

Unequal effects of anterior thalamic nuclei and mammillothalamic tract lesions

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Introduction

The anterior thalamic nuclei (ATN), and the mammillothalamic tract (MTT) projection to the ATN from the mammillary bodies (MB), are key parts of the extended hippocampal system. The MTT are associated with diencephalic amnesia after stroke, whereas a combination of ATN degeneration and MB injury is associated with the amnesic Korsakoff's syndrome. Separate rat studies suggest that ATN lesions may produce more severe memory deficits than MTT lesions. Here, for the first time, the effects of ATN and MTT lesions were directly contrasted on spatial memory tasks and the functional integrity of other structures in the extended hippocampal circuit.

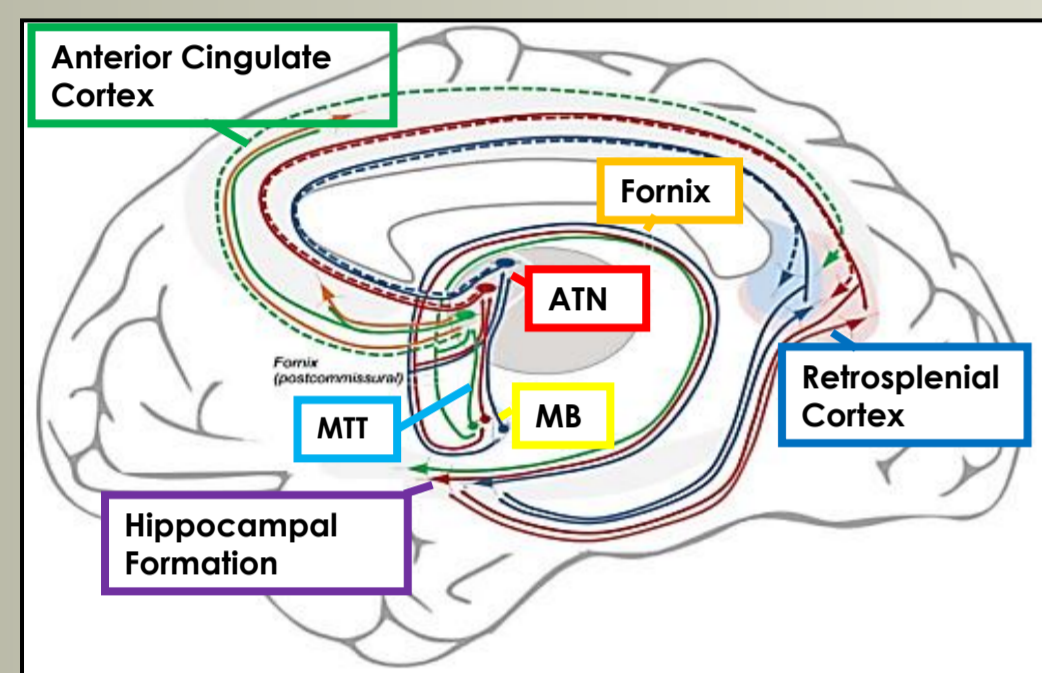


Figure 1. The extended hippocampal system in the human brain (Adapted from Child and Benarroch, 2013). This system is relevant to memory loss in neurodegenerative disorders stroke and KS.

Methods

Surgery

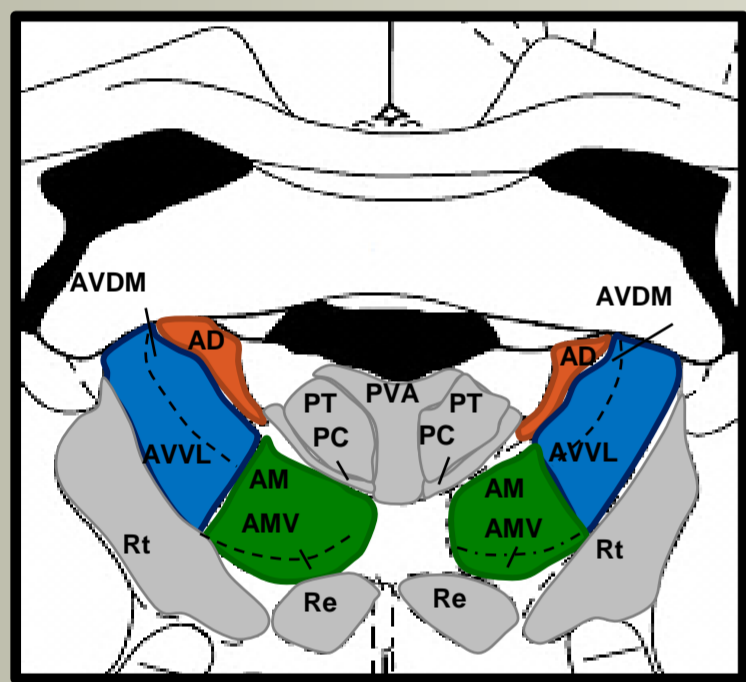


Figure 2. ATN lesion. Target site for neurotoxic (NMDA) ATN lesions (orange, blue & green) (n = 14). Control (n = 11). (Paxinos's & Watson, 1998)

