Neuroscience and Biobehavioral Reviews 54 (2015) 145–160

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

# Anterior thalamic nuclei lesions and recovery of function: Relevance to cognitive thalamus

John C. Dalrymple-Alford[a,b,*], Bruce Harland[a], Elena A. Loukavenko[a], Brook Perry[a], Stephanie Mercer[a], David A. Collings[c], Katharina Ulrich[d], Wickliffe C. Abraham[d], Neil McNaughton[d], Mathieu Wolff[e,f]

[a] New Zealand Brain Research Institute, and Department of Psychology, University of Canterbury, Christchurch 8140, New Zealand
[b] Department of Medicine, University of Otago, Christchurch, New Zealand
[c] School of Biological Sciences, University of Canterbury, Christchurch, New Zealand
[d] Department of Psychology and Brain Health Research Centre, University of Otago, Dunedin, New Zealand
[e] University of Bordeaux, INCIA, UMR 5287, F-33400 Talence, France
[f] CNRS, INCIA, UMR 5287, F-33400 Talence, France

ARTICLE INFO

*Article history:*
Received 13 July 2014
Received in revised form 2 November 2014
Accepted 4 December 2014
Available online 29 January 2015

*Keywords:*
Thalamic amnesia
Enrichment
Spines
Retrosplenial
CA1
Cerebrolysin

ABSTRACT

Injury to the anterior thalamic nuclei (ATN) and their neural connections is the most consistent neuropathology associated with diencephalic amnesia. ATN lesions in rats produce memory impairments that support a key role for this region within an extended hippocampal system of complex overlapping neural connections. Environmental enrichment is a therapeutic tool that produces substantial, although incomplete, recovery of memory function after ATN lesions, even after the lesion-induced deficit has become established. Similarly, the neurotrophic agent cerebrolysin, also counters the negative effects of ATN lesions. ATN lesions substantially reduce c-Fos expression and spine density in the retrosplenial cortex, and reduce spine density on CA1 neurons; only the latter is reversed by enrichment. We discuss the implications of this evidence for the cognitive thalamus, with a proposal that there are genuine interactions among different but allied thalamo-cortical systems that go beyond a simple summation of their separate effects.



**Contents**



* Corresponding author at: University of Canterbury, Psychology, 20 Kirkwood Avenue, Christchurch 8041, New Zealand. Tel.: +64 3 364 2998; fax: +64 03 364 2181.
*E-mail addresses:* jc.dalrymple.alford@gmail.com, john.dalrymple-alford@canterbury.ac.nz (J.C. Dalrymple-Alford).

http://dx.doi.org/10.1016/j.neubiorev.2014.12.007
0149-7634/

## 1. Introduction

Diencephalic amnesia is associated with injury to thalamic nuclei and associated fibre tracts (Markowitsch, 1988; Kopelman, 2014). Recognised by clinical studies long before attention became focused on the hippocampal formation and medial temporal lobe, this subcortical pathology is increasingly viewed as an important field of study if we are to achieve a full understanding of the neuroanatomical basis of memory, and episodic memory in particular (Aggleton, 2014; Carlesimo et al., 2014; Child and Benarroch, 2013; Kopelman et al., 2009). Several thalamic structures within the diencephalon have been implicated, most commonly the mediodorsal nucleus (MD), the midline and intralaminar nuclei (ILN), the anterior thalamic nuclei (ATN), and the fibre pathways associated with these nuclei (Aggleton et al., 2011; Dillingham et al., 2014; Mitchell and Chakraborty, 2013; Pergola and Suchan, 2013; Savage et al., 2012; Vann, 2013). It is likely that human cases of amnesia involve damage to multiple thalamic sites and fibre tracts, some of which may affect many cognitive processes in addition to their influence on memory (Carlesimo et al., 2014; Carrera and Bogousslavsky, 2006; Cipolotti et al., 2008; Mennemeier et al., 1992; Nishio et al., 2014). Nonetheless, the bulk of human evidence for impaired recollection and episodic memory dysfunction (the hallmark of anterograde amnesia) most strongly implicates the ATN, the mammillary bodies (MB), and the mammillothalamic tract, a unique tract among limbic system neurocircuits because it provides a unidirectional link from the MB to ATN (Aggleton et al., 2011; Carlesimo et al., 2011; Harding et al., 2000; Van der Werf et al., 2003; Vann et al., 2009).

The variability of unintended brain injury to closely adjacent nuclei and tracts in people with diencephalic amnesia has naturally led to a variety of animal lesion models. These animal models aim to test a circumspect injury and thus identify the region most likely to cause human memory loss. As with the analysis of human cases, this evidence supports an influence on memory of injury to many thalamic nuclei. When highly localised lesions have been made to different limbic thalamic structures, the animal studies generally suggest selectivity for, or differences in, the type of memory that is affected (Alcaraz et al., 2014; Bailey and Mair, 2005; Burk and Mair, 1998; Burk and Mair, 1999; Chudasama et al., 2001; Corbit et al., 2003; Mair et al., 2003; Mitchell and Dalrymple-Alford, 2005; Mitchell and Dalrymple-Alford, 2006; Wolff et al., 2008). For example, Moreau et al. (2013) trained rats with either neurotoxic ILN lesions or ATN lesions in two discrimination learning tasks, using the water maze protocols devised by Packard and McGaugh (1992) in which one of two visual cues was present with one arbitrary cue attached to a submerged escape platform. Irrespective of the order of testing, Moreau et al. (2013) showed that only rats with ATN lesions experienced impaired acquisition of the spatial task, in which the fixed location of a hidden platform was guided by a redundant visual cue, whereas neither lesion impaired acquisition of the specific correct visual cue when spatial information was redundant (Fig. 1). Others have shown that both MD and ILN lesions impaired performance of a delayed matching task trained with retractable levers, producing delay-dependent (MD) and delay-independent (ILN) deficits, respectively (Bailey and Mair, 2005). By contrast, localised MD or ILN lesions did not affect a varying choice radial maze delayed non-matching task, which instead was impaired by ATN and hippocampal system lesions (Bailey and Mair, 2005; Mair et al., 2003).

These and other observations align with a growing body of literature that supports Aggleton and Brown's (1999) initial focus on the ATN as a key site for injury or disconnection that disrupts a functionally inter-dependent extended hippocampal system. Specifically, ATN injury often produces spatial and temporal memory deficits that overlap with those found after explicit hippocampal system injury (Aggleton, 2008; Aggleton et al., 2011; Aggelton and Nelson, 2014; Dumont and Aggleton, 2013; Wolff et al., 2006). Likewise, disconnection and electrophysiological studies show that interactions between the ATN, retrosplenial cortex and hippocampal formation support learning and retrieval of events linked with spatial and context-dependent information (Gabriel, 1993; Henry et al., 2004; Smith et al., 2002; Warburton et al., 2001).

## 2. The anterior thalamic nuclei (ATN)

This idea of an extended hippocampal system with the ATN as a nodal point in the exchange of both cortical and subcortical information relevant to episodic memory receives considerable support from anatomical descriptions of the neural connections of the ATN (Aggleton et al., 2010; Dillingham et al., 2014; Jankowski et al., 2013; Wright et al., 2013). The three subnuclei of the ATN have a substantial number of reciprocal connections with the subicular cortex of the hippocampus and with the prefrontal cortex. They also exert an influence through reciprocal connections with the different regions of the retrosplenial cortex, thereby making major contributions to serial connections across the extended circuit. An excellent summary of these and other ATN connections was provided by Jankowski et al. (2013) see also, Dillingham et al. (2014). Rather than a purely passive role, however, the ATN may provide a strategic influence on the hippocampal system, perhaps on the basis of the unique modulation made on the ATN by its connections with the MB and brainstem tegmental nuclei (Vann, 2013; see Fig. 2). In addition, the apparent segregation of information transfer to the ATN, both directly from the hippocampal formation and from the MB, as well as from the prefrontal cortex, suggests the potential for subcircuit specificity (Jankowski et al., 2013; Wright et al., 2013).

These descriptions imply that the ATN are a pivotal – and perhaps critical – node in the extended hippocampal system. Thus both lesion and neuroanatomical evidence is consistent with the fact that dysfunction of the ATN has multiple ramifications on the network of brain structures associated with episodic memory. Conversely, the multitude of overlapping pathways and connections across the extended hippocampal system may also permit a degree of functional redundancy across ATN neurocircuitry, and perhaps the extended system as a whole. Indeed, evidence that other structures are failing as a consequence of distal injury to the ATN, MTT and even the ventral tegmental nucleus of Gudden (Dumont et al., 2012; Dupire et al., 2013; Garden et al., 2009; Jenkins et al., 2004; Mendez-Lopez et al., 2013; Poirier and Aggleton, 2009; Reed et al., 2003; Vann, 2013; Vann and Albasser, 2009), raises an interesting question that is relevant to memory impairment associated with lesions to components of the extended hippocampal system and its related neurocircuitry. Can we reverse some of the seemingly permanent memory deficits produced by ATN lesions (and other system lesions)? That is, after ATN injury, can other cortical and subcortical structures retain neuroplasticity and so have the capacity to respond to suitable treatments?

## 3. Recovery of function after ATN lesions

The prospect of some recovery or sparing of function after thalamic injury may explain some of the variability in memory deficits evident after thalamic injury in humans (Carlesimo et al., 2014; Carrera and Bogousslavsky, 2006; Pergola and Suchan, 2013; Van der Werf et al., 2003). Even in the context of the Korsakoff syndrome, in which permanently impaired memory is regarded as the defining symptom, and loss of ATN neurons the most prominent feature (Harding et al., 2000), only 25% of patients show no

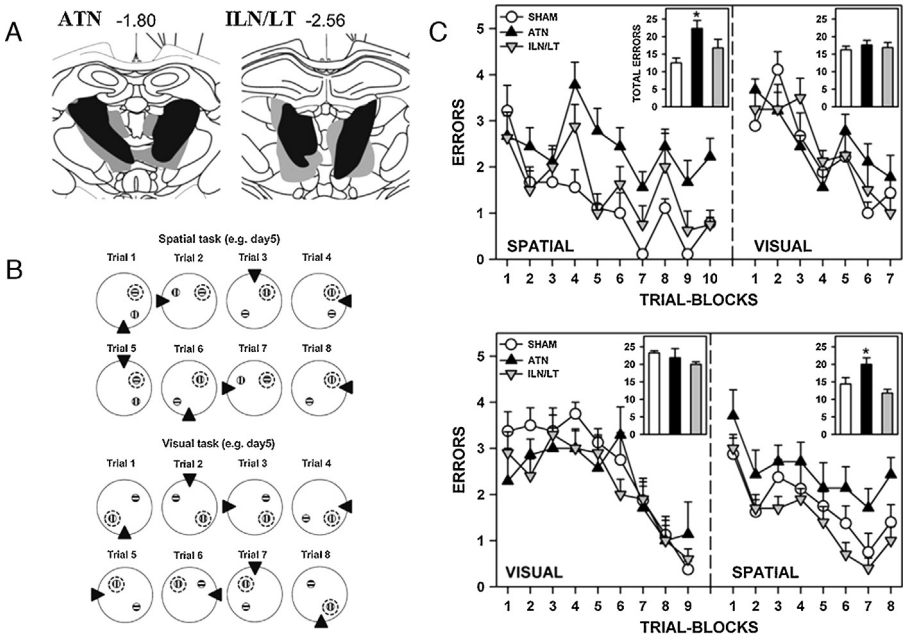


**Fig. 1.** Moreau et al. (2013) compared the effects of neurotoxic anterior thalamic nuclei (ATN) lesions and intralaminar/lateral thalamic nuclei (ILN/LT) lesions (A) on a spatial task and a visual task (B) in which two visual cues were present in the water maze, one of which signalled the presence of a submerged escape platform (dashed circle). The ATN lesions produced an acquisition impairment on the spatial task, irrespective of the order of testing (C).

improvement, while memory improves slowly over time in 50–75% of cases with perhaps as many as 25% showing relatively good recovery (Kopelman et al., 2009; Victor et al., 1971). Although seldom explicitly tested, deficits found after ATN lesions in rats appear to be permanent, at least with various spatial memory tasks. For example, evidence from the forced alternation spatial working memory task was instrumental in developing the idea of the extended hippocampal–diencephalic axis (Aggleton and Brown, 1999) and ATN lesions produce severe deficits on this task that persist for up to 4 months postsurgery despite repeated exposure to spatial memory training (Loukavenko et al., 2007; Ulrich et al., 2014; Warburton et al., 2000). That is, in standard-housed laboratory rats, there appears to be little spontaneous recovery after ATN lesions. In this context, evidence of some recovery of function after experimental treatment strategies in robust animal models of ATN lesions would encourage formal therapeutic intervention in clinical cases of diencephalic amnesia. The current review summarises studies that have used environmental enrichment to address this question.

### *3.1. Environmental enrichment and recovery of function after brain injury*

Enriched environments are a proven therapeutic tool to ameliorate learning and memory deficits after many types of brain injury (Alwis and Rajan, 2014; Will et al., 2004; Nithianantharajah and Hannan, 2006; Hannan, 2014; Pang and Hannan, 2013). An enriched environment for rats in a laboratory setting is generally one in which a moderately large (10–12) group of animals is housed in a large cage in which they are exposed to stimulation far beyond that afforded by the standard empty laboratory cages that often house 3 or 4 rats (Simpson and Kelly, 2011). Such enrichment generally includes multiple objects within the cage that are regularly replaced with new objects, often on a daily basis. It provides a complex mixture of informal cognitive stimulation and learning, plus physical, motor, multisensory, social and emotional experiences. Unlike natural (feral) conditions, laboratory enrichment establishes a safe complex environment that has relatively stable social conditions but the inanimate physical conditions are frequently changing. The benefits of enrichment are thought to arise from a combination of increased exercise, socialisation, and novelty, producing stronger effects than each of these components administered individually (Cracchiolo et al., 2007; Einon et al., 1980; Olson et al., 2006; Sozda et al., 2010; Will et al., 1986). These effects are likely to be mediated byincreased activation of multiple brain networks, including changesto their recruitment during behavioural tasks, together with neurobiological effects that range from the size and morphology ofbrain regions to the survival and complexity of neurons, adult neu-rogenesis, enhanced cell excitability and synaptic plasticity, anda wide array of neuroprotective molecular responses that reflectmultiple genetic processes, including neuroinflammation and lev-els of trophic factors (Alwis and Rajan, 2014; Bonaccorsi et al.,2013; Briones et al., 2013; Eckert and Abraham, 2013; Hirase and Shinohara, 2014; Leger et al., 2012; Rampon et al., 2000a,b; Will et al., 2004).

