FULL-LENGTH ORIGINAL RESEARCH

Modulation of epileptiform EEG discharges in juvenile myoclonic epilepsy: An investigation of reflex epileptic traits

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SUMMARY

Purpose: Previous studies have suggested that cognitive tasks modulate (provoke or inhibit) the epileptiform electroencephalography (EEG) discharges (EDs) in patients with juvenile myoclonic epilepsy (JME). Their inhibitory effect was found to be especially frequent (64–90%). These studies arbitrarily defined modulation as a >100% increase or >50% decrease of the EDs compared with baseline, which may not sufficiently distinguish from spontaneous fluctuations. The aim of our study was to assess the modulation of EDs and the precipitation of myoclonic seizures by cognitive tasks and by conventional provocation methods, taking into account also the spontaneous fluctuation of EDs.
Method: Sixty patients with JME underwent video-EEG recordings including 50-min baseline, sleep, hyperventilation, intermittent photic stimulation (IPS), and cognitive tasks. To account for spontaneous fluctuations of the EDs we divided the baseline period into 5-min epochs and calculated the 95% confidence interval for the baseline EDs in each patient. Modulation was assumed when the number of EDs during any 5-min test period was outside the 95% confidence interval.
Key Findings: Using the arbitrary method, our results were similar to previous publications: Cognitive tasks seemed to inhibit the EDs in 94% of the patients, and to provoke them in 22%. However, when the spontaneous fluctuations were accounted for, inhibition was found in only 29% of the patients and provocation in 18%. A nonspecific effect of any cognitive task seemed to account for the observed significant inhibition in two-thirds of the cases, but was observed in only one of the patients with significant provocation. Photoparoxysmal response was observed in 23% of the patients. When accounting for the spontaneous occurrence of EDs, IPS had provocative effect in 10% of the patients. Hyperventilation and sleep had provocative effect on EDs to an extent similar to the cognitive tasks (hyperventilation: 22%; sleep: 18%). The conventional provocation methods tended to be more efficient in patients who were not seizure free. Myoclonia were recorded most often during the cognitive tasks (10 patients).
Significance: Spontaneous fluctuations of EDs account for most of the previously described inhibitory effect of the cognitive tasks. The provocative effect of the cognitive tasks is task-specific, whereas the inhibitory effect seems to be related to cognitive activation in general.
KEY WORDS: Cognitive tasks, EEG, Juvenile myoclonic epilepsy, External modulation, Reflex epilepsy, Photoparoxysmal response.

Reflex epileptic seizures are defined as seizures that can reproducibly and immediately be triggered by some well-defined sensory or cognitive stimulus (Wolf & Koepp, 2012). Many varieties have been described in all types of epilepsy, and juvenile myoclonic epilepsy (JME) stands out by its relation to no less than four different reflex epileptic traits, all rather common: photosensitivity (Wolf & Goosses, 1986), praxis induction (Matsuoka et al., 1988; Inoue et al., 1994), language-induced perioral reflex myoclonia (Mayer et al., 2006), and eye closure sensitivity (Sevgi et al., 2007). Of these, photosensitivity is so common and well-described that use of intermittent photic stimulation (IPS) to identify it is part of the standard protocol of electroencephalography (EEG) in the diagnostics of epilepsy.

Recently, several groups have reported that the same stimuli that typically produce reflex epileptic seizures and epileptiform EEG discharges (EDs) in patients at risk, can

also inhibit or prevent seizures and EDs. In some studies (Matsuoka et al., 2000, 2005; Mayer et al., 2006; Guaranha et al., 2009), the inhibitory effect was a surprisingly frequent finding, occurring in 64–90% of patients. These studies arbitrarily defined the level of provocation and inhibition. The rate of EDs during stimulation was calculated. A test was considered to have an inhibitory effect when this was half or less of the mean rate of EDs during the baseline. In contrast, an increased rate to at least twice the mean baseline value was considered a provocative effect. However, this rating does not take into account that spontaneous fluctuations in the occurrence of EDs also could exceed double or half of the average.

To clarify whether the reported modulation of EDs by cognitive tasks is a true phenomenon, we applied a study protocol designed to allow for a statistical comparison of spontaneous fluctuations and responses to cognitive tasks. In addition to the cognitive tasks, we included the conventional modulators (hyperventilation, IPS, sleep).

We included patients with JME because previous studies suggested that modulation by cognitive tasks occurs mainly among patients with idiopathic generalized epilepsy, and especially JME (Matsuoka et al., 1988, 2000, 2005; Mayer et al., 2006; Guaranha et al., 2009), although JME is clinically and genetically heterogeneous (Zifkin et al., 2005).

Elucidation of external factors that modulate ictogenesis would help in a better understanding of the underlying pathomechanisms and in defining clinical/electrographic endophenotypes in JME.

