The Reticular Thalamic Nucleus is involved in Interhemispheric Synchronization of the EEG

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The thalamic origin of sleep spindles is well established. Old and recent theories acknowledge the existence of a thalamic pacemaker, most likely to be located in the reticular thalamic nucleus (RTN). The evidence is based on surgical isolation studies, multiple and single unit studies and intracellular recordings in cats. The RTN plays also an important role in the pathogenesis of generalized absence epilepsy in the feline model (Steriade and Contreras 1995). It is suggested that the RTN serves as a pacemaker for sleep spindles, which form a carrier, or rider for generalized absence epilepsy characteristic spike-wave discharges (SWD). These spindles may or may not be transferred to SWD through changes of excitability in the thalamo-cortico-thalamic network.

The RTN is part of the anterodorsolateral thalamus; it has the shape of a thin sheet. It contains GABA-ergic cells, which encapsulate most of the anterior and lateral borders of the thalamus. The principal inputs of the RTN in the rat are from the ipsilateral cerebral cortex and the ipsilateral thalamo-cortical relay (TCR) cells. The RTN also receives inputs from the ventral striatum, various brainstem regions, substantia nigra, the globus pallidus and the dorsal raphe nucleus (Cornwall et al., 1990) These projections provide cholinergic, serotonergic and GABA-ergic inputs to the RTN that, in turn, modulate the physiological activity of the TCR cells through GABA-ergic projections in the dorsal thalamus (Battaglia et al, 1994). Most of the projections to and from the RTN are ipsilateral. However, RTN neurons also project to contralateral dorsal thalamic domains. Commissural connections from the RTN to selected nuclei of the contralateral thalamus have been reported in different mammalian species including the rat (Chen et al, 1992; Raos and Bentivoglia, 1993). Commissural neurons are concentrated in two parts of the RTN. Neurons in the rostral part of the RTN project to the contralateral central lateral (CL) and paracentral (Pc) nuclei of the thalamus, neurons in the

ventromedial sector of the middle third of RTN project to the contralateral VM nucleus of the thalamus and posterior part of CL and Pc. It seems that bilateral RTN connections with the dorsal thalamus provide a channel for interthalamic cross talk (Raos and Bentivoglio, 1993; Battaglia et al, 1994; Kolmac and Mitrofanis, 1997). Through the bilateral connections with thalamic VM and intralaminar neurons, the rostral pole of the RTN could influence through diffuse projections the activity of wide territories of the cerebral cortex of both hemispheres. However, there are no physiological data that show that this is actually the case.
In the present experiment it will be investigated whether lesions of the lateral thalamus including the rostral pole of the RTN would, besides having an effect on sleep spindles and SWD, change the synchronicity in the EEG between the left and right hemisphere. Such a possibility is feasible considering the connections of the rostral pole of the RTN to the contralateral intralaminar and medial nuclei with their diffuse projections to broad cortical areas.
Synchronization between two signals is commonly visually determined. This is particularly used in EEG research, where patterns such as spikes, spindles, burst of oscillations, etc. have been used to show synchronized (or de-synchronized) activity between different locations. However, not all forms of synchronization can be determined by visual inspection of the recordings. For this reason, measures of synchronization such as the cross-correlation or its Fourier domain version, the coherence, where introduced (for review see Lopes da Silva, 1993). These methods allow a quantitative analysis of synchronization but with the drawback that they are only sensitive to linear interdependences. In the context of the analysis of EEG signals of epileptic patients, a non-linear measure of interdependence was introduced by Arnhold et al (1999) and further studied with simple models (Quian Quiroga et al., 2000). The main advantages over previous approaches are its asymmetry, (that could eventually give information on driver-response relationships) and its sensitivity to non-linear synchronization.

Materials and Methods

Subjects

Adult male WAG/Rij rats, born and raised under standard conditions in the laboratory of the Department of Comparative and Physiological Psychology of Nijmegen University, were used. At the time of surgery, they were over 6 months old, their body weight ranged from 265-325 g.

