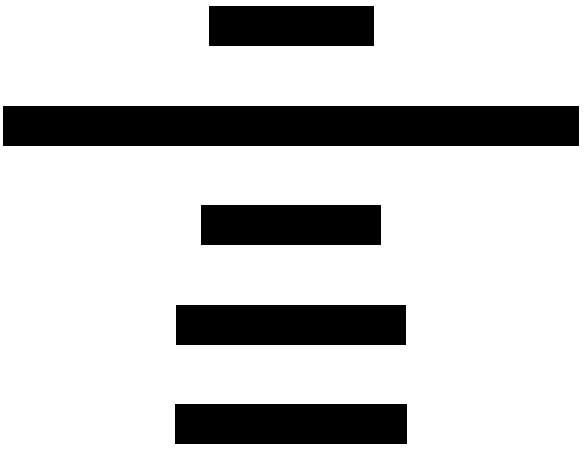
Variations in Neuroplasticity following Traumatic Brain Injury: A Comparison across the Life Span



Abstract

Traumatic brain injury (TBI) represents a significant worldwide health concern, resulting in long-term disability and/or mortality. Annually, it is estimated that approximately 64-74 million individuals experience a TBI, impacting cognition, emotions, and motor abilities throughout all life stages. The main causes of TBI are demographic ageing, increased use of motorized vehicles, and road traffic incidents. Neuroplasticity enables the brain to reorganise itself through the formation of new neural connections, essential for recovery after a TBI, although the effectiveness of this process differs with age. The effect of traumatic brain injury on plasticity is not properly understood across different age groups. This literature review examines the variations in brain plasticity throughout an individual's life (specifically children, adolescents, adults, and the elderly) following a traumatic brain injury. Evidence indicates that, although children and adolescents exhibit increased neural adaptability and higher plasticity, it does not consistently lead to the most effective functional recovery. Conversely, adults and seniors typically exhibit more limited yet stable plasticity and reorganization. This theory is based on the analysis of current academic research, including neuroimaging studies, clinical trials, and long-term examinations of TBI and neuroplasticity among various age groups. In general, it is crucial to understand age-related variations in neuroplasticity following a TBI. This is essential for developing recovery strategies and enhancing future clinical and research techniques related to traumatic brain injury.

Keywords: traumatic brain injury, neuroplasticity, age, children, adolescents, adults, elderly, recovery

Introduction

Traumatic brain injury (TBI) is a major global health problem and it is one of the leading causes of mortality (Maas et al., 2017) across all age groups. It refers to the alteration of how the brain functions or other signs of brain disease caused by an outside force that can happen on the road, at home, at work, during war, or even while playing sports (Manley & Maas, 2013). This can lead to physical, social, cognitive and emotional impairments of different severities. Following a brain injury, the brain undergoes a process called neuroplasticity which causes the brain to undergo adaptive functional and structural modifications. It is described as the nervous system's capacity to reorganize its structure, functions, or connections in response to internal or external stimuli following injuries like TBI or stroke (Puderbaugh & Emmady, 2023).

According to Zamani et al. (2020), the effects of traumatic brain injury present variably across developmental stages, with some cognitive and behavioral abnormalities only appearing around adolescence or early adulthood, even though children's brains usually show higher flexibility.

In children, early traumatic brain injury can affect how the brain normally functions and the creation of neural networks which are needed for a variety of different social behaviours; however, plasticity is affected based on multiple factors for example, existing conditions, individual traits, circumstances before and after the injury, age, and the type of injury itself, which can impact the prolonged effects of pediatric TBI (Zamani et al., 2020).

In adolescents, traumatic brain injury can lead to constant executive functioning deficits in everyday life (Catharine et al., 2019). Linking to plasticity, it may not always be defined as beneficial for adolescents as it consists of multiple processes needed to be regulated (Giza and Prins, 2006).

In adults, TBI increases the risk of neurodegradation which could include Alzheimer's. Therefore, this could negatively affect the recovery of adults in the cognitive and neurological aspect (Rajan, 2025) but full recovery is completely possible (depending on the severity of the injury and other personal factors).

For the elderly, Tan et al. (2025) found that across 18 of their studies, fewer than half regained full functional independence which shows that older adults have the greatest difficulty recovering completely compared to other age groups.

Understanding how neuroplasticity functions across developmental stages is crucial for evaluating recovery results following traumatic brain injury (TBI) in light of these age-related differences. This literature review will contrast a variety of academic studies examining children, adolescents, adults and the elderly. It focuses on how brain plasticity is affected following traumatic brain injury. The paper will first look at neuroplastic responses in children and adolescents and then analyse recovery pattens in adults and the elderly. Each component will assess how the developmental stage affects recovery outcomes by interacting with variables such as injury severity and timing of injury. Furthermore, in order to find broad trends in neuroplasticity throughout the lifetime, the review will synthesise the similarities and differences between age groups. Finally, this paper will analyse how this information can help to provide more insight into future endeavors in this specific field of neuroscience.

Traumatic brain injury and neuroplasticity

Neuroplasticity underlies recovery following traumatic brain injury, but the extent of these neural changes is influenced by factors such as age, injury severity, and stage of rehabilitation. In the context of TBI, immediately after injury, there is cell death, along with a reduction in cortical inhibitory pathways, for 1 to 2 days, which may facilitate the recruitment of new neural networks and promote early circuit reorganization (Su et al., 2016). Cortical circuits gradually shift from inhibitory to excitatory activity; surviving neurons initiate axonal sprouting and synaptogenesis, forming new connections that help repair damaged circuits and restore functional pathways (Su et al., 2016). Neuronal and nonneuronal cells – such as the endothelial progenitors, glial cells, and inflammatory cells – are brought in to replace the weakened cells, promote gliotic scar formation – the creation of dense glial tissue that isolates the injury and inhibits regrowth of neurons (Wang et al., 2018) – and support revascularisation (Su et al., 2016). Circulating endothelial progenitor cells (EPCs) may be crucial for both healthy and pathological angiogenesis in adults (Wei et al., 2010). Angiogenesis is a complex process of forming new blood vessels and is essential for growth and balance (Swerlick, 1995). This is necessary for recovery after TBI. Additionally, glial cells actively influence neuroplasticity, which enables extreme adaptable control over neuronal excitability, synaptic transmission, and network synchronization (Dzyubenko and Hermann, 2023). These processes, including angiogenesis supported by EPCs and the neuroplasticity influenced by glial cells, together play a crucial role in recovery after TBI. Several weeks after the injury, increased expression of synaptic markers and enhanced axonal sprouting is observed. This enables neural remodeling and cortical reorganization that contributes to functional recovery. (Su et al., 2016).

In individuals with brain injuries, adaptive neuroplasticity can be modulated by rehabilitation procedures, increasing everyday life activities and lowering motor impairment (Johnsen and Cohen, 2022). Therefore after TBI, rehabilitation can be done, which is dependent on the

recovery stage of the patient, such as immediately after the injury (acute stage), the main goal of the treatment would be to prevent injury and calm the patient down. After this stage (chronic stages of recovery), there can be many rehabilitation strategies put into place. However, recovery is complicated by age-related variations in plasticity, with younger people showing more plasticity and older adults showing less plasticity and a higher risk of maladaptive alterations (Rajan, 2025).

In general, neuroplastic mechanisms promote recovery after traumatic brain damage because they allow for the gradual structural and functional reorganization of neuronal networks. In order to enhance adaptive neural pathways and increase functional improvement, biological processes like synaptogenesis, angiogenesis, and glial-cell regulation work together with rehabilitation interventions. The efficacy of these neuroplastic mechanisms varies because age, the severity of the injury, and the stage of recovery all affect how well rehabilitation can support long-term recovery results.

Neuroplasticity in Children and Adolescents after TBI

In children and adolescents, the degree and effectiveness of neuroplasticity after TBI are strongly dependent on developmental stage and injury severity. Neuroplasticity after traumatic brain injury differs significantly between children and adolescents, demonstrating that the degree and efficacy of plasticity vary across the lifetime. Various processes play a role in this mechanism of neuroplasticity of younger individuals, such as the excessive production and removal of neurons and synapses, along with the stabilization of synapses depending on the activity (Johnston et al., 2009). The activity-dependent stabilization is the strengthening of circuits that are repeatedly activated, shaping long-term connectivity (Chaudhury et al., 2016). However, the molecular mechanisms for synapses depending on activity are still being found (Johnston et al., 2009). Age of injury is a very important factor because younger children have a higher risk of diffuse brain injury, the process of

widespread axonal damage in the aftermath of TBI (E. Su and Bell, 2016), and this can have dangerous effects on their growth and development (Treble-Barna et al., 2017). The severity of TBI is also a crucial factor, as significant severity is associated with long-term damage (Treble-Berna et al., 2017). A study showed that children who had a severe TBI when they were young showed impairments in adaptive functioning as a result of neuropsychological tests and interviews after 6.9 years of injury (Chan et al., 2024; Tomar et al., 2018). Observing the results, the children in this study showed deficiencies in processing speed and fluid reasoning. Slowing down of processing speeds can make it difficult to do everyday tasks such as understanding verbal remarks or dealing with a fast work environment (Chan et al., 2024; Treble-Barna et al., 2017). Integrating both age and severity, younger age at injury was linked to little to no recovery for children who have severe traumatic brain injury, but older children showed better results. Although newborns (ages 0-2.11 years) with moderate TBI had a worse outcome than older children with injuries of similar severity (Anderson et al., 2005).

During adolescence, ongoing synaptic pruning (the targeted elimination of functional synapses; Sakai, 2020) and cortical maturation (enabling cognitive and behavioral functioning, measured by thickness and curvature; Deoni et al., 2015) make the brain more sensitive to TBI, resulting in more consistent deficits compared with injuries sustained earlier in childhood. Due to continuous neuronal growth during this delicate developmental stage, reviews by Mulligan et al. (2021) and Chan et al. (2024) show that traumatic brain damage received throughout adolescence is associated with worse recovery results than injuries sustained earlier in childhood. Through the process of synaptic pruning, cortical structures undergo significant remodeling, and this results in a decrease in cortical gray matter, an acceleration of axon density and myelination, the formation of a specialized myelin membrane around axons, and an increase in white matter volume. These processes can lead to better cognitive abilities and social cognition (Mulligan et al., 2021). Therefore, any interruptions to these processes can lead to harmful consequences (Chan et al., 2024).

Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be associated with mainly improved functional outcome; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition. Also, a population-based outcome study conducted in Norway presented that 87% of all the children/adolescents included in the study with a mild TBI showed improved recovery compared to the 59% of adolescents with severe TBI (Olsen et al., 2022).

Overall, the relationship between developmental stage and injury severity shapes neuroplasticity in children and adolescents after traumatic brain injury. Disturbances during crucial stages like adolescence can result in long-lasting neurological and cognitive impairments even if ongoing neuronal reorganization in the growing brain might aid in healing. As a result, recovery results depend not only on neuroplastic potential but also on the timing and severity of the damage.

Neuroplasticity in Adults after TBI

In adults, neuroplasticity following TBI is present but happens more slowly and with greater limitations compared to earlier stages of development. In order to preserve cognitive function, adults rely on compensatory processes (Rajan, 2025), which occur when the body tries to readjust and compensate for the stresses it is under (Kauffman, 2015). Even though plasticity decreases with age, new neurons can still be created throughout life; therefore, it does not completely stop generating (Rajan, 2025). The brain's tendency toward neuroplasticity enables it to partially compensate for these disruptions caused by traumatic brain injury by creating new connections and rerouting neural pathways. Neuroplasticity plays a role in both compensatory behaviour and potential functional maladaptation in the process of recovering from brain damage in adults. Compensating is when the brain shifts activities to unaffected areas to retain or restore function after brain damage. This adaptive reaction often results in enhanced performance in previously degraded tasks. On the other

hand, maladaptation refers to the traits or characteristics that reduce fitness or performance in a population (Brady et al., 2019) and can occur when compensatory processes inadvertently prevent optimal healing (Zotey et al., 2023). There is also a significant difference related to recovery and severity of TBI in adults. A study conducted by Othman et al. (2022) showed that out of all the adults with mild TBI, 19.2% showed cognitive damage 3 months after the injury and 19.2% showed neuropsychiatric manifestations. After 6 months of injury, most of the patients exhibited recovery, while some continued to experience cognitive damage (Chan et al., 2024). However, in the same study by Othman et al. (2022), out of all adults with moderate TBI, 39.3% exhibited cognitive impairment, whereas 25% showed neuropsychiatric manifestations (such as agitation, depression, anxiety, apathy, hallucinations, impulsivity, and aggression; Maristany et al., 2024) after 3 months of having the injury. In the case of 6 months post injury, none of the patients showed continued cognitive damage or neuropsychiatric manifestations. According to a review by Wilkins et al. (2019), long-term results after severe traumatic brain damage might be better than previously proposed recovery models. In the study conducted by Wilkins et al. (2019), it is seen that the mortality rate of severe TBI patients was high 3 months after injury; however, for long-term TBI patients, there was significant improvement in functional results 3-24 months after injury which shows that the long-term prognosis in adults with severe TBI was higher than expected.

After traumatic brain injury (TBI), adults' neuroplasticity is generally slower and less extensive than that of younger individuals; however, compensatory neuronal reorganization still allows a partial functional recovery. The degree of an injury has a significant impact on recovery results: minor injuries typically improve more quickly, whereas severe injuries show gradual, long-term improvements. Adults still have some capacity for brain adaptation, although the degree and quality of recovery are influenced by both maladaptive and compensatory processes.

Neuroplasticity in the Elderly after TBI

Older adults exhibit the slowest and least effective neuroplastic responses after a TBI, leading to poorer functional outcomes, higher mortality rates and higher vulnerabilities to even mild injuries. Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates. Atrophy is a condition where the loss of brain cells and neural connections causes brain tissues to decrease (Joseph et al., 2023), and this occurs in the brain as people age. It causes the distance between the brain and skull to expand. This increases the risk of shearing damage to the dural vessels. Also, due to their diminished cerebral reserve, elderly individuals are more susceptible to mild injuries, and many of them have underlying medical issues that are concealed by TBIs (Prasad et al., 2018; Chan et al., 2024). A study conducted by Race et al. (2024) on rodents came to the conclusion that aged rodents had difficulties related to reduced neuroplasticity, dysregulated inflammation, and age-regulated cellular changes, which can affect their recovery after TBI.

In older patients, this leads to poor functional results and higher mortality rates (Chan et al., 2024). Additionally, the elderly have slower plasticity rates because long-term potentiation (LTP) is decreased while long-term depression (LTD) is enhanced (Ridderinkhof and Krugers, 2022). LTP is the lasting increase in synaptic strength caused by repeated high-frequency stimulation of input fibers (Shors & Matzel, 1997), whereas LTD is the reduction of efficacy in synaptic transmission (Bliss & Cooke, 2011). Impaired glutamatergic transmission (the synaptic signalling between neurons mediated by glutamate; Zhou & Danbolt, 2014), cholinergic hypofunction (when the cholinergic system shows reduced function; Schliebs and Arendt, 2010), and significant changes in the dopaminergic system (the neural signalling mediated by dopamine that regulates movement, reward and cognition; Klein et al., 2018) all hinder inter-neuronal interaction and may contribute to learning and

memory deficits as well as decreased cognitive flexibility as age increases (Ridderinkhof and Krugers, 2022). A review by Winter et al. (2022) found consistent evidence, considering the severity of TBI, showing worse results for older patients, even though they have milder TBIs. In a comparison of older and younger adults with mild TBI, Thompson et al. (2020) discovered that older adults consistently exhibited lower overall physical health-related quality of life than their counterparts from one week to one year after injury (Chan et al., 2024). Older patients with severe TBI exhibited unfavorable results and a very high mortality rate of 83.3% (Utomo et al., 2009; Chan et al., 2024). Moreover, the treatment of elderly traumatic brain injury lacks precise guidelines, and those that do exist are mainly based on research involving younger people (Chan et al., 2024).

In comparison to younger age groups, neuroplasticity is generally significantly diminished in the elderly following traumatic brain injury (TBI), which results in a delayed and less successful recovery. Even in mild TBI patients, age-related brain alterations, reduced cerebral reserve, and altered neurotransmission restrict functional results and increase vulnerability to injury. Because there are no age-specific rehabilitation criteria, older persons experience greater mortality rates, worse recovery, and more difficulties.

Conclusion

In conclusion, neuroplasticity provides the biological basis for recovery after traumatic brain injury; however, both the developmental stage and the severity of the injury influence its effectiveness. In individuals of all ages, TBI gives rise to a series of plastic changes (such as synaptogenesis, axonal growth, and cortical reorganization) that may help in functional recovery (Su et al., 2016). Even though this mechanism is common, the ability to tackle neuroplasticity changes throughout life. Children and teenagers usually exhibit higher baseline plasticity because their brains are still developing, but serious injuries in early

childhood or adolescence can hinder essential maturation processes, leading to lasting cognitive and adaptive challenges (Anderson et al., 2005; Treble-Barna et al., 2017; Mulligan et al., 2021). In adults, neuroplasticity occurs at a slower pace and with greater limitations, primarily depending on compensatory reorganization instead of complete functional recovery, while results significantly rely on the severity of the injury and the interaction between adaptive and maladaptive plastic alterations (Zotey et al., 2023; Rajan et al., 2025). In older adults, age-related declines in synaptic plasticity, neurotransmitter function, and brain reserve further constrain recovery ability, leading to worse functional results and increased mortality even after mild TBI (Prasad et al., 2018; Ridderinkhof & Krugers, 2022; Chan et al., 2024)

For rehabilitation strategies, the primary goal of treatment during the acute phase (which occurs in the hours right after an accident) is to stabilize the patient and concentrate on preventing additional harm. Treatment is usually administered in an intensive care unit and then a neurosurgery ward. Rehabilitation is the primary treatment for chronic stages of recovery, and there are numerous treatment and rehabilitation methods (Chan et al., 2024). The results of a study done by Winter et al. (2022) verify that age moderates the impact of injury severity on functional trajectory. Therefore, an individual's age at the time of injury determines the predictive validity of injury severity for functional trajectories; older individuals have worse functional outcomes. This suggests that age is a major factor in recovery after TBI. However, most rehabilitation strategies are based on severity and are dependent on the recovery stage of the patient (Chan et al., 2024). These results point to a discrepancy between current clinical practice and study findings. By highlighting age as a critical component of recovery in addition to injury severity, this study aims to optimise functional results across various age groups and influence future rehabilitation efforts. In other words, future rehabilitation strategies should focus greatly on age due to it being a crucial factor in recovery.

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Title: Variations in neuroplasticity following Traumatic Brain Injury: A Comparison across the Life Span

Comments:

This manuscript addresses an important and timely topic by examining age-related differences in recovery following traumatic brain injury. The lifespan perspective adopted by the authors provides a useful framework for understanding how recovery trajectories may vary across developmental and aging stages. Additionally, the manuscript synthesizes a range of clinical findings, helping to highlight broader patterns of cognitive outcomes after traumatic brain injury across different age groups. Overall, this review is well written and provides valuable information. However, several issues need to be addressed before the manuscript can be accepted.

Major comments:

1. The manuscript aims to compare neuroplasticity across the lifespan following traumatic brain injury. However, the current analysis primarily reports age-related differences in cognitive outcomes. While these findings are valuable, they do not directly demonstrate alterations in neuroplasticity.

