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The pathways connecting the hippocampal formation, the thalamic reuniens nucleus and the thalamic reticular nucleus in the rat

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Abstract

Most dorsal thalamic nuclei send axons to specific areas of the neocortex and to specific sectors of the thalamic reticular nucleus; the neocortex then sends reciprocal connections back to the same thalamic nucleus, directly as well indirectly through a relay in the thalamic reticular nucleus. This can be regarded as a 'canonical' circuit of the sensory thalamus. For the pathways that link the thalamus and the hippocampal formation, only a few comparable connections have been described. The reuniens nucleus of the thalamus sends some of its major cortical efferents to the hippocampal formation. The present study shows that cells of the hippocampal formation as well as cells in the reuniens nucleus are retrogradely labelled following injections of horseradish peroxidase or fluoro-gold into the rostral part of the thalamic reticular nucleus in the rat. Within the hippocampal formation, labelled neurons were localized in the subiculum, predominantly on the ipsilateral side, with fewer neurons labelled contralaterally. Labelled neurons were seen in the hippocampal formation and nucleus reuniens only after injections made in the rostral thalamic reticular nucleus (1.6–1.8 mm caudal to bregma). In addition, the present study confirmed the presence of afferent connections to the rostral thalamic reticular nucleus from cortical (cingulate, orbital and infralimbic, retrosplenial and frontal), midline thalamic (paraventricular, anteromedial, centromedial and mediodorsal thalamic nuclei) and brainstem structures (substantia nigra pars reticularis, ventral tegmental area, periaqueductal grey, superior vestibular and pontine reticular nuclei). These results demonstrate a potential for the thalamo-hippocampal circuitry to influence the functional roles of the thalamic reticular nucleus, and show that thalamo-hippocampal connections resemble the circuitry that links the sensory thalamus and neocortex.

Key words fluoro-gold; horseradish peroxidase; midline thalamic nuclei; retrograde transport; subiculum.

Introduction

The thalamic reticular nucleus (TRN) is a derivative of the ventral thalamus. It is a sheet of cells that surrounds the dorsal thalamus and lies between the external medullary lamina and the internal capsule. The TRN is traversed by axons of thalamocortical and corticothalamic fibres, many of which give collaterals to the TRN itself, providing the nucleus with both a dorsal thalamic and a cortical innervation (Jones, 1975; Yen et al. 1985). The majority of the outputs of the TRN are to the dorsal thalamus (Ohara & Lieberman, 1985; De Biasi et al. 1986). Furthermore, it has been shown that TRN connections with the thalamus and the cortex are organized in a topographic manner with single sectors of the TRN having two-way connections to distinct groups of thalamic nuclei and also receiving afferents from the related cortical areas (Carman & Powell, 1964; Jones, 1975; Crabtree & Killackey, 1989; Crabtree, 1992, 1996; Guillery & Harting, 2003).

Although there are many structural and functional studies of the TRN, its precise role remains under debate. Crick (1984) postulated that the TRN acts to mediate selective attention by specifically gating dorsal thalamic inputs to the cerebral cortex. It has also been suggested that the TRN is involved in a modulation of thalamic and/or cortical neuronal firing patterns and in the generation of oscillatory activity responsible for cortical spindles during the early stage of sleep (Steriade & Deschenes, 1984; Steriade et al. 1984, 1986, 1987). The TRN is also critically implicated in the oscillatory thalamo-cortico-thalamic loop relevant to the spike-and-wave discharge characteristics of absence epilepsy.

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Previous anatomical and experimental studies have demonstrated a thalamo-hippocampal pathway from the thalamic reuniens nucleus, including a termination in the subiculum (Herkenham, 1978; Van Groen et al. 1986; Yanagihara et al. 1987; Su & Bentivoglio, 1990; Van Groen & Wyss, 1990; Wouterlood et al. 1990; Dolleman-van der Weel & Witter, 1996; Dolleman-van der Weel et al. 1997; Bertram & Zhang, 1999; Vertes et al. 2006, 2007). There is also evidence that the nucleus reuniens sends axons to the TRN (Cornwall et al. 1990; Vertes et al. 2006). However, connections of the hippocampal formation to the TRN, which would complete the pattern of connections summarized above, have not been previously described.

