Mammillothalamic tract lesions and spatial memory in rats

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Introduction

In humans, damage to the mammillothalamic tract (MTT), which provides a unidirectional connection between the mammillary bodies and the anterior thalamus (ATN), may be a critical site that causes stroke-induced diencephalic amnesia (Carlesimo et al., 2011). Both the MTT and the adjacent ATN are key nodes in an extended hippocampal circuit for episodic memory (Aggleton et al., 2011). Unlike lesions to the ATN, MTT lesions produce mixed results or only mild deficits in animal lesion models. The current study used total or near total bilateral radiofrequency lesions of the MTT to test their effects on several spatial memory tasks. As a comparison, ATN lesions were made in additional rats to determine the relative contributions of the ATN and MTT to spatial memory.

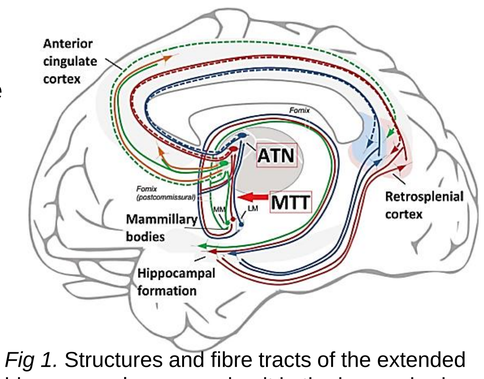


Fig 1. Structures and fibre tracts of the extended hippocampal memory circuit in the human brain (adapted from Child & Benarroch, 2013).

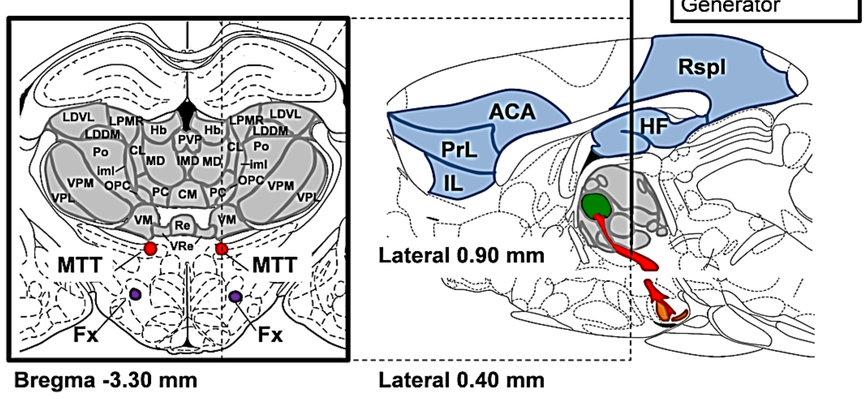
Method

Surgery + Recovery (weeks 0 - 3)

MTT lesion (n = 16): A radiofrequency probe was raised to 63° C for 60 secs.
MTT control (n = 14): The radiofrequency probe was lowered to 1mm above the lesion site and the temperature was not raised.

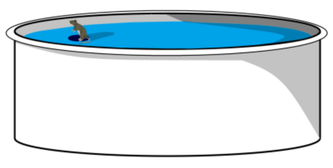
Fig 2. Coronal and sagittal atlas plates (Paxinos and Watson, 1998) showing the MTT in rat brain and site of MTT lesions.

Key
- anterior thalamic nuclei
- mammillothalamic tract
- fornix
- HPF circuit structures
- thalamic structures
- medial mammillary bodies

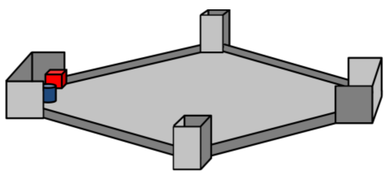


Behavioural tasks

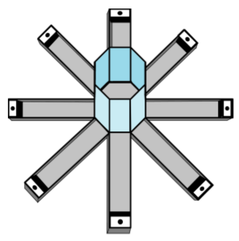
Water-maze (weeks 4 – 7)
Reference memory (12 days)
Fixed platform location. Four trials a day, four start points.
Working memory (12 days)
Platform fixed within session, varied between sessions.
Four trials a day, from three start points (Trial 1 & 2 same start point).



Diamond: object-place association (weeks 8 – 14)
Two different objects were presented at one location per trial. The rats had to learn to associate one object with reward in one spatial location and the other object with reward in other location. Rats received 6 trials per day.



