The Neural Economics of Brain Aging

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The Neural Economics of Brain Aging

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Abstract

Human brain aging is a true spectrum across the population, ranging from minimal changes on the microscopic level to full-blown neurodegenerative disease with accumulation of pathology, neuronal loss, dysfunctional large-scale brain networks, and progressive functional decline. Although much is known about the individual mechanisms involved in brain aging, a convincing framework that ties these highly related processes together is lacking. Herein, using mathematical modeling, I sought to understand decline with brain aging by capturing the essential macro-level processes that shape how a brain changes over the lifetime. I develop ABC (*A*ging *B*rain *C*apital), a simple linear simultaneous-equation model that unites aspects of neuroscience, economics, and thermodynamics to explain the evolution of brain pathology and human brain capital, the infrastructure and processes that underlie brain function, over the lifespan. The results of this model suggest that aging-associated decline in brain function is inevitable, driven by the finite nature of the brain's pathology-clearance capacity. Furthermore, age-related neurodegenerative diseases can be understood as part of this aging process, explaining the spectrum of pathology and neurodegeneration across the population. I demonstrate that several essential aspects of the pathogenesis of Alzheimer disease (AD) can be likewise explained in this framework incorporating amyloid-tau interaction, the emerging concept that amyloid pathology accelerates tau pathology. The conception of Alzheimer pathogenesis that I present not only explains and unifies the basis for familial AD, primary-age-related tauopathy (PART), and late-onset AD (LOAD), but also reconciles amyloid-centered, tau-centered, and synergistic models of AD. Finally, I describe the possible implications of these results for future therapeutic development across neurodegenerative disease.

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1. Introduction

The brain is humanity's all-important asset, responsible for our complex behavior and hence, the success of our species. As our brains age, our cognitive functions decline, especially in neurodegenerative diseases such as Alzheimer disease (AD) [23]. Despite amazing advance in the understanding of individual features and mechanisms of aging, there is still significant debate on basic questions regarding the nature of brain aging. Is decline with aging 'natural' or pathologic? Endogenous to the brain or due to environmental factors? Distinct from, or part of a spectrum with neurodegenerative disease? Effective neurodegenerative disease therapy remains one of the greatest challenges of modern medicine[2], and thus the need for definitive answers on these conceptual issues is paramount.

Herein, I develop a mathematical model, ABC (*A*ging *B*rain *C*apital), which unites neuroscience, economics, and thermodynamics to explain the essential processes that determine how brain infrastructure develops and evolves over an individual's lifetime. From this model, a simple, elegant, and unifying explanation for brain aging and neurodegenerative disease emerges. I suggest that these results have crucial implications for future therapeutic development in these settings, especially Alzheimer disease (AD).

2. Results and Discussion

The basis for brain aging emerges from the ABC model

To model the complexities of brain aging, I sought to capture the essential processes that determine how the brain changes, develops, and evolves over an individual's lifespan. Although details are far from clear, brain functions are known to be crucially based on the state of the underlying brain infrastructure—for example, the activation of large-scale neural networks underlies almost every type of behavior[4, 18, 36]. Humans learn through our interactions with the environment, developing language, complex behavior, decision-making paradigms, knowledge, and memories. I reasoned that the underlying brain infrastructure and processes (which I collectively define as human brain capital) must correspondingly develop to accommodate this functional maturation. The development of brain capital is the central process that enables functional growth. Likewise, a decline in this brain capital necessitates corresponding functional decline[28, 41]. In this framework, the brain is a physical asset that supports and maintains brain capital by providing space, 'maintenance', and resources. As an example of these concepts, plastic changes in the activity of neuronal networks are thought to underpin the formation and retrieval of memory[47]. In this system, the neurons themselves represent the brain asset and are the resources that enable plasticity. This asset supports the development of functionally relevant networks, representing the formation of brain capital. It is this brain capital that ultimately underlies memory, brain function. Thus, I suggest a basic set of relationships linking the brain, the development of brain capital, and changes in brain function.

To mathematically model how brain capital (K_t) evolves over the lifetime, I utilized basic principles from economics. In ABC, the brain is treated as a physical asset that generates a stream of resources over time (endowment, E_t) that support the development and maintenance of brain capital. Brain endowment can be used as investment (I_t) to generate new brain capital or to replace depreciated capital:

$$K_t = \alpha \times K_{t-1} + I_t \quad (\mathbf{1})$$

where α is a parameter associated with capital depreciation and K_0 represents starting brain capital at the beginning of life. I next considered the impact of the development and usage of brain capital on the brain

itself that 'houses' the capital. Any production process generates unwanted byproducts such as pollution or heat. Likewise, I reasoned that the deployment of human brain capital generates unwanted byproducts within the brain, which I collectively define as pathology (P_t). This concept has extensive biological precedent, such as the creation of reactive oxygen species (ROS), misfolded proteins, and waste products in the course of regular biological function[31]. The brain redirects available resources (a portion of endowment) as pathology control (PC_t) to consistently clear this pathology. In the brain, the efficient removal and repurposing of unwanted byproducts is a must. Unlike many real-world systems, the brain cannot easily externalize a number of byproducts, which would otherwise accumulate in limited space and cause significant damage[46]. Importantly, however, thermodynamics dictates that pathology control processes cannot be fully efficient. Furthermore, certain types of pathology within the brain are known to resist common clearance mechanisms and persist after they are formed[7]. I modeled these critical considerations by representing pathology in two forms—short-term pathology (P^{ST}_t) that the brain can clear and long-term pathology (P^{LT}_t) that persists. Cellular correlates of these pathologies include the distinction between misfolded proteins, short-term pathology that the cell compensates for and clears, and resilient protein aggregates, long-term pathology that effectively persists[7, 34]. Both forms of pathology are assumed to be cumulative and are produced in linear proportion to brain capital:

$$P^{ST}_t = P^{ST}_{t-1} + \gamma_{ST} \times K_t - PC_t \quad (\mathbf{2})$$

$$P^{LT}_t = P^{LT}_{t-1} + \gamma_{LT} \times K_t \quad (\mathbf{3})$$

where the γ's are parameters representing the rate of production of pathology. Lastly, ABC explores the impact of produced pathology. Pathologies are known to be directly detrimental to the brain via a number of biological mechanisms[31, 32, 37, 50]. I captured these complex relationships by representing the damage done to the quality of the brain asset by a decline proportional to current pathology burden. This would manifest as a proportional decline in brain endowment:

$$E_t = E_0 - \beta \times (P^{ST}_t + P^{LT}_t) \quad (\mathbf{4})$$

where β is a parameter representing the brain's vulnerability to pathology and E_0 represents the endowment generated by the brain in its mint condition. The pathology-mediated impact on brain endowment in turn determines the brain's resource budget available to either develop brain capital or clear short-term pathology over the lifespan:

$$E_t = I_t + PC_t \quad (\mathbf{5})$$

Thus, the complete ABC model ties together several crucial, dynamic, co-evolving processes within the brain—the development of brain capital, the production and clearance of pathology, and pathology-mediated damage to brain asset quality (**Figure 1A**). Obtaining an analytical solution to this simultaneous-equation system (**Methods**), I simulated several scenarios of human brain capital across an

approximate lifetime. In the first scenario, I explored the development of capital in the complete absence of pathology (both values of γ set to zero). In this scenario, capital increases until it plateaus after a certain time period (**Supplementary Fig. 1A**). Thus, even in the absence of pathologies, there is a finite upper limit to the levels of capital our brains can attain due to capital depreciation—in essence, as brain capital grows, the brain's resources must be used more and more to maintain current levels as opposed to forming new capital (**Supplementary Fig. 1B**). I next considered the scenario where short-term but not long-term pathology was generated over time. Capital once again developed in early-life and plateaued (**Supplementary Fig. 1C**), with the need for pathology control limiting both the upper limit to brain capital and the total resources devoted to investment (**Supplementary Fig.1C-D**). Importantly, the brain in this state does not accumulate any pathology, as pathology control is always capable of matching and clearing any pathology generated (i.e. clearance matches pathology).

I then simulated ABC in full by including the production of long-term pathology. The results of this scenario are remarkable for three major deviations from previous scenarios: firstly, long-term pathology accumulates over the lifespan (**Figure 1B-C**, **Supplementary Fig. 1E**); secondly, endowment declines over the lifespan (**Supplementary Fig. 1F**), representing pathology-mediated damage to the brain; lastly, although capital develops and plateaus as before, it declines in late life (**Figure 1B-C**, **Supplementary Fig. 1E**). I found these general results to be remarkably robust to reasonable ranges for all model parameters (**Supplementary Table 1**). In this complete model, long-term pathology accumulates in an age-driven manner as a natural consequence of the usage and development of brain capital. This accumulating pathology causes a proportional decline in endowment, representing depletion in the brain asset's quality and resources. As brain capital plateaus, decline in endowment crosses a crucial threshold where available investment is no longer sufficient to maintain depreciating levels of brain capital (**Supplementary Fig. 1F**) and consequently, capital in turn declines. This late-life decline in capital would manifest as brain network dysfunction and escalating functional decline in the affected systems. As the brain continues to decline, it generates fewer resources and thus progressively loses its ability to clear short-term pathologies, which may in turn accumulate (**Supplementary Fig. 1G**) and cause additional damage (**Supplementary Fig. 1H**).

Thus, the accumulation of persistent pathology and functional decline with brain aging both emerge as endogenous and inevitable consequences of the finite nature of the brain's pathology-clearance capacity. This simple, general process that emerges from ABC is strikingly consistent with studies examining changes in human brain function across the lifespan[16, 31, 40]. In reality, brain pathology takes multiple forms, each with unique patterns of accumulation and impact across pathologies, brain regions, and

individuals. As a simplistic yet essential basic framework, I suggest that these distinct pathologies represent manifestations of a common process and collectively underpin the spectrum of observable brain aging (**Supplementary Fig. 2**).

ABC-ND suggests that age-related neurodegenerative diseases are driven in common by aging

I next sought to understand how neurodegenerative diseases relate to the ABC framework of brain aging. Although their pathogenesis is complex and heterogenous, the accumulation of protein aggregates is a striking common pathological feature of these diseases[15, 19, 33, 38, 43] and in many ways epitomizes pathology accumulation within ABC. Just as pathology is produced by the deployment of brain capital in the model, abnormally processed protein pathologies are well-established byproducts of cellular functioning[31, 38], and many are produced in proportion to neuronal activity[5, 49]. Misfolded proteins can be adaptively cleared by a number of cellular mechanisms[7, 10, 21], in line with the concept of short-term pathology. On the other hand, protein aggregates are largely resilient to cellular clearance[7], accumulate in an age-dependent manner across the lifespan[8, 9], and are highly consistent with the concept of long-term pathology. Although exact mechanisms remain contentious, accumulating protein aggregates cause damage to neurons and ultimately lead to irreversible neuronal death[7, 50]. Neurodegeneration is fully compatible with the concept of pathology-mediated damage to the brain's available resources—realistically, neurodegeneration represents a special case of decline in brain-asset quality due to pathology because it is inherently persistent[3]. I straightforwardly integrated the concept of neurodegeneration into ABC to create ABC-ND (ABC-*n*euro*d*egeneration, **Methods**) and applied this derivative model as a specific explanation for how protein aggregate pathologies accumulate with aging to drive neurodegeneration and corresponding functional decline.