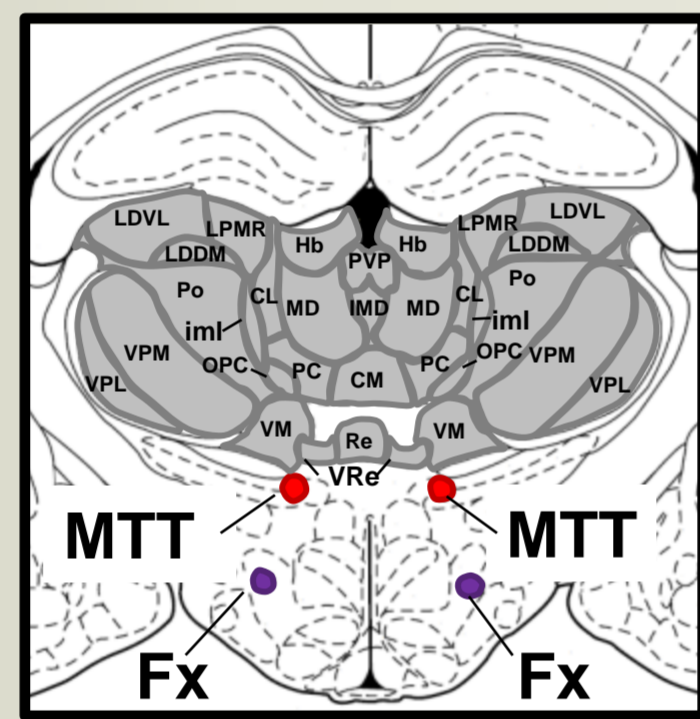


Figure 3. MTT lesion. Site of radiofrequency MTT lesions (red; n = 16). Control (n = 14)



Behaviour Presurgery

Radial arm maze

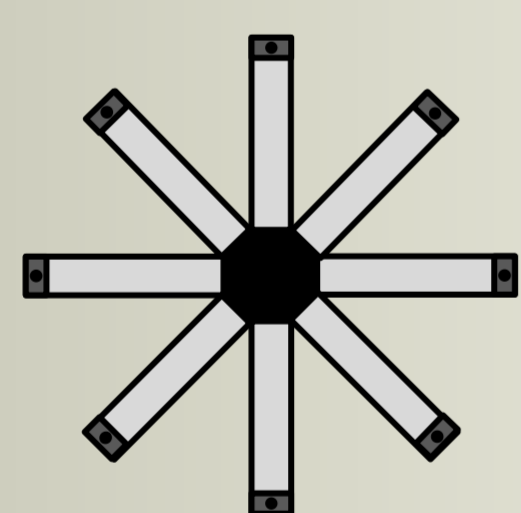


Figure 4. Standard working memory (12 days) All eight arms baited: find all eight baits without re-visits. Used to equate spatial memory for surgery groups

Postsurgery

Water maze

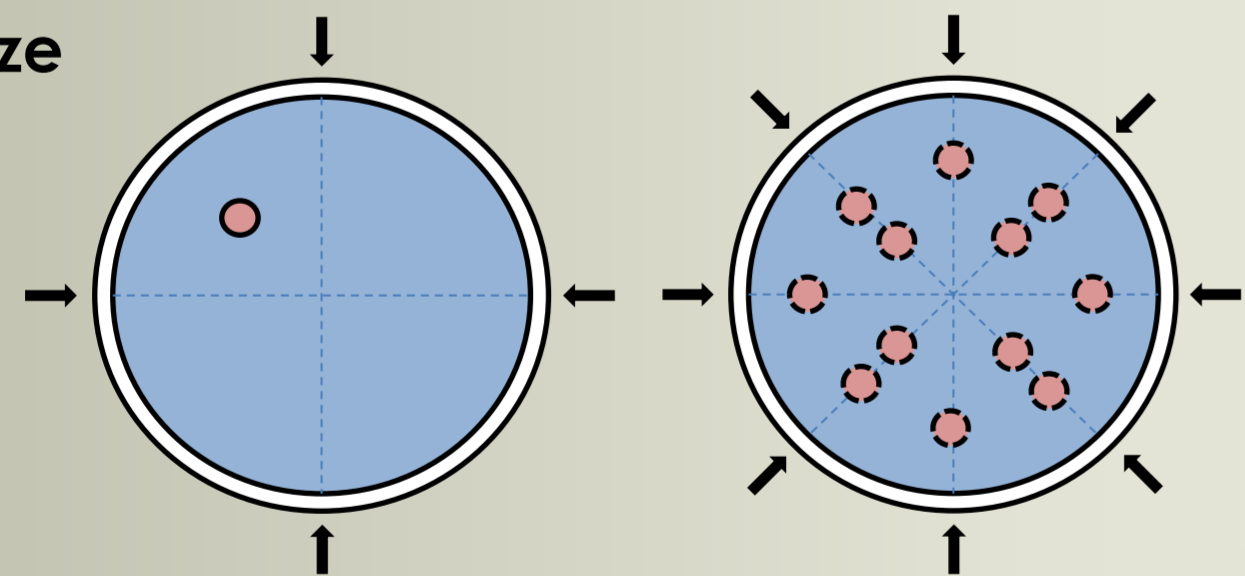


Figure 5. #1 Reference memory (12 days) Fixed platform location. Four trials a day, four start points.

Figure 6. #2 Working memory (12 days) Platform varied between daily sessions. Four trials a day, from three start points (Trial 1 & 2 same start point).