In an earlier study dealing with other issues (Aker et al. 2006a), the hippocampal formation was listed (Table 1, p. 217) as contributing afferents to the TRN, but was not considered in further detail. We have now confirmed these earlier results using a different tracer (fluoro-gold, FG) and a lateral approach to the TRN that avoided passage of the pipette through the hippocampus and the fornix system. In addition, we have shown a pathway from the reuniens nucleus to the TRN on the basis of the same injections. These observations demonstrate that the rostral part of the TRN provides a link between the hippocampal formation and the thalamus comparable with the canonical circuits that link sensory thalamus and cortex. They also show a link between hippocampal and thalamic circuitry that may play an important role in clinical conditions such as epilepsy.

Materials and methods

Wistar albino rats weighing 250–400 g were fed with a standard laboratory rat chow and tap water *ad libitum*, and housed in Plexiglass cages with a 12-h light/dark cycle in a temperature-controlled room (20 ± 3 °C). The Institutional Animal Care and Use Committee of Marmara University approved all procedures. A total of 18 animals were used [ten animals for horseradish peroxidase (HRP), eight animals for FG experiments]. Of the ten HRP experiments, four were successful in reaching the rostral TRN; and of the eight FG injections, four were successful in reaching the rostral TRN.

Rats were anaesthetized deeply with ketamine (100 mg kg^{-1}, intraperitoneally) and chlorpromazine (1 mg kg^{-1}, intraperitoneally). The heads of the animals were placed in a stereotaxic frame (Stoelting Model 51600, Wood Dale, IL, USA). The scalp was incised longitudinally, and the skull was exposed between lambda and bregma. A small hole was drilled in the skull at a position appropriate for the unilateral injection of tracer into the rostral TRN.

HRP injections

A glass micropipette (30–50 μm tip diameter) containing 25% HRP solution was lowered into the right rostral TRN according to the atlas of Paxinos and Watson (1998). The coordinates were selected as follows: rostral TRN –1.8 mm posterior to bregma, 2.8 mm lateral to midline and 5.4 mm ventral to the surface of the skull.

The tip of the micropipette was filled with air (20 nL) to avoid diffusion of HRP to unwanted areas of the brain during the passage of the pipette to the TRN. A volume of 60 nL of HRP was applied by pressure injection via a Hamilton microsyringe through a cannula connected to an infusion pump (Kd Scientific, Holliston, MA, USA). The injections were delivered during a period of 20 s with the aid of the pump. Following the injection, the pipette remained in the target location for 1.5 h to avoid loss of tracer during the removal of the pipette.

After 2–3 days' survival, the animals were deeply anaesthetized with ketamine (100 mg kg^{-1}, intraperitoneally) and perfused transcardially with 350–500 mL, depending on body weight, of saline solution, and an equal volume of a mixture of 1% paraformaldehyde and 1.25% glutaraldehdyde in 0.05 M phosphate buffer. Brains were removed and postfixed for 24 h at 4 °C. Coronal sections (40 μm) were cut using a cryostat (Microtom, Waldorf, Germany). Every third section was collected in phosphate buffer (1 M, pH 7.2). The sections were treated with tetramethylbenzidine as described by Mesulam (1978). Sections showing the HRP injection sites were stained with thionin and examined microscopically to verify the location of the injection.

Fluoro-gold injections

A lateral oblique approach at an angle of 27.5° to the vertical was used to avoid direct involvement of the hippocampus and fornix system and also to prevent the diffusion of the tracer into the ventricle. FG solution (2%, FluoroChrome Inc., Englewood, CO, USA) in 0.1 M cacodylic acid sodium salt was injected iontophoretically into the right rostral TRN through a glass micropipette (30–50 μm tip diameter) by passing a 5-μA positive current pulse, for alternating 7-s on and off periods, over a total of 20 min. After 5–7 days' survival the animals were deeply anaesthetized with ketamine (100 mg kg^{-1}, intraperitoneally) and perfused transcardially with 350–500 mL saline solution, followed by 2.5% paraformaldehyde and 1.25% glutaraldehdyde in 0.1 M phosphate buffer (350–500 mL). Brains were removed and postfixed for 24 h at 4 °C. Coronal sections (40 μm) were cut on a cryostat (Microtom). Every third section was placed on gelatin subbed glass slides, dehydrated and cleared, covered with DPX and examined under a fluorescence microscope. To determine the extent of each injection site the boundary of the TRN was assessed by using cresyl violet counterstaining. The results presented are selected from animals in which the centres of the injection sites were optimal with minimal contamination of the adjacent structures or along the pipette tract (Fig. 1).