Although the majority of recent studies examined the beneficial effect environmental enrichment in animal models of relatively diffuse brain injury, such as stroke, traumatic brain injury and various neurodegenerative diseases (Alwis and Rajan, 2014; Hannan, 2014; Johansson, 2004; Pang and Hannan, 2013), this therapeutic approach to recovery began with the study of acute localised lesions in cortical regions and the hippocampal formation (Will and Kelche, 1992; Will et al., 2004). Behavioural deficits in spontaneous alternation, the Hebb-Williams maze and radial arm maze after lesions to the dorsal hippocampus and the subiculum have been reduced when rats were subsequently housed in enriched environments, although the beneficial effects of enrichment are less common in the Morris water maze with these lesions, and there are mixed findings after fimbria-fornix lesions and as yet no identified benefit after lesions to the entorhinal cortex (Bindu et al., 2007; Dhanushkodi et al., 2007; Galani et al., 1998; Will and Kelche, 1992; Will et al., 2004). The reduced impairments after hippocampal lesions have been associated with both social housing by comparsion with individual housing conditions as well as enrichment relative to standard group housing (Will et al., 2004).

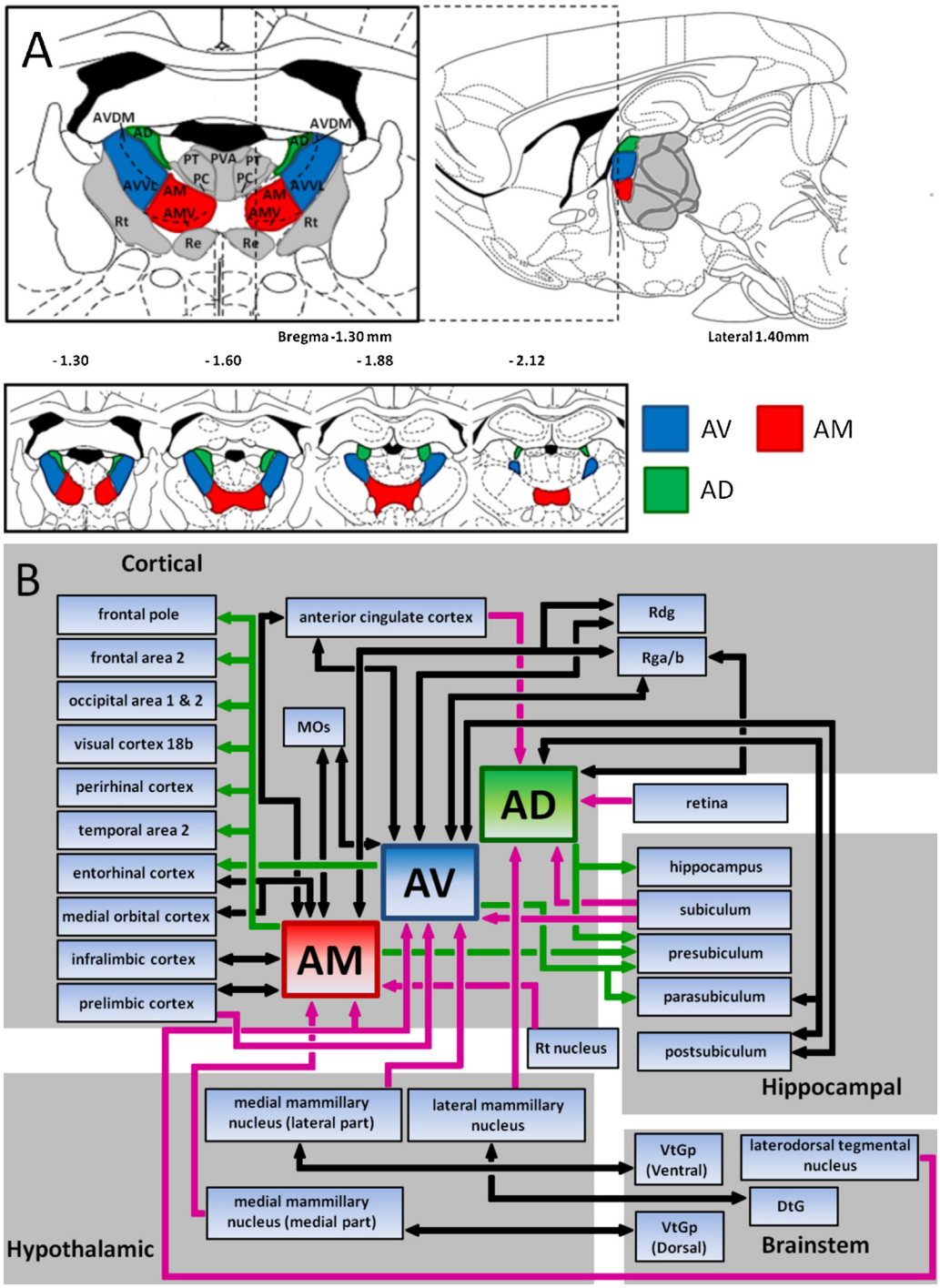


**Fig. 2.** Location (A) and connections (B) of the anterior thalamic nuclei (ATN), adapted from Jankowski et al. (2013), Wright et al. (2013), van Groen et al. (1999), and Vann (2013). The coronal and sagittal sections (Paxinos and Watson, 1998) depicted in (A) show the anterior-posterior and medial-lateral extent of the anteroventral (AV), anteromedial (AM), and anterodorsal (AD) subnuclei of the ATN. The enlarged coronal section indicates the subdivisions of the AV, the anteroventral dorsomedial region (AVDM), the anteroventral ventrolateral region (AVVL); and the anteromedial ventral region (AMV); grey regions indicate adjacent thalamic structures: reticular nucleus of the thalamus (Rt), nucleus reuniens (Re), paratenial thalamic nucleus (PT), paraventricular thalamic nucleus (PVA), and paracentral thalamic nucleus. The main neural connections of the AM, AV and AD in the rat brain are shown in (B). Black arrows represent reciprocal connections, pink arrows afferents, and green arrows efferents, of the three ATN subnuclei. Connecting structures have been grouped into cortical, hippocampal, hypothalamic and brainstem regions. The reciprocal projections from the ventral (VtGp) and dorsal tegmental nucleus of Gudden (DtG) to the mammillary bodies have been included because of their unique non-hippocampal contribution conveyed directly (to AV) or indirectly, via the mammillary bodies, to the ATN and beyond. Additional abbreviations: MOs, secondary motor cortex; Rdg, retrosplenial dysgranular cortex; Rga, caudal retrosplenial granular cortex; Rgb, rostral retrosplenial granular cortex.

### *3.2. Enriched environment and recovery of the flexible use of spatial memory after ATN lesions*

An important feature of the episodic memory system is its ability to synthesise relational representations that can be used flexibly in novel test conditions to generate novel behaviour (Eichenbaum, 2000). A convincing example of this ability in the context of spatial memory was established by a modified water maze procedure introduced by Eichenbaum et al. (1990). Rats with fornix or hippocampal lesions were able to learn the location of a fixed platform

location using a fixed (i.e. constant) start point at the edge of the pool, but then performed extremely poorly when challenged with new start points; intact rats showed little disruption during these probe trials (Compton et al., 1997; Eichenbaum et al., 1990). This procedure provides a particularly clear test of the flexible use of relational spatial representations and thus a useful measure of recovery of a critical facet of the declarative memory system.

Wolff et al. (2008) tested the flexible use of allocentric spatial representations to determine whether the expected deficits after hippocampal–diencephalic injury, caused by neurotoxic ATN lesions, were amenable to therapeutic intervention using a postoperative enriched environment. The results were clear. Over the 10-day acquisition period, the standard-housed rats with ATN lesions (AT-Std; 3 to 4 ATN and sham rats in a standard cage) acquired the initial task using a fixed start position, albeit at a severely impaired rate compared to the other three groups (Fig. 3A). By contrast, the Enriched group with ATN lesions (AT-Enr; 12 ATN and sham rats in a large cage with multiple objects all changed on a daily basis) acquired this task at a similar rate to the intact SHAM-Std housed group; the best rate of acquisition was displayed by the SHAM-Enr group. The critical probes using novel start positions on the third and sixth trial on three subsequent days produced a mild increase in path length in the intact sham groups by comparison to trials using the originally-trained start position. By contrast, a clear impairment was evident in the AT-Std housed group during these probe trials, shown by a substantial increase in path length. Recovery of function on these critical probe trials was, however, evident in the AT-Enr group because these rats were not disproportionately affected by the novel start positions (Fig. 3B). When switched to the acquisition of a new platform position and the conventional procedure of using four different start points across the four daily trials, substantial impairment, and recovery of spatial memory, was again evident in the AT-Std and AT-Enr groups, respectively (Fig. 3C). A residual impairment on this second task remained in the AT-Enr group, showing that recovery was incomplete.

The findings reported by Wolff et al. (2008) show that postoperative enrichment can promote the recovery of allocentric spatial memory in rats with ATN lesions including the flexible use of spatial representations in novel task conditions. Although a diversity of strategies may help a rat learn the location of a platform (e.g., Oswald and Good, 2000; Zheng et al., 2003), probe testing was introduced only after substantial training from a constant start point. It was therefore unlikely that these findings could be explained by possibility that the improvement in the AT-Enr group reflected the engagement of multiple strategies during acquisition that were then transferred to solve the probe task. Hence enriched housing conditions provided an experimental therapy that countered the negative effects of ATN lesions on the establishment of a spatial representation. Given the earlier summary (Section 3.1) of the influence of enriched environments after brain injury, it is possible that the beneficial effect on spatial memory in the water maze after ATN lesions depends on the integrity of the hippocampus and/or the entorhinal cortex.

### 3.3. Recovery from prior memory impairment

One important question in terms of improved performance with an experimental therapy after lesions is whether the treatment effect is primarily due to a "recovery from deficit" or the "sparing of a deficit." Sparing of function would occur when, for example, early treatment minimises the subsequent severity of the deficit; such early intervention can be highly pertinent in the context of the Korsakoff syndrome (Kopelman et al., 2009). Recovery of function from a prior, established condition would be relevant to many clinical situations, because essential medical treatment is often necessary, and the person's condition stabilised, before attention is given to potential cognitive rehabilitation.

The answer to this question came from a study conducted by Loukavenko et al. (2007). Their first experiment showed that rats with ATN lesions produced severe deficits in spatial working memory using a preoperatively trained T-maze non-matching-to-place task. As mentioned earlier, this reinforced spatial alternation task provides a sensitive behavioural assay of dysfunction in the extended hippocampal system (Warburton and Aggleton, 1999; Warburton et al., 1999; Ward-Robinson et al., 2002). The deficit is especially severe when a cross-maze apparatus is used that emphasises the use of extramaze cues (e.g. allocentric spatial cues) and minimises the benefit of a directional strategy or potential egocentric (response-based) strategy (Aggleton et al., 1996; Warburton et al., 1997). In the study by Loukavenko et al. (2007), thirty days of enrichment was introduced either soon after surgery (Experiment 1) or only after the spatial working memory deficit induced by ATN lesions had already been established by postoperative testing (Experiment 2).

Rats with ATN lesions that were housed in standard conditions (SC-ATN) showed only chance levels of performance in spatial working memory when tested in the cross-maze apparatus (Fig. 4). These rats did not benefit from repeated experience in the task as the deficit showed little sign of changing across tests conducted 14 days, 75 days and 120 days postsurgery. Rats with ATN lesions that were housed postoperatively in enriched environments (EE-ATN) showed intermediate performance relative to the sham-lesion groups and the SC-ATN group. This improved spatial memory was evident both when enrichment was introduced soon after surgery (Experiment 1; not shown) and when enrichment was delayed 40 days post-surgery, which was after the spatial working memory deficit induced by ATN lesions had already been well-characterised by postoperative testing (Experiment 2, Fig. 4B). The improved spatial working memory in the EE-ATN group also persisted beyond the period of enrichment, which suggests that some (unspecified) biological changes were maintained in rats with ATN lesions after a period of environmental enrichment.

