Motor evoked potential polyphasia

A novel endophenotype of idiopathic generalized epilepsy

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ABSTRACT

Objective: We compared the motor evoked potential (MEP) phases using transcranial magnetic stimulation in patients with idiopathic generalized epilepsy (IGE), their relatives, and healthy controls, hypothesizing that patients and their unaffected relatives may share a subtle pathophysiologic abnormality.

Methods: In a cross-sectional study, we investigated 23 patients with IGE, 34 first-degree relatives, and 30 matched healthy controls. Transcranial magnetic stimulation was performed to produce a series of suprathreshold single-pulse MEPs. A semiautomated method was used to count phases. We compared between groups the mean number of MEP phases, the stimulus-to-stimulus variability in MEP phases, and the proportion of polyphasic MEPs within subjects.

Results: Patients with IGE and their relatives had a significantly increased number of MEP phases (median for patients 2.24, relatives 2.17, controls 2.01) and a significantly higher proportion of MEPs with more than 2 phases than controls (median for patients 0.118, relatives 0.088, controls 0.013). Patients had a greater stimulus-to-stimulus variability in number of MEP phases than controls. There were no differences between patients and relatives.

Conclusion: Increased MEP polyphasia in patients with IGE and their first-degree relatives may reflect transient abnormal evoked oscillations. The presence of polyphasic MEPs in relatives as well as patients suggests that MEP polyphasia is not related to treatment, and is in isolation insufficient to predispose to epilepsy. Polyphasic MEP may be a novel endophenotype in IGE.
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GLOSSARY

AED = antiepileptic drug; **ALS** = amyotrophic lateral sclerosis; **FDI** = first dorsal interosseus; **IGE** = idiopathic generalized epilepsy; **IQR** = interquartile range; **MEP** = motor evoked potential; **TMS** = transcranial magnetic stimulation.

The excessive, synchronous discharges characterizing most seizures may arise through cortical hyperexcitability.[1] Idiopathic generalized epilepsy (IGE) presents with complex genetics and distinct phenotypes.[2] Transcranial magnetic stimulation (TMS) is a noninvasive technique for measuring cortical excitability; using TMS, abnormalities of cortical excitability have been reported in drug naive[3] and medicated[4] IGE.

A little-studied phenomenon in TMS not previously reported in epilepsy is the occurrence of polyphasic oscillations within the motor evoked potential (MEP) (figure 1). In amyotrophic lateral sclerosis (ALS), they may reflect central corticospinal abnormality,[5] and in myoclonus dystonia, they may reflect abnormal variability in the patterning of descending corticospinal volleys evoked by TMS (so-called I waves)[6] and hence alteration in the pattern and timing of recruitment of spinal motor neurons.[7,8] Polyphasic responses have also been observed in healthy children[9] becoming less polyphasic with age.

Asymptomatic relatives of patients with IGE may share an endophenotype that alone is not sufficient to cause seizures. EEG abnormalities have been found in unaffected siblings,[10] and

