Original article

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RTTBD-like activity in association with hippocampal ictal discharges in patients with temporal lobe epilepsy

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ABSTRACT – *Aim.* To determine clinical and intracranial EEG correlates of rhythmic temporal theta bursts of drowsiness (RTTBD) and assess its clinical significance in patients with temporal lobe epilepsy (TLE).
Methods. A retrospective review of simultaneous scalp and intracranial video-EEG recordings from 28 patients with TLE was evaluated for epilepsy surgery. Scalp RTTBD patterns were identified and their clinical and intracranial EEG correlates were then determined on video-EEG recording using depth and subdural electrodes.
Results. Thirty-one RTTBD patterns on scalp EEG were observed in six (21%) of the 28 patients. Five (16%) of the RTTBD patterns occurred during wakefulness and 26 (84%) occurred during drowsiness and light sleep. The mean duration of RTTBD was 10 seconds (range: 3-28 seconds). RTTDB consistently correlated with hippocampal ictal discharges and was time-locked to the hippocampal seizures in which the ictal discharges evolved into rhythmic theta frequency (4-7-Hz) range. Ictal automatisms were observed during five (16%) RTTBD patterns, while cognitive impairment was observed in four (13%) of the 31 RTTBD patterns.
Conclusion. Our findings show that scalp EEG correlates of hippocampal ictal discharges can resemble RTTBD and may be associated with ictal symptoms and cognitive impairment, indicating that RTTBD may rarely be an ictal EEG pattern in patients with TLE.

Key words: rhythmic temporal theta bursts of drowsiness (RTTBD), rhythmic mid-temporal discharges (RMTD), "psychomotor" variant (PV), hippocampal epileptiform discharges, temporal lobe epilepsy (TLE), subclinical seizures

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Rhythmic temporal theta bursts of drowsiness (RTTBD), or rhythmic mid-temporal discharges (RMTD), is currently considered a benign non-epileptiform EEG pattern (Lipman and Hughes, 1969), but its clinical relevance has been debated ever since it was first described by Gibbs (Gibbs and Gibbs, 1952; Gutmann, 2007). The pattern manifests as sharply contoured, flat-topped or notched waves in the theta frequency band (4-7 Hz) over the mid-temporal region unilaterally or bilaterally. It usually occurs in brief runs lasting a few seconds and rarely lasts longer than one minute (Gibbs *et al*., 1963; Tatum *et al*., 2006). The pattern was originally called "psychomotor variant" because of its morphological resemblance to the ictal EEG pattern seen with temporal lobe seizures, which at the time were called "psychomotor" seizures.(Gibbs *et al*., 1963) However, the term "psychomotor variant" fell out of favor because the pattern was not consistently associated with epileptic seizures (Chatrian *et al*., 1974). RTTBD differs from classic ictal EEG patterns as it is monomorphic without significant evolution in frequency or amplitude, and does not spread to adjacent electrodes or disturb the EEG background. The incidence of this pattern ranges between 0.2% and 0.5% in patients referred for routine EEG studies (Gibbs *et al*., 1963;Garvin, 1968; Lipman and Hughes, 1969).

Patients with RTTBD often have a history of traumatic brain injury, infection, cerebrovascular disease, epilepsy or multiple sclerosis (Gibbs and Gibbs, 1989). This EEG pattern has been linked consistently to neurovegetative or psychiatric symptoms including headache, dizziness, panic episodes, nervousness, nausea, vomiting, blurred vision and syncope, but rarely with frank psychosis (Garvin, 1968; Hughes and Olson, 1981; Hughes and Hermann, 1984; Boutros *et al*., 1986). However, no consistent correlation between RTTBD and epileptic seizures has been found (Lipman and Hughes, 1969). This waveform also appears in 2% of normal young adults (Maulsby, 1979). As such, RTTDB is generally considered to be a non-specific, non-epileptiform EEG phenomenon, or benign EEG variant (Klass and Westmoreland, 1985).

Emerging evidence, however, suggests that benign EEG variants, such as small sharp spike (SSS), can rarely be epileptiform EEG markers (Issa *et al*., 2018). RTTBD has been associated with ictal symptomatology in several reports, and it is clear that many electrographic seizures can be subclinical (Velkey *et al*., 2011), leaving open the question of how tightly coupled RTTBD is to seizures (Hughes and Cayaffa, 1973; Klass and Westmoreland, 1985; Gibbs and Gibbs, 1989). The main objective of this study was to determine whether RTTBD is associated with intracranial ictal epileptiform discharges using simultaneous scalp and intracranial EEG recordings, which has not been investigated previously.

Methods

Subjects

The study data were collected from a retrospective review of patients who underwent pre-surgical evaluation at the University of Chicago adult epilepsy center between January 2014 and December 2017. Patients who met the following criteria were included:

– simultaneous scalp and intracranial EEG were recorded;

– at least one depth electrode targeted the amygdalohippocampal complex (AHC) through an occipital approach;

– and intracranial ictal epileptiform discharges were recorded. Patients with significant structural lesions, such as tumors, strokes and vascular malformations, were excluded. The University of Chicago Institutional Review Board (IRB) approved the study.