One issue is whether the recovery observed includes some return to the processes or strategies associated with normal function, in this case the presumed spatial and temporal functions associated with the extended hippocampal system. The findings reported by Wolff et al. (2008) mentioned above are consistent with a return to normal function. The study by Loukavenko et al. (2007) also provided evidence that a degree of normalised function was present in the enriched rats with lesions. The cross maze used in this study enabled trials in which both the sample and test runs of the trial used either the same start position (e.g. both runs from the South start arm) or a test run that used the opposite start position (e.g. test run from the North start arm that follows a sample run from the South start arm; Fig. 4A). All groups, especially rats with ATN lesions when standard-housed, showed better performance on the same start position trials than on the opposite start position trials (Fig. 4C). If the rats were using consistent directional and olfactory cues at the choice point, then they would be unimpaired or at least show similar levels of performance on the two types of trial. A reliance on egocentric (body orientation) cues at the choice point is consistent with good performance on the same start position trials and, because such a strategy would then lead to a return to the previously visited arm, poor performance on the opposite start position trials. While rats with hippocampal system lesions may be more reliant on egocentric strategies, or at least unimpaired on tasks that explicitly test such strategies (Aggleton et al., 1995; Mitchell and Dalrymple-Alford, 2006; Warburton et al., 1997; Wolff et al., 2008), an egocentric strategy appears to be seldom used by intact rats in spatial alternation working memory tasks (Aggelton and Nelson, 2014; Baird et al., 2004; Dudchenko, 2001;

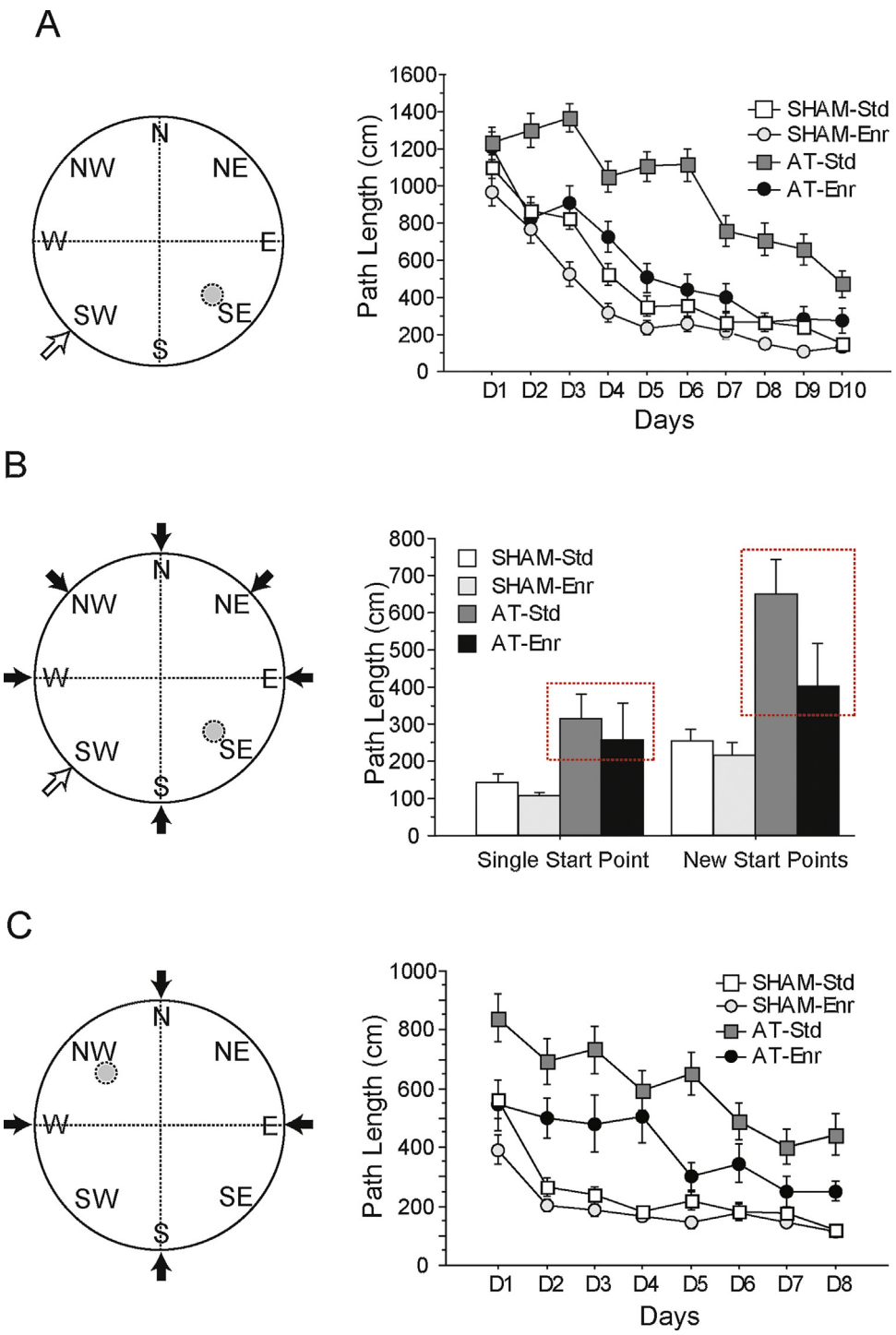


**Fig. 3.** Spatial reference memory in the water maze, adapted from Wolff et al. (2008). (A) Schematic representation of the constant start reference memory procedure used for task 1 (left panel) showing the location of the constant start position (white arrow) and the submerged platform location (grey circle). The right panel depicts the mean (±SEM) path length of each group to reach the platform across the 10 blocks (mean of four daily trials) of acquisition. (B) Schematic representation of the testing procedure used across the three days of probe testing (left panel). For this task the platform location remained fixed as for acquisition testing (grey circle), but now two of the six daily trials (trials 3 & 6) were started from novel positions (black arrows) with the remaining trials (1, 2, 4 & 5) starting from the constant position used during acquisition testing (white arrow). The right panel depicts the mean (±SEM) path length of the four groups to locate the submerged platform for both constant and novel start point trials across the three days of probe testing. (C) Schematic representation of the standard spatial reference memory procedure used for task 2 (left panel). The four different start points were used per day (black arrows) and the submerged platform (grey circle) was now located in the opposite quadrant. The right panel depicts the mean (±SEM) path length of the four groups across the 10 acquisition blocks (mean of four daily trials). Abbreviations: AT, neurotoxic lesions to the anterior thalamic nuclei; ENR, enriched environment; Std, housed in standard group conditions.

Pothuizen et al., 2008). The differential performance of standard-housed rats with ATN lesions across the two types of trial may also reflect susceptibility to retroactive interference from cues of various kinds when traversing the stem on the test trial for the opposite start position trails. The ATN rats that were housed in environmental enrichment showed improvements on both types of trial. The improvement on opposite start position trials in particular suggests that the use of extramaze place cues was to some extent restored

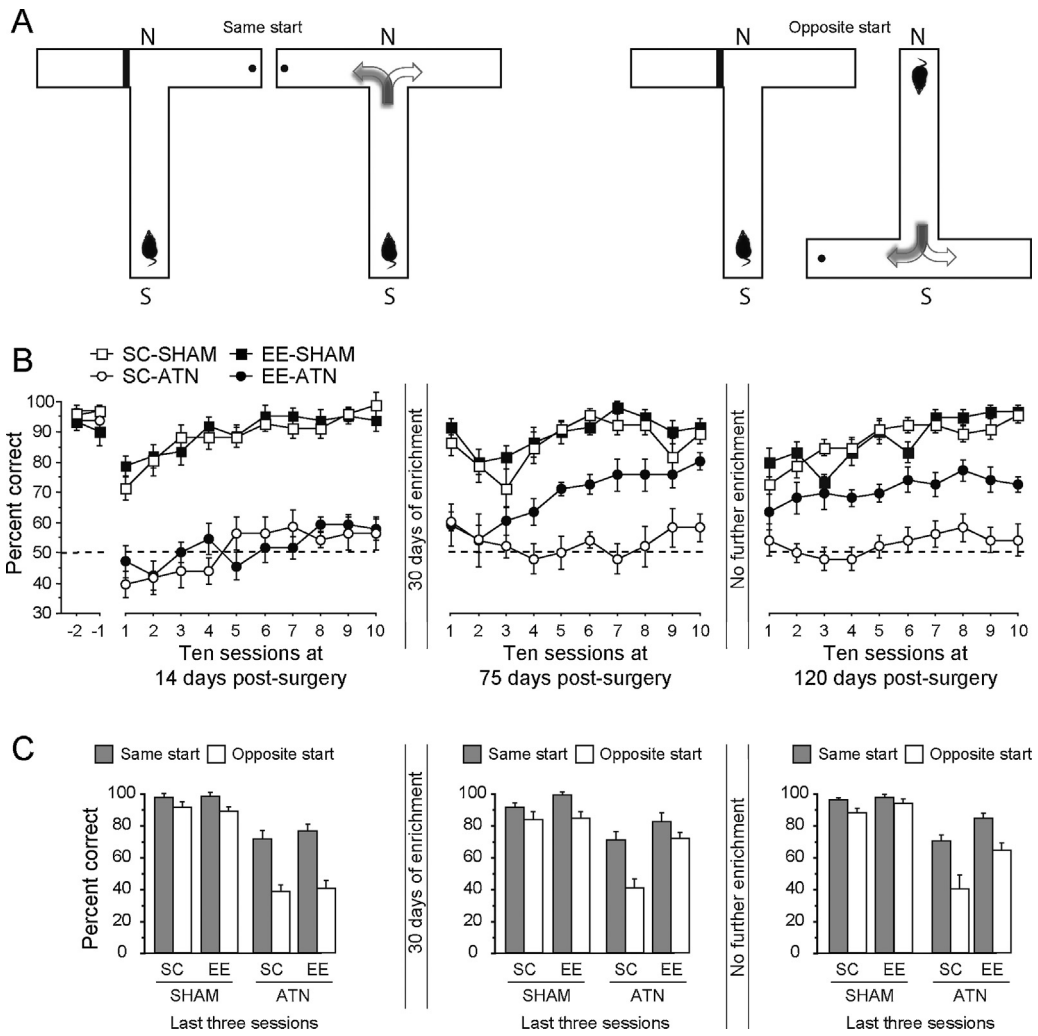


**Fig. 4.** Spatial working memory in the cross-maze, adapted from Loukavenko et al. (2007), Experiment 2. (A) Depicts the cross maze procedure, which consisted of two trial types, 'same start position' trials (left panel) and 'opposite start position' trials (right panel). On 'same start position' trials the sample run (far left; with forced choice of arm) and the test run (second from left; free choice) were run from the same start area requiring rats to alternate the goal arm for reward on the test run (shaded arrow). On 'opposite start position' trials the sample run (second from right) and test run (far right) were started from opposite ends of the cross-maze. Baited arms for sample runs were counterbalanced across all trials. (B) Mean (±SEM) performance for the last two sessions of pre-surgery testing (−1, −2) and 10 sessions of post-surgery testing prior to the enrichment period (left panel), after the 30-day period of enrichment (middle panel) and at 120 days post-surgery (right panel). (C) Performance for the last three sessions of each test expressed separately for the 'same start position' trials and 'opposite start position' trials on these three tests. Abbreviations: ATN, neurotoxic lesions to the anterior thalamic nuclei; EE, enriched environment; SC, housed in standard group conditions.

by this treatment, perhaps in part through reduced susceptibility to retroactive interference.

### 3.4. Recovery using cerebrolysin, a neurotrophic drug

The afore-going behavioural recovery in spatial memory from ATN lesions after enrichment is encouraging. Pharmacological treatments may, however, be more feasible from a clinical perspective. We examined the potential for recovery after ATN lesions using the neurotrophic drug, cerebrolysin (Loukavenko et al., in press). This compound offers a unique pharmacotherapeutic option as it is a parenterally-administered mixture of different active fragments of neurotrophic factors and small peptides, including nerve growth factor and brain derived neurotrophic factor (Sharma et al., 2012; Windisch, 2000). Cerebrolysin has many pleiotropic actions, similar to those of enrichment: it reduces apoptosis, promotes neurogenesis, improves glucose transport across the blood-brain barrier, improves cerebral vasculature, increases dendritic complexity, and facilitates behavioural recovery in models of neurodegeneration and hippocampal lesions (Francis-Turner and Valouskova, 1996; Hartbauer et al., 2001; Juarez et al., 2011; Rockenstein et al., 2006; Ubhi et al., 2013; Vázquez-Roque et al., 2012). Cerebrolysin has also received favourable reports in Alzheimer's disease clinical trials (Plosker and Gauthier, 2009).

The primary aim of this study was to determine whether cerebrolysin (Cere, 2.5 ml/kg i.p., daily), starting 3 days post-surgery for a thirty day period, either alone or in combination with postoperative enrichment (starting at 5 days), produced better recovery of spatial working memory after ATN lesions than enrichment alone. As before, spatial working memory was assessed postoperatively using a preoperatively trained T-maze non-matching-to-place task, embedded within a cross-maze apparatus.

The second aim was to examine whether functional recovery of spatial working memory associated with cerebrolysin or enrichment after ATN lesions coincided with improved expression of c-Fos in the retrosplenial cortex. One of the most interesting consequences of ATN dysfunction in rats, discovered by John Aggleton, Seralynne Vann and their colleagues, is that ATN and mammillothalamic tract lesions (and lesions to the ventral tegmental nucleus of Gudden, the brain stem nucleus that projects to the MB) produce a

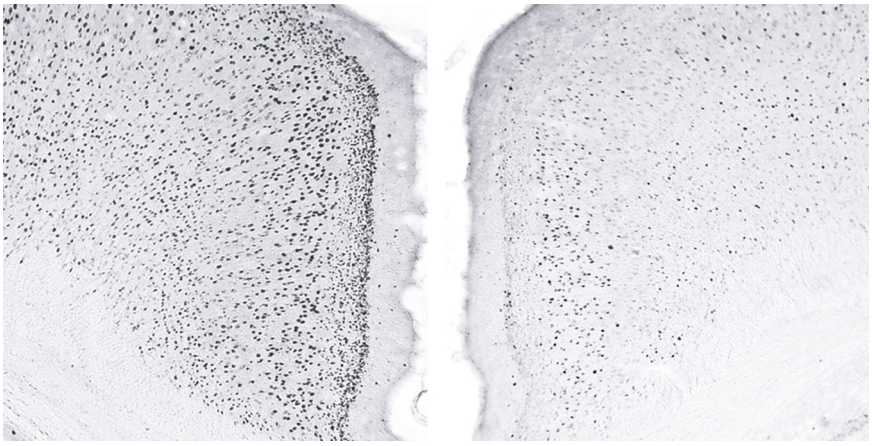

**Fig. 5.** Aggleton, Vann and colleagues discovered that ATN lesions dramatically reduce the immediate early gene, c-Fos, in the retrosplenial cortex. The pattern of Fos-positive neurons in the rostral retrosplenial cortex is shown in a sham-control rat (left panel), which contrasts with the marked loss of c-Fos staining in the retrosplenial cortex of the rat with an ATN lesion, especially in the (medial) superficial layers (right panel). The restrosplenial cortex is intact in both sections, Nissl cell counts are unchanged, and this region retains numerous inputs from other sites. Figure courtesy of (personal communication).

dramatic, enduring and exacerbating reduction in the expression of immediate-early gene products (IEG), c-Fos and Zif268, in the retrosplenial cortex (Fig. 5) (Aggleton, 2008; Albasser et al., 2007; Amin et al., 2010; Dumont et al., 2012; Jenkins et al., 2002a,b; Jenkins et al., 2004; Poirier and Aggleton, 2009; Vann, 2013; Vann and Albasser, 2009).