Methods

Chronic stainless steel electrodes (Plastic One Inc., MS303/2) and a guide cannula were implanted under isoflurane anaesthesia (~240-320 cc/min). Elec-

trodes were placed at the frontal cortex, coordinates AP= 2.0, L= +/- 3.5 (Paxinos and Watson, 1986) and two other electrodes were aimed at the cerebellum, which served as reference and ground. The guide cannula (inner diameter (ID)= 0.5 mm, outer diameter (OD)=1.0 mm, length = 3.5mm) was aimed at the rostral pole of the RTN of the right hemisphere (AP= -1.6, L=-1.8) to enable needle penetration for ibotenic acid injections later in the experiment. The whole assembly was fixed to the skull with three stainless steel screws and dental cement.

Synchronization measure

If one assumes two simultaneously measured univariate time series corresponding to two systems X and Y, than the easiest measure of interdependence between them is given by the *cross-correlation*:

$$C(X \mid Y) = \frac{1}{N}\sum_{i=1}^{N}(x_i - \hat{x})\cdot(y_i - \hat{y})$$

This measure is symmetric and has the disadvantage that it is not sensitive to non-linear interdependences. Recently, a non-linear measure of synchronization was proposed (Arnhold et al, 1999; Quian Quiroga et al, 2000).

First one has to define for the two signals *m-dimensional* phase spaces by using delay vectors (Takens, 1981) $\bar{x}_n = (x_n, x_{n+\tau}, \ldots, x_{n+(m-1)\cdot\tau})$ and $\bar{y}_n = (y_n, y_{n+\tau}, \ldots, y_{n+(m-1)\cdot\tau})$, where m is the embedding dimension, τ the time lag and n=1,...,N. Let $r_{n,j}$ and $s_{n,j}$, j=1,...,k, denote the time indices of the k nearest neighbours in phase space of $\bar{x}_n$ and $\bar{y}_n$, respectively. Then, for each $\bar{x}_n$, the squared mean Euclidean distance to its k neighbours is defined as

$$R_n^{(k)}(X) = \frac{1}{k}\sum_{j=1}^{k}(\bar{x}_n - \bar{x}_{r_{n,j}})^2 \,.$$

where the neighbours should not be temporally correlated with $\bar{x}_n$; i.e. $|n - r_{n,j}| > T$ (Theiler, 1986). Similarly, the *y-conditioned* squared mean Euclidean distance is defined by replacing the nearest neighbours by the equal time partners of the closest neighbours of $\bar{y}_n$,

$$R_n^{(k)}(X \mid Y) = \frac{1}{k}\sum_{j=1}^{k}(\bar{x}_n - \bar{x}_{s_{n,j}})^2 \,.$$

If the point cloud of the embedding vectors $\bar{x}_n$ has average squared radius

$$R(X) \equiv \frac{1}{N}\sum_{n=1}^{N} R_n^{(N-1)}(X),$$

then $R_n^{(k)}(X \mid Y) << R(X)$ if the systems are strongly correlated, while $R_n^{(k)}(X \mid Y) \approx R(X)$ if they are independent.

Accordingly, we can define an interdependence measure $H^{(k)}(X \mid Y)$; i.e. the dependence of X on Y, as

$$H^{(k)}(X \mid Y) = \frac{1}{N}\sum_{n=1}^{N} \ln\left(\frac{R_n(X)}{R_n^{(k)}(X \mid Y)}\right).$$

This is zero is X and Y are completely independent, while it is positive if they are synchronized. The opposite interdependence $H^{(k)}(Y \mid X)$ is defined in complete analogy. It is in general not equal to $H^{(k)}(X \mid Y)$ and this asymmetry could in principle be used to study driver-response relationships (Quian Quiroga et al, 2000).

Procedure

Experimentation took place during the middle part of the dark phase. The animals were habituated to the experimental set-up, including the EEG leads for 12 hours prior to EEG recording. The base-line EEG was recorded for two hours. Signals were fed into a multi-channel differential amplifier, filtered between 1-100 Hz, digitised with 200 samples/second and stored onto optical disk. The behaviour of the rats was observed and encoded on disk to measure/determine passive behaviour after recording. Furthermore, a band pass filter (7-14 Hz) for the EEG channels was used to facilitate the detection and analysis of the sleep spindles.

