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Review

# Why do lesions in the rodent anterior thalamic nuclei cause such severe spatial deficits?

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ABSTRACT

Lesions of the rodent anterior thalamic nuclei cause severe deficits to multiple spatial learning tasks. Possible explanations for these effects are examined, with particular reference to T-maze alternation. Anterior thalamic lesions not only impair allocentric place learning but also disrupt other spatial processes, including direction learning, path integration, and relative length discriminations, as well as aspects of nonspatial learning, e.g., temporal discriminations. Working memory tasks, such as T-maze alternation, appear particularly sensitive as they combine an array of these spatial and nonspatial demands. This sensitivity partly reflects the different functions supported by individual anterior thalamic nuclei, though it is argued that anterior thalamic lesion effects also arise from covert pathology in sites distal to the thalamus, most critically in the retrosplenial cortex and hippocampus. This two-level account, involving both local and distal lesion effects, explains the range and severity of the spatial deficits following anterior thalamic lesions. These findings highlight how the anterior thalamic nuclei form a key component in a series of interdependent systems that support multiple spatial functions.



**Contents**



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## 1. Introduction

On reflection, it is remarkable that lesions in the anterior thalamic nuclei (ATN) produce severe, long lasting deficits in rodents on a such wide range of spatial memory tests (e.g., Aggleton et al., 1995a, 1996; Aggleton and Sahgal, 1993; Beracochea and Jaffard, 1994; Byatt and Dalrymple-Alford, 1996; Célérier et al., 2000; Dumont et al., 2014a; Loukavenko et al., 2007; Mair et al., 2003; Mitchell and Dalrymple-Alford, 2005, 2006; Sutherland and Rodriguez, 1989; Sziklas and Petrides, 1999; Van Groen et al., 2002a). There are many different forms of spatial learning, which are supported by a multiplicity of brain sites (Mizumori et al., 2000; Taube, 2007; Moser et al., 2008), so why should these thalamic nuclei be so important? The finding is all the more extraordinary as animals can often switch between different strategies, thereby, counteracting impairments to specific spatial abilities. The implication is, therefore, that the ATN must either be critical for a range of spatial processes or that these thalamic lesions disrupt a fundamental process upon which multiple forms of spatial learning then depend. An example of the second account might be that the ATN are required for integrating intrinsic body signals with extrinsic spatial information.

This review provides a two-level explanation for why anterior thalamic lesions have such disruptive effects on spatial learning. The first level concerns the loss of functions provided by the anterior thalamic nuclei themselves, with the conclusion that these nuclei have multiple functions that contribute to effective spatial learning. The second level concerns the loss of function following 'covert pathologies' found in sites distal to the anterior thalamic nuclei, sites that normally support spatial learning. Because these same distal sites also appear to support multiple aspects of spatial learning, the impact of ATN lesions across a range of spatial processes is further exacerbated.

Reflecting this two-level account, the early sections of this review are concerned with the impact of lesions in the anterior thalamic nuclei. Some additional evidence comes from studies into the effects of mammillary body lesions as these hypothalamic nuclei have very dense projections focussed on the anterior thalamic nuclei. Particular attention is given to tests of T-maze alternation. This spatial test is readily learnt, has been used in many experiments, and is highly sensitive to anterior thalamic damage. Although spatial alternation is a test of 'working memory' (see Section 2.1), this feature is in itself not critical as anterior thalamic nuclei lesions also impair 'reference memory' tasks, such as learning the location of a submerged platform in the Morris water pool (Sutherland and Rodriguez, 1989; Warburton and Aggleton, 1999; Warburton et al., 1999; Wolff et al., 2008a,b). Later sections are concerned with the visualisation and mapping of neuronal dysfunctions beyond the thalamus, caused by anterior thalamic lesions. The implication from these latter experiments is that the spatial deficits following anterior thalamic lesions reflect a much broader array of brain dysfunctions than those evident from classic histological methods.