As expected, rats with ATN lesions that were housed in standard cages, in this instance with saline control injections, showed severely impaired spatial working memory (Fig. 6A, left panel). Other groups with ATN lesions that were standard housed but given cerebrolysin, enrichment with saline injections, or the combination of cerebrolysin with enrichment, all showed substantially improved spatial working memory. Fewer errors on the same start position trials were shown by these three treatment groups at the start of training; improved performance on the opposite start trials was evident by the end of training (not shown). The pattern of performance in untreated, standard-housed ATN rats (untreated) replicated our previous study, with improvement across training on the same start position trials but consistently poor performance (chance level) on trials that used the opposite start position for the test runs. When the interval between sample and test run was increased from the standard 5 s ITI to 40 s ITI, the performance of the group with the combination treatment of cerebrolysin plus enrichment was similar to that of the sham standard housed control group whereas the single-treated groups had lower performance (Fig. 6A, right panel).

ATN lesions in standard-housed groups produced a substantial reduction in c-Fos expression by comparison with the levels of this IEG product expressed by rostral retrosplenial cortex and superficial layers of caudal retrosplenial cortex in intact rats. Unlike their behavioural recovery, however, the three treatment groups maintained low expression of c-Fos in the retrosplenial cortex (Fig. 6B). The study by Loukavenko et al. (in press) only used a single (reference) control group that was housed in standard conditions; it is possible that sham-lesion rats given cerebrolysin or enrichment would have a lower level of c-Fos expression than standard-housed rats, which would temper the apparent failure to reverse low c-Fos in the retrosplenial cortex in treated ATN groups. However, a second study showed that c-Fos expression in the retrosplenial cortex was not reduced in sham-enriched rats compared to sham-standard rats and again remained low in ATN rats housed in an enriched environment (Dupire et al., 2013). The latter authors also reported, however, evidence that the phosphorylated cAMP response element-binding protein (pCREB) in the granular retrosplenial cortex is reduced by ATN lesions, but there was some evidence that this marker increased in sham-lesion and ATN-lesion enriched rats. Increased expression of pCREB in the retrosplenial cortex has been linked with encoding and storage of spatial memory (Czajkowski et al., 2014) and warrants further study in the context of recovery of function after ATN lesions. Nonetheless, the failure to find increased c-Fos expression in the retrosplenial cortex in rats with ATN lesions after environmental enrichment suggests that this molecular marker of spatial memory in the extended hippocampal system may have a limited or task-dependent utility.

### 3.5. Recovery of neuronal microintegrity in hippocampal CA1

The IEG data on the effects of ATN (and mammillothalamic tract) lesions represents an intriguing feature of recent developments of the extended hippocampal system hypothesis as it shows that diencephalic injury has a direct, and potentially powerful, influence on the functional integrity of other components of a distributed system. An extension of this idea, which has received less attention, is the suggestion that the ATN primarily influence the hippocampus, rather than vice versa, through various direct and indirect routes (Aggleton et al., 2010; Dillingham et al., 2014; Vann, 2010;Fig. 2). Functional changes in the hippocampus after ATN lesions have been reported, such as reduced phosphorylated CREB (pCREB) as well as IEG markers (c-Fos; zif268), but these are generally weaker (and sometimes not evident in the case of IEG markers) compared with changes in the retrosplenial cortex (Jenkins et al., 2002a,b; Dumont et al., 2012; Dupire et al., 2013). In the dorsal hippocampal CA1, enrichment increases pCREB in sham-lesion rats only, while both sham-lesion and ATN-lesion rats show a small reduction in c-Fos expression (Dupire et al., 2013).

Another example that dovetails with the suggestion that the ATN have a greater influence on the hippocampus than vice versa comes from the medial thalamus injury produced by pyrithiamine-induced thiamine deficiency in rats, a model for the Korsakoff syndrome (PTD; Savage et al., 2012). While the PTD model produces diffuse injury, there is prominent neuronal loss in the anteroventral subnucleus of the ATN, the medial mammillary bodies and the ILN. Rats with PTD-induced brain injury have adequate basal levels of hippocampal acetylcholine efflux, but they show a task-related functional impairment in acetylcholine release that correlates with poor performance on spatial memory tasks (Savage et al., 2012). Conversely, intrahippocampal infusions of the acetylcholinesterase inhibitor physostigmine eliminated the

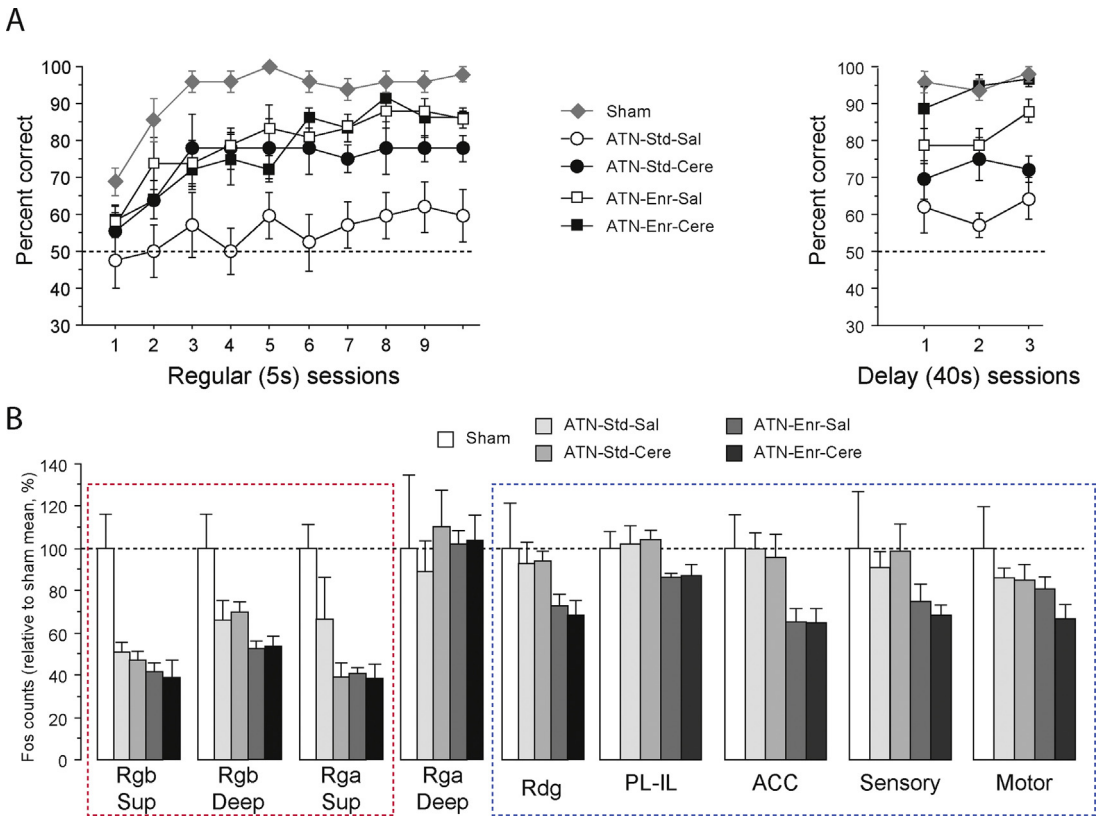


**Fig. 6.** (A) Spatial working memory in the cross-maze, adapted from Loukavenko et al. (in press) showing recovery of function when either cerebrolysin, enrichment or the combination of these two treatments were employed in rats with ATN lesions. Performance is shown when a regular (5 s) delay was used between the sample and test runs (left panel) and when a longer (40 s) delay was used (right panel). (B) Group effects on c-Fos counts in the retrosplenial cortex (granular rostral, Rgb; granular caudal, Rga; dysgranular, Rdg), prefrontal cortex (prelimbic–infralimbic, PL–IL), and primary sensory and primary motor cortex. C-Fos in the sham group was expressed as a mean of 100%. Severely reduced c-Fos in retrosplenial cortex compared to controls was evident in all groups with ATN lesions. ATN, neurotoxic lesions to the anterior thalamic nuclei; Enr, enriched environment; Std, housed in standard group conditions; cere, cerebrolysin; sal, saline.

PTD-associated behavioural impairment, as did intraseptal inhibition of GABA to increase hippocampal acetylcholine release (Roland et al., 2008; Roland and Savage, 2009).

We reasoned that a convincing test of the idea that the ATN have a strong influence on hippocampal function would be to evaluate the impact of ATN lesions on the microstructural integrity of CA1 pyramidal neurons in the hippocampus (Harland et al., 2014). The CA1 cells are a primary source of hippocampal outputs with collateral projections to multiple brain regions (Cenquizca and Swanson, 2006; Aggleton, 2012), and thus may be a good barometer of the overall well-being of the hippocampal system. We asked whether postoperative enrichment would also affect CA1 neurons in rats with ATN lesions. Environmental enrichment is known to affect hippocampal neurons, including CA1 spine density after subiculum lesions (Bindu et al., 2007; Eckert and Abraham, 2013). As enrichment seemed not to cause increases in c-Fos expression in the retrosplenial cortex (Dupire et al., 2013; Loukavenko et al., in press), the second objective of this study was to determine whether ATN lesions and enrichment produced changes in the microstructural integrity of neurons in the superficial layer of the rostral granular retrosplenial cortex.

Once again, ATN lesions produced substantial impairments in standard-housed rats, which were not ameliorated by lengthy testing using both reinforced spatial alternation in the cross maze and spatial memory in the radial arm maze. Spatial memory improved in rats with ATN lesions that were subsequently housed in an enriched environment. On this occasion, we employed a more standardised enrichment protocol in which thirteen objects were introduced each day, no single object was repeated within five days, and one day with no enrichment objects was programmed every 8th day; placement of the enrichment cages within the colony room was changed every fourth day (http://www.psyc.canterbury.ac.nz/StandardizedEnrichment.shtml) (Fig. 7). Golgi staining revealed a remarkable reduction in CA1 spine density after ATN lesions in the standard-housed rats, with virtually no overlap (~6%) in the distribution of spine counts in these rats compared to the distribution of spine counts in sham-lesion controls (Fig. 8). Reflecting the impact of ATN lesions on CA1 neurons, the effect size for the reduction in basal CA1 spines (Cohen's $d = 3.77$, CI 2.89–4.65) was greater than that of the spatial working memory deficit in the cross maze ($d = 2.40$, CI 1.80–3.00). Enrichment increased CA1 spine density in both sham rats and those with ATN lesions; this measure in the latter group approached that found in the sham standard-housed rats (Fig. 8D and E, left four groups). Spine density was related to spatial learning in enriched rats, because CA1 neurons in trained rats showed significantly more spines than in rats that received only pseudo-training in the memory tasks (Fig. 8E and D, right four groups).

In terms of the second question, ATN lesions also substantially reduced the density of apical spines of fusiform pyramidal neurons whose cell bodies are found in layers II/III of the rostral retrosplenial cortex (Fig. 9). The greater variation in spine number across rats resulted in a smaller effect size of ATN lesions ($d = 1.88$) than was evident for CA1 neurons. In this instance, however, there were no effects of enrichment in either rats with ATN lesions or sham rats, and no difference between trained as opposed to pseudo-trained rats. Together with the low c-Fos expression in the retrosplenial

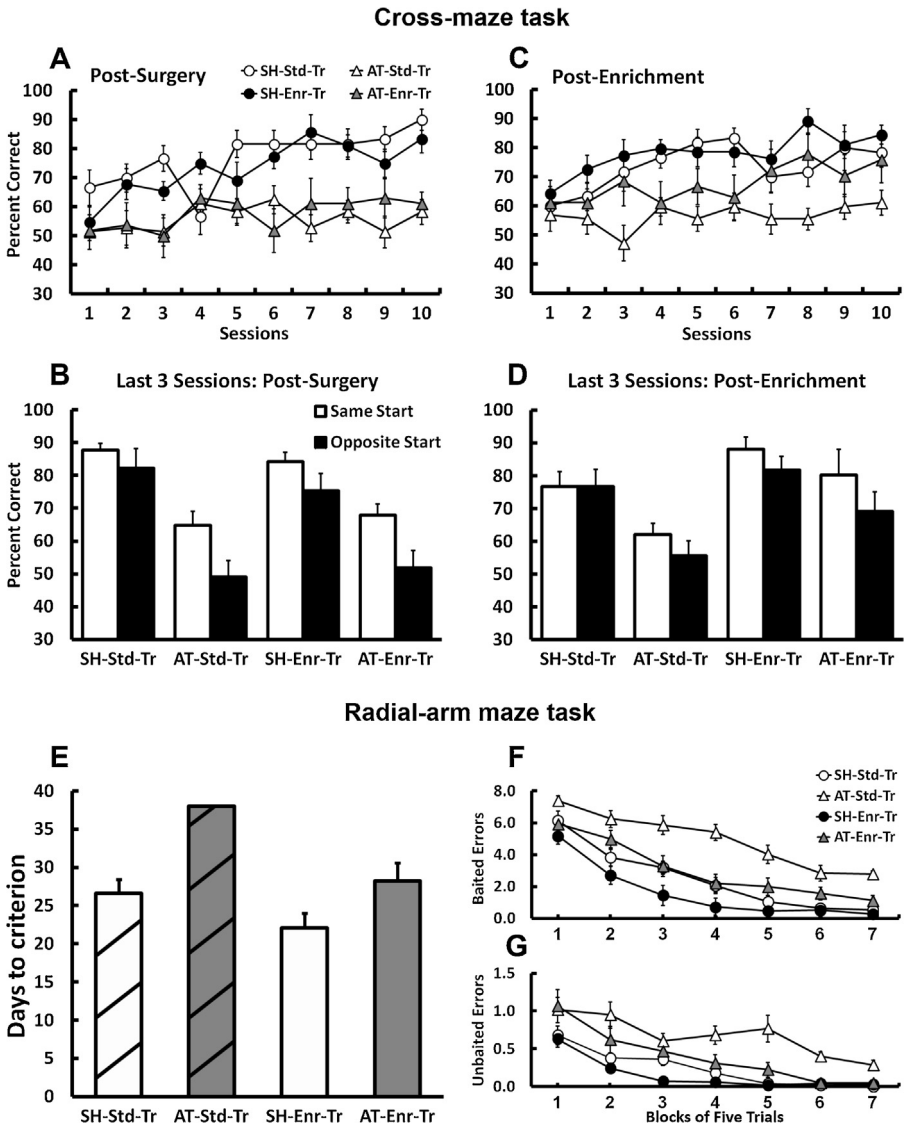


**Fig. 7.** Spatial working memory in the cross-maze, adapted from Harland et al. (2014) after lesion surgery but before differential housing (A) and after the enrichment period (B); Impaired performance on both the 'same start position' trials and 'opposite start trials' that was impaired post-surgery (C) improved after enrichment (D). A similar enrichment-induced reversal of a spatial memory impairment produced by ATN lesions was evident in the radial arm maze when one of the 8 arms was unbaited (E–G). AT, neurotoxic lesions to the anterior thalamic nuclei; SH, sham; Enr, enriched environment; Std, housed in standard group conditions.

cortex in treated ATN rats despite showing recovery of spatial memory, the lack of enrichment effect in restoring spine number in the superficial layers of this limbic cortex leaves open the question of the significance for memory of the reduced c-Fos evident after ATN lesions. This question is addressed below.