The main results of this model are highly consistent with the base ABC model (**Supplementary Fig. 3A-F**). Protein aggregate pathologies accumulate as long-term pathologies over the course of the lifetime (**Supplementary Fig. 3E**), causing progressive neurodegeneration (**Supplementary Fig. 3F**). As neurons degenerate, the brain's ability to support brain capital (e.g. large-scale networks) declines, with severe consequences for brain functioning. This sequence of pathological events, albeit simplistic, is nonetheless highly consistent with previous work in a number of neurodegenerative disease settings[19, 22, 25, 28, 30, 33, 35, 37, 42, 45] . I therefore suggest that the ABC-ND model captures the general aspects of pathogenesis that are shared across neurodegenerative disease (**Figure 2A**).

To test this assertion, I applied ABC-ND to explain the spectrum of neurodegeneration observed across the aging population[1, 15, 24, 26]. Generally, I suggest that the variability in the extent of a specific

pathology's accumulation can be explained by variation in the production of and vulnerability to that pathology between individuals. In ABC-ND, healthy aging (i.e. aging without significant pathology accumulation or decline) can be simulated as a case of low production (γ) of pathology, leading to minimal loss of brain capital in late life (**Figure 2B**). Pathological aging (aging with significant pathology accumulation but little neurodegeneration or decline)[11, 13, 24, 26] can be simulated as a case of higher production and lower vulnerability (β) to that pathology (**Figure 2C**). Late-onset neurodegenerative disease can be conceptualized as brain aging with high pathology production and normal vulnerability to that pathology (**Figure 2D**). Furthermore, the accelerated decline observed in patients with familial forms of neurodegenerative disease[15] can be likewise explained. Such patients have genetic mutations that accelerate the production of a particular pathology[15, 42]. Modeling this in ABC-ND, pathology accumulates at much higher rates, driving a relatively early and progressive decline in the brain's resources, brain capital, and consequently, brain function (**Figure 2E**), as is clinically observed[27].

I suggest that neurodegenerative diseases do not represent distinct clinico-pathological entities from aging—rather, as the ABC-ND model demonstrates, the same underlying aging-driven process drives a spectrum of functional decline across individuals. As such, on a basic level, neurodegenerative diseases are manifestations of severe aging caused by extensive lifelong accumulation of specific pathologies.

Uniting ABC-ND with amyloid-tau interaction theory explains the neuropathological basis for Alzheimer's disease

Alzheimer's disease (AD) is the most significant cause of dementia worldwide, yet a universally accepted disease mechanism is lacking[13, 22, 30, 45, 48]. Part of the complexity of AD stems from the presence of two forms of pathology within AD brains—senile plaques containing amyloid-β (Aβ) and neurofibrillary tangles containing hyper-phosphorylated tau[43]. The classical amyloid hypothesis of AD suggests that Aβ-related pathology (AβRP) directly causes tau-related pathology (TRP), explaining many elements of disease pathogenesis[42]. This paradigm has nevertheless been criticized for failing to explain the frequent observation of TRP accumulation in the absence of AβRP[13, 48], ranging from primary-age related tauopathy (PART)[11, 13] to severe neurodegenerative tauopathies[15]. Extensive precedent has suggested a relationship between the two pathologies, however[6, 20, 28]. Expanding on the classical amyloid hypothesis, which would suggest TRP is completely dependent on AβRP[42], I propose a theory of amyloid-tau interaction which postulates that the pre-existing production of TRP is *accelerated* by the presence of AβRP (**Figure 3A**). This relation is justified by several lines of research including previously enumerated mechanistic links at the cellular and brain network levels[6, 20, 28], and as I describe below, provides a convincing model of the entire spectrum of AD pathogenesis.

I sought to adapt ABC-ND to capture the essential aspects of AD pathobiology and maintain consistency with the entire clinico-pathological spectrum of AD. Although the precise nature of AβRP and TRP remains unclear[29, 32, 34, 42], pathological evidence suggests that each form of pathology is independently consistent with the concept of pathology accumulation and impact in ABC[8]. Preserving the basic architecture of ABC-ND, I integrated amyloid-tau interaction by including the production of both AβRP and TRP and introducing a simple linear relationship between the rate of production of TRP and AβRP burden (**Methods**).

Obtaining an exact analytic solution, I examined the behavior of this simplistic integrated model (ABC-AD). In the absence of either form of long-term pathology, the evolution of brain capital was highly consistent with ABC and ABC-ND as expected (**Supplementary Fig 4A-D**). In the presence of long-term TRP alone, ABC-AD reduced to the generalized single-pathology form of ABC-ND—TRP gradually accumulated as brain capital developed, driving a decline in brain resources and capital (**Supplementary Fig. 4E-F**). Thus, at a basic level, ABC-AD is able to robustly explain how TRP may accumulate and cause neurodegeneration in the absence of AβRP, as is the case in primary age-related tauopathy (PART)[11] and other tauopathies[15]. In the reverse scenario (AβRP without TRP), the same results are expected (**Supplementary Fig. 4G-H**). However, patterns of pathology accumulation across the population[8, 9] suggest that the prevalence of TRP is significantly greater than AβRP and that the latter pathology is rarely present without the former[8], making an AβRP-alone scenario less clinically relevant. I then considered the most realistic scenario of ABC-AD with both long-term forms of AβRP and TRP present. In this case, both AβRP and TRP gradually accumulate as a natural consequence of aging as expected. Because of amyloid-tau interaction, the building presence of AβRP accelerates the production of TRP (**Figure 3B**, **Supplementary Fig. 5A-B**). As in the base models, the accumulation of pathology drives a progressive decline in brain resources and consequently, a late-life decline in brain capital (**Supplementary Fig. 6A-B**).

Importantly, ABC-AD does not constrain the relative impact of AβRP and TRP in driving decline, a controversial question in AD research[13, 25, 42, 48]. Current evidence suggests that in AD, neurodegeneration correlates strongly with TRP both temporally and spatially[27], and that AβRP accrues for many years without causing observable neurodegeneration or functional decline[24, 27, 42]. Using the conceptual framework of ABC-AD, these observations suggest that the brain's vulnerability to TRP exceeds its vulnerability to AβRP. In such a scenario, although TRP ultimately contributes more to

neurodegeneration (**Supplementary Fig. 6B**), AβRP has both a direct and indirect impact through amyloid-tau interaction (**Supplementary Fig. 6B**).

Explaining the complete spectrum of AD-related pathological change in the aging population has remained one of the greatest hurdles for contemporary theories of AD pathogenesis[24, 26, 28, 42]. As a testament to the validity of the amyloid-tau interaction theory, I found that this spectrum naturally emerges from ABC-AD. Healthy aging can be simulated as brain capital evolution with low production of both forms of pathology, resulting in fairly stable brain capital levels persisting through old age (**Figure 3C**). AD-related pathological change can be plausibly explained as being driven by increased accumulation of AβRP, causing neurodegeneration and late-life decline in brain capital both directly and indirectly through acceleration of TRP accumulation. In a brain that is relatively resistant to TRP (low vulnerability), this manifests as pathological aging, with both pathologies accumulating in the relative absence of neurodegeneration[24, 26] (**Figure 3D**). Otherwise, the accumulation of both pathologies causes severe late-life decline, conceivably the basis for late-onset AD (LOAD) (**Figure 3E**). Importantly, familial AD (fAD)[15, 27, 42] emerges straightforwardly from this framework. Patients with fAD have mutations strongly promoting the formation of AβRP[34, 42]. In ABC-AD, a substantial increase in the rate of production of AβRP is sufficient to drive both an acceleration in TRP and a severe, early-onset decline in capital (**Figure 3F**), as is observed[25, 27, 42]. Importantly, these findings are entirely consistent with TRP-mediated neurodegeneration in the absence of AβRP[11]. An AβRP-independent increase in the rate of TRP accumulation may conceivably drive the range of functional decline from PART (**Figure 3G**) to late-onset tauopathy (**Figure 3H**).

Thus, I propose ABC-AD as a basic framework for the pathoetiology of AD. I suggest that the aging-driven accumulation of AβRP and TRP are both endogenous and inevitable consequences of brain functioning. I propose that AβRP is indeed the crucial etiological driver of AD, causing an accelerated accumulation of TRP via amyloid-tau interaction, neurodegeneration, a late-life collapse in brain capital, and functional decline. In this framework, the pathogenesis of AD (**Supplementary Fig. 6C-D, 7A**) represents a distinct but overlapping clinico-pathological entity from purely tau-driven decline (**Supplementary Fig. 6E-F, 7B**). I do not constrain the relative role of AβRP and TRP in driving neurodegeneration, but suggest that TRP may play the more significant role, in line with spatiotemporal data[27]. I emphasize that pathological aging and neurodegenerative disease are not distinct clinico-pathological entities but are differential manifestations of the same underlying process. As such, amyloid-tau interaction may finally represent a complete reconciliation of Aβ- and tau-centered theories of AD

pathobiology[48], providing a unifying mechanistic basis explaining how aging, AβRP, and TRP intersect over the lifespan to cause the entire observable spectrum of AD-related change.

Implications for therapy in neurodegeneration and AD

At a fundamental level, the ABC-based models suggest a common mechanism by which pathologies accumulate within the brain to cause aging-driven decline. In a final investigation, I sought to translate these findings by simulating how therapeutic intervention may be expected to alter or reverse disease pathogenesis. In ABC-ND, I represented neurodegenerative disease-targeting therapy as an instantaneous modification to model parameters at a particular time period (**Methods**). I tested 'perfect' therapies representing several rational approaches[3, 17, 50] (**Supplementary Fig. 8A**) in prototypical disease simulations and was thus defined the 'maximum' efficacy of each therapeutic strategy. Although this is at best a simplistic representation of therapeutic effectiveness in these diseases, I nonetheless was able to define unexplored and noteworthy limitations in several classes of therapy. For example, halting the production of new neurodegenerative pathology is a logical therapeutic approach that has received much attention[17, 30, 42]. However, I found that even a therapeutic that completely eliminated any production of new short-term and long-term pathology failed to stop consequent decline in brain capital (**Figure 4A**)—the rate of decline was slowed, but pre-existing pathology continued to cause accumulating damage to the brain's resources, leading to continued capital (and therefore cognitive) collapse. In contrast, I found that with a pathology-clearing therapeutic—one that physically clears the offending long-term pathology, removing or otherwise repurposing all of it by a novel mechanism[17, 42, 44]—further decline in capital was completely stopped (**Figure 4B**), the brain eventually reaching a steady-state where its depleted resources were balanced to maintain levels of brain capital. The same result was reached by a therapeutic that blocked the impact of pathology on the brain[17], eliminating the brain's vulnerability. In this scenario, brain capital stabilized despite the growing presence of pathology (**Figure 4C**).