Radial arm maze (RAM) (weeks 15 – 17)
Standard working memory (12 days)
All eight arms baited: find all eight baits without re-visits.
Delay and rotation task
Delay (4 days) 60 sec delay mid-trial to find the last 4 baits.
Rotation (4 days) 60 sec delay mid-trial, maze rotated, then find remaining 4 baits.



Results

Lesion Verification

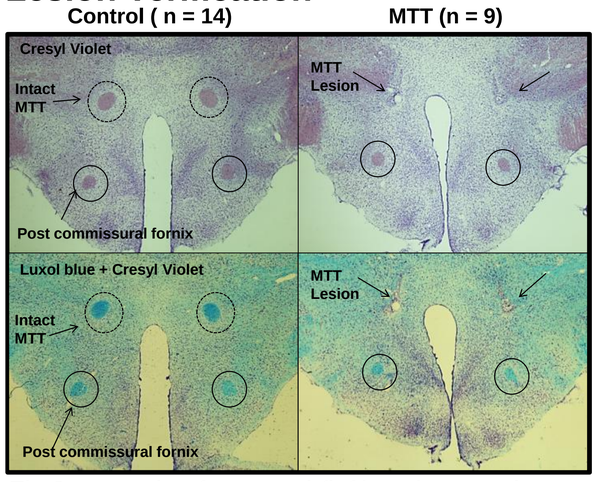


Fig 3. example of a control (left) and a complete bilateral lesion MTT lesion (right) at ~bregma -3.3 stained with both a nissl (top) and myelin-specific stain (bottom). Seven other MTT lesions failed.

Behaviour

Fig 4. **Water maze-reference memory**: MTT lesions did not impair acquisition of a fixed platform location (Lesion, $p > 0.20$).

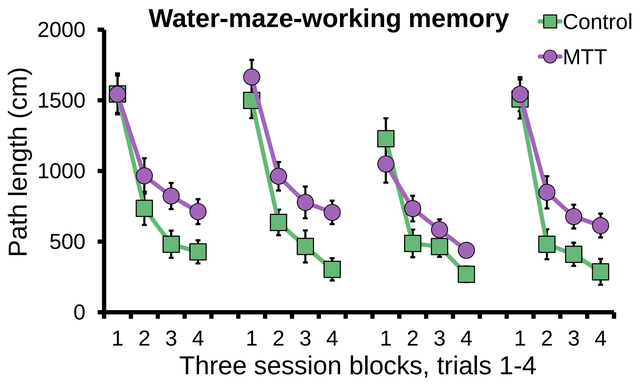


Fig 5. **Water maze-working memory:** MTT lesions impaired performance (Lesion, ($F(1, 21) = 13.04$, $p > 0.001$).