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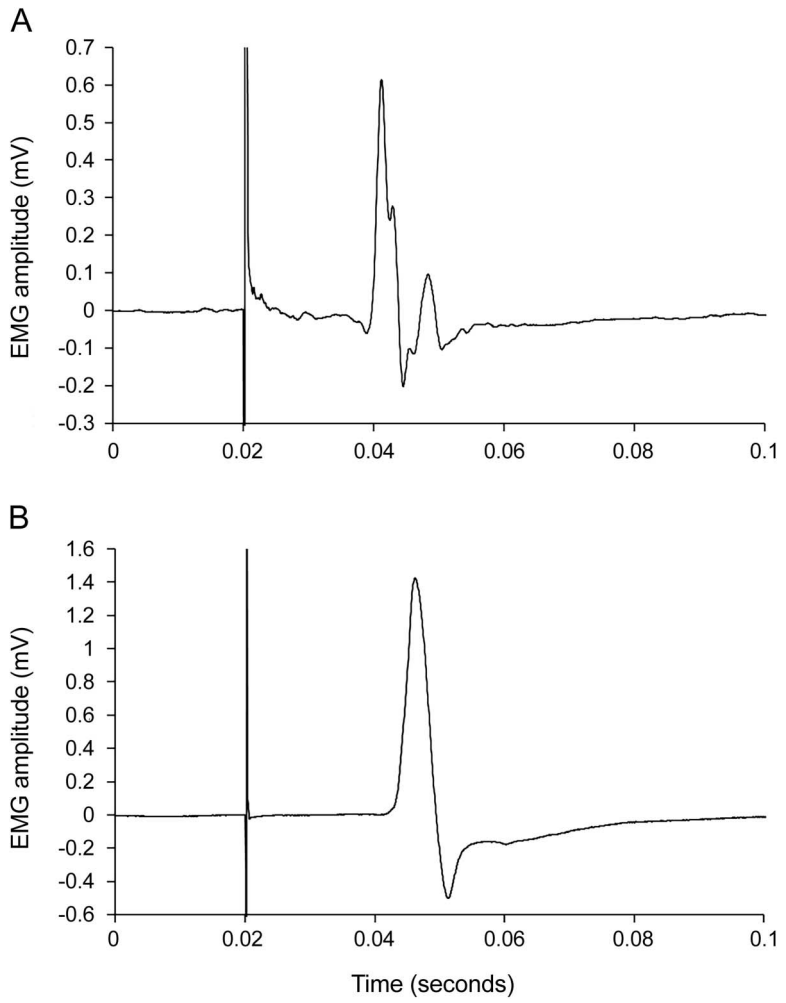
Figure 1 Motor evoked potential (MEP) from single transcranial magnetic stimulation pulse over contralateral motor cortex, recorded using surface EMG from first dorsal interosseus muscle



(A) A polyphasic MEP from a patient with idiopathic generalized epilepsy with a count of 4 phases. (B) A normal MEP from a healthy control subject.

TMS has revealed altered cortical excitability in patients with IGE and their asymptomatic relatives, in particular an impairment of intracortical inhibition.[11,12] Thus, a neurophysiologic marker present in patients and unaffected relatives might be useful in characterizing a genetically inherited predisposition to epilepsy.

Based on the observation of polyphasic MEPs in other patient groups, and that this may be a central phenomenon, we hypothesized that polyphasic MEP activity would be more prominent in IGE compared with controls, and would be present as an endophenotype in asymptomatic first-degree relatives.

METHODS

Subjects. We studied 23 right-handed patients with IGE (12 women, mean age 29 years, range 18–59, SD 11.14), 34 first-degree relatives (13 women, mean age 35.4 years, range 18–68, SD 14.8), and 30 age- and sex-matched healthy controls (17 women, mean age 29.3 years, range 18–52, SD 8.69) with no history of neurologic illness. In this exploratory study, we chose group sizes to allow detection of a large effect size (0.8) with 80% power and α of 0.05. Patients were recruited from outpatient clinics at several London hospitals, controls from a local research volunteer database. Diagnoses of IGE were made by experienced epileptologists (L.N., R.D.C.E., M.P.R.), based on a combination of clinical presentation, EEG, and neuroimaging data. Patients were subdivided into clinical syndromes: 5 with juvenile myoclonic epilepsy, 1 with juvenile absence epilepsy, 4 with childhood absence epilepsy, 9 with generalized tonic-clonic seizures only, 1 with eyelid myoclonia and absences, and 3 IGE unclassified. Basic clinical and demographic data are shown in table 1. This cohort has been previously described.[13] No relatives had a diagnosis of epilepsy; 2 had generalized discharges on EEG.

Standard protocol approvals, registrations, and patient consents. The study was approved by the research ethics committee at King's College Hospital (ethics reference 08/H0808/157). All participants gave written informed consent.

