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Neurogenesis is the process by which new neurons are formed in the brain. Neurogenesis is crucial when an embryo is developing, but also continues in certain brain regions after birth and throughout lifespan. The mature brain has many specialised areas of function, and neurons that differ in structure and connections. The hippocampus, for example, which is a brain region that plays an important role in memory and spatial navigation, alone has at least 122 different types of neurons^[1]

Adult neurogenesis in the dentate gyrus of the hippocampus is highly regulated by several external conditions and cell-intrinsic factors to adapt to environmental changes.

Accumulating evidence suggests that adult-born neurons may play distinct physiological roles in hippocampus-dependent functions, such as memory encoding and mood regulation^[2].

Adult hippocampal neurogenesis is a process that describes the generation of new functional dentate granule cells (DGCs) from adult neural stem cells through the amplification of intermediate progenitors and neuroblasts, as well as the differentiation and integration of these new neurons into the existing neural circuits^[3].

Diagram I

Outline of the scheme of lineage progression and fate decisions during adult hippocampal neurogenesis.

A astrocyte;
GC granule cell;
NSC neural stem cell^[4].

Diagram II

As part of this process the newly generated granule cells then extend axons or dendritic branches to integrate themselves in the pre-existing network of cells that compose the hippocampal. Again, the integration relies on newly formed dendritic branches of pre-matured neurons that reach the dentate gyrus (DG) molecular layer (ML) from granule cell layer (GCL) and upon reaching the molecular layer (ML) layer these dendritic branches reach out to entorhinal cortex (EC) and lateral (LPP) and medial (MPP) path, forming novel synaptic connections^[5].

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These cells can then project their axons to the *Cornu Ammonis 3* (CA3), further establishing the hippocampal circuitry; hence maintaining or improving dendritic complexity is key to hippocampal function, a brain region important for spatial information, learning and memory functions. When there is a malfunction in any of the processes, then a subsequent breakdown can be expected in either the quiescent pool (stem cell generator), loss of dendritic complexity (**Diagram III**), angiogenesis or neuroplasticity leading to a loss of memory.

Diagram III displays impaired morphology and activity in dentate gyrus granule cells in depression. In the healthy state, the granule cells have long thick apical dendrites ^[6].

Importance to Maintain Healthy Hippocampal Neurogenesis

Brain cognitive reserve reflects the brains capacity to preserve normal functions, and has been used to explain the gap between tissue damage and clinical symptoms that has been observed in dementia and Alzheimer's disease (AD)⁸. In early/moderate stages of Alzheimer's disease, cognitive reserve compensates neurodegeneration and allows the maintenance of patients' cognitive performance⁷. As outlined in **Table I**, there are several factors that modulate cognitive reserve:

Table I The impact of the aforementioned factors can translate into physical changes in brain morphology as outlined in Table II ^[9] .	Beneficial Factors	Deleterious Factors
	Cognitive Exercises i.e. crossword, puzzles	Sedative Mental Activity i.e. excessive television viewing
	Education levels	Illiteracy
	Creative activities	Inadequate diet
	Diet	Solitude
	Regular Physical Exercise	Little Physical Exercise
	Social stimulus i.e. Bridge club	
Table II Physical changes in brain morphology	Improvement of cognitive reserve	Decline of cognitive reserve
	Increased brain size	Reduction in brain size
	Increase in the number of neurons	Reduction in the number of neurons
	Increased synaptic density	Reduction in synaptic density

Neurogenesis decreases with aging and declines may be linked to compromised cognitive-emotional resilience. Older individuals have less angiogenesis and neuroplasticity and a smaller quiescent progenitor pool. In these AD patients there is a malfunction of the growth stages of hippocampal neurons or an unexplained severe deletion of these neurons or inability of these neurons to establish an integration within the existing circuitry of hippocampal function. Due to the aforementioned malfunction and unexplained deletion of these neurons the continued pharmaceutical focus on the reduction of Tau and β -Amyloid proteins may be in need of review. Attempts

to treat Alzheimer's disease with a "reduction" approach to Tau and β -Amyloid proteins has been disappointing ^[9]. Until a pharmaceutical solution can be proven, could mushroom nutrition act as a disease modifying therapy by nutritionally targeting neurogenesis? How? By focusing on:
1. Reduction of neuroinflammation by increasing Lipoxin A4. Lipoxin A4 (LXA4) is an endogenously produced eicosanoid that inhibits neutrophil recruitment and activation and blocks the generation of pro-inflammatory proteins. LXA4 acts as an endogenous "breaking signal" in the inflammatory process. Biomass

forms of *Coriolus versicolor* and *Hericium erinaceus* increased Lipoxin A4 and A β uptake by phagocytic cells in rats which is recognized as a potential therapeutic target for AD treatment^{[10][11]}.