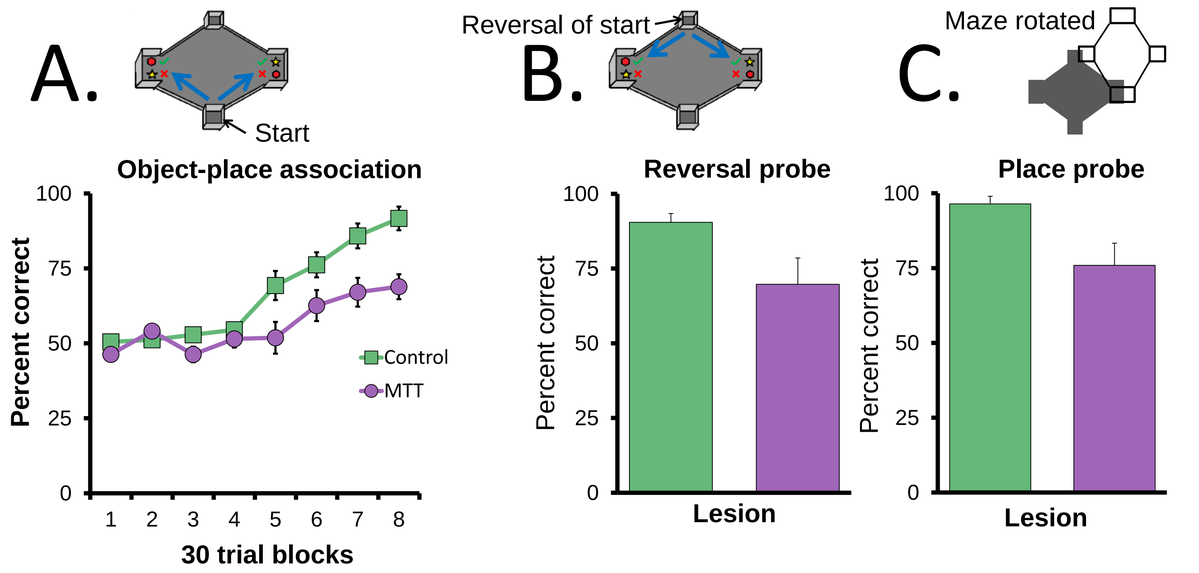


Fig 6a. **Object-place association :** MTT lesions impaired acquisition (Lesion, $F(1,21) = 12.66$, $p < 0.005$).

Fig 6b & 6c. **Object-place association reversal probe & place probe:** MTT lesions impaired performance on both probe trials $t(1,21) = 3.83$, $p < 0.001$ & $t(1,21) = 3.06$, $p < 0.006$ respectively. The probes showed that control lesion rats used allocentric memory.

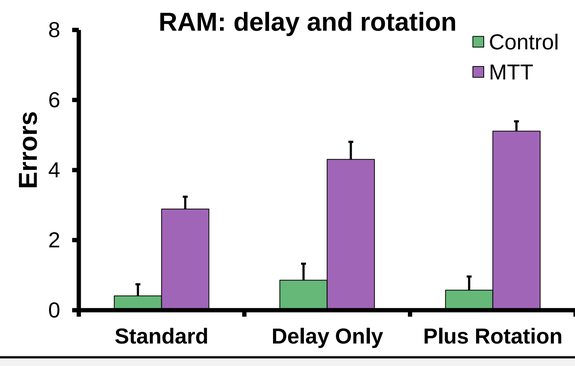


Fig 7. **RAM: delay and rotation:** Rats with MTT lesions made significantly more errors across all three conditions (Lesion, $F(1, 21) = 85.99$, $p < 0.001$ especially when a delay and delay plus rotation was added (Condition × lesion, $F(2, 42) = 6.17$, $p < 0.005$.

MTT VS ATN deficits

Surgery

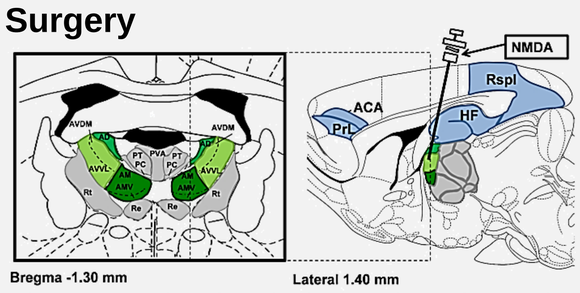


Fig 8. Coronal and sagittal atlas plates (Paxino's & Watson, 1998) indicating the extent of the ATN in the rat brain and the approximate target site for ATN lesions. Control (n = 11), ATN (n = 14).

Lesion verification

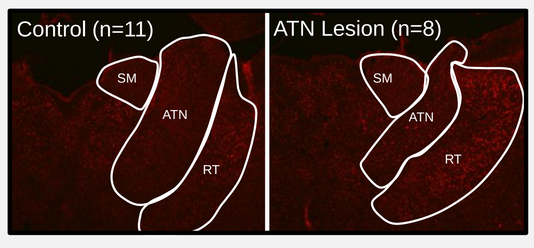


Fig 9. Example of a control (left) and ATN lesion (right) at ~ bregma -1.40 stained with propidium iodide (cell stain).