I applied this same approach in ABC-AD to understand how therapeutic approaches can be predicted to shape functional decline in AD, assuming amyloid-tau interaction. Again, I found that stopping the production of AβRP, TRP, or both pathologies together was not sufficient to prevent decline (**Supplementary Fig. 8A**), an important potential explanation for the failure of drugs targeting the production of Aβ in recent clinical trials[14]. Results for pathology-clearing therapeutics in this model were more nuanced. Crucially, I found that even complete clearance of AβRP was not sufficient to prevent capital decline (**Supplementary Fig. 8B**)—in the absence of Aβ, TRP continued to accumulate and cause damage, although the rate and extent of decline was reduced. These results may explain the recent failure of several anti:Aβ therapeutics[12, 39, 44]. On the contrary, TRP-clearing therapeutics[17]

would be expected to more significantly slow neurodegeneration and functional decline assuming the brain's vulnerability to TRP is higher (**Supplementary Fig. 8B**), although I found that only combination-clearance therapy of both pathologies halts AD-related decline entirely (**Supplementary Fig. 8B**). Amyloid-tau interaction theory suggests that AD pathogenesis is driven by the combination of AβRP and TRP—as such, I propose that therapeutics designed to target only a single pathology cannot be expected to fully address decline, regardless of the brain's relative vulnerability to each[27]. These general findings were replicated for vulnerability-targeting approaches in ABC-AD (**Supplementary Fig. 8C**).

Thus, I observed that even complete clearance of pathology in ABC-ND or combination-clearance in ABC-AD was not sufficient to reverse lost brain capital (and hence function). Rather, these approaches may represent means to prevent further decline by stopping the accumulation of pathology (and hence disease progression) at an early stage (**Supplementary Fig. 9A**), making continued efforts into early identification of individuals at high risk for severe disease of considerable importance[25]. The ABC-ND or ABC-AD brain cannot reverse pathology-driven decline because neurodegeneration is inherently an irreversible form of brain damage[3, 38, 50]. I found that in both ABC-ND and ABC-AD, regenerating brain endowment—that is, developing and administering a model therapeutic that recovers the brain's lost resources (i.e. regenerative medicine)[3]—appears to be the only approach to reverse severe decline in brain capital (**Figure 4D**, **Supplementary Fig. 8D**). Due to the progressive nature of neurodegenerative diseases, their cure lies in regenerative medicine (**Supplementary Fig. 9B**).

3. Methods

Solutions to ABC, ABC-ND, and ABC-AD behavior. The behavior of the ABC model is determined by the brain's resource budget-constraint (Equation 5). In the complete absence of pathology, the brain's endowment devotes entirely to investment and is constant over time. In the presence of short-term pathology, the brain must 'choose' its prioritization of investment and pathology control. I specified two assumptions in order to arrive at model behavior. Firstly, I assumed that the brain will distribute its endowment to maximize brain capital. Secondly, I made an assumption about the impact of pathology on the brain. I believe that the presence of pathology costs the brain more resources than those required to clear that pathology—in other words, it pays for the brain to clear pathology. Mathematically, I specified this by constraining the parameter β to be greater than one across all models. From these assumptions, Three conceivable cases may then emerge over an individual simulation—firstly, a case where the brain is capable of clearing all short-term pathology; secondly, where the brain can only partially clear pathology; and lastly, where the brain has no resources to clear short-term pathology.

Case 1: In the first case, sufficient resources are devoted to pathology control and the remainder to investment, such that:

$$I_t > 0 \quad (\mathbf{6})$$

$$PC_t = \gamma_{ST} \times K_t + P_{t-1}^{ST} \quad (\mathbf{7})$$

$$P_t^{ST} = 0 \quad (\mathbf{8})$$

A recursive solution to the evolution of capital over time can be obtained:

$$K_t = \frac{\alpha \times K_{t-1} + E_0 - \beta \times P_{t-1}^{LT}}{1 + \gamma_{ST} + \beta \times \gamma_{LT}} \quad (\mathbf{9})$$

Long-term pathologies, endowment, investment, and pathology control can all be solved for simultaneously given Equations 6-9.

Case 2: In the second case, all available endowment is directed to pathology control. Investment is therefore zero:

$$I_t = 0 \quad (\mathbf{10})$$

$$PC_t = E_t \quad (\mathbf{11})$$

$$P_t^{ST} = \gamma_{ST} \times K_t + P_{t-1}^{ST} - E_t \quad (\mathbf{12})$$

In this case, the evolution of capital over time is simply determined by capital depreciation:

$$K_t = \alpha \times K_{t-1} \quad (\mathbf{13})$$

Again, the co-evolution of other variables in the system can be analytically solved based on Equations 10-13.

Case 3: In the last case, the brain has no resources to clear pathology, and the brain's endowment reduces below zero:

$$I_t < 0 \quad (\mathbf{14})$$

$$PC_t = 0 \quad (\mathbf{15})$$

$$P_t^{ST} = \gamma_{ST} \times K_t + P_{t-1}^{ST} \quad (\mathbf{16})$$

I interpreted a negative endowment as representing a fundamental crisis in the brain—the underlying asset that supports capital is collapsing, and so effectively the contribution from the brain itself is negative. As such, capital takes the following solution:

$$K_t = \frac{\alpha \times K_{t-1} + E_0 - \beta \times (P_{t-1}^{LT} + P_{t-1}^{ST})}{1 + \beta \times (\gamma_{ST} + \gamma_{LT})} \quad (\mathbf{17})$$

Given Equation 17, the continued decline in endowment and accumulation of pathologies can be solved for to yield the complete behavior of the system. In each simulation of ABC and subsequent models, the system's behavior in terms of the above scenarios was simultaneously determined at a given time point. The system's evolution through each case naturally emerged and was not arbitrarily determined.

Neurodegeneration represents a unique case of damage to brain asset quality because it is in itself cumulative[38, 50]. In ABC, long-term pathologies are effectively equivalent to the damage they cause to the brain. Applying ABC specifically to neurodegenerative disease, the long-term pathologies (protein aggregates) and the damage they cause (neurodegeneration) are distinct. Because the brain cannot seem to reverse pathology-associated neuronal loss[3], it is more realistic to assume that neurodegeneration-causing protein aggregates cause damage in a given period that is proportional to total pathology load and that this damage in itself accumulates. The sole difference between the generalized framework of aging in ABC and the derivative model ABC-ND is specifically how the impact of pathology is modeled:

$$E_t = E_{t-1} - \beta \times (P_t^{ST} + P_t^{LT}) \quad (\mathbf{18})$$

compared to the form of endowment in the ABC model (Equation 4). The budget-constraint aspect of ABC-ND is identical to the original model, and the dynamic behavior of the solution is again determined by the value of endowment relative to total produced short-term pathology. The equivalent forms of Equations 9, 13, and 17 can be solved to obtain Equations 19-21, respectively, and yield highly comparable behavior:

Case 1: $$K_t = \frac{\alpha \times K_{t-1} + E_{t-1} - \beta \times P_{t-1}^{LT}}{1 + \gamma_{ST} + \beta \times \gamma_{LT}} \quad (\mathbf{19})$$

Case 2: $$K_t = \alpha \times K_{t-1} \quad (\mathbf{20})$$

Case 3: $$K_t = \frac{\alpha \times K_{t-1} + E_{t-1} - \beta \times (P_{t-1}^{LT} + P_{t-1}^{ST})}{1 + \beta \times (\gamma_{ST} + \gamma_{LT})} \quad (\mathbf{21})$$

ABC-AD expands upon ABC-ND in two major points: firstly, pathology is split into two components (AβRP and TRP) with each having short-term and long-term forms; secondly, amyloid-tau interaction is assumed[6, 20, 28] (Figure 3A). The exact quantitative relationship between AβRP and TRP is not currently known and is likely complex[28]. I assumed that amyloid-tau interaction manifests as acceleration in the rate of long-term TRP directly proportional to AβRP burden up to the previous time-period:

$$\gamma_t^{TRPLT} = \gamma_0^{TRPLT} \times \left(1 + \delta \times A\beta RP_{t-1}^{LT}\right) \quad (\mathbf{22})$$

where δ represents the degree of amyloid-tau interaction. The resource-budget constraint is slightly more complex in ABC-AD compared to the base models. Endowment distributes between investment, AβRP control, and TRP control. In the scenario where endowment is greater than the sum of total produced short-term pathologies, the solution for capital evolution over time is akin to Equations 9 and 19 (ABC and ABC-ND, respectively):

$$K_t = \frac{\alpha \times K_{t-1} + E_{t-1} - \beta_{A\beta} \times A\beta RP_{t-1}^{LT} - \beta_{Tau} \times TRP_{t-1}^{LT}}{1 + \gamma_{ST}^{A\beta RP} + \gamma_{ST}^{TRP} + \beta_{A\beta} \times \gamma_{LT}^{A\beta RP} + \beta_{Tau} \times \gamma_t^{TRPLT}} \quad (\mathbf{23})$$

When endowment is insufficient to clear both AβRP and TRP, the brain prioritizes clearance of the pathology to which it has higher vulnerability (β). For example, in the simulations where brain vulnerability to TRP is greatest, investment is zero, PC first distributes to short-term TRP, and the remainder to short-term AβRP. In the case that endowment is lower than short-term TRP and greater than zero, all endowment is distributed to TRP control, investment is zero, short-term TRP becomes the difference between produced and cleared, and short-term AβRP is produced without clearance. In each of these scenarios, capital evolution takes the form of Equations 13 and 20. Finally, in the case where endowment is negative, the evolution of capital over time takes the following form, akin to Equations 8 and 12 in ABC and ABC-ND, respectively:

$$K_t = \frac{\alpha \times K_{t-1} + E_{t-1} - \beta_{A\beta} \times \left(A\beta RP_{t-1}^{LT} + A\beta RP_{t-1}^{ST}\right) - \beta_{Tau} \times \left(TRP_{t-1}^{LT} + TRP_{t-1}^{ST}\right)}{1 + \beta_{A\beta} \times \left(\gamma_{LT}^{A\beta RP} + \gamma_{ST}^{A\beta RP}\right) + \beta_{Tau} \times \left(\gamma_t^{TRPLT} + \gamma_{ST}^{TRP}\right)} \quad (\mathbf{24})$$

Simulating ABC, ABC-ND, and ABC-AD. In all simulations, parameters are assumed to be constant (i.e. equivalent to their initial value) over the lifetime, ensuring that the behavior of the system is truly endogenous. Appropriate, reasonable values for initial parameters were estimated based on known information about the underlying process. **Supplementary Table 1** provides the 'hard' constraints I applied on model parameters.