## 4. Limitations and future directions

The tasks on recovery of function after ATN lesions have thus far addressed spatial memory, most often reinforced alternation using spatial working memory. One limitation, therefore, concerns the relatively narrow range of behavioural tests employed, so the generality of these findings awaits further validation. The tasks used suggest a degree of generalisation in terms of recovery of function, but a broader range of both spatial and non-spatial tasks, including conditional learning tasks, would provide a more convincing basis for translational work to commence in a clinical context. For example, lesions of the retrosplenial cortex have limited effects on reinforced spatial alternation, whereas deficits occur more reliably when there is a conflict between intramaze and extramaze cues, such as when maze rotation is introduced after the first four choices of a radial arm maze test (Pothuizen et al., 2008, 2010; Vann and Aggleton, 2005). Thus this maze rotation task would be useful to examine the influence of experimental therapeutic intervention on both memory and IEG expression in the retrosplenial cortex in rats with ATN lesions. Similarly, it would be valuable to learn how the electrophysiology of retrosplenial cortex and hippocampal neurons during encoding, consolidation, and reconsolidation of spatial and contextual tasks (Miller et al., 2014; Smith et al., 2012) is affected by ATN lesions and enrichment. Conversely, it is possibile that environmental enrichment will be able to reverse some of the effects of lesions to the retrosplenial cortex, perhaps through changes to the MB-ATN neuroaxis.

The failure to find recovery of IEG expression in the retrosplenial cortex may also be associated with the incomplete recovery that has been observed thus far in experimental studies, so tools are needed that restore this dysfunction after hippocampal–diencephalic system lesions. It would also be interesting to know whether enrichment alters any of the other changes evident in the retrosplenial

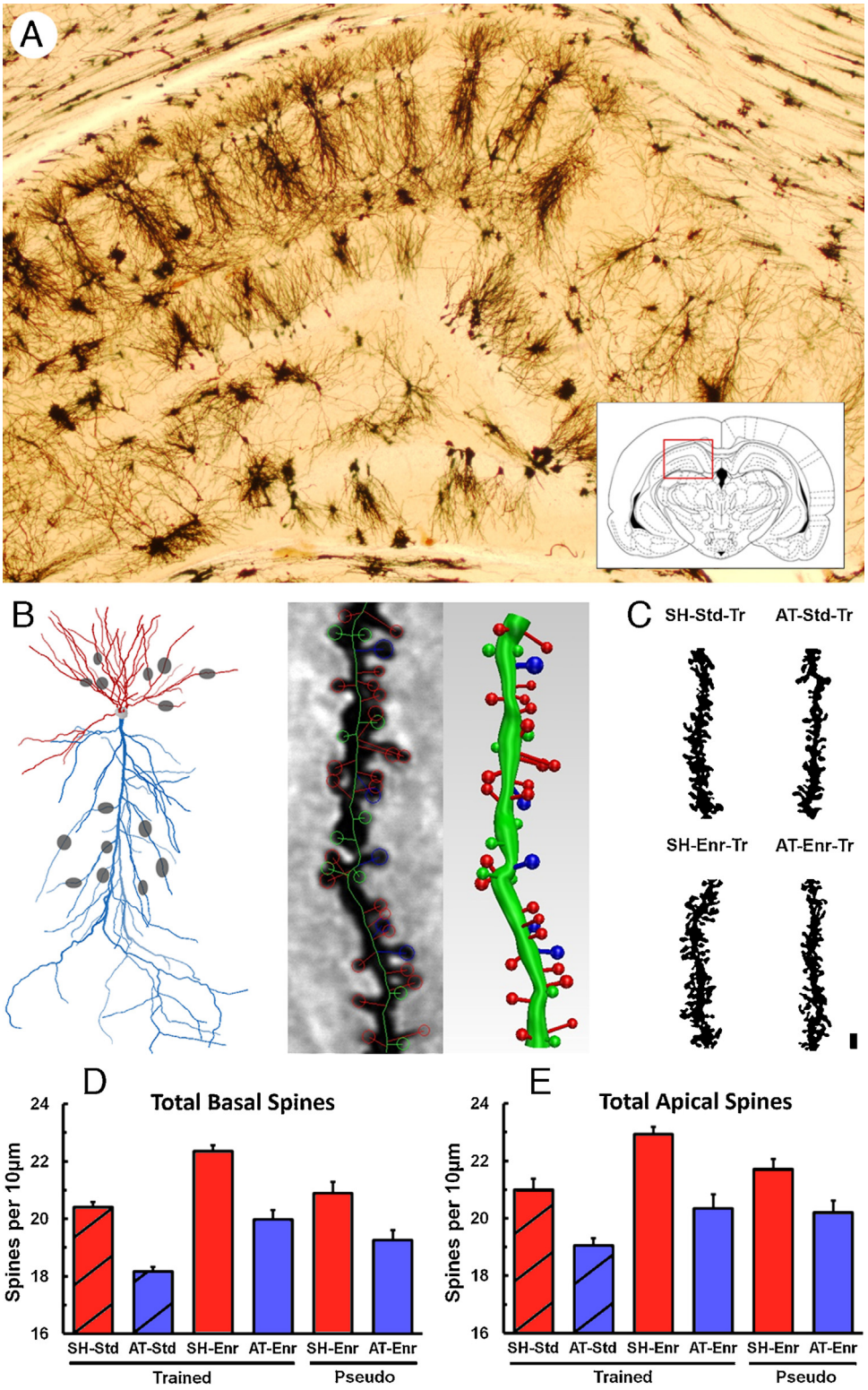


**Fig. 8.** Adapted from Harland et al. (2014). Golgi staining of the dorsal hippocampus (A) was used to examine basal and apical dendritic segments of CA1 pyramidal neurons processed using Neurolucida (B) to count spine density (per 10 µ) in sham and ATN-lesion groups housed in either standard conditions or enrichment (C). Both basal (D) and apical (E) spine density in CA1 was reduced by ATN lesions and increased by enrichment (four groups on left of each panel), and increased by formal spatial memory training compared to pseudotraining in enriched groups (four groups on right of each panel). AT, neurotoxic lesions to the anterior thalamic nuclei; SH, sham; Enr, enriched environment; Std, housed in standard group conditions.

cortex produced by ATN lesions, such as loss of electrophysiological neuroplasticity, reduced pCREB (see Dupire et al., 2013) and transcriptome disturbances such as GABA-A *receptor delta subunit*, *serotonin receptor 2c, zif268*, *fra-2*, *kcnab2*, *cox6b, mmp9*, *cghB*, or *ruvbl1* (Amin et al., 2010; Dumont et al., 2012; Dupire et al., 2013; Garden et al., 2009; Poirier et al., 2008). Similarly, a host of neurobiological changes are associated with enrichment, including increases in neurogenesis and trophic factors (Will et al.,

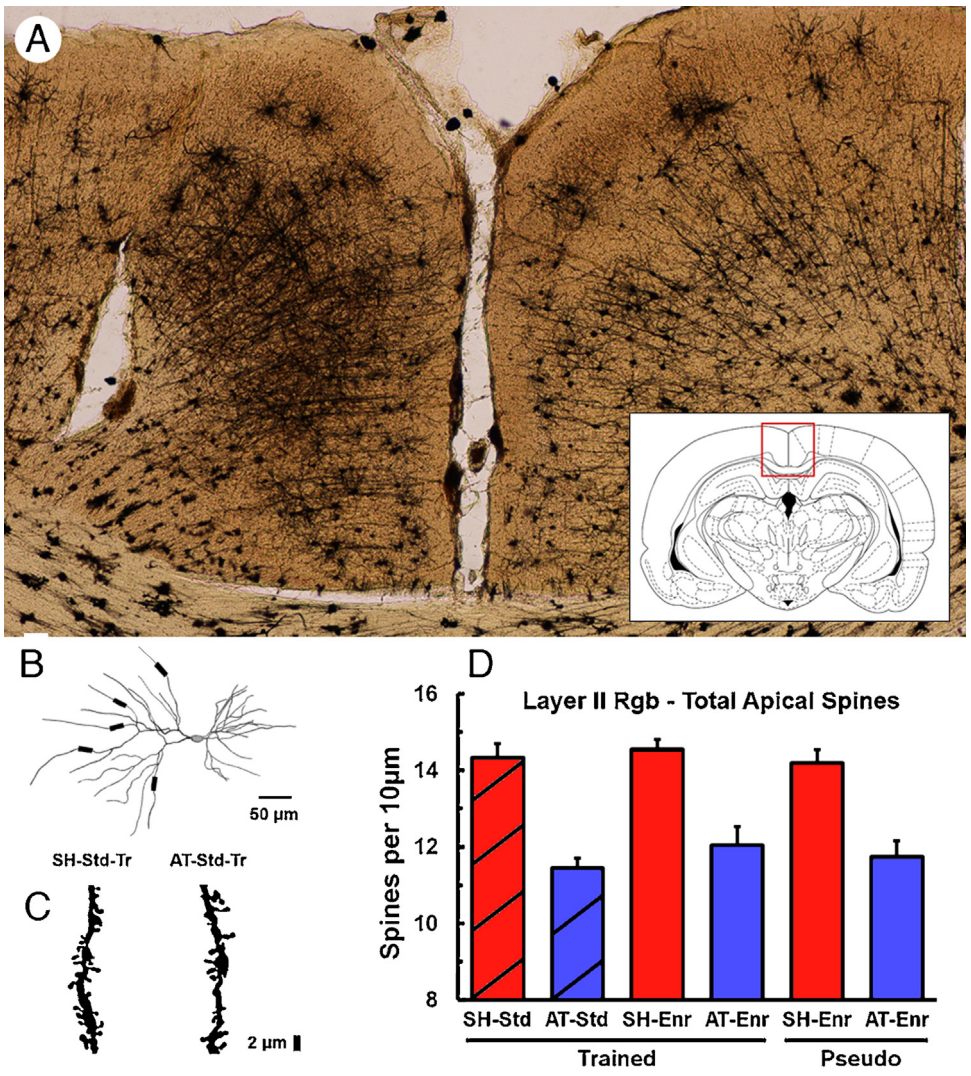


**Fig. 9.** Adapted from Harland et al. (2014). Golgi staining of the rostral retrosplenial cortex (A) was used to examine apical dendritic segments of fusiform layer II/III pyramidal neurons processed using Neurolucida (B) to count spine density (per 10 µ) in sham and ATN-lesion groups (C). Apical spine density (D) was reduced by ATN lesions, but not changed by enrichment (four groups on left of each panel), or by formal spatial memory training when compared to pseudotraining in enriched groups (four groups on right of each panel). AT, neurotoxic lesions to the anterior thalamic nuclei; SH, sham; Enr, enriched environment; Std, housed in standard group conditions.

2004), so it would be interesting to know whether any of these mechanisms are associated with recovery of function after diencephalic lesions.

A second issue concerns recovery of function in other models of diencephalic injury. One obvious question is whether damage to ATN connections are also sensitive to the effects of therapeutic treatments. Lesions to the mammillary bodies, mammillothalamic tract and the brainstem projections to the ATN and mammillary bodies would be key contenders for this approach (see Vann, 2013). In these instances the ATN are intact but presumably have some lesion-related dysfunction that might be reversed, especially after lesions of the ventral tegmental nucleus of Gudden that leaves the classic Papez circuitry intact.

Deficits after other thalamic lesions (e.g. MD, ILN) that are associated with various memory deficits should also be investigated, as well as the potentials for exacerbation or compensation of memory impairments when multiple thalamic regions show dysfunction. One question, for example, is whether MD function is enhanced by enrichment in the presence of an ATN lesion. Other work has shown that low levels of thalamic stimulation can enhance conditional discrimination, which may provide additional tools for cognitive neuro-rehabilitation (Mair and Hembrook, 2008; Mair et al., 2011; Shah and Schiff, 2012). Savage and her colleagues have already produced novel evidence of recovery of function in PTD model of the Wernicke–Korsakoff syndrome. Aside from optimizing the balance of acetylcholine-GABA interactions in the septohippocampal circuit in PTD to recover spontaneous spatial alternation in a plus-maze (Roland and Savage, 2009), Savage and colleagues have shown that this behaviour in PTD rats was increased by acetylcholine in the anterior cingulate cortex, but not the retrosplenial cortex. Similarly, they have shown that voluntary exercise (running wheel) recovered spatial alternation in PTD rats and that this improvement was related to increased oligodendrocyte precursors and elevated brain-derived neurotrophic factor and nerve growth factor in the frontal cortex, but not in the restrosplenial cortex (Hall et al., 2014). Clearly, similar approaches would be interesting to examine in the context of enrichment or cerebrolysin after localised thalamic lesions, including ATN lesions.