Cognitive recovery following traumatic brain injury can be influenced by multiple factors, including baseline cognitive reserve, comorbidities, rehabilitation exposure, and psychosocial variables. Therefore, interpreting age-related differences in cognitive outcomes as evidence of altered neuroplasticity may be an overextension.

Given that the manuscript focuses on variations in neuroplasticity across the lifespan following traumatic brain injury, the mechanistic basis of neuroplasticity is not sufficiently addressed. The current discussion primarily focuses on age-related differences in cognitive outcomes without clearly linking these findings to the underlying biological mechanisms of neuroplasticity.

To strengthen the manuscript's central claim, the authors should consider incorporating mechanistic evidence supporting age-related changes in neuroplasticity (e.g., molecular markers of synaptic plasticity, experimental animal studies, or relevant mechanistic literature). Alternatively, the authors may consider moderating their conclusions and framing the findings as age-related differences in functional recovery rather than direct evidence of altered neuroplasticity.

2. To strengthen the conceptual framework of the manuscript, the authors may consider including an additional section (e.g., “Mechanisms of Neuroplasticity: From Molecules to Circuits”) that outlines the molecular, cellular, and circuit-level processes involved in neuroplasticity. Incorporating evidence from molecular studies, animal models, or other mechanistic research would help bridge the gap between clinical outcomes and the proposed neuroplasticity-based interpretation.

3. Another concern is that several statements referring to specific experimental findings cite review articles rather than the original research papers in which those findings were first reported. While review articles are useful for providing general background, citing the primary studies would provide more direct support for the claims made in the manuscript and improve the scientific rigor of the discussion.

243 e.g) line 246 Additionally, the elderly have slower plasticity rates because long-term potentiation (LTP) is decreased while long-term depression (LTD) is enhanced (Ridderinkhof and Krugers, 2022).

4. Use of visual materials: Including figures such as an age-related neuroplasticity curve or a diagram illustrating recovery stages after traumatic brain injury (e.g., acute vs. chronic phases) would help improve reader comprehension.

Minor Comments:

1. Even if the paper has already been mentioned earlier, a citation should still be added at the end of the sentence.

e.g.) Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be
156 associated with mainly improved functional outcome; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition(add reference).

2. The abbreviation for traumatic brain injury (TBI) is defined earlier in the manuscript; however, the full term “traumatic brain injury” is used again in subsequent sections. Once the abbreviation has been defined, it would be preferable to use “TBI” consistently throughout the manuscript to improve clarity and maintain consistency.

3. Ensure consistent and complete referencing throughout the manuscript

Final Recommendation

- Accept with major revisions (acceptance conditional on satisfactory major revisions)

SUBMISSION 100154: Reviewer Comments and Feedback:
The manuscript is very interesting and well-researched. The author clearly has a strong grasp of the subject matter. However, the unique contribution or "novel perspective" of this review needs to be more clearly defined, as the topic of neuroplasticity across the lifespan is well-documented in existing literature.

Overall Recommendation: Accept with Minor Revisions.

Streamline the Abstract: Remove the specific causes of Traumatic Brain Injury (TBI); these are better suited for the introduction.
Abstract Phrasing: Remove the sentence "This theory is based on..." as it is redundant following the statement "Evidence indicates that..."
Citations: Please ensure the abstract follows standard journal guidelines regarding citations (typically, they are omitted or kept to an absolute minimum).
Mechanism Integration: Consider introducing LTP and LTD much earlier. These mechanisms would significantly strengthen your initial arguments regarding neuroplasticity in children and adolescents.

While children, adolescents, adults, and the elderly are referenced throughout, specific age brackets (e.g., 0–12, 13–19) should be defined early on for scientific rigor.
TBI is defined early in the paper. Use the acronym consistently in lines 72, 85, and 86 rather than writing out the full term.

Line-Specific Corrections:
Line 50: This sentence is quite long; please split or shorten it to improve readability.
Line 57: The meaning of this paragraph is currently unclear. Please rephrase to clarify the central point.
Line 95: Change "brought in" to "recruited."
Line 138: Change "are still being found" to "have yet to be elucidated" or "have yet to be fully understood."

Synthesize the Argument: The conclusion is currently quite long. Instead of summarizing, focus on tying the manuscript's findings together into a cohesive argument.
Clinical Implications: To highlight the importance of this work, include 1–2 sentences on how these findings might impact current clinical practices or neurological standards.
General Proofreading: There are several run-on sentences throughout the manuscript. I recommend a thorough "read-aloud" of the paper to identify grammar mistakes and improve the overall flow.

Variations in neuroplasticity following Traumatic Brain Injury: A Comparison across the Life Span

[Author name redacted]

[School redacted]

[Mentor name redacted]

Abstract

Traumatic brain injury (TBI) represents a significant worldwide health concern, resulting in long-term disability and/or mortality. Annually, it is estimated that approximately 64-74 million individuals experience a TBI, impacting cognition, emotions, and motor abilities throughout all life stages. Recovery depends largely on neuroplasticity, which enables the brain to reorganise itself through the formation of new neural connections, although the effectiveness of this process differs with age. The effect of TBI on plasticity is not properly understood across different age groups. This literature review examines the variations in brain plasticity throughout an individual's life (specifically children, adolescents, adults, and the elderly) following a TBI. Evidence indicates that, although children and adolescents exhibit increased neural adaptability and higher plasticity, it does not consistently lead to the most effective functional recovery. Conversely, adults and seniors typically exhibit more limited yet stable plasticity and reorganization. This is based on the analysis of current academic research, including neuroimaging studies, clinical trials, and long-term examinations of TBI and neuroplasticity among various age groups. In general, it is crucial to understand age-related variations in neuroplasticity following a TBI. This is essential for developing recovery strategies and enhancing future clinical and research techniques related to TBI.

Keywords: traumatic brain injury, neuroplasticity, age, children, adolescents, adults, elderly, recovery

Introduction

Traumatic brain injury (TBI) is a major global health problem and it is one of the leading causes of mortality (Maas et al., 2017) across all age groups. It refers to alterations in brain function or other signs of brain disease caused by an external force, which can occur on the road, at home, at work, during war, or even while playing sports (Manley & Maas, 2013). This can lead to physical, social, cognitive and emotional impairments of different severities. Following a brain injury, the brain undergoes a process called neuroplasticity, resulting in adaptive functional and structural modifications. It is described as the nervous system's capacity to reorganise its structure, functions, or connections in response to internal or external stimuli following injuries like TBI or stroke (Puderbaugh & Emmady, 2025). This process is supported by molecular and

cellular mechanisms such as synaptic plasticity (e.g., long-term potentiation and depression), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and structural changes including synaptogenesis, all of which may vary across the lifespan (Bear & Malenka, 1994; Gustafsson et al., 2021; Su et al., 2016).

According to Zamani et al. (2020), the effects of TBI vary across developmental stages. While children's brains generally show higher flexibility, some of the cognitive and behavioural abnormalities only emerge during adolescence or early adulthood.

In this review, children are defined as individuals aged 0-12, adolescents as 13-18 years, adults as 19-64 years, and the elderly as 65 years and above.

In children, early TBI can disrupt normal brain function and hinder the development of neural networks crucial for social behaviour. However, the effectiveness of neuroplasticity in helping recovery depends on various factors such as pre-existing conditions, individual characteristics, the circumstances surrounding and following the injury, age and the nature of the injury itself (Zamani et al., 2020)

In adolescents, TBI can lead to consistent executive functioning deficits in everyday life (Catharine et al., 2019). Linking to plasticity, it may not always be defined as beneficial for adolescents as it consists of multiple processes needed to be regulated (Giza & Prins, 2006).

In adults, TBI increases the risk of neurodegradation which could include Alzheimer's. Consequently, this could negatively affect the recovery of adults in the cognitive and neurological aspects (Sivaprasad et al., 2005; Rajan, 2025). However, full recovery remains possible, depending on the severity of the injury and other personal factors.

For the elderly, Tan et al. (2025) found that across 18 of their studies, fewer than half regained full functional independence, which shows that older adults have the greatest difficulty recovering completely compared to other age groups.

Understanding how neuroplasticity functions across developmental stages is crucial for evaluating recovery results following TBI in light of these age-related differences. This literature review will contrast a variety of academic studies examining children, adolescents, adults and the elderly. It focuses on how brain plasticity is affected following TBI. The paper will first look at neuroplastic responses in children and adolescents and then analyse recovery patterns in adults and the elderly. Each component will assess how the developmental stage affects recovery outcomes by interacting with variables such as injury severity and timing of injury. Furthermore, in order to find broad trends in neuroplasticity throughout the lifetime, the review will synthesise the similarities and differences between age groups. Finally, this paper will analyse how this information can help to provide more insight into future endeavours in this specific field of neuroscience.

Traumatic brain injury and neuroplasticity

Neuroplasticity underlies recovery following TBI, but the extent of these neural changes is influenced by factors such as age, injury severity, and stage of rehabilitation.

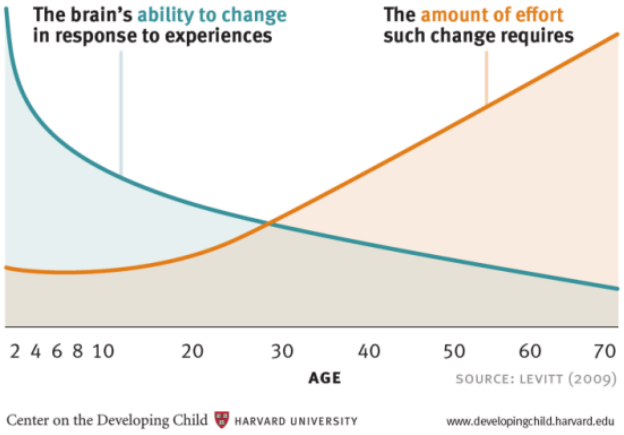

Figure 1. Age-related neuroplasticity graph
Source: Harvard University (2024)

As seen in Figure 1, the brain's capacity to adapt in response to experiences diminishes with age, while the effort required to achieve functional recovery increases (Harvard University, 2024). This indicates that younger individuals may exhibit greater neuroplastic potential following TBI, enabling more efficient neural reorganisation whereas older individuals may require more intensive rehabilitation to achieve comparable recovery outcomes.

In the context of TBI, immediately after injury, there is cell death, along with a reduction in cortical inhibitory pathways for 1 to 2 days, which may facilitate the recruitment of new neural networks and promote early circuit reorganization (Nahmani & Turrigiano, 2014; Su et al., 2016). Cortical circuits gradually shift from inhibitory to excitatory activity; surviving neurons initiate axonal sprouting and synaptogenesis, forming new connections that help repair damaged circuits and restore functional pathways (Su et al., 2016). Neuronal and non-neuronal cells, including endothelial progenitors, glial cells, and inflammatory cells, are recruited to replace weakened cells and support revascularization (Burda & Sofroniew, 2014; Su et al., 2016). Additionally, these cells promote gliotic scar formation—a process where dense glial tissue isolates the injury but also inhibits the regrowth of neurons (Wang et al., 2018). At the cellular level, microglia and astrocytes initiate an inflammatory response after injury. These cells will then secrete a variety of cytokines, chemokines, and growth factors, which determine the extent of the damage and the following repair (Karve et al., 2016). Circulating endothelial progenitor cells (EPCs) may be crucial for both healthy and pathological angiogenesis in adults (Wei et al., 2010). Angiogenesis is a complex process of forming new blood vessels and is essential for growth and balance (Swerlick, 1995). It is regulated by molecular signals such as vascular endothelial growth factor, which help in endothelial cell proliferation, promoting angiogenesis (Johnson & Wilgus, 2014). Additionally, glial cells actively influence neuroplasticity, which enables highly adaptable control over neuronal excitability, synaptic transmission, and network synchronization (Dzyubenko and Hermann, 2023). At the circuit level, these processes lead to large-scale cortical reorganisation, including the recruitment of intracortical circuits to support recovery (Mohammed & Hollis, 2018).

Therefore, these processes, including angiogenesis supported by EPCs and the neuroplasticity influenced by glial cells, together play a crucial role in recovery after TBI. Several weeks after the injury, increased expression of synaptic markers and enhanced axonal sprouting is observed. This enables neural remodelling and cortical reorganization that contribute to functional recovery (Su et al., 2016).

In individuals with brain injuries, adaptive neuroplasticity can be modulated by rehabilitation procedures, increasing everyday life activities and lowering motor impairment (Johnson and Cohen, 2022). Therefore, after TBI, rehabilitation can be done, which is dependent on the recovery stage of the patient, such as immediately after the injury (acute stage), the main goal of the treatment would be to prevent injury and calm the patient down. After this stage (the chronic stages of recovery), many rehabilitation strategies can be implemented. However, recovery is complicated by age-related variations in plasticity, with younger people showing more plasticity and older adults showing less plasticity and a higher risk of maladaptive alterations (Rajan, 2025).

In general, neuroplastic mechanisms promote recovery after traumatic brain damage because they allow for the gradual structural and functional reorganization of neuronal networks. To enhance adaptive neural pathways and improve function, biological processes such as synaptogenesis, angiogenesis, and glial cell regulation work together with rehabilitation interventions. The efficacy of these neuroplastic mechanisms varies because age, the severity of the injury, and the stage of recovery all affect how well rehabilitation can support long-term recovery results.

Neuroplasticity in Children and Adolescents after TBI

In children and adolescents, the degree and effectiveness of neuroplasticity after TBI are strongly dependent on developmental stage and injury severity. Neuroplasticity after TBI differs significantly between children and adolescents, demonstrating that the degree and efficacy of plasticity vary across the lifetime. Various processes play a role in this mechanism of neuroplasticity of younger individuals, such as the excessive production and removal of neurons and synapses, along with the stabilization of synapses depending on the activity (Johnston et al., 2009). The activity-dependent stabilization is the strengthening of circuits that are repeatedly activated, shaping long-term connectivity (Chaudhury et al., 2016). The pediatric brain exhibits greater neuroplasticity compared to the adult brain, facilitating the rapid acquisition of new skills and the recovery from cerebral injuries (Johnston et al., 2009). Mechanistically, this heightened plasticity is supported by LTP and LTD. LTP is a process that helps in synaptic enhancement and increases synaptic strength (Bear & Malenka, 1994; Johnston et al., 2009), whereas LTD is the process of the reduction of synaptic efficacy (Bliss & Cooke, 2011). Interruption of these processes by TBI in children can disrupt normal circuit maturation, leading to prolonged cognitive and adaptive impairments. Additionally, experimental animal models of TBI using juvenile rats show that injury alters brain-derived neurotrophic factor (BDNF), a crucial factor for activity-dependent synaptic plasticity. These changes are observed in both mRNA and protein levels in the hippocampal and cortical areas following the injury (Gustafsson et al., 2021). This suggests that the developing brain may sometimes recover slowly or incompletely, possibly indicating age-related disruptions in synaptic plasticity mechanisms, rather than solely reflecting observed cognitive deficits.

However, the molecular mechanisms for synapses depending on activity have yet to be elucidated (Johnston et al., 2009). Age of injury is a very important factor because younger children have a higher risk of diffuse brain injury, the process of widespread axonal damage in the aftermath of TBI (Su & Bell, 2016), and this can have dangerous effects on their growth and development (Treble-Barna et al., 2017). The severity of TBI is also a crucial factor, as significant severity is associated with long-term damage (Treble-Barna et al., 2017). A study showed that children who had a severe TBI when they were young showed impairments in adaptive functioning as a result of neuropsychological tests and interviews after 6.9 years of injury (Tomar et al., 2018). Observing the results, the children in this study showed deficiencies in processing speed and fluid reasoning. Slowing down of processing speeds can make it difficult to do everyday tasks such as understanding verbal remarks or dealing with a fast work environment (Treble-Barna et al., 2017). Integrating both age and severity, younger age at injury was linked to little to no recovery for children who have severe TBI, but older children showed better results. Although newborns (ages 0-2.11 years) with moderate TBI had a worse outcome than older children with injuries of similar severity (Anderson et al., 2005).

During adolescence, ongoing synaptic pruning (the targeted elimination of functional synapses; Sakai, 2020) and cortical maturation (enabling cognitive and behavioral functioning, measured by thickness and curvature; Deoni et al., 2015) make the brain more sensitive to TBI, resulting in more consistent deficits compared with injuries sustained earlier in childhood. Due to continuous neuronal growth during this delicate developmental stage, reviews by Mulligan et al. (2022) and Chan et al. (2024) show that traumatic brain damage received throughout adolescence is associated with worse recovery results than injuries sustained earlier in childhood. Through the process of synaptic pruning, cortical structures undergo significant remodelling. This process results in a decrease in cortical grey matter alongside an acceleration of axon density and myelination - the formation of a specialized myelin membrane around axons – leading to an increase in white matter volume. These processes can lead to better cognitive abilities and social cognition (Mulligan et al., 2022). Therefore, any interruptions to these processes can lead to harmful consequences (Chan et al., 2024). These developmental processes are closely connected to underlying synaptic plasticity mechanisms, and disruptions with pruning and myelination may impair activity-dependent plasticity. Thus, this contributes to poorer recovery outcomes following TBI during adolescence (Sakai, 2020; Mulligan et al., 2022).

Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be associated with mainly improved functional outcome; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition (Kolstø et al., 2025). Also, a population-based outcome study conducted in Norway presented that 87% of all the children/adolescents included in the study with a mild TBI showed improved recovery compared to the 59% of adolescents with severe TBI (Olsen et al., 2022).

Overall, the relationship between developmental stage and injury severity shapes neuroplasticity in children and adolescents after TBI. Disturbances during crucial stages like adolescence can result in long-lasting neurological and cognitive impairments even if ongoing neuronal reorganization in the growing brain might aid in healing. As a result,

recovery results depend not only on neuroplastic potential but also on the timing and severity of the damage.

Neuroplasticity in Adults after TBI

In adults, neuroplasticity following TBI is present but happens more slowly and with greater limitations compared to earlier stages of development. In order to preserve cognitive function, adults rely on compensatory processes (Rajan, 2025), which occur when the body tries to readjust and compensate for the stresses it is under (Kauffman, 2015). Even though plasticity decreases with age, new neurons can still be created throughout life; therefore, it does not completely stop generating (Rajan, 2025). Mechanistically, adult neuroplasticity involves activity-dependent processes such as LTP. A study conducted by Weston et al. (2021) investigated adult male rats that received a moderate TBI. Measurements of LTP showed prolonged impairment, which worsened between 30-60 days (Weston et al., 2021). In addition, adult TBI causes a neurological deficit through complex mechanisms including glutamate excitotoxicity, inflammation, demyelination, programmed cell death and the development of edema. This is caused by glial cells and they play a crucial role in the CNS response, damage control and regeneration. In response to tissue damage, these cells activate, undergo hypertrophy and proliferate, eventually forming a glial scar. This scar acts as a barrier within the damaged tissue, protecting the CNS during the acute phase following the injury (Amlerova et al., 2024). These molecular and cellular mechanisms provide a biological basis for the partial functional recovery seen in adults.