Procedure. TMS recordings were obtained in a single session. All subjects were seated, relaxed, and alert. EMG was recorded by positioning silver/silver chloride EMG disc electrodes in a belly-tendon montage on the first dorsal interosseus (FDI) muscle bilaterally. TMS pulses were delivered by a figure-of-8 coil (9-cm external loop diameter) using a Magstim BiStim unit (Magstim Company, Dyfed, UK) connected to 2 Magstim 200 stimulators. EMG signals were filtered and amplified (CED 1902; Cambridge Electronic Design, Cambridge, UK) using a sampling rate of 15 kHz, a bandwidth of 10–5,000 Hz, and a gain of 1,000 (CED 1401), and traces were recorded using data capture and signals processing software (Signal 3.10; Cambridge Electronic Design).

The coil was placed tangentially to the scalp with the handle facing backward and angled at approximately 45° to the midline so as to provide an optimal posterior-to-anterior current flow across the motor cortex, as per previously established methods.[14] The optimal site for stimulating the FDI was established for each hemisphere and marked on the scalp to ensure consistency during recording. Resting motor threshold was recorded according to previously established protocols.[14] The threshold is defined as the lowest stimulator output capable of eliciting an MEP of at least 50 μV amplitude in 50% of pulses. Resting motor threshold was recorded with patients completely relaxed whereas active motor threshold was recorded during voluntary contraction of the FDI. Contraction force was standardized using a manometer, with subjects squeezing at 20% of their maximum voluntary contraction. These data were collected as part of a larger dataset, and for the measurement of polyphasic activity, the unconditioned single pulses from a larger paired-pulse dataset were analyzed. These pulses were delivered at 120% of resting motor threshold to ensure an MEP would be consistently evoked across the trials. A total of 20 unconditioned MEPs were recorded for each subject.

Data analysis. MEPs were analyzed for polyphasic activity in Signal 3.13 using a semiautomated custom script. First, every MEP in every subject was visually inspected for the presence of 50-Hz line noise. If present, the maximum and minimum values of the 50-Hz oscillation were determined in the EMG data beyond the termination of the MEP. These maximum and minimum threshold values were entered into the automated analysis of MEP phases. The analysis script was designed to first identify the highest peak (the point of

Table 1 Description of the patient group

Age, y	Sex	Epilepsy syndrome	Age at onset	Seizure frequency/y	Medication	EEG	MRI
53	F	IGE GTCS	3 y	ABS 5–10 daily, GTCS SF	Nil	GSW (with Ph+)	Normal
20	F	JME	13 y	SF	VAL	GSW (front max)	Normal
20	F	IGE GTCS	6 mo	SF	Nil	—	
39	F	IGE GTCS	22 y	GTCS SF	CBZ	GSW	Normal
18	F	JME	15 y	MJ	LEV, LTG, ZON	GSW	—
18	F	CAE	7 y	GTCS 12, ABS	ETX, LTG	GSW	Normal
21	F	JAE	10 y	GTCS, ABS SF	LTG, ETX	GSW	Normal
32	F	CAE	4 y	ABS (weekly)	NA	GSW	—
19	F	IGE GTCS	15 y	GTCS 6	LEV	GSW	Normal
45	F	IGE GTCS	2 y	GTCS SF	Nil	—	—
21	F	AEM	6 y	52	LTG	PSW	—
28	M	GTCS	8 y	1	VAL	GSW	—
31	M	IGE	8 y	GTCS SF	VAL	Normal	Normal
28	M	CAE	4 y	GTCS SF, ABS SF	VAL, LEV, LTG	GSW	—
30	M	IGE	11 y	ABS SF	Nil	—	—
28	M	JME	17 y	GTCS 12, MJ frequent	VAL	Frequent GSW	Normal
25	M	JME	14 y	GTCS 3 MJ	VAL	GSW	Normal
25	M	IGE GTCS	11 y	GTCS 24	VAL	GSW	Normal
59	M	JME	14 y	MJ+, GTCS SF	Nil	—	—
26	M	CAE	5 y	SF	VAL, TOP, LTG	GSW	—
28	M	IGE	20 y	SF	CBZ	Normal	Normal
31	M	GTCS (Ph+)	8 y	GTCS 6	VAL, ZON, LEV, LTG	GSW Ph+	—
45	M	CAE	3 y	SF	VAL, LEV	GSW	—

