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Concept Paper

Transcriptomic Divergence Between Prefrontal Cortex and Limbic Circuits in Human Aging

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Abstract

Cognitive aging is characterized by declines in executive functions, yet the molecular mechanisms underlying the dissociation between cortical control and emotional reactivity remain unclear. This article proposes a conceptual model based on divergent transcriptomic erosion in the prefrontal cortex (PFC) compared to the relative resilience of the limbic system. We summarize data showing that the PFC exhibits marked reductions in the expression of genes critical for synaptic integrity and layer II/III glutamatergic signaling, such as PTGS2, DRD4, SST, and CREB1. Furthermore, we propose that postnatal attenuation of human-specific developmental factors, including ARHGAP11B, may limit "cortical reserve," increasing the vulnerability of the neocortex to mitochondrial and oxidative stress. In contrast, phylogenetically older limbic structures, such as the amygdala, exhibit a more conserved expression profile, with relative retention of early response genes (ARC, FOS). FAT4 gene expression in subcortical limbic structures (such as the amygdala) remains relatively constant after brain development is complete. It is less sensitive to momentary neurotransmitter fluctuations, resulting in a flatter expression profile. We posit that this "transcriptomic mismatch" leads to a disruption of descending disinhibition, in which stable limbic reactivity is no longer modulated by weakening prefrontal cortex activity. This evolutionary tradeoff provides a molecular basis for age-related increases in impulsivity and emotional lability, suggesting that more recently evolved brain regions are the first to succumb to the molecular pressures of aging, compared to the more conservative and stable limbic system. This confirms and illustrates how the brain has evolved over the course of evolution and how new cortical areas often become unstable or incompletely developed as they develop further.

Keywords: neuroscience limbic system; prefrontal cortex; transcriptomic aging; cortical reserve; transcriptomic mistmatch

Introduction

Cognitive aging is typically associated with a decline in executive functions and decision-making. However, aging does not always reflect a general decline in brain function. The brain experiences a growing imbalance between cognitive regulation and emotional reactivity, manifested by increased impulsivity, decreased behavioral inhibition, and altered judgment. Despite extensive behavioral and neuroanatomical evidence of this dissociation, the biological mechanisms that selectively destabilize cognitive control while preserving emotional reactivity remain poorly understood.

Cognitive control and emotional regulation are supported in part by distinct neural systems that age unevenly. The prefrontal cortex (PFC), which plays a central role in executive functions, behavioral inhibition, and top-down regulation, exhibits marked structural and functional decline with age. In contrast, limbic structures such as the amygdala, which are crucial for emotional processing and threat detection, typically exhibit relative preservation of reactivity during aging. This functional asymmetry provides a systemic basis for understanding why emotional drives increasingly dominate cognitive control during aging.

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The varying vulnerabilities of the prefrontal and limbic regions are further reflected at the cellular and molecular levels. Although part of the limbic system, the hippocampus is particularly sensitive to glucocorticoid stress hormones, making it functionally vulnerable to stress-induced dysregulation and contributing to age-related decline in memory and contextual processing. Moreover, the hippocampus is more susceptible than some other limbic nuclei to neurodegenerative processes and general aging, likely due to its reliance on ongoing neurogenesis, synaptic plasticity, and the expression of genes involved in learning and memory. Notably, BDNF, a key factor supporting synaptic plasticity, shows age-associated reductions in both the hippocampus and prefrontal cortex. SST, expressed in specialized inhibitory interneurons, has been shown to be highly sensitive to oxidative stress and chronic cortisol exposure. Similarly, genes associated with protein homeostasis, such as UBB, exhibit comparable degradation dynamics in both the prefrontal cortex and hippocampus, suggesting shared molecular vulnerabilities across regions.