The brain's tendency toward neuroplasticity enables it to partially compensate for these disruptions caused by TBI by creating new connections and rerouting neural pathways. Neuroplasticity plays a role in both compensatory behaviour and potential functional maladaptation in the process of recovering from brain damage in adults. Compensating is when the brain shifts activities to unaffected areas to retain or restore function after brain damage. This adaptive reaction often results in enhanced performance in previously degraded tasks. On the other hand, maladaptation refers to the traits or characteristics that reduce fitness or performance in a population (Brady et al., 2019) and can occur when compensatory processes inadvertently prevent optimal healing (Zotey et al., 2023). There is also a significant difference related to recovery and severity of TBI in adults. A study conducted by Othman et al. (2022) showed that out of all the adults with mild TBI, 19.2% showed cognitive damage 3 months after the injury and 19.2% showed neuropsychiatric manifestations (Othman et al., 2022). After 6 months of injury, most of the patients exhibited recovery, while some continued to experience cognitive damage (Othman et al., 2022). However, in the same study by Othman et al. (2022), out of all adults with moderate TBI, 39.3% exhibited cognitive impairment, whereas 25% showed neuropsychiatric manifestations (such as agitation, depression, anxiety, apathy, hallucinations, impulsivity, and aggression; Maristany et al., 2024) after 3 months of having the injury. In the case of 6 months post injury, none of the patients showed continued cognitive damage or neuropsychiatric manifestations (Othman et al., 2022). According to a review by Wilkins et al. (2019), long-term results after severe traumatic brain damage might be better than previously proposed recovery models. In the study conducted by Wilkins et al. (2019), it is seen that the mortality rate of severe TBI patients was high 3 months after injury; however, for long-term TBI patients, there was significant improvement in functional results 3-24 months after injury which shows

that the long-term prognosis in adults with severe TBI was higher than expected (Wilkins et al., 2019).

After TBI, adults' neuroplasticity is generally slower and less extensive than that of younger individuals; however, compensatory neuronal reorganization still allows a partial functional recovery. The degree of an injury has a significant impact on recovery results: minor injuries typically improve more quickly, whereas severe injuries show gradual, long-term improvements. Adults still have some capacity for brain adaptation, although the degree and quality of recovery are influenced by both maladaptive and compensatory processes.

Neuroplasticity in the Elderly after TBI

Older adults exhibit the slowest and least effective neuroplastic responses after a TBI, leading to poorer functional outcomes, higher mortality rates and higher vulnerabilities to even mild injuries. Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates. Atrophy is a condition where the loss of brain cells and neural connections causes brain tissues to decrease (Joseph et al., 2023), and this occurs in the brain as people age. It causes the distance between the brain and skull to expand. This increases the risk of shearing damage to the dural vessels. Also, due to their diminished cerebral reserve, elderly individuals are more susceptible to mild injuries, and many of them have underlying medical issues that are concealed by TBIs (Prasad et al., 2018; Chan et al., 2024). A study conducted by Race et al. (2024) on rodents came to the conclusion that aged rodents had difficulties related to reduced neuroplasticity, dysregulated inflammation, and age-regulated cellular changes, which can affect their recovery after TBI (Race et al., 2024).

In older patients, this leads to poor functional results and higher mortality rates (Chan et al., 2024). Additionally, numerous studies have demonstrated that aged rodents have slower plasticity rates because LTP is decreased while LTD is enhanced (Rapp et al., 1987; Ridderinkhof and Krugers, 2022). Impaired glutamatergic transmission (the synaptic signalling between neurons mediated by glutamate; Zhou & Danbolt, 2014), cholinergic hypofunction (the reduction of cholinergic system activity; Schliebs and Arendt, 2010), and significant changes in the dopaminergic system (the neural signalling mediated by dopamine that regulates movement, reward and cognition; Klein et al., 2019) all hinder inter-neuronal interaction and may contribute to learning and memory deficits as well as decreased cognitive flexibility as age increases (Wong et al., 2021; Ridderinkhof and Krugers, 2022). These changes reflect a decline in the efficiency of synaptic plasticity mechanisms, which could limit the brain's ability for flexible reorganisation after TBI in older adults. A review by Winter et al. (2022) found consistent evidence, considering the severity of TBI, showing worse results for older patients, even though they have milder TBIs (Winter et al., 2022). In a comparison of older and younger adults with mild TBI, Thompson et al. (2020) discovered that older adults consistently exhibited lower overall physical health-related quality of life than their counterparts from one week to one year after injury (Thompson et al., 2020; Chan et al., 2024). Older patients with severe TBI exhibited unfavorable results and a very high mortality rate of 83.3% (Utomo et al., 2009; Chan et al., 2024). Moreover, the treatment

of elderly TBI lacks precise guidelines, and those that do exist are mainly based on research involving younger people (Chan et al., 2024).

In comparison to younger age groups, neuroplasticity is generally significantly diminished in the elderly following TBI, which results in a delayed and less successful recovery. Even in mild TBI patients, age-related brain alterations, reduced cerebral reserve, and altered neurotransmission restrict functional results and increase vulnerability to injury. Because there are no age-specific rehabilitation criteria, older persons experience greater mortality rates, worse recovery, and more difficulties.

Conclusion

In conclusion, neuroplasticity provides an important biological framework for recovery after TBI; however, both the developmental stage and severity of the injury influence the extent to which functional recovery occurs. While these neuroplastic mechanisms develop throughout the lifespan, much of the existing evidence reflects age-related differences in functional outcomes, which are likely influenced by, rather than direct measures of, underlying neuroplastic processes (Su et al., 2016). Younger individuals show greater baseline plasticity but this does not always lead to better recovery. Early disruptions can interfere with important development processes (Anderson et al., 2005; Mulligan et al., 2022).

For rehabilitation strategies, the primary goal of treatment during the acute phase (which occurs in the hours right after an accident) is to stabilize the patient and concentrate on preventing additional harm. The results of a study done by Winter et al. (2022) verify that age moderates the impact of injury severity on functional trajectory (Winter et al., 2022). Therefore, an individual's age at the time of injury determines the predictive validity of injury severity for functional trajectories. However, most rehabilitation strategies are based on severity and are dependent on the recovery stage of the patient (Chan et al., 2024). These results point to a discrepancy between current clinical practice and study findings. Incorporating both age and injury severity into rehabilitation planning allows clinicians to optimise recovery outcomes. By tailoring interventions to a patient's developmental stage and the extent of their injury, functional improvements can be enhanced and long-term deficits reduced.

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Variations in neuroplasticity following Traumatic Brain Injury: A Comparison across the Life Span

[Author name redacted]

[School redacted]

[Mentor name redacted]

Abstract

Traumatic brain injury (TBI) represents a significant worldwide health concern, resulting in long-term disability and/or mortality. Annually, it is estimated that approximately 64-74 million individuals experience a TBI, impacting cognition, emotions, and motor abilities throughout all life stages. ~~The main causes of TBI are demographic ageing, increased use of motorized vehicles, and road traffic incidents~~ Recovery depends largely on neuroplasticity, which ~~. Neuroplasticity~~ enables the brain to reorganise itself through the formation of new neural connections, ~~, essential for recovery after a TBI,~~ although the effectiveness of this process differs with age. The effect of TBI ~~traumatic brain injury~~ on plasticity is not properly understood across different age groups. This literature review examines the variations in brain plasticity throughout an individual's life (specifically children, adolescents, adults, and the elderly) following a ~~-~~ TBI~~traumatic brain injury~~. Evidence indicates that, although children and adolescents exhibit increased neural adaptability and higher plasticity, it does not consistently lead to the most effective functional recovery. Conversely, adults and seniors typically exhibit more limited yet stable plasticity and reorganization. This~~This theory~~ is based on the analysis of current academic research, including neuroimaging studies, clinical trials, and long-term examinations of TBI and neuroplasticity among various age groups. In general, it is crucial to understand age-related variations in neuroplasticity following a TBI. This is essential for developing recovery strategies and enhancing future clinical and research techniques related to TBI~~traumatic brain injury~~.

Keywords: traumatic brain injury, neuroplasticity, age, children, adolescents, adults, elderly, recovery

Introduction

Traumatic brain injury (TBI) is a major global health problem and it is one of the leading causes of mortality (Maas et al., 2017) across all age groups. It refers to alterations in brain function or other signs of brain disease caused by an external force, which can occur~~the alteration of how the brain functions or other signs of brain disease caused by an outside force that can happen~~ on the road, at home, at work, during war, or even while playing sports (Manley & Maas, 2013). This can lead to physical, social, cognitive and emotional impairments of different severities. Following a brain injury, the brain undergoes a process called neuroplasticity, ~~which causes the brain to~~resulting

~~undergo~~in adaptive functional and structural modifications. It is described as the nervous system's capacity to ~~reorganize~~ reorganise its structure, functions, or connections in response to internal or external stimuli following injuries like TBI or stroke (Puderbaugh & Emmady, 2025~~3~~). This process is supported by molecular and cellular mechanisms such as synaptic plasticity (e.g., long-term potentiation and depression), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and structural changes including synaptogenesis, all of which may vary across the lifespan (Bear & Malenka, 1994; Gustafs~~ff~~son et al., 2021; Su et al., 2016).

According to Zamani et al. (2020), the effects of TBI ~~traumatic brain injury~~ vary across ~~present variably across~~ developmental stages. ~~, with some cognitive and behavioral abnormalities only appearing around adolescence or early adulthood, even though children's brains usually show higher flexibility~~While children's brains generally show higher flexibility, some of the cognitive and behavioural abnormalities only emerge during adolescence or early adulthood.

In this review, children are defined as individuals aged 0-12, adolescents as 13-18 years, adults as 19-64 years, and the elderly as 65 years and above.

~~In children, early traumatic brain injury can affect how the brain normally functions and the creation of neural networks which are needed for a variety of different social behaviours; however, plasticity is affected based on multiple factors for example, existing conditions, individual traits, circumstances before and after the injury, age, and the type of injury itself, which can impact the prolonged effects of pediatric TBI (Zamani et al., 2020). ¶~~
In children, early TBI can disrupt normal brain function and hinder the development of neural networks crucial for social behaviour. However, the effectiveness of neuroplasticity in helping recovery depends on various factors such as pre-existing conditions, individual characteristics, the circumstances surrounding and following the injury, age and the nature of the injury itself (Zamani et al., 2020)

In adolescents, TBI ~~traumatic brain injury~~ can lead to consistent~~tant~~ executive functioning deficits in everyday life (Catharine et al., 2019). Linking to plasticity, it may not always be defined as beneficial for adolescents as it consists of multiple processes needed to be regulated (Giza &~~and~~ Prins, 2006).

In adults, TBI increases the risk of neurodegradation which could include Alzheimer's. Consequently, ~~Therefore,~~ this could negatively affect the recovery of adults in the cognitive and neurological aspects (Sivaprasad et al., 2005; Rajan, 2025). ~~However,~~~~but~~ full recovery remains ~~is completely~~ possible, ~~(~~depending on the severity of the injury and other personal factors~~)~~.

For the elderly, Tan et al. (2025) found that across 18 of their studies, fewer than half regained full functional independence, which shows that older adults have the greatest difficulty recovering completely compared to other age groups.

Understanding how neuroplasticity functions across developmental stages is crucial for evaluating recovery results following TBI ~~traumatic brain injury (TBI)~~ in light of these age-related differences. This literature review will contrast a variety of academic studies

examining children, adolescents, adults and the elderly. It focuses on how brain plasticity is affected following TBI~~traumatic brain injury~~. The paper will first look at neuroplastic responses in children and adolescents and then analyse recovery patterns in adults and the elderly. Each component will assess how the developmental stage affects recovery outcomes by interacting with variables such as injury severity and timing of injury. Furthermore, in order to find broad trends in neuroplasticity throughout the lifetime, the review will synthesise the similarities and differences between age groups. Finally, this paper will analyse how this information can help to provide more insight into future endeavours in this specific field of neuroscience. ¶

Traumatic brain injury and neuroplasticity

Neuroplasticity underlies recovery following TBI~~traumatic brain injury~~, but the extent of these neural changes is influenced by factors such as age, injury severity, and stage of rehabilitation.

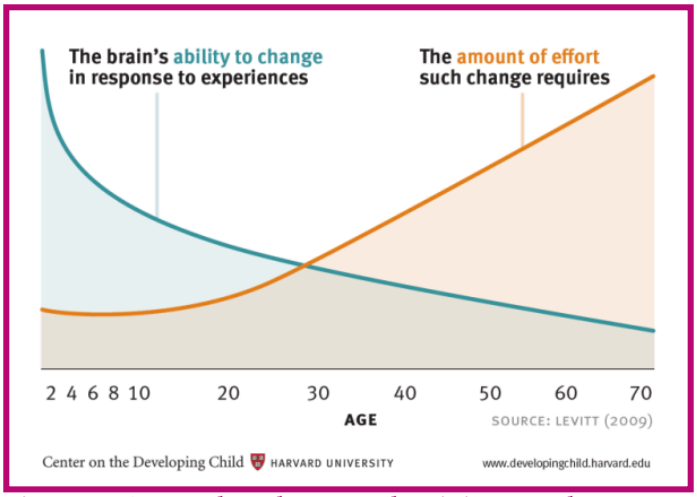

Figure 1. Age-related neuroplasticity graph
Source: Harvard University (2024)

As seen in Figure 1, the brain's capacity to adapt in response to experiences diminishes with age, while the effort required to achieve functional recovery increases (Harvard University, 2024). This indicates that younger individuals may exhibit greater neuroplastic potential following TBI, enabling more efficient neural reorganisation whereas older individuals may require more intensive rehabilitation to achieve comparable recovery outcomes.

In the context of TBI, immediately after injury, there is cell death, along with a reduction in cortical inhibitory pathways for 1 to 2 days, which may facilitate the recruitment of new neural networks and promote early circuit reorganization (Nahmani & Turrigiano, 2014; Su et al., 2016). Cortical circuits gradually shift from inhibitory to excitatory activity; surviving neurons initiate axonal sprouting and synaptogenesis, forming new connections that help repair damaged circuits and restore functional pathways (Su et al., 2016). Neuronal and non-neuronal cells, including endothelial progenitors, glial cells, and inflammatory cells, are recruited to replace weakened cells and support revascularization (Burda & Sofroniew, 2014; Su et al., 2016). Additionally, these cells promote gliotic scar formation—a process where dense glial tissue isolates the injury

but also inhibits the regrowth of neurons (Wang et al., 2018). ~~Neuronal and nonneuronal cells – such as the endothelial progenitors, glial cells, and inflammatory cells – are brought in to replace the weakened cells, promote gliotic scar formation – the creation of dense glial tissue that isolates the injury and inhibits regrowth of neurons (Wang et al., 2018) – and support revascularisation (Su et al., 2016).~~ At the cellular level, microglia and astrocytes initiate an inflammatory response after injury. These cells will then secrete a variety of cytokines, chemokines, and growth factors, which determine the extent of the damage and the following repair (Karve et al., 2016). Circulating endothelial progenitor cells (EPCs) may be crucial for both healthy and pathological angiogenesis in adults (Wei et al., 2010). Angiogenesis is a complex process of forming new blood vessels and is essential for growth and balance (Swerlick, 1995). It is regulated by molecular signals such as vascular endothelial growth factor, which help in endothelial cell proliferation, promoting angiogenesis (Johnson & Wilgus, 2014). ~~This is necessary for recovery after TBI.~~ Additionally, glial cells actively influence neuroplasticity, which enables highly~~extreme~~ adaptable control over neuronal excitability, synaptic transmission, and network synchronization (Dzyubenko and Hermann, 2023). At the circuit level, these processes lead to large-scale cortical reorganisation, including the recruitment of intracortical circuits to support recovery (Mohammed & Hollis, 2018).

Therefore, t~~T~~hese processes, including angiogenesis supported by EPCs and the neuroplasticity influenced by glial cells, together play a crucial role in recovery after TBI. Several weeks after the injury, increased expression of synaptic markers and enhanced axonal sprouting is observed. This enables neural remodelling and cortical reorganization that contribute~~s~~ to functional recovery ~~.~~(Su et al., 2016).¶

In individuals with brain injuries, adaptive neuroplasticity can be modulated by rehabilitation procedures, increasing everyday life activities and lowering motor impairment (Johnso~~e~~n and Cohen, 2022). Therefore, after TBI, rehabilitation can be done, which is dependent on the recovery stage of the patient, such as immediately after the injury (acute stage), the main goal of the treatment would be to prevent injury and calm the patient down. After this stage (the chronic stages of recovery), ~~there can be~~ many rehabilitation strategies ~~put~~can ~~into~~be ~~place~~implemented. However, recovery is complicated by age-related variations in plasticity, with younger people showing more plasticity and older adults showing less plasticity and a higher risk of maladaptive alterations (Rajan, 2025).

In general, neuroplastic mechanisms promote recovery after traumatic brain damage because they allow for the gradual structural and functional reorganization of neuronal networks. To enhance adaptive neural pathways and improve function, biological processes such as synaptogenesis, angiogenesis, and glial cell~~In order to enhance adaptive neural pathways and increase functional improvement, biological processes like synaptogenesis, angiogenesis, and glial cell~~ regulation work together with rehabilitation interventions. The efficacy of these neuroplastic mechanisms varies because age, the severity of the injury, and the stage of recovery all affect how well rehabilitation can support long-term recovery results.

Neuroplasticity in Children and Adolescents after TBI

In children and adolescents, the degree and effectiveness of neuroplasticity after TBI are strongly dependent on developmental stage and injury severity. Neuroplasticity after TBI~~traumatic brain injury~~ differs significantly between children and adolescents, demonstrating that the degree and efficacy of plasticity vary across the lifetime. Various processes play a role in this mechanism of neuroplasticity of younger individuals, such as the excessive production and removal of neurons and synapses, along with the stabilization of synapses depending on the activity (Johnston et al., 2009). The activity-dependent stabilization is the strengthening of circuits that are repeatedly activated, shaping long-term connectivity (Chaudhury et al., 2016). The pediatric brain exhibits greater neuroplasticity compared to the adult brain, facilitating the rapid acquisition of new skills and the recovery from cerebral injuries (Johnston et al., 2009). Mechanistically, this heightened plasticity is supported by LTP and LTD. LTP is a process that helps in synaptic enhancement and increases synaptic strength (Bear & Malenka, 1994; Johnston et al., 2009), whereas LTD is the process of the reduction of synaptic efficacy (Bliss & Cooke, 2011). Interruption of these processes by TBI in children can disrupt normal circuit maturation, leading to prolonged cognitive and adaptive impairments. Additionally, experimental animal models of TBI using juvenile rats show that injury alters brain-derived neurotrophic factor (BDNF), a crucial factor for activity-dependent synaptic plasticity. These changes are observed in both mRNA and protein levels in the hippocampal and cortical areas following the injury (Gustafsson et al., 2021). This suggests that the developing brain may sometimes recover slowly or incompletely, possibly indicating age-related disruptions in synaptic plasticity mechanisms, rather than solely reflecting observed cognitive deficits.

However, the molecular mechanisms for synapses depending on activity have yet to be elucidated~~are still being found~~ (Johnston et al., 2009). Age of injury is a very important factor because younger children have a higher risk of diffuse brain injury, the process of widespread axonal damage in the aftermath of TBI (~~E.~~ Su ~~&and~~ Bell, 2016), and this can have dangerous effects on their growth and development (Treble-Barna et al., 2017). The severity of TBI is also a crucial factor, as significant severity is associated with long-term damage (Treble-B~~a~~erna et al., 2017). A study showed that children who had a severe TBI when they were young showed impairments in adaptive functioning as a result of neuropsychological tests and interviews after 6.9 years of injury (~~Chan et al., 2024;~~ Tomar et al., 2018). Observing the results, the children in this study showed deficiencies in processing speed and fluid reasoning. Slowing down of processing speeds can make it difficult to do everyday tasks such as understanding verbal remarks or dealing with a fast work environment (~~Chan et al., 2024;~~ Treble-Barna et al., 2017). Integrating both age and severity, younger age at injury was linked to little to no recovery for children who have severe TBI~~traumatic brain injury~~, but older children showed better results. Although newborns (ages 0-2.11 years) with moderate TBI had a worse outcome than older children with injuries of similar severity (Anderson et al., 2005).