Radial arm maze

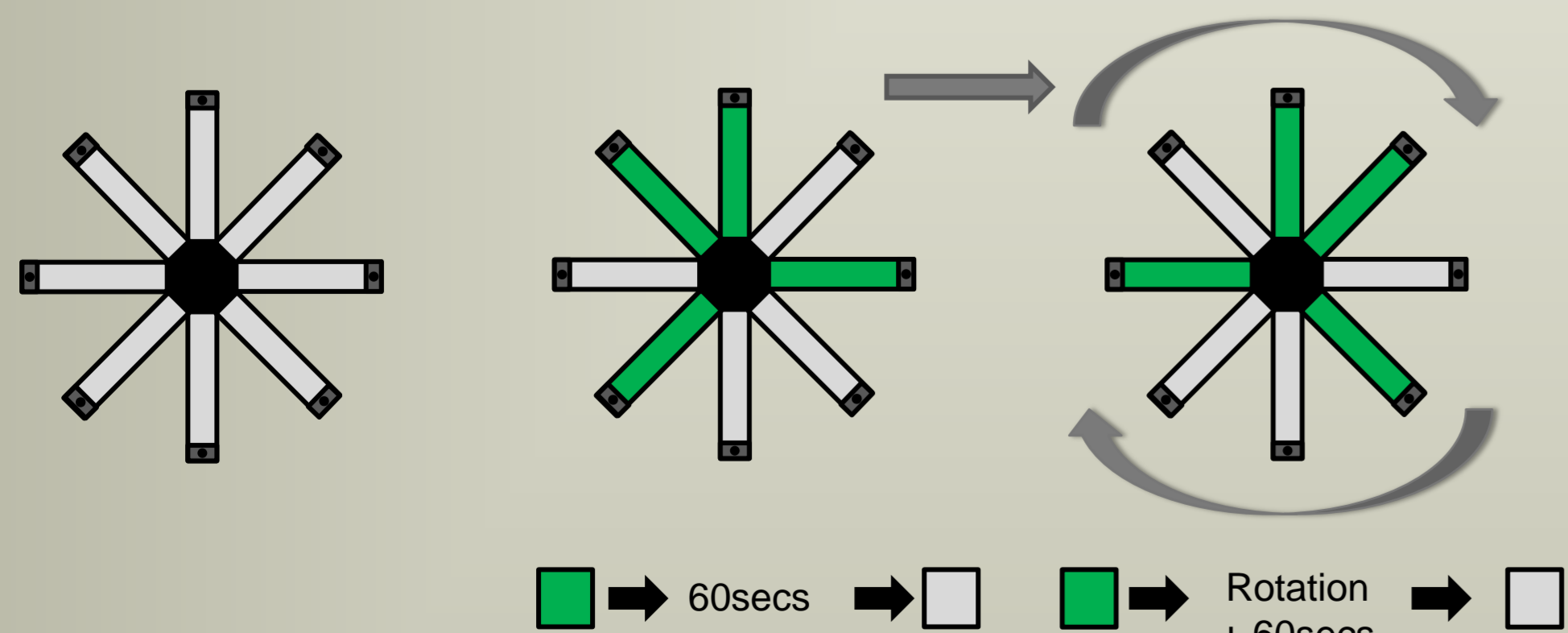


Figure 7. #3 Standard working memory (12 days) Same as presurgery

Figure 8. #4a Delay task (example) (4 days) 60 sec delay mid-trial after 4 visits.

Figure 9. #4b Rotation task (example) (4 days) Maze rotated 45° during the 60 sec delay.

Methods

IEG expression (zif268)

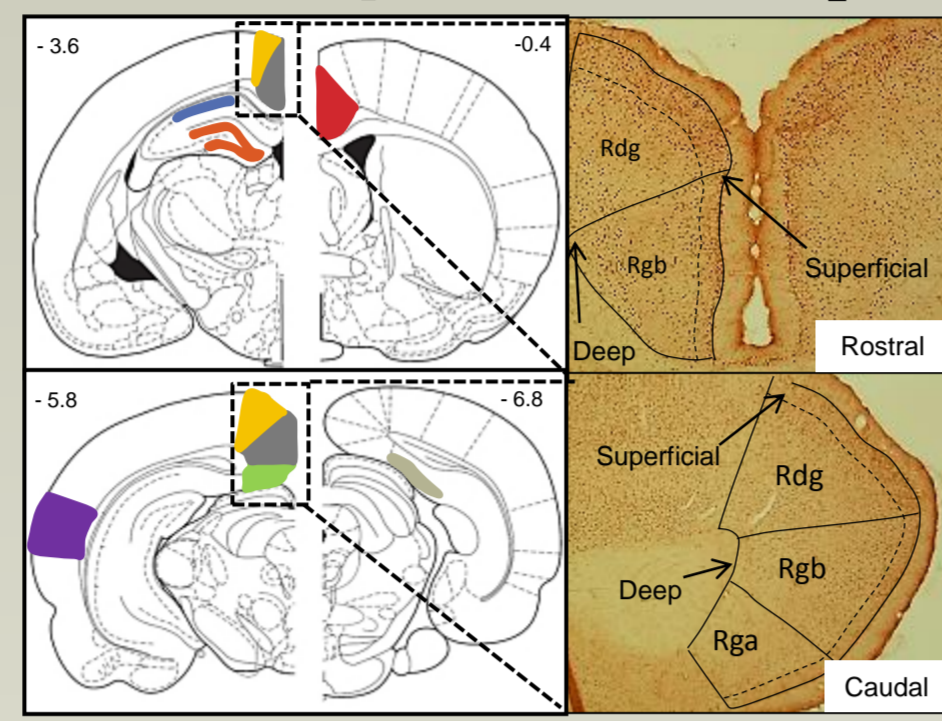
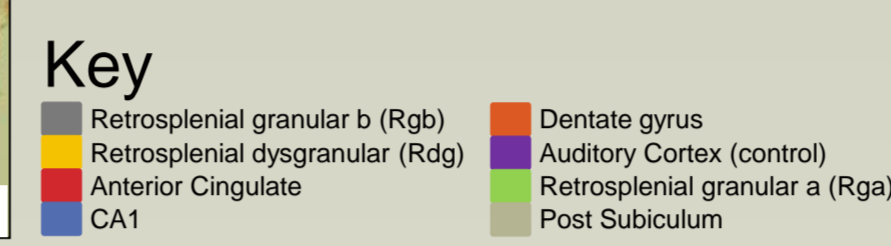


Figure 10. ROI's for zif268 IHC. In retrosplenial cortex, a key site in the extended hippocampal system (left) photomicrographs indicate subregions and layers of the retrosplenial cortex (right).



