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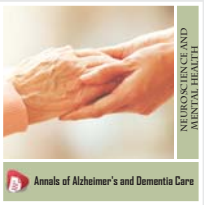

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Letter to Editor

Why Does Neuroplasticity Fail to Rescue the Alzheimer's Brain? Biological Brakes and Philosophical Reflections

Beyza Aksu[1] and Bekir Faruk Erden[2]*

[1]Department of Health Care Services, Division of Podiatry, Vocational School of Health Services, Kocaeli University, Kocaeli, Türkiye

[2]Department of Pharmacology, Kocaeli University Medical Faculty, Kocaeli, Türkiye

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***Corresponding author:** Bekir Faruk Erden, Department of Pharmacology, Kocaeli University Medical Faculty, Kocaeli, Türkiye, E-mail: berden@kocaeli.edu.tr

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Abstract

Alzheimer's disease represents a paradox in which the brain's intrinsic capacity for neuroplasticity fails to prevent progressive decline. Unlike stroke, where intact circuits can reorganize and restore function, AD is marked by diffuse degeneration and active molecular brakes that suppress recovery. This article reviews the dual barriers of myelin-associated inhibitors and chronic neuroinflammation, and further considers the philosophical implications of conditional plasticity. Therapeutic strategies must therefore aim both to release inhibitory signaling pathways and to support the structural substrate of cognition.

Alzheimer's disease embodies a striking paradox: the human brain's famed capacity for neuroplasticity simply fails when it is needed most. After a stroke, patients can relearn to walk or speak; cortical maps reshape, and function returns. Yet in Alzheimer's disease (AD), this restorative force does not emerge. The obvious question arises-why?

We argue that the explanation lies in the "brakes" of neuroplasticity. Far from being a free-flowing repair system, the adult brain is actively restrained by molecular gatekeepers. Myelin-associated inhibitors such as Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp) activate the Nogo receptor, triggering RhoA/ROCK signaling to collapse neurites and block sprouting [1]. At the same time, chronic neuroinflammation in AD amplifies the blockade: cytokines such as interleukin-1β and tumor necrosis factor-α impair long-term potentiation and memory consolidation [2]. In addition, recent evidence shows that network instability and the collapse of homeostatic mechanisms further restrict adaptive remodeling [3].

This dual inhibition explains the paradox. Stroke represents an acute focal insult, sparing networks that can reorganize. Alzheimer's, however, is a slow and diffuse degeneration—eroding not only neurons but also the scaffolds on which plasticity depends. Thus, the very conditions that foster recovery in stroke are absent in AD.

Beyond biology, this raises a philosophical challenge. Neuroplasticity is not a universal healing principle; it is conditional. In some diseases, the brain is permitted to rescue itself; in others, it is forbidden. The stroke brain benefits from plasticity; the Alzheimer's brain is locked out of its own defense. This perspective forces us to abandon overly romantic notions of neuroplasticity and face its limits.

For therapy, this means that simply "boosting plasticity" in AD will not suffice. Instead, strategies must combine two steps: first, releasing the brakes (for example, using ROCK inhibitors or anti-Nogo agents) [4]; second, nurturing the substrate with trophic factors, enriched environments, or cognitive interventions [5,6]. Clinical neuroscience has increasingly emphasized that harnessing neuroplasticity requires both molecular interventions and structured rehabilitation paradigms [7]. Without lifting the restraints, plasticity remains a locked door in a collapsing house.

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Conclusion

Neuroplasticity is not inherently protective; its efficacy depends on biological permissiveness, disease context, and timing. In stroke, preserved networks enable adaptive remodeling, but in AD, diffuse degeneration and active molecular brakes deny the brain this opportunity. Recognizing these constraints allows the field to move beyond over-romanticized views of plasticity and to pursue realistic therapeutic strategies that integrate molecular, cognitive, and environmental interventions. In this context, deficits in neurotrophin signaling [8] and variations in cognitive reserve [9] highlight why neuroplasticity alone cannot explain resilience in Alzheimer's disease.

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