Simultaneous scalp and intracranial video-EEG recordings

Standard scalp EEG electrodes were placed in the 26-channel international 10-20 arrangement plus supplementary sub-temporal electrodes, F9, T9, F10, T10, from the 10-10 system, and mastoid electrodes, M1, M2 (Tao *et al*., 2007). Mid and posterior temporal electrodes, T3, T5, T4 and T6, in the 10-20 system have been renamed as T7, P7, T8 and P8, respectively, in the 10-10 system. Electrodes T7/T9 and T8/T10 localize to the left and right mid-temporal areas, respectively. In our standard intracranial implantation, one depth electrode was implanted through an occipital approach along the longitudinal axis of AHC to sample the AHC ipsilateral to the side of seizure onset. Bilateral hippocampal depth electrodes were placed in patients with possible bilateral temporal ictal onsets. Three lateral temporal depth or strip electrodes were implanted to sample the anterior, mid and posterior temporal cortices. Additional frontal, orbitofrontal or posterior temporal strips or depth electrodes were placed as clinically indicated if extra-temporal epileptic focus was a concern (Tao *et al*., 2018).

All the electrodes were implanted through burr holes, typically one in the occipital and one in the lateral temporal region for each patient. A craniotomy was not performed in any of the patients in this study. Breach rhythm due to burr hole was not clearly observed in this study. Locations of the electrodes were reconstructed using intraoperative stereotactic CT scans co-registered with pre-implantation volumetric MRI

(Brang *et al*., 2016). EEG signals were acquired at a sampling rate of 1 kHz using a Natus Neurolink EEG amplifier (Natus Neurology Incorporated, Middleton, WI). Scalp electrode FCz was used as the reference for both scalp and intracranial EEG recordings. The scalp and intracranial EEG signals were viewed using a common average referential montage, in which the average reference was constructed using all the scalp electrodes except Fp1, Fp2, M1, and M2; none of the intracranial electrodes were included. Muscle artifacts were appropriately filtered to improve the signal-to-noise ratio. RTTBD patterns with significant artifacts obscuring the evolution and termination of RTTBD patterns were excluded in this study.

Clinical and intracranial EEG correlates of scalp RTTBD

Three experienced electroencephalographers (TS, XL and JXT) visually interpreted the archived simultaneous scalp and intracranial EEG recordings with differences resolved by consensus. The archived EEG files consisted of segmented EEG data including the first hour of sleep EEG, interictal discharges, events, runs, and subclinical and clinical seizures. The mean duration of the archived EEG recordings available for review was nine hours, ranging from 6 to 18 hours. For each patient, scalp EEG recordings were reviewed simultaneously with the intracranial EEG recordings. The frequency, duration, location and morphology of RTTBD on scalp EEG were characterized. RTTBD was defined as rhythmic 4-7-Hz discharges that stood out from the EEG background and lasted ≥three seconds in the temporal region, with maximal amplitude in the mid-temporal region (Gibbs *et al*., 1963).

The clinical accompaniments of RTTBD were then reviewed on video recordings. For this study, clinical seizures were defined as events with auras (psychic, autonomic or somatosensory), automatisms, or sensorimotor symptoms with or without impairment of awareness and secondary generalization (Luders *et al*., 1998). The intracranial EEG correlates of RTTBD were determined based on the recordings of depth and subdural electrodes. The intracranial ictal patterns were defined as rhythmic epileptiform discharges lasting ≥10 seconds and involving ≥three contacts on the depth or strip electrodes with clear ictal onset and offset. The total number of intracranial seizures was also determined.

The presence of high frequency oscillations (HFOs) was assessed during hippocampal ictal discharges that stood out from background activity. HFOs were identified when there were at least four cycles of 80 Hz or higher activity. Digital filters were set to optimize detection by:

– turning off the low-pass filter;
– setting the high-pass filter at sequentially higher cut-off frequencies starting at 80 Hz;
– and turning off the 60-Hz notch filter, which if active would produce a ringing artifact ≥60 Hz.

Results

Patient characteristics

A total of 28 patients were included in the study. Their mean age was 40 years, ranging from 16 to 61 years. Ten patients were males and 18 were females. The mean duration of epilepsy was 20 years, ranging from 3 to 41 years. All patients had medically intractable temporal lobe epilepsy (TLE). Twenty-seven patients had mesial TLE and one patient had both mesial and neocortical TLE. RTTBD was observed in six of the 28 patients. The mean age of these six patients was 51 years, ranging from 29 to 61 years, and three patients were males. Of the six patients with RTTBD patterns, five underwent laser amygdalohippocampectomy, and two of the five patients have remained seizure free after one year of follow-up. One of the six patients underwent responsive nerve stimulation (RNS) treatment for bilateral temporal ictal onset with 90% seizure reduction after two years of follow-up.

