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Altered cortical excitability in tuberous sclerosis and the effect of mTOR inhibitors: An intracranial electrical stimulation study

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ABSTRACT

Objective: We used electrical stimulation mapping (ESM) of functional responses, after-discharges (ADs), and unwanted electrical stimulation-induced seizures (EIS) to explore differences in cortical excitability in tuberous sclerosis complex (TSC) patients on mTOR inhibitors, TSC patients not on mTOR inhibitors, and drug-resistant epilepsy (DRE) of unknown etiology.

Methods: In 20 patients with TSC and 10 patients with DRE of unknown etiology, incidence and current thresholds of physiologic (language and motor) and pathologic (ADs, EIS) responses were analyzed using mixed effects models against disease phenotype (TSC vs unknown) and use of mTOR inhibitors.

Results: Patients with TSC showed a higher incidence and required a lower threshold current to elicit motor responses and ADs compared to those with DRE of unknown etiology. In TSC patients, mTOR inhibitors increased the threshold for motor responses and ADs, and decreased the incidence of face motor responses, language responses, and ADs.

Conclusions: TSC patients exhibit higher physiologic and pathologic cortical excitability evidenced by a higher incidence and lower current thresholds of ESM responses, which appears to be mitigated by mTOR inhibitors.

Significance: To our knowledge, this is the first study providing direct intracranial evidence for altered cortical excitability in TSC and the corrective effect of mTOR inhibitors.

1. Introduction

Tuberous sclerosis complex (TSC) is a genetic multisystem disorder associated with a high incidence of epilepsy and neurodevelopmental comorbidities. The incidence of epilepsy in TSC is 70–90 %, and up to 70 % of TSC patients may have drug-resistant epilepsy (DRE) (Specchio et al., 2023). Epilepsy in TSC stems from the development of hyperexcitable cortical tubers (Feliciano, 2020; Jozwiak et al., 2020). Studies examining TSC1 knockout mice models have showed that depletion of TSC1 protein, hamartin, in cortical pyramidal neurons leads to enhanced glutamatergic synaptic transmission, reduction in GABA receptor expression, and increased seizure activity (Wu et al., 2022; Zhao and Yoshii, 2019). Similar cellular alterations in synaptic excitation have also been noted in human tissue (Wang et al., 2007). TSC is often regarded as an ideal model to study epileptogenesis at the cellular level due to knowledge of the underlying gene changes and the downstream molecular pathways. Inactivating mutations in TSC1 and TSC2 cause sustained activation of the mechanistic target of rapamycin (mTOR) pathway, leading to a spectrum of neuroanatomical changes including cortical malformations and epileptogenesis (Aronica et al., 2023; Feliciano, 2020; Jozwiak et al., 2020; Schubert-Bast and Strzelczyk, 2021). These epileptogenic changes have been noted to occur in early infancy and even begin in-utero (Aronica et al., 2023; Lasarge and Danzer, 2014; Tsai et al., 2014). Thus, the mTOR pathway has been studied as a therapeutic target for epileptogenesis (Franz and Capal, 2017; Galanopoulou et al., 2012; Krueger et al., 2013; Moloney et al.,

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2021; Schubert-Bast and Strzelczyk, 2021). There is evidence from mouse models and human pyramidal cortical tissue that suggests use of mTOR inhibitors can alter cell membrane excitability (Lasarge and Danzer, 2014; Wu et al., 2022; Zhao and Yoshii, 2019).

However, to date, there have been no *in vivo* human studies, to our knowledge, investigating altered cortical excitability in TSC and the effect of mTOR inhibitors on those alterations. We used intracranial electrical stimulation mapping (ESM) of functional responses, after-discharges (ADs), and unwanted electrical stimulation-induced seizures (EIS) to measure alterations in cortical excitability in TSC patients compared to those with DRE of unknown etiology, and the impact of mTOR inhibitors in TSC. We hypothesized that ESM current thresholds would be lower and the incidence of ESM-induced responses, both physiologic (motor and language responses) and pathologic (ADs, EIS), would be higher, in patients with TSC suggesting cortical hyperexcitability. We further investigated if mTOR inhibitor therapy would modify this altered cortical excitability.

2. Methods

2.1. Patient sample

Using the epilepsy surgery database at the Cincinnati Children's Hospital, patients who underwent subdural electrode (SDE) or stereotactic EEG (SEEG) monitoring between January 2007 and December 2020 and completed ESM were identified. Of these, patients who had TSC and unknown etiology DRE were selected for the study. Patients with unknown etiology were defined as those with no epileptogenic lesion on brain MRI (Bernasconi et al., 2019), no identified genetic etiology for their epilepsy, *and* no specific etiology (e.g., cortical dysplasia) determined on postsurgical histology.

The study was approved by the Institutional Review Board.

2.2. Intracranial EEG recordings

Intracranial electrode placement was customized for each patient by reviewing the noninvasive presurgical data in a multidisciplinary conference. Due to evolving institutional practices, we used SDE before 2016 and SEEG after 2016 as the preferred intracranial modality. Intracranial recordings with both SDE and SEEG used a standardized approach described in our previous study (Aungaroon et al., 2023).

2.3. Electrical stimulation mapping

The decision to perform ESM was taken by the clinical team independent of this study. Selection of electrode contacts for stimulation was individualized for each patient based on the presumptive seizure-onset zone and its proximity to putative motor and language areas. For TSC patients all stimulations analyzed in this study were outside the MRI-identified tubers. We used bipolar stimulation with both SEEG and SDE using 50 Hz, 250–350 μs, biphasic, square wave pulses. The stimulation began with 1–2 mA and followed a stepwise increment of 0.5–2 mA unless a functional response, evolving ADs, or EIS were encountered. Note that all stimulations included in this study were for functional mapping and not for seizure induction. Therefore, all EIS documented herein were "unwanted". The train duration was 2–3 s for motor ESM and 5 s for language ESM. The maximum current strength differed between the two electrode types being 15 mA for SDE ESM and 8 mA for SEEG ESM. Additional details of our ESM protocol have been published previously (Arya et al., 2020, 2019; Aungaroon et al., 2023, 2017; Zea Vera et al., 2017). In this manuscript, we have regarded elicitation of functional responses, ADs, or EIS at a lower current strength to indicate higher excitability of the stimulated region (Corley et al., 2017; Lesser et al., 1984; Momi et al., 2024).