METHODS

Patients

Sixty patients with JME (36 female) from six centers were recruited to the study. The patients gave their informed consent, and the study was approved by the ethics committees. All patients had a diagnosis of JME based on clinical and EEG data (Janz & Durner, 1998). The demographic and clinical data of the patients are summarized in Table 1.

Reflex epileptic traits

Twenty patients (33%) were historically known to be photosensitive based upon at least one EEG recording with photoparoxysmal response. At present, no established protocols exist for the assessment of eye closure sensitivity, orofacial reflex myoclonias, and praxis induction; therefore, no systematic historical data on these traits exist in our patients.

Recordings

To increase the probability of recording EDs in the baseline period (for assessing inhibition) the patients were sleep-deprived, and all recordings were performed in the morning (Labate et al., 2007). Patients were excluded if they had a generalized tonic–clonic seizure during the day preceding

Table 1. Demographic and clinical data of the 60 patients with JME	
Gender	
Male (%)	23 (40)
Female (%)	36 (60)
Age	
Range	14–50 years
Mean	28 years
Median	28 years
Family history	
Epilepsy (%)	21 (35)
JME (%)	9 (15)
Duration of JME	
Range	1–36 years
Mean	12.9 years
Median	12 years
Antiepileptic drug (AED) therapy	
Without AED (%)	4 (7)
Appropriate AED (%)	49 (82)
Inappropriate (%)	7 (11)
Seizure control	
Seizure-free (%)	35 (58)
Not seizure-free (%)	25 (42)

the recording. None of the recruited patients had generalized tonic–clonic seizure during the recording session. Video-EEG was recorded using 19–32 EEG electrodes placed according to the International 10-20 or 10-10 electrode system. The protocol is summarized in Table 2. The recording started with the patient lying on a bed, in a dark room with eyes closed. If the patient fell asleep during the first 30 min, a sleep period of 50 min was registered at the beginning of the recording. This was followed by a baseline period of 50 min, with the patient sitting in a chair, relaxed, and with eyes open. The EEG during the baseline period was continuously monitored to ensure that drowsiness or sleep did not occur during this period. After the baseline period, the conventional provocation methods (hyperventilation, IPS), and the cognitive tasks were performed. IPS was done according to standard protocol (Kasteleijn-Nolst Trenité et al., 1999) adjusted to a total duration of 5 min. Each test condition was of 5 min duration, separated by 2-min intervals. If EDs were absent in the baseline period and occurred during a test condition, this test was repeated at the end of the protocol to exclude a chance relation. The total duration of the recording was 3–4 h per patient. All recordings were video documented, which allowed precise assignment of any seizures occurring during the investigation to the various test conditions. The number of patients experiencing seizures was compared among the different types of provocation methods.

As in previous publications (Matsuoka et al., 2000, 2005; Guaranha et al., 2009) the different types of cognitive tasks were categorized in two ways:

1 Action-programming: reading aloud a difficult text in their own language, speaking, copying a text in Hungarian

Table 2. Video-EEG protocol
Sleep period (50 min)
Baseline period, awake with eyes open (50 min)
Conventional provocation methods (5 min each; 2-min interval between them)
Hyperventilation (HV)
Intermittent photic stimulation (IPS)
Cognitive tasks (5 min each, in random order; separated by 2-min interval between the tests)
Read silently a difficult text in the patient's first language
Read aloud (continue with the same text)
Speak: the patient looks into the camera and tells about his/her medical history, life, etc.
Writing (copying a text in Hungarian)
Mental calculations (e.g.: $8 - 7$, $35 - 17$, $23 + 48$, 11×11, 147×2, 123×3, $125/5$, $369/3$, $621/3$, $425 - 148$, $128/4$)
Drawing: copy Rey-Osterrieth complex figure; fish; face; car; house; cat; dog; apple; star; moon; etc.
Playing with Rubik's cube
Written calculations (e.g.: $419 + 728$; $256 - 179$; $3,248 - 1,359$; 124×46; 135×112; $1,656/34$; $6,268/72$; $4,273 \times 324$; $83,426/219$; $1,964 \times 625$; $411/24$)

(which for all was an unintelligible language; Japanese patients copied a text consisting mainly of Kanji signs), written calculation, drawing, and Rubik's cube versus thinking-activity: reading silently and mental calculation.

2 Tasks related to visuospatial functions: drawing, writing as above, written calculation, Rubik's cube versus linguistic functions: reading aloud and silently, speaking. The protocol is based on the one used by Matsuoka et al. (2000) with the extensions of linguistic testing that were introduced by Mayer et al. (2006) and also applied by Guaranha et al. (2009).

The task of copying an unintelligible text has both spatial and linguistic aspects. Therefore, in addition to the procedural categorizations described, we also evaluated the visuospatial group excluding the writing.

EDs fulfilling established criteria (Gloor, 1977; Noachtar et al., 1999) were visually identified and marked in the recordings. The number of EDs was determined for each test condition (of 5 min each) and for 10 consecutive 5-min epochs (time-windows) during the baseline period and during sleep. When EDs were present in the baseline period, we calculated the provocative and the inhibitory effect, applying (for comparison) both the previously used arbitrary and a statistical method as described below.

