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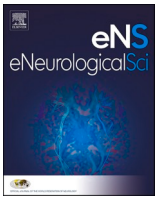

Temporal intermittent rhythmic theta activity (TIRTA): A marker of epileptogenicity?

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ABSTRACT

Objective: To describe a novel EEG rhythm, temporal intermittent rhythmic theta activity (TIRTA), and its potential association with epilepsy.
Methods: We report TIRTA on scalp EEG in a series of 12 patients, all of whom were found to have epilepsy. The clinical and electroencephalographic characteristics of each patient were reviewed. In addition, features that may distinguish TIRTA from benign EEG patterns, including rhythmic temporal theta bursts of drowsiness (RTTBD), were identified.
Results: TIRTA was unilateral in all cases. For all patients, TIRTA was seen in the awake and drowsy states. Eight patients also had TIRTA observed during N2 sleep. The average frequency of TIRTA was 5.5 Hz and the average duration of a train of TIRTA was 5.25 s. In seven cases the morphology was notched in appearance. Temporal intermittent rhythmic delta activity (TIRDA) was seen in seven patients on the same side as TIRTA. Eleven patients also had ipsilateral temporal sharp waves. Abnormal MRI (6/12) and or PET (5/5) findings were ipsilateral to TIRTA.
Conclusions: In this preliminary report we suggest that TIRTA may be a novel marker of potential epileptogenicity, possibly representing a higher frequency variant of TIRDA.

1. Introduction

Temporal intermittent rhythmic delta activity (TIRDA) is an EEG pattern that is associated with temporal lobe epilepsy [1–4]. It was originally reported in 1989 as an intermittent ≥3 seconds, rhythmic, sinusoidal 1 to 4 Hz activity in the anterior-mid-temporal region [4]. TIRDA is associated with ipsilateral interictal epileptiform discharges maximal in the anterior-mid-temporal region [1]. It is typically state-independent and unilateral. While TIRDA has a frequency of 1 to 4 Hz, it would not be surprising that a faster frequency rhythm may have the same significance.

We describe a pattern of temporal intermittent rhythmic theta activity (TIRTA) in twelve patients with epilepsy, reviewing its association with other markers of epilepsy.

2. Methods

Twelve patients with epilepsy at Vanderbilt University Medical Center were identified with TIRTA on scalp EEG during routine clinical work. TIRTA was first noted by the senior author (BAK) as a pattern in some patients with temporal lobe epilepsy. EEG samples were then collected by BAK over approximately thirteen years each time that TIRTA was noted on EEG review. No instances of TIRTA were excluded from the study. Nine of the EEGs were EMU studies; three were only 2-h EEG studies; Seven patients had both 2-h EEG studies and EMU recordings (supplementary material). The medical records of all patients were retrospectively reviewed, and clinical, neurophysiologic, and imaging characteristics were assessed, including age at time of recording; epilepsy risk factors; epilepsy duration; seizure and aura types, frequency, and semiology; presence of TIRDA; sharp waves; laterality and duration of TIRTA as well as the state in which it was recorded. MRI and PET findings were evaluated when available.

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Table 1
Clinical and electrographic characteristics.