## 5. Implications for cognitive thalamus and a proposal

We stated earlier that the orderly segregation of information transfer between the hippocampal formation and the ATN, suggested by neuroanatomy, may not necessarily translate to specific,

segregated functions. Instead, these separate pathways may share a degree of functional overlap, generating redundancy. A middle view would be that the parallel pathways may support a mixture of globally overlapping outputs that can result from locally segregated connections. Such a functional arrangement could extend beyond the classic regions of the extended hippocampal system to overlapping connections with the prefrontal cortex or even other cortical regions, including the retrosplenial cortex. This type of organisation could further extend, in a presumably increasingly graded fashion, to include the mediodorsal nuclei (and its subcomponents), the intralaminar and midline nuclei (especially the reuniens), and potentially other thalamic nuclei that are less frequently implicated in memory, particularly the laterodorsal nuclei and lateral posterior nuclei (in the rat; pulvinar in the human) (Aggleton et al., 2011). The perspective being proposed here is that there are genuine interactions among different but allied thalamo-cortical systems that go beyond a simple summation of their separate effects. For example, severe deficits may emerge or be exacerbated when partial lesion occurs in each of two relevant thalamic structures, whereas each lesion alone may produce only a mild deficit. Indeed, this may be true even within the components of the ATN (Aggleton et al., 1996; van Groen et al., 2002).

There are two reasons for this proposal. First, these possibilities are stimulated by the nature of the sparing and recovery of function described above with respect to ATN lesions. The studies summarised earlier suggest that recovery from ATN-related dysfunction may be mediated in part by changes in the hippocampal formation, at least at the level of CA1 neurons. However, some of the changes in the retrosplenial cortex caused by ATN lesions may not need to be reversed for recovery, although it remains an open question whether other therapeutic tools to reverse these changes, alternative behavioural tasks, or other molecular changes in the retrosplenial cortex might be associated with recovery of function after these lesions. But it is also possible that more effective therapeutic tools induce changes that shift the balance of graded functions in other structures, and their interconnections.

At least two lines of evidence support the prospect that changes to an anterior cortical limbic system can compensate for ATN lesions that predominantly affect a posterior cortical limbic system. The work on recovery of spatial alternation in the PTD model, mentioned above, indicated that the observed deficits can be reversed by changes either directly to the prefrontal (cingulate) cortex or the hippocampus. Secondly, a large body of electrophysiological evidence of training-induced activity (TIA) in retrosplenial cortex neurons during discrimination learning is consistent with a model (Gabriel, 1993) in which a gradient of thalamo-cortical activity exists between an anterior circuit, involving the MD and the anterior cingulate, and a posterior circuit involving in particular the anteroventral nucleus of the ATN and the retrosplenial cortex. Stage-specific and context-specific peaks of training-induced excitation in the anterior circuit precede the development of similar peaks in the posterior circuit, including hippocampal CA1. There is more temporal overlap during appetitive than during avoidance learning and a different ordering of TIA within each circuit between approach and avoidance tasks with thalamic involvement earlier for appetitive learning and cortical earlier for avoidance learning (Freeman et al., 1996a,b). The bigger picture, however, is that both circuits become engaged during learning in an inversely related fashion over time, such that the anterior circuit is normally dominant during the initial stages of new learning and the posterior circuit is normally dominant during the later stages of learning (Gabriel, 1993). Different neurons within a cortical region may contribute unequally to this scenario, with rapidly-forming discriminative activity occurring in deep layers of the retrosplenial cortex and the anterodorsal nucleus of the ATN, and late-developing discriminative activity occurring in superficial layers of the retrosplenial cortex and the anteroventral nucleus of the ATN (Gabriel et al., 1991). When recovery of spatial memory has been observed after ATN lesions, these generally follow a pattern in which the treated rats with ATN lesions are primed to better learn the association or task over time, rather than starting from the same vantage point of an intact animal. In other words, rather than the various detailed circuits making either unique or redundant contributions to memory, their influence may be shifted by suitable treatments so that they can accommodate the neural plasticity required for partial reinstatement of the impaired function. It is hard to determine what a critical test might be in this regard, but one possibility would be to examine an object-place association as this is impaired by both selective ATN and selective MD lesions (Cross et al., 2013; Wilton et al., 2001) and to determine whether the loss of one circuit changes the behaviour of the alternate circuit in animals showing recovery as opposed to those not showing recovery.

Another possibility that may reflect the balance of interactions across anterior and posterior thalamo-cortical circuits concerns the brain's low frequency rhythmicity, "theta". The prefrontal cortex and hippocampal formation show coupling of theta rhythm when they are interacting to process information (Young and McNaughton, 2009). Reinstatement of theta rhythmicity can recover memory function (McNaughton et al., 2006) and prefrontal coupling with hippocampal theta may produce stronger memory traces (Colgin, 2011; Fell and Axmacher, 2011; Hyman et al., 2010; Jones and Wilson, 2005). The MD and the anteroventral nucleus of the ATN (and anteromedial nucleus) are key nodes in two separate and potentially mutually supportive theta pathways that may coordinate information processing across the prefrontal cortex, retrosplenial cortex and hippocampal formation (Kirk and Mackay, 2003; Tsanov et al., 2011). Preliminary data (Ulrich et al., in preparation) suggest that improved anterior cingulate-CA1 communication, as measured by coherence, occurs in enriched rats, even superimposed on the effects of an ATN lesion (the ATN lesion reduced theta power while enrichment tended to increase power in lesioned rats and decrease it in sham rats). This enhanced prefrontal–hippocampal communication may contribute to the improved cognitive performance found in enriched rats with ATN lesions. Thus, enrichment may improve the anterior thalamo-cortical circuit and so compensate for the disruption that occurs in the posterior thalamo-cortical circuit after ATN lesions. This may provide a route towards normality after ATN lesions, and the potential for modulation of the posterior thalamo-cortical circuit to influence recovery after MD lesions. Additional work on theta across different brain networks, and across different tasks and therapies may flesh out this hypothetical scenario and help direct potential therapies in the future.

The second reason is that amnesic pathology in humans always involves a mixture of damaged circuits. Hence our explanations must go beyond single nuclei. Severe human amnesia, probably in all cases, appears to depend on disruption to more than one nucleus, more than one system. As these systems are generally seen as entirely separate, it is usually assumed that only one of those affected systems must be *the* cause of memory loss. Some twenty-five years ago, Markowitsch (1988) explained that searching for specific diencephalic loci that are critical for memory loss did not accord with the majority of clinical evidence. Instead, thalamic amnesia most likely occurs when injury disrupts more than one thalamic circuit. While more recent reviews emphasise that the ATN and especially the mammillothalmic tract are most consistently associated with human amnesia, even the most circumspect injury in humans is associated with subtle damage to adjacent structures and passing fibre systems, and other evidence still strongly implicates the MD as well as other thalamic structures (Aggleton et al., 2011; Carlesimo et al., 2011; Harding et al., 2000; Mitchell and Chakraborty, 2013; Pergola and Suchan, 2013; Savage

et al., 2012; Van der Werf et al., 2003; Wolff et al., 2014). For example, while severe disruption to the ATN appears to be the critical difference between those Korsakoff patients with severe memory loss and those Wernicke cases without significant memory loss, these amnesic patients always have additional injury and dysfunction beyond the ATN, even beyond the diencephalon (Harding et al., 2000; Kopelman et al., 2009; Kopelman, 2014).

Evidence that recovery of function can be elicited after ATN lesions in rats encourages us to look beyond the extended hippocampal system and ask whether changes to other systems may contribute to the improved function observed. This, in turn, generates the more fundamental scientific question of how the various "thalamic players on the memory stage" (Pergola and Suchan, 2013) integrate their functions in the service of everyday memory. This attention may elaborate a theoretical framework aiming to consider multi-effect multi-nuclei models of memory. We would be better prepared to think more positively about how to reverse or ameliorate the dysfunctional memory evident in many clinical cases of diencephalic injury, a disorder that was first acknowledged about 125 years ago (Aggleton, 2014).

## Acknowledgements

This paper acknowledges the tremendous inspiration and memory of our colleague and friend, Professor Bruno Will. The authors also gratefully acknowledge the financial support of Neurex (Neuroscience Upper Rhine Network), the Health Research Council of New Zealand International Investment Opportunities Fund (No. 09/051) and the University of Canterbury, New Zealand. EAL received personal support from the Foundation for Research Science and Technology, New Zealand. We are also grateful to Dr Moessler of EBEWE Arzneimittel, Austria, for supply and unrestricted use of cerebrolysin. None of these funding sources had any role in study design, collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

## References

Aggelton, J.P., Nelson, A.J.D., 2014. Why do lesions in the rodent anterior thalamic nuclei cause such severe spatial memory deficits. Neurosci. Biobehav. Rev., http://dx.doi.org/10.1016/j.neubiorev.2014.08.013.

Aggleton, J.P., 2008. Understanding anterograde amnesia: disconnections and hidden lesions. Q. J. Exp. Psychol. 61 (10), 1441–1471, http://dx.doi.org/10.1080/17470210802215335.

Aggleton, J.P., 2012. Multiple anatomical systems embedded within the primate medial temporal lobe: implications for hippocampal function. Neurosci. Biobehav. Rev. 36, 1579–1596.

Aggleton, J.P., 2014. Looking beyond the hippocampus: old and new neurological targets for understanding memory disorders. Proc. R. Soc. London, Ser. B 281, 20140565, http://dx.doi.org/10.1098/rspb.2014.0565.

Aggleton, J.P., Brown, M.W., 1999. Episodic memory, amnesia and the hippocampal–anterior thalamic axis. Behav. Brain Sci. 22, 425–444.

Aggleton, J.P., Neave, N., Nagle, S., Sahgal, A., 1995. A comparison of the effects of medial prefrontal, cingulate cortex, and cingulum bundle lesions on tests of spatial memory: evidence of a double dissociation between frontal and cingulum bundle contributions. J. Neurosci. 15, 7270–7281.

Aggleton, J.P., Hunt, P.R., Nagle, S., Neave, N., 1996. The effects of selective lesions within the anterior thalamic nuclei on spatial memory in the rat. Behav. Brain Res. 81, 189–198.

Aggleton, J.P., O'Mara, S.M., Vann, S.D., Wright, N.F., Tsanov, M., Erichsen, J.T., 2010. Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. Eur. J. Neurosci. 31, 2292–2307, http://dx.doi.org/10.1111/j.1460-9568.2010.07251.x.

Aggleton, J.P., Dumont, J.R., Warburton, E.C., 2011. Unravelling the contributions of the diencephalon to recognition memory: a review. Learn. Mem. 18, 384–400.

Albasser, M.M., Poirier, G.L., Warburton, E., Aggleton, J.P., 2007. Hippocampal lesions halve immediate-early gene protein counts in retrosplenial cortex: distal dysfunctions in a spatial memory system. Eur. J. Neurosci. 26 (5), 1254–1266.

Alcaraz, F., Naneix, F., Desfosses, E., Marchand, A.R., Wolff, M., Coutureau, E., 2014. Dissociable effects of anterior and mediodorsal thalamic lesions on spatial goal-directed behaviour. Brain Struct. Funct., 10.1007/s00429-014-0893-7.

Alwis, D.S., Rajan, R., 2014. Environmental enrichment and the sensory brain: the role of enrichment in remediating brain injury. Front. Syst. Neurosci. 8, 156, http://dx.doi.org/10.3389/fnsys.2014.00156.

Amin, E., Wright, N., Poirier, G.L., Thomas, K.L., Erichsen, J.T., Aggleton, J.P., 2010. Selective lamina dysregulation in granular retrosplenial cortex (area 29) after anterior thalamic lesions: an in situ hybridization and *trans*-neuronal tracing study in rats. Neuroscience 169 (3), 1255–1267, S0306-4522(10)00795-5[pii].

Bailey, K.R., Mair, R.G., 2005. Lesions of specific and nonspecific thalamic nuclei affect prefrontal cortex-dependent aspects of spatial working memory. Behav. Neurosci. 119, 410–419.

Baird, A.L., Putter, J.E., Muir, J.L., Aggleton, J.P., 2004. On the transience of egocentric working memory: evidence from testing the contribution of limbic brain regions. Behav. Neurosci. 118 (4), 785–797, 10.1037/0735-7044.118.4.785.

Bindu, B., Alladi, P.A., Mansooralikhan, B.M., Srikumar, B.N., Raju, T.R., Kutty, B.M., 2007. Short-term exposure to an enriched environment enhances dendritic branching but not brain-derived neurotrophic factor expression in the hippocampus of rats with ventral subicular lesions. Neuroscience 144, 412–423.

Bonaccorsi, J., Cintoli, S., Mastrogiacomo, R., Baldanzi, S., Braschi, C., Pizzorusso, T., Cenni, M.C., Berardi, N., 2013. System consolidation of spatial memories in mice: effects of enriched environment. Neural Plast., http://dx.doi.org/10.1155/2013/956312.

Briones, T.L., Woods, J., Rogozinska, M., 2013. Decreased neuroinflammation and increased brain energy homeostasis following environmental enrichment after mild traumatic brain injury is associated with improvement in cognitive function. Acta Neuropathol. Commun. 1, 57.

Burk, J.A., Mair, R.G., 1998. Thalamic amnesia reconsidered: excitotoxic lesions of the intralaminar nuclei, but not the mediodorsal nucleus disrupt place DMTS performance in the rat (*Rattus norvegicus*). Behav. Neurosci. 112, 54–67.

Burk, J.A., Mair, R.G., 1999. Delayed matching-to-sample trained with retractable levers is impaired by lesions of the intralaminar or ventromedial but not the laterodorsal thalamic nuclei. Psychobiology 27, 351–363.

Carlesimo, G.A., Lombardi, M.G., Caltagirone, C., 2011. Vascular thalamic amnesia: a reappraisal. Neuropsychologia 49, 777–789.

Carlesimo, G.A., Lombardi, M.G., Caltagirone, C., Barban, F., 2014. Recollection and familiarity in the human thalamus. Neurosci. Biobehav. Rev., http://dx.doi.org/10.1016/j.neubiorev.2014.09.006.

Carrera, E., Bogousslavsky, J., 2006. The thalamus and behavior: effects of anatomically distinct strokes. Neurology 66, 1817–1823.

Cenquizca, L.A., Swanson, L.W., 2006. An analysis of direct hippocampal cortical field CA1 axonal projections to the diencephalon in rats. J. Comp. Neurol. 497, 101–114.

Child, N.D., Benarroch, E.E., 2013. Anterior nucleus of the thalamus: functional organization and clinical implications. Neurology 81, 1869–1876.

Chudasama, Y., Bussey, T.J., Muir, J.L., 2001. Effects of selective thalamic and prelimbic cortex lesions on two types of visual discrimination and reversal learning. Eur. J. Neurosci. 14, 1009–1020.