Neurotoxic lesions were made four days after baseline registration under isoflurane anaesthesia. Ibotenic acid (RBI, I-116), dissolved in phosphate buffer (pH= 7.3) was injected through the cannula through the injection needle (OD= 0.4 mm) connected via a polyethyleen tube to a 2ul Hamilton microsyringe.

A total volume of 1 µl was infused at two different depths (6.5 and 7.5 mm from skull surface). The concentration ibotenic acid was 5µg/µl or 6.5 µg/µl.

Three days after the ibotenic acid lesion a two hour post-lesion EEG recording was made under identical circumstances as the baseline recording. Next, the animals were deeply anaesthetized with Nembutal (100mg/kg i.p.) and intracardially perfused with saline followed by 4% paraformaldehyde solution. Brains were removed and stored in 4% paraformaldehyde solution. Three days before sectioning, the brains were transferred to 30% buffered sucrose. Serial coronal sections of 60µm were cut on a vibratome. Each section was mounted on gelatine-coated glasses, stained with 0.1% cresyl violet and cover slipped with Entallan. The sections were examined on a light microscope to determine the damage of the ibotenic lesion.

The RTN was divided in a rostral and a caudal area. The rostral area was defined from AP= -1.3 to AP= -1.8. The caudal area started from AP= -2.12.

The number and duration of sleep spindles and SWD were quantified. These data will not be reported here in detail. For the synchronization study, four condi-

tions for all rats were studied: i.e. for the pre- and post-lesion condition, segments with and without SWD (for criteria see van Luijtelaar and Coenen, 1986). For each condition and rat, synchronization values were calculated as the average of 5 segments of 10 seconds each. An embedding dimension m=10, a time lag $\tau = 5$ in order to avoid oversampling, k=10 nearest neighbours and a correction for temporal correlations of T = 50 were used. These parameters were chosen heuristically in order to maximize the sensitivity of the method to the underlying synchronizations. These values were kept fixed for all the calculations done, thus allowing comparisons between the different conditions.

Results

From behavioral and EEG observation it was clear that the rats displayed all states of the sleep-wake cycle. All rats showed also sleep spindles and SWD in their baseline EEG record. The sleep spindles did not always occur bilateral symmetrically. The SWD were always bilateral symmetrical and looked synchronously.

Post-mortem verification of the lesion showed that the area of the lesion was characterized by complete loss or shrinkage of neurons and a general presence of gliosis, which was seen as little dark cells between the (remainders) of neurons. The lesioned area was centered around the injection side and no distant lesions were found. From detailed analyses it appeared that 7 out of 9 animals had a lesion in the rostral pole of the RTN. They were considered as the lesion group. Two of these rats had a small rostral RTN lesion, two rats had a 75% rostral RTN lesion and three rats had a near complete lesioned rostral RTN. None of the rats had any damage to the caudal part of the RTN. Damage to the rostral pole of the RTN was always accompanied by damage to anterior as well as lateral thalamic nuclei.

Two rats a complete intact RTN, they were considered as controls. These two rats showed a normal EEG pattern and synchronous, bilaterally symmetrical SWD after the lesion procedure. The SWD had a normal frequency of 7-10Hz. Various types of changes were found postlesion in the EEG of the lesioned hemisphere in the seven experimental rats. There seemed to be a decrease in the number of sleep spindles in the lesioned hemisphere only. Six of the seven rats with the lesion in the RTN showed a decrease in the number of SWD, in one subject the number was unchanged. The decrease was the same in both hemispheres. The two control rats showed an increase in SWD's from pre- to postlesion. The difference in the number of SWD in the lesioned as well in the intact hemisphere between the lesioned and control rats was significant. During EEG registration the occurrence of mobile behavior (behavioral activity such as walking, grooming and rearing) was scored in order to control for behavioral effects of the

lesion. As the vast majority of the number of sleep spindles and SWD occurs when the animal is passive and the level of vigilance is low (Coenen et al 1991), a decrease in immobility could explain a decrease in the number of sleep spindles and SWDs. After correction for the duration of immobility after the lesion the above-described effects persisted.
The amount of left-right non-linear synchronicity H in epochs with and without SWD is presented in Table I. H was found to vary in the human EEG from 0 (no synchronization) to 2.5-3.0 (during epochs with extremely high synchronization as seen during some tonic-clonic seizures).