Patient #	Age (at time of EEG)	Age of Onset (years)	Epilepsy Risk factors	Seizure types	Baseline Seizure Frequency	Seizure semiology	MRI/PET findings	State at TIRTA appearance	Laterality of TIRTA	TIRTA duration (seconds)	Frequency (Hz)	Co-existing TIRDA, laterality	Interictal Epileptiform Abnormalities	Electrographic Seizure onset
1	20	19	head injury	FAS, FIAS	3–4 FAS or FIAS/week	auditory aura, arm clenching, impaired awareness	MRI: Normal PET: N/A	awake, drowsy	Left	2	5.5	no	none	no seizures recorded
2	70	69	dural venous thrombosis/ hemorrhage	FAS, FIAS	daily FAS or FIAS	right arm paresthesia, aphasia, post-ictal RUE paresis	MRI: Left temporo-occipital encephalomalacia PET: N/A MRI: relatively small left hippocampus & hyperintense FLAIR signal	awake, drowsy and sleep	Left	13	5.5	yes, ipsilateral	Left anterior-mid-temporal	left parieto-occipital
3	19	12	dural venous thrombosis	FAS, FIAS	3–5 FIAS/ week	butterflies in the stomach, impaired awareness, oromanual automatisms	PET: Left mesial temporal hypometabolism	awake, drowsy and sleep	Left	2	5.0	yes, ipsilateral	Left anterior-mid-temporal	left temporal
4	18	10	none	FAS, FIAS, FBTC	1–2 FIAS/ week, 1 FBTC/ lifetime	lightheadedness, ringing in ears, goosebumps, sweating, impaired awareness, rare BTC activity	MRI: Normal PET: anterior bilateral hypometabolism	awake, drowsy and sleep	Left	3	5.5	yes, ipsilateral	Independent anterior bitemporal	no seizures captured
5	24	18	viral encephalitis	FAS, FIAS, FBTC	1–4 FIAS/ month, 5 FBTC lifetime	olfactory-gustatory aura, aphasia, impaired awareness	MRI: left hippocampal atrophy PET: N/A	awake, drowsy and sleep	Left	5	5.5	no	Left anterior mid-temporal	no seizures captured
6	52	51	none	FAS, FIAS, FTBC	multiple FIAS per day	epigastric rising sensation, déjà vu, behavior arrest, impaired awareness, rare BTC	MRI: normal PET: N/A	awake, drowsy	Left	7	5.0	yes. Bilateral	Independent anterior bitemporal	independent bitemporal
7	27	26	none	FIAS, FTBC	5–10 FIAS/ month, 5 lifetime FBTC	staring, freezing, oromanual automatisms, RUE RINCH	MRI: normal PET: Left mesial temporal hypometabolism	awake, drowsy and sleep	Left	5	7.0	no	Left anterior mid-temporal	independent bitemporal
8	22	6	none	FAS, FIAS, FTBC	3 FIAS /week, 1 FBTC/ month	Chest discomfort, anxiety, blinking, ictal cough, LUE dystonic posturing	MRI: normal PET: N/A MRI: left partial temporal lobectomy	awake, drowsy and sleep	Right	8	4.5	yes, ipsilateral	Independent anterior bitemporal	right temporal
9	58	26	viral encephalitis	FAS, FIAS, FBTC	2 FIAS/ month, 4 FTBTC/ week	staring, oral automatisms	PET (prior to surgery): left temporal-parietal hypometabolism	awake, drowsy and sleep	Left	5	7.0	no	Left anterior mid-temporal	no seizures recorded
10	27	1	family history of epilepsy	FAS, FIAS, FBTC	1 FIAS/ month, rare FBTC	scary feeling at the pit of the stomach, light-headednes, rare evolution to BTC activity	MRI: normal PET: N/A	awake, drowsy and sleep	Right	3	5.5	yes, ipsilateral	Right anterior mid-temporal	right anterior mid-temporal
11	30	1				discomfort in the stomach, impaired	MRI: colpocephaly and right temporal	awake, drowsy	Right	7	6.0	no	Right posterior temporal	no seizures recorded

(*continued on next page*)

Table 1 (*continued*)

