larger volumes in A+ as compared to A-normal elderly<sup>e2</sup> ([links.lww.com/WNL/A347](https://links.lww.com/WNL/A347)). Results providing insights into the determinants of resistance include evidence of fewer risk factors and chronic conditions in very old adults without ADP<sup>31,e3,e4</sup> or greater brain structure and lower ADP in very old individuals with unusually high cognitive performances, namely super agers.<sup>e3,e4</sup> Limitations of these types of studies concern notably the sampling: due to their retrospective nature, they are especially prone to selection bias. The lack of representativeness of the sample also affects the generalizability of the findings. Moreover, temporal sequence between the outcome and exposure would be difficult to establish and thus they do not address causality.

### Longitudinal study designs

Finally, longitudinal cohort studies might be used to evaluate the relationship between the hypothesized determinants of resistance and resilience and cognitive and biomarker changes longitudinally. This design would be particularly useful to investigate a sequence of events and provide relevant information about possible causation; for example, evaluation of a slower rate of cognitive decline with higher intellectual enrichment<sup>e5</sup> ([links.lww.com/WNL/A347](https://links.lww.com/WNL/A347)). Findings from longitudinal studies in line with resistance hypothesis would show slower rates of atrophy or  $A\beta$  deposition with higher intellectual enrichment.<sup>27,e6</sup> Evidence in line with cognitive resilience would come from studies showing effects of intellectual enrichment on cognitive trajectories but not on biomarker trajectories.<sup>e5</sup> Possible selection bias can be seen with retrospective cohort studies in longitudinal study designs. In addition, longitudinal study designs are subject to bias due to differential loss to follow up (drop-out cases or loss to mortality).

### Additional approaches specific to resilience

Several studies have reported factors that may contribute to resistance by studying individuals with exceptional cognitive capacities or lower than expected ADP, i.e., super agers or exceptional agers. One of the important challenges in the field of resilience, however, is to identify individuals who do not progress to AD, notably when long follow-up data are not available. Here we present recent approaches that have been developed to capture the notion of resilience including residual and risk approaches.

## Residual approaches

Residual approaches study measurements reflect the discordance between ADP or neurodegeneration and cognition or between several AD processes (e.g., ADP and neurodegeneration). Such an approach reflects the discordance between predicted and observed measurements. These kinds of approaches were initially proposed within the framework of cognitive reserve<sup>e7</sup> ([links.lww.com/WNL/A347](http://links.lww.com/WNL/A347)) and have been used in several investigations.<sup>15,17,e8</sup> A strength of this approach includes the quantification of resilience as a continuous variable allowing its use at different disease stages. It has recently shown great utility for clinical research, as it may predict cognitive decline.<sup>17</sup> A shortcoming of this approach, however, is that it is reductionist. Resilience is defined by the error that is not explained in the model, and thus it depends on the large number of inputs included in the model (which may be incomplete or poor surrogates), which may lead to noisy residual measurements. To date, these approaches have been less informative about the underlying brain mechanisms, as often brain measurements (structure or function) are included as inputs in the model, which does not allow for studying brain measurements that contribute to resilience.

## Risk approaches

Risk approaches rely on the assumption that known risk factors for AD (e.g., *APOE4* or age) are related to negative outcomes (such as cognitive decline or ADP) (for example, references 12 and 31). These approaches allow for better characterization of brain mechanisms as individuals can be identified based solely on risk factors. The limitations are that the relationships between risk factors and outcomes are typically complex (especially with increasing age) and long follow-up times may be needed to reliably identify non-declining individuals.

## Discussion

Several concepts have been proposed to date aiming at explaining the disconnect between ADP levels and cognition. There is now emerging evidence that lifestyle and behavioral modifications can slow or halt ADP progression, which is theoretically distinct from the concept of pathology and cognition disconnect. The present article represents an effort to integrate previous concepts in a common framework and nomenclature that can aid researchers to investigate these 2 distinct aspects under the notions of resilience and resistance to AD. This framework will facilitate preclinical AD studies and aid in distinguishing between the behavioral/lifestyle, genetic, and brain determinants of resistance vs resilience. It complements previous approaches, where factors such as lifestyle variables are used as convenient proxies to study the concepts (e.g., cognitive reserve).

The application of the proposed framework for proposing hypotheses, study design, and interpretation of results in

preclinical AD studies can provide a common research ground for understanding the mechanisms underlying the maintenance of normal cognition. This will ultimately help advance the field from observational research towards developing effective intervention and prevention strategies.

## Author contributions

E.M. Arenaza-Urquijo: study concept, interpretation of data, drafting the manuscript. P. Vemuri: study concept, interpretation of data, drafting the manuscript, revising the manuscript for content.

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