Arbitrary method

The total number of EDs during a condition (test or baseline) is divided by the duration (in minutes) of that condition. Provocation is considered when the number of EDs/time during a test condition is greater than twice that during the baseline. Inhibition is considered when the number of EDs/time during a test condition is less than half that of the baseline period (Matsuoka et al., 2000, 2005; Guaranha et al., 2009).

Statistical method

The 95% CI was determined from the EDs counted per 5 min epoch in the baseline period of each patient (Fisher & van Belle, 1993; NIST/SEMATECH 2011). A test condition was considered as having provocative effect when the number of EDs during that test exceeded the upper limit of the 95% CI; inhibition was considered when it was below this interval. The 95% CI accounts for the spontaneous fluctuation of the EDs in the baseline period of each patient. The normality of the data distribution was assessed using the Kolmogorov-Smirnoff test. We used the Wilcoxon test to compare the occurrence of EDs among the baseline period, sleep, and the whole period of cognitive tasks.

To compare the results obtained with the arbitrary and the statistical method, and among the different categories of cognitive tasks, Fisher's exact test was used. Data analysis was done using MATLAB 7.6 software (MathWorks, Natick, MA, U.S.A.).

The primary end point of this study was thus undertaken to establish, with exact statistical methods, the modulation (provocation and inhibition) of ED in JME by cognitive tasks as compared with standard provocation methods. The secondary end point was to measure the occurrence of epileptic seizures during a prolonged video documented exposition of an unselected group of JME patients to a standardized rigorous protocol of multimodal activation.

Results

Modulation of the EDs

EDs were present during the baseline period in 31 patients (52%). Of the 29 patients (48%) with normal EEG studies in the baseline period, 9 had EDs during sleep. Considerable spontaneous fluctuation in the occurrence of EDs was observed in the baseline periods (Fig. 1).

The modulation of the EDs during the different conditions is summarized in Table 3.

Cognitive tasks had provocative effect in 13 patients (22%) according to the arbitrary method, and 11 patients (18%) using the statistical method (p = 0.8). Of the 31 patients who had EDs in the baseline period, cognitive tasks had inhibitory effect in 29 patients (94%) according to the
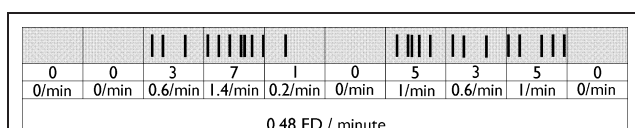
Figure 1.

Spontaneous fluctuation of the EDs. The black vertical bars in the upper line correspond to EDs occurring during the baseline period of 50 min (horizontal time axis) in one of the patients. This is segmented in 10 epochs of 5 min each, equal to one test period. Second line: numbers of EDs occurring in each epoch. Third line: number of EDs/min in each epoch. The mean frequency of the EDs in the baseline period is 0.48/min. This evens out the spontaneous fluctuations. Therefore, with application of the arbitrary method (twice, respectively half of the baseline mean frequency) 4 epochs would be considered "inhibited," and 3 would be considered as "provoked," although they are just part of the baseline.

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Table 3. Number of patients in which the different conditions had provocative or inhibitory effect on the occurrence of EDs, as concluded by the arbitrary and the statistical method

Conditions	Modulation	Method of data analysis		
		Arbitrary (%)	Statistical (%)	p-Value
CTs	Provocative	13 (22)	11 (18)	0.8
	Inhibitory	29 (94)	9 (29)	<0.0001
HV	Provocative	15 (25)	13 (22)	0.8
	Inhibitory	9 (29)	1 (3)	0.01
IPS	Provocative	8 (13)	6 (10)	0.77
	Inhibitory	17 (55)	2 (6)	0.0001
Sleep	Provocative (n = 54)	18 (33)	11 (18)	0.19
	Inhibitory (n = 26)	11 (42)	3 (12)	0.03

CT, cognitive task; HV, hyperventilation.

Percentages for the provocative effects are calculated from the total number of patients (n = 60), whereas for the inhibitory effect percentages are calculated from the number of patients who had EDs in the baseline period (n = 31).

Figure 2.

Number of patients who had statistically significant provocative (**A**) and inhibitory (**B**) effects in the different categories of cognitive tasks.

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arbitrary method, and in 9 patients (29%) according to the statistical method (p < 0.0001).

Figure 2 shows the modulating effects according to the different types of cognitive tasks. There was no significant difference between the categories of cognitive tasks: action programming versus thinking activity; visuomotor/spatial versus linguistic functions concerning the number of patients with provocative or with inhibitory effect (p > 0.08). Four patients had EDs provoked by linguistic tasks, two patients by spatial tasks, and four patients by tasks in both of these categories.

To assess the global effect of cognitive tasks, we compared the whole period of cognitive tasks (all tests, all epochs) with the va