NeuN cell counts in the MB

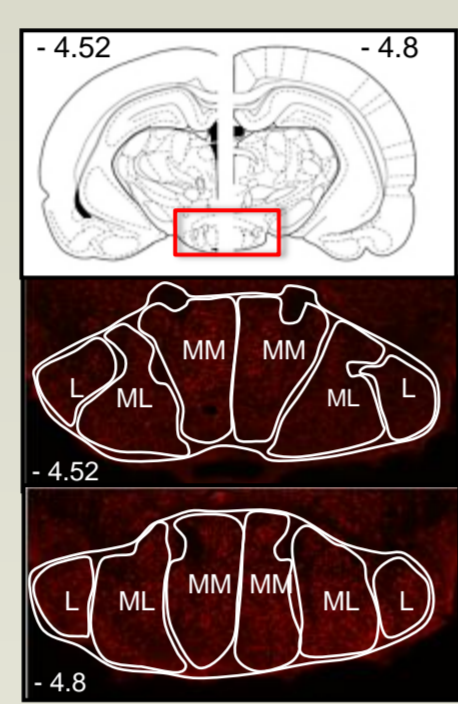


Figure 11. ROI's for NeuN IF. MTT lesions remove the primary efferents of the MB, and ATN lesions the primary efferent target. MB integrity was examined with the neuron specific marker NeuN in three subregions (at two AP coordinates (left)). MM = medial mammillary nucleus, ML = medial lateral mammillary nucleus, L = lateral mammillary nucleus.

Results

Histology

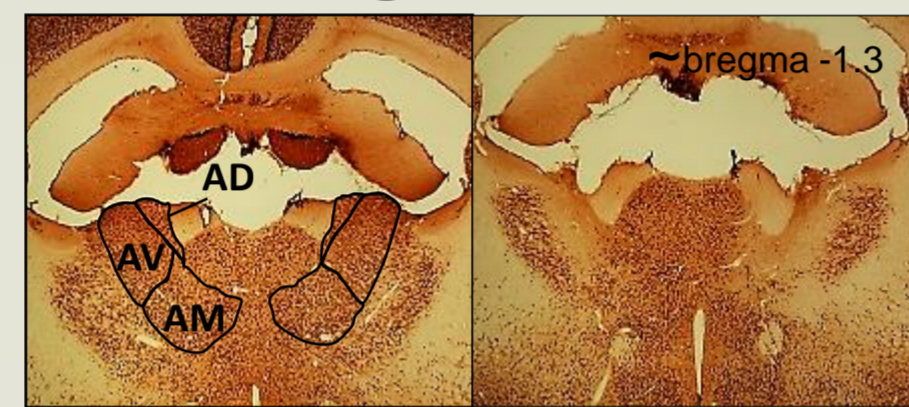


Fig 12. ATN Lesion Example of a control (left) and 1 of 8 ATN lesions (right). NeuN stain.

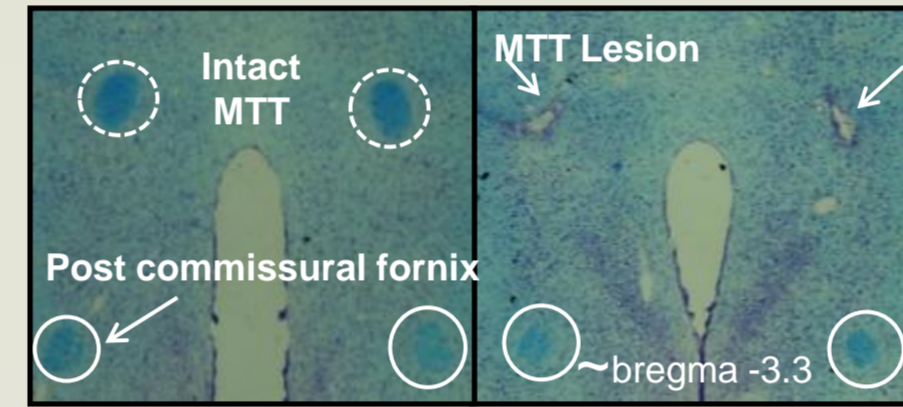


Fig 13. MTT Lesion example of a control (left) and 1 of 9 complete bilateral MTT lesion (right). Luxol blue + Cresyl violet stain.

Behaviour

Post surg. Water maze Reference Memory

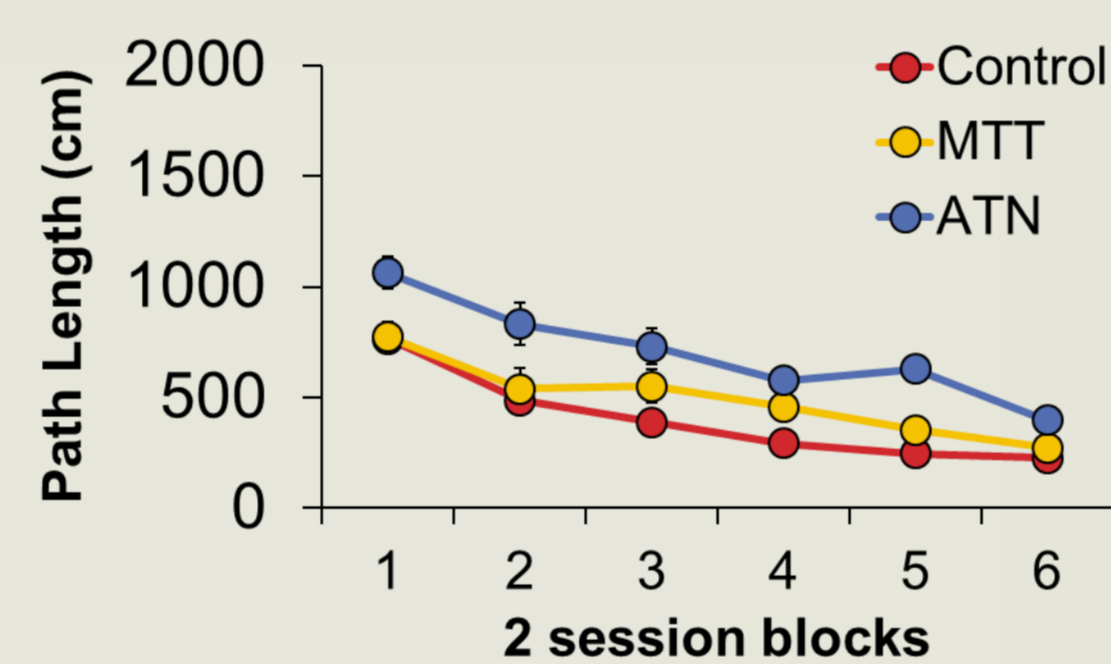


Figure 14. ATN, but not MTT lesions, impaired reference memory (p 's < 0.001 c.f. control and MTT).

