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Comment on: RTTBD-like activity in association with hippocampal ictal discharges in patients with temporal lobe epilepsy by Sun *et al*.

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Rhythmic mid-temporal theta bursts in drowsiness (RTTBD) is an EEG phenomenon considered a *benign variant of uncertain significance* (Klass and Westmoreland, 1985; Tatum *et al*., 2006). Pathogenicity of RTTBD has been long debated since the initial description (Gibbs and Gibbs, 1952). Originally termed "psychomotor variant" (Gibbs *et al*., 1963) to reflect similarity with the seizure-like pattern seen on EEG in people with "psychomotor seizures", RTTBD was often linked with other paroxysmal patterns on EEG such as epilepsy neurovegetative and psychiatric symptoms, headache, and non-specific symptoms to garnish diagnostic support (Lipman and Hughes, 1969; Hughes and Cayaffa, 1973). However, early reports of RTTBD and other benign variants had little or no use of an appropriate comparison of populations or knowledge of the clinical context.

Later, EEG variants were considered as normal because they were rare with similar prevalence to that of control populations without epilepsy (Lombroso *et al*., 1966; White *et al*., 1977; Klass and Westmoreland, 1985; Santoshkumar *et al*., 2009). Benign variants appear as epileptiform and rhythmic patterns (Tatum *et al*., 2006). E-consults revolving around diagnostic tests such as EEG are one of the top five reasons prompting reevaluation (Tatum and Shellhaas, 2020). A large review of 35,249 routine EEGs performed over 35 years (Santoshkumar *et al*., 2009) using standardized definitions to delineate epileptiform patterns (Chatrian *et al*., 1974) found benign variants in 3.4% of the recordings and RTTBD in 0.12%. A prospective study examining EEGs in healthy teens reported another variant in 58% of records (Lombroso *et al*., 1966). Benign epileptiform transients of sleep were seen in 20% of consecutive EEGs performed for a variety of symptoms compared with 24% in healthy teenagers (White *et al*., 1977).

In this issue of Epileptic Disorders, Sun *et al*. revitalize the controversy around RTTBD as an ictal rhythm in patients with temporal lobe epilepsy (TLE).

And so, the debate continues...

A single-center, retrospective review of 28 patients with drug-resistant TLE undergoing presurgical evaluation used simultaneous scalp and intracranial video-EEG and identified 31 RTTBD-like activities on scalp ictal EEG in 6/28 (21%) patients. Rhythmic 4-7-Hz temporal theta recorded on scalp EEG over 3-28 seconds was time-locked to hippocampal seizures recorded by depth electrocorticography. The authors concluded that RTTBD on standard EEG is a rare surrogate for a temporal epileptic seizure. Cognitive impairment was present in only 4/28 (13%), suggesting a principal association with focal aware seizures approximating the spatially limited temporal distribution on scalp EEG. In a similar report by the same group, benign epileptiform transients of sleep (a.k.a. small sharp spikes) were reported as abnormal interictal epileptiform discharges and a biomarker for mesio-temporal lobe epilepsy using scalp-intracranial EEG recording in drug-resistant epilepsy patients (Issa *et al*., 2018).

The results reported by Sun *et al*., should not surprise us given the cohort of patients evaluated. In practice, temporal patterns are commonplace for benign (normal) EEG variants and abnormal electrographic patterns (Benbadis and Lin, 2008). It is therefore incumbent upon every EEG interpreter to assess EEG in the proper clinical context of recording for accurate clinical correlation. For example, theta frequencies are normal in the context of drowsiness, in children and the elderly, and abnormal in patients with a focal structural lesion or diffuse encephalopathy. In practice, most rhythmic mid-temporal theta would be expected to occur as interictal "focal slowing" associated with temporal delta/temporal intermittent rhythmic delta activity and spikes/sharp waves during standard EEG and evolving rhythmic theta or alpha over a hemispheric or bihemispheric spatial field of distribution with post-ictal slowing on ictal EEG recorded in garden-variety mesial TLE (Tatum, 2012).

After reading the report by Sun *et al*., it is important to recall that epileptiform transients occur in people without epilepsy (Koepp *et al*., 2016). Beun *et al*. found that only 4/60 (6.7%) sleep recordings did not show paroxysmal EEG phenomena and 8/60

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(13%) had "true" epileptiform discharges (benign EEG variants) recorded during the initial non-REM sleep (Beun *et al*., 1998), which underscores the need for conservative interpretation (Benbadis and Tatum, 2003; Krauss *et al*., 2005). Early "rules" to identify features of abnormal epileptiform discharges acknowledged physiologic variants as epileptic mimics (Maulsby, 1971). Future applications of machine learning using novel automated source space methods will help identify abnormal epileptiform activity with high specificity and sensitivity, to minimize spurious interpretations of putative abnormality (Kural *et al*., 2020) because "it just looks that way".

The importance of EEG rests upon its accurate diagnostic interpretation to impart proper treatment (Tatum, 2013). Correctly identifying RTTBD as a benign EEG variant can avert misdiagnosis and unnecessary investigations (Benbadis and Tatum, 2003; Santoshkumar *et al*., 2009; Tatum, 2013). Adequate neuroimaging is necessary to exclude a structural lesion before defining RTTBD as a variant of "uncertain significance" (Hennessy *et al*., 2001). The challenge separating normal from abnormal is understandable given the lack of specificity for EEG waveforms using visual inspection (Maulsby, 1971; Tatum, 2013). Criteria to establish waveforms as epileptiform are in part specific (*i.e*., spikes are 20-70 msec.) but relatively insensitive to separate normal from abnormal (IFECN, 1966; Maulsby, 1971; Lesser *et al*., 1985). As a result, significant inter-observer variability for EEG interpretation exists (van Donselaar *et al*., 1992). Further, RMTTBD may coexist with abnormal EEG features in TLE (Lin *et al*., 2003). Using simultaneous MEG and EEG recordings from three patients, RTTBD localized to the posterior inferior temporal cortex and remained following temporal lobectomy (Lin *et al*., 2003).

There are limitations to the study by Sun *et al*. As the authors point out, the retrospective design without a control group exhibits substantial selection bias toward finding an association in patients with TLE. The lack of a comparative cohort further prevents identifying dissimilarity of RTTBD in normal and abnormal states of health. Might there not be some features that distinguish them? The association of RTTBD with TLE should not bias us towards equating RTTBD or other benign variants with abnormality. Rather, the association should encourage us to personalize EEG interpretation of waveforms that are "suspicious" (Tatum, 2013) by associating them with the patient's clinical condition.

The findings by Sun *et al*. add to the literature on benign EEG variants by contributing to our knowledge of intracerebral generators for scalp-derived waveforms. The authors should be commended for expanding our current knowledge on benign rhythmic EEG variants beyond benign epileptiform variants as a more common point of confusion. Ultimate recognition of RTTBD-like ictal activity as an epileptic correlate should rarely require confirmation by video-EEG when the clinical history includes seizures to provide support for the diagnosis of TLE. The need to be conservative when interpreting benign EEG variants remains despite the association reported by Sun *et al*. When in doubt, a normal interpretation should be the result. With the limited "language" of EEG to segregate normalcy from abnormality using current methods of standard EEG recording, we can expect the debate to continue. As Sun *et al*. have taught us, in the case of RTTBD, a rose is a rose but not always rosy. □

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