During adolescence, ongoing synaptic pruning (the targeted elimination of functional synapses; Sakai, 2020) and cortical maturation (enabling cognitive and behavioral functioning, measured by thickness and curvature; Deoni et al., 2015) make the brain more sensitive to TBI, resulting in more consistent deficits compared with injuries sustained earlier in childhood. Due to continuous neuronal growth during this delicate developmental stage, reviews by Mulligan et al. (2021) and Chan et al. (2024) show that

traumatic brain damage received throughout adolescence is associated with worse recovery results than injuries sustained earlier in childhood. Through the process of synaptic pruning, cortical structures undergo significant remodelling. ~~,~~This process ~~and this~~ results in a decrease in cortical ~~gray~~ grey matter alongside~~,~~ an acceleration of axon density and myelination ~~-~~ ~~,~~the formation of~~-~~ a specialized myelin membrane around axons ~~–,~~ leading to ~~and~~ an increase in white matter volume. These processes can lead to better cognitive abilities and social cognition (Mulligan et al., 2022~~1~~). Therefore, any interruptions to these processes can lead to harmful consequences (Chan et al., 2024). These developmental processes are closely connected to underlying synaptic plasticity mechanisms, and disruptions with pruning and myelination may impair activity-dependent plasticity. Thus, this contributes to poorer recovery outcomes following TBI during adolescence (Sakai, 2020; Mulligan et al., 2022~~1~~).

Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be associated with mainly improved functional outcome; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition (Kolstø et al., 2025). Also, a population-based outcome study conducted in Norway presented that 87% of all the children/adolescents included in the study with a mild TBI showed improved recovery compared to the 59% of adolescents with severe TBI (Olsen et al., 2022).

Overall, the relationship between developmental stage and injury severity shapes neuroplasticity in children and adolescents after TBI~~traumatic brain injury~~. Disturbances during crucial stages like adolescence can result in long-lasting neurological and cognitive impairments even if ongoing neuronal reorganization in the growing brain might aid in healing. As a result, recovery results depend not only on neuroplastic potential but also on the timing and severity of the damage.

Neuroplasticity in Adults after TBI

In adults, neuroplasticity following TBI is present but happens more slowly and with greater limitations compared to earlier stages of development. In order to preserve cognitive function, adults rely on compensatory processes (Rajan, 2025), which occur when the body tries to readjust and compensate for the stresses it is under (Kauffman, 2015). Even though plasticity decreases with age, new neurons can still be created throughout life; therefore, it does not completely stop generating (Rajan, 2025). Mechanistically, adult neuroplasticity involves activity-dependent processes such as LTP. A study conducted by Weston et al. (2021) investigated adult male rats that received a moderate TBI. Measurements of LTP showed prolonged impairment, which worsened between 30-60 days (Weston et al., 2021). In addition, adult TBI causes a neurological deficit through complex mechanisms including glutamate excitotoxicity, inflammation, demyelination, programmed cell death and the development of edema. This is caused by glial cells and they play a crucial role in the CNS response, damage control and regeneration. In response to tissue damage, these cells activate, undergo hypertrophy and proliferate, eventually forming a glial scar. This scar acts as a barrier within the damaged tissue, protecting the CNS during the acute phase following the injury (Amlerova et al., 2024). These molecular and cellular mechanisms provide a biological basis for the partial functional recovery seen in adults.

The brain's tendency toward neuroplasticity enables it to partially compensate for these disruptions caused by TBI~~traumatic brain injury~~ by creating new connections and rerouting neural pathways. Neuroplasticity plays a role in both compensatory behaviour and potential functional maladaptation in the process of recovering from brain damage in adults. Compensating is when the brain shifts activities to unaffected areas to retain or restore function after brain damage. This adaptive reaction often results in enhanced performance in previously degraded tasks. On the other hand, maladaptation refers to the traits or characteristics that reduce fitness or performance in a population (Brady et al., 2019) and can occur when compensatory processes inadvertently prevent optimal healing (Zotey et al., 2023). There is also a significant difference related to recovery and severity of TBI in adults. A study conducted by Othman et al. (2022) showed that out of all the adults with mild TBI, 19.2% showed cognitive damage 3 months after the injury and 19.2% showed neuropsychiatric manifestations (Othman et al., 2022). After 6 months of injury, most of the patients exhibited recovery, while some continued to experience cognitive damage (Othman et al., 2022~~Chan et al., 2024~~). However, in the same study by Othman et al. (2022), out of all adults with moderate TBI, 39.3% exhibited cognitive impairment, whereas 25% showed neuropsychiatric manifestations (such as agitation, depression, anxiety, apathy, hallucinations, impulsivity, and aggression; Maristany et al., 2024) after 3 months of having the injury. In the case of 6 months post injury, none of the patients showed continued cognitive damage or neuropsychiatric manifestations (Othman et al., 2022). According to a review by Wilkins et al. (2019), long-term results after severe traumatic brain damage might be better than previously proposed recovery models. In the study conducted by Wilkins et al. (2019), it is seen that the mortality rate of severe TBI patients was high 3 months after injury; however, for long-term TBI patients, there was significant improvement in functional results 3-24 months after injury which shows that the long-term prognosis in adults with severe TBI was higher than expected (Wilkins et al., 2019).

After TBI~~traumatic brain injury (TBI)~~, adults' neuroplasticity is generally slower and less extensive than that of younger individuals; however, compensatory neuronal reorganization still allows a partial functional recovery. The degree of an injury has a significant impact on recovery results: minor injuries typically improve more quickly, whereas severe injuries show gradual, long-term improvements. Adults still have some capacity for brain adaptation, although the degree and quality of recovery are influenced by both maladaptive and compensatory processes.

Neuroplasticity in the Elderly after TBI

Older adults exhibit the slowest and least effective neuroplastic responses after a TBI, leading to poorer functional outcomes, higher mortality rates and higher vulnerabilities to even mild injuries. Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates. Atrophy is a condition where the loss of brain cells and neural connections causes brain tissues to decrease (Joseph et al., 2023), and this occurs in the brain as people age. It causes the distance between the brain and skull to expand. This increases the risk of shearing damage to the dural vessels. Also, due to their diminished cerebral reserve, elderly individuals are more susceptible to mild injuries, and many of them have underlying medical issues that are concealed by TBIs (Prasad et al., 2018; Chan et al., 2024). A study conducted by Race et al. (2024) on rodents came to the conclusion that

aged rodents had difficulties related to reduced neuroplasticity, dysregulated inflammation, and age-regulated cellular changes, which can affect their recovery after TBI (Race et al., 2024).

In older patients, this leads to poor functional results and higher mortality rates (Chan et al., 2024). Additionally, numerous studies have demonstrated that aged rodents~~, the elderly~~ have slower plasticity rates because ~~long-term potentiation (~~LTP~~)~~ is decreased while ~~long-term depression (~~LTD~~)~~ is enhanced (Rapp et al., 1987; Ridderinkhof and Krugers, 2022). ~~LTP is the lasting increase in synaptic strength caused by repeated high-frequency stimulation of input fibers (Shors & Matzel, 1997), whereas LTD is the reduction of efficacy in synaptic transmission (Bliss & Cooke, 2011).~~ Impaired glutamatergic transmission (the synaptic signalling between neurons mediated by glutamate; Zhou & Danbolt, 2014), cholinergic hypofunction (~~when~~ the reduction of cholinergic system~~-~~ activity~~shows reduced function~~; Schliebs and Arendt, 2010), and significant changes in the dopaminergic system (the neural signalling mediated by dopamine that regulates movement, reward and cognition; Klein et al., 2019~~8~~) all hinder inter-neuronal interaction and may contribute to learning and memory deficits as well as decreased cognitive flexibility as age increases (Wong et al., 2021; Ridderinkhof and Krugers, 2022). These changes reflect a decline in the efficiency of synaptic plasticity mechanisms, which could limit the brain's ability for flexible reorganisation after TBI in older adults. A review by Winter et al. (2022) found consistent evidence, considering the severity of TBI, showing worse results for older patients, even though they have milder TBIs (Winter et al., 2022). In a comparison of older and younger adults with mild TBI, Thompson et al. (2020) discovered that older adults consistently exhibited lower overall physical health-related quality of life than their counterparts from one week to one year after injury (Thompson et al., 2020; Chan et al., 2024). Older patients with severe TBI exhibited unfavorable results and a very high mortality rate of 83.3% (Utomo et al., 2009; Chan et al., 2024). Moreover, the treatment of elderly TBI ~~traumatic brain injury~~ lacks precise guidelines, and those that do exist are mainly based on research involving younger people (Chan et al., 2024).

In comparison to younger age groups, neuroplasticity is generally significantly diminished in the elderly following TBI~~-traumatic brain injury (TBI)~~, which results in a delayed and less successful recovery. Even in mild TBI patients, age-related brain alterations, reduced cerebral reserve, and altered neurotransmission restrict functional results and increase vulnerability to injury. Because there are no age-specific rehabilitation criteria, older persons experience greater mortality rates, worse recovery, and more difficulties.

Conclusion

In conclusion, neuroplasticity provides an important~~the~~ biological framework~~basis~~ for recovery after TBI~~traumatic brain injury~~; however, both ~~the~~ the developmental stage and ~~the~~ severity of the injury influence the extent to which functional recovery occurs~~its effectiveness~~. While these neuroplastic mechanisms develop throughout the lifespan, much of the existing evidence reflects age-related differences in functional outcomes, which are likely influenced by, rather than direct measures of, underlying neuroplastic processes (Su et al., 2016). ~~In individuals of all ages, TBI gives rise to a series of plastic changes (such as synaptogenesis, axonal growth, and cortical reorganization) that may~~

help in functional recovery (Su et al., 2016). Even though this mechanism is common, the ability to tackle neuroplasticity changes throughout life. Children and teenagers usually exhibit higher baseline plasticity because their brains are still developing, but serious injuries in early childhood or adolescence can hinder essential maturation processes, leading to lasting cognitive and adaptive challenges (Anderson et al., 2005; Treble-Barna et al., 2017; Mulligan et al., 2021). In adults, neuroplasticity occurs at a slower pace and with greater limitations, primarily depending on compensatory reorganization instead of complete functional recovery, while results significantly rely on the severity of the injury and the interaction between adaptive and maladaptive plastic alterations (Zotey et al., 2023; Rajan et al., 2025). In older adults, age-related declines in synaptic plasticity, neurotransmitter function, and brain reserve further constrain recovery ability, leading to worse functional results and increased mortality even after mild TBI (Prasad et al., 2018; Ridderinkhof & Krugers, 2022; Chan et al., 2024)Younger individuals show greater baseline plasticity but this does not always lead to better recovery. Early disruptions can interfere with important development processes (Anderson et al., 2005; Mulligan et al., 2022).

For rehabilitation strategies, the primary goal of treatment during the acute phase (which occurs in the hours right after an accident) is to stabilize the patient and concentrate on preventing additional harm. . Treatment is usually administered in an intensive care unit and then a neurosurgery ward. Rehabilitation is the primary treatment for chronic stages of recovery, and there are numerous treatment and rehabilitation methods (Chan et al., 2024). The results of a study done by Winter et al. (2022) verify that age moderates the impact of injury severity on functional trajectory (Winter et al., 2022). Therefore, an individual's age at the time of injury determines the predictive validity of injury severity for functional trajectories.; older individuals have worse functional outcomes. This suggests that age is a major factor in recovery after TBI. However, most rehabilitation strategies are based on severity and are dependent on the recovery stage of the patient (Chan et al., 2024). These results point to a discrepancy between current clinical practice and study findings. Incorporating both age and injury severity into rehabilitation planning allows clinicians to optimise recovery outcomes. By tailoring interventions to a patient's developmental stage and the extent of their injury, functional improvements can be enhanced and long-term deficits reduced. By highlighting age as a critical component of recovery in addition to injury severity, this study aims to optimise functional results across various age groups and influence future rehabilitation efforts. In other words, future rehabilitation strategies should focus greatly on age due to it being a crucial factor in recovery.

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Title: Variations in neuroplasticity following Traumatic Brain Injury:
A Comparison across the Life Span

Comments:
This manuscript addresses an important and timely topic by examining age-related differences in recovery following traumatic brain injury. The lifespan perspective adopted by the authors provides a useful framework for understanding how recovery trajectories may vary across developmental and aging stages. Additionally, the manuscript synthesizes a range of clinical findings, helping to highlight broader patterns of cognitive outcomes after traumatic brain injury across different age groups. Overall, this review is well written and provides valuable information. However, several issues need to be addressed before the manuscript can be accepted.

Major comments:
1. The manuscript aims to compare neuroplasticity across the lifespan following traumatic brain injury. However, the current analysis primarily reports age-related differences in cognitive outcomes. While these findings are valuable, they do not directly demonstrate alterations in neuroplasticity.

Cognitive recovery following traumatic brain injury can be influenced by multiple factors, including baseline cognitive reserve, comorbidities, rehabilitation exposure, and psychosocial variables. Therefore, interpreting age-related differences in cognitive outcomes as evidence of altered neuroplasticity may be an overextension.

Given that the manuscript focuses on variations in neuroplasticity across the lifespan following traumatic brain injury, the mechanistic basis of neuroplasticity is not sufficiently addressed. The current discussion primarily focuses on age-related differences in cognitive outcomes without clearly linking these findings to the underlying biological mechanisms of neuroplasticity.

To strengthen the manuscript's central claim, the authors should consider incorporating mechanistic evidence supporting age-related changes in neuroplasticity (e.g., molecular markers of synaptic plasticity, experimental animal studies, or relevant mechanistic literature). Alternatively, the authors may consider moderating their conclusions and framing the findings as age-related differences in functional recovery rather than direct evidence of altered neuroplasticity.

- Thank you for this comment. I have included a range of mechanistic evidence across all paragraphs – particularly in those on children, adolescents, and adults. I have included information about LTP and LTD in all of those paragraphs and how they link to the conclusion I came to. Additionally, I have fixed the phrasing of my conclusion so it does not come across too strongly.

2. To strengthen the conceptual framework of the manuscript, the authors may consider including an additional section (e.g., "Mechanisms of Neuroplasticity: From Molecules to Circuits") that outlines the molecular, cellular, and circuit-level processes involved in neuroplasticity. Incorporating evidence from molecular studies, animal models, or other mechanistic research would help bridge the gap between clinical outcomes and the proposed neuroplasticity-based interpretation.

- Thank you for this comment. I already had a section named "traumatic brain injury and neuroplasticity" with a paragraph discussing the biological mechanisms involved in neuroplasticity. However, I have built on it and added more information about cellular, molecular, and circuit-level mechanisms.

3. Another concern is that several statements referring to specific experimental findings cite review articles rather than the original research papers in which those findings were first reported. While review articles are useful for providing general background, citing the primary studies would provide more direct support for the claims made in the manuscript and improve the scientific rigor of the discussion.

- 243 e.g) line 246 Additionally, the elderly have slower plasticity rates because long-term potentiation (LTP) is decreased while long-term depression (LTD) is enhanced (Ridderinkhof and Krugers, 2022).

- Thank you so much for this comment. I have done my best to cite all the primary research articles that presented the first findings of the evidence I have used in my paper. I have also cited the review papers from where I first discovered the findings.

4. Use of visual materials: Including figures such as an age-related neuroplasticity curve or a diagram illustrating recovery stages after traumatic brain injury (e.g., acute vs. chronic phases) would help improve reader comprehension.

- Thank you for this comment. I have inserted an image from research conducted by Harvard University in 2024, which illustrates how neuroplasticity decreases with age.

Minor Comments:

1. Even if the paper has already been mentioned earlier, a citation should still be added at the end of the sentence.
e.g.) Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be 156 associated with mainly improved functional outcome; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition(add reference).

- Thank you for this comment. I have added citations after I mention “a study conducted by…” throughout the whole paper

2. The abbreviation for traumatic brain injury (TBI) is defined earlier in the manuscript; however, the full term “traumatic brain injury” is used again in subsequent sections. Once the abbreviation has been defined, it would be preferable to use “TBI” consistently throughout the manuscript to improve clarity and maintain consistency.

- Thank you for this comment. After defining it once, I have changed the wording from ‘Traumatic brain injury’ to ‘TBI’ throughout the manuscript.

3. Ensure consistent and complete referencing throughout the manuscript
- I have gone over and checked the referencing and have done my best to make sure that every fact and outside information is cited and referenced.

Final Recommendation
● Accept with major revisions (acceptance conditional on satisfactory major revisions)

SUBMISSION 100154: Reviewer Comments and Feedback:
The manuscript is very interesting and well-researched. The author clearly has a strong grasp of the subject matter. However, the unique contribution or "novel perspective" of this review needs to be more clearly defined, as the topic of neuroplasticity across the lifespan is well-documented in existing literature.

Overall Recommendation: Accept with Minor Revisions.

Streamline the Abstract: Remove the specific causes of Traumatic Brain Injury (TBI); these are better suited for the introduction.

- Thank you for the comment. I have removed the causes of TBI from the abstract and included them in the introduction.

Abstract Phrasing: Remove the sentence "This theory is based on..." as it is redundant following the statement "Evidence indicates that..."

- I have rephrased the sentence so it does not contradict my previous point

Citations: Please ensure the abstract follows standard journal guidelines regarding citations (typically, they are omitted or kept to an absolute minimum).

- No in-text citations were included in the abstract, in line with standard academic interventions

Mechanism Integration: Consider introducing LTP and LTD much earlier. These mechanisms would significantly strengthen your initial arguments regarding neuroplasticity in children and adolescents.

- Thank you for this comment. I have introduced LTP and LTD in the paragraph named ‘Neuroplasticity in Children and Adolescents’. I have also explained the effects of TBI on these 2 processes.

While children, adolescents, adults, and the elderly are referenced throughout, specific age brackets (e.g., 0–12, 13–19) should be defined early on for scientific rigor.

- I have added 2 lines in the paper (lines 56-57) defining the ages for all 4 age groups. In this review, children are defined as individuals aged 0-12, adolescents as 13-18 years, adults as 19-64 years, and the elderly as 65 years and above.

TBI is defined early in the paper. Use the acronym consistently in lines 72, 85, and 86 rather than writing out the full term.

- Thank you for this comment. I have replaced ‘Traumatic brain injury’ with ‘TBI’ in the entire paper

Line-Specific Corrections:
Line 50: This sentence is quite long; please split or shorten it to improve readability.

- Thank you for the comment. I split the sentence into 2. It reads “According to Zamani et al. (2020), the effects of TBI vary across developmental stages. While children’s brains generally show higher flexibility, some of the cognitive and behavioural abnormalities only emerge during adolescence or early adulthood. “

Line 57: The meaning of this paragraph is currently unclear. Please rephrase to clarify the central point.

- I have broken down the paragraph and reordered the structure. The sentences are not too long and easier for the reader to understand.