Cipolotti, L., Husain, M., Crinion, J., Bird, C.M., Khan, S.S., Losseff, N., Howard, R.S., Leff, A.P., 2008. The role of the thalamus in amnesia: a tractography, high-resolution MRI and neuropsychological study. Neuropsychologia 46, 2745–2758.

Colgin, L.L., 2011. Oscillations and hippocampal–prefrontal synchrony. Curr. Opin. Neurobiol. 21, 467–474.

Compton, D.M., Griffith, H.R., McDaniel, W.F., Foster, R.A., Davis, B.K., 1997. The flexible use of multiple cue relationships in spatial navigation: a comparison of water maze performance following hippocampal, medial septal, prefrontal cortex, or posterior parietal cortex lesions. Neurobiol. Learn. Mem. 68, 117–132.

Corbit, L.H., Muir, J.L., Balleine, B.W., 2003. Lesions of mediodorsal thalamus and anterior thalamic nuclei produce dissociable effects on instrumental conditioning in rats. Eur. J. Neurosci. 18, 1286–1294.

Cracchiolo, J.R., Mori, T., Nazian, S.J., Tan, J., Potter, H., Arendash, G.W., 2007. Enhanced cognitive activity–over and above social or physical activity–is required to protect Alzheimer's mice against cognitive impairment, reduce Abeta deposition, and increase synaptic immunoreactivity. Neurobiol. Learn. Mem. 88, 277–294.

Cross, L., Brown, M.W., Aggleton, J.P., Warburton, E.C., 2013. The medial dorsal thalamic nucleus and the medial prefrontal cortex of the rat function together to support associative recognition and recency but not item recognition. Learn. Mem. 20, 41–50.

Czajkowski, R., Jayaprakash, B., Wiltgen, B., Rogerson, T., Guzman-Karlsson, M.C., Barth, A.L., Trachtenberg, J.T., Silva, A.J., 2014. Encoding and storage of spatial information in the retrosplenial cortex. Proc. Natl. Acad. Sci. 111, 8661–8666, 10.1073/pnas.1313222111.

Dhanushkodi, A., Bindu, B., Raju, T.R., Kutty, B.M., 2007. Exposure to enriched environment improves spatial learning performances and enhances cell density but not choline acetyltransferase activity in the hippocampus of ventral subicular-lesioned rats. Behav. Neurosci. 121, 491–500.

Dillingham, C.M., Frizzati, A., Nelson, A.J.D., Vann, S.D., 2014. How do mammillary body inputs contribute to anterior thalamic function? Neurosci. Biobehav. Rev., http://dx.doi.org/10.1016/j.neubiorev.2014.07.025.

Dudchenko, P.A., 2001. How do animals actually solve the T maze? Behav. Neurosci. 115, 850–860.

Dumont, J.R., Aggleton, J.P., 2013. Dissociation of recognition and recency memory judgments after anterior thalamic nuclei lesions in rats. Behav. Neurosci. 127, 415–431, 10.1037/a0032750.

Dumont, J.R., Amin, E., Poirier, G.L., Albasser, M.M., Aggleton, J.P., 2012. Anterior thalamic nuclei lesions in rats disrupt markers of neural plasticity in

distal limbic brain regions. Neuroscience 224, 81–101, http://dx.doi.org/10.1016/j.neuroscience.2012.08.027.
Dupire, A., Kant, P., Mons, N., Marchand, A.R., Coutureau, E., Dalrymple-Alford, J., Wolff, M., 2013. A role for anterior thalamic nuclei in affective cognition: interaction with environmental conditions. Hippocampus 23, 392–404, 10.1002/hipo.22098.
Eckert, M.J., Abraham, W.C., 2013. Effects of environmental enrichment exposure on synaptic transmission and plasticity in the hippocampus. Curr. Top. Behav. Neurosci. 15, 165–187, 10.1007/7854_2012_215, Review.
Einon, D.F., Morgan, M.J., Will, B.E., 1980. Effects of post-operative environment on recovery from dorsal hippocampal lesions in young rats: tests of spatial memory and motor transfer. Q. J. Exp. Psychol. 32, 137–148.
Eichenbaum, H., 2000. A cortical–hippocampal system for declarative memory. Nat. Rev. Neurosci. 1, 41–50.
Eichenbaum, H., Stewart, C., Morris, R.G., 1990. Hippocampal representation in place learning. J. Neurosci. 10, 3531–3542.
Fell, J., Axmacher, N., 2011. The role of phase synchronization in memory processes. Nat. Rev. Neurosci. 12, 105–118.
Francis-Turner, L., Valouskova, V., 1996. Nerve growth factor and nootropic drug Cerebrolysin but not fibroblast growth factor can reduce spatial memory impairment elicited by fimbria-fornix transection: short-term study. Neurosci. Lett. 202 (3), 193–196.
Freeman Jr., J.H., Cuppernell, C., Flannery, K., Gabriel, M., 1996a. Context-specific multi-site cingulate cortical, limbic thalamic and hippocampal neuronal activity during concurrent discriminative approach and avoidance training in rabbits. J. Neurosci. 16, 1538–1549.
Freeman Jr., J.H., Cuppernell, C., Flannery, K., Gabriel, M., 1996b. Limbic thalamic, cingulate cortical and hippocampal neuronal correlates of discriminative approach learning in rabbits. Behav. Brain Res. 80, 123–136.
Gabriel, M., 1993. Discriminative avoidance learning: a model system. In: Vogt, B.A., Gabriel, M. (Eds.), Neurobiology of Cingulate Cortex and Limbic Thalamus. Birkhäuser, Boston, MA, pp. 478–523.
Gabriel, M., Vogt, B.A., Kubota, Y., Poremba, A., Kang, E., 1991. Training-stage related neuronal plasticity in limbic thalamus and cingulated cortex during learning: a possible key to mnemonic retrieval. Behav. Brain Res. 46, 175–185.
Galani, R., Coutureau, E., Kelche, C., 1998. Effects of enriched postoperative housing conditions on spatial memory deficits in rats with selective lesions of either the hippocampus, subiculum or entorhinal cortex. Restor. Neurol. Neurosci. 13, 173–184.
Garden, D., Massey, P.V., Caruana, D.A., Johnson, B., Warburton, E.C., Aggleton, J.P., Bashir, Z.I., 2009. Anterior thalamic lesions stop synaptic plasticity in retrosplenial cortex slices: expanding the pathology of diencephalic amnesia. Brain 132, 1847–1857, http://dx.doi.org/10.1093/brain/awp090.
Hall, J.M., Vetreno, R.P., Savage, L.M., 2014. Differential cortical neurotrophin and cytogenetic adaptation after voluntary exercise in normal and amnestic rats. Neuroscience 258, 131–146, 10.1016/j.neuroscience.2013.10.075.
Hannan, A.J., 2014. Environmental enrichment and brain repair: harnessing the therapeutic effects of cognitive stimulation and physical activity to enhance experience-dependent plasticity. Neuropathol. Appl. Neurobiol. 40, 13–25, 10.1111/nan.12102.
Harding, A., Halliday, G., Caine, D., Kril, J., 2000. Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. Brain 123, 141–154.
Harland, B.C., Collings, D.A., McNaughton, N., Abraham, W.C., Dalrymple-Alford, J.C., 2014. Anterior thalamic lesions reduce spine density in both hippocampal CA1 and retrosplenial cortex, but enrichment rescues CA1 spines only. Hippocampus 24, 1232–1247.
Hartbauer, M., Hutter-Paier, B., Skofitsch, G., Windisch, M., 2001. Antiapoptotic effects of the peptidergic drug cerebrolysin on primary cultures of embryonic chick cortical neurons. J. Neural. Transm. 108 (4), 459–473.
Henry, J., Petrides, M., St-Laurent, M., Sziklas, V., 2004. Spatial conditional associative learning: effects of thalamo-hippocampal disconnection in rats. NeuroReport 15, 2427–2431, http://dx.doi.org/10.1097/00001756-200410250-00025.
Hirase, H., Shinohara, Y., 2014. Transformation of cortical and hippocampal neural circuit by environmental enrichment. Neuroscience, http://dx.doi.org/10.1016/j.neuroscience.2014.09.031.
Hyman, J.M., Zilli, E.A., Paley, A.M., Hasselmo, M.E., 2010. Working memory performance correlates with prefrontal–hippocampal theta interactions but not with prefrontal neuron firing rates. Front. Integr. Neurosci. 4, 1–13.
Johansson, B.B., 2004. Functional and cellular effects of environmental enrichment after experimental brain infarcts. Restor. Neurol. Neurosci. 22, 163–174.
Jankowski, M.M., Ronnqvist, K.C., Tsanov, M., Vann, S.D., Wright, N.F., Erichsen, J.T., Aggleton, J.P., O'Mara, S.M., 2013. The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation. Front. Syst. Neurosci. 7, 45.
Jenkins, T.A., Dias, R., Amin, E., Brown, M.W., Aggleton, J.P., 2002a. Fos imaging reveals that lesions of the anterior thalamic nuclei produce widespread limbic hypoactivity in rats. Neuroscience 22 (12), 5230–5238.
Jenkins, T.A., Dias, R., Amin, E., Aggleton, J.P., 2002b. Changes in Fos expression in the rat brain after unilateral lesions of the anterior thalamic nuclei. Eur. J. Neurosci. 16 (8), 1425–1432.
Jenkins, T.A., Vann, S.D., Amin, E., Aggleton, J.P., 2004. Anterior thalamic lesions stop immediate early gene activation in selective laminae of the retrosplenial cortex: evidence of covert pathology in rats? Eur. J. Neurosci. 19, 3291–3304, http://dx.doi.org/10.1111/j.0953-816X.2004.03421.x.
Jones, M.W., Wilson, M.A., 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. PLoS Biol. 3, e402.
Juarez, I., Gonzalez, D.J., Mena, R., Flores, G., 2011. The chronic administration of cerebrolysin induces plastic changes in the prefrontal cortex and dentate gyrus in aged mice. Synapse 65 (11), 1128–1135, http://dx.doi.org/10.1002/syn.20950.
Kirk, I.J., Mackay, J.C., 2003. The role of theta-range oscillations in synchronising and integrating activity in distributed mnemonic networks. Cortex 39, 993–1008.
Kopelman, M.D., 2014. What does a comparison of the alcoholic Korsakoff syndrome and thalamic infarction tell us about thalamic amnesia? Neurosci. Biobehav. Rev., http://dx.doi.org/10.1016/j.neubiorev.2014.08.014.
Kopelman, M.D., Thomson, A., Guerrini, I., Marshall, E.J., 2009. The Korsakoff syndrome: clinical aspects, psychology and treatment. Alcohol Alcohol. 44, 148–154.
Leger, M., Quiedeville, A., Paizanis, E., Natkunarajah, S., Freret, T., Boulouard, M., Schumann-Bard, P., 2012. Environmental enrichment enhances episodic-like memory in association with a modified neuronal activation profile in adult mice. PloS One 7 (10), e48043.
Loukavenko, E.A., Ottley, M.C., Moran, J.P., Wolff, M., Dalrymple-Alford, J.C., 2007. Towards therapy to relieve memory impairment after anterior thalamic lesions: improved spatial working memory after immediate and delayed postoperative enrichment. Eur. J. Neurosci. 26, 3267–3276.
Loukavenko, E.A., Wolff, M., Poirier, G.L., Dalrymple-Alford, J.C., Impaired spatial working memory after anterior thalamic lesions: Recovery with cerebrolysin and enrichment. Brain Struct. Funct. (in press).
Mair, R.G., Hembrook, J.R., 2008. Memory enhancement with event-related stimulation of the rostral intralaminar thalamic nuclei. J. Neurosci. 28, 14293–14300.
Mair, R.G., Burk, J.A., Porter, M.C., 2003. Impairment of radial maze delayed nonmatching after lesions of anterior thalamus and parahippocampal cortex. Behav. Neurosci. 117, 596–605.
Mair, R.G., Onos, K.D., Hembrook, K.D., 2011. Cognitive activation by central thalamic stimulation: the Yerkes–Dodson law revisited. Dose Response 9, 313–331.
Markowitsch, H.J., 1988. Diencephalic amnesia: a reorientation towards tracts? Brain Res. 472, 351–370.
McNaughton, N., Ruan, M., Woodnorth, M.A., 2006. Restoring theta-like rhythmicity in rats restores initial learning in the Morris water maze. Hippocampus 16, 1102–1110.
Mendez-Lopez, M., Arias, J.L., Bontempi, B., Wolff, M., 2013. Reduced cytochrome oxidase activity in the retrosplenial cortex after lesions to the anterior thalamic nuclei. Behav. Brain Res. 250, 264–273.
Mennemeier, M., Fennell, E., Valenstein, E., Heilman, K.M., 1992. Contributions of the left intralaminar and medial thalamic nuclei to memory: comparisons and a case report. Arch. Neurol. 49, 1050–1058.
Miller, A.M.P., Vedder, L.C., Law, M., Smith, D.M., 2014. Cues, context, and long-term memory: the role of the retrosplenial cortex in spatial cognition. Front. Hum. Neurosci. 8, 586, 10.3389/fnhum.2014.00586, (eCollection 2014. Review).
Mitchell, A.S., Chakraborty, S., 2013. What does the mediodorsal thalamus do? Front. Syst. Neurosci. 7, 37.
Mitchell, A.S., Dalrymple-Alford, J.C., 2005. Dissociable memory effects after medial thalamus lesions in the rat. Eur. J. Neurosci. 22, 973–985.
Mitchell, A.S., Dalrymple-Alford, J.C., 2006. Lateral and anterior thalamic lesions impair independent memory systems. Learn. Mem. 13, 388–396.
Moreau, P.H., Tsenkina, Y., Lecourtier, L., Lopez, J., Cosquer, B., Wolff, M., Dalrymple-Alford, J.C., Cassel, J.C., 2013. Lesions of the anterior thalamic nuclei and the intralaminar thalamic nuclei: place and visual discrimination learning in the water maze. Brain Struct. Funct. 218, 657–667.
Nishio, Y., Hashimoto, M., Ishii, K., Ito, D., Mugikura, S., Takahashi, S., Mori, E., 2014. Multiple thalamo-cortical disconnections in anterior thalamic infarction: implications for thalamic mechanisms of memory and language. Neuropsychologia 53, 264–273.
Nithianantharajah, J., Hannan, A.J., 2006. Enriched environments, experience-dependent plasticity and disorders of the nervous system. Nat. Rev. Neurosci. 7, 697–709, http://dx.doi.org/10.1038/nrn1970.
Olson, A.K., Eadie, B.D., Ernst, C., Christie, B.R., 2006. Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways. Hippocampus 16, 250–260.
Oswald, C.J.P., Good, M., 2000. The effects of combined lesions of the subicular complex and the entorhinal cortex on two forms of spatial navigation in the water maze. Behav. Neurosci. 14, 211–217.
Packard, M.G., McGaugh, J.L., 1992. Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: further evidence for multiple memory systems. Behav. Neurosci. 106, 439–446.
Pang, T.Y., Hannan, A.J., 2013. Enhancement of cognitive function in models of brain disease through environmental enrichment and physical activity. Neuropharmacology 64, 515–528.
Paxinos, G., Watson, C., 1998. The Rat Brain in Stereotaxic Coordinates, fourth ed. Academic Press, San Diego, CA.
Pergola, G., Suchan, B., 2013. Associative learning beyond the medial temporal lobe: many actors on the memory stage. Front. Behav. Neurosci. 7, 162.
Plosker, G.L., Gauthier, S., 2009. Cerebrolysin: a review of its use in dementia. Drugs and aging. , 893–915.
Poirier, G.L., Aggleton, J.P., 2009. Post-surgical interval and lesion location within the limbic thalamus determine extent of retrosplenial cortex immediate-early gene hypoactivity. Neuroscience 160 (2), 452–469, http://dx.doi.org/10.1016/j.neuroscience.2009.02.021.
Poirier, G.L., Shires, K.L., Sugden, D., Amin, E., Thomas, K.L., Carter, D.A., Aggleton, J.P., 2008. Anterior thalamic lesions produce chronic and profuse