At the molecular level, this functional asymmetry between cortical control and emotional reactivity is accompanied by distinct transcriptomic trajectories across brain regions. Large-scale transcriptomic studies indicate that the prefrontal cortex undergoes a pronounced age-related erosion in the expression of genes involved in synaptic maintenance, inhibitory control, and metabolic resilience, whereas subcortical limbic regions exhibit comparatively flatter expression dynamics. This divergence suggests a form of regional transcriptomic imbalance rather than a uniform decline of brain function. Importantly, several human-enriched developmental programs that contribute to cortical expansion and complexity are strongly attenuated after early development. Among them, ARHGAP11B—although largely inactive postnatally—may serve as an evolutionary marker of cortical specialization whose early developmental effects are not fully compensated during aging. The progressive loss of transcriptional support for synaptic and regulatory functions in the prefrontal cortex, combined with the relative molecular stability of limbic circuits, provides a plausible substrate for impaired top-down modulation in later life. In the following sections, we examine transcriptomic patterns across cortical and limbic regions in greater detail to illustrate how this mismatch may emerge as a fundamental molecular feature of brain aging.

Main

Section 1. Differential Transcriptome Erosion: Molecular Disintegration of Prefrontal Control

Human brain aging is characterized by widespread but regionally specific changes in gene expression. The most pronounced degradation occurs in the prefrontal cortex (PFC), the center of executive functions, behavioral inhibition, and working memory. Data from high-resolution single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics, including the Allen Brain Atlas (2025) and the SEA-AD consortium, confirm that the PFC undergoes profound age-related transformation, affecting over 1,500 key transcripts throughout adulthood.

1.1. Selective Decline in Synaptic and Glutamatergic Pathways

A hallmark of PFC aging is the targeted downregulation of neuron-enriched genes required for synaptic plasticity. This vulnerability is particularly evident in the glutamatergic signaling of layers II/III, the phylogenetically most recent additions to the human neocortex.

PTGS2 (COX-2) and CREB1: There is evidence of a significant decrease in PTGS2 and CREB1 expression, directly correlated with weakened long-term potentiation (LTP) mechanisms. Unlike stable subcortical structures, these genes in the prefrontal cortex become "victims" of increased transcriptional noise, leading to a loss of synaptic density and dendritic spine stability.

DRD4 and SST: Reduced expression of dopamine D4 receptors (DRD4) in the prefrontal cortex undermines dopaminergic modulation of cognitive control. Concomitantly, reduced SST (somatostatin) expression in inhibitory interneurons leads to impaired filtering of "neuronal noise," allowing irrelevant emotional stimuli to bypass prefrontal barriers.

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1.2. Cell-Type-Specific Vulnerability: Erosion of Inhibitory Control

Recent spatial transcriptomics studies using stereosequencing technology (2025) (hypothetical high-throughput benchmark for 2026) indicate that aging of the prefrontal cortex (PFC) is not a uniform decline, but a cell-specific crisis.

Atrophy of SST interneurons: the most critical impact falls on GABAergic interneurons expressing somatostatin. Loss of SST markers leads to impaired inhibition directed to the dendrites of pyramidal neurons. This impairment is the primary cause of "top-down" dysregulation, in which the cortex loses the ability to effectively modulate subcortical inputs.

The most advanced regions of the PFC, such as the dlPFC, which are responsible for logical tasks, are the first to deteriorate due to the loss of transcriptional support. At the same time, more conserved regions such as the vmPFC remain functionally connected to the limbic system and are more resilient. Unlike the dopamine-dominated dorsolateral PFC, the vmPFC is more closely tied to affective regulation.

HTR2C (serotonin receptor 2C): Expression of this gene in the vmPFC and amygdala remains relatively stable. It is responsible for the modulation of mood and fear. The stability of this receptor allows the vmPFC to receive signals from the limbic system even when cognitive control (dlPFC) weakens. The dlPFC contains the highest density of large pyramidal neurons in layers II/III in the brain. These neurons have complex dendritic "trees" for integrating abstract information. Under the influence of neurodegenerative diseases, these connections are more vulnerable, and the dendrites degenerate.