Abbreviations: ABS = absence seizures; AEM = absences with eyelid myoclonia; CAE = childhood absence epilepsy; CBZ = carbamazepine; ETX = ethosuximide; GSW = generalized spike and wave; GTCS = generalized tonic-clonic seizures; IGE = idiopathic generalized epilepsy; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; LEV = levetiracetam; LTG = lamotrigine; MJ = myoclonic jerks; ph+ = photic stimulation; SF = seizure free (if >12 months without any seizure); TOP = topiramate; Val = valproate; ZON = zonisamide.

maximum amplitude) of the MEP waveform. Then, a time window was automatically placed around the peak during which polyphasic activity would be detected. Based on a prior analysis of all MEPs across all subjects, a time window of 7.5 milliseconds before and 15 milliseconds after the peak was chosen because it encompassed 100% of the observable polyphasic activity in every subject. Within this time window, peaks and troughs of the waveform were automatically counted if they exceeded the thresholds set according to the amplitude of the line noise, or if the peak/trough had an amplitude exceeding 0.4 μV if no visible line noise was present. It is conceivable that some peaks and troughs may, in some instances, have had an amplitude less than the line noise, and therefore not detected, but it should be noted that in such case our estimate of MEP phases may be conservative. It should also be noted that the presence of line noise was similar between groups of subjects.

We did not use a 50-Hz notch filter. This is because the MEP has frequency components in this range, and hence using a notch filter creates very prominent ringing in the MEP waveform, which would artifactually create a polyphasic signal. Although we did everything feasible to reduce line noise, the presence of some line noise in some subjects' data is inevitable given that we did not have access to an electrically shielded recording room or to a Faraday cage. We emphasize that line noise was always of very low amplitude and was not visually detectable in many subjects.

Once a count of phases was obtained for each MEP, the total number of phases was averaged for all 20 MEPs for each subject; this mean MEP phase count was used for between-group comparisons. We also calculated the within-subjects interquartile range (IQR) of the number of MEP phases to assess whether the presence of polyphasic responses in patients and relatives was more variable from trial to trial than in control participants. Finally, we examined the proportion of all MEPs in each subject that demonstrated polyphasic activity (i.e., the number of frames that showed more than 2 phases as a proportion of the total number of MEPs recorded per subject).

All data were analyzed using SPSS 21.0 (IBM UK, London). Nonparametric Kruskal–Wallis test was adopted to compare groups for each measure (mean number of phases; between-trials IQR of the number of MEP phases; proportion of polyphasic MEPs), and post hoc nonparametric Mann–Whitney test was used to further explore the data if a significant effect was found for Kruskal–Wallis test.

RESULTS There were no significant differences in polyphasic activity between hemispheres in any subject group; therefore, the number of phases was

Table 2 Summary of data obtained for each group

Within-subjects measure	Minimum	25th centile	Median	75th centile	Maximum
Patients					
Mean no. of MEP phases	2.000	2	2.235	2.8	3.813
IQR of no. of MEP phases	0	0	0	1.5	3
Proportion of MEPs with >2 phases	0	0	0.118	0.388	0.688
Relatives					
Mean no. of MEP phases	1.95	2	2.179	2.429	4.325
IQR of no. of MEP phases	0	0	0	0	2
Proportion of MEPs with >2 phases	0	0	0.088	0.222	0.925
Controls					
Mean no. of MEP phases	1.85	2	2.013	2.099	2.609
IQR of no. of MEP phases	0	0	0	0	1.5
Proportion of MEPs with >2 phases	0	0	0.013	0.071	0.391

Abbreviations: IQR = interquartile range; MEP = motor evoked potential.

averaged within subjects between hemispheres. Age was not significantly different between groups.