transcriptional de-regulation in retrosplenial cortex: a model of retrosplenial hypoactivity and covert pathology. Thalamus Relat. Syst. 4 (1), 59–77, 10.1017/S1472928808000368.
Pothuizen, H.H., Aggleton, J.P., Vann, S.D., 2008. Do rats with retrosplenial cortex lesions lack direction? Eur. J. Neurosci. 28, 2486–2498, 10.1111/j.1460-9568.2008.06550.x, EJN6550 [pii].
Pothuizen, H.H., Davies, M., Aggleton, J.P., Vann, S.D., 2010. Effects of selective granular retrosplenial cortex lesions on spatial working memory in rats. Behav. Brain Res. 208 (2), 566–575, 10.1016/j.bbr.2010.01.001, S0166-4328(10)00018-5[pii].
Rampon, C., Jiang, C.H., Dong, H., Tang, Y.P., Lockhart, D.J., Schultz, P.G., Tsien, J.Z., Hu, Y., 2000a. Effects of environmental enrichment on gene expression in the brain. Proc. Natl. Acad. Sci. U.S.A. 97, 12880–12884.
Rampon, C., Tang, Y.P., Goodhouse, J., Shimizu, E., Kyin, M., Tsien, J.Z., 2000b. Enrichment induces structural changes and recovery from nonspatial memory deficits in CA1 NMDAR1-knockout mice. Nat. Neurosci. 3, 238–244.
Reed, L.J., Lasserson, D., Marsden, P., Stanhope, N., Stevens, T., Bello, F., Kingsley, D., Colchester, A., Kopelman, M.D., 2003. FDG-PET findings in the Wernicke–Korsakoff syndrome. Cortex 39, 1027–1045, http://dx.doi.org/10.1016/S0010-9452(08)70876-1.
Rockenstein, E., Torrance, M., Mante, M., Adame, A., Paulino, A., Rose, J.B., Crews, L., Moessler, H., Masliah, E., 2006. Cerebrolysin decreases amyloid-beta production by regulating amyloid protein precursor maturation in a transgenic model of Alzheimer's disease. J. Neurosci. Res. 83 (7), 1252–1261, http://dx.doi.org/10.1002/jnr.20818.
Roland, J.J., Savage, L.M., 2009. Blocking GABA-A receptors in the medial septum enhances hippocampal acetylcholine release and behavior in a rat model of diencephalic amnesia. Pharmacol. Biochem. Behav. 92, 480–487, 10.1016/j.pbb.2009.01.022.
Roland, J.J., Mark, K., Vetreno, R.P., Savage, L.M., 2008. Increasing hippocampal acetylcholine levels enhance behavioral performance in an animal model of diencephalic amnesia. Brain Res. 1234, 116–127.
Savage, L.M., Hall, J.M., Resende, L.S., 2012. Translational rodent models of Korsakoff syndrome reveal the critical neuroanatomical substrates of memory dysfunction and recovery. Neuropsychol. Rev. 22, 195–209.
Shah, S.A., Schiff, N.D., 2012. Central thalamic deep brain stimulation for cognitive neuromodulation—a review of proposed mechanisms and investigational studies. Eur. J. Neurosci. 32, 1135–1144.
Sharma, H.S., Sharma, A., Mossler, H., Muresanu, D.F., 2012. Neuroprotective effects of cerebrolysin, a combination of different active fragments of neurotrophic factors and peptides on the whole body hyperthermia-induced neurotoxicity: modulatory roles of co-morbidity factors and nanoparticle intoxication. Int. Rev. Neurobiol. 102, 249–276, http://dx.doi.org/10.1016/B978-0-12-386986-9.00010-7.
Simpson, J., Kelly, J.P., 2011. The impact of environmental enrichment in laboratory rats–behavioural and neurochemical aspects. Behav. Brain Res. 222, 246–264.
Smith, D.M., Freeman Jr., J.H., Nicholson, D., Gabriel, M., 2002. Limbic thalamus lesions, appetitively motivated discrimination learning, and training-induced neuronal activity in rabbits. J. Neurosci. 22, 8212–8221.
Smith, D.M., Barredo, J., Mizumori, S.J., 2012. Complimentary roles of the hippocampus and retrosplenial cortex in behavioral context discrimination. Hippocampus 22, 1121–1133, 10.1002/hipo.20958.
Sozda, C.N., Hoffman, A.N., Olsen, A.S., Cheng, J.P., Zafonte, R.D., Kline, A.E., 2010. Empirical comparison of typical and atypical environmental enrichment paradigms on functional and histological outcome after experimental traumatic brain injury. J. Neurotrauma 27, 1047–1057.
Tsanov, M., Wright, N., Vann, S.D., Erichsen, J.T., Aggleton, J.P., O'Mara, S.M., 2011. Hippocampal inputs mediate theta-related plasticity in anterior thalamus. Neuroscience 187, 52–62, 10.1016/j.neuroscience.2011.03.055.
Ubhi, K., Rockenstein, E., Vazquez-Roque, R., Mante, M., Inglis, C., Patrick, C., Adame, A., Fahnestock, M., Doppler, E., Novak, P., Moessler, H., Masliah, E., 2013. Cerebrolysin modulates pronerve growth factor/nerve growth factor ratio and ameliorates the cholinergic deficit in a transgenic model of Alzheimer's disease. J. Neurosci. Res. 91 (2), 167–177, http://dx.doi.org/10.1002/jnr.23142.
Ulrich, K., Aitken, P.N., Abraham, W.C., Dalrymple-Alford, J.C., McNaughton, N., 2014. Effects of thalamic lesions on repeated relearning of a spatial working memory task. Behav. Brain Res. 261, 56–59.
Van der Werf, Y., Scheltens, P., Lindeboom, J., Witter, M.P., Uylings, H.B.M., Jolles, J., 2003. Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localized lesions. Neuropsychologia 41, 1330–1344.
van Groen, T., Kadish, I., Wyss, J.M., 1999. Efferent connections of the anteromedial nucleus of the thalamus of the rat. Brain Res. Rev. 30, 1–26.
van Groen, T., Kadish, I., Michael Wyss, J., 2002. Role of the anterodorsal and anteroventral nuclei of the thalamus in spatial memory in the rat. Behav. Brain Res. 132, 19–28.
Vann, S.D., 2010. Re-evaluating the role of the mammillary bodies in memory. Neuropsychologia 48, 2316–2327.
Vann, S.D., 2013. Dismantling the Papez circuit for memory in rats. eLife 2, e00736.
Vann, S.D., Aggleton, J.P., 2005. Selective dysgranular retrosplenial cortex lesions in rats disrupt allocentric performance of the radial-arm maze task. Behav. Neurosci. 119 (6), 1682–1686, 10.1037/0735-7044.119.6.1682.
Vann, S.D., Albasser, M.M., 2009. Hippocampal, retrosplenial, and prefrontal hypoactivity in a model of diencephalic amnesia: evidence towards an interdependent subcortical–cortical memory network. Hippocampus 19 (11), 1090–1102, http://dx.doi.org/10.1002/hipo.20574.
Vann, S.D., Tsivilis, D., Denby, C.E., Quamme, J., Yonelinas, A.P., Aggleton, J.P., Montaldi, D., Mayes, A.R., 2009. Impaired recollection but spared familiarity in patients with extended hippocampal system damage: convergence across three methods. Proc. Natl. Acad. Sci. U.S.A. 106, 5442–5447, http://dx.doi.org/10.1073/pnas.0812097106.
Vázquez-Roque, R.A., Ramos, B., Tecuatl, C., Juárez, I., Adame, A., de la Cruz, F., Zamudio, S., Mena, R., Rockenstein, E., Masliah, E., Flores, G., 2012. Chronic administration of the neurotrophic agent cerebrolysin ameliorates the behavioral and morphological changes induced by neonatal ventral hippocampus lesion in a rat model of schizophrenia. J. Neurosci. Res. 90, 288–306, http://dx.doi.org/10.1002/jnr.22753.
Victor, M., Adams, R.D., Collins, G.H., 1971. The Wernicke–Korsakoff Syndrome. F.A. Davis, Philadelphia, PA.
Warburton, E.C., Aggleton, J.P., 1999. Differential deficits in the Morris water maze following cytotoxic lesions of the anterior thalamus and fornix transection. Behav. Brain Res. 98, 27–38.
Warburton, E.C., Baird, A.L., Aggleton, J.P., 1997. Assessing the magnitude of the allocentric spatial deficit associated with complete loss of the anterior thalamic nuclei in rats. Behav. Brain Res. 87, 223–232.
Warburton, E.C., Morgan, A., Baird, A.L., Muir, J.L., Aggleton, J.P., 1999. Does pretraining spare the spatial deficit associated with anterior thalamic damage in rats? Behav. Neurosci. 113 (5), 956–967.
Warburton, E.C., Baird, A.L., Morgan, A., Muir, J.L., Aggleton, J.P., 2000. Disconnecting hippocampal projections to the anterior thalamus produces deficits on tests of spatial memory in rats. Eur. J. Neurosci. 12, 1714–1726.
Warburton, E.C., Morgan, A., Baird, A., Muir, J.L., Aggleton, J.P., 2001. The conjoint importance of the hippocampus and anterior thalamic thalamic nuclei for allocentric spatial learning: evidence from a disconnection study in the rat. J. Neurosci. 21, 7323–7330.
Ward-Robinson, J., Wilton, L.A.K., Muir, R.C., Honey, S.D., Vann, S.D., Aggleton, J.P., 2002. Sensory preconditioning in rats with lesions of the anterior thalamic nuclei: evidence for intact nonspatial "relational" processing. Behav. Brain Res. 133, 125–133.
Will, B., Kelche, C., 1992. Environmental approaches to recovery of function from brain damage: a review of animal studies (1981 to 1991). Adv. Exp. Med. Biol. 325, 79–103.
Will, B., Toniolo, G., Kelche, C., Pallage, V., Deluzarche, F., Misslin, R., 1986. The effects of postoperative physical environment on novelty seeking behaviour and maze learning in rats with hippocampal lesions. Behav. Brain Res. 19, 233–240.
Will, B., Galani, R., Kelche, C., Rosenzweig, M.R., 2004. Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990–2002). Prog. Neurobiol. 72 (3), 167–182, http://dx.doi.org/10.1016/j.pneurobio.2004.03.00.
Wilton, L.A.K., Baird, A.L., Muir, J.L., Honey, R.C., Aggleton, J.P., 2001. Loss of the thalamic nuclei for "head direction" produces impaired spatial memory in rats. Behav. Neurosci. 115, 861–869.
Windisch, M., 2000. Approach towards an integrative drug treatment of Alzheimer's disease. J. Neural. Transm. Suppl. 59, 301–313.
Wolff, M., Gibb, S.J., Dalrymple-Alford, J.C., 2006. Beyond spatial memory: the anterior thalamus and memory for the temporal order of a sequence of odor cues. J. Neurosci. 26, 2907–2913.
Wolff, M., Gibb, S.J., Cassel, J.C., Dalrymple-Alford, J.C., 2008. Anterior but not intralaminar thalamic nuclei support allocentric spatial memory. Neurobiol. Learn. Mem. 90, 71–80.
Wolff, M., Alcaraz, F., Marchand, A.R., Coutureau, E., 2014. Functional heterogeneity of the limbic thalamus: From hippocampal to cortical functions. Neurosci. Biobehav. Rev.
Wright, N.F., Vann, S.D., Erichsen, J.T., O'Mara, S.M., Aggleton, J.P., 2013. Segregation of parallel inputs to the anteromedial and anteroventral thalamic nuclei of the rat. J. Comp. Neurol. 521 (13), 2966–2986, http://dx.doi.org/10.1002/cne.23325.
Young, C.K., McNaughton, N., 2009. Coupling of theta oscillations between anterior and posterior midline cortex and with the hippocampus in freely behaving rats. Cerebral Cortex 19, 24–40.
Zheng, Y., Pearce, J.M., Vann, S.D., Good, M., Jenkins, T.A., Smith, P.F., Aggleton, J.P., 2003. Using idiothetic cues to swim a path with a fixed trajectory and distance: necessary involvement of the hippocampus, but not the retrosplenial cortex. Behav. Neurosci. 117, 1363–1377.