Electrophysiological features of RTTBD

A total of 31 RTTBD patterns were observed in six patients. The predominant frequency within the pattern ranged from 4 to 7 Hz, with the majority in the range of 5 to 7 Hz (*table 1*). The morphology of the RTTBD was sharply contoured, flat-topped or notched waves (*figure 1, 2, 3*). Five (16%) of 31 RTTBD were observed during wakefulness. In all five patterns observed during wakefulness, the patients were asleep at the time of hippocampal ictal onset and were woken by the seizure at the time when scalp RTTBD was recordable. The frequency of the five RTTBD patterns was 4-5 Hz, 5-6 Hz, 4-5 Hz, 6-7 Hz, 6-7 Hz, respectively. In the same patient, the frequency of RTTBD during wakefulness and sleep was similar (*table 1*). The remaining 26 (84%) occurred during drowsiness or light sleep. Twenty-seven (87%) were unilateral and four (13%) were bilateral and independent (*table 1*). RTTBD were typically maximal on mid-temporal electrodes, T7/T9 or T8/T10, but also involved anterior temporal electrodes, F7/F9 and F8/F10. Compared to lateral temporal electrodes, F7/T7 and F8/T8, the pattern was typically more pronounced on subtemporal electrodes, F9/T9 and F10/T10, which are more sensitive in detecting signals arising from the mesiobasal temporal cortex (*figure 1*).

Table 1. Clinical and EEG characteristics of RMTD.

Patient (age/sex)	No. of PV	Location of PV	Frequency of PV (Hz)	Duration of PV(s)	Delay of PV (s)	Onset of IC seizure	Duration of IC seizure(s)	Sleep or drowsinsess?
1 (58yr/F)	1	RT	4-5	16	11	R hippo	44	N
	2	RT	5-6	10	37	R hippo	115	Y
	3	BT	5-6	9	48	R hippo	214	Y
	4	RT	5-6	10	38	R hippo	81	Y
	5	RT	4-5	5	17	R hippo	22	Y
2 (29yr/M)	6	LT	5-6	13	18	L hippo	32	Y
	7	LT	5-6	3	30	L hippo	33	Y
3 (63yr/M)	8	LT	6-7	7	14	L hippo	78	Y
	9	LT	5-6	7	15	L hippo	68	Y
	10	LT	5-6	18	19	L hippo	85	N
	11	LT	4-5	11	13	L hippo	52	Y
	12	LT	5-6	7	18	L hippo	80	Y
	13	LT	4-5	5	16	L hippo	21	Y
	14	LT	5-6	14	19	L hippo	49	Y
	15	LT	6-7	11	18	L hippo	46	Y
	16	LT	5-6	5	17	L hippo	59	Y
	17	LT	4-5	4	49	L hippo	67	N
	18	BT	5-6	3	14	L hippo	17	Y
4 (42yr/F)	19	LT	5-6	4	2	L hippo	11	Y
	20	LT	5-6	5	2	L hippo	12	Y
5 (61yr/F)	21	LT	6-7	5	4	L hippo	12	Y
	22	BT	6-7	10	15	R hippo	35	N
	23	LT	6-7	14	7	L hippo	25	Y
	24	RT	6-7	9	19	R hippo	48	Y
	25	LT	6-7	3	18	L hippo	21	Y
	26	RT	6-7	15	16	R hippo	71	Y
	27	RT	6-7	17	17	R hippo	69	Y
	28	RT	6-7	28	14	R hippo	67	Y

Table 1. Clinical and EEG characteristics of RMTD (*Continued*).

Patient (age/sex)	No. of PV	Location of PV	Frequency of PV (Hz)	Duration of PV(s)	Delay of PV (s)	Onset of IC seizure	Duration of IC seizure(s)	Sleep or drowsinsess?
6 (50yr/M)	29	BT	6-7	18	19	R hippo	43	Y
	30	RT	5-6	8	15	R hippo	45	Y
	31	RT	6-7	4	17	R hippo	39	N

RMTD: rhythmic mid-temporal discharge; PV: psychomotor variant;; F: female; M: male; yr: year; S: seconds; RT: right temporal; LT: left temporal; BT: bilateral temporal; R: right; L: left; hippo: hippocampus; IC: intracranial; N: no; Y: yes.