There was a significant difference in the average number of MEP phases between groups (Kruskal–Wallis $p = 0.027$). Patients with epilepsy had a significantly increased average number of phases compared with controls (Mann–Whitney $p = 0.010$; median for patients 2.24, controls 2.01) (see figure 1, and tables 2 and 3). Relatives also had a significantly increased number of phases compared with controls (Mann–Whitney 0.048; median 2.18).

Table 3 Summary of comparison of measures among groups

Group comparison	Statistical test	*p*
Within-subjects mean no. of phases in MEP		
Comparing all 3 groups	Kruskal-Wallis	0.027[a]
Patient vs normal control	Mann-Whitney	0.010[a]
Relative vs normal control	Mann-Whitney	0.048[a]
Patient vs relative	Mann-Whitney	0.466
Within-subjects IQR of no. of phases in MEP		
Comparing all 3 groups	Kruskal-Wallis	0.033[a]
Patient vs normal control	Mann-Whitney	0.009[a]
Relative vs normal control	Mann-Whitney	0.138
Patient vs relative	Mann-Whitney	0.175
Within-subjects proportion of MEPs with >2 phases		
Comparing all 3 groups	Kruskal-Wallis	0.030[a]
Patient vs normal control	Mann-Whitney	0.012[a]
Relative vs normal control	Mann-Whitney	0.044[a]
Patient vs relative	Mann-Whitney	0.527

Abbreviations: IQR = interquartile range; MEP = motor evoked potential.
[a] Significant value.

There was a significant difference in the variability of the number of MEP phases between the groups, measured by examining the within-subjects IQR of the number of MEP phases across the 20 trials (Kruskal–Wallis $p = 0.033$). Patients with epilepsy had a significantly increased IQR of the number of MEP phases compared with controls (Mann–Whitney $p = 0.009$; patients 25th centile 0, 75th centile 1.5; controls 25th centile 0, 75th centile 0). Relatives and controls were not significantly different.