2.4. Data extraction

The following data were extracted for each patient: DRE etiology (TSC or unknown), age, duration of epilepsy, whether the language dominant side was stimulated, if mTOR inhibitor was used for $\geq$ 1 month, and electrode type (SDE or SEEG). To further quantify the effect of mTOR inhibitors, an "exposure" variable was calculated by multiplying the average serum level of mTOR inhibitor (ng/mL) by the duration of treatment (days). Because it is our standard practice to stop mTOR inhibitors two weeks prior to surgery, patients were not on mTOR inhibitors during the ESM, and the data is based on presurgical mTOR inhibitor use. Hemispheric language dominance was based on functional MRI, if not available, only left-handed patients with left *peri*-sylvian epileptogenic tubers were regarded as having atypical language dominance (Nakai et al., 2017).

2.5. Outcomes

We analyzed the incidence and current thresholds for functional responses (motor and language), ADs, and EIS. Motor responses consisted of involuntary movement of upper extremity (UE), lower extremity (LE), or facial muscles, that were visually ascertained by the bedside team. Language responses were assessed using an overt picture naming task (Snodgrass and Vanderwart, 1980). Paraphasic errors, aphasia, anomia, dysarthria, and speech interruptions were scored as speech/language responses per standard clinical practice (Hamberger, 2007). All functional responses were verified for reproducibility.

ADs were defined as epileptiform discharges that occurred immediately after electrical stimulation and were clearly distinct from pre-stimulation electrographic activity (Aungaroon et al., 2017; Blume et al., 2004). EIS was defined as a train of ADs that evolved in distribution, morphology, or frequency and was associated with clinical changes. Current thresholds were defined as minimum stimulation currents (mA) that resulted in functional responses, ADs, or EIS.

2.6. Statistical analysis

Because the maximum currents were different between SEEG and SDE, we scaled the currents by subtracting the mean and dividing by standard deviation, separately for each electrode type, converting them into z-scores, to ensure comparability. TSC and unknown etiology groups were then compared using t-tests for independent samples (for continuous variables) and Fisher exact tests (for categorical variables).

The incidence and current thresholds for functional responses, ADs, and EIS were analyzed using generalized linear and linear mixed effects models respectively, with etiology of epilepsy (TSC/unknown), scaled current strength, age, duration of epilepsy, and whether the language dominant hemisphere was stimulated, as fixed effects and "patient" as the random effect. In addition, the TSC and unknown etiology groups were also analyzed separately using similar mixed effects models, where use of mTOR inhibitors for $\geq$ 1 month (binary) and mTOR exposure (continuous) were included as fixed effects in the TSC group. All analyses were performed with R version 4.3 using "lme4" and "lmerTest" libraries for mixed effects modeling (Bates et al., 2015).

3. Results

We analyzed 20 patients with TSC and 10 patients with DRE of unknown etiology. The cohorts were comparable in terms of age, gender, language dominant hemisphere, stimulated side, use of premedication, and electrode type (Table S1). Although the duration of epilepsy was longer (7.77 years) in TSC patients than the unknown etiology group (4.08 years), the standardized mean difference (SMD) was not statistically significant (SMD–1.79; 95 % CI–7.92, −0.53; $p = 0.084$). An mTOR inhibitor was used in 11/20 patients with TSC. Of these, 7 had been on everolimus, 2 on sirolimus, and 2 had been on both at different times.

Locations of ESM-induced functional responses on a standard brain space are illustrated for all patients in Fig. S1 with incidence and raw current strengths provided in Table S2.

3.1. Incidence and thresholds of functional responses

3.1.1. Motor

Mixed models showed a significantly higher incidence of motor responses in the TSC patients compared to unknown etiology DRE (OR 4.46; 95 % CI 1.89 to 11.17; $p < 0.001$; Table 1). TSC patients also had a lower current threshold to elicit motor responses compared to the unknown etiology group (slope = −1.15; 95 % CI–1.31 to −0.99; p = 0.037, Table 2).

While the incidence of face motor responses was higher in the TSC group (OR 3.74; 95 % CI 1.31 to 11.80; p = 0.017), the face motor current threshold was not significantly different between TSC and the unknown etiology groups. In contrast, there was no significant difference between the two groups in the incidence of UE motor responses, however, lower currents were needed to elicit UE motor responses in the TSC patients (slope = −1.02; 95 % CI–2.70 to −0.65; $p < 0.001$).

Older age was associated with a higher incidence of motor responses (OR 1.21; 95 % CI 1.06 to 1.35; p = 0.006), and a lower motor threshold (slope = −1.00; 95 % CI–1.04 to −0.96; p = 0.013). Similarly, longer duration of epilepsy was associated with a higher incidence of motor responses (OR 1.23; 95 % CI 1.03 to 1.52; p = 0.036) and a lower motor threshold (slope = −0.16; 95 % CI–0.24 to −0.08; $p < 0.001$). Increasing current strengths led to a higher incidence of face motor responses (OR 1.50; 95 % CI 1.02 to 2.23; p = 0.039), but decreased the incidence of UE motor responses (OR 0.65; 95 % CI 0.47 to 0.89; p = 0.009). Neither the electrode type (SEEG or SDE) nor the stimulated hemisphere (language dominant or not) showed a significant effect on motor thresholds.

3.1.2. Language

There was no significant difference between the TSC and unknown etiology groups in either the incidence or the current thresholds for language responses (Tables 1, 2).

Again, higher current strength was associated with a greater incidence of language responses (OR 2.03; 95 % CI 1.38 to 3.04; $p < 0.001$). Similar to motor responses, the incidence of language responses (OR 1.13; 95 % CI 1.00 to 1.27; p = 0.040) increased, while the current thresholds decreased (slope–0.14; 95 % CI–0.25 to −0.04; $p < 0.001$) with increasing age. ESM of the language dominant hemisphere was associated with a higher incidence of language responses (OR 41.02; 95 % CI 7.71 to 765.35; $p < 0.001$) whereas increased duration of epilepsy was associated with lower thresholds for eliciting language interference (slope–0.15, 95 % CI–0.20 to −0.10; $p < 0.001$).