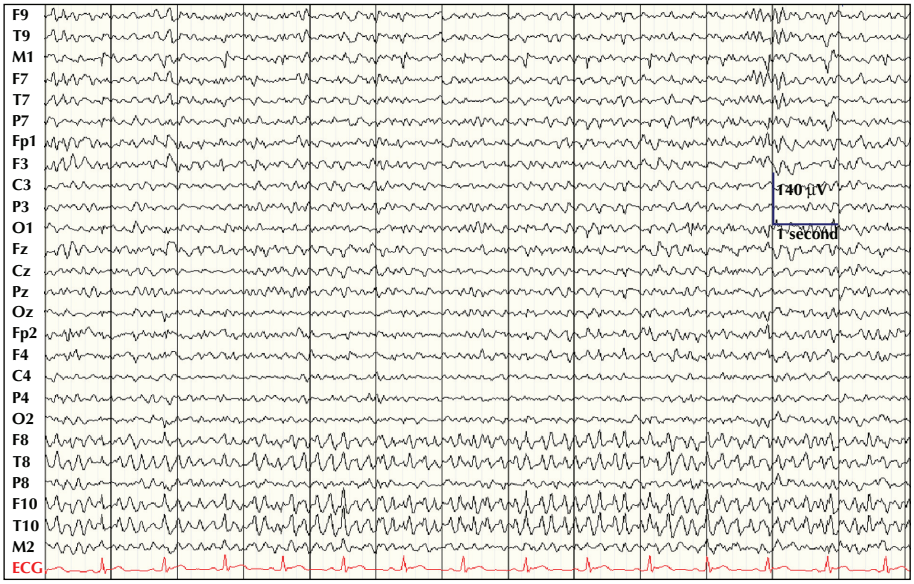

Figure 1. RTTBD on scalp EEG recording. A sharply contoured RTTBD (5-6Hz) was present in the right temporal lobe on scalp EEG during Phase I pre-surgical video-EEG monitoring prior to the intracranial study. The RTTBD appeared sharply contoured or notched and maximal in the mid-temporal region at electrodes T10 and T8, but also involved the anterior temporal region at electrodes F10 and F8. It was more prominent over the subtemporal region at electrodes F10 and T10 than the lateral temporal region at electrodes F8 and T8. Filters: LF=2 Hz; HF=30 Hz.

RTTBD patterns did not involve extra-temporal electrodes. There was no postictal slowing following the RTTBD patterns.

Clinical correlates of RTTBD

Video-EEG recordings were reviewed to determine clinical correlates of the RTTBD. Of 31 RTTBD, patients were not disturbed by caretakers and nurses, and did not have any noticeable body movements during 19 episodes. During the remaining12 episodes, patients had voluntary or involuntary body movements, such as body repositioning and limb movements. Ictal automatisms including lip-smacking and ipsilateral limb fumbling were observed during five episodes of RTTBD; three over the left temporal region and two over the right temporal region. Physical examination was conducted by nurses during or immediately after nine episodes. Patients were responsive and coherent during five events with RTTBD over the right temporal lobe, whereas patients were unable to answer nurses' questions, such as name, time and location (receptive aphasia), in four episodes over the left temporal lobe, but they were alert and did not appear to have impaired consciousness during these episodes. Twenty-three of 31 RTTBD patterns occurred during sleep and light drowsiness without cognitive impairment.

Intracranial EEG correlates of RTTBD

The mean duration of the intracranial seizures associated with RTTBD was 54 seconds; ranging from 11 to 214 seconds. The mean duration of RTTBD was 10 seconds; ranging from 3 to 28 seconds. All RTTBD patterns