Post surg. Water maze Working Memory

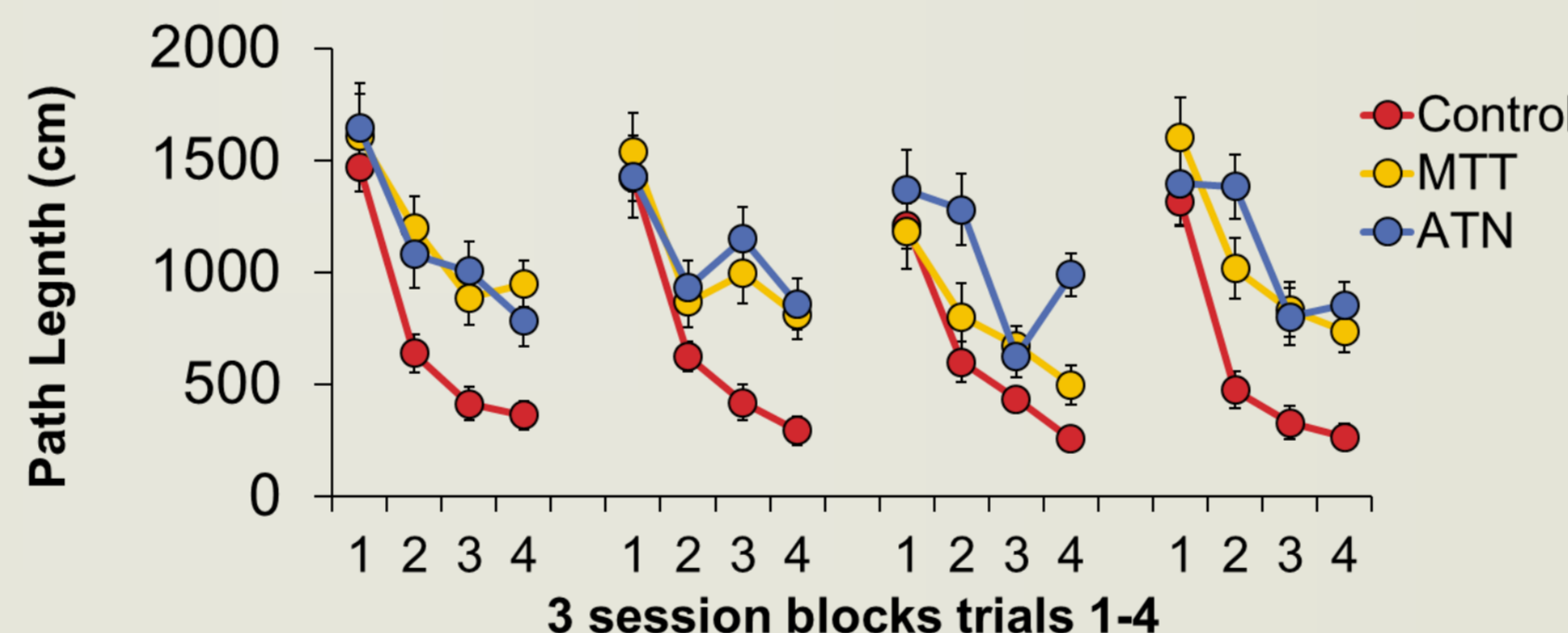


Figure 15. Both ATN and MTT lesions equally impaired performance (p < 0.001)