3.2. Incidence and thresholds of ADs and unwanted EIS

TSC was associated with both a higher incidence of ADs compared to unknown etiology DRE (OR 1.75; 95 % CI 1.55 to 2.02; p = 0.006, Table 1) as well as a lower current thresholds to induce ADs (slope = −0.71; 95 % CI–0.99 to −0.43; $p < 0.001$, Table 2). Higher incidence of ADs was also seen with increasing age (OR 1.13; 95 % CI 1.08 to 1.18; $p < 0.001$) and longer duration of epilepsy (OR 1.89; 95 % CI 1.85 to 1.93; $p < 0.001$). Likewise, both older age (slope = −0.08; −0.11 to −0.05; $p < 0.001$) and longer duration of epilepsy (slope = −0.05; 95 % CI–0.08 to −0.02; p = 0.007) were also associated with lower threshold currents to induce ADs. Higher current strength was associated with increased incidence of ADs (OR 1.19; 95 % CI 1.06 to 1.33; p = 0.002) and EIS (OR 1.68; 95 % CI 1.17 to 2.19; p = 0.012). Stimulation of the language dominant side and electrode type did not significantly affect either AD or EIS thresholds.

Table 1
Incidence of responses as a function of etiology, age, scaled current, duration of epilepsy, and stimulated side, analyzed using generalized linear mixed effects models.

Response	Variable	Odds Ratio	95 % Confidence Interval	p–value
Face Motor	TSC vs unknown	3.744	1.306 to 11.799	0.017 *
	Current scaled	1.503	1.024 to 2.232	0.039 *
	Age	0.942	0.746 to 1.133	0.569
	Duration of Epilepsy	1.109	0.919 to 1.413	0.336
	Language Dominant Side Stimulated	1.495	0.607 to 3.848	0.390
Upper Extremity Motor	TSC vs unknown	0.864	0.405 to 1.814	0.702
	Current scaled	0.653	0.470 to 0.892	0.009 *
	Age	0.838	0.558 to 1.118	0.138
	Duration of Epilepsy	1.165	0.997 to 1.424	0.087
	Language Dominant Side Stimulated	0.629	0.325 to 1.203	0.163
All Motor	TSC vs unknown	4.458	1.892 to 11.170	<0.001 *
	Current scaled	0.865	0.617 to 1.215	0.400
	Age	1.205	1.062 to 1.347	0.006 *
	Duration of Epilepsy	1.232	1.030 to 1.519	0.036 *
	Language Dominant Side Stimulated	0.971	0.814 to 1.302	0.199
Language	TSC vs unknown	1.245	0.432 to 3.585	0.682
	Current scaled	2.025	1.381 to 3.039	<0.001 *
	Age	1.127	0.999 to 1.272	0.040 *
	Duration of Epilepsy	0.875	0.675 to 1.075	0.059
	Language Dominant Side Stimulated	41.023	7.714 to 765.345	<0.001 *
After-discharges	TSC vs unknown	1.746	1.551 to 2.015	0.006 *
	Current scaled	1.187	1.064 to 1.325	0.002 *
	Age	1.132	1.083 to 1.183	<0.001 *
	Duration of Epilepsy	1.891	1.853 to 1.931	<0.001 *
	Language Dominant Side Stimulated	0.744	0.244 to 1.244	0.295
ESM-induced seizures	TSC vs unknown	0.290	0.073 to 1.254	0.080
	Current scaled	1.679	1.169 to 2.190	0.012 *
	Age	1.199	0.979 to 1.472	0.071
	Duration of Epilepsy	0.886	0.730 to 1.087	0.217
	Language Dominant Side Stimulated	0.760	0.632 to 1.203	0.111

Notes: 1. Data for lower extremity motor responses cannot be analyzed separately because of paucity of these responses. 2. Current strengths were separately scaled for electrode types by subtracting the mean and dividing by standard deviation for the respective electrode type, converting raw current values to z-scores. 3. *$p \leq 0.05$. 4. Unknown implies drug-resistant epilepsy of unknown etiology as defined in the text.
Abbreviations: TSC tuberous sclerosis complex, ESM electrical stimulation mapping.

3.3. ESM responses in TSC

3.3.1. Effect of mTOR inhibitors

In TSC patients, mTOR inhibitors significantly decreased the incidence of face motor responses (OR 0.09, 95 % CI 0.02 to 0.34, p <

Table 2
Current thresholds, scaled separately for electrode types, as a function of etiology, age, duration of epilepsy, and electrode type analyzed using linear mixed effects models.

Response	Variable	Slope	95 % Confidence Interval	p-value
Face Motor	TSC (vs Unknown)	−0.936	−2.084 to 0.213	0.108
	Age	0.013	−0.131 to 0.156	0.861
	Duration of Epilepsy	−0.049	−0.209 to 0.111	0.538
	SEEG (vs SDE)	−0.258	−0.826 to 0.310	0.365
Upper Extremity Motor	TSC (vs Unknown)	−1.027	−2.699 to −0.645	<0.001 *
	Age	−0.064	−0.210 to 0.083	0.389
	Duration of Epilepsy	−0.001	−0.144 to 0.142	0.986
	SEEG (vs SDE)	0.232	−0.188 to 0.651	0.275
All Motor	TSC (vs Unknown)	−1.148	−1.307 to −0.988	0.037 *
	Age	−0.999	−1.041 to −0.957	0.013 *
	Duration of Epilepsy	−0.159	−0.242 to −0.078	<0.001 *
	SEEG (vs SDE)	0.174	−0.119 to 0.468	0.242
Language	TSC (vs Unknown)	−0.230	−0.769 to 0.308	0.392
	Age	−0.144	−0.251 to −0.038	<0.001 *
	Duration of Epilepsy	−0.149	−0.198 to −0.100	<0.001 *
	SEEG (vs SDE)	0.406	−0.068 to 0.880	0.091
After-discharges	TSC (vs Unknown)	−0.711	−0.989 to −0.433	<0.001 *
	Age	−0.080	−0.112 to −0.048	<0.001 *
	Duration of Epilepsy	−0.050	−0.077 to −0.024	0.007 *
	SEEG (vs SDE)	0.182	−0.031 to 0.396	0.094
ESM-induced seizures	TSC (vs Unknown)	−0.993	−2.271 to 0.286	0.116
	Age	−0.136	−0.274 to 0.003	0.054
	Duration of Epilepsy	−0.003	−0.175 to 0.169	0.972
	SEEG (vs SDE)	−0.402	−1.526 to 0.721	0.450

Notes: 1. Data for lower extremity motor responses cannot be analyzed separately because of paucity of these responses. 2. Current strengths were separately scaled for electrode types by subtracting the mean and dividing by standard deviation for the respective electrode type, converting raw current values to z-scores. 3. *p ≤ 0.05. 4. Unknown implies drug-resistant epilepsy of unknown etiology as defined in the text.
Abbreviations: TSC tuberous sclerosis complex, ESM electrical stimulation mapping, SDE subdural electrodes, SEEG stereo-electroencephalography.