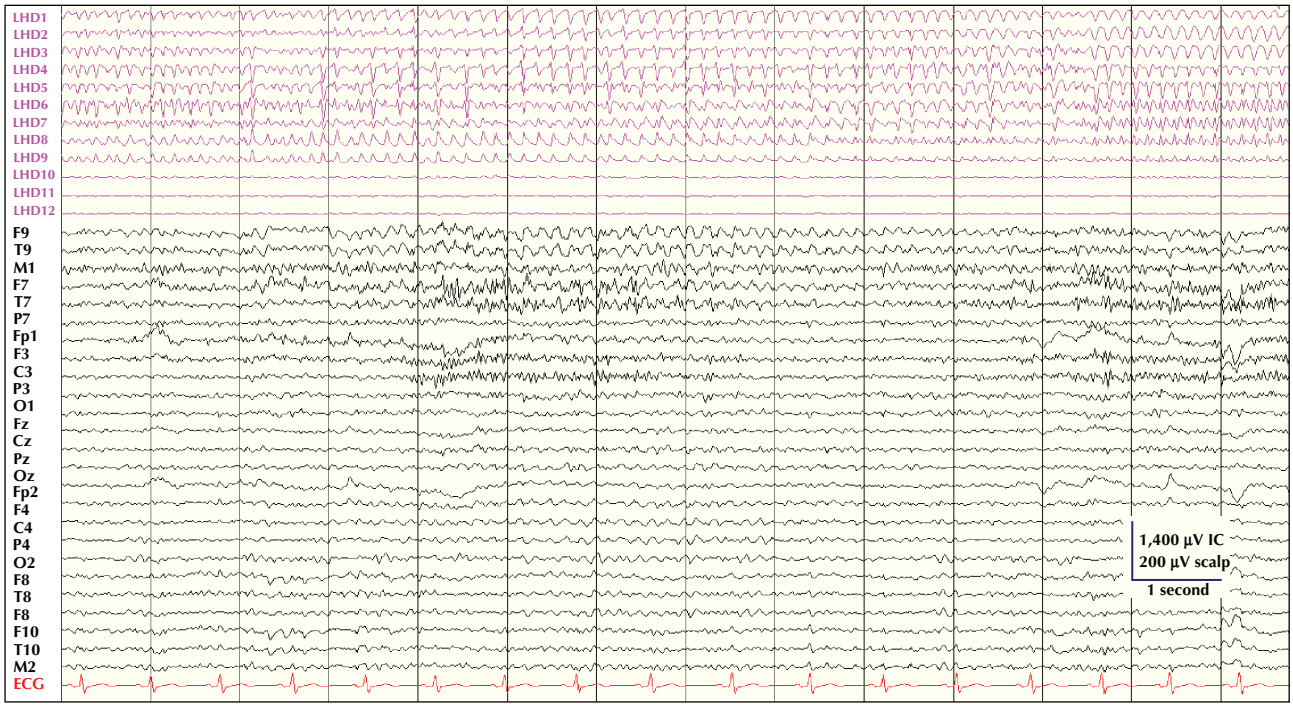

Figure 2. RTTBD correlating with a hippocampal seizure. Simultaneous scalp (black) and hippocampal (pink) EEG recordings in a patient with left mesial TLE during sleep. The RTTBD (5-6 Hz) with flat-toped or notched appearance was present in the left temporal lobe on scalp EEG and correlated with the middle part of a left hippocampal seizure recorded on a single depth electrode placed along the longitudinal axis of the left hippocampus without lateral temporal bone defect. On scalp EEG, the RTTBD was more prominent over the subtemporal region at electrodes F9 and T9, compared to the lateral temporal region at electrodes F7 and T7. LHD: left hippocampus depth electrode. Filters: LF=2 Hz; HF=30 Hz.

were correlated with the middle part of hippocampal seizures, in which the ictal discharges gradually evolved to rhythmic theta frequency. These rhythmic theta ictal discharges in the hippocampus achieved sufficient synchrony, and commonly appeared sharply contoured or had a spike-wave pattern, correlating with sharply contoured, flat-topped or notched discharges on scalp EEG. The cycles of the scalp RTTBD were time-locked to the intracranial ictal epileptiform discharges (*figure 2, 3*). These hippocampal seizures propagated minimally to basolateral and anterior temporal cortices (*figure 3*). The mean latency from hippocampal seizure onset to RTTBD onset on scalp EEG was 18 seconds; ranging from 3 to 115 seconds. The mean number of the implanted intracranial electrodes was five in the six patients with RTTBD patterns. Two (Patient 2 and 3) of these six patients had extratemporal (orbitofrontal and parietal) depth electrodes that did not show any extra-temporal propagation correlating with scalp RTTBD patterns (*supplementary figure 1*).

Interictal and ictal HFOs in the hippocampus were observed in all six patients in whom RTTBD were identified. Of the 31 hippocampal ictal discharges associated RTTBD, 27 had HFOs associated with these hippocampal ictal discharges. There was no direct association between HFOs and RTTBD observed in this study. A total of 1,024 intracranial seizures were observed in the 28 patients with TLE. The sensitivity of scalp RTTBD for detecting hippocampal seizures was 3%.

Discussion

We determined the clinical manifestations and intracranial EEG correlates of the scalp RTTBD pattern observed in six patients with medically intractable TLE. The morphological characteristics of RTTBD in this study were similar to those reported in previous studies, as demonstrated in both non-invasive and invasive settings, including a Phase 1 EEG study without any burr hole (*figure 1*), with only an occipital burr hole without lateral temporal burr holes (*figure 2*), and with both occipital and lateral temporal burr holes (*figure 3*) during the Phase II invasive study. The pattern manifested as sharply contoured, flat-topped or notched waves in the theta frequency band (4-7 Hz) over the mid-temporal region. It usually occurred in brief runs lasting a few seconds and rarely lasted longer than a minute. The pattern occurred unilaterally or bilaterally during in drowsiness, sleep and wakefulness. The notch or the fast component was considered a

