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Letter to the Editor

DOES HIPPOCAMPAL THETA EXISTS IN THE HUMAN BRAIN? (Comment to the paper of Uchida et al. 2001)

R. BODIZS, ANNA SZUCS, P. HALASZ
Epilepsy Center, National Institute of Psychiatry and Neurology, Budapest, Hungary

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The hidden surface of the human medial temporal lobe (MTL) and its inaccessibility by traditional EEG recording procedures produced a large gap between human and animal data regarding hippocampal activity patterns. A wide-range of state-specific activity patterns of the hippocampal formation were established in animal studies, but few of them were unambiguously detected in humans. Two papers of Uchida et al. (Brain Research, 2001, 891:7-19 and Neurobiology of Sleep-Wakefulness Cycle, 2001, 1(1):1-8) present data with the explicit intention of reducing the gap between human and animal studies and "establishing human MTL activity patterns", which we agree "is of utmost importance" in "unveiling the enigma of human brain function" (Uchida et al 2001a, p. 8.). These and the previously reported data of the same group (Hirai et al., 1999a, b) are major advances in the field. They exceed previous studies in relatively high number of subjects, high frequency sampling and quantitative analysis of the electrocorticogram (ECoG), as well as careful avoidance of epileptic activity in the analyzed ECoG segments. In spite of these major advances, we disagree with the recording technique and the interpretation of the data, presented in their papers in Neurobiology of Sleep-Wakefulness Cycle and Brain Research. The authors invoke the phenomenon of hippocampal theta (also known as hippocampal rhythmic slow activity or hippocampal RSA) as one of the major starting point of their study and the basis of the interpretation of their results. Hippocampal RSA is a basic neurophysiologic feature of waking- and REM sleep related arousal (and perhaps cognition) in animal models. It is unclear whether similar theta activity exists in primates including humans. However, recording of hippocampal RSA has its indispensable conditions, which were established on the basis of a large number of animal experiments (Robinson, 1980). Perhaps the most important condition is related to the reference point. As hippocampal RSA is synchronous over large mediotemporal areas, it can be recorded in monopolar derivation, provided that the reference point is distant from the hippocampal formation. Bipolar recordings detect hippocampal RSA only when the referred points are below and above the pyramidal layer respectively. It is hard to imagine, how this latter criterion can be met in human studies, but clearly the subdural electrodes presented in the study of Uchida et al. (2001a) are inappropriate for bipolar recording of hippocampal RSA. Given this fact and the intention of the authors to detect hippocampal RSA, it is surprising that they used bipolar recordings in their study. This could lead them to erroneous assumptions regarding the frequency of human hippocampal RSA.

Presenting the logaritmized spectral plots of a single subject's monopolarly referred ECoG is (Uchida et al. 2001a, Fig. 9.) not convincing because of three reasons: (1) the distance between the reference point (ipsilateral basal temporal lobe) and the parahippocampal contact point is probably not sufficient (theta activity can be still detected in the basal temporal cortex of rats); (2) log-transformed spectral plots up to the 200 Hz value reported in figure 9. (p. 17.) did not allow visual inspection in the 1-5 Hz frequency range, which is most frequently found to behave like hippocampal RSA in human studies cited by Uchida et al. (2001a, b); (3) statistical analysis is based only on bipolar signals, which are unsuitable for detecting hippocampal RSA, so we do not know if the similar statistical analysis of the monopolar signals would produce significant state-specific differences in other frequency bands too. Otherwise it is quite improbable that a synchronized rhythmic activity would appear in a similar way in bipolar and monopolar derivations. It is more probable that the 10-20 Hz activity reported by Uchida et al. (2001a, b) is not synchronous over the parahippocampal gyrus, which is not the case for hippocampal RSA.

When used in animal studies, bipolar recordings produced signals which were rich in fast activity (Robinson 1980). This is exactly what we see in the records presented by Uchida et al. (2001a). In a similar study (Bodizs et al. 2001), using mediotemporal corticography with foramen oval electrodes in 12 epilepsy patients, we also found relatively low amplitude, fast activity in bipolar recordings during REM sleep. But when the same records were reanalyzed in extracranial reference they showed synchronized, rhythmic slow activity of 1.50-3.00 Hz. Our present database contain multiple all-night recordings from 14 patients, who all had this 1.50-3.00 Hz monopolarly recorded rhythmic activity during REM sleep. Other studies reporting hippocampal RSA-like patterns in human subjects always found frequencies below 10 Hz. Some of these papers were cited by Uchida et al. (2001a, b; but see also Wieser 1984 and Mann et al. 1997). Given these reports and the huge data coming from animal experiments we feel it is premature to consider beta-1 activity as the "functional equivalent of the animal hippocampal theta rhythm" (Uchida et al. 2001b).

Correspondence: Robert Bodizs
Epilepsy Center, National Institute of Psychiatry and Neurology
Huvösvölgyi út 116. H-1021 Budapest, Hungary
E-mail: rbodizs@opni.hu

Interestingly, many of the human studies share the above mentioned methodological problem (they report bipolar hippocampal recordings). It would be interesting to see this carefully selected ECoG-s with monopolar, extracranial reference, focusing on the low frequency components (< 10 Hz) of the signals.