Three radial arm maze tasks

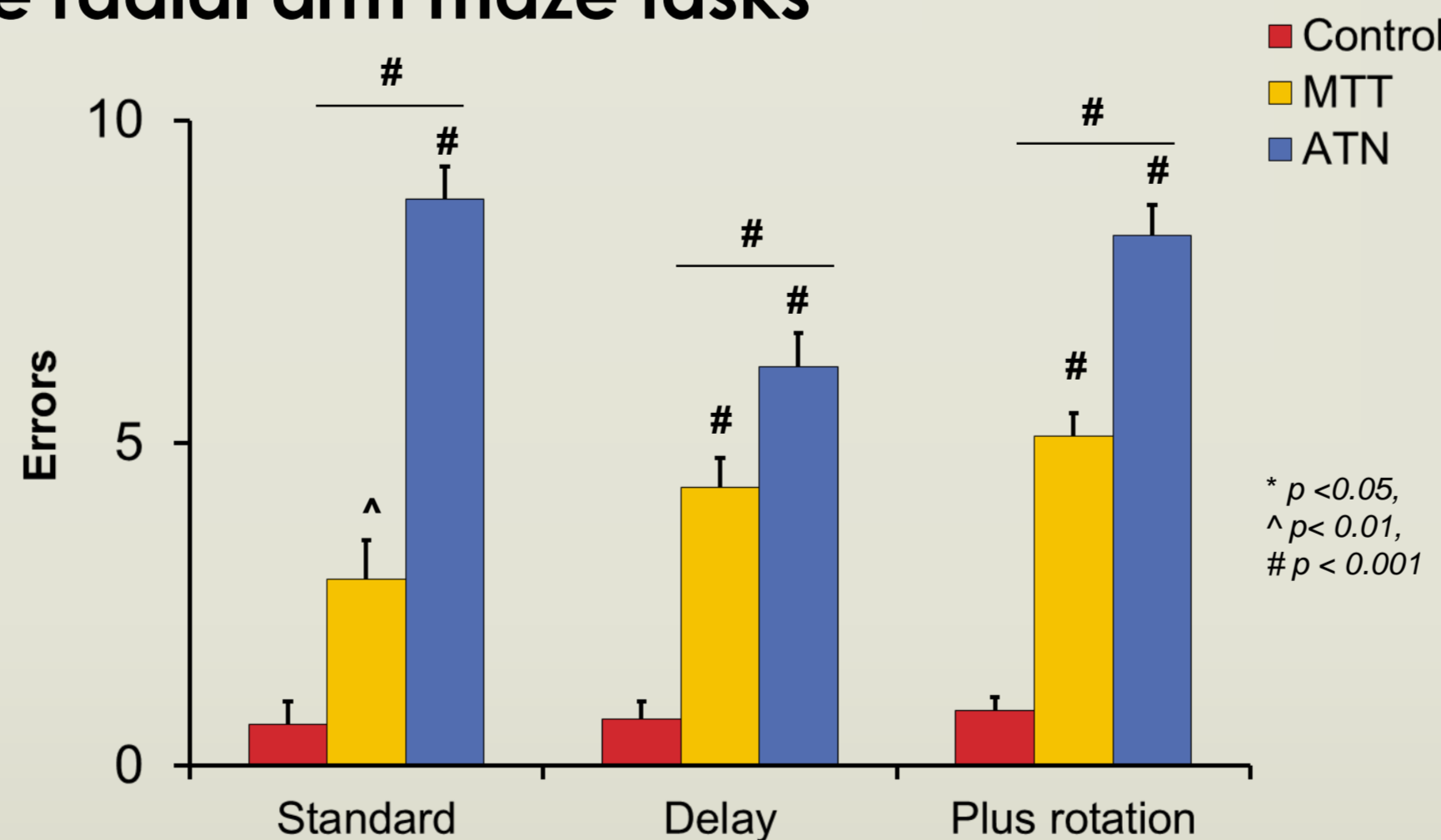


Fig 16. A graded lesion effect was found: ATN lesions produced significantly more errors than MTT lesions across conditions (p 's < 0.05). But both ATN and MTT rats made substantially more errors than controls across conditions (p 's < 0.001).

Results

Reduced IEG expression (zif268) Rostral Retrosplenial

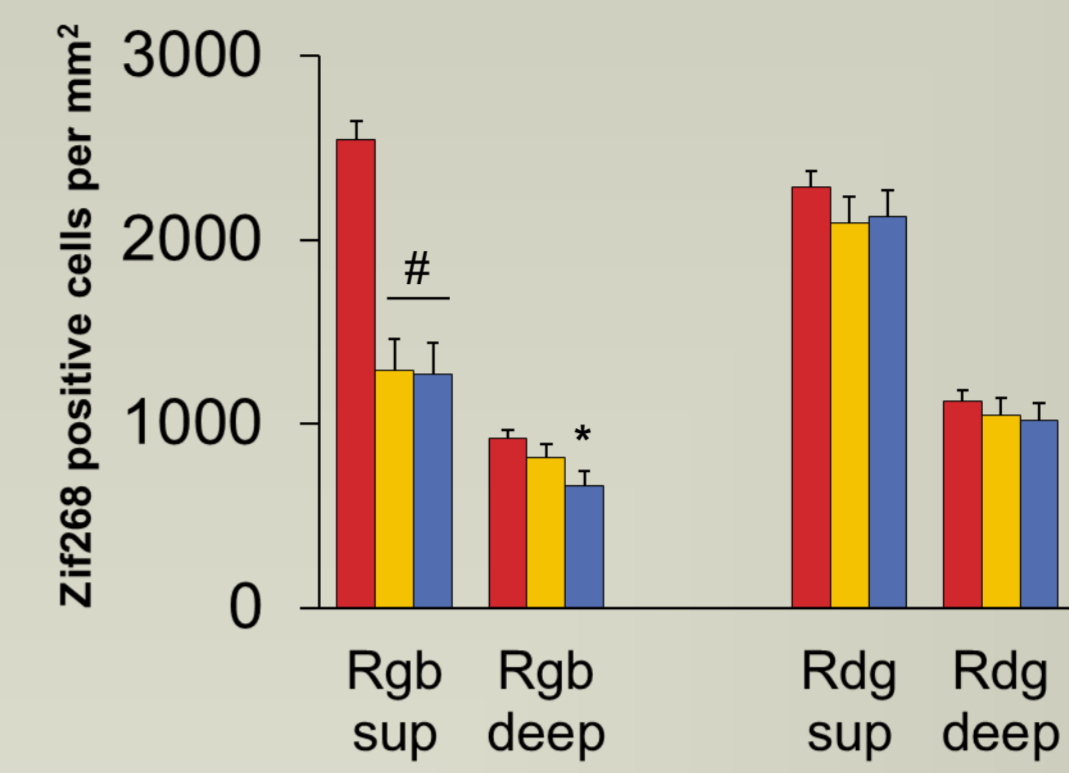


Figure 17. ATN and MTT lesions substantially reduced zif268 in the superficial layers of granular b (Rgb) (p < 0.001). Only ATN lesions reduced zif268 expression in the deep Rgb (p < 0.01).