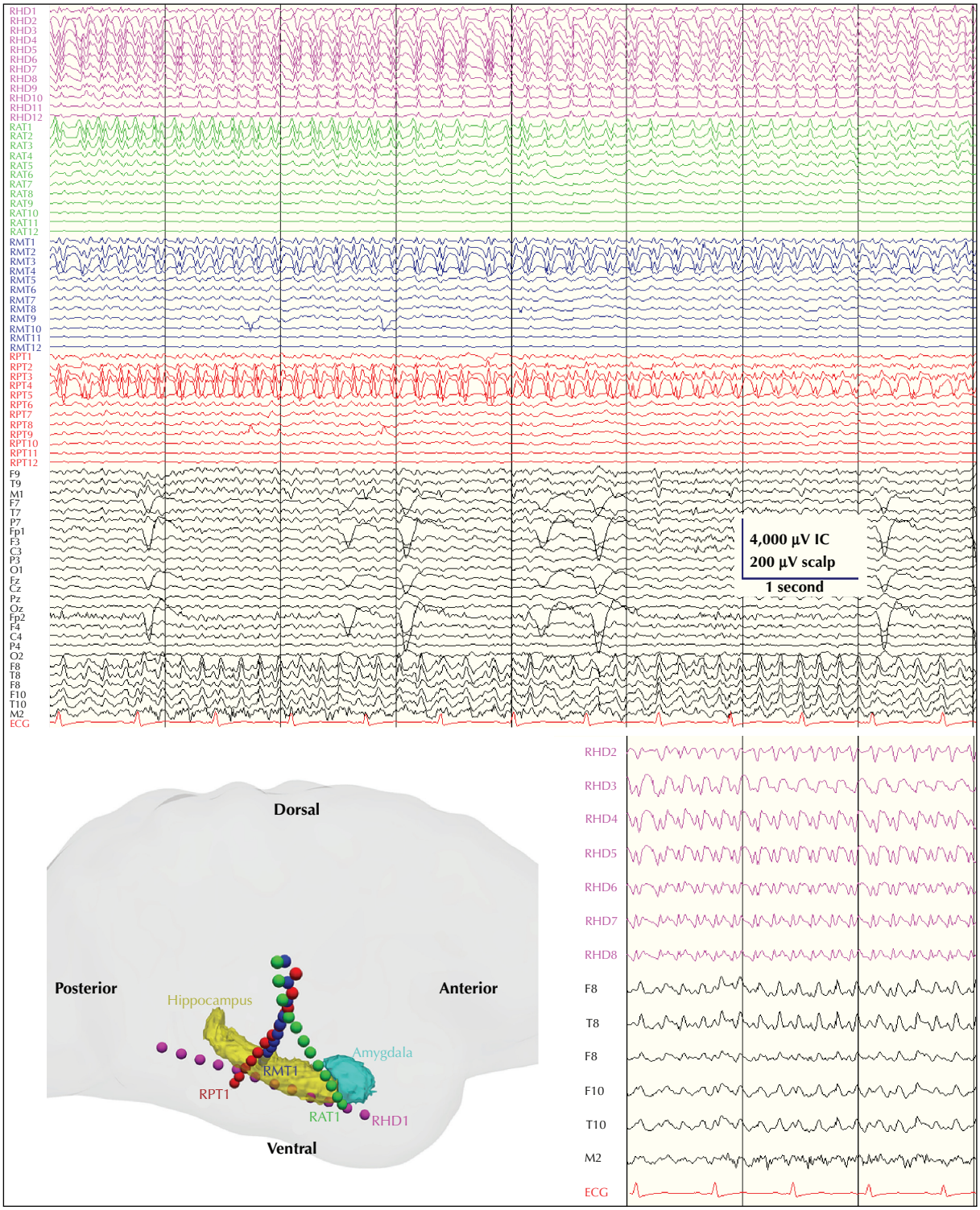

Figure 3. RTTBD correlating with a hippocampal seizure with minimal ictal propagation; simultaneous scalp and hippocampal EEG recordings in a patient with right mesial TLE during wakefulness. The RTTBD (5-6 Hz) was present in the right temporal lobe on scalp EEG and correlated with the middle part of a right hippocampal seizure recorded on depth electrodes placed along the longitudinal axis of the right hippocampus and lateral temporal depth electrodes. On scalp EEG, the RTTBD was sharply contoured and notched. Upper panel: simultaneous recording with full sets of depth and scalp electrodes. Lower left panel: 3D-reconstructed depth electrodes. Lower right panel: correlation between the right temporal scalp RTTBD and right hippocampal ictal discharges is highlighted. RHD: right hippocampal depth electrode; RAT: right anterior temporal; RMT: right medial temporal; RPT: right posterior temporal. Filters: LF=2 Hz; HF=30 Hz.

prominent morphological feature of RTTBD (*figure 3*) (Gibbs and Gibbs, 1989). The morphological features of RTTBD patterns appeared heterogeneous from patient to patient. Achieving sufficient synchrony of hippocampal ictal discharges was imperative for the recording of scalp RTTBD correlates (*supplemental material; Seizure 1*). Although not significant, some variations in amplitude and frequency were observed in some of the 31 RTTBD patterns, which was consistent with the RTTBD patterns described in previous classic studies (Gibbs *et al*., 1963; Lipman and Hughes, 1969; Gibbs and Gibbs, 1989). We reviewed the published studies on RTTBD and found that the vast majority of published RTTBD patterns had noticeable variations in frequency and amplitude, and RTTBD patterns without such variations were relatively rare.