Patient #	Age (at time of EEG)	Age of Onset (years)	Epilepsy Risk factors	Seizure types	Baseline Seizure Frequency	Seizure semiology	MRI/PET findings	State at TIRTA appearance	Laterality of TIRTA	TIRTA duration (seconds)	Frequency (Hz)	Co-existing TIRDA, laterality	Interictal Epileptiform Abnormalities	Electrographic Seizure onset
						awareness, oral automatisms	lobectomy with residual superior temporal gyrus PET (prior to surgery): right temporal hypometabolism							
			developmental delay, colpocephaly	FAS, FIAS, FBTC	seizure free for 20 years									
						nausea, excessive spitting, word finding problem, aphasia, rush of warmth, impaired awareness	MRI: mild gliosis and volume loss within the left mesial temporal lobe PET: N/A	awake, drowsy	Left	5	4.5	yes, ipsilateral	Left anterior temporal	no seizures recorded
					4–5 FAS/ month, 4–5 FBTC/ month									
12	46	36	CNS vasculitis with biopsy	FAS, FBTC						5.4	5.5			
Mean	***34.4***	***19.7***	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*			*N/A*	*N/A*	*N/A*

Key: BTC = bilateral tonic clonic, FAS = focal aware seizures, FIAS = focal impaired aware seizures, FBTC = focal to bilateral tonic clonic seizure, LUE = Left upper extremity, RUE = Right upper extremity RINCH = rhythmic ictal non-clonic hand movements.

Scalp EEG-video monitoring was reviewed by two board-certified neurologists (BAK and NS). The international 10–20 system was used for all patients, as were T1/T2 electrodes ("true anterior temporal" electrodes). In addition, in certain instances, sphenoidal (infero-mesial temporal) or zygomatic (infero-lateral temporal) electrodes were used, as were additional inferior temporal chain electrodes of the 10–10 system (i.e. F9/F10, T9/T10, P9/P10).

The study was approved by the Vanderbilt University Institutional Review Board.

3. Results

3.1. Patient clinical features

Patient clinical features are summarized in Table 1. The diagnosis of epilepsy was supported by clinical history in all patients, by interictal sharp waves in 11 patients and by ictal recordings in seven patients. The investigations suggested temporal lobe epilepsy in all patients, although there was some incongruence in one patient. The average age of patients at the time the EEG was obtained was 34.4 years (IQR = 20.5–50.5 years), with an average age of onset of epilepsy of 19.7 years (IQR = 7–24.3 years). The average duration of epilepsy was 14.8 years (IQR = 1–26.8 years). Risk factors for epilepsy included head injury; venous sinus thrombus with associated hemorrhage; viral encephalitis; family history of epilepsy; developmental delay; no definite risk factors were identified in four cases.

3.2. Neurophysiologic features

TIRTA was consistently unilateral and localized to the anterior-mid-temporal region. TIRTA was lateralized to the left in nine cases, and to the right in three cases. The average TIRTA frequency was 5.5 Hz (Fig. 1). The average duration was 5.25 s. Seven patients also had TIRDA ipsilateral to TIRTA. Eleven patients had focal temporal sharp waves ipsilateral to TIRTA. All patients had TIRTA in the awake and drowsy states. Eight also had TIRTA in N2 sleep. Supplemental material contains additional clinical and neurophysiologic details as well as EEG samples from each patient.

3.3. Imaging findings

The source images were available for all but three patients, whose imaging reports were available for review. MRI was abnormal in 6/12 patients. In all cases with abnormal MRI findings, the imaging abnormality was ipsilateral to TIRTA and included the ipsilateral temporal lobe. PET was abnormal in all five with PET scans. PET hypometabolism was in the ipsilateral temporal lobe in all cases; in one case it was bilateral. The imaging findings are summarized in the Table.

4. Discussion

In this preliminary report we raise the possibility that TIRTA may be a marker of potential epileptogenicity given its association with clinical seizures, and its co-localization with other established markers of epilepsy such as sharp waves and TIRDA. TIRTA, like TIRDA, may be seen during wakefulness, drowsiness and sleep. In our study, TIRTA was seen exclusively unilaterally. Half of patients with TIRTA had an abnormal MRI finding involving the same temporal lobe. A similar association between the location of abnormal MRI findings and TIRDA has been observed [1]. TIRDA is often associated with ipsilateral anterior temporal sharp waves and we found that this may also be the case with TIRTA in our selected sample. TIRDA has been repeatedly demonstrated through multiple lines of evidence to serve as an indicator of potential epileptogenicity in the temporal lobe [1–4]. The source of TIRDA remains incompletely understood and it is not clear if it is produced by mesial or neocortical temporal structures. There is some evidence that