0.001), language responses (OR 0.16, 95 % CI 0.03 to 0.70, p = 0.022), and ADs (OR 0.40, 95 % CI 0.28 to 0.52, p < 0.001, Table 3). The incidence of EIS was also decreased by mTOR inhibitors but fell short of statistical significance (OR 0.72, 95 % CI 0.37 to 1.07, p = 0.058). Current thresholds for motor responses (slope 0.24, 95 % CI 0.19 to 0.28, p = 0.008), particularly face motor (slope 1.54, 95 % CI 1.01 to 2.07, p < 0.001), and ADs (slope 0.11, 95 % CI 0.03 to 0.18, p = 0.006) significantly increased with use of mTOR inhibitors (Table 4, Fig. 1). Moreover, higher exposure to mTOR inhibitors was associated with increased current thresholds to induce motor responses (slope 0.15; 95 % CI 0.08 to 0.22; p = 0.042, Fig. 2) and ADs (slope = 0.71; 95 % CI 0.11 to 1.30; p = 0.009).

3.3.2. *Motor*

Within the cohort of TSC patients, longer duration of epilepsy increased the incidence of face motor responses (OR 6.39; 95 % CI 1.95 to 27.56; p = 0.009, Table 3) and lowered the thresholds to induce face motor (slope = −1.02; 95 % CI–1.33 to −0.70; p < 0.001, Table 4) and all motor responses (slope = −0.14; 95 % CI–0.24 to −0.04; p < 0.001). Increasing age was associated with a reduced threshold to induce all motor responses (slope = −0.16; 95 % CI–0.2 to −0.12; p < 0.001) and UE motor responses (slope = −0.20; 95 % CI–0.34 to −0.06; p = 0.007). Increased incidence of UE motor responses were seen with decreasing current strengths (OR 0.57; 95 % CI 0.34 to 0.91; p = 0.022). SEEG ESM, compared to SDE ESM, was associated with lower facial motor thresholds (slope = −1.26; 95 % CI–1.74 to −0.79; p < 0.001).

3.3.3. *Language*

Older age was associated with an increased incidence (OR 1.74; 95 % CI 1.28 to 2.42; p < 0.001; Table 3) and a lower current threshold (slope = −0.20; 95 % CI–0.34 to −0.06; p = 0.001) to induce language responses (Table 4). Longer duration of epilepsy was associated with a reduced threshold to elicit language responses (slope = −0.18; 95 % CI–0.29 to −0.08; p = 0.002).

3.3.4. *ADs and EIS*

Older age was associated with an increased incidence of ADs (OR 1.28; 95 % CI 1.14 to 1.43; p < 0.001; Table 3) and a decreased current threshold to induce ADs (slope = −0.14; 95 % CI–0.21 to −0.06; p = 0.006; Table 4).

3.4. *ESM responses in DRE of unknown etiology*

3.4.1. *Motor*

Higher current strength was associated with an increase in face motor responses (OR 2.55; 95 % CI 1.15 to 7.08; p = 0.036; Table 3). Increasing age (slope = −0.03; 95 % CI–0.06 to −0.01; p = 0.014) and duration of epilepsy (slope = −0.05; 95 % CI–0.09 to −0.01; p = 0.026) were associated with a decreased threshold to induce all motor responses (Fig. 1), the decrease being most prominent for UE responses with respect to both age (slope = −0.36; 95 % CI–0.52 to −0.20; p = 0.001) and longer duration of epilepsy (slope = −1.43; 95 % CI–2.19 to −0.68; p < 0.001; Table 4). SEEG ESM was associated with a lower motor threshold compared to SDE ESM (slope = −0.48; 95 % CI–0.75 to −0.21; p < 0.001).

3.4.2. *Language*

Higher current strengths (OR 6.60; 95 % CI 3.10 to 17.97; p < 0.001) and stimulation of the language dominant hemisphere (OR 195.08; 95 % CI 12.56 to 16161.50; p = 0.002) were associated with increased incidence of language responses (Table 3). Also, increasing age was associated with a decrease in threshold to induce language responses (slope = −0.04; 95 % CI–0.06 to −0.03; p = 0.034; Table 4).

3.4.3. *ADs **and** EIS*

Higher current strengths (OR 1.95; 95 % CI 1.58 to 2.44; p < 0.001) and older age (OR 1.16; 95 % CI 1.10 to 1.22; p < 0.001) were associated with increased occurrence of ADs (Table 3). Increasing age was also associated with lower threshold currents to induce both ADs (slope = −0.08; 95 % CI–0.13 to −0.02; p = 0.006) and EIS (slope = −0.18; 95 % CI–0.26 to −0.10; p = 0.001; Table 4). Also, longer duration of epilepsy was associated with a lower EIS threshold (slope = −0.16; 95 % CI–0.29 to −0.04; p = 0.019).

4. Discussion

We have generated *in vivo* evidence for cortical hyperexcitability in TSC compared to unknown etiology DRE, which further increases in a duration-dependent manner and is partly mitigated by mTOR inhibitors (Fig. 1). Ours is probably the first study to demonstrate this cortical hyperexcitability in TSC both for functional (motor, language) and aberrant (ADs, EIS) responses elicited by intracranial ESM.

4.1. *Increased cortical excitability in TSC*

TSC patients exhibited a higher incidence and a lower current threshold for motor responses when compared to the unknown etiology

Table 3
Incidence of responses, analyzed separately for Tuberous Sclerosis Complex and unknown etiology DRE groups, as a function of age, scaled current, duration of epilepsy, mTOR inhibitor use, and stimulated side using generalized linear mixed effects models.