2. Combating viral infections that could be responsible for triggering dementia

Mushroom nutrition can be a source of natural bioactive compounds responsible for prevention and treatment of viral diseases through improvement of human immunomodulation. They boost antiviral cytokines or prevent the entry of the virus into the human cell that are responsible for triggering neurodegeneration^{[12][13][14][15]}.

3. Rebalancing the microbiota in dementia diagnosed patients

Food needs to cover the requirements of the human body and of the microbiota and ensure homeostasis. Mushrooms supply numerous enzymes, nucleosides, nucleotides and secondary metabolites essential for microbiota contributing to cell cycle regulation, apoptosis, autophagy, angiogenesis, metastasis, and signal transduction cascades^[16].

4. Reducing oxidative and cellular stress response

Mushroom nutrition reduces oxidative stress and free radical-induced cell damage in neurodegenerative conditions^[17].

5. Maintaining hippocampal neurogenesis by supporting Wnt/ β -catenin signalling?

The Wnt/ β -catenin signalling pathway involves secreted glycoproteins acting through transduction pathways signalling cascade and ligands, controlling carcinogenesis, embryonic development, and tissue regeneration^[18].

They are dual function proteins, involved in regulation and coordination of cell–cell adhesion and gene transcription^[19], playing an important role in neurogenesis by enhancing the maturation of the newly generated dendritic network^[20]. In fact, β -catenin is a protein with numerous functions in different cellular locations and its regulation is dependent of the action of several interplayers.

An important regulator of β -catenin is the glycogen synthase kinase-3 β (GSK3 β) that promotes β -catenin degradation through

its phosphorylation^[21]. In pathological conditions in which GSK3 β is highly activated, β -catenin is degraded, impairing the cellular processes dependent on its normal function. This degradation is evident in AD where both Wnt/ β -catenin signalling pathway and β -catenin levels were shown to be decreased in the brain of AD patients^[22].

Thus, β -catenin is a powerful therapeutic target, as its overexpression may function as a promoter of maturation and functional integration of immature neurons into the hippocampus. This possible therapeutic intervention may thus counterbalance scenarios where β -catenin is abnormally degraded and dysfunctional.

Study Design

In 2018, researchers at the Institute for Pharmacology and Experimental Therapeutics (IBILI), Faculty of Medicine at the University of Coimbra Portugal and in the Centre for Neuroscience and Cell Biology at the University of Coimbra led by Professors Frederico C. Pereira and A. Cristina Rego performed the following study on mice to evaluate the impact of mushroom nutrition on hippocampal neurogenic reserve^[23].

Using *Coriolus versicolor* (CV) biomass supplementation, the researchers took two groups of 2.5-month-old mice divided into one group taking 200 mg/kg every day for 2.5 months while the control group took saline. After 2.5 months the mice were sacrificed, and the following parameters were measured and compared between the two groups^[23].

While there was no change in the dentate gyrus volume or proliferation in newly generated neurons, it was found that mice treated with *Coriolus versicolor* biomass supplementation had a significant increase in the complexity of the long and short immature neurons (increase in dendritic complexity)^[23].

Table III: Summary of changes in the parameters

1	Changes in volume of granular cell layer (GCL) and sub granular zone (SGZ) of the hippocampal dentate gyrus (DG)	None
2	Changes in proliferation of DCX-positive cells	None
3	Changes on number and nucleus area of immature neurons in the DG of mouse hippocampus	None
4	Changes in differentiation features of DG short immature neurons of mouse hippocampus	Yes
5	Changes in differentiation features of DG long immature neurons of mouse hippocampus	Yes
6	Changes in Wnt/ β -catenin signalling	Yes

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Image 1

Of additional interest there was the fact that mice treated with *Coriolus versicolor* biomass had increased cytoplasmic and nuclear levels of β -catenin in immature neurons from hippocampal DG, suggesting that this protein may be a key molecule responsible for the increase in dendritic complicity in these cells.

Conclusion

The researchers demonstrated that supplementation with *Coriolus versicolor* biomass in mice promotes:

- Increased dendritic arborization and complexity of newly generated neurons (short and long); and
- Increase in the levels of β -catenin in the nucleus and cytoplasm of hippocampal newly generated neurons.

This indicates that *Coriolus versicolor* biomass promotes hippocampal neurogenic reserve in mice by increasing levels of β -catenin that may translate into enhanced cognitive reserve essential for learning and memory⁽²⁴⁾.

Further clinical research is required to reconfirm these results.

The *Coriolus versicolor* biomass used in this study was supplied by Mycology Research Laboratories Ltd. (Luton, UK). (www.mycologyresearch.com).

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