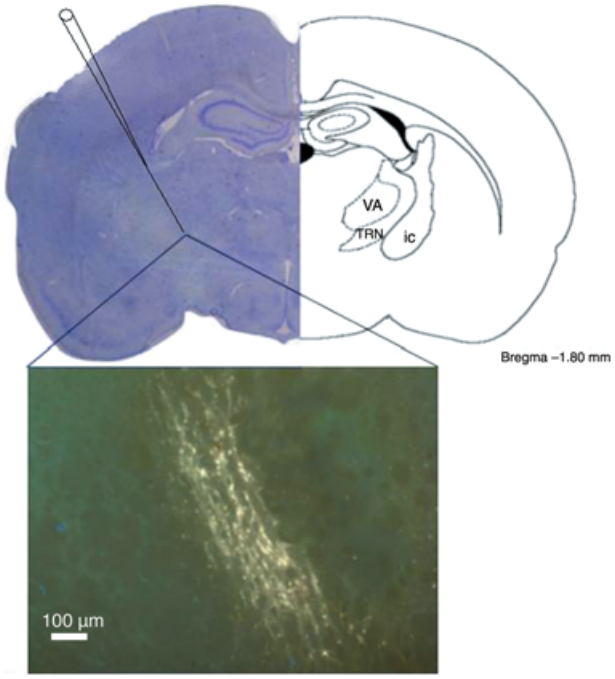

Fig. 1 Photomicrograph and schematic drawing of a coronal section (bregma –1.80 mm) of the brain with a high-power view of the injection site into the TRN in the rat. VA, ventral anterior thalamic nucleus; ic, internal capsule; TRN, thalamic reticular nucleus.

Labelled neuron counts

The HRP/FG-labelled neurons in the subicular cortex were counted at 400× magnification on each side of the brain in order to show the extent of asymmetry of the pathways. At least four adjacent sections of a 1 in 3 series through the dense labelled part of the subiculum on each side were surveyed and the mean and the standard error of the number of labelled neurons were calculated for both sides of each animal (Table 1).

As these numbers provide information about the degree of asymmetry only, and as corrections (Abercrombie, 1946) would be comparable for the two sides, no corrections have been made. The actual number of labelled cells depends on the size of the injections, so that these numbers should not be interpreted as representing the size of the projections.

Results

An example of an injection site is shown in Fig. 1. No labelled neurons were detected in any region of the hippocampus or reuniens nucleus subsequent to TRN injections other than those 1.6–1.8 mm caudal to bregma. In four of the HRP experiments and in four of the FG experiments we succeeded in obtaining injections restricted to this rostral part of the TRN. Both the vertical microinjections of HRP and the FG injections with an oblique approach into the specific rostral (1.6–1.8 mm caudal to bregma) parts of the TRN resulted in labelled neurons in the subicular cortex (Figs 2a,b and 3a,b) of the hippocampal formation and in the nucleus reuniens (Fig. 4). Note that labelled neurons were seen in the ipsilateral nucleus reuniens in all of the experiments that showed subicular labelling, and vice versa, indicating that the pathways from the subiculum and the reuniens nucleus terminated in the same parts of the reticular nucleus. Labelled neurons were more numerous on the ipsilateral side than on the contralateral side in all of the experiments (Figs 2a,b and 3a,b). The ratios of ipsilateral to contralateral labelled cells in each of the animals are shown for the subicular cortex. The counts for both HRP and FG showed that the ipsilateral and contralateral sides of the subicular cortex differed significantly ($P < 0.05$) and the ratios were all close to 5 : 1 (Table 1, Fig. 5). It can be seen that the uncrossed connections greatly outnumber the crossed connections for the subicular TRN pathway.