Simulating Therapeutic Intervention in ABC-ND and ABC-AD. Real therapeutics have complex, uncertain, and imperfect impact on variables within a physiological system such as the brain[17]. I sought

to define the upper limits of achievable therapeutic possibilities by simulating the effects of 'perfect' therapeutics—that is, interventions that achieve 100% efficacy. Rather than predicting the effectiveness of specific therapeutics, I used the ABC models to delineate the promise of a certain therapeutic approach. For example, I simulated a perfect therapeutic that aims to stop the production of pathology by reducing the γ parameter associated with that pathology to zero at a particular time-point and following the behavior of the simulation following this intervention. I simulated complete clearance of pathology by instantaneously reducing total pathology levels to zero, and simulated eliminating the brain's vulnerability to pathology by reducing the β parameter to zero. I modeled regeneration of the brain asset as an instantaneous recovery of endowment back to E_0, the brain's endowment in its mint condition. I modeled these interventions in ABC-ND and ABC-AD in the context of simulations of familial neurodegenerative disease and fAD respectively (**Figure 2E**, **3F**).

Data Availability Statement. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. Model solutions, parameter values, and simulations will all be made available upon reasonable request.

***Declarations/Conflict of Interest Statement*.** Disclosures of interest: none.

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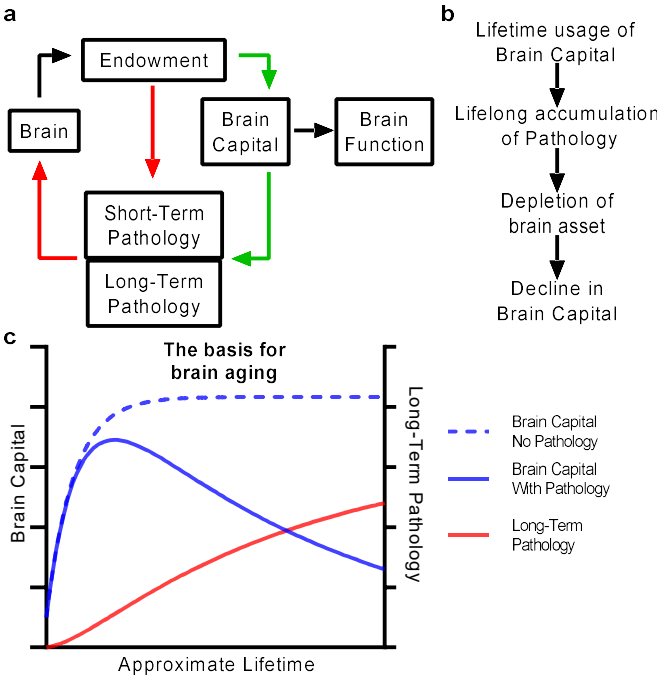

Figure 1. The ABC model defines a general mechanism for brain aging.

Figure 1. The ABC model defines a general mechanism for brain aging. a, Relationships between variables in the ABC model. Green arrows represent positive contributions (e.g. endowment increases brain capital over time via investment) whereas red arrows represent negative contributions (e.g. endowment clears short-term pathology via pathology control). **b**, A simplified model for the basis of brain aging as emerges from ABC. **c**, A representative simulation of brain capital and pathology evolution over an individual's lifetime in ABC. In the absence of long-term pathology, brain capital reaches an upper limit. With the accumulation of long-term pathology, brain capital declines after reaching a peak. All axes have arbitrary units.

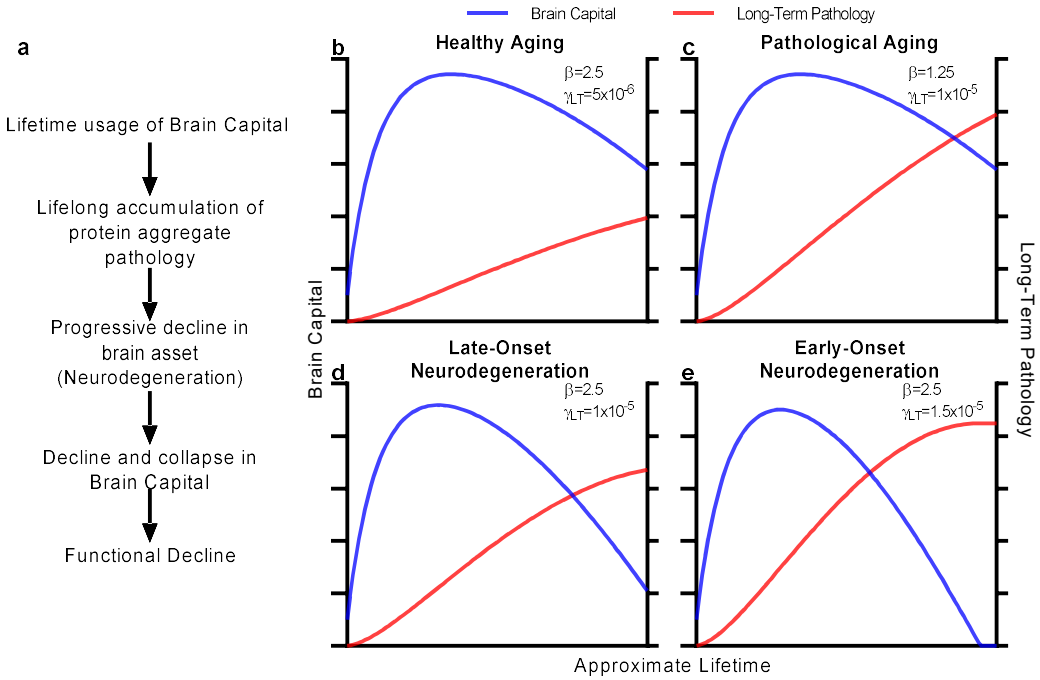

Figure 2. ABC-ND provides a unifying framework for neurodegenerative disease.

Figure 2. ABC-ND provides a unifying framework for neurodegenerative disease. a, A generalized conceptual framework for aging-driven accumulation of protein aggregate pathologies, neurodegeneration, and late-life functional decline. **b**-**d**, Simulations of the ABC-ND model representing plausible scenarios for healthy aging (**b**), pathological aging (**c**), late-onset neurodegenerative disease (**d**), and familial disease (**e**). Parameters values varied between simulations are provided in the corresponding panels.

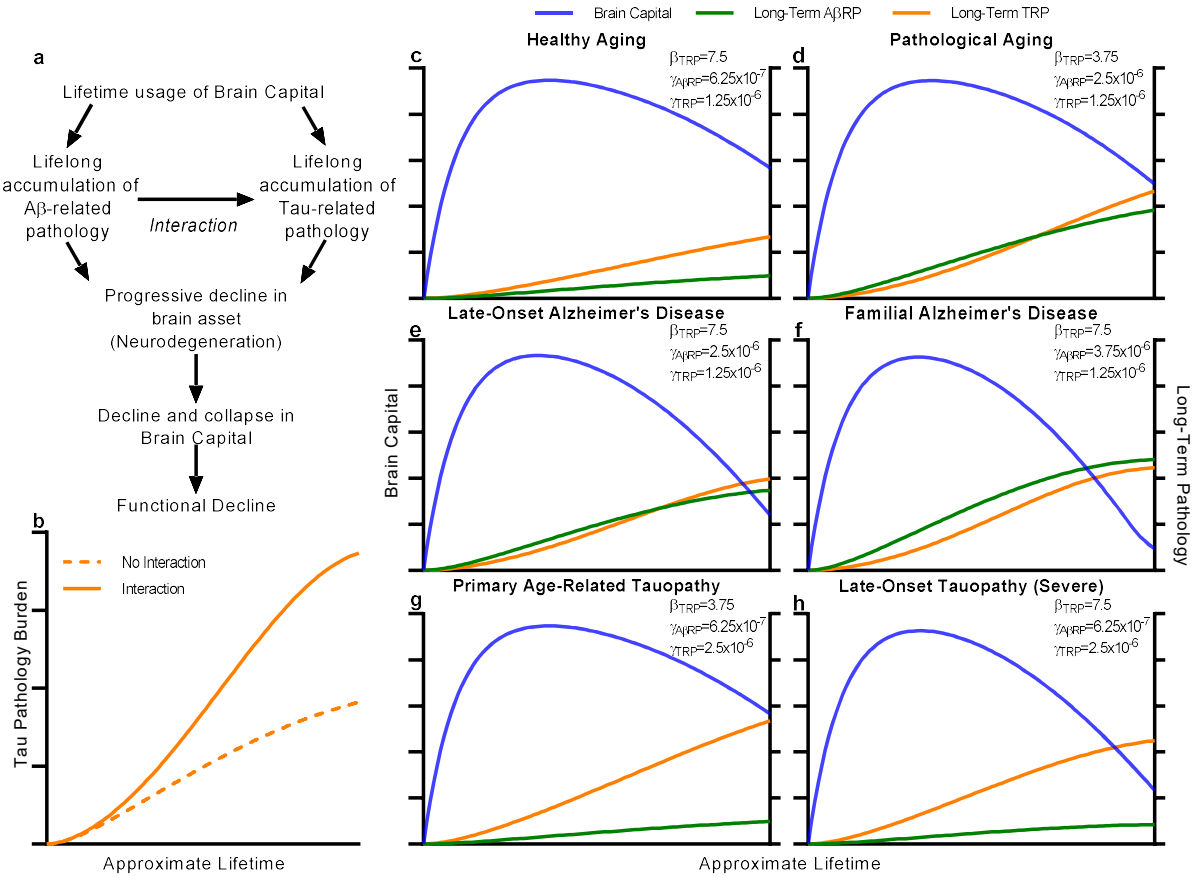

Figure 3. ABC-AD provides a basic unifying framework for the pathogenesis of Alzheimer's disease.