Line 95: Change "brought in" to "recruited."

- I have changed the wording from “brought in” to “recruited”

Line 138: Change "are still being found" to "have yet to be elucidated" or "have yet to be fully understood."

- I have changed the wording from “are still being found” to “have yet to be elucidated”

Synthesize the Argument: The conclusion is currently quite long. Instead of summarizing, focus on tying the manuscript’s findings together into a cohesive argument.

- I have removed the parts of the conclusion where I summarise the paper and have cut it down to 2 sentences to tie the manuscript findings.

Clinical Implications: To highlight the importance of this work, include 1–2 sentences on how these findings might impact current clinical practices or neurological standards.

- I have integrated the improvements that can be made to clinical practices into the conclusion (final two sentences)

General Proofreading: There are several run-on sentences throughout the manuscript. I recommend a thorough "read-aloud" of the paper to identify grammar mistakes and improve the overall flow.

- Thank you for this comment. I have read through and edited the run-on sentences. I have broken them down into 2 sentences to improve readability.

Comments:

The section describing age-related differences in neuroplasticity is well done. A well-written and timely review on age-related differences in recovery after traumatic brain injury, offering a useful lifespan perspective and synthesizing clinical findings, but requiring several revisions before it can be accepted.

Main issue:

The added figure presents a serious issue, and there are still multiple missing citations throughout the manuscript. These issues need to be addressed.

Regarding Figure 1, permission must be obtained from Harvard University before the image is used. More importantly, in academic writing, sources should primarily be limited to peer-reviewed articles rather than website-based materials, which are generally considered informal and not appropriate for scholarly work. Furthermore, the author has used the website-based figure to support explanations in the main text. This is highly unprofessional and raises serious concerns. The figure should either be replaced with one from a peer-reviewed review or research article or be recreated by the author. In addition, any text based on the website figure should be removed or substantially revised.

Specific Comments:

- **Line 186:** The full terms for LTP and LTD should be provided at first mention.

(probably line 46?)

- **Line 260:** “A study conducted by Weston et al. (2021) investigated adult male rats that received a moderate TBI.” → A citation should be added at the end of the sentence.
- **Line 311:** “Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates.” → A citation should be added at the end of the sentence.
- **Line 324:** “Additionally , numerous studies have demonstrated that aged rodents, the elderly have slower plasticity rates because long-term potentiation (LTP) is decreased while long-term depression (LTD) is enhanced (Rapp et al., 1987; Ridderinkhof and Krugers, 2022)”. -> Again, Ridderinkhof and Krugers (2022 is a review paper. The author can cite the review paper as well, but the author needs to add the original paper. Eg). In parallel, LTP, an important experimental model for learning and memory (Nabavi et al., **2014**), at peri-threshold stimulation paradigms is decreased in aged rodents, while LTD is enhanced (Burke and Barnes, **2006**; Kumar, **2011**; Sikora et al., **2021**).

Final Recommendation
Accept with major revisions (acceptance is contingent upon satisfactory completion of the required revisions)

This is a very well researched paper with wonderfully implemented edits. Some constructive feedback:

1. Consider a comparative table to summarize key differences in neuroplastic mechanisms across the lifespan as a quick reference guide for the reader.
2. Figure 1 is well integrated in the text. Make sure you have permission from Harvard University to utilize in your publication (is it open access free to use?)
3. Line 335 is an example of when explicitly writing "a study by Winter" you do not have to use paratheses to site them again at the end of the sentence.
4. What does "age-specific rehabilitation" look like? Be more specific here.

Final decision: **Accept with minor revisions.**

I have reviewed Jadah and Daniel's comments and the updated manuscript and responses to the initial feedback. The author has done a relatively good job in responding to the initial comments However, some comments remain and some new ones have been appropriately raised by reviewers. After addressing the new (and some same from first round...) comments raised by the reviewers, I would say the paper is at a "Accept with minor revisions" stage.

My additional comments from an editorial perspective:

- There are no methods in the paper. Can authors please include information on how this review was conducted? eg. What keywords were used in the search? What databases were searched? What types of articles were included?
- Change Conclusion to "Discussion", and do not start with "In conclusion" as that is not how journal articles are written. A short Conclusion section (approx a paragraph) can be included at the paper's end, after the Discussion as a concise summary of the findings and their implications to this research area.
- The Discussion does not explore and expand on the paper's findings enough. Authors needs to show what their work adds to the existing literature, keeping in mind the aim of the paper: "This literature review examines the variations in brain plasticity throughout an individual's life... following a TBI". The Discussion should link back to this aim.
- Include strengths and limitations of the study in the Discussion.

Variations in neuroplasticity following Traumatic Brain Injury: A Comparison across the Life Span

Jagriti Khare

Dover Court International School, Singapore

Dr Kimberly Clark

Abstract

Traumatic brain injury (TBI) represents a significant worldwide health concern, resulting in long-term disability and/or mortality. Annually, it is estimated that approximately 64-74 million individuals experience a TBI, impacting cognition, emotions, and motor abilities throughout all life stages. Recovery depends largely on neuroplasticity, which enables the brain to reorganise itself through the formation of new neural connections, although the effectiveness of this process differs with age. The effect of TBI on plasticity is not properly understood across different age groups. This literature review examines the variations in brain plasticity throughout an individual's life (specifically children, adolescents, adults, and the elderly) following a TBI. Evidence indicates that, although children and adolescents exhibit increased neural adaptability and higher plasticity, it does not consistently lead to the most effective functional recovery. Conversely, adults and seniors typically exhibit more limited yet stable plasticity and reorganization. This is based on the analysis of current academic research, including neuroimaging studies, clinical trials, and long-term examinations of TBI and neuroplasticity among various age groups. In general, it is crucial to understand age-related variations in neuroplasticity following a TBI. This is essential for developing recovery strategies and enhancing future clinical and research techniques related to TBI.

Keywords: traumatic brain injury, neuroplasticity, age, children, adolescents, adults, elderly, recovery

Methodology

A narrative literature review approach was used here to investigate age-related variations in neuroplasticity following TBI. Some of the databases used for the literature searches were Google Scholar, PubMed, ScienceDirect, and APA PsycNet. Key terms included traumatic brain injury, TBI, neuroplasticity, ageing, children, adolescents, adults, elderly, recovery, long-term depression, long-term potentiation, brain-derived neurotrophic factor (BDNF), diffuse brain injury, synaptogenesis, etc. Studies that were analysed include peer-reviewed articles, longitudinal studies, clinical studies, neuroimaging studies, and experimental studies published primarily in English. Articles that specifically examined neuroplastic mechanisms and recovery outcomes following TBI across different age groups were prioritised.

Introduction

Traumatic brain injury (TBI) is a major global health problem and it is one of the leading causes of mortality (Maas et al., 2017) across all age groups. It refers to alterations in brain function or other signs of brain disease caused by an external force, which can occur on the road, at home, at work, during war, or even while playing sports (Manley & Maas, 2013). This can lead to physical, social, cognitive and emotional impairments of different severities. Following a brain injury, the brain undergoes a process called neuroplasticity, resulting in adaptive functional and structural modifications. It is described as the nervous system's capacity to reorganise its structure, functions, or connections in response to internal or external stimuli following injuries like TBI or stroke (Puderbaugh & Emmady, 2025). This process is supported by molecular and cellular mechanisms such as synaptic plasticity (e.g., long-term potentiation and depression), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and structural changes including synaptogenesis, all of which may vary across the lifespan (Bear & Malenka, 1994; Gustafsson et al., 2021; Su et al., 2016).

According to Zamani et al. (2020), the effects of TBI vary across developmental stages. While children's brains generally show higher flexibility, some of the cognitive and behavioural abnormalities only emerge during adolescence or early adulthood.

In this review, children are defined as individuals aged 0-12, adolescents as 13-18 years, adults as 19-64 years, and the elderly as 65 years and above.

In children, early TBI can disrupt normal brain function and hinder the development of neural networks crucial for social behaviour. However, the effectiveness of neuroplasticity in helping recovery depends on various factors such as pre-existing conditions, individual characteristics, the circumstances surrounding and following the injury, age and the nature of the injury itself (Zamani et al., 2020)

In adolescents, TBI can lead to consistent executive functioning deficits in everyday life (Catharine et al., 2019). Linking to plasticity, it may not always be defined as beneficial for adolescents as it consists of multiple processes needed to be regulated (Giza & Prins, 2006).

In adults, TBI increases the risk of neurodegradation which could include Alzheimer's. Consequently, this could negatively affect the recovery of adults in the cognitive and neurological aspects (Sivaprasad et al., 2005; Rajan, 2025). However, full recovery remains possible, depending on the severity of the injury and other personal factors.

For the elderly, Tan et al. (2025) found that across 18 of their studies, fewer than half regained full functional independence, which shows that older adults have the greatest difficulty recovering completely compared to other age groups.

Understanding how neuroplasticity functions across developmental stages is crucial for evaluating recovery results following TBI in light of these age-related differences. This literature review will contrast a variety of academic studies examining children, adolescents, adults and the elderly. It focuses on how brain plasticity is affected following TBI. The paper will first look at neuroplastic responses in children and adolescents and then analyse recovery patterns in adults and the elderly. Each component will assess how the developmental stage affects recovery outcomes by

interacting with variables such as injury severity and timing of injury. Furthermore, in order to find broad trends in neuroplasticity throughout the lifetime, the review will synthesise the similarities and differences between age groups. Finally, this paper will analyse how this information can help to provide more insight into future endeavours in this specific field of neuroscience.

Traumatic brain injury and neuroplasticity

Neuroplasticity underlies recovery following TBI, but the extent of these neural changes is influenced by factors such as age, injury severity, and stage of rehabilitation.

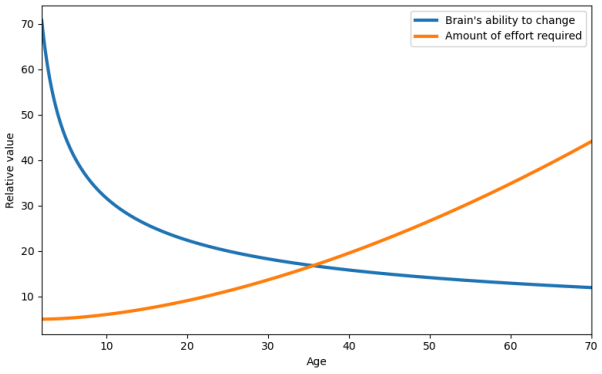

Figure 1. Author-generated illustration showing the inverse relationship between the brain's capacity for change and the effort required for such change across age. The figure is adapted conceptually from Levitt (2019).

Existing literature suggests that the brain's capacity to adapt in response to experiences diminishes with age, while the effort required to achieve functional recovery increases (Figure 1). This indicates that younger individuals may exhibit greater neuroplastic potential following TBI, enabling more efficient neural reorganization whereas older individuals may require more intensive rehabilitation to achieve comparable recovery outcomes.

In the context of TBI, immediately after injury, there is cell death, along with a reduction in cortical inhibitory pathways for 1 to 2 days, which may facilitate the recruitment of new neural networks and promote early circuit reorganization (Nahmani & Turrigiano, 2014; Su et al., 2016). Cortical circuits gradually shift from inhibitory to excitatory activity; surviving neurons initiate axonal sprouting and synaptogenesis, forming new connections that help repair damaged circuits and restore functional pathways (Su et al., 2016). Neuronal and non-neuronal cells, including endothelial progenitors, glial cells, and inflammatory cells, are recruited to replace weakened cells and support revascularization (Burda & Sofroniew, 2014; Su et al., 2016). Additionally, these cells promote gliotic scar formation—a process where dense glial tissue isolates the injury but also inhibits the regrowth of neurons (Wang et al., 2018). At the cellular level, microglia and astrocytes initiate an inflammatory response after injury. These cells will then secrete a variety of cytokines, chemokines, and growth factors, which determine the extent of the damage and the following repair (Karve et al., 2016). Circulating endothelial progenitor cells (EPCs) may be crucial for both healthy and pathological angiogenesis in adults (Wei et al., 2010). Angiogenesis is a complex process of forming new blood vessels and is essential for growth and balance (Swerlick, 1995). It is regulated by molecular signals such as vascular endothelial growth factor, which help in

endothelial cell proliferation, promoting angiogenesis (Johnson & Wilgus, 2014). Additionally, glial cells actively influence neuroplasticity, which enables highly adaptable control over neuronal excitability, synaptic transmission, and network synchronization (Dzyubenko and Hermann, 2023). At the circuit level, these processes lead to large-scale cortical reorganization, including the recruitment of intracortical circuits to support recovery (Mohammed & Hollis, 2018).

Therefore, these processes, including angiogenesis supported by EPCs and the neuroplasticity influenced by glial cells, together play a crucial role in recovery after TBI. Several weeks after the injury, increased expression of synaptic markers and enhanced axonal sprouting is observed. This enables neural remodeling and cortical reorganization that contribute to functional recovery (Su et al., 2016).

In individuals with brain injuries, adaptive neuroplasticity can be modulated by rehabilitation procedures, increasing everyday life activities and lowering motor impairment (Johnson and Cohen, 2022). Therefore, after TBI, rehabilitation can be done, which is dependent on the recovery stage of the patient, such as immediately after the injury (acute stage), the main goal of the treatment would be to prevent injury and calm the patient down. After this stage (the chronic stages of recovery), many rehabilitation strategies can be implemented. However, recovery is complicated by age-related variations in plasticity, with younger people showing more plasticity and older adults showing less plasticity and a higher risk of maladaptive alterations (Rajan, 2025).

In general, neuroplastic mechanisms promote recovery after traumatic brain damage because they allow for the gradual structural and functional reorganization of neuronal networks. To enhance adaptive neural pathways and improve function, biological processes such as synaptogenesis, angiogenesis, and glial cell regulation work together with rehabilitation interventions. The efficacy of these neuroplastic mechanisms varies because age, the severity of the injury, and the stage of recovery all affect how well rehabilitation can support long-term recovery results.

Neuroplasticity in Children and Adolescents after TBI

In children and adolescents, the degree and effectiveness of neuroplasticity after TBI are strongly dependent on developmental stage and injury severity. Neuroplasticity after TBI differs significantly between children and adolescents, demonstrating that the degree and efficacy of plasticity vary across the lifetime. Various processes play a role in this mechanism of neuroplasticity of younger individuals, such as the excessive production and removal of neurons and synapses, along with the stabilization of synapses depending on the activity (Johnston et al., 2009). The activity-dependent stabilization is the strengthening of circuits that are repeatedly activated, shaping long-term connectivity (Chaudhury et al., 2016). The pediatric brain exhibits greater neuroplasticity compared to the adult brain, facilitating the rapid acquisition of new skills and the recovery from cerebral injuries (Johnston et al., 2009). Mechanistically, this heightened plasticity is supported by LTP (Long-term potentiation) and LTD (Long-term depression). LTP is a process that helps in synaptic enhancement and increases synaptic strength (Bear & Malenka, 1994; Johnston et al., 2009), whereas LTD is the process of the reduction of synaptic efficacy (Bliss & Cooke, 2011). Interruption of these processes by TBI in children can disrupt normal circuit maturation, leading to prolonged cognitive and adaptive impairments. Additionally, experimental animal

models of TBI using juvenile rats show that injury alters brain-derived neurotrophic factor (BDNF), a crucial factor for activity-dependent synaptic plasticity. These changes are observed in both mRNA and protein levels in the hippocampal and cortical areas following the injury (Gustafsson et al., 2021). This suggests that the developing brain may sometimes recover slowly or incompletely, possibly indicating age-related disruptions in synaptic plasticity mechanisms, rather than solely reflecting observed cognitive deficits.

However, the molecular mechanisms for synapses depending on activity have yet to be elucidated (Johnston et al., 2009). Age of injury is a very important factor because younger children have a higher risk of diffuse brain injury, the process of widespread axonal damage in the aftermath of TBI (Su & Bell, 2016), and this can have dangerous effects on their growth and development (Treble-Barna et al., 2017). The severity of TBI is also a crucial factor, as significant severity is associated with long-term damage (Treble-Barna et al., 2017). A study showed that children who had a severe TBI when they were young showed impairments in adaptive functioning as a result of neuropsychological tests and interviews after 6.9 years of injury (Tomar et al., 2018). Observing the results, the children in this study showed deficiencies in processing speed and fluid reasoning. Slowing down of processing speeds can make it difficult to do everyday tasks such as understanding verbal remarks or dealing with a fast work environment (Treble-Barna et al., 2017). Integrating both age and severity, younger age at injury was linked to little to no recovery for children who have severe TBI, but older children showed better results. Although newborns (ages 0-2.11 years) with moderate TBI had a worse outcome than older children with injuries of similar severity (Anderson et al., 2005).

During adolescence, ongoing synaptic pruning (the targeted elimination of functional synapses; Sakai, 2020) and cortical maturation (enabling cognitive and behavioral functioning, measured by thickness and curvature; Deoni et al., 2015) make the brain more sensitive to TBI, resulting in more consistent deficits compared with injuries sustained earlier in childhood. Due to continuous neuronal growth during this delicate developmental stage, reviews by Mulligan et al. (2022) and Chan et al. (2024) show that traumatic brain damage received throughout adolescence is associated with worse recovery results than injuries sustained earlier in childhood. Through the process of synaptic pruning, cortical structures undergo significant remodeling. This process results in a decrease in cortical gray matter alongside an acceleration of axon density and myelination - the formation of a specialized myelin membrane around axons – leading to an increase in white matter volume. These processes can lead to better cognitive abilities and social cognition (Mulligan et al., 2022). Therefore, any interruptions to these processes can lead to harmful consequences (Chan et al., 2024). These developmental processes are closely connected to underlying synaptic plasticity mechanisms, and disruptions with pruning and myelination may impair activity-dependent plasticity. Thus, this contributes to poorer recovery outcomes following TBI during adolescence (Sakai, 2020; Mulligan et al., 2022).

Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be associated with mainly improved functional outcomes; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition. Also, a population-based outcome study conducted in Norway

presented that 87% of all the children/adolescents included in the study with a mild TBI showed improved recovery compared to the 59% of adolescents with severe TBI (Olsen et al., 2022).

Overall, the relationship between developmental stage and injury severity shapes neuroplasticity in children and adolescents after TBI. Disturbances during crucial stages like adolescence can result in long-lasting neurological and cognitive impairments even if ongoing neuronal reorganization in the growing brain might aid in healing. As a result, recovery results depend not only on neuroplastic potential but also on the timing and severity of the damage.

Neuroplasticity in Adults after TBI

In adults, neuroplasticity following TBI is present but happens more slowly and with greater limitations compared to earlier stages of development. In order to preserve cognitive function, adults rely on compensatory processes (Rajan, 2025), which occur when the body tries to readjust and compensate for the stresses it is under (Kauffman, 2015). Even though plasticity decreases with age, new neurons can still be created throughout life; therefore, it does not completely stop generating (Rajan, 2025). Mechanistically, adult neuroplasticity involves activity-dependent processes such as LTP. A study conducted by Weston et al. (2021) investigated adult male rats that received a moderate TBI. Measurements of LTP showed prolonged impairment, which worsened between 30-60 days (Weston et al., 2021). In addition, adult TBI causes a neurological deficit through complex mechanisms including glutamate excitotoxicity, inflammation, demyelination, programmed cell death and the development of edema. This is caused by glial cells and they play a crucial role in the CNS response, damage control and regeneration. In response to tissue damage, these cells activate, undergo hypertrophy and proliferate, eventually forming a glial scar. This scar acts as a barrier within the damaged tissue, protecting the CNS during the acute phase following the injury (Amlerova et al., 2024). These molecular and cellular mechanisms provide a biological basis for the partial functional recovery seen in adults.