## 2. T-maze alternation and the anterior thalamic nuclei (ATN)

### 2.1. The reinforced T-maze alternation task

One of the most widely studied spatial abilities in rodents is T-maze alternation (Dember and Fowler, 1958; Dudchenko, 2001; Lalonde, 2002). Each alternation trial is in two stages (Fig. 1). For reinforced alternation, used in the large majority of lesion studies, the rat or mouse first runs up the stem of the T-maze and is only allowed to enter one of the two cross arms ('sample' run). In that arm the animal receives a reward. Next, the rodent is picked up and placed back at the start of the T-maze and, after a delay, is allowed a free choice between the two cross arms ('choice' test). The rodent is rewarded for selecting the arm opposite to that entered in the sample run, i.e., nonmatching-to-place. The choice of sample arm (and, hence, the rewarded arm on the choice test) is independent of the preceding trial. For this reason the task taxes 'working memory' (Olton et al., 1979).

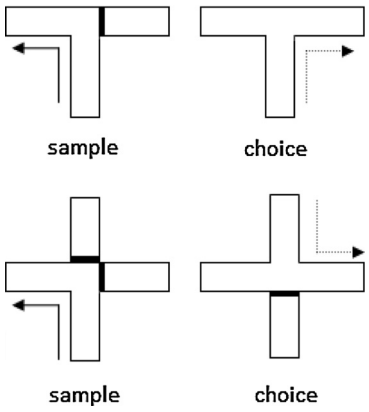


**Fig. 1.** T-maze (upper) and cross-maze (lower) arrangements used to test spatial alternation. The bold line depicts the barrier used on sample runs (solid arrow) to control the arm choice by the animal. The dashed arrow shows the correct arm in the choice test. The cross-mazes show how opposing start positions can be used for the sample run and choice test in order to disrupt egocentric and directional alternation.

It has been repeatedly shown that T-maze alternation is highly sensitive to ATN damage in rats (Aggleton et al., 1995a, 1996, 2009; Dumont and Aggleton, 2013; Loukavenko et al., 2007; Warburton and Aggleton, 1999; Warburton et al., 1997, 1999) and mice (Beracochea and Jaffard, 1994; Célérier et al., 2000). Following ATN lesions in rats, alternation performance often starts close to chance levels. Although an improvement is sometimes seen, the animals fail to reach normal levels of accuracy. Even when rats with ATN lesions are given environmental enrichment, which improves spatial alternation performance, the rats remain impaired with respect to their enriched controls (Loukavenko et al., 2007). Likewise, rats trained on T-maze alternation prior to their ATN lesions are still severely impaired when subsequently re-tested on spatial alternation after surgery (Warburton et al., 1999). This robust alternation impairment is all the more striking given that the task is so easy for intact rats to solve, sometimes resulting in near-ceiling levels of performance. An analysis of this task should, therefore, cast light on the wider spatial functions of the anterior thalamic nuclei.

It has long been known that rats will spontaneously avoid the arm of a T-maze last visited, instead preferring the novel arm or the arm that had been visited longer ago in time (Dember and Fowler, 1958; Dudchenko, 2001). This spontaneous preference reflects a bias to approach stimuli that are novel (Dember, 1956; Kivy et al., 1956). It is clear, however, that anterior thalamic lesions do not affect the tendency to detect and approach novel stimuli per se, as shown when testing object recognition memory (Mitchell and Dalrymple-Alford, 2005; Warburton and Aggleton, 1999; Wilton et al., 2001b). A different issue relates to the likelihood that testing in the T-maze, at least initially, may be anxiogenic. If anterior thalamic lesions affect anxiety then it is possible that such nonspatial changes could indirectly disrupt spatial memory. In fact, when tested in an elevated plus-maze, rats with anterior thalamic lesions appear to show reduced anxiety, as measured both by behaviour and by levels of corticosterone (Dupire et al., 2013). The implication is, therefore, that the lesion-induced alternation deficits principally arise from the spatial demands of the task.