Figure 3. ABC-AD provides a basic, unifying framework for the pathogenesis of Alzheimer's disease. a, The conceptual framework for amyloid-tau interaction theory, linking aging-driven accumulation of AβRP and TRP, neurodegeneration, and functional decline. **b**, A representative simulation of the effect of amyloid-tau interaction on the accumulation of TRP. **c-h**, Simulations of ABC-AD representing plausible scenarios for healthy aging (**c**), pathological aging (**d**), LOAD (**e**), fAD (**f**), PART (**g**), and late-onset tauopathy (**h**). Parameters values varied between simulations are shown in the corresponding panels. The value for δ (strength of amyloid-tau interaction) was taken to equal 1500 in all simulations.

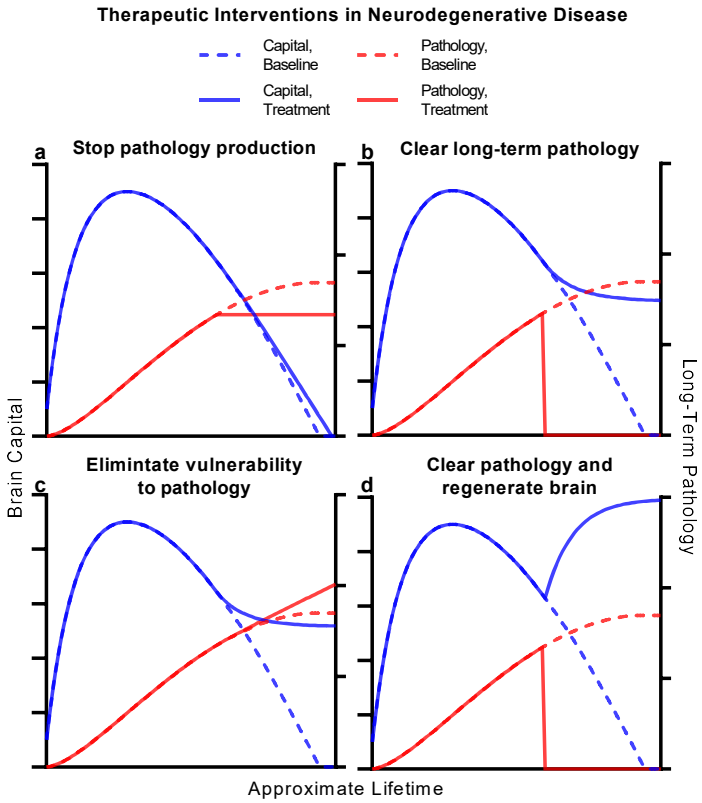

Figure 4. Simulating Therapeutic Effectiveness in ABC-ND.

Figure 4. Simulating Therapeutic Effectiveness in ABC-ND. a-d, Simulations of 'perfect' therapeutic intervention in ABC-ND. The evolution of brain capital and pathology burden was simulated after stopping pathology production (**a**), permanently clearing all pathology (**b**), eliminating the brain's vulnerability to pathology (**c**), or clearing pathology and permanently regenerating brain endowment (**d**). Initial model parameters are identical across simulations in each model and correspond to a familial neurodegenerative disease scenario (**Figure 2E**). Endogenous behavior in the absence of intervention is demonstrated in each panel by the dotted curves.

Supplementary Information

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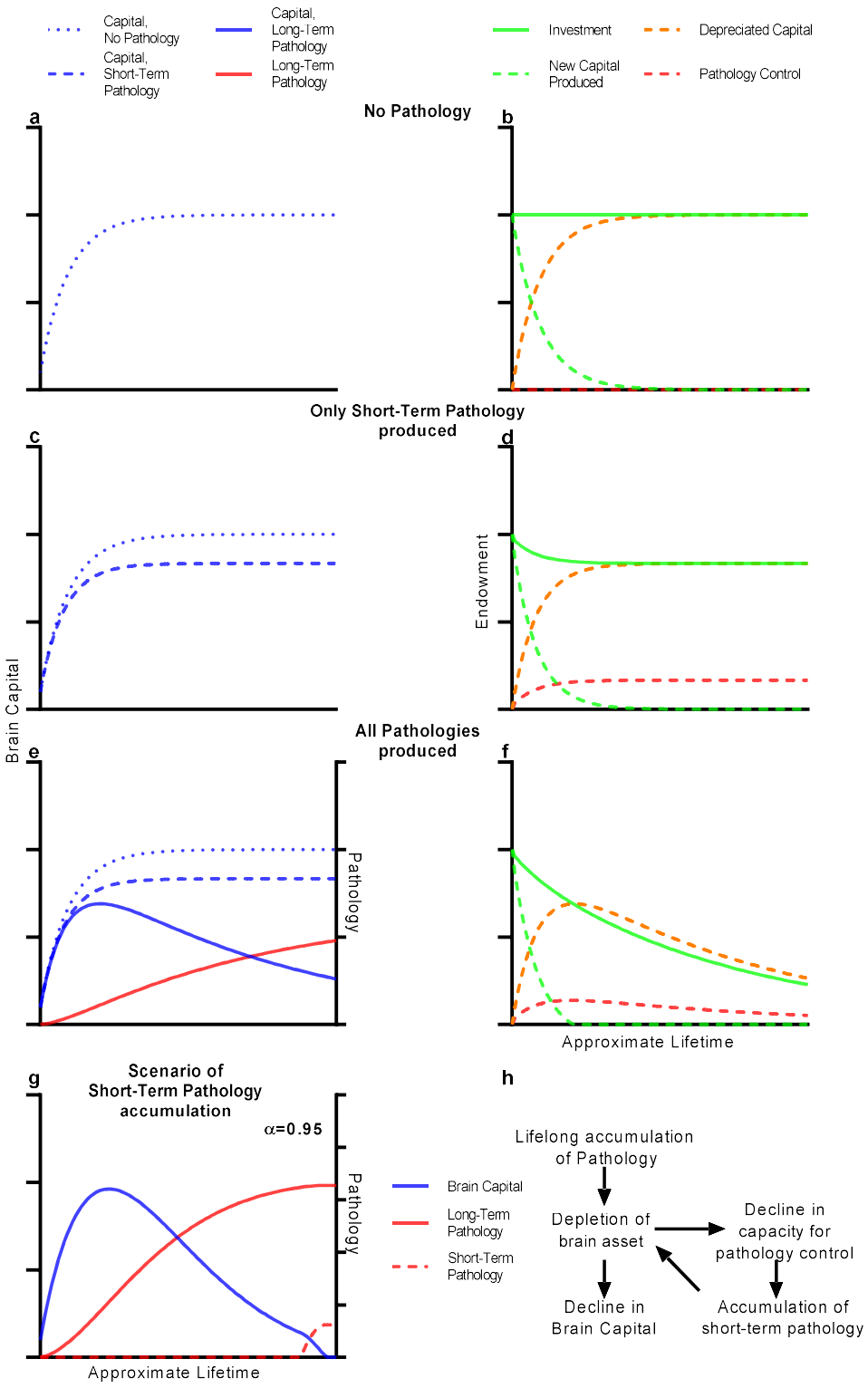
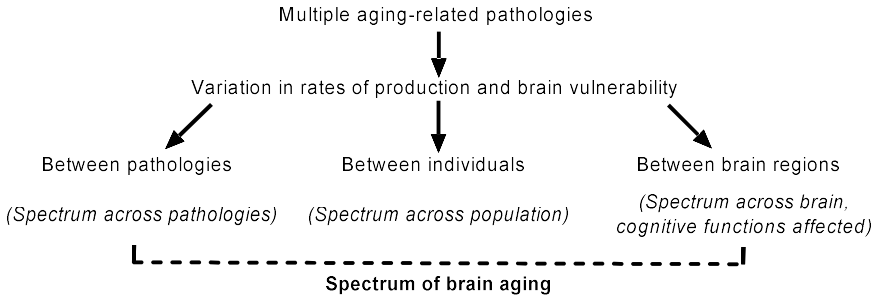


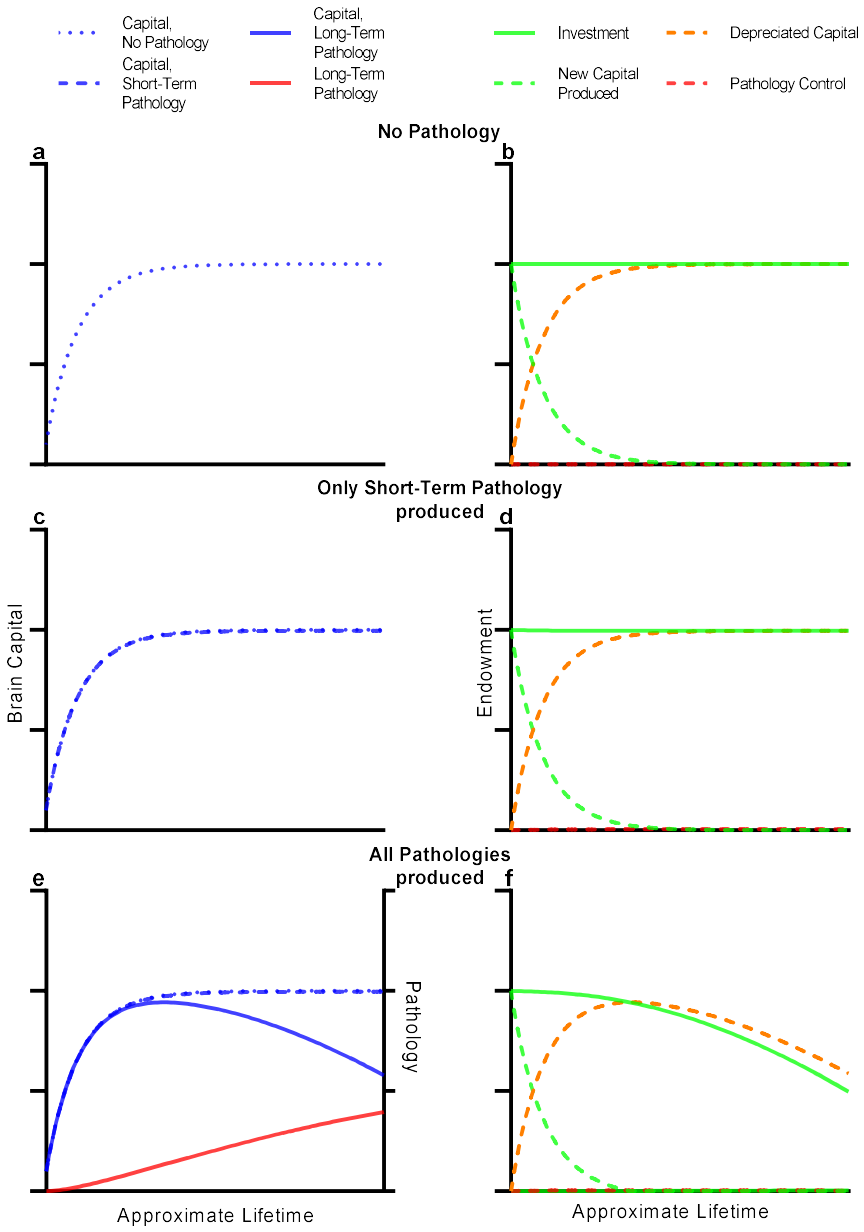
Supplementary Figure 1. Behavior of the ABC model.