The brain's tendency toward neuroplasticity enables it to partially compensate for these disruptions caused by TBI by creating new connections and rerouting neural pathways. Neuroplasticity plays a role in both compensatory behavior and potential functional maladaptation in the process of recovering from brain damage in adults. Compensating is when the brain shifts activities to unaffected areas to retain or restore function after brain damage. This adaptive reaction often results in enhanced performance in previously degraded tasks. On the other hand, maladaptation refers to the traits or characteristics that reduce fitness or performance in a population (Brady et al., 2019) and can occur when compensatory processes inadvertently prevent optimal healing (Zotey et al., 2023). There is also a significant difference related to recovery and severity of TBI in adults. A study conducted by Othman et al. (2022) showed that out of all the adults with mild TBI, 19.2% showed cognitive damage 3 months after the injury and 19.2% showed neuropsychiatric manifestations. After 6 months of injury, most of the patients exhibited recovery, while some continued to experience cognitive damage (Othman et al., 2022). However, in the same study by Othman et al. (2022), out of all adults with moderate TBI, 39.3% exhibited cognitive impairment, whereas 25% showed neuropsychiatric manifestations (such as agitation, depression, anxiety, apathy, hallucinations, impulsivity, and aggression; Maristany et al., 2024) after 3 months of

having the injury. In the case of 6 months post injury, none of the patients showed continued cognitive damage or neuropsychiatric manifestations (Othman et al., 2022). According to a review by Wilkins et al. (2019), long-term results after severe traumatic brain damage might be better than previously proposed recovery models. In the study conducted by Wilkins et al. (2019), it is seen that the mortality rate of severe TBI patients was high 3 months after injury; however, for long-term TBI patients, there was significant improvement in functional results 3-24 months after injury which shows that the long-term prognosis in adults with severe TBI was higher than expected.

After TBI, adults' neuroplasticity is generally slower and less extensive than that of younger individuals; however, compensatory neuronal reorganization still allows a partial functional recovery. The degree of an injury has a significant impact on recovery results: minor injuries typically improve more quickly, whereas severe injuries show gradual, long-term improvements. Adults still have some capacity for brain adaptation, although the degree and quality of recovery are influenced by both maladaptive and compensatory processes.

Neuroplasticity in the Elderly after TBI

Older adults exhibit the slowest and least effective neuroplastic responses after a TBI, leading to poorer functional outcomes, higher mortality rates and higher vulnerabilities to even mild injuries. Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates. Atrophy is a condition where the loss of brain cells and neural connections causes brain tissues to decrease (Joseph et al., 2023), and this occurs in the brain as people age. It causes the distance between the brain and skull to expand. This increases the risk of shearing damage to the dural vessels. Also, due to their diminished cerebral reserve, elderly individuals are more susceptible to mild injuries, and many of them have underlying medical issues that are concealed by TBIs (Prasad et al., 2018; Chan et al., 2024). A study conducted by Race et al. (2024) on rodents came to the conclusion that aged rodents had difficulties related to reduced neuroplasticity, dysregulated inflammation, and age-regulated cellular changes, which can affect their recovery after TBI.

In older patients, this leads to poor functional results and higher mortality rates (Chan et al., 2024). Additionally, numerous studies have demonstrated that aged rodents have slower plasticity rates because LTP is decreased while LTD is enhanced (Burke and Barnes, 2006; Kumar, 2011; Sikora et al., 2021; Ridderinkhof and Krugers, 2022). Impaired glutamatergic transmission (the synaptic signaling between neurons mediated by glutamate; Zhou & Danbolt, 2014), cholinergic hypofunction (the reduction of cholinergic system activity; Schliebs and Arendt, 2010), and significant changes in the dopaminergic system (the neural signalling mediated by dopamine that regulates movement, reward and cognition; Klein et al., 2019) all hinder inter-neuronal interaction and may contribute to learning and memory deficits as well as decreased cognitive flexibility as age increases (Wong et al., 2021; Ridderinkhof and Krugers, 2022). These changes reflect a decline in the efficiency of synaptic plasticity mechanisms, which could limit the brain's ability for flexible reorganisation after TBI in older adults. A review by Winter et al. (2022) found consistent evidence, considering the severity of TBI, showing worse results for older patients, even though they have milder TBIs. In a

comparison of older and younger adults with mild TBI, Thompson et al. (2020) discovered that older adults consistently exhibited lower overall physical health-related quality of life than their counterparts from one week to one year after injury (Thompson et al., 2020; Chan et al., 2024). Older patients with severe TBI exhibited unfavorable results and a very high mortality rate of 83.3% (Utomo et al., 2009; Chan et al., 2024). Moreover, the treatment of elderly TBI lacks precise guidelines, and those that do exist are mainly based on research involving younger people (Chan et al., 2024).

In comparison to younger age groups, neuroplasticity is generally significantly diminished in the elderly following TBI, which results in a delayed and less successful recovery. Even in mild TBI patients, age-related brain alterations, reduced cerebral reserve, and altered neurotransmission restrict functional results and increase vulnerability to injury. Because rehabilitation programs are not sufficiently tailored to the cognitive and functional needs of older adults (e.g. slower recovery rates, higher fall risk), older persons experience greater mortality rates, worse recovery, and more difficulties.

Discussion

Although each age group demonstrates different neuroplastic responses following TBI, there are several common trends that emerge across the lifespan. The evidence reviewed suggests that recovery does not depend solely on the degree of neuroplasticity but also by factors such as developmental stage, injury severity, and age-related biological mechanisms. To provide a clearer comparison of the findings, Table 1 summarises the key differences across different stages of life

Lifespan stage	**Neuroplasticity level**	**Key mechanisms**	**Typical TBI response**	**Main limiting factors**
Children and adolescents	High but developmentally sensitive	Synaptogenesis, synaptic pruning, LTP/LTD, activity-dependent stabilisation, BDNF-mediated plasticity	Potential for strong recovery, but risk of disrupted development if injury is severe or early	Injury during critical developmental windows, diffuse brain injury, severity of TBI
Adults	Moderate, declining with age	Compensatory reorganisation, LTP-dependent plasticity, limited neurogenesis, glial responses	Partial recovery via rerouting and compensation	Excitotoxicity, inflammation, demyelination, slower synaptic remodelling

Elderly	low	Reduced LTP, increased LTD, neurotransmitter decline (dopamine, acetylcholine, glutamate), reduced cerebral reserve	Poorer recovery, higher mortality even in mild mortality	Brain atrophy, vascular fragility, reduced synaptic efficiency comorbidities

Table 1. Comparison of neuroplastic mechanisms and recovery characteristics across the lifespan following TBI

A key contribution of this review is the integration of evidence directly addressing its aim: to examine variations in neuroplasticity across the lifespan following TBI. The findings show that while neuroplasticity is a universal biological response to TBI, its nature and functional outcome differ significantly between children, adolescents, adults and the elderly. Children and adolescents demonstrate heightened synaptic activity, BDNF-mediated plasticity, and synaptogenesis, but early or severe TBI can disrupt healthy-brain maturation leading to deficits (Anderson et al., 2005; Mulligan et al., 2022). In adults, neuroplasticity remains in a more limited and compensatory form where the same mechanisms that support recovery can sometimes cause dysfunctional pathways (Zotey et al., 2023). For the elderly, there is reduced LTP, neurotransmitter decline, and brain atrophy which produces a poor neuroplastic environment for recovery even after mild TBI (Burke and Barnes, 2006; Chan et al., 2024). Clinical data for this group is largely extrapolated from younger patient data which shows a large gap in research. Altogether, these findings directly address the aim of this paper.

For rehabilitation strategies, the primary goal of treatment during the acute phase (which occurs in the hours right after an accident) is to stabilize the patient and concentrate on preventing additional harm. The results of a study done by Winter et al. (2022) verify that age moderates the impact of injury severity on functional trajectory. Therefore, an individual's age at the time of injury determines the predictive validity of injury severity for functional trajectories. However, most rehabilitation strategies are based on severity and are dependent on the recovery stage of the patient (Chan et al., 2024). These results point to a discrepancy between current clinical practice and study findings. Incorporating both age and injury severity into rehabilitation planning allows clinicians to optimise recovery outcomes. By tailoring interventions to a patient's developmental stage and the extent of their injury, functional improvements can be enhanced and long-term deficits reduced.

Strengths and Limitations

A key strength of this review is its holistic and integrative scope. By synthesising evidence across molecular and cellular levels of analysis in 4 different age groups, this review provides a comprehensive framework for understanding age-dependent neuroplasticity after TBI. The inclusion of both human and animal studies strengthens the mechanistic explanations offered in the paper.

However, the limitations must be acknowledged. The review is narrative rather than systematic so the search and selection process is not entirely replicable, introducing the possibility of selection bias. Second, much of the mechanistic evidence such as evidence regarding LTP, LTD, and BDNF is drawn from animal models (primarily rodents) which may not fully represent human neurophysiology. Additionally, only a few of the studies compared neuroplastic outcomes across all 4 age groups under controlled conditions. This means that the cross-group comparisons are inferential rather than directly evidenced.

Conclusion

Overall, neuroplasticity provides an important biological framework for recovery after TBI; however, both the developmental stage and severity of the injury influence the extent to which functional recovery occurs. While these neuroplastic mechanisms operate throughout the lifespan, much of the existing evidence reflects age-related differences in functional outcomes, which are likely influenced by, rather than direct measures of, underlying neuroplastic processes (Su et al., 2016). Younger individuals show greater baseline plasticity but this does not always lead to better recovery. Early disruptions can interfere with important development processes (Anderson et al., 2005; Mulligan et al., 2022). Adults show moderate compensatory reorganization; and the elderly display the most limited neuroplastic capacity. These age-related differences have meaningful implications for clinical practice, particularly in rehabilitation. Future research should, therefore, prioritise age-specific longitudinal studies, greater inclusion of elderly populations and the development of targeted therapeutic strategies that use neuroplastic mechanisms at every stage of life.

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Variations in neuroplasticity following Traumatic Brain Injury: A Comparison across the Life Span

Jagriti Khare

Dover Court International School, Singapore

Dr Kimberly Clark

Abstract

Traumatic brain injury (TBI) represents a significant worldwide health concern, resulting in long-term disability and/or mortality. Annually, it is estimated that approximately 64-74 million individuals experience a TBI, impacting cognition, emotions, and motor abilities throughout all life stages. ~~The main causes of TBI are demographic ageing, increased use of motorized vehicles, and road traffic incidents~~ Recovery depends largely on neuroplasticity, which . ~~Neuroplasticity~~ enables the brain to reorganise itself through the formation of new neural connections, , ~~essential for recovery after a TBI,~~ although the effectiveness of this process differs with age. The effect of TBI ~~traumatic brain injury~~ on plasticity is not properly understood across different age groups. This literature review examines the variations in brain plasticity throughout an individual's life (specifically children, adolescents, adults, and the elderly) following a TBI~~traumatic brain injury~~. Evidence indicates that, although children and adolescents exhibit increased neural adaptability and higher plasticity, it does not consistently lead to the most effective functional recovery. Conversely, adults and seniors typically exhibit more limited yet stable plasticity and reorganization. This~~This theory~~ is based on the analysis of current academic research, including neuroimaging studies, clinical trials, and long-term examinations of TBI and neuroplasticity among various age groups. In general, it is crucial to understand age-related variations in neuroplasticity following a TBI. This is essential for developing recovery strategies and enhancing future clinical and research techniques related to TBI~~traumatic brain injury~~.

Keywords: traumatic brain injury, neuroplasticity, age, children, adolescents, adults, elderly, recovery

Methodology

A narrative literature review approach was used here to investigate age-related variations in neuroplasticity following TBI. Some of the databases used for the literature searches were Google Scholar, PubMed, ScienceDirect, and APA PsycNet. Key terms included traumatic brain injury, TBI, neuroplasticity, ageing, children, adolescents, adults, elderly, recovery, long-term depression, long-term potentiation, brain-derived neurotrophic factor (BDNF), diffuse brain injury, synaptogenesis, etc. Studies that were analysed include peer-reviewed articles, longitudinal studies, clinical studies, neuroimaging studies, and experimental studies published primarily in English. Articles that specifically examined neuroplastic mechanisms and recovery outcomes following TBI across different age groups were prioritised.

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Introduction

Traumatic brain injury (TBI) is a major global health problem and it is one of the leading causes of mortality (Maas et al., 2017) across all age groups. It refers to alterations in brain function or other signs of brain disease caused by an external force, which can occur~~the alteration of how the brain functions or other signs of brain disease caused by an outside force that can happen~~ on the road, at home, at work, during war, or even while playing sports (Manley & Maas, 2013). This can lead to physical, social, cognitive and emotional impairments of different severities. Following a brain injury, the brain undergoes a process called neuroplasticity, ~~which causes the brain to~~resulting ~~undergo~~in adaptive functional and structural modifications. It is described as the nervous system's capacity to ~~reorganize~~ reorganise its structure, functions, or connections in response to internal or external stimuli following injuries like TBI or stroke (Puderbaugh & Emmady, 2025~~3~~). This process is supported by molecular and cellular mechanisms such as synaptic plasticity (e.g., long-term potentiation and depression), neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and structural changes including synaptogenesis, all of which may vary across the lifespan (Bear & Malenka, 1994; Gustafsffson et al., 2021; Su et al., 2016).

According to Zamani et al. (2020), the effects of TBI ~~traumatic brain injury~~ vary across ~~present variably across~~ developmental stages. ~~, with some cognitive and behavioral abnormalities only appearing around adolescence or early adulthood, even though children's brains usually show higher flexibility~~While children's brains generally show higher flexibility, some of the cognitive and behavioural abnormalities only emerge during adolescence or early adulthood.

In this review, children are defined as individuals aged 0-12, adolescents as 13-18 years, adults as 19-64 years, and the elderly as 65 years and above.

~~In children, early traumatic brain injury can affect how the brain normally functions and the creation of neural networks which are needed for a variety of different social behaviours; however, plasticity is affected based on multiple factors for example, existing conditions, individual traits, circumstances before and after the injury, age, and the type of injury itself, which can impact the prolonged effects of pediatric TBI (Zamani et al., 2020).~~
In children, early TBI can disrupt normal brain function and hinder the development of neural networks crucial for social behaviour. However, the effectiveness of neuroplasticity in helping recovery depends on various factors such as pre-existing conditions, individual characteristics, the circumstances surrounding and following the injury, age and the nature of the injury itself (Zamani et al., 2020)

In adolescents, TBI ~~traumatic brain injury~~ can lead to consistent~~tant~~ executive functioning deficits in everyday life (Catharine et al., 2019). Linking to plasticity, it may not always be defined as beneficial for adolescents as it consists of multiple processes needed to be regulated (Giza ~~&and~~ Prins, 2006).

In adults, TBI increases the risk of neurodegradation which could include Alzheimer's. Consequently, ~~Therefore,~~ this could negatively affect the recovery of adults in the cognitive and neurological aspects (Sivaprasad et al., 2005; Rajan, 2025). ~~However,but~~ full

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recovery remains ~~is completely~~ possible, ~~(~~depending on the severity of the injury and other personal factors~~)~~.

For the elderly, Tan et al. (2025) found that across 18 of their studies, fewer than half regained full functional independence, which shows that older adults have the greatest difficulty recovering completely compared to other age groups.

Understanding how neuroplasticity functions across developmental stages is crucial for evaluating recovery results following TBI ~~traumatic brain injury (TBI)~~ in light of these age-related differences. This literature review will contrast a variety of academic studies examining children, adolescents, adults and the elderly. It focuses on how brain plasticity is affected following TBI~~traumatic brain injury~~. The paper will first look at neuroplastic responses in children and adolescents and then analyse recovery patterns in adults and the elderly. Each component will assess how the developmental stage affects recovery outcomes by interacting with variables such as injury severity and timing of injury. Furthermore, in order to find broad trends in neuroplasticity throughout the lifetime, the review will synthesise the similarities and differences between age groups. Finally, this paper will analyse how this information can help to provide more insight into future endeavours in this specific field of neuroscience.

Traumatic brain injury and neuroplasticity

Neuroplasticity underlies recovery following TBI~~traumatic brain injury~~, but the extent of these neural changes is influenced by factors such as age, injury severity, and stage of rehabilitation.

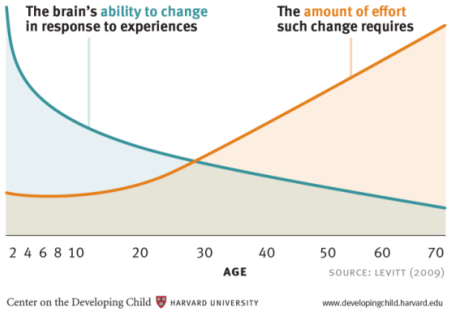

Figure 1. Age-related neuroplasticity graph
~~Source: Harvard University (2024)~~

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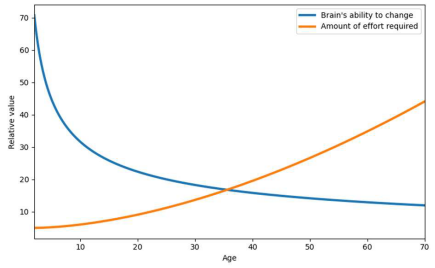

Figure 1. Author-generated illustration showing the inverse relationship between the brain's capacity for change and the effort required for such change across age. The figure is adapted conceptually from Levitt (2019).

~~As seen in Figure 1, Existing literature suggests that t~~The brain's capacity to adapt in response to experiences diminishes with age, while the effort required to achieve functional recovery increases (Figure 1) ~~(Harvard University, 2024)~~. This indicates that younger individuals may exhibit greater neuroplastic potential following TBI, enabling more efficient neural reorganizsation whereas older individuals may require more intensive rehabilitation to achieve comparable recovery outcomes.

In the context of TBI, immediately after injury, there is cell death, along with a reduction in cortical inhibitory pathways ~~,~~ for 1 to 2 days, which may facilitate the recruitment of new neural networks and promote early circuit reorganization (Nahmani & Turrigiano, 2014; Su et al., 2016). Cortical circuits gradually shift from inhibitory to excitatory activity; surviving neurons initiate axonal sprouting and synaptogenesis, forming new connections that help repair damaged circuits and restore functional pathways (Su et al., 2016). Neuronal and non-neuronal cells, including endothelial progenitors, glial cells, and inflammatory cells, are recruited to replace weakened cells and support revascularizsation (Burda & Sofroniew, 2014; Su et al., 2016). Additionally, these cells promote gliotic scar formation—a process where dense glial tissue isolates the injury but also inhibits the regrowth of neurons (Wang et al., 2018). ~~Neuronal and nonneuronal cells – such as the endothelial progenitors, glial cells, and inflammatory cells – are brought in to replace the weakened cells, promote gliotic scar formation – the creation of dense glial tissue that isolates the injury and inhibits regrowth of neurons (Wang et al., 2018) – and support revascularisation (Su et al., 2016).~~ At the cellular level, microglia and astrocytes initiate an inflammatory response after injury. These cells will then secrete a variety of cytokines, chemokines, and growth factors, which determine the extent of the damage and the following repair (Karve et al., 2016). Circulating endothelial progenitor cells (EPCs) may be crucial for both healthy and pathological angiogenesis in adults (Wei et al., 2010). Angiogenesis is a complex process of forming new blood vessels and is essential for growth and balance (Swerlick, 1995). It is regulated by molecular signals such as vascular endothelial growth factor, which help in endothelial cell proliferation, promoting angiogenesis (Johnson & Wilgus, 2014). ~~This is necessary for recovery after TBI.~~ Additionally, glial cells actively influence neuroplasticity, which enables highly~~extreme~~ adaptable control over neuronal excitability, synaptic transmission, and network synchronization (Dzyubenko and Hermann, 2023). At the circuit level, these processes lead to large-scale cortical reorganizsation, including the recruitment of intracortical circuits to support recovery (Mohammed & Hollis, 2018).