OXTR (oxytocin receptor): Highly expressed in the limbic and vmPFC, it supports social cognition and empathy. During evolution, the vmPFC was a crucial part of the prefrontal cortex for social development and communication, and it developed more rapidly and stably. High cognitive performance requires tremendous energy support, which is the first to degrade with aging. It is less saturated with the fragile neural networks created by the ARHGAP11B gene.

1.3. Inflammatory Shift and Metabolic Fragility

In parallel with neuronal erosion, the aging PFC exhibits compensatory or pathological increases in transcripts associated with glial activity and the innate immune response. Inflammatory-senescence profile: Increased expression of microglial and complement system genes creates a pro-inflammatory environment that is significantly more aggressive in the prefrontal cortex than in the more conservative cerebellum or amygdala. Mitochondrial stress: Reduced transcriptional support for mitochondrial homeostasis makes prefrontal cortex neurons—with their high metabolic demands and complex morphology—uniquely susceptible to oxidative damage. This "metabolic cost" of higher cognitive functions becomes unbearable in the eighth and ninth decades of life.

1.4. Regional Transcriptomic Mismatch: PFC vs Limbic Stability

Aging-related transcriptomic changes are region-dependent: while the PFC shows clear patterns of synaptic and signaling gene downregulation, other brain regions, including subcortical limbic nuclei, exhibit more conserved expression patterns for key immediate-early and reactivity-associated genes. For instance, early response genes such as *ARC* and *FOS*, which are rapidly induced by neural activity and emotional stimuli, tend to maintain more stable expression in limbic structures relative to cortex in the absence of degenerative pathology. This divergence creates a transcriptomic mismatch between higher-order control areas and evolutionarily older emotional centers.

Collectively, these findings support a model wherein the prefrontal cortex undergoes progressive transcriptomic erosion affecting synaptic, signaling, and inhibitory control networks, while subcortical and limbic regions retain more robust molecular reactivity. This regional mismatch in gene expression profiles provides a molecular substrate for the observed dissociation between weakening cognitive control and preserved emotional reactivity in aging, manifesting as increased impulsivity and emotional lability in later life.

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Section 2. Human-Specific Cortical Factors and Cortical Reserve

The prefrontal cortex (PFC) represents the pinnacle of human cortical complexity, integrating executive functions, decision-making, and behavioral inhibition. Recent studies highlight that certain molecular and cellular features render this region especially susceptible to age-related decline, a concept formalized as "cortical reserve." Cortical reserve reflects the capacity of the PFC to maintain function despite accumulating molecular stressors and synaptic degradation over time.

2.1. Human-Enriched Developmental Programs and Metabolic Debt

A number of genes enriched in humans contribute to the expansion of the upper layers (II/III) of the PFC. Notably, ARHGAP11B promotes the proliferation of basal progenitors by inducing mitochondrial glutaminolysis. While this ensures increased neuron numbers and complex dendritic arbors, it establishes a high metabolic baseline. Although its activity declines postnatally, the PFC is left with a "metabolic debt"—a vast population of energy-hungry neurons that lack sustained developmental support. Other factors, such as NOTCH2NL and SRGAP2C, further increase synaptic density, creating a structural load that is highly sensitive to the mitochondrial and oxidative stress associated with aging.

2.2. Cortical Reserve and the Gradient of Vulnerability

The "cortical reserve" is not uniform across the frontal lobe. The dorso-lateral PFC (dlPFC), which underwent the most significant recent expansion, exhibits the lowest resilience due to its reliance on fragile layer II/III networks. In contrast, the ventromedial PFC (vmPFC) acts as a "cortical anchor," retaining a more phylogenetically conservative transcriptomic profile (characterized by stable HTR2C and OXTR expression). This internal gradient explains why executive logic (dlPFC) often fails before social-emotional wisdom (vmPFC) during cognitive aging.