In summary, we think that the papers of Uchida et al. (2001a, b) present very intriguing data on human MTL activity, but this is more related to the high frequency components and not to the hippocampal RSA. This means that the significance of beta-1 (10-20 Hz) activity in the human MTL during waking and REM sleep needs further discussion before being considered as a functional equivalent of hippocampal RSA.

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RESPONSE TO THE COMMENTS OF DRS. ROBERT BODIZS, ANNA SZUCS, PETER HALASZ

SUNAO UCHIDA[1], NOBUHIDE HIRAI[1], MASAKI NISHIDA[1], KENSUKE KAWAI[2], TAKETOSHI MAEHARA[3], HIROYUKI SHIMIZU[2]

[1]Department of Sleep Disorders Research, Tokyo Institute of Psychiatry, Tokyo; [2]Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo; [3]Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo

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We are grateful that our paper (Uchida et al. 2001b) in the first issue of this journal was read with interest by Bodizs et al. (2001b). It is surely useful to discuss data interpretation with researchers in a similar field. The number of researchers studying the human electrocorticogram is so small that it is important to exchange ideas. For this reason, the stimulating comments by Bodizs et al. were extremely valuable for our future research, and we deeply appreciate their efforts in writing us. We are also grateful that this new journal has been used for this valuable discussion.

In summary, they pointed out that our medial and basal temporal lobe (MTL and BTL) recordings were performed using a cortico-cortical bipolar technique, so that oscillatory activity will not be detected when it occurs in unison in the two cortical fields where electrodes were attached. They further commented on our intra-cortical monopolar recordings that the reference

Correspondence: Uchida Sunao, MD., PhD.,
Department of Sleep Disorders Research, Tokio Institute of Psychiatri,
2-1-8 Kamikitazawa, Setagaya-ku, Tokio, 156-8585, Japan.
E-mail: sunao@uchidae.com

on the most lateral electrode in the basal temporal lobe (Uchida et al. 2001a) was not far enough to avoid this cancellation effect. In conclusion, they stated that we should have failed to detect the lower frequency oscillation (1.5-3 Hz) that they recently reported (Bodizs et al. 2001a), which is probably the same activity described in two cases in a preliminary report (Mann et al. 1997). Thus, they claimed "that the significance of beta-1 (10-20 Hz) activity in the human MTL during waking and REM sleep needs further discussion before being considered as a functional equivalent of hippocampal RSA (rhythmic slow activity) (Bodizs et al. 2001b)".

We fully understand that bipolar recording can cause such a cancellation effect. In order to avoid this possibility, monopolar recording should be used. Since the primary purpose of our electrocorticogram (ECoG) recording was to detect high frequency (gamma) activity in the human cortex, we used cortico-cortical bipolar recording and high frequency (1500-3000 Hz) sampling, as an extra-cortical reference easily picks up muscle activities. We have, in fact, succeeded in detecting high frequency activity in the medial temporal lobe (Hirai et al 1999a). In addition, we have unexpectedly detected very regular beta-1 (10-20 Hz) rhythmic oscillation in the human medial temporal lobe, primarily during wakefulness (Hirai et al. 1999b) and during REM sleep in the human MTL (Uchida et al. 2001a). In these bipolar recordings, we failed to find the 1.5-3 Hz regular oscillation during REM sleep.

So, the question arises why we could not find 1.5-3 Hz. We use cortical surface electrodes, while Bodizs et al. (2001a) used wire electrodes with four contacts, which penetrate foramen ovale into the ambient cistern. The recording points seemed similar. We record cortical activities on four points (about 5 mm apart) along the long axis of the parahippocampal gyrus surface. Four electrodes were on a soft flexible plastic sheet, so that the contacts were good. Bodizs et al. also contact four points on the parahippocampal gyrus. Their four contact points were on a wire. In addition to the differences between monopolar and bipolar recording, these differences might account for the different results.

We think it important to emphasize that Bodizs et al. do not reject our evidence the beta-1 oscillation exists in the human medial temporal lobe during wakefulness and REM sleep. Since beta-1 appears during wakefulness and REM when animal RSA is observed, we consider beta-1 a possible homologue of animal RSA activity.

At this moment both beta-1 activity and 1.5-3 Hz activity remain on a descriptive level. No functional significance has been elucidated for either the slow or fast frequencies. As Bodizs et al. (2001b) and we (Uchida et al 2001b) pointed out, further studies to examine physiological or functional significance of these frequencies should be pursued.

It has been stated that the basic connections and role of brain structures is very similar in humans and rodents (Eichenbaum 2000). However, despite the topological similarities, the more developed higher brain functions in humans may need different physiological properties. More specifically, it may be that no single oscillation frequency in humans plays the role of animal hippocampal theta. Thus, we need further careful studies on human cortical activity.

Human studies of brain electrophysiology obviously are far more difficult to perform than animal studies. Subjects are not always available, and electrode placements are determined by clinical needs. Experimental designs are also limited because subjects primarily hospitalized for clinical evaluation and treatment. In spite of these difficulties we strongly agree with Bodizs et al. that human studies are essential to integrate the observations made in animal research.

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