NORMAL EEG SEGMENTS				
	H(X|Y)	H(Y|X)	H(X|Y)	H(Y|X)
	Pre	Pre	Post	Post
Lesion	0.44 (0.16)	0.44 (0.15)	0.28 (0.09)	0.28 (0.09)
Control	0.49 (0.01)	0.47 (0.02)	0.47 (0.01)	0.45 (0.02)
SWD SEGMENTS				
	H(X|Y)	H(Y|X)	H(X|Y)	H(Y|X)
	Pre	Pre	Post	Post
Lesion	0.65 (0.20)	0.64 (0.21)	0.38 (0.08)	0.35 (0.16)
Control	1.19 (0.20)	1.10 (0.02)	1.08 (0.16)	0.94 (0.18)

Table 1: Mean and SD of the non-linear synchronicity in normal episodes of EEG and during periods with SWD before and after a unilateral RTN lesion (Lesioned group, n=7) and in the two control animals. X is the lesioned hemisphere.

The data from Table I were analysed with an analysis of variance with lesion-non-lesion as between group factor and Pre/Post, type of EEG segment and Driver/Follower as within group factors. There was a significant effect for the type of EEG segment ($F=46.06$, df 1,7, $p<.001$), demonstrating that the synchronicity was higher during the segments with SWD than during the normal segments. Next, there was a main effect for the difference Pre/Post lesion ($F=26.50$, df 1,7, $p<.001$), a significant group effect ($F=19.48$, df 1,7, $p<.01$) and an interaction between group and pre-post ($F=6.05$, df 1,7, $p<.05$). This significant interaction demonstrates that the lesion had a different effect in the two groups. This implies that the synchronicity was decreased post-lesion in the experimental group, not in the control group. There was neither effect of the factor Driver/Follower nor interactions with this factor.

	NORMAL EEG SEGMENTS		SWD SEGMENTS	
	Pre	Post	Pre	Post
Lesion		0.61 (0.10)	0.46 (0.13)	0.63 (0.13) 0.46 (0.12)
Control	0.59 (0.01)	0.61 (0.01)	0.76 (0.02)	0.71 (0.03)

Table 2: Mean and SD of the cross correlations of normal EEG segments and SWD segments, before and after a unilateral RTN lesion in experimental and control rats.

The cross correlation data are presented in Table II, they were also analysed with an analysis of variance with group as between group factor and Pre/Post and type of segment as within group factors. The outcomes of this analyses showed only a significant main effect for Pre/Post ($F=7.14$, df 1,7, $p<.05$) and trends ($p<.1$) for a) type of segment: a tendency for more synchronization in the SWD segments, b) interactions between group and Pre/Post (only a decrease in the lesioned group after the lesion) and between group and type, suggesting that the control group had a higher left-right synchronicity for the segments with SWD. Note that cross-correlation decreases post-lesion are relatively lower (even in normal and in SWD segments) than with the non-linear measure, thus stressing the higher sensitivity of the latter.

Discussion

A lesion in the rostral pole of the RTN tended to show a decrease in the number of sleep spindles in the lesioned hemisphere only, while no such effects were seen in the non-lesioned hemisphere. Next, a bilateral decrease in the number of SWD was found after the lesion. The diminishment of sleep spindles as well as SWD after a unilateral lesion of the rostral pole of the RTN suggest a similar role for the rostral pole of the RTN in the generation of both types of oscillations. The differential effect with respect to whether the abolishment occurs in the lesioned or in both hemispheres demonstrates that the mechanism for bilateral synchronization of the two phenomena is different. A close link between sleep spindles and SWD has been shown to exist in humans (Kellaway et al., 1990) and in the feline penicillin generalized epilepsy model (Kostopoulos and Gloor, 1982). Gloor and co-workers (1969) demonstrated that spindles can be transformed into SWD when they reach a diffusely hyperexcitable cortex. Moreover, van Luijtelaar (1997) showed in rats, under pharmacological manipulation, the existence of an inverse relationship between sleep spindles and SWD. The present results are in agreement with the above findings, which