Although RTTBD is commonly seen in adolescents and young adults (Hughes and Cayaffa, 1973; Klass and Westmoreland, 1985), the patients in this study who displayed RTTBD were adults (21 to 61 years old), likely because enrollment was restricted to patients who were 16 years and above with medically intractable epilepsy. The incidence of RTTBD was reported to be between 0.2% and 0.5% in patients with routine EEG studies and was 27-36% in patients with epilepsy (Gibbs *et al*., 1963; Lipman and Hughes, 1969). The incidence of RMTD in our study was 21% (6/28) in patients with medically refractory TLE, which is consistent with previous studies.

Location of RTTBD

On scalp EEG, RTTBD was maximal over the mid-temporal area, at T7 or T8 electrodes based on the 10-20 international system, and commonly involved the anterior temporal region at F7 and F8 electrodes. This is consistent with the traditionally described location of the RTTBD. Additionally, RTTBD was more pronounced over the subtemporal region at electrodes F9/T9 and F10/T10, as compared to the anterior and lateral temporal region at electrodes F7/T7 and F8/T8. Subtemporal electrodes, F9/T9 and F10/T10, were more sensitive in sampling the EEG potentials arising from the mesiobasal temporal cortex. The subtemporal region was not recorded in the previous studies using standard 10-20 electrodes (Lipman and Hughes, 1969).

RTTBD as a potential ictal EEG pattern

RTTBD has been considered a benign EEG variant because it has a monomorphic appearance, often does not have significant clinical manifestations, exhibits poor correlation with epilepsy, and can be observed in 2% of normal healthy individuals (Klass and Westmoreland, 1985). Nevertheless, several lines of evidence suggest that RTTBD can be an ictal EEG pattern:

– RTTBD was associated with ictal automatisms during the period of psychomotor seizures (Gibbs *et al*., 1937), and was found during the interictal period in patients with "psychomotor" seizures (Gibbs *et al*., 1938). Additionally, 98 (17%) of 591 episodes of the "psychomotor" variants (or RTTBD) were associated with some ictal symptomatology (Gibbs and Gibbs, 1989). In this study, ictal automatisms were observed in four (13%) of 31 episodes of RTTBD.

– RTTBD was commonly observed in 27-36% patients with epilepsy (Lipman and Hughes, 1969; Hughes and Cayaffa, 1973; Hughes and Olson, 1981), and the incidence of seizures was significantly higher ($p<0.001$) in patients exhibiting RTTBD than in those with normal EEG (Hughes and Olson, 1981).

– Patients with RTTBD might have subtle clinical accompaniments such as cognitive impairment, and showed a statistically significant increase in latency of response to photic stimulation, and significantly decreased incidence in the ability to respond at all during the burst (Lipman and Hughes, 1969). Patients with prolonged RTTBD discharges during wakefulness reported clinical symptoms such as a floating feeling and heaviness in the head (Lipman and Hughes, 1969). Similarly, patients in this study were unable to follow commands and were disoriented during and immediately after five (16%) of 31 left hippocampal seizures associated with RTTBD on scalp EEG.

– Most importantly, we found that scalp RTTBD patterns were consistently correlated with hippocampal ictal epileptiform discharges. Intracranial ictal discharges correlated with the scalp RTTBD and ictal discharges originated from the same hippocampal seizure onset in the amygdalohippocampal complex; they were associated with ictal HFOs. The location and morphology of scalp RTTBD were also similar to those of the onset of classic ictal EEG patterns in patients with mesial TLE, in whom initial rhythmic theta discharges are common ictal onset patterns (Ebersole and Pacia, 1996; Tao *et al*., 2007). It is interesting to compare RTTBD to temporal intermittent rhythmic delta activity (TIRDA), since both rhythmic theta and delta ictal patterns are common ictal onset patterns in patients with TLE. TIRDA is implicated as an epileptiform EEG pattern (Geyer *et al*., 1999; Tao *et al*., 2011), and our study raised the possibility that RTTBD may rarely be an epileptic pattern.