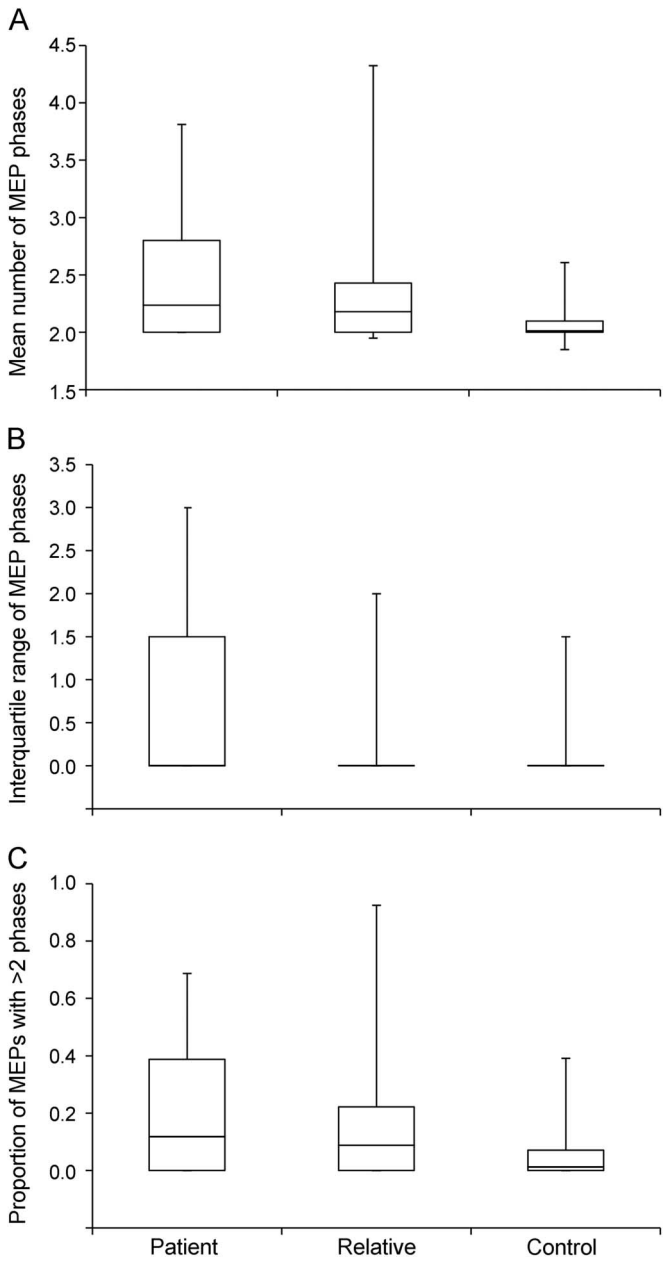
There was a significant difference in the proportion of MEPs from each subject with more than 2 phases (polyphasic activity) across the groups (Kruskal–Wallis $p = 0.030$) (see figure 2). The proportion of MEPs with more than 2 phases was greater in patients compared with controls (Mann–Whitney $p = 0.012$; median for patients 0.118, median for controls 0.013). The proportion of MEPs with more than 2 phases was also greater in relatives compared with controls (Mann–Whitney $p = 0.044$; median 0.088).

Note that there were no significant differences between patients and relatives on any measures.

These findings are summarized in figure 3, which shows the proportion of MEPs within the 20 trials for each subject that had between 1 and 6 phases (no subject had any MEP with >6 phases). Group-level minimum, 25th centile, median, 75th centile, and maximum are illustrated for each number of MEP phases, providing a summary overview of the entire dataset.

Finally, we examined an established measure of cortical excitability (resting motor threshold) as a separate intergroup comparison. Left- and right-hemisphere resting motor threshold was averaged and intergroup differences were assessed. There were no significant differences between any of the groups.

Figure 2 **Patients with idiopathic generalized epilepsy and first-degree relatives have significantly more polyphasic motor evoked potentials (MEPs) than healthy controls**



(A) Within-subjects mean number of MEP phases across the 20 MEPs, illustrated for the patient, relative, and control groups. Box-and-whisker plot showing group median (horizontal line in box), 25th and 75th centiles (bottom and top of box), and minimum and maximum values (lower and upper whiskers). (B) Within-subjects interquartile range of the number of MEP phases across the 20 MEPs, illustrated for the patient, relative, and control groups. Box-and-whisker plot showing group median (horizontal line in box), 25th and 75th centiles (bottom and top of box), and minimum and maximum values (lower and upper whiskers). (C) Within-subjects proportion of MEPs with >2 phases across the 20 MEPs, illustrated for the patient, relative, and control groups. Box-and-whisker plot showing group median (horizontal line in box), 25th and 75th centiles (bottom and top of box), and minimum and maximum values (lower and upper whiskers).