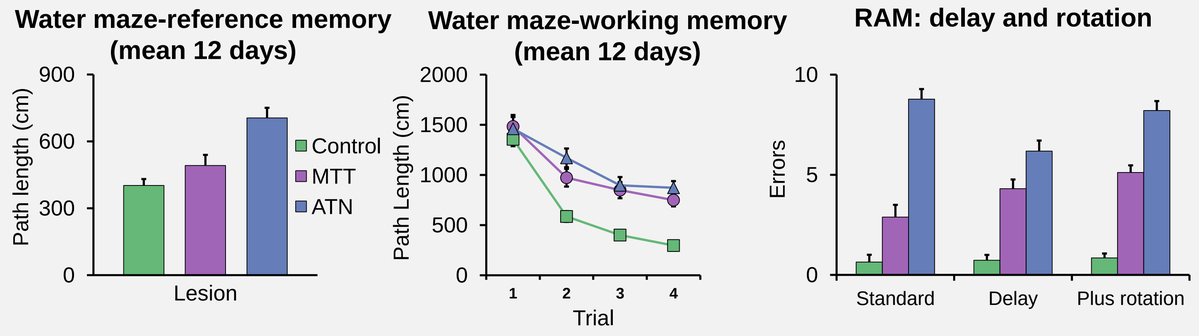


Fig 10. **Water maze-reference memory**: Only ATN lesions impaired acquisition of a fixed platform location (Lesion, $F(1,39) = 18.64$, $p < 0.001$).

Fig 11. **Water maze-working memory**: Both lesions impaired performance (Lesion, $F(1,39) = 20.53$, $p < 0.001$).

Fig 12. **RAM: delay and rotation:** Both lesion groups made more errors (Lesion, $F(1,39) = 102.2$, $p < 0.001$. ATN were more impaired than MTT lesions (Condition × lesion, $F(4,78) = 9.59$, $p < 0.001$).

Preliminary Immunofluorescence

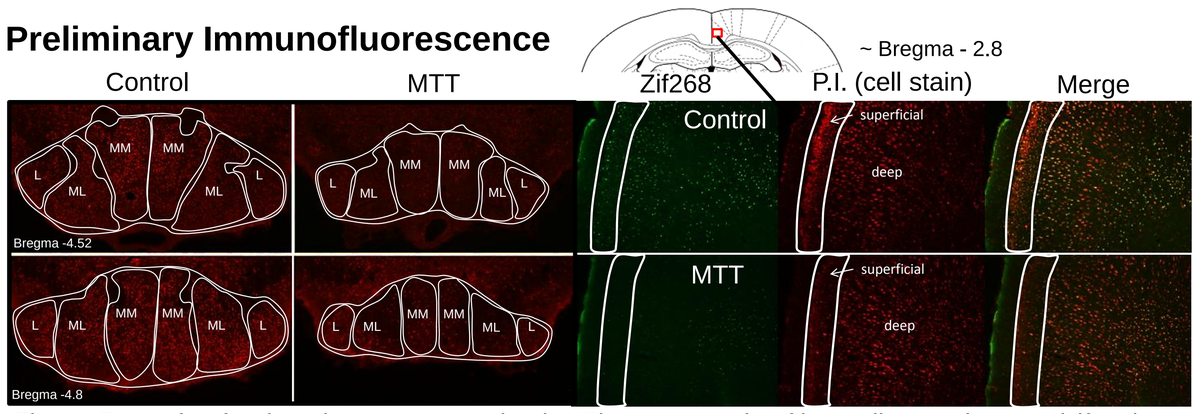


Fig 13. Example of reduced NeuN expression in the mammillary bodies following an MTT lesion.
MM = medial mammillary nucleus medial part; ML = medial mammillary nucleus lateral part; L = lateral mammillary nucleus.

Fig 14. example of immediate early gene (zif268) expression in the retrosplenial (Rgb) cortex in a control (top) and MTT lesion rat (bottom). The atlas plate above shows the region of interest (red box).

Conclusions

MTT lesions resulted in working memory and associative memory deficits. By comparison, rats with ATN lesions showed greater deficits, plus impairment in water maze reference memory. Substantial injury to the MTT contributes to diencephalic amnesia, but perhaps the severity of deficits in human cases is worsened by additional damage to adjacent structures.

References: Aggleton JP, Dumont JR, Warburton EC. (2011)Unravelling the contributions of the diencephalon to recognition memory: a review. *Learn Mem*, 18:384-400.: Carlesimo, G. A., Lombardi, M. G., & Caltagirone, C. (2011). Vascular thalamic amnesia : A reappraisal. *Neuropsychologica, 49*, 777-789; Child ND, Benarroch EE. (2013). Anterior nucleus of the thalamus: functional organization and clinical implications. *Neurology*; 81:1869-1876; Paxinos, G., & Watson, C. (1998). *The rat brain in stereotaxic coordinates* (4th ed.). San Diego: Academic Press.