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Therefore, t~~T~~hese processes, including angiogenesis supported by EPCs and the neuroplasticity influenced by glial cells, together play a crucial role in recovery after TBI. Several weeks after the injury, increased expression of synaptic markers and enhanced axonal sprouting is observed. This enables neural remodelling and cortical reorganization that contribute~~s~~ to functional recovery ~~.~~(Su et al., 2016).

In individuals with brain injuries, adaptive neuroplasticity can be modulated by rehabilitation procedures, increasing everyday life activities and lowering motor impairment (Johns~~o~~en and Cohen, 2022). Therefore, after TBI, rehabilitation can be done, which is dependent on the recovery stage of the patient, such as immediately after the injury (acute stage), the main goal of the treatment would be to prevent injury and calm the patient down. After this stage (the chronic stages of recovery), ~~there can be~~ many rehabilitation strategies ~~put~~can ~~into~~be ~~place~~implemented. However, recovery is complicated by age-related variations in plasticity, with younger people showing more plasticity and older adults showing less plasticity and a higher risk of maladaptive alterations (Rajan, 2025).

In general, neuroplastic mechanisms promote recovery after traumatic brain damage because they allow for the gradual structural and functional reorganization of neuronal networks. To enhance adaptive neural pathways and improve function, biological processes such as synaptogenesis, angiogenesis, and glial cell~~In order to enhance adaptive neural pathways and increase functional improvement, biological processes like synaptogenesis, angiogenesis, and glial cell~~ regulation work together with rehabilitation interventions. The efficacy of these neuroplastic mechanisms varies because age, the severity of the injury, and the stage of recovery all affect how well rehabilitation can support long-term recovery results.

Neuroplasticity in Children and Adolescents after TBI

In children and adolescents, the degree and effectiveness of neuroplasticity after TBI are strongly dependent on developmental stage and injury severity. Neuroplasticity after TBI~~traumatic brain injury~~ differs significantly between children and adolescents, demonstrating that the degree and efficacy of plasticity vary across the lifetime. Various processes play a role in this mechanism of neuroplasticity of younger individuals, such as the excessive production and removal of neurons and synapses, along with the stabilization of synapses depending on the activity (Johnston et al., 2009). The activity-dependent stabilization is the strengthening of circuits that are repeatedly activated, shaping long-term connectivity (Chaudhury et al., 2016). The pediatric brain exhibits greater neuroplasticity compared to the adult brain, facilitating the rapid acquisition of new skills and the recovery from cerebral injuries (Johnston et al., 2009). Mechanistically, this heightened plasticity is supported by LTP (Long-term potentiation) and LTD (Long-term depression). LTP is a process that helps in synaptic enhancement and increases synaptic strength (Bear & Malenka, 1994; Johnston et al., 2009), whereas LTD is the process of the reduction of synaptic efficacy (Bliss & Cooke, 2011). Interruption of these processes by TBI in children can disrupt normal circuit maturation, leading to prolonged cognitive and adaptive impairments. Additionally, experimental animal models of TBI using juvenile rats show that injury alters brain-derived neurotrophic factor (BDNF), a crucial factor for activity-dependent synaptic plasticity. These changes are observed in

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both mRNA and protein levels in the hippocampal and cortical areas following the injury (Gustafsson et al., 2021). This suggests that the developing brain may sometimes recover slowly or incompletely, possibly indicating age-related disruptions in synaptic plasticity mechanisms, rather than solely reflecting observed cognitive deficits.

However, the molecular mechanisms for synapses depending on activity have yet to be elucidatedare still being found (Johnston et al., 2009). Age of injury is a very important factor because younger children have a higher risk of diffuse brain injury, the process of widespread axonal damage in the aftermath of TBI (E. Su &and Bell, 2016), and this can have dangerous effects on their growth and development (Treble-Barna et al., 2017). The severity of TBI is also a crucial factor, as significant severity is associated with long-term damage (Treble-Baerna et al., 2017). A study showed that children who had a severe TBI when they were young showed impairments in adaptive functioning as a result of neuropsychological tests and interviews after 6.9 years of injury (Chan et al., 2024; Tomar et al., 2018). Observing the results, the children in this study showed deficiencies in processing speed and fluid reasoning. Slowing down of processing speeds can make it difficult to do everyday tasks such as understanding verbal remarks or dealing with a fast work environment (Chan et al., 2024; Treble-Barna et al., 2017). Integrating both age and severity, younger age at injury was linked to little to no recovery for children who have severe TBItraumatic brain injury, but older children showed better results. Although newborns (ages 0-2.11 years) with moderate TBI had a worse outcome than older children with injuries of similar severity (Anderson et al., 2005).

During adolescence, ongoing synaptic pruning (the targeted elimination of functional synapses; Sakai, 2020) and cortical maturation (enabling cognitive and behavioral functioning, measured by thickness and curvature; Deoni et al., 2015) make the brain more sensitive to TBI, resulting in more consistent deficits compared with injuries sustained earlier in childhood. Due to continuous neuronal growth during this delicate developmental stage, reviews by Mulligan et al. (20224) and Chan et al. (2024) show that traumatic brain damage received throughout adolescence is associated with worse recovery results than injuries sustained earlier in childhood. Through the process of synaptic pruning, cortical structures undergo significant remodelling. ;This process and this results in a decrease in cortical gray graey matter alongside, an acceleration of axon density and myelination - , the formation of a specialized myelin membrane around axons –; leading to and an increase in white matter volume. These processes can lead to better cognitive abilities and social cognition (Mulligan et al., 20221). Therefore, any interruptions to these processes can lead to harmful consequences (Chan et al., 2024). These developmental processes are closely connected to underlying synaptic plasticity mechanisms, and disruptions with pruning and myelination may impair activity-dependent plasticity. Thus, this contributes to poorer recovery outcomes following TBI during adolescence (Sakai, 2020; Mulligan et al., 20221).

Comparing the severity of TBI, a study conducted by Kolstø et al. (2025) showed that a mild TBI in adolescence can be associated with mainly improved functional outcomes; however, patients (from age 0 to 17) showed more neurological damage and a more severe clinical condition (Kolstø et al., 2025). Also, a population-based outcome study conducted in Norway presented that 87% of all the children/adolescents included in the study with a mild TBI showed improved recovery compared to the 59% of adolescents with severe TBI (Olsen et al., 2022).

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Overall, the relationship between developmental stage and injury severity shapes neuroplasticity in children and adolescents after TBI~~traumatic brain injury~~. Disturbances during crucial stages like adolescence can result in long-lasting neurological and cognitive impairments even if ongoing neuronal reorganization in the growing brain might aid in healing. As a result, recovery results depend not only on neuroplastic potential but also on the timing and severity of the damage.

Neuroplasticity in Adults after TBI

In adults, neuroplasticity following TBI is present but happens more slowly and with greater limitations compared to earlier stages of development. In order to preserve cognitive function, adults rely on compensatory processes (Rajan, 2025), which occur when the body tries to readjust and compensate for the stresses it is under (Kauffman, 2015). Even though plasticity decreases with age, new neurons can still be created throughout life; therefore, it does not completely stop generating (Rajan, 2025). Mechanistically, adult neuroplasticity involves activity-dependent processes such as LTP. A study conducted by Weston et al. (2021) investigated adult male rats that received a moderate TBI. Measurements of LTP showed prolonged impairment, which worsened between 30-60 days (Weston et al., 2021). In addition, adult TBI causes a neurological deficit through complex mechanisms including glutamate excitotoxicity, inflammation, demyelination, programmed cell death and the development of edema. This is caused by glial cells and they play a crucial role in the CNS response, damage control and regeneration. In response to tissue damage, these cells activate, undergo hypertrophy and proliferate, eventually forming a glial scar. This scar acts as a barrier within the damaged tissue, protecting the CNS during the acute phase following the injury (Amlerova et al., 2024). These molecular and cellular mechanisms provide a biological basis for the partial functional recovery seen in adults.

The brain's tendency toward neuroplasticity enables it to partially compensate for these disruptions caused by TBI~~traumatic brain injury~~ by creating new connections and rerouting neural pathways. Neuroplasticity plays a role in both compensatory behavio~~u~~r and potential functional maladaptation in the process of recovering from brain damage in adults. Compensating is when the brain shifts activities to unaffected areas to retain or restore function after brain damage. This adaptive reaction often results in enhanced performance in previously degraded tasks. On the other hand, maladaptation refers to the traits or characteristics that reduce fitness or performance in a population (Brady et al., 2019) and can occur when compensatory processes inadvertently prevent optimal healing (Zotey et al., 2023). There is also a significant difference related to recovery and severity of TBI in adults. A study conducted by Othman et al. (2022) showed that out of all the adults with mild TBI, 19.2% showed cognitive damage 3 months after the injury and 19.2% showed neuropsychiatric manifestations. ~~(Othman et al., 2022).~~ After 6 months of injury, most of the patients exhibited recovery, while some continued to experience cognitive damage (Othman et al., 2022~~Chan et al., 2024~~). However, in the same study by Othman et al. (2022), out of all adults with moderate TBI, 39.3% exhibited cognitive impairment, whereas 25% showed neuropsychiatric manifestations (such as agitation, depression, anxiety, apathy, hallucinations, impulsivity, and aggression; Maristany et al., 2024) after 3 months of having the injury. In the case of 6 months post injury, none of the patients showed continued cognitive damage or neuropsychiatric manifestations (Othman et al., 2022). According to a review by Wilkins et al. (2019), long-term results

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after severe traumatic brain damage might be better than previously proposed recovery models. In the study conducted by Wilkins et al. (2019), it is seen that the mortality rate of severe TBI patients was high 3 months after injury; however, for long-term TBI patients, there was significant improvement in functional results 3-24 months after injury which shows that the long-term prognosis in adults with severe TBI was higher than expected. ~~(Wilkins et al., 2019).~~

After TBI~~traumatic brain injury (TBI)~~, adults' neuroplasticity is generally slower and less extensive than that of younger individuals; however, compensatory neuronal reorganization still allows a partial functional recovery. The degree of an injury has a significant impact on recovery results: minor injuries typically improve more quickly, whereas severe injuries show gradual, long-term improvements. Adults still have some capacity for brain adaptation, although the degree and quality of recovery are influenced by both maladaptive and compensatory processes.

Neuroplasticity in the Elderly after TBI

Older adults exhibit the slowest and least effective neuroplastic responses after a TBI, leading to poorer functional outcomes, higher mortality rates and higher vulnerabilities to even mild injuries. Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates. Atrophy is a condition where the loss of brain cells and neural connections causes brain tissues to decrease (Joseph et al., 2023), and this occurs in the brain as people age. It causes the distance between the brain and skull to expand. This increases the risk of shearing damage to the dural vessels. Also, due to their diminished cerebral reserve, elderly individuals are more susceptible to mild injuries, and many of them have underlying medical issues that are concealed by TBIs (Prasad et al., 2018; Chan et al., 2024). A study conducted by Race et al. (2024) on rodents came to the conclusion that aged rodents had difficulties related to reduced neuroplasticity, dysregulated inflammation, and age-regulated cellular changes, which can affect their recovery after TBI. ~~(Race et al., 2024).~~

In older patients, this leads to poor functional results and higher mortality rates (Chan et al., 2024). Additionally, numerous studies have demonstrated that aged rodents~~, the elderly~~ have slower plasticity rates because ~~long-term potentiation (~~LTP~~)~~ is decreased while ~~long-term depression (~~LTD~~)~~ is enhanced (Burke and Barnes, 2006; Kumar, 2011; Sikora et al., 2021; ~~Rapp et al., 1987;~~ Ridderinkhof and Krugers, 2022). ~~LTP is the lasting increase in synaptic strength caused by repeated high-frequency stimulation of input fibers (Shors & Matzel, 1997), whereas LTD is the reduction of efficacy in synaptic transmission (Bliss & Cooke, 2011).~~ Impaired glutamatergic transmission (the synaptic signal~~l~~ing between neurons mediated by glutamate; Zhou & Danbolt, 2014), cholinergic hypofunction (~~when~~ the reduction of cholinergic system ~~activityshows reduced function~~; Schliebs and Arendt, 2010), and significant changes in the dopaminergic system (the neural signalling mediated by dopamine that regulates movement, reward and cognition; Klein et al., 201~~9~~8) all hinder inter-neuronal interaction and may contribute to learning and memory deficits as well as decreased cognitive flexibility as age increases (Wong et al., 2021; Ridderinkhof and Krugers, 2022). These changes reflect a decline in the efficiency of synaptic plasticity mechanisms, which could limit the brain's ability for flexible reorganisation after TBI in older adults. A review by Winter et al. (2022) found consistent evidence, considering the severity of TBI, showing worse results for older

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patients, even though they have milder TBIs ~~(Winter et al., 2022)~~. In a comparison of older and younger adults with mild TBI, Thompson et al. (2020) discovered that older adults consistently exhibited lower overall physical health-related quality of life than their counterparts from one week to one year after injury (Thompson et al., 2020; Chan et al., 2024). Older patients with severe TBI exhibited unfavorable results and a very high mortality rate of 83.3% (Utomo et al., 2009; Chan et al., 2024). Moreover, the treatment of elderly TBI ~~traumatic brain injury~~ lacks precise guidelines, and those that do exist are mainly based on research involving younger people (Chan et al., 2024).

In comparison to younger age groups, neuroplasticity is generally significantly diminished in the elderly following TBI ~~traumatic brain injury (TBI)~~, which results in a delayed and less successful recovery. Even in mild TBI patients, age-related brain alterations, reduced cerebral reserve, and altered neurotransmission restrict functional results and increase vulnerability to injury. Because rehabilitation programs are not sufficiently tailored to the cognitive and functional needs of older adults (e.g. slower recovery rates, higher fall risk) ~~there are no age-specific rehabilitation ,criteria ,~~ older persons experience greater mortality rates, worse recovery, and more difficulties.

Discussion

Although each age group demonstrates different neuroplastic responses following TBI, there are several common trends that emerge across the lifespan. The evidence reviewed suggests that recovery does not depend solely on the degree of neuroplasticity but also by factors such as developmental stage, injury severity, and age-related biological mechanisms. To provide a clearer comparison of the findings, Table 1 summarises the key differences across different stages of life

Lifespan stage	**Neuroplasticity level**	**Key mechanisms**	**Typical TBI response**	**Main limiting factors**
Children and adolescents	High but developmentally sensitive	Synaptogenesis, synaptic pruning, LTP/LTD, acitivity-dependent stabilisation, BDNF-mediated plasticity	Potential for strong recovery, but risk of disrupted development if injury is severe or early	Injury during critical developmental windows, diffuse brain injury, severity of TBI
Adults	Moderate, declining with age	Compensatory reorganisation, LTP-dependent plasticity, limited neurogenesis, glial responses	Partial recovery via rerouting and compensation	Excitotoxicity, inflammation, demyelination, slower synaptic remodelling

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Elderly	low	Reduced LTP, increased LTD, neurotransmitter decline (dopamine, acetylcholine, glutamate), reduced cerebral reserve	Poorer recovery, higher mortality even in mild mortality	Brain autrophy, vascular fragility, reduced synaptic efficiency comorbidities

Table 1. Comparison of neuroplastic mechanisms and recovery characteristics across the lifespan following TBI

~~Conclusion~~

A key contribution of this review is the integration of evidence directly addressing its aim: to examine variations in neuroplasticity across the lifespan following TBI. The findings show that while neuroplasticity is a universal biological response to TBI, its nature and functional outcome differ significantly between children, adolescents, adults and the elderly. Childrem and adolescents demonstrate heightened synaptic acitivity, BDNF-mediated plasticity, synaptogenesis, but early or sever TBI can disrupt healthy-brain maturation leading to deficits (Anderson et al., 2005; Mulligan et al., 2022). In adults, neuroplasticity remains in a more limited and compensatory form where the same mechanisms that support recovery can sometimes cause dysfunctional pathways (Zotey et al., 2023). For the elderly, there is reduced LTP, neurotransmitter decline, and brain atrophy which produces a poor neuroplastic environment for recovery even after mild TBI (Burke and Barnes, 2006; Chan et al., 2024). Clinical data for this group is largely extrapolated from younger patient data which shows a large gap in research. Altogether, these findings directly address the aim of this paper.

~~In conclusion, neuroplasticity provides an importantthe biological frameworkbasis for recovery after TBItraumatic brain injury; however, both the the developmental stage and the severity of the injury influence the extent to which functional recovery occurs its effectiveness. While these neuroplastic mechanisms develop throughout the lifespan, much of the existing evidence reflects age-related differences in functional outcomes, which are likely influenced by, rather than direct measures of, underlying neuroplastic processes (Su et al., 2016). In individuals of all ages, TBI gives rise to a series of plastic changes (such as synaptogenesis, axonal growth, and cortical reorganization) that may help in functional recovery (Su et al., 2016). Even though this mechanism is common, the ability to tackle neuroplasticity changes throughout life. Children and teenagers usually exhibit higher baseline plasticity because their brains are still developing, but serious injuries in early childhood or adolescence can hinder essential maturation processes, leading to lasting cognitive and adaptive challenges (Anderson et al., 2005; Treble-Barna et al., 2017; Mulligan et al., 2021). In adults, neuroplasticity occurs at a slower pace and with greater limitations, primarily depending on compensatory reorganization instead of complete functional recovery, while results significantly rely on the severity of the injury and the interaction between adaptive and maladaptive plastic alterations (Zotey et al., 2023; Rajan et al., 2025). In older adults, age-related declines in synaptic plasticity, neurotransmitter function, and brain reserve further constrain recovery ability, leading to worse functional results and increased mortality even after mild TBI (Prasad et al., 2018;~

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~~Ridderinkhof & Krugers, 2022; Chan et al., 2024)~~Younger individuals show greater baseline plasticity but this does not always lead to better recovery. Early disruptions can interfere with important development processes (Anderson et al., 2005; Mulligan et al., 2021).