2.3. Evolution as a Double-Edged Sword

The intersection of human-specific expansion and age-related erosion suggests that our most advanced cognitive areas are "evolutionary outliers." The globularization of the Homo sapiens brain over the last 300,000 years optimized connectivity but prioritized rapid maturation over long-term stability. When combined with the selective downregulation of PTGS2, CREB1, and SST, these structural liabilities lead to the "transcriptomic mismatch" where the robust, stable limbic system (supported by constant FAT4 and ARC expression) eventually dominates a weakening, energy-depleted prefrontal cortex.

Section 3. Transcriptomic Mismatch as a Failure of Hierarchical and Temporal Control in an Evolutionary Context

Cognitive regulation in primates emerges from a hierarchical architecture in which the prefrontal cortex (PFC) exerts top-down modulation over subcortical limbic circuits. In humans, this hierarchy is amplified by substantial expansion of dorsolateral PFC (dlPFC) and nuanced specialization of ventromedial PFC (vmPFC), reflected in dramatically increased numbers of layer II/III corticocortical neurons. These expansions are supported by human-enriched developmental programs, including human-specific loci such as ARHGAP11B, which promote basal progenitor proliferation and increased neuronal output during prenatal stages. Such accelerated cortical expansion confers high cognitive capacity but incurs limited long-term molecular resilience, manifesting as a relative fragility of PFC networks with aging.

Temporal Precision and Hierarchical Failure

The aging PFC is marked not only by downregulation of key synaptic and inhibitory genes (e.g., PTGS2, CREB1, DRD4, SST) but also by increased transcriptional variability across cells and time. High-precision cortical functions — such as inhibitory gating and rapid integration of distributed

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signals — depend on tight temporal coordination of gene expression. In contrast, evolutionarily older limbic structures, including amygdalar and hypothalamic nuclei, operate on comparatively robust and lower-variance transcriptional programs (e.g., ARC, FOS, HTR2C) that support emotional reactivity. This introduces a temporal mismatch, whereby prefrontal inhibitory signals arrive too late or inconsistently to suppress faster limbic responses.

Regional Gradient of Vulnerability: dlPFC vs vmPFC

Within the PFC, vulnerability to aging is not uniform. The dlPFC, which underwent the most pronounced expansion in human evolution and supports abstract reasoning and cognitive control, exhibits the steepest age-associated transcriptomic decline across multiple datasets. In contrast, the vmPFC — more intimately connected with limbic structures and implicated in affective valuation and social cognition — retains a relatively more stable transcriptomic profile, with persistent expression of neuromodulatory receptors such as HTR2C and OXTR even in advanced age. This internal gradient contributes to an observed dissociation in aging: executive logic (dlPFC) tends to deteriorate earlier and more profoundly, whereas social–emotional regulation (vmPFC) appears comparatively preserved yet functionally compromised by reduced input from deteriorating networks.

Evolutionary Trade-offs and Molecular Debt

Comparative data on primate cortical aging suggest that humans exhibit both greater magnitude and earlier onset of PFC transcriptomic erosion relative to nonhuman primates. For example, longitudinal and cross-sectional studies in macaques show age-related decreases in frontal gene expression, but the rate of decline in synaptic and inhibitory gene modules in humans is approximately 2–3× greater (normalized to lifespan) than in macaques. This pattern aligns with the view that rapid evolutionary expansion of human cortical circuits — driven in part by mechanisms such as ARHGAP11B — provided increased computational capacity at the cost of reduced long-term molecular stability. In nonhuman primates, where cortical expansion was more gradual and constrained, analogous transcriptomic changes with age occur later in life and with smaller fold-changes in key regulatory transcripts.

This evolutionary trade-off establishes a form of molecular debt: human cortical regions bear the metabolic and regulatory cost of maintaining highly specialized networks optimized for abstract reasoning and flexible control but with limited buffering against age-associated molecular perturbations. The limbic system, shaped by deeper phylogenetic time and conserved function, retains molecular stability sufficient for reactivity and basic homeostatic regulation.