		Tuberous Sclerosis Complex			Unknown Etiology DRE		
Response	Variable	Odds ratio	95 % Confidence Interval	p-value	Odds ratio	95 % Confidence Interval	p-value
Face Motor	Current scaled	1.206	0.736 to 1.992	0.457	2.554	1.145 to 7.083	0.036 *
	Age	0.898	0.554 to 1.242	0.310	1.172	0.892 to 1.530	0.216
	Duration of Epilepsy	6.394	1.947 to 27.559	0.009 *	0.890	0.512 to 1.450	0.631
	Language Dominant Side Stimulated	0.376	0.056 to 2.196	0.296	0.445	0.051 to 3.787	0.439
	mTOR inhibitor	0.091	0.020 to 0.343	<0.001 *			
Upper Extremity Motor	Current scaled	0.567	0.342 to 0.909	0.022 *	0.468	0.244 to 0.822	0.013
	Age	0.947	0.679 to 1.298	0.740	0.792	0.431 to 1.033	0.240
	Duration of Epilepsy	0.969	0.706 to 1.352	0.848	0.838	0.545 to 1.525	0.458
	Language Dominant Side Stimulated	2.045	0.551 to 8.154	0.294	0.851	0.515 to 1.186	0.107
	mTOR inhibitor	0.784	0.336 to 1.232	0.152			
Language	Current scaled	0.684	0.331 to 1.330	0.278	6.603	3.103 to 17.966	<0.001 *
	Age	1.737	1.277 to 2.418	<0.001 *	0.961	0.782 to 1.141	0.672
	Duration of Epilepsy	0.929	0.445 to 1.412	0.534	1.776	0.980 to 3.430	0.056
	Language Dominant Side Stimulated				195.08	12.557 to 16161.5	0.002 *
	mTOR inhibitor	0.156	0.027 to 0.696	0.022 *			
Afer-discharges	Current scaled	0.951	0.825 to 1.096	0.491	1.954	1.583 to 2.437	<0.001 *
	Age	1.276	1.138 to 1.427	<0.001 *	1.156	1.096 to 1.220	<0.001 *
	Duration of Epilepsy	0.736	0.462 to 1.010	0.166	1.770	0.695 to 2.846	0.057
	Language Dominant Side Stimulated	0.828	0.597 to 1.060	0.205	0.986	0.103 to 1.868	0.095
	mTOR inhibitor	0.397	0.275 to 0.520	<0.001 *			
ESM-induced seizures	Current scaled	2.288	0.918 to 6.650	0.094	1.872	0.845 to 5.278	0.159
	Age	0.922	0.701 to 1.171	0.545	1.255	1.009 to 1.657	0.059
	Language Dominant Side Stimulated	0.639	0.034 to 7.856	0.736	1.000	0.722 to 1.425	0.999
	mTOR inhibitor	0.721	0.374 to 1.068	0.058	0.213	0.016 to 2.220	0.182

Notes: 1. Data for lower extremity motor responses cannot be analyzed separately because of paucity of these responses. 2. Current strengths were separately scaled for electrode types by subtracting the mean and dividing by standard deviation for the respective electrode type, converting raw current values to z-scores. 3. $^{*}p \leq 0.05$. 4. Unknown implies drug-resistant epilepsy of unknown etiology as defined in the text.
Abbreviations: DRE drug-resistant epilepsy, ESM electrical stimulation mapping.

Table 4
Current thresholds, scaled separately for electrode types, analyzed separately for Tuberous Sclerosis Complex and unknown etiology DRE groups, as a function of etiology, age, duration of epilepsy, and electrode type, using linear mixed effects models.

		Tuberous Sclerosis Complex			Unknown Etiology DRE		
	Variable	Slope	95 % Confidence Intervals	p-value	Slope	95 % Confidence Intervals	p-value
Face Motor	Age	0.888	−0.275 to 2.050	0.499	−0.213	−0.779 to 0.353	0.354
	Duration of Epilepsy	−1.015	−1.334 to −0.696	<0.001 *	0.931	−2.398 to 4.259	0.481
	SEEG (vs SDE)	−1.264	−1.738 to −0.789	<0.001 *			
	mTOR inhibitor use	1.540	1.007 to 2.072	<0.001 *			
Upper Extremity Motor	Age	−0.200	−0.342 to −0.058	0.007 *	−0.360	−0.522 to −0.197	0.001 *
	Duration of Epilepsy	0.128	−0.014 to 0.270	0.076	−1.433	−2.186 to −0.681	<0.001 *
	SEEG (vs SDE)	0.219	−0.201 to 0.638	0.299			
	mTOR inhibitor use	−0.321	−0.735 to 0.094	0.127			
All Motor	Age	−0.161	−0.202 to −0.120	<0.001 *	−0.031	−0.055 to −0.006	0.014 *
	Duration of Epilepsy	−0.140	−0.238 to −0.043	<0.001 *	−0.046	−0.086 to −0.005	0.026 *
	SEEG (vs SDE)	−0.027	−0.126 to 0.723	0.594	−0.481	−0.751 to −0.210	<0.001 *
	mTOR inhibitor use	0.235	0.189 to 0.281	0.008 *			
	mTOR inhibitor exposure	0.153	0.084 to 0.222	0.042 *			
Language	Age	−0.197	−0.336 to −0.057	0.001 *	−0.042	−0.056 to −0.028	0.034 *
	Duration of Epilepsy	−0.182	−0.289 to −0.076	0.002 *	1.364	−0.263 to 2.991	0.095
	SEEG (vs SDE)	0.144	−0.574 to 0.863	0.679	−1.595	−5.019 to 1.830	0.340
After-discharges	Age	−0.138	−0.211 to −0.064	<0.001 *	−0.078	−0.133 to −0.023	0.006 *
	Duration of Epilepsy	−0.077	−0.325 to 0.171	0.544	−0.014	−0.032 to 0.004	0.065
	SEEG (vs SDE)	0.173	−0.058 to 0.405	0.142	−0.0004	−0.710 to 0.719	0.999
	mTOR inhibitor use	0.105	0.030 to 0.179	0.006 *			
	mTOR inhibitor exposure	0.706	0.115 to 1.296	0.009 *			
ESM-induced seizures	Age				−0.178	−0.256 to −0.100	0.001 *
	Duration of Epilepsy				−0.161	−0.285 to −0.038	0.019 *
	SEEG (vs SDE)				−0.221	−1.080 to −0.639	0.553