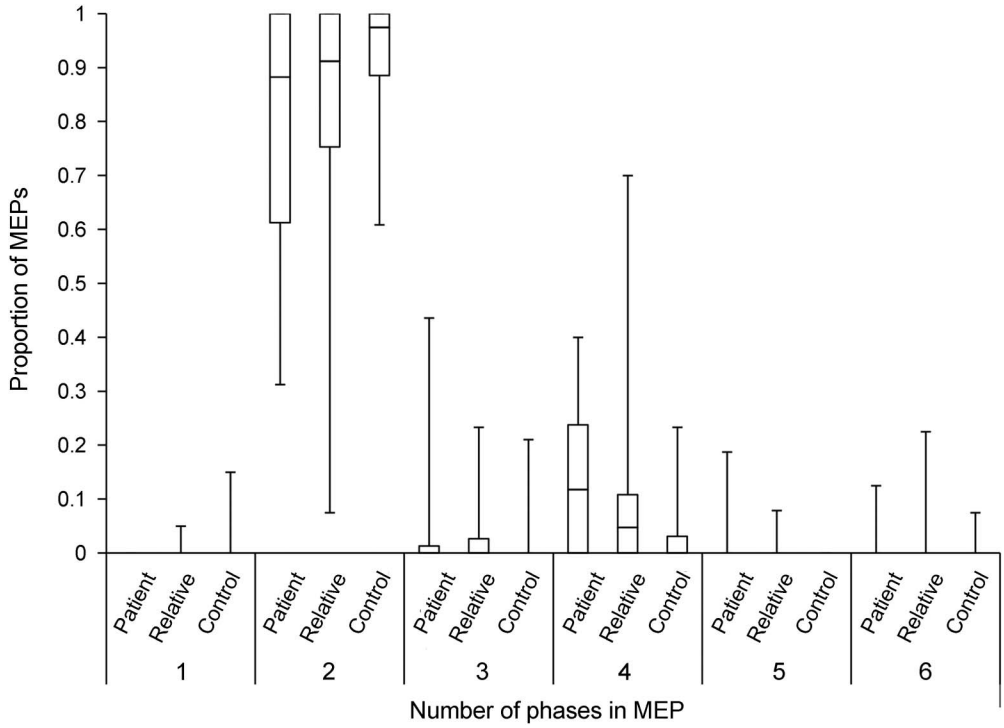
DISCUSSION The current study revealed that MEPs evoked by TMS show increased polyphasia in patients with IGE and their relatives compared with healthy controls. We also found that the variability in the number of MEP phases, across a series of MEPs within each subject, was greater in patients compared with controls and that the proportion of MEPs with more than 2 phases was also significantly higher in patients and relatives compared with controls.

Our finding adds to previous studies showing differences in TMS measures between patients with IGE receiving antiepileptic drug (AED) therapy and controls,[4,12] revealing abnormalities of a novel aspect of cortical physiology in patients with IGE and their relatives. The presence of increased polyphasic activity in unaffected relatives of patients with IGE suggests that polyphasic responses may represent an electrophysiologic characteristic related to underlying cortical pathophysiology, even in the absence of a manifest epilepsy syndrome.

The underlying cortical mechanisms responsible for the polyphasic phenomena remain unclear. To our knowledge, this is the first report of polyphasic MEPs in epilepsy, although they have previously been documented in ALS[5] and myoclonus dystonia.[7,8] In these studies, the polyphasia was attributed to central mechanisms. We speculate that this is due to abnormal timing and patterning of the descending volleys in the corticospinal tract, termed I waves. Computational modeling at a cellular level suggests that dysfunction in local circuits can be amplified at a network level, causing asynchronicity in population oscillations and a tendency for modeled seizures to arise.[15] We speculate that this abnormal timing of I waves could be attributable to recurrent volleys of I waves being fired from motor cortex due to a TMS-induced oscillation that continues within the dysfunctional circuits of patients and relatives. This might recurrently fire I waves at a longer delay than normal, ultimately being detected as polyphasic MEPs. Patients show higher variability between different MEPs in the same subject, suggesting that the central phenomenon responsible for generating the polyphasic MEPs might be related to such asynchronous oscillations, where stimulation fails to reliably elicit the same response with each trial. However, because this is the first instance of the observed phenomenon in epilepsy, greater elucidation is required of both the neurophysiologic differences between groups as well the putative computational models before a plausible mechanism can be proposed.