Supplementary Figure 1. Behavior of the ABC model. a, Representative simulation of the evolution of brain capital over the lifespan in the absence of either short-term or long-term pathology. **b**, Investment gradually distributes from producing new capital to maintaining current levels, driving the plateau in total capital. **c**, In the presence of short-term pathology, capital again plateaus, although at a lower level than the no-pathology scenario. **d**, Total investment declines and plateaus as the need for pathology control increases. **e**, As long-term pathology is produced, it accumulates over the lifespan, driving a decline in brain capital. **f**, Resources available for investment into capital decline and are outstripped by capital depreciation. This difference drives the loss of brain capital (**e**). **g**, In simulations of less capital depreciation, short-term pathology accumulates at the end of life as long-term pathology-mediated damage to brain endowment impairs the brain's pathology control, as is described in **h**.



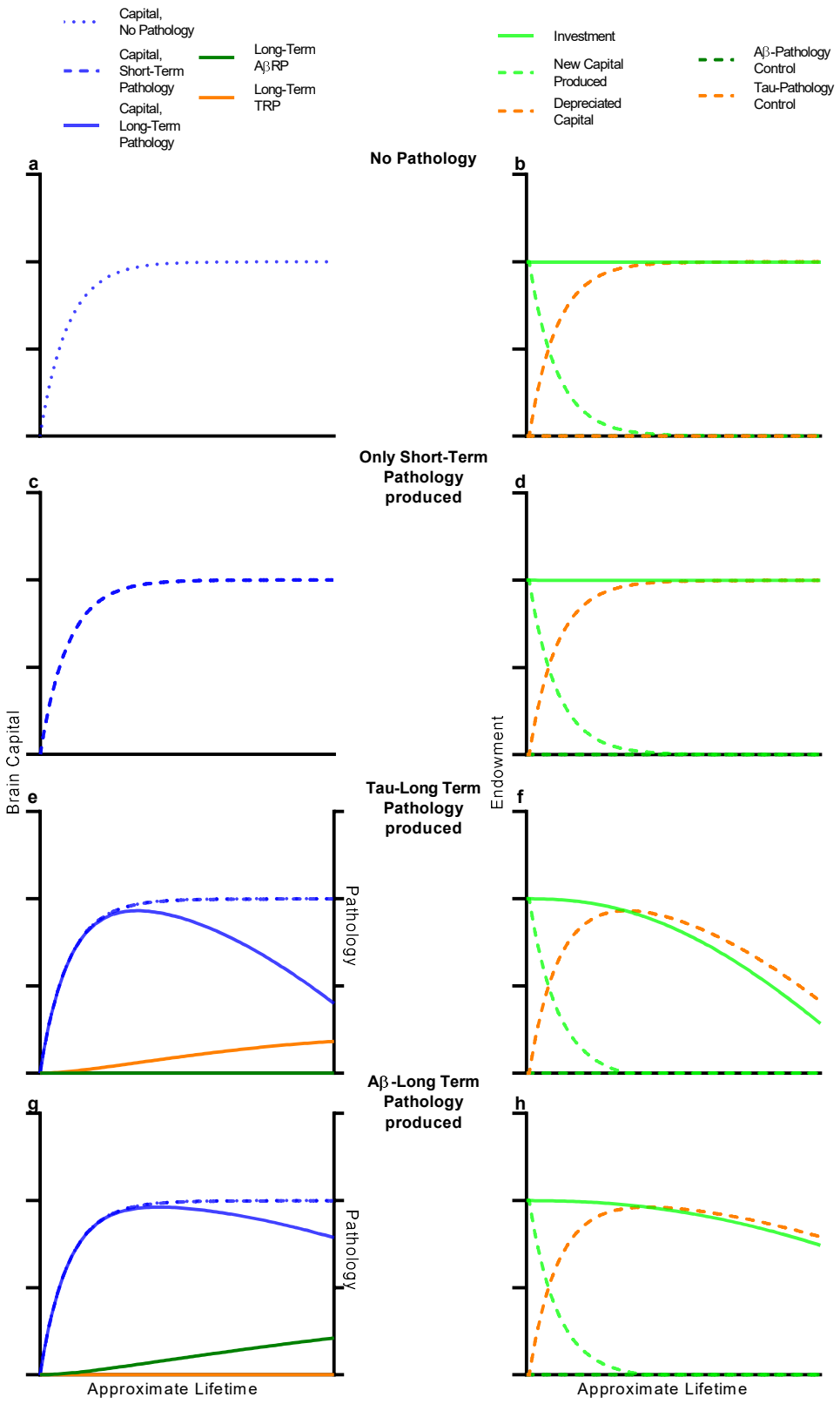
Supplementary Figure 2. A simplified model of the spectrum of brain aging.

Supplementary Figure 2. A simplified model of the spectrum of brain aging. The complete set of aging-related long-term pathologies accumulates in every individual and brain region at potentially different rates. Conceivably, the observed clinico-pathologic spectrum of brain aging could emerge from this variability.



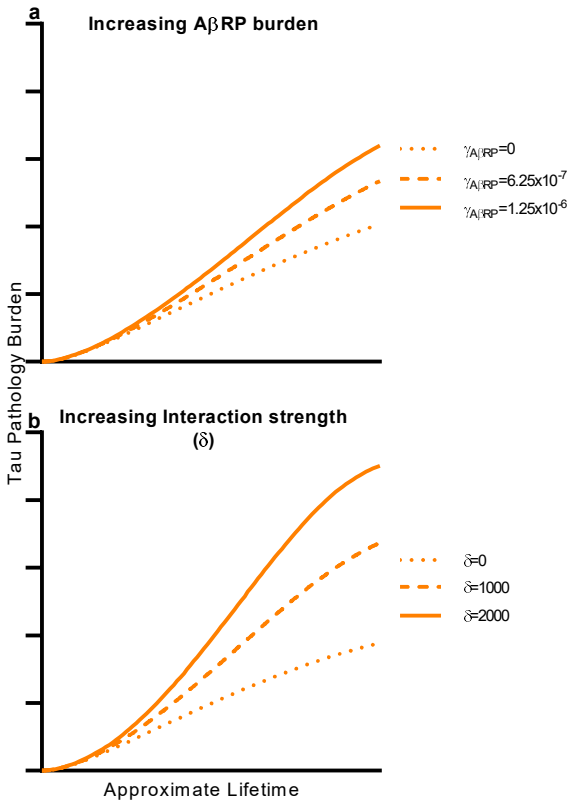
Supplementary Figure 3. Behavior of the ABC-ND model.

Supplementary Figure 3. Behavior of the ABC-ND model. a, Representative simulation of the evolution of brain capital over the lifespan in the absence of either short-term or long-term pathology. **b**, Investment gradually distributes from producing new capital to maintaining current levels, driving the plateau in total capital. **c**, In the presence of short-term pathology, capital again plateaus. **d**, The clearance of pathology does not become a significant portion of endowment (~0.5%), and there is only a marginal decrease in investment this scenario compared to **b**. **e**, As long-term pathology is produced, it accumulates over the lifespan, driving a progressive decline in brain capital. **f**, Resources available for investment into capital decline and are outstripped by capital depreciation. This difference drives the loss of brain capital (**e**).



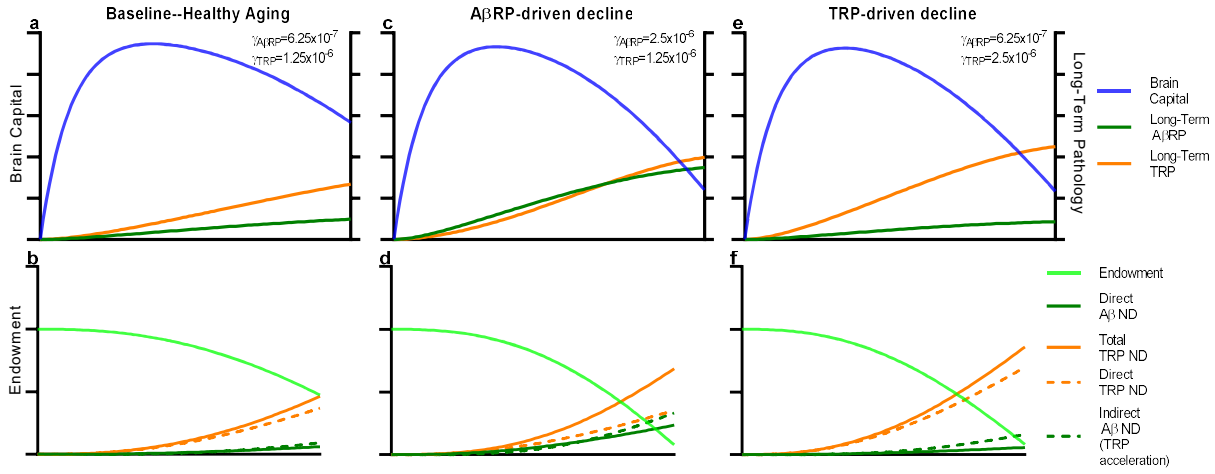
Supplementary Figure 4. Basic behavior of the ABC-AD model.

Supplementary Figure 4. Basic behavior of the ABC-AD model. a, Representative simulation of the evolution of brain capital over the lifespan in the absence of either short-term or long-term pathology. **b**, Investment gradually distributes from producing new capital to maintaining current levels, driving the plateau in total capital. **c**, In the presence of AβRP and TRP short-term pathologies, capital again plateaus. **d**, The clearance of individual pathologies does not become a significant portion of endowment (~0.1-0.5% for each pathology), and there is only a marginal decrease in investment this scenario compared to **b**. This is why maximum capital is only marginally affected (**c**). **e**, As long-term TRP is produced, it accumulates over the lifespan, driving a progressive decline in brain capital. **f**, Resources available for investment into capital decline and are outstripped by capital depreciation. This difference drives the loss of brain capital (**e**). These trends are also observed with AβRP (**g-h**), although to a lesser extent.



Supplementary Figure 5. The impact of amyloid-tau interaction.