Notes: 1. Data for lower extremity motor responses cannot be analyzed separately because of paucity of these responses. 2. Current strengths were separately scaled for electrode types by subtracting the mean and dividing by standard deviation for the respective electrode type, converting raw current values to z-scores. 3. $^{*}p \leq 0.05$. 4. Unknown implies drug-resistant epilepsy of unknown etiology as defined in the text. 5. mTOR inhibitor use and exposure variables are not applicable to the unknown group.
Abbreviations: DRE drug-resistant epilepsy, ESM electrical stimulation mapping, SDE subdural electrodes, SEEG stereo-electroencephalography.

DRE group (Tables 1, 2). This suggests a heightened excitability of the motor cortex in patients with TSC compared to other patients with DRE. Also, while the incidence of face motor responses was higher in the TSC group, the thresholds were not significantly different from the unknown etiology DRE group. In contrast, the incidence of UE motor responses was not significantly different between the two groups but the

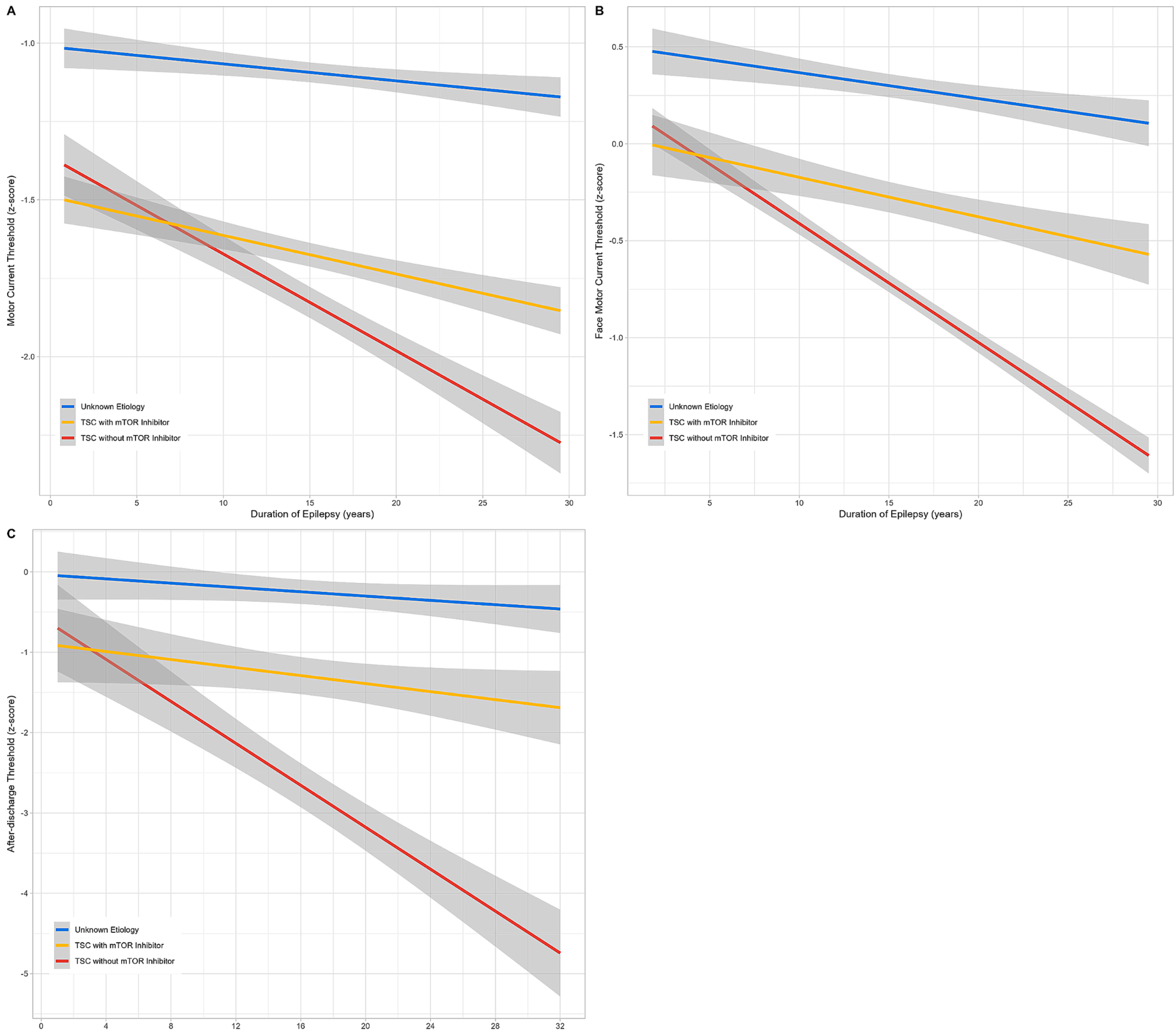

Fig. 1. Current thresholds (z-scores) for all motor responses (A) and face motor responses (B) as function of duration of epilepsy and for inducing after-discharges (C) as function of age in DRE of unknown etiology (blue), TSC patients on mTOR inhibitor (yellow), and TSC patients not on mTOR inhibitor (red). Note a faster rate of fall in threshold currents, suggestive of duration-dependent increase in cortical excitability, in TSC, and the corrective effect of mTOR inhibitors. Note: Although the data were analyzed using mixed effects models, ordinary least square lines, obtained from the coefficients and standard errors of mixed effects models, are shown for clarity. Abbreviations: TSC Tuberous Sclerosis Complex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

thresholds to induce UE motor responses were lower in the TSC group. These findings suggest regional differences in motor cortex excitability, which we and others have identified previously (Aungaroon et al., 2023; Kanno et al., 2018; Muster et al., 2021). In TSC patients, this regional variation in motor cortex excitability may be due to differential distribution of areas of cortical dysplasia, because epileptogenic tubers may have a predilection for the central sulcus and inferior parietal lobe (Cohen et al., 2021; Doherty et al., 2005; Ellingson et al., 2016). However, our study was not designed to test this because we excluded stimulations within tubers. Rather, our study shows that motor thresholds, particularly face motor thresholds, are not only lower in TSC patients than unknown etiology DRE but this difference exacerbates over time with increased duration of epilepsy (Fig. 1).