Neurovegetative and psychiatric symptoms associated with RTTBD

RTTBD is strongly correlated with "neurovegetative" symptoms, which were characterized as alterations

of a broad spectrum of neurological, autonomic and psychiatric symptoms including headache, dizziness, panic episodes, anxiety, nausea, palpitations, vomiting, blurred vision and syncope (Garvin, 1968; Lipman and Hughes, 1969; Gibbs and Gibbs, 1989). Based on the analysis of 55 RTTBD patterns observed in 16,800 EEG records, 60% of RTTBD were associated with "neurovegetative" symptoms, 46% with psychiatric symptoms, and 36% with seizures (Lipman and Hughes, 1969). Although the lack of strong correlation between RTTBD and epilepsy has been the main reason why RTTBD is considered a benign EEG variant, these "neurovegetative" and psychiatric symptoms can be observed in up to 80% of patients with TLE as interictal and ictal symptoms (Flor-Henry, 1969; Gupta *et al*., 1983; Beyenburg *et al*., 2005; Beletsky and Mirsattari, 2012). Fear, panic attacks and syncope can be the main symptoms in the early stages of TLE (McLachlan and Blume, 1980; Hermann *et al*., 2000; Biraben *et al*., 2001), which can often lead to misdiagnosis as primary psychiatric disorders for years prior to the development of more classic ictal semiologies (Thompson *et al*., 2000; Mintzer and Lopez, 2002; Sazgar *et al*., 2003; Kanner, 2011). After treatment with antiseizure medications, the majority (68%) of patients with "neurovegetative" and psychiatric symptoms, with RTTBD patterns on EEG, improved clinically, and the RTTBD pattern became less frequent or disappeared (Stone *et al*., 1986; Muller *et al*., 1988; Gibbs and Gibbs, 1989). This suggests that RTTBD might be an early ictal EEG marker for TLE, which would account for the poor correlation between the incidence of RTTBD on EEG and epilepsy. As such, the strong association of RTTBD with neuro-vegetative and psychiatric symptoms should not undermine the clinical significance of the RTTBD as an epileptiform EEG pattern. Neither should the presence of the RTTBD in 2% normal healthy individuals mitigate its use as a marker for TLE (Maulsby, 1979), as epileptiform EEG discharges are present in 5% of normal healthy children (Okubo *et al*., 1994), and in 12.3% of patients without a clinical diagnosis of epilepsy (Sam and So, 2001).

Study limitations

This study is limited by its retrospective design and the population preselection bias of patients with established TLE. Because patients in the study were exclusively pre-surgical candidates, intracranial electrodes consistently targeted the AHC but inconsistently sampled other areas. As result, other intracranial sources that might also generate RTTBD, such as extratemporal cortex, cannot be ruled out. Depth electrode placement can sometimes produce theta activity in the neocortex (Tatum *et al*., 2019), but this is unlikely to be the origin of the scalp RTTBD-like pattern observed. The pattern was not found in association with isolated theta on neocortical intracranial channels, but instead was correlated with hippocampal seizure activity in the theta range. Additionally, patients with RTTBD without interictal epileptiform discharges or a diagnosis of epilepsy were not included in this study. Therefore, it is possible that both benign and pathological RTTBD may exist. Although the recommendations to distinguish the benign from pathological RTTBD are beyond the scope of this study, the evaluation of RTTBD with sharp morphology, clinical correlates (automatisms and cognitive impairment) and occurrence during wakefulness should raise caution in interpreting this pattern as a "benign variant". The pre-selection of subjects based on TLE means that the true incidence of RTTBD and the specificity of RTTBD for hippocampal seizures cannot be estimated. However, it is clear that RTTBD is not readily associated with subclinical hippocampal seizures, with only 3% of the seizures detected on intracranial channels producing RTTBD on scalp EEG. These findings are analogous to the situation with small sharp spikes, another scalp EEG pattern typically considered benign, but which have recently been found to correlate with pathological hippocampal spikes (Issa *et al*., 2018). If RTTBD is consistently associated with hippocampal seizures, it may represent an early stage of the disease that does not manifest a classical ictal pattern on scalp EEG, however, this would not be evident in our sample of patients with established epilepsy. For these reasons, a large prospective and longitudinal study including patients with RTTBD, but without a diagnosis of epilepsy, is necessary to determine whether these patients will eventually become epileptic.

Conclusions

In our study, we identified a possible association between scalp RTTBD-like activity and a subset of hippocampal ictal discharges in patients with mesial TLE. Hippocampal ictal discharges correlated with scalp RTTBD, propagated minimally to anterior and basolateral temporal cortex. RMTD is usually subclinical, but may be associated with ictal symptoms and cognitive impairment. These findings suggest that RTTBD is rarely an ictal EEG pattern for mTLE, and the specificity of RTTBD, correlating with intracranial ictal patterns, remains to be determined in future studies. □

Supplementary data.
Summary didactic slides and supplementary figures are available on the www.epilepticdisorders.com website.

Highlights

- Rhythmic temporal theta bursts of drowsiness (RTTBD) are traditionally considered a benign EEG variant.
- Hippocampal seizures exhibited scalp EEG correlates mimicking RTTBD.
- RTTBD might rarely represent an intracranial ictal EEG pattern on standard EEG recordings in some people.

Editorial comment linked to this article on page 473-475.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What are the characteristics of rhythmic temporal theta bursts of drowsiness (RTTBD)?

(2) What symptoms are related to RTTBD?

(3) Is RTTBD only a benign EEG variant?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".