For rehabilitation strategies, the primary goal of treatment during the acute phase (which occurs in the hours right after an accident) is to stabilize the patient and concentrate on preventing additional harm. ~~. Treatment is usually administered in an intensive care unit and then a neurosurgery ward. Rehabilitation is the primary treatment for chronic stages of recovery, and there are numerous treatment and rehabilitation methods (Chan et al., 2024).~~ The results of a study done by Winter et al. (2022) verify that age moderates the impact of injury severity on functional trajectory (Winter et al., 2022). Therefore, an individual's age at the time of injury determines the predictive validity of injury severity for functional trajectories.~~; older individuals have worse functional outcomes. This suggests that age is a major factor in recovery after TBI.~~ However, most rehabilitation strategies are based on severity and are dependent on the recovery stage of the patient (Chan et al., 2024). These results point to a discrepancy between current clinical practice and study findings. Incorporating both age and injury severity into rehabilitation planning allows clinicians to optimise recovery outcomes. By tailoring interventions to a patient's developmental stage and the extent of their injury, functional improvements can be enhanced and long-term deficits reduced. ~~By highlighting age as a critical component of recovery in addition to injury severity, this study aims to optimise functional results across various age groups and influence future rehabilitation efforts. In other words, future rehabilitation strategies should focus greatly on age due to it being a crucial factor in recovery.~~

Strengths and Limitations

A key strength of this review is its holistic and integrative scope. By synthesising evidence across molecular and cellular levels of analysis in 4 different age groups, this review provides a comprehensive framework for understanding age-dependent neuroplasticity after TBI. The inclusion of both human and animal studies strengthens the mechanistic explanations offered in the paper.

However, the limitations must be acknowledged. The review is narrative rather than systematic so the search and selection process is not entirely replicable, introducing the possibility of selection bias. Second, much of the mechanistic evidence such as evidence regarding LTP, LTD, and BDNF is drawn from animal models (primarily rodents) which may not fully represent human neurophysiology. Additionally, only a few of the studies compared neuroplastic outcomes across all 4 age groups under controlled conditions. This means that the cross-group comparisons are inferential rather than directly evidenced.

Conclusion

Overall, neuroplasticity provides an important biological framework for recovery after TBI; however, both the developmental stage and severity of the injury influence the extent to which functional recovery occurs. While these neuroplastic mechanisms operate throughout the lifespan, much of the existing evidence reflects age-related

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differences in functional outcomes, which are likely influenced by, rather than direct measures of, underlying neuroplastic processes (Su et al., 2016). Younger individuals show greater baseline plasticity but this does not always lead to better recovery. Early disruptions can interfere with important development processes (Anderson et al., 2005; Mulligan et al., 2022). Adults show moderate compensatory reorganisation; and the elderly display the most limited neuroplastic capacity. These age-related differences have meaningful implications for clinical practice, particularly in rehabilitation. Future research should, therefore, prioritise age-specific longitudinal studies, greater inclusion of elderly populations and the development of targeted therapeutic strategies use neuroplastic mechanisms at every stage of life.

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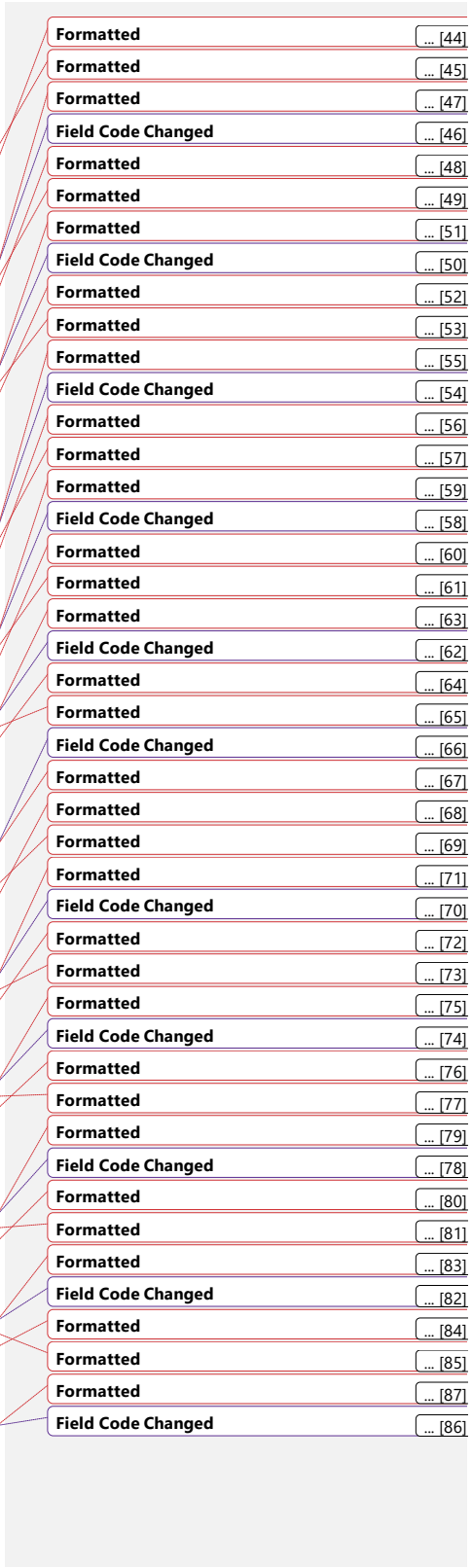

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Comments:

The section describing age-related differences in neuroplasticity is well done. A well-written and timely review on age-related differences in recovery after traumatic brain injury, offering a useful lifespan perspective and synthesizing clinical findings, but requiring several revisions before it can be accepted.

Main issue:

The added figure presents a serious issue, and there are still multiple missing citations throughout the manuscript. These issues need to be addressed.

Regarding Figure 1, permission must be obtained from Harvard University before the image is used. More importantly, in academic writing, sources should primarily be limited to peer-reviewed articles rather than website-based materials, which are generally considered informal and not appropriate for scholarly work. Furthermore, the author has used the website-based figure to support explanations in the main text. This is highly unprofessional and raises serious concerns. The figure should either be replaced with one from a peer-reviewed review or research article or be recreated by the author. In addition, any text based on the website figure should be removed or substantially revised.

- Thank you for this comment. I have removed the original website image and replaced it with an image I generated. This is the python code I used:

```
import numpy as np

import matplotlib.pyplot as plt


# Age range

age = np.linspace(2,70,500)


# Approximate trends

brain_change = 100/(age**0.5)

effort = 0.03*(age-2)**1.7 + 5


plt.figure(figsize=(8,5))


plt.plot(age, brain_change,

label="Brain's ability to change",

linewidth=3)


plt.plot(age, effort,

label="Amount of effort required",
```

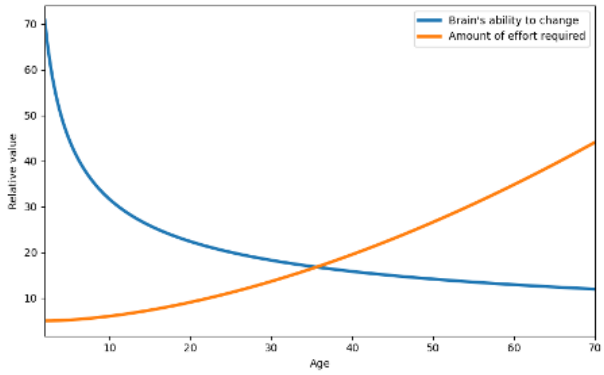
```
linewidth=3)


plt.xlabel("Age")
plt.ylabel("Relative value")
plt.xlim(2,70)


plt.legend()
plt.tight_layout()


plt.savefig("recreated_figure.png", dpi=300)
plt.show()
```

- Additionally, the text relying on the website figure has been revised, and relevant explanations have been rewritten.
- Image generated:



Specific Comments:

- **Line 186:** The full terms for LTP and LTD should be provided at first mention.
    - Thank you for this comment. The manuscript has been revised to include the full terms for LTP (Long-term potentiation) and LTD (long-term depression) at first mention.

(probably line 46?)

- **Line 260:** “A study conducted by Weston et al. (2021) investigated adult male rats that received a moderate TBI.” → A citation should be added at the end of the sentence.
- **Line 311:** “Chan et al. (2024) reported that TBI recovery declines with age, with older patients showing poorer functional outcomes and higher mortality rates.” → A citation should be added at the end of the sentence.
    - Thank you for this comment. I looked through the APA 7th edition citation guidelines here (https://apastyle.apa.org/style-grammar-guidelines/citations/basic-principles/pare

nthetical-versus-narrative) and it mentions that narrative citations do not require an additional parenthetical citation at the end of the sentence. Therefore, I have maintained the original format.

- **Line 324:** “Additionally , numerous studies have demonstrated that aged rodents, the elderly have slower plasticity rates because long-term potentiation (LTP) is decreased while long-term depression (LTD) is enhanced (Rapp et al., 1987; Ridderinkhof and Krugers, 2022)”. -> Again, Ridderinkhof and Krugers (2022 is a review paper. The author can cite the review paper as well, but the author needs to add the original paper. Eg). In parallel, LTP, an important experimental model for learning and memory (Nabavi et al., **2014**), at peri-threshold stimulation paradigms is decreased in aged rodents, while LTD is enhanced (Burke and Barnes, **2006**; Kumar, **2011**; Sikora et al., **2021**).
    - Thank you for this comment. The citation has been revised to include the suggested primary literature (Burke and Barnes. 2006; Kumar, 2011; Sikora et al., 2021) while keeping Ridderinkhof and Krugers (2022) as a review source.
    - Additionally, numerous studies have demonstrated that aged rodents have slower plasticity rates because LTP is decreased while LTD is enhanced (Burke and Barnes, 2006; Kumar, 2011; Sikora et al., 2021; Ridderinkhof and Krugers, 2022).

Final Recommendation

Accept with major revisions (acceptance is contingent upon satisfactory completion of the required revisions)

This is a very well researched paper with wonderfully implemented edits. Some constructive feedback:

1. Consider a comparative table to summarize key differences in neuroplastic mechanisms across the lifespan as a quick reference guide for the reader.
    - Thank you for this comment. I created a new section in the paper titled 'Discussion' and have included the table there:
    -

Lifespan stage	**Neuroplasticity level**	**Key mechanisms**	**Typical TBI response**	**Main limiting factors**
Children and adolescents	High but developmentally sensitive	Synaptogenesis, synaptic pruning, LTP/LTD, acitivity-dependent stabilisation, BDNF-mediated plasticity	Potential for strong recovery, but risk of disrupted development if injury is severe or early	Injury during critical developmental windows, diffuse brain injury, severity of TBI
Adults	Moderate, declining with age	Compensatory reorganisation, LTP-dependent plasticity, limited neurogenesis, glial responses	Partial recovery via rerouting and compensation	Excitotoxicity, inflammation, demyelination, slower synaptic remodelling
Elderly	low	Reduced LTP, increased LTD, neurotransmitter decline (dopamine, acetylcholine, glutamate), reduced cerebral reserve	Poorer recovery, higher mortality even in mild mortality	Brain autrophy, vascular fragility, reduced synaptic efficiency comorbidities

2. Figure 1 is well integrated in the text. Make sure you have permission from Harvard University to utilize in your publication (is it open access free to use?)

- Thank you for this comment. I have changed the image from the website image to an image I recreated using python. I also mentioned that the image is adapted from the original creator but the image is free to copy.

3. Line 335 is an example of when explicitly writing "a study by Winter" you do not have to use paratheses to site them again at the end of the sentence.
    - Thank you for this comment. I have removed all the parenthetical citations at the end of the narrative citations.
4. What does "age-specific rehabilitation" look like? Be more specific here.
    - Thank you for this comment. I have rephrased the sentence to - Because rehabilitation programs are not sufficiently tailored to the cognitive and functional needs of older adults (e.g. slower recovery rates, higher fall risk), older persons experience greater mortality rates, worse recovery, and more difficulties.

Final decision: **Accept with minor revisions.**

I have reviewed Jadah and Daniel's comments and the updated manuscript and responses to the initial feedback. The author has done a relatively good job in responding to the initial comments However, some comments remain and some new ones have been appropriately raised by reviewers. After addressing the new (and some same from first round...) comments raised by the reviewers, I would say the paper is at a "Accept with minor revisions" stage.

My additional comments from an editorial perspective:

- There are no methods in the paper. Can authors please include information on how this review was conducted? eg. What keywords were used in the search? What databases were searched? What types of articles were included?
    - Thank you for this comment. I have added a methodology section after the introduction and answered all the questions given above.
    - Methodology

      A narrative literature review approach was used here to investigate age-related variations in neuroplasticity following TBI. Some of the databases used for the literature searches were Google Scholar, PubMed, ScienceDirect, and APA PsycNet. Key terms included traumatic brain injury, TBI, neuroplasticity, ageing, children, adolescents, adults, elderly, recovery, long-term depression, long-term potentiation, brain-derived neurotrophic factor (BDNF), diffuse brain injury, synaptogenesis, etc. Studies that were analysed include peer-reviewed articles, longitudinal studies, clinical studies, neuroimaging studies, and experimental studies published primarily in English. Articles that specifically examined neuroplastic mechanisms and recovery outcomes following TBI across different age groups were prioritised.
- Change Conclusion to "Discussion", and do not start with "In conclusion" as that is not how journal articles are written. A short Conclusion section (approx a paragraph) can be included at the paper's end, after the Discussion as a concise summary of the findings and their implications to this research area.
    - Thank you for this comment. I Have added an additional ‘discussion’ section and changed the phrasing for the short conclusion paragraph at the end.
- The Discussion does not explore and expand on the paper's findings enough. Authors needs to show what their work adds to the existing literature, keeping in mind the aim of the paper: "This literature review examines the variations in brain plasticity throughout an individual's life... following a TBI". The Discussion should link back to this aim.
    - Thank you for this comment. I have included a comparison table as mentioned by reviewer 2 and also expanded the paper’s findings while linking it vack to the aim.
    - Discussion: Although each age group demonstrates different neuroplastic responses following TBI, there are several common trends that emerge across the lifespan. The evidence reviewed suggests that recovery does not depend solely on the degree of neuroplasticity but also by factors such as developmental stage, injury severity, and age-related biological mechanisms. To provide a clearer comparison of the findings, Table 1 summarises the key differences across different stages of life

Lifespan stage	Neuroplasticity level	Key mechanisms	Typical TBI response	Main limiting factors
Children and adolescents	High but developmentally sensitive	Synaptogenesis, synaptic pruning, LTP/LTD, acitivity-dependent stabilisation, BDNF-mediated plasticity	Potential for strong recovery, but risk of disrupted development if injury is severe or early	Injury during critical developmental windows, diffuse brain injury, severity of TBI
Adults	Moderate, declining with age	Compensatory reorganisation, LTP-dependent plasticity, limited neurogenesis, glial responses	Partial recovery via rerouting and compensation	Excitotoxicity, inflammation, demyelination, slower synaptic remodelling
Elderly	low	Reduced LTP, increased LTD, neurotransmitter decline (dopamine, acetylcholine, glutamate), reduced cerebral reserve	Poorer recovery, higher mortality even in mild mortality	Brain autrophy, vascular fragility, reduced synaptic efficiency comorbidities

- Table 1. Comparison of neuroplastic mechanisms and recovery characteristics across the lifespan following TBI

- A key contribution of this review is the integration of evidence directly addressing its aim: to examine variations in neuroplasticity across the lifespan following TBI. The findings show that while neuroplasticity is a universal biological response to TBI, its nature and functional outcome differ significantly between children, adolescents, adults and the elderly. Childrem and adolescents demonstrate heightened synaptic acitivity, BDNF-mediated plasticity, synaptogenesis, but early or sever TBI can disrupt healthy-brain maturation leading to deficits (Anderson et al., 2005; Mulligan et al., 2022). In adults, neuroplasticity remains in a more limited and compensatory form where the same mechanisms that support recovery can sometimes cause dysfunctional pathways (Zotey et al., 2023). For the elderly, there is reduced LTP, neurotransmitter decline, and brain atrophy which produces a poor neuroplastic environment for recovery even after mild TBI (Burke and Barnes, 2006; Chan et al., 2024). Clinical data for this

group is largely extrapolated from younger patient data which shows a large gap in research. Altogether, these findings directly address the aim of this paper.

-

- For rehabilitation strategies, the primary goal of treatment during the acute phase (which occurs in the hours right after an accident) is to stabilize the patient and concentrate on preventing additional harm. The results of a study done by Winter et al. (2022) verify that age moderates the impact of injury severity on functional trajectory. Therefore, an individual's age at the time of injury determines the predictive validity of injury severity for functional trajectories. However, most rehabilitation strategies are based on severity and are dependent on the recovery stage of the patient (Chan et al., 2024). These results point to a discrepancy between current clinical practice and study findings. Incorporating both age and injury severity into rehabilitation planning allows clinicians to optimise recovery outcomes. By tailoring interventions to a patient's developmental stage and the extent of their injury, functional improvements can be enhanced and long-term deficits reduced.

- Include strengths and limitations of the study in the Discussion.
  - Thank you for this comment. I have included a section titled "strengths and limitations" in the revised manuscript
  - Strengths and Limitations
  - A key strength of this review is its holistic and integrative scope. By synthesising evidence across molecular and cellular levels of analysis in 4 different age groups, this review provides a comprehensive framework for understanding age-dependent neuroplasticity after TBI. The inclusion of both human and animal studies strengthens the mechanistic explanations offered in the paper.

  - However, the limitations must be acknowledged. The review is narrative rather than systematic so the search and selection process is not entirely replicable, introducing the possibility of selection bias. Second, much of the mechanistic evidence such as evidence regarding LTP, LTD, and BDNF is drawn from animal models (primarily rodents) which may not fully represent human neurophysiology. Additionally, only a few of the studies compared neuroplastic outcomes across all 4 age groups under controlled conditions. This means that the cross-group comparisons are inferential rather than directly evidenced.
  -

Decision: Accept with Minor Revisions

This manuscript presents a narrative literature review examining age-related differences in neuroplasticity and recovery following TBI across children, adolescents, adults, and elderly populations. The paper synthesizes evidence from molecular, cellular, clinical, and psychological studies to evaluate how the developmental stage influences functional recovery outcomes after TBI.

Overall, the revised manuscript demonstrates substantive improvement compared to the previous version and responds well to the concerns raised by the reviewers and Action Editor. The author has clearly engaged with the feedback and made meaningful revisions to the structure, discussion, and methodology of the paper, including a comparative lifespan table and acknowledged inclusion of strengths and limitations.

However, there are still some minor issues. Several citations require correction or replacement before publication:

- Sivaprasad et al. (2005) appears inappropriate for the claim it supports, as it concerns age-related macular degeneration rather than traumatic brain injury or neurodegeneration after TBI. This citation should be removed or replaced with a more relevant source.
- Tomar et al. (2018) is a real TBI-related paper, but I am not sure how well it directly supports the long-term adaptivity claims made in the manuscript. A more directly relevant citation would strengthen this section.
- Mohammed & Hollis (2018) focuses primarily on spinal cord injury rather than TBI. While potentially acceptable for general neuroplasticity concepts, a more TBI-specific reference would be preferable.
- Johnson & Wilgus (2014) relates to angiogenesis in wound healing rather than TBI-specific angiogenesis and may not be the strongest support for the discussion presented.

Furthermore:

- A small number of citation formatting inconsistencies remain and should be corrected during copyediting.
- The discussion could still provide a somewhat deeper mechanistic synthesis explaining why greater neuroplasticity in younger individuals does not necessarily produce superior long-term outcomes.
- The section on age-specific rehabilitation strategies could benefit from slightly more concrete examples.

These issues are relatively minor and do not substantially detract from the quality or publishability of the manuscript, which still presents a well-developed and timely narrative review addressing an important topic in neurorehabilitation and developmental neuroscience. Provided the citation issues noted above are corrected during the final manuscript preparation, I believe the manuscript is suitable for publication.