Caudal Retrosplenial

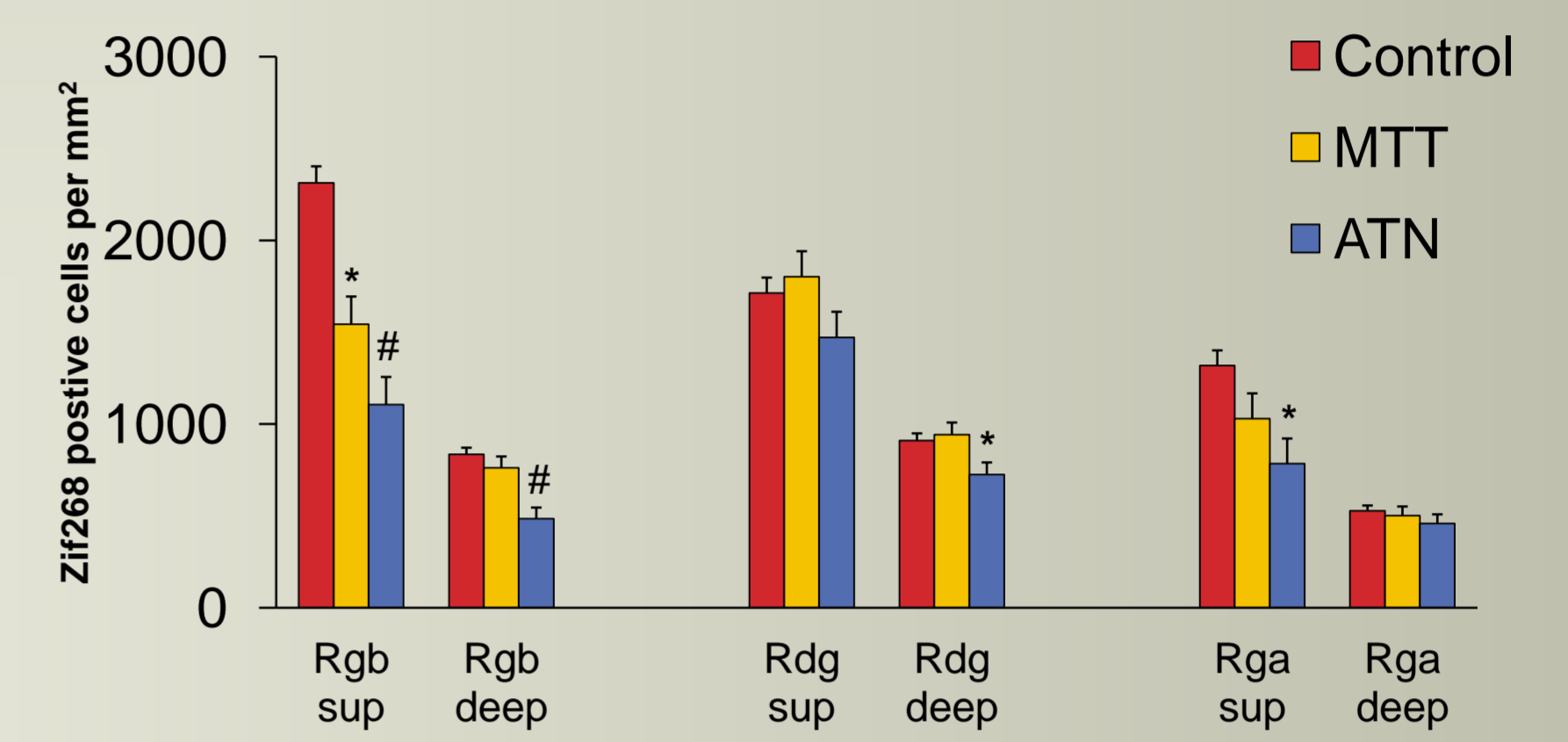


Figure 18. ATN and MTT lesions reduced zif268 in the superficial layers of granular b (p < 0.001) in a graded fashion ATN < MTT (p < 0.001). However, only ATN lesions reduced zif268 in the deep Rgb, (p < 0.001), deep dysgranular (Rdg) (p < 0.05) and the superficial Rga regions (p < 0.02).

Dorsal hippocampus

ATN lesions and MTT lesions reduced zif268 expression in CA1 only in a graded fashion ATN < MTT (p < 0.001).

Anterior cingulate

Only ATN lesions reduced zif268 expression in the anterior cingulate cortex (p < 0.05 c.f. control).

Cortical control region

No differences in the control region (p = 0.14).