Supplementary Figure 5. The impact of amyloid-tau interaction. **a**, Acceleration of long-term TRP over the lifespan at different rates of production of AβRP. **b**, Acceleration of long-term TRP over the lifespan at different values for δ (parameter representing the strength of amyloid-tau interaction).

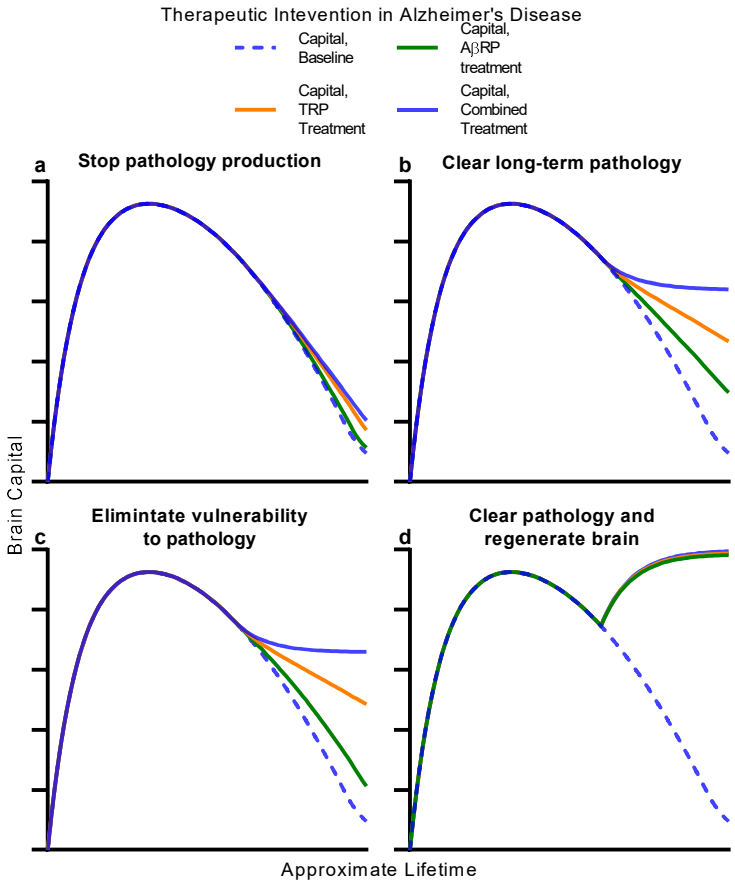


Supplementary Figure 6. Contributions of AβRP and TRP to functional decline in the complete ABC-AD model.

Supplementary Figure 6. Contributions of AβRP and TRP to functional decline in the complete ABC-AD model. Simulation of the evolution of brain capital over the lifespan in the presence of both AβRP and TRP in a representation of healthy aging with minimal pathology accumulation and capital decline. **b**, Endowment decline (neurodegeneration, ND) is mediated directly by AβRP and by TRP, which has both a direct component reflecting the inherent production of TRP and an AβRP-indirect component representing acceleration of TRP due to amyloid-tau interaction. **c**, When AβRP is over-produced in a conceivable scenario for AD, TRP is accelerated from baseline and severe capital decline is observed. **d**, TRP contributes most significantly to decline in brain asset quality (neurodegeneration), although the acceleration of decline from baseline is mediated directly and indirectly by AβRP. **e**, When TRP is over-produced in a conceivable scenario for tauopathy, it accumulates over the lifespan, driving a progressive decline in brain capital. **f**, In tauopathy, TRP contributes most significantly to neurodegeneration independent of AβRP.

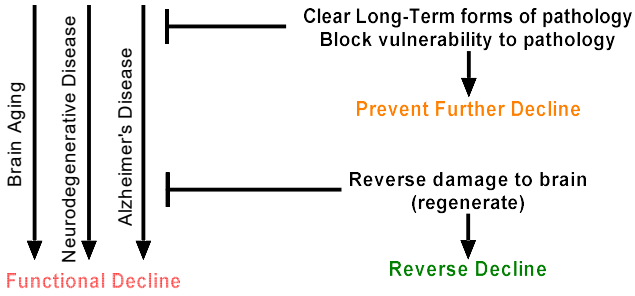
Supplementary Figure 7. A simplified model for the pathoetiology of Alzheimer's disease and tauopathy.

Supplementary Figure 7. A simplified model for the pathoetiology of Alzheimer's disease and tauopathy. a, In AD, genetic and environmental risk factors promote the formation of AβRP in an individual's brain. This leads to accelerated functional decline with aging both directly and indirectly via amyloid-tau acceleration (red arrows). **b,** In tauopathy, genetic and environmental risk factors directly promote the formation of TRP which directly contributes to decline (red arrows). Thus, the pathogenesis of AD and that of tauopathy are distinct but overlapping.



Supplementary Figure 8. Simulations of therapeutic intervention in ABC-AD.

Supplementary Figure 8. Simulations of therapeutic intervention in ABC-AD. The evolution of brain capital and pathology burden was simulated after stopping pathology production (**a**), permanently clearing all pathology (**b**), eliminating the brain's vulnerability to pathology (**c**), or clearing pathology and permanently regenerating brain endowment (**d**). Initial model parameters are identical across simulations in each model and correspond to a familial Alzheimer's disease (fAD) scenario (**Figure 3F**). Endogenous behavior in the absence of intervention is demonstrated in each panel by the dotted curves.



Supplementary Figure 9. A general direction for future neurodegenerative disease intervention.

Supplementary Figure 9. A general direction for future neurodegenerative disease intervention. Therapies that physically clear the offending neurodegenerative pathologies or block the brain's vulnerability have the potential to stop disease progression. With earlier prediction and diagnosis, this could be implemented early in the aging process as a means to prevent severe decline. Ultimately, regenerative medicine that reverses pathology-mediated damage to the brain could conceivably allow for the reversal of decline.

Supplementary Table 1. Interpretation and summary of model parameters across ABC, ABC-ND, and ABC-AD

Parameter/Variable	Meaning	Reasonable Values Explored
K_t	Brain Capital	K_0>**0**
E_t	Brain Endowment	E_0>**0**
I_t	Investment	N/A
PC_t	Pathology Control	N/A
P^{ST}_t	Short-Term Pathology	P^{ST}_0=0
P^{LT}_t	Long-Term Pathology	P^{LT}_0=0
α	Rate of Capital depreciation	**<1,** >0.6
β	Brain vulnerability to pathology	>**1**
γ	Rate of production of Pathology	>**0**
δ	Strength of amyloid-tau interaction	**>0**

Figures

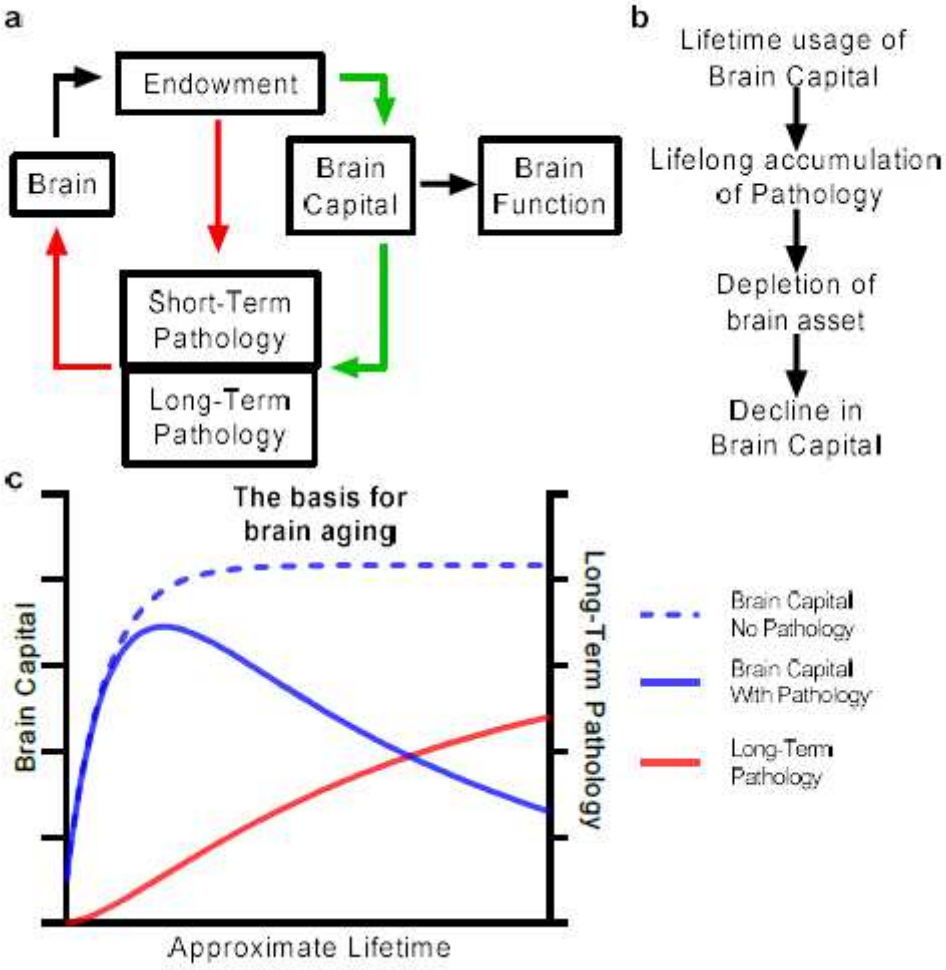


Figure 1

The ABC model defines a general mechanism for brain aging. a, Relationships between variables in the ABC model. Green arrows represent positive contributions (e.g. endowment increases brain capital over time via investment) whereas red arrows represent negative contributions (e.g. endowment clears short-term pathology via pathology control). b, A simplified model for the basis of brain aging as emerges from ABC. c, A representative simulation of brain capital and pathology evolution over an individual's lifetime in ABC. In the absence of long-term pathology, brain capital reaches an upper limit. With the accumulation of long-term pathology, brain capital declines after reaching a peak. All axes have arbitrary units.