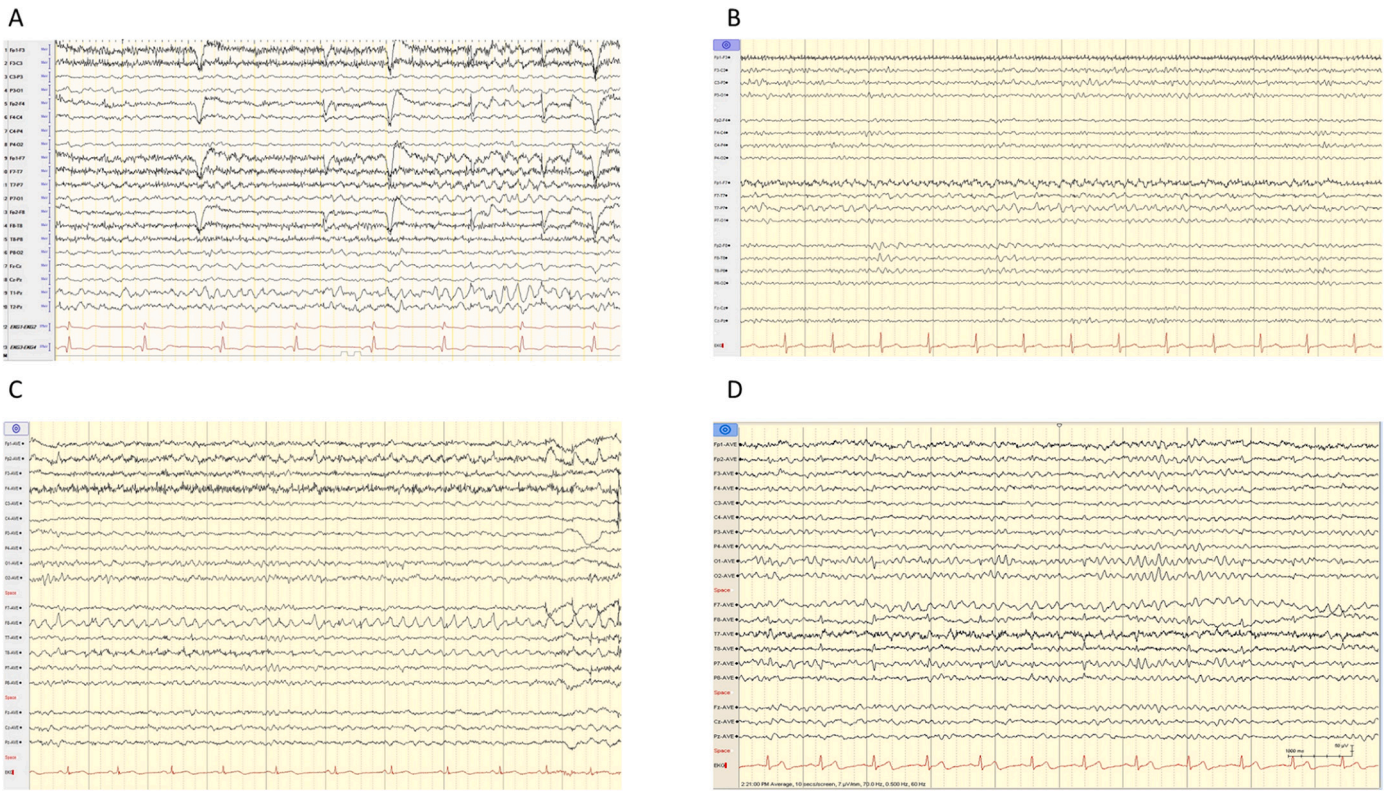

Fig. 1. Examples of TIRTA.
A: EEG sample of TIRTA from patient 1–5-6 Hz activity in left anterior-midtemporal region (longitudinal bipolar reference, 7 uV/mm, 60 mm/s, HFF 70 Hz, LFF 1 Hz).
B: EEG sample of TIRTA from patient 2–5.5-7 Hz activity in the left anterior-midtemporal region (longitudinal bipolar reference, 7 uV/mm, 60 mm/s, HFF 70 Hz, LFF 1 Hz).
C: EEG sample of TIRTA from patient 3–4.5-5 Hz activity in the right anterior-midtemporal region (average reference, 5 uV/mm, 60 mm/s, HFF 70 Hz, LFF 1 Hz).
D: EEG sample of TIRTA from patient 10–5.5–6 Hz activity in the left anterior-midtemporal region (average reference, 60 mm/s, HFF 70 Hz, LFF 0.5 Hz, 60 Hz notch filter).

TIRDA occurs in patients with mesial temporal lobe epilepsy but is produced by associated dysfunction in the neocortical regions [5]. Others have suggested that TIRDA is produced by repetitive spiking in deep mesial temporal structures [2]. TIRTA may represent a higher frequency variant of TIRDA.

Theta activity is a predominant rhythm in the hippocampus that has been associated with multiple cognitive processes such as those related to memory [6]. Seizures with onset in the hippocampus have been shown to be associated with theta ictal rhythm compared to seizures with onset in the neocortical temporal lobe [7]. A recent simultaneous scalp and intracranial EEG study provided evidence that rhythmic temporal theta bursts seen with surface electrodes were time-locked to hippocampal seizures [8]. The underlying physiology of TIRTA will need to be confirmed in future research.

Another temporal theta rhythm that needs to be distinguished from TIRTA is rhythmic temporal theta bursts of drowsiness (RTTBD), also previously referred to as rhythmic mid-temporal discharge (RMTD) [9]. It was originally named psychomotor variant and described by Gibbs and Gibbs in 1941 as “bursts of flat-topped, but notched 5-6 per second waves, maximal in the mid-temporal area and less