Although changes similar to motor cortex excitability were also seen in the language responses (increased incidence and reduced thresholds), the difference between TSC and unknown etiology DRE were not statistically significant. One possible explanation for this observation may be because of a higher likelihood of atypical language representation in patients with TSC (Gallagher et al., 2013, 2012). Due to early epileptogenesis, there is a higher propensity for cerebral reorganization of language areas and therefore the areas stimulated during anatomically-directed ESM may not have reflected “true” language sites in some TSC patients (Litwa, 2022). Another contributory factor may be due to the inherent differences between language and motor responses induced by ESM. ESM-induced language interference is an inhibitory phenomenon relying on stimulation currents to create a transient lesion, whereas motor ESM relies on direct excitation. We speculate that in TSC patients, compared to other DRE patients, there may be an intrinsic increase in

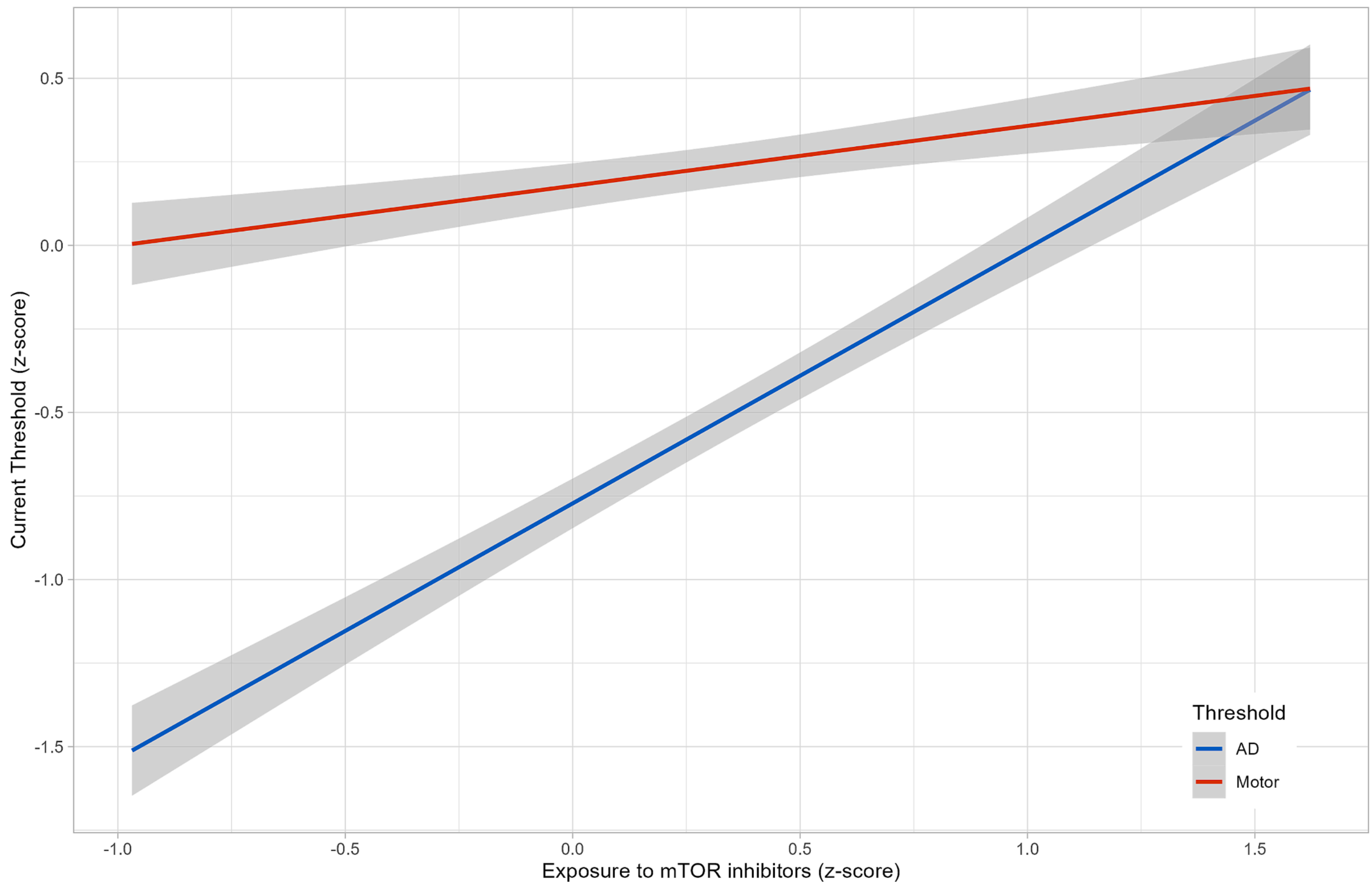

Fig. 2. Current thresholds for inducing motor responses (red) and after-discharges (blue) as function of exposure to mTOR inhibitors. Note the preferential effect of mTOR inhibitors on after-discharge thresholds. Notes: 1. Exposure to mTOR inhibitors was calculated as a product of the average serum level of the mTOR inhibitor and the period over which it was used. 2. Although the data were analyzed using mixed effects models, ordinary least square lines, obtained from the coefficients and standard errors of mixed effects models, are shown for clarity. Abbreviations: AD after-discharge. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cortical excitability. It is also important to recall that ESM language mapping is task-dependent, and a broader protocol, with multiple language tasks may have highlighted additional differences in language cortex excitability, however, such testing is often not feasible in pediatric patients.

Similar to the increased excitability in functional cortical regions, particularly motor cortex, TSC was also associated with a higher incidence and lower current thresholds for inducing ADs during ESM. Again the difference in AD thresholds increased over time between patients with TSC and unknown etiology DRE (Fig. 1), further supporting our hypothesis that TSC globally increases cortical excitability in a duration-dependent manner.