Previous research also concluded that the polyphasic activity identified by TMS in patients with myoclonus dystonia may be related to mutations in the *SGCE* gene encoding a transmembrane protein, thereby increasing synaptic instability within the corticospinal tract.[7,8] While *SCGE* is not recognized as a genetic contributor to IGE, further corroboration of these results might motivate the hypothesis that this gene could provide a potential putative central

Figure 3 Motor evoked potential (MEP) data for all subjects are summarized



For each subject, the proportion of MEPs with each specific number of phases (1 phase to 6 phases) was calculated; across each group of subjects, the median proportion of MEPs with each specific number of phases was estimated, and in addition the group minimum, 25th centile, 75th centile, and maximum. The data are displayed as box-and-whisker for each group and each number of MEP phases. The horizontal line in the box indicates the median proportion across the group, lower and upper limits of the box represent group 25th and 75th centiles, and the lower and upper whiskers represent the group minimum and maximum. Note that for most subjects in all groups, the proportion of MEPs with 2 phases is >0.8, whereas for most subjects in all groups, the proportion of MEPs with 1, 5, or 6 phases is zero. Note that compared with healthy control subjects, patients and relatives have a reduced proportion of MEPs with 2 phases, and an increased proportion of MEPs with >2 phases (especially 4 phases).

mechanism. However, further investigation is certainly required before its pathophysiologic mechanism can be better understood.

It was noted in the study of patients with ALS that resting motor threshold in the patients was higher than in controls.[5] It could be argued that the relatively higher motor threshold in patients with ALS, and hence the higher simulation intensity required to elicit an MEP, may activate additional motor pathways responsible for MEP polyphasia in patients with ALS compared with controls. Given that there were no significant differences in motor thresholds (and therefore no significant difference in stimulation intensity) between the groups, this would not explain the current findings. In particular, thresholds in controls and relatives were identical.

While the observed differences between patients and controls may be partly attributable to the action of AED medication, which is known to alter TMS measurements,[15] asymptomatic relatives were all untreated; therefore, the actions of AEDs cannot explain our findings in the relatives. It is proposed that these differences in MEP polyphasia may represent an endophenotype, observable by TMS, which implies a degree of shared cortical pathophysiology in patients with IGE and their close relatives, but which cannot be attributed to AED therapy.

None of the relatives had any evidence of prior seizures on the basis of history, assessed by an epilepsy-trained neurologist (F.A.C.). All relatives underwent EEG, which revealed generalized spike and wave associated with photic stimulation or hyperventilation in 2; exclusion of these 2 did not alter the results.

In this study, we did not use peripheral motor nerve stimulation to assess nerve conduction and muscle properties independently from central stimulation via TMS. We cannot exclude that the patients with IGE and relatives differed from controls because of a lower motor neuron or muscle property. Although such an explanation would be out of keeping with the conventionally understood pathophysiology of epilepsy, future work should address this gap in evidence.

We studied a heterogeneous group of patients with IGE, and did not seek to power the study to examine individual IGE syndromes. Future work

should clarify whether polyphasic MEPs are an endophenotype of all IGEs, or relatively specific for one or more syndromes. Furthermore, it would be of great interest to examine whether this phenomenon associates with specific seizure types, or with other subtle abnormalities in IGE such as cognitive dysfunction.

We describe here a novel endophenotype of IGE, namely, polyphasia of TMS-evoked MEPs, which is present in patients and their unaffected untreated relatives. We speculate that this finding is attributable to abnormal intracortical oscillation induced by TMS, but its detailed pathophysiology remains to be established.

AUTHOR CONTRIBUTIONS

F. Chowdhury: recruitment, data collection, reviewing of manuscript. A. Pawley: study design, data analysis, writing the manuscript. B. Ceronie: data analysis, contributed to writing of manuscript. L. Nashef and R.D.C. Elwes: study design, recruitment, reviewing of manuscript. M.P. Richardson: principal investigator, study design, supervision of data collection, reviewing and redrafting of manuscript.

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DISCLOSURE

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