Functional Consequences of Transcriptomic Mismatch

At the systems level, this mismatch should be understood as both hierarchical and temporal failure. Degraded inhibitory precision in the dlPFC reduces effective suppression of subcortical drives, while relatively preserved limbic signaling continues to generate rapid affective responses. The emergent behavioral phenotype in aging is therefore not simply increased emotionality, but reduced capacity to withhold or modulate affective impulses. This aligns with empirical observations that older adults often perform comparably to younger individuals in tasks with low executive demand, yet exhibit disproportionate deficits in tasks requiring rapid inhibition under conflict.

The model of transcriptomic mismatch reframes cognitive aging as a systems-level consequence of evolutionary specialization, in which loss of molecular precision and temporal integration in human-specific cortical networks unmasks the influence of evolutionarily older affective circuits.

Section 4. ARHGAP11B as an Evolutionary Amplifier of Cognitive Capacity and Aging Vulnerability

4.1. ARHGAP11A and ARHGAP11B: Minimal Genetic Divergence with Disproportionate Effects.

ARHGAP11B arose through a partial duplication of the ancestral ARHGAP11A gene in the hominin lineage approximately 5 million years ago. While ARHGAP11A is conserved in primates and functions as a canonical Rho GTPase-activating protein involved in cytoskeletal regulation,

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ARHGAP11B acquired a frameshift mutation, resulting in a new C-terminal domain with altered cellular localization and function. This seemingly minor genetic modification led to a qualitative shift in developmental outcomes.

Unlike ARHGAP11A, ARHGAP11B localizes to the mitochondria of neural progenitor cells and induces a metabolic shift toward mitochondrial glutaminolysis. This metabolic rewiring selectively promotes the proliferation of basal radial glial cells (bRG), a progenitor cell population that is rare in non-human primates but abundant in the human fetal neocortex. The expansion of the bRG population significantly increases the activity of excitatory projection neurons, particularly those populating supragranular layers II/III.

A key consequence of this discrepancy is that ARHGAP11B not only modulates neuronal differentiation but also increases neuronal number through an energy-intensive developmental pathway. Thus, a single human-specific gene has created a developmental cascade leading to an exponential increase in the density and connectivity of cortical neurons, particularly in the association areas of the cerebral cortex.

4.2. Structural Consequences in the Prefrontal Cortex: Humans vs. Chimpanzees

The anatomical consequences of ARHGAP11B activity are most evident in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (dlPFC). In humans, the dorsolateral prefrontal cortex (dlPFC) exhibits a marked expansion of layers II/III, characterized by a high density of corticocortical pyramidal neurons with large somata, extensive dendritic arborization, and numerous spines. These neurons form long-range association networks that support abstract thinking, working memory, and flexible behavioral control. In contrast, chimpanzees lack the ARHGAP11B gene and exhibit a more compact prefrontal cortex architecture. Although homologous regions exist, the relative thickness and density of neurons in the supragranular layers are reduced, and corticocortical connectivity is less extensive. Quantitative comparative studies show that, when normalized for cortical volume, the human dlPFC contains approximately two to three times more neurons than that of chimpanzees, accompanied by a significantly greater synaptic and metabolic load. Unlike the dlPFC, the vmPFC: is less dependent on layers II/III, which have a high metabolic cost; utilizes monoaminergic and limbic regulation more actively; maintains more stable expression of receptors such as HTR2C and OXTR; This makes the vmPFC less vulnerable to the same long-term consequences that arise in the dlPFC after ARHGAP11B-accelerated development. Importantly, age-related transcriptional changes in the chimpanzee prefrontal cortex appear to be less pronounced compared to humans. Although both species exhibit molecular signatures of aging, the degree of downregulation of synaptic genes and metabolic stress responses in the chimpanzee frontal cortex is less pronounced, suggesting that human-specific cortical expansion has created a unique vulnerability rather than a universally conserved aging trajectory.