4.2. *Effect of mTOR inhibitors on cortical excitability in TSC*

While TSC appears to be associated with enhanced cortical excitability, use of mTOR inhibitors apparently reduces this excitability. Our findings suggest that mTOR inhibitors "course correct" cortical excitability in TSC in a duration-dependent manner, aligning it with that in unknown etiology DRE (Fig. 1).

mTOR inhibitors significantly decreased the incidence and increased the current thresholds for face motor responses in TSC patients suggestive of decreased motor cortex excitability. This aligns well with *in vitro* studies demonstrating the hyperexcitability of cortical dysplasia in TSC secondary to the mTOR pathway activation (Nguyen et al., 2019; Pineau et al., 2024; Wu et al., 2022; Zhao and Yoshii, 2019). It is noteworthy that while the motor thresholds decreased with longer duration of epilepsy both in patients with TSC and unknown etiology DRE, the slope of motor threshold change with duration of epilepsy was similar in TSC patients on mTOR inhibitors and those with unknown etiology DRE (Fig. 1). This suggests that although changes in cortical excitability that have already occurred in TSC patients may not be reversed, the exacerbation of this change with longer duration of epilepsy can be corrected, to some extent, with mTOR inhibitors.

An analogous effect of mTOR inhibitors was seen on AD thresholds. Fig. 1C shows that AD thresholds are lower for TSC patients than those with unknown etiology DRE at a younger age, and that the rate of decrease is significantly faster in TSC suggesting an age-dependent increase in cortical excitability. However, mTOR inhibitors alter the slope of this change to reflect more similarly the change in excitability with age for patients with unknown etiology DRE. Importantly, the effect of mTOR exposure on increasing the AD threshold is higher than it is on increasing the motor threshold (Fig. 2), suggesting that mTOR inhibitors may have a greater effect on cortical excitability in abnormal than on physiologic (functional) cortices. This ability of mTOR inhibitors to correct heightened cortical excitability in TSC, with a preferential effect on aberrant cortical excitability, probably provides a neurophysiologic basis for the effectiveness of mTOR inhibitors in TSC-related DRE (Franz and Capal, 2017; French et al., 2016; Krueger et al., 2013; Overwater et al., 2016). Prolonged treatment and higher dosage of mTOR inhibitors are known to improve seizure control in patients with TSC, suggesting an exposure-dependent suppression of pathological cortical excitability, aligning with the observed decrease in ADs with increased mTOR inhibitors exposure in our study (Franz et al., 2021; French et al., 2016).

4.3. Duration of Epilepsy, Age, and cortical excitability

Older age was associated with higher incidence and lower current thresholds for motor responses, language responses, and ADs in both the TSC and unknown etiology DRE groups (Tables 3, 4). This global increase in cortical excitability with age has been previously documented by us and others and is often attributed to an increase in the proportion of myelinated neurons with age, which require lower currents for excitation (Arya et al., 2020, 2019; Aungaroon et al., 2023, 2017; Chitoku et al., 2001; Jayakar et al., 1992; Zea Vera et al., 2017). In this study, we tried to discern the effect of duration of epilepsy separate from age. Overall, the duration of epilepsy mirrored the effect of age, as a longer duration of epilepsy corresponded to a higher incidence and lower thresholds for motor responses, language responses, and ADs in both groups. However, the correlation between age and duration of epilepsy was significant in TSC (slope $= 0.98$; $p < 0.001$) compared to unknown etiology DRE (slope $= 0.26$; $p = 0.127$, *post hoc* analysis, Fig. S2). This likely reflects early onset of epilepsy in a majority of TSC patients whereas the onset of epilepsy in patients with unknown epilepsy DRE is more variable (Berg et al., 1996; Litwa, 2022; de Saint Martin et al., 2022; Specchio et al., 2023). Moreover, there appears to be a significant effect on cortical excitability of the duration of epilepsy in TSC patients rather than those with unknown etiology DRE independent of age, which further supports the potential benefits of early intervention with mTOR inhibitors given the duration-dependent correction of aberrant cortical excitability.

4.4. Limitations

Like any other human subjects research, our study had some inadvertent limitations, being a single-center, retrospective study, with a limited sample size. In TSC patients, the location and degree of tuber burden had intrinsic variability that can potentially affect localization of language and motor responses. To ensure comparability of ESM between TSC and unknown etiology DRE groups, we ensured coverage of *peri*-rolandic and *peri*-sylvian regions-of-interest with intracranial electrodes in all patients, albeit only visually (Fig. S1). To some extent, use of mixed effects models partly adjusts for this inherent variability in electrode placement across patients. For language ESM, reliance only on visual naming is another concern, however, it is challenging in pediatric patients to use multiple language tasks for ESM, an optimal pediatric language ESM protocol being undefined (Hamberger, 2007). Also, we did not analyze gray and white matter contacts separately because in our previous work, ESM language and sensorimotor thresholds were not significantly different between gray and white matter (Arya et al., 2020, 2019). In general, several factors can potentially affect ESM results and interpretation, including electrical propagation, co-occurrence of functional responses and ADs in pediatric patients, underlying pathology, heterogeneity in coverage in individual patients and proximity to epileptogenic zone, effect of anti-seizure medications, etc. Such granular data extraction and analyses were beyond the scope of our study.

An additional limitation stems from the necessity to withhold mTOR inhibitor up to 2 weeks prior to the intracranial monitoring. However, we posit that because we found evidence of altered cortical excitability in TSC patients who had been on mTOR inhibitors despite this limitation, it supports a longer-term disease modifying effect of mTOR inhibitors that persists even upon recent discontinuation.

5. Conclusions

We found that patients with TSC have increased cortical excitability for both functional (language and motor) and aberrant (ADs) ESM-induced responses compared to a similar cohort of unknown etiology DRE. In TSC, this cortical excitability further increases at a higher rate with age or duration of epilepsy compared to the unknown etiology DRE group. mTOR inhibitors appear to correct the longitudinal course of this altered cortical excitability and greater mTOR inhibitor exposure may preferentially reduce aberrant over functional cortical excitability. This study provides a neurophysiologic basis for the effect of mTOR inhibitors for improving seizure control in TSC and supports earlier use of mTOR inhibitors in TSC to potentially prevent the duration-dependent alterations in cortical excitability.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2025.02.001.

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