Reduced NeuN Counts in the MB

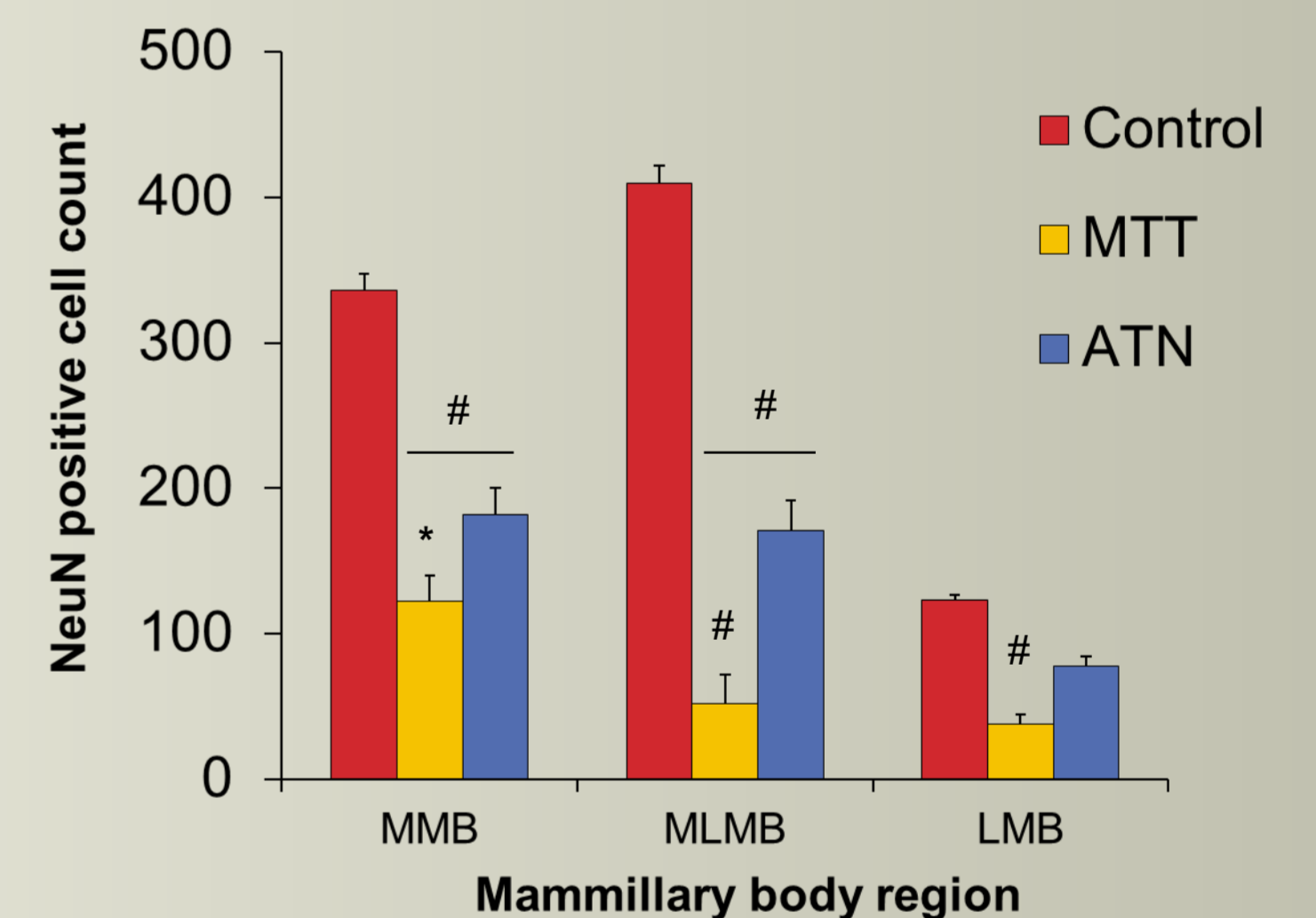


Figure 19. ATN and especially MTT lesions reduced overall NeuN positive cell counts in the MB.

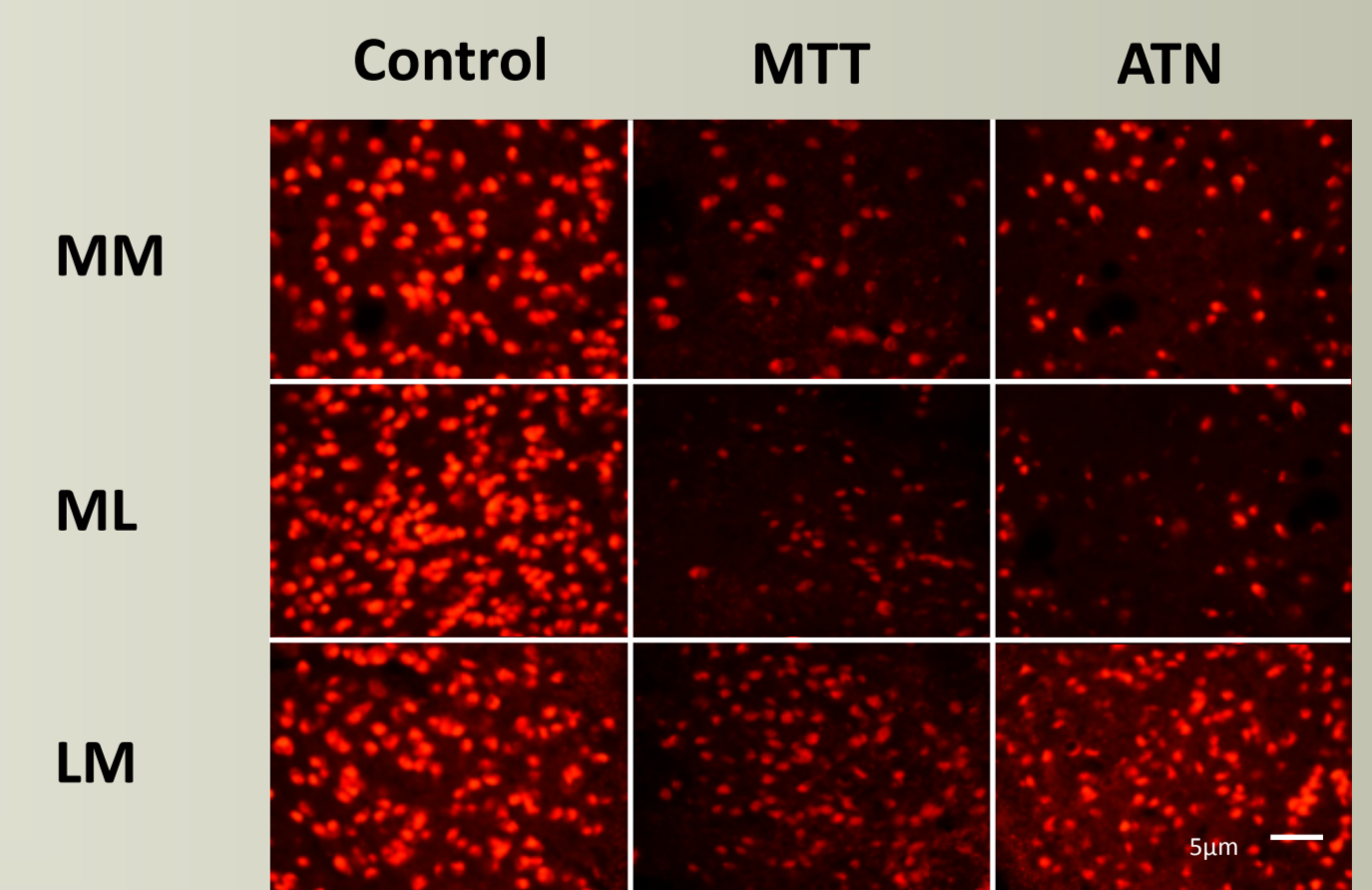


Figure 20. NeuN staining in the mammillary bodies. In MB subregions of a control, MTT and ATN rat at ~ bregma - 4.8.

Conclusions

- These findings suggest that amnesia associated with MTT lesions in humans may depend on the extent of direct additional injury to the ATN and/or other adjacent nuclei.
- ATN and MTT lesions do not result in equivalent spatial memory impairments.
- ATN lesions produced greater impairments in reference memory in the water maze and in the RAM.
- ATN lesions resulted in greater and more widespread zif268 hypoactivation than MTT lesions, in extended hippocampal structures.
- Mammillary body atrophy is more severe following MTT, than ATN lesions.