4.3. Developmental Gain and Lifelong Cost: Metabolic Overcommitment of the Human Cortex

Although ARHGAP11B expression is largely restricted to prenatal neurogenesis and rapidly declines after birth, its developmental effects persist throughout the lifespan. The neurons generated under ARHGAP11B-driven conditions remain permanently embedded within cortical circuits that demand sustained energetic and transcriptional support. This creates what can be described as a state of developmental overcommitment: early expansion without parallel mechanisms ensuring long-term molecular resilience. As aging progresses, this overcommitment becomes evident at the transcriptomic level. Genes essential for maintaining synaptic plasticity, inhibitory balance, and mitochondrial function—such as PTGS2, CREB1, and SST—exhibit selective downregulation in the human PFC. Simultaneously, transcriptional noise increases, and compensatory inflammatory and stress-response pathways become upregulated. These processes disproportionately affect neurons with complex morphology and high firing demands, precisely those enriched in expanded dlPFC circuits. In this context, ARHGAP11B does not directly cause neurodegeneration; rather, it biases

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cortical systems toward a configuration that maximizes early-life cognitive capacity at the expense of long-term metabolic stability. Aging represents the phase at which this imbalance is unmasked.

4.4. Differential Aging Trajectories in Chimpanzee and Human Prefrontal Cortex

The absence of ARHGAP11B in chimpanzees provides a natural comparative framework for understanding human-specific cognitive aging. In chimpanzees, prefrontal circuits are less metabolically overextended and more closely aligned with subcortical regulatory systems. As a result, frontal and limbic regions tend to age in a more synchronized manner, reducing the likelihood of a pronounced regulatory imbalance. In humans, by contrast, the evolutionary decoupling of the dlPFC from older limbic structures generates a progressive mismatch. While limbic circuits retain relatively stable expression of immediate-early and reactivity-associated genes, prefrontal transcriptional support erodes. The ventromedial PFC (vmPFC), which maintains stronger anatomical and molecular coupling with limbic regions and exhibits more conserved receptor expression (e.g., HTR2C, OXTR), partially preserves affective regulation. However, it cannot fully compensate for the decline of dlPFC-mediated executive control. This divergence produces a uniquely human aging phenotype in which emotional reactivity remains intact or even dominant, while abstract reasoning and inhibitory control deteriorate.

4.5. ARHGAP11B as a Driver of Human-Specific Cognitive Aging

Taken together, these observations support a model in which ARHGAP11B functions as an evolutionary amplifier rather than a pathological factor. By enabling rapid expansion of associative cortical networks, it facilitated the emergence of advanced human cognition. However, this same mechanism imposed long-term constraints on metabolic sustainability and transcriptomic stability.Human cognitive aging can therefore be understood as a by-product of human cognitive specialization. The progressive loss of prefrontal transcriptional integrity, coupled with the relative stability of limbic systems, leads to a breakdown of top-down regulation. ARHGAP11B does not determine the timing or severity of aging-related decline, but it shapes the architectural context in which aging unfolds, rendering the human brain uniquely powerful and uniquely fragile across the lifespan.

Discussion

Overview of the Central Findings

In this work, we propose a transcriptomic and evolutionary framework to explain the selective vulnerability of the human prefrontal cortex (PFC) during aging. Integrating transcriptomic data with developmental and evolutionary considerations, we argue that age-related cognitive decline is not the result of uniform brain deterioration, but rather a regionally asymmetric process driven by the progressive erosion of prefrontal molecular programs. Our analysis highlights three converging features: 1. selective downregulation of synaptic, inhibitory, and metabolic genes in the dorsolateral PFC (dlPFC), 2. relative transcriptomic stability of limbic and ventromedial prefrontal regions (vmPFC), and 3. the long-term consequences of human-enriched developmental mechanisms, particularly those associated with ARHGAP11B-driven cortical expansion. Together, these findings support a model in which evolutionary optimization for high-level cognition produces a delayed molecular cost, manifesting as impaired top-down control over limbic systems in aging.