evident in the anterior temporal area… It appears usually during drowsiness and light sleep, only rarely awake and never during deep sleep” [10,11]. It was initially associated with temporal lobe epilepsy, however subsequent studies demonstrated that it was a normal variant [12]. We found several unique characteristics of TIRTA which may distinguish it from RTTBD. Unlike RTTBD, TIRTA was exclusively unilateral. Also, unlike RTTBD which is typically seen during drowsiness, TIRTA was seen during wakefulness in all patients and during sleep in two-thirds.

TIRTA is also distinguished from subclinical rhythmic EEG discharges in adults (SREDA), a rare benign variant characterized by bilateral evolving rhythmic delta-theta activity that is usually maximal over the parietal and posterior temporal regions [13]. TIRTA was seen exclusively unilaterally, had a different distribution compared to SREDA, and also has no evolution.

5. Conclusion

We described a distinct rhythm, TIRTA, that may be a marker of potential epileptogenicity. Notable features include unilaterality, presence during wakefulness, co-occurrence with sharp waves, as well as TIRDA in some patients. This report is preliminary and the study has limitations including the absence of a large control group of normal subjects. Larger controlled studies will be needed to assess the prevalence of TIRTA and its localizing significance, and test our preliminary findings.

CRediT authorship contribution statement

Jonah Fox: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Niyatee Samudra:** Conceptualization, Investigation, Writing – original draft. **Michael Johnson:** Investigation, Visualization. **Mohammad Junaid Humayun:** Investigation. **Bassel W. Abou-Khalil:** Conceptualization, Investigation, Writing – review & editing, Supervision, Data curation.

Declaration of Competing Interest

None.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ensci.2022.100433.

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