In order to compare our results with the connectional patterns described by others, we also surveyed relevant cortical regions, thalamic nuclei and brainstem structures and identified a wide distribution of labelled cells in the HRP and the FG material. Our material confirms the presence of connections from many different regions to the relevant rostral part of the TRN. Labelled cells were identified in the following structures: cingulate (Fig. 6), orbital, infralimbic, retrosplenial and frontal cortex; paraventricular, anteromedial, centromedial and mediodorsal thalamic nuclei, as well as substantia nigra pars reticularis, ventral tegmental area, periaqueductal grey, superior vestibular and pontine reticular nuclei in the brainstem. The distribution of these labelled cells agrees with earlier accounts (Jones, 1975; Ohara & Lieberman, 1985; Cornwall et al. 1990;

Table 1 Labelled neuron counts in the ipsilateral and contralateral subicular cortex subsequent to FG and HRP injections into the rostral TRN

	Number of HRP-labellled neurons in the subicular cortex				Number of FG-labelled neurons in the subicular cortex		
	Ipsilateral	Contralateral	*P*	Ratio	Ipsilateral	Contralateral	Ratio
1	62.8 ± 8.8	11.5 ± 3.7	0.0039	5.4	128.5 ± 25.9	22.0 ± 6.2	5.8
2	87.0 ± 17.3	16.3 ± 4.4	0.03	5.3	92.3 ± 11.3	18.0 ± 2.6	5.2
3	76.3 ± 11.9	14.0 ± 3.5	0.0079	5.2	153.5 ± 16.3	30.2 ± 6.8	5.1
4	82.2 ± 9.4	18.3 ± 9.4	0.017	4.5	128.0 ± 17.6	29.7 ± 7.1	4.3

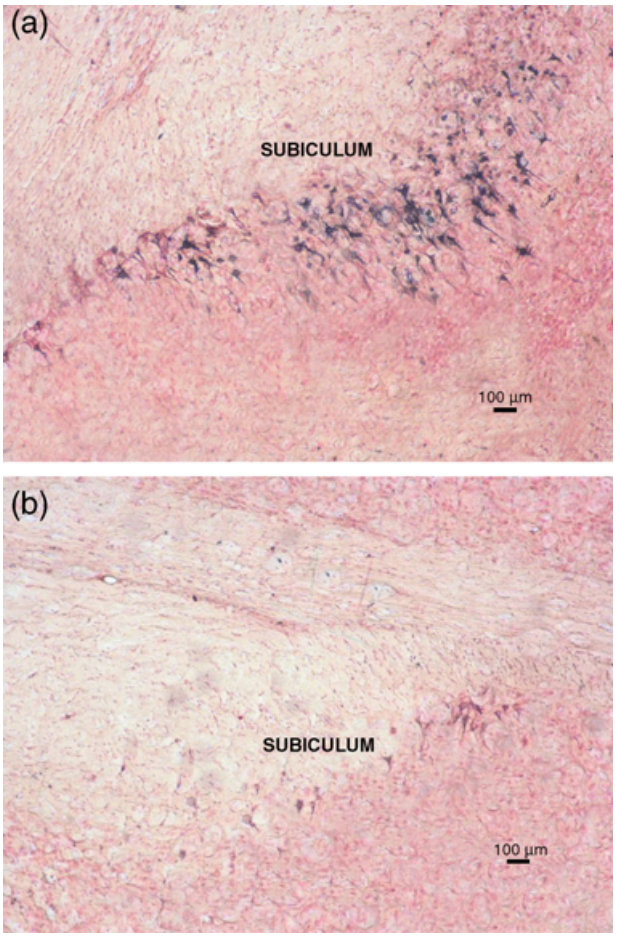

Fig. 2 Photomicrograph showing numerous ipsilateral (a) and scarce contralateral (b) HRP-labelled neurons within the subiculum subsequent to HRP injections into TRN 1.8 mm caudal to bregma.

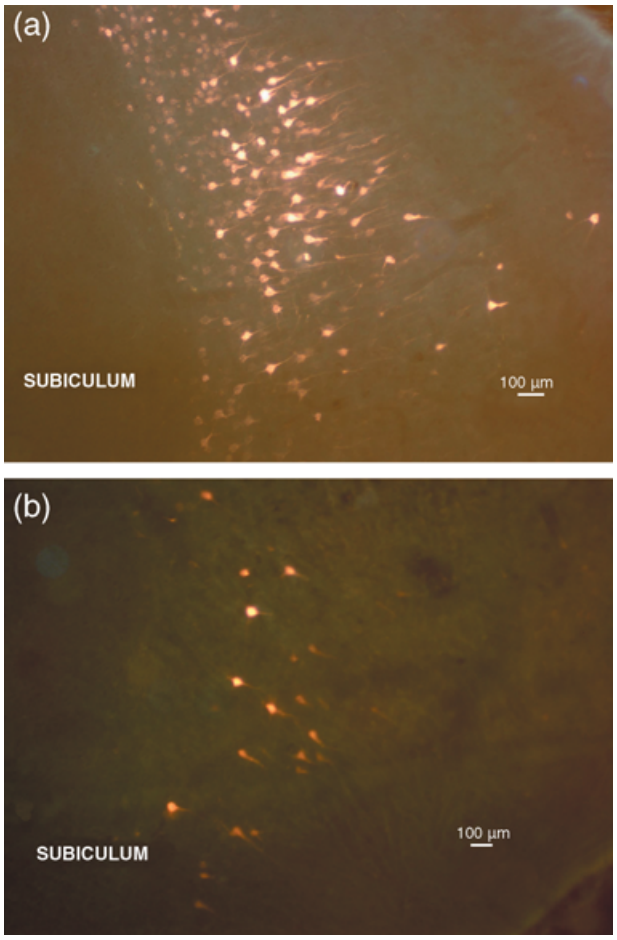

Fig. 3 Photomicrograph showing numerous ipsilateral (a) and scarce contralateral (b) FG-labelled neurons within the subiculum subsequent to FG injections into TRN 1.8 mm caudal to bregma.

Lozsádi, 1994, 1995; Ilinsky et al. 1995), confirming that the injections were correctly placed. As this part of the study does not add to the previously published results, and does not add to the main focus of this report on the connections of the hippocampal formation and the reuniens nuclei, only a summary of these observations is presented here.

Discussion

The present study demonstrates projections from the hippocampal formation to the rostral TRN in the rat and also shows that the same sector of the TRN receives input from the reuniens nucleus. To our knowledge the pathway from the hippcampal formation has not been decribed before but the connections from the reuniens nucleus have previously been described (Cornwall et al. 1990; Vertes et al. 2006). Various aspects of the data obtained in this study suggest that these are functionally significant pathways and not merely the consequence of technical artefacts.

It is important to recognize that the pattern of labelling we have reported cannot have been produced by inadvertent labelling of adjacent structures or of fimbrial fibres traversed by the pipette. The possible contamination by diffusion of the tracer from the injection site in the rostral TRN to neighbouring structures has to be considered; anteriorly the tracer could have reached the ventral anterior thalamic nucleus and posteriorly it could have reached the internal capsule. Neither the ventral anterior thalamic nucleus nor the internal capsule has any known afferent connections from the hippocampal formation. Furthermore, no retrogradely labelled neurons were found in the deep cerebellar nuclei or the globus pallidus, thus indicating that the injection site did not encroach upon the ventral anterior thalamic nucleus. So far as we are aware, all of the long descending efferents from the hippocampal formation described previously pass medially through the fimbria or fornix (Guillery, 1956; Nauta, 1956; Swanson & Cowan, 1977) and do not pass in the internal capsule close to the TRN. HRP could have entered the lateral ventricle and reached the fimbria by diffusion, or could have labelled fornix fibres as the pipette descended to the thalamus. However, the FG injections avoided the fimbria and fornix

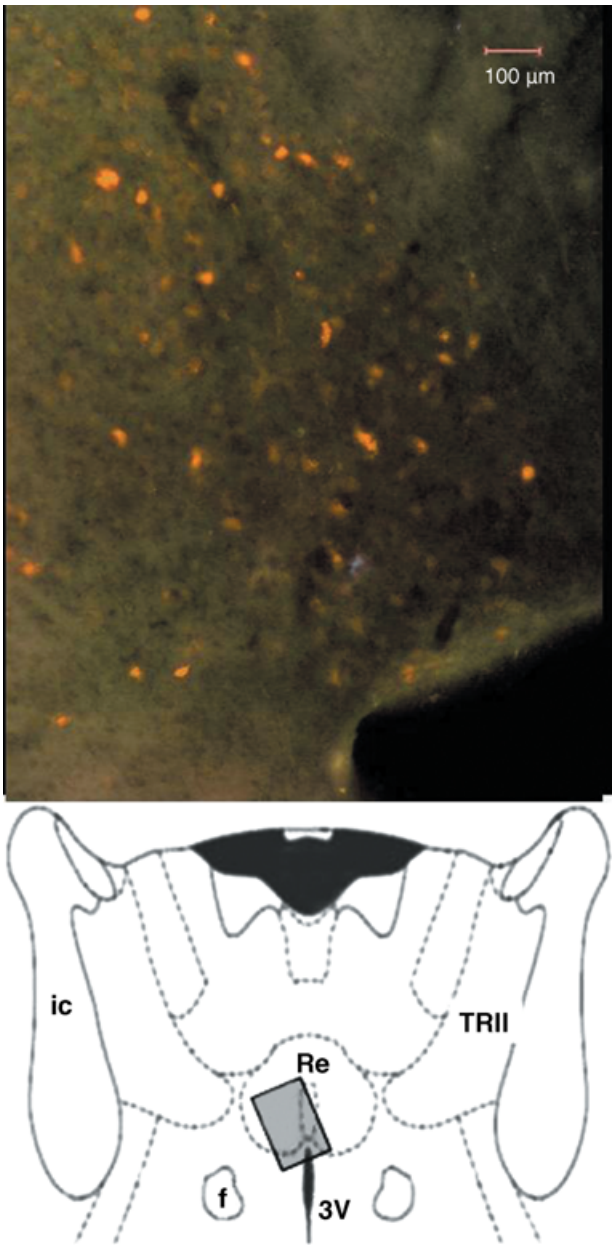

Fig. 4 Photomicrograph showing labelled cells in the reuniens nucleus of the thalamus subsequent to FG injections into the rostral TRN.

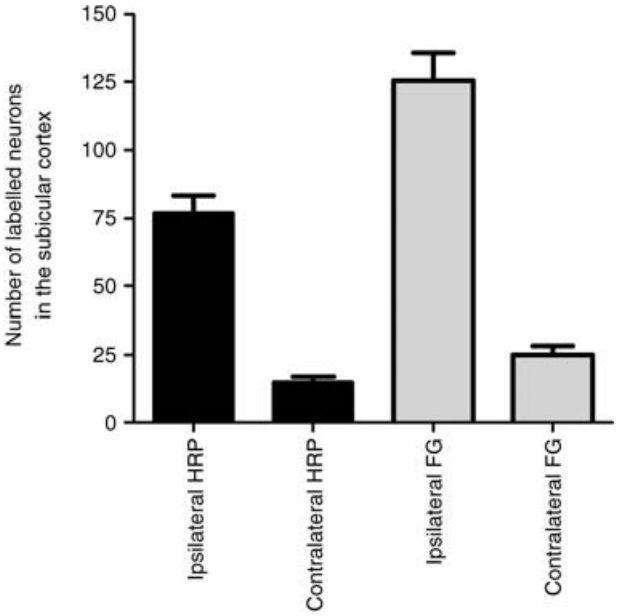

Fig. 5 The number of labelled neurons per section on the ipsilateral and contralateral subicular cortex, subsequent to HRP and FG injections into the rostral TRN. The error bars on the graph give the SE, which was calculated from the average numbers of HRP- and FG-labelled neurons for each animal.

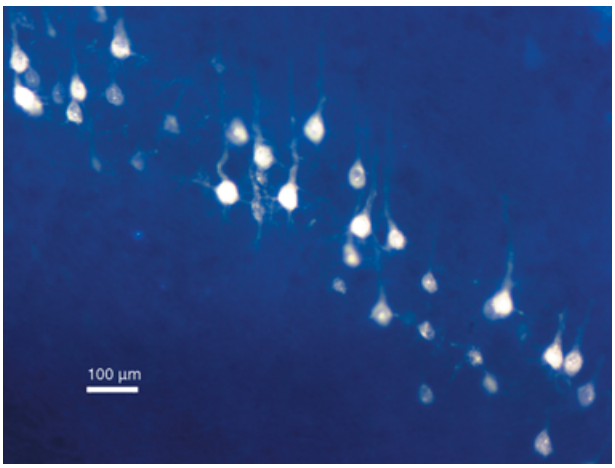

Fig. 6 Photomicrograph of one of the most important afferent connections of the rostral TRN is from layer V of the cingulate cortex.

and also avoided the ventricle (Fig. 1); furthermore, the fact that no cells were labelled in the hippocampal formation when injections involved the caudal sectors of the TRN argues against this interpretation.

The pathway from the subicular cortex to the TRN can be viewed in relation to the basic pattern of connections that link thalamic relay nuclei, the TRN and areas of neocortex (Carman & Powell, 1964; Jones, 1975; Conley & Diamond, 1990; Conley et al. 1991; Crabtree, 1992, 1996; Lozsádi, 1994; see Fig. 7). Each thalamic relay nucleus sends an axon to a particular neocortical area with a branch going to a specific related sector of the TRN. The same cortical area sends a modulatory corticothalamic axon back to the same thalamic nucleus and also has a branch that innervates the same sector of the TRN. This sector of the TRN, in turn, sends inhibitory axons back to the same thalamic nucleus. Our results show that the thalamic connections of the subicular cortex follow this same pattern. Figure 7 shows pathways from the reuniens nucleus to the hippocampal formation, including the subiculum (Herkenham, 1978; Yanagihara et al. 1987; Su and Bentivoglio, 1990; Wouterlood et al. 1990; Dolleman-van Weel et al. 1996, 1997; Bertram & Zhang, 1999; Dolleman-van der Weel & Witter,