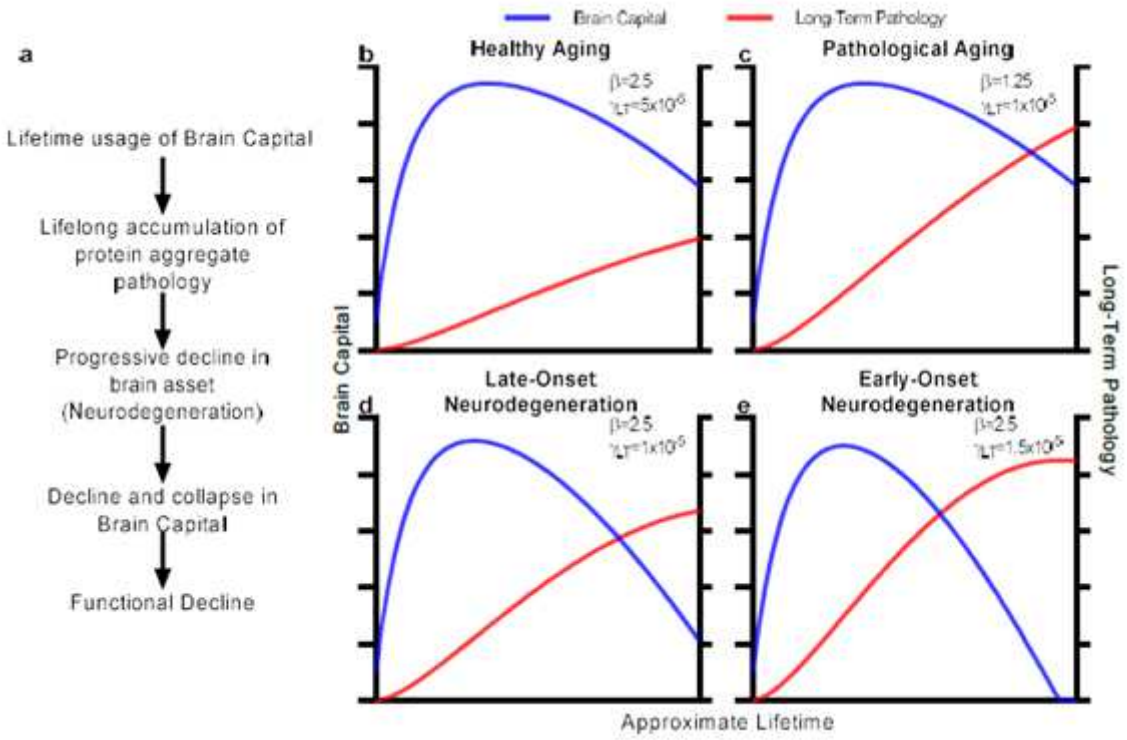


Figure 2

ABC-ND provides a unifying framework for neurodegenerative disease. a, A generalized conceptual framework for aging-driven accumulation of protein aggregate pathologies, neurodegeneration, and late-life functional decline. b-d, Simulations of the ABC-ND model representing plausible scenarios for healthy aging (b), pathological aging (c), late-onset neurodegenerative disease (d), and familial disease (e). Parameters values varied between simulations are provided in the corresponding panels.

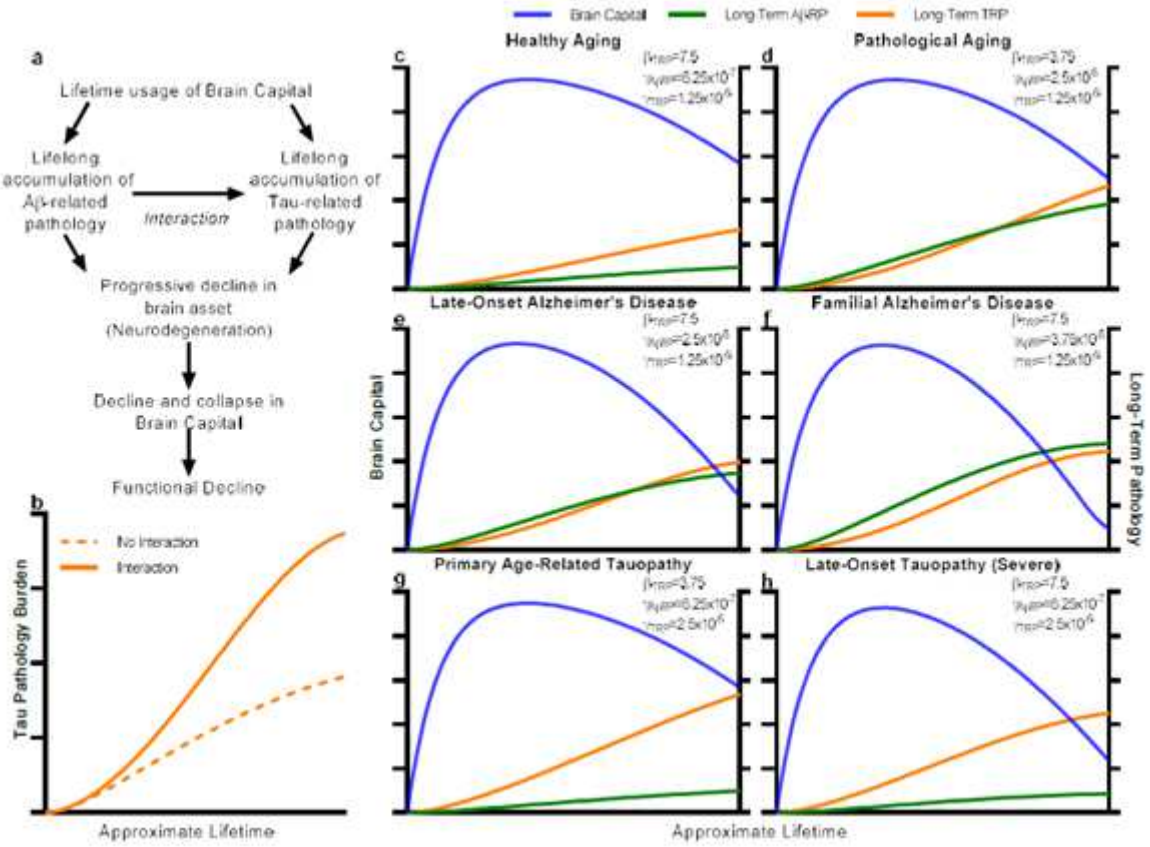


Figure 3

ABC-AD provides a basic, unifying framework for the pathogenesis of Alzheimer's disease. a, The conceptual framework for amyloid-tau interaction theory, linking aging-driven accumulation of AβRP and TRP, neurodegeneration, and functional decline. b, A representative simulation of the effect of amyloid-tau interaction on the accumulation of TRP. c-h, Simulations of ABC-AD representing plausible scenarios for healthy aging (c), pathological aging (d), LOAD (e), fAD (f), PART (g), and late-onset tauopathy (h). Parameters values varied between simulations are shown in the corresponding panels. The value for δ (strength of amyloid-tau interaction) was taken to equal 1500 in all simulations.

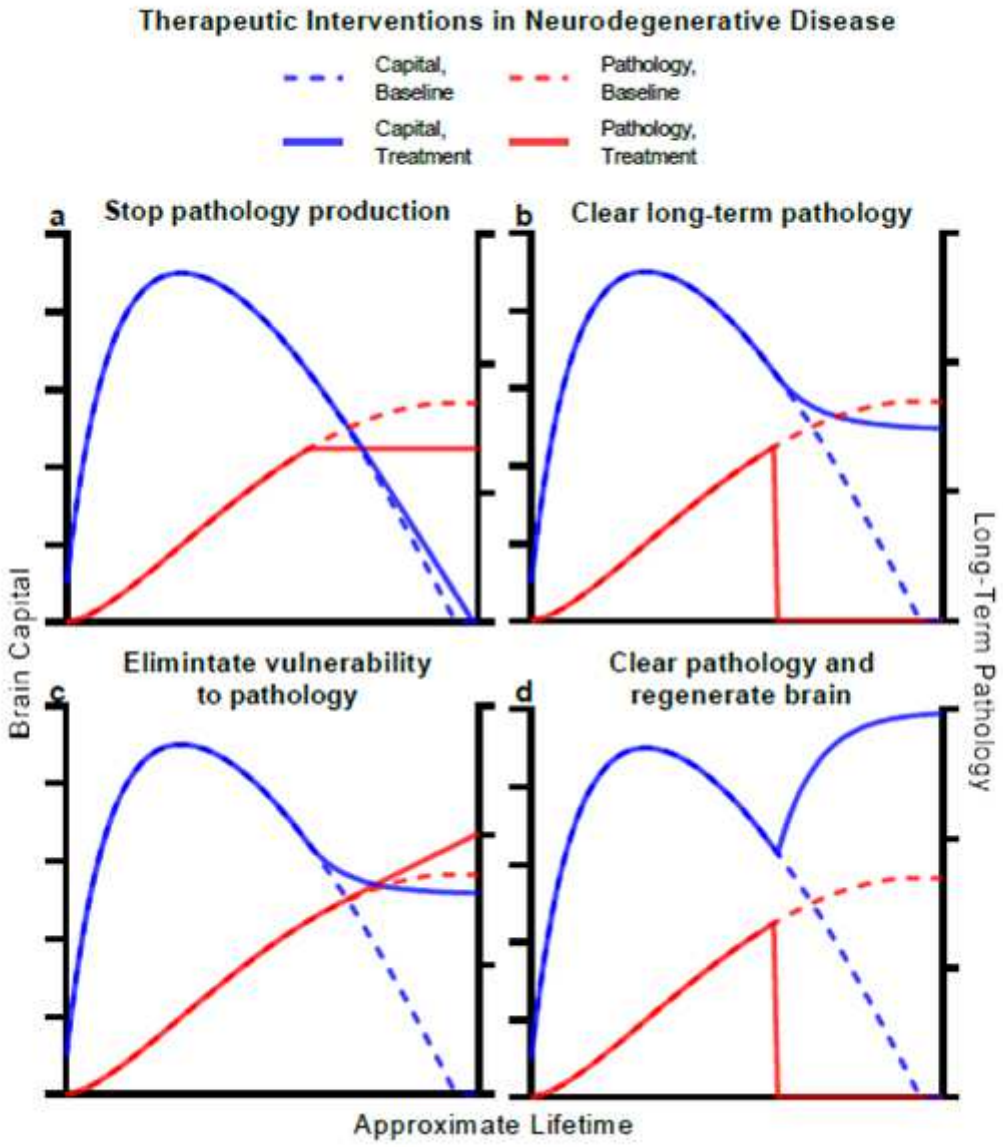


Figure 4

Simulating Therapeutic Effectiveness in ABC-ND. a-d, Simulations of ‘perfect’ therapeutic intervention in ABC-ND. The evolution of brain capital and pathology burden was simulated after stopping pathology production (a), permanently clearing all pathology (b), eliminating the brain’s vulnerability to pathology (c), or clearing pathology and permanently regenerating brain endowment (d). Initial model parameters are identical across simulations in each model and correspond to a familial neurodegenerative disease scenario (Figure 2E). Endogenous behavior in the absence of intervention is demonstrated in each panel by the dotted curves.