suggests that a single controlling system or pacemaker in the rostral pole of the RTN controls SWD and spindles. The present results confirm also Meeren et al. data (1998). They made thalamic lesions that included the whole RTN and a total abolishment of SWD was found in rats with a complete RTN lesion. The present data suggest that the Meeren et al. data should be interpreted according to the view that in rats the rostral pole seems to be the pacemaker for the thalamic oscillations. This seems to be different from what has been suggested in the ferret: here the perigeniculate nucleus, which is part of the caudal RTN, is considered to play a significant role in driving the TCR cells in the spindle rhythm (McCormick and Huguenard, 1992; McCormick and Bal, 1997).

In some individual cases, the segments without SWD showed a larger synchronization than the ones with SWD (individual data not reported) although larger synchronizations were found in SWD than in normal EEG segments. The usefulness of the synchronization measure is also illustrated by the fact that it showed synchronizations hardly seen by visual inspection. Next, the non-linear association measure was much more sensitive than the classical cross-correlation, stressing not only the presence of non-linear interdependence between the two hemispheres but also the sensitivity of this new variable. Damage to the rostral pole of the RTN reduces the linear cross-correlation but even more the non-linear interdependency of the synchronicity between the left and right hemisphere. Apparently, the rostral RTN is involved in the synchronization processes between the two hemispheres. The rostral pole of the RTN is, together with ventromedial sector of the middle third of the RTN, responsible for the commissural projection to contralateral ventromedial and anterior intralaminar thalamic nuclei (Chen et al., 1992; Raos and Bentivoglio, 1993; Kolmac and Mitrofanis, 1997). At their turn these areas provide the cerebral cortex with diffuse projection. Neurotoxic lesions do not, in contrast to electrolytic lesion, affect axons and dendrites and although axons and dendrites may be part of this commissar pathways and pass the lesioned parts of the thalamus, it may be assumed that it are indeed the lesions of the cell bodies in the rostral pole of the RTN which are causing the decrease in left-right synchronisation.

A leading role of one of the hemispheres in the picrotoxin model of generalized 5-7 Hz SWD that were accompanied by myoclonic jerks, was proposed (Medvedev et al., 1996). However it should be kept in mind that there are many peculiarities in the picrotoxin model that are different from those of genetic models: the induction method, the involvement of the hippocampus, the slower frequencies of the SWD, and the presence of myoclonic jerks accompanying SWD.

The number of SWD after the lesion appeared to be reduced in an equal amount in both hemispheres. It must therefore be that the both cortices work as a single system during SWD, irrespective of damage to the rostral pole of the RTN. It is thought that only complete or nearly complete transsections of the

corpus callosum may break up this single system in two parts since in GAERS (another commonly used rat model for generalized absence epilepsy) it was found that transsections of the corpus callosum resulted in a 90% partial abolition of the bilateral synchronism during SWD. Also unilateral SWD occurred (Vergnes et al., 1989). This suggests that each hemisphere has its own SWD generating system, but that these two generators normally act together as one through the strong interplay of the corpus callosum and the commissural fibres between the rostral RTN poles. Therefore, it seems that SWD from the intact generating hemisphere are spread through the corpus callosum to the other hemispheres, which causes an equal amount of SWDs in both hemispheres. Interestingly, the number of sleep spindles was only reduced at the lesioned site, not at the intact hemisphere. This discrepancy between the decrease in spindles and sleep spindles might agree with another important characteristic difference between the two types of oscillations: SWD are much more generalized and always bilateral symmetrical. Sleep spindles are less generalized and may even appear locally (Terrier and Gottesmann, 1978).

In conclusion, the brain contains two pacemaking systems, one in the left and one in the right hemisphere: the rostral pole of the RTN. This area is involved in the generation of sleep spindles and SWD. The rostral RTN poles of both hemispheres are connected via the reticulo-reticular commissure, which regulates the synchronization between the two hemispheres. While sleep spindles may occur independently in the left and right hemispere, SWD are more generalized and occur bilateral synchronously. The corpus callosum is responsible for the transfer of SWD from the intact to the lesioned hemisphere and thus for the bilaterally of SWD between both hemispheres.

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