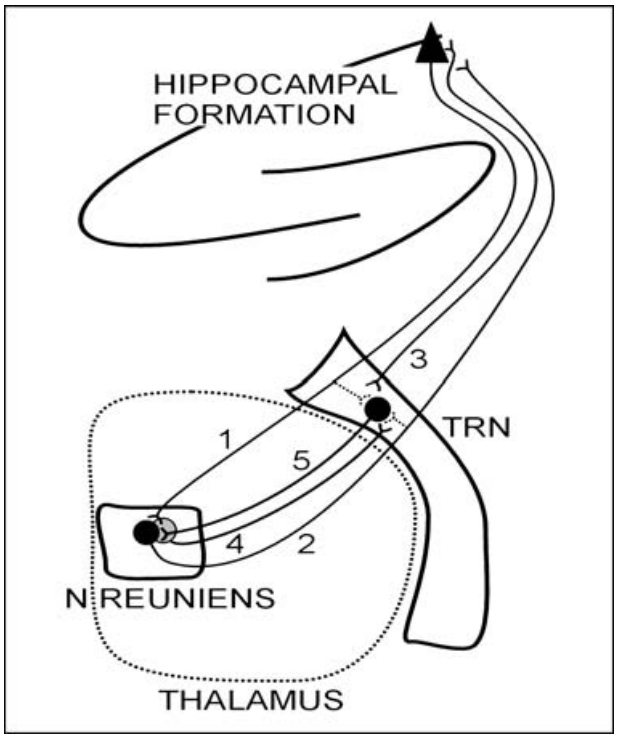

Fig. 7 Schematic illustration of the ipsilateral pathways between hippocampal formation, TRN and the reuniens nucleus. Solid line indicates the known connections; dotted line indicates the unknown collateral connections of the hippocampal–reuniens and reuniens–hippocampal formation connections (see text). 1. Reuniens–hippocampal formation connections (Herkenham, 1978; Yanagihara et al. 1987; Su and Bentivoglio, 1990; Wouterlood et al. 1990; Dolleman-van der Weel et al. 1996, 1997; Bertram and Zhang, 1999; Dolleman-van der Weel and Witter, 2000; Vertes et al. 2007). 2. Hippocampal formation–reuniens (Aggleton et al. 1986). 3. Hippocampal formation–TRN (present study). 4. TRN–reuniens (Mckenna and Vertes, 2004). 5. Reuniens–TRN (Cornwall et al. 1990; Vertes et al. 2006; present study).

2000; Vertes et al. 2007); it shows a pathway from the TRN to the reuniens nucleus (Mckenna & Vertes, 2004), and from the hippocampal formation to the reuniens nucleus (Aggleton et al. 1986). Our present results provide evidence for the existence of a pathway from the hippocampal formation to the TRN and confirm the earlier accounts of a pathway from the reuniens nucleus to the relevant part of the TRN (Cornwall et al. 1990; Vertes et al. 2006). These connections indicate that the thalamo-hippocampal connections resemble the thalamo-neocortical connections summarized above. At present we have no information about the branching patterns of the hippocampo-thalamic axons, although evidence from other thalamic nuclei would suggest that the hippocampo-reticular axons are likely to be branches of the hippocampo-reuniens axons as indicated by the dotted lines in Fig. 7.

Anatomical studies have demonstrated the existence of seven main sectors in the TRN, five sensory (auditory, gustatory, somatosensory, visceral and visual), one motor and one limbic (Carman & Powell, 1964; Jones, 1975; Conley & Diamond, 1990; Conley et al. 1991; Crabtree, 1992, 1996; Lozsádi, 1994). The most rostral part of the TRN, which receives the subicular and reuniens inputs demonstrated by our experiments, is connected to the motor and limbic centres. However, within this sector we have not been able to demonstrate any more detailed topography.

The connections that have been shown here may be relevant in the production or control of absence seizures. Several recent studies (Nanobashvili et al. 2003; Manning et al. 2003; Aker et al. 2006b; Tolmacheva & Luijtelaar, 2007) have shown that the hippocampal formation may be involved in the genesis of cortico-thalamo-cortical seizures. The TRN plays a crucial role in the pathogenesis of absence epilepsy (Avanzini et al. 1992) and the circuitry shown in Fig. 4 may account for some of the functional links that have been found between the hippocampal formation and mechanisms concerned with absence seizures (Manning et al. 2003). For example, Nanobashvili et al. (2003) showed that stimulation in the TRN affects the development of temporal lobe seizures in the rat. Their results showed that TRN stimulation can act to supress limbic motor seizures produced by hippocampal kindling. Consistent with those results, it has been shown that genetic strains of rat subject to absence seizures (GAERS and WAG/Rij models) fail to develop temporal lobe epilepsy in response to kindling stimulation (Aker et al. 2006b). This suggests a possible role of the thalamus in the neuronal circuits that involve the hippocampus and are responsible for limbic seizure generalization, In addition, Tolmacheva & Luijtelaar (2007) have shown that injections of anti-epileptic drugs into the hippocampal formation of WAG/Rij rats reduce the occurrence of spike-and-wave discharges generated within the thalamic circuits. Furthermore, one of these genetic strains of rat (GAERS) also shows that the density of glutamate immunolabelling in the mossy fibre terminals in the hilar region of the hippocampus is decreased compared with the control animals (Sirvanci et al. 2005). Taken together, this evidence suggests possible links between temporal lobe structures and TRN circuitry.

The results reported here suggest that the hippocampal formation is involved in thalamocortical circuitry that links the reuniens nucleus and the TRN in a pattern generally characteristic for thalamocortical relays to the neocortex. This allows the hippocampal formation access to the rostral sector of the TRN and through it to the whole of the thalamocortical circuitry relevant for attentional mechanisms, sleep–wake cycles and absence epilepsy.

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