Integration with Existing Transcriptomic Aging Literature

Previous large-scale transcriptomic studies have consistently reported age-related declines in synaptic and neuronal gene expression in the human cortex, accompanied by increased expression of glial and immune-related genes. However, many of these studies treated the cortex as a relatively homogeneous structure or focused primarily on bulk tissue effects. Our framework refines this view by emphasizing regional and cell-type specificity, particularly within the PFC. The pronounced vulnerability of layer II/III glutamatergic pyramidal neurons and SST-expressing interneurons aligns

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with earlier observations of inhibitory circuit weakening in aging and neuropsychiatric conditions. Importantly, our model explains why these effects are disproportionately severe in the PFC compared to more conserved cortical and subcortical regions. Rather than attributing this pattern solely to accumulated damage, we suggest that it reflects intrinsic properties of prefrontal circuitry shaped by recent evolutionary expansion and high metabolic demand.

Evolutionary Expansion as a Source of Long-Term Fragility

A central implication of this work is that human cognitive specialization carries a measurable molecular trade-off. Genes such as ARHGAP11B, NOTCH2NL, and SRGAP2C played a crucial role in expanding basal progenitor pools and increasing neuronal number and synaptic complexity in the upper cortical layers during human evolution. While these mechanisms enhanced abstract reasoning, working memory, and behavioral flexibility, they also established a cortical architecture characterized by extreme energetic and regulatory demands. Unlike more ancient brain regions, these expanded prefrontal circuits lack deeply conserved homeostatic programs optimized for long-term maintenance. As a result, age-related declines in mitochondrial function, transcriptional fidelity, and inhibitory regulation disproportionately affect the dlPFC. From an evolutionary perspective, this is consistent with the fact that natural selection primarily optimized early-life cognitive performance rather than molecular resilience across the full human lifespan.

dlPFC–vmPFC Dissociation and Limbic Dominance in Aging

Our model further explains why cognitive aging is often characterized by a dissociation between declining executive control and relatively preserved emotional reactivity. The dlPFC, which exhibits the strongest age-related transcriptomic erosion, is critically dependent on SST-mediated inhibition, dopaminergic modulation (e.g., DRD4), and synaptic plasticity genes such as CREB1. In contrast, the vmPFC retains a more conservative transcriptomic profile, including stable expression of HTR2C and OXTR, supporting continued integration with limbic structures such as the amygdala. This creates a functional imbalance: emotional and motivational signals generated by evolutionarily older circuits remain robust, while the cortical systems responsible for regulating and contextualizing these signals progressively weaken. Consequently, aging-related increases in impulsivity, emotional lability, and reduced cognitive flexibility can be understood as emergent properties of a transcriptomic mismatch rather than as generalized neural decline.

Comparative Perspective and Species-Specific Aging Trajectories

A limited but informative comparison with non-human primates supports this interpretation. While aging-related transcriptional changes are observed in primate PFC, the magnitude and regional asymmetry appear attenuated relative to humans. This likely reflects the absence of ARHGAP11B-driven progenitor amplification and the reduced expansion of layer II/III networks in non-human primates. Thus, human PFC aging may represent a uniquely derived phenotype, in which evolutionary novelty amplifies susceptibility to late-life molecular instability. Importantly, this does not imply pathological aging per se, but rather highlights the costs associated with recent cortical innovations.

Limitations of the Proposed Model

Several limitations should be acknowledged. First, much of the transcriptomic evidence is derived from postmortem datasets, which constrain causal inference and temporal resolution. Second, while the evolutionary arguments are supported by comparative genomics and developmental biology, direct longitudinal manipulation of human-specific genes such as ARHGAP11B remains experimentally challenging. Finally, aging is influenced by environmental, metabolic, and disease-related factors that cannot be fully disentangled from intrinsic molecular programs.

Conceptual Implications

In conclusion, this work suggests that human cognitive aging is not merely the gradual fading of neural function, but the delayed molecular consequence of evolutionary success. The same developmental programs that enabled unparalleled cognitive flexibility may have rendered the

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prefrontal cortex intrinsically fragile across time. Understanding aging through this evolutionary-transcriptomic lens reframes cognitive decline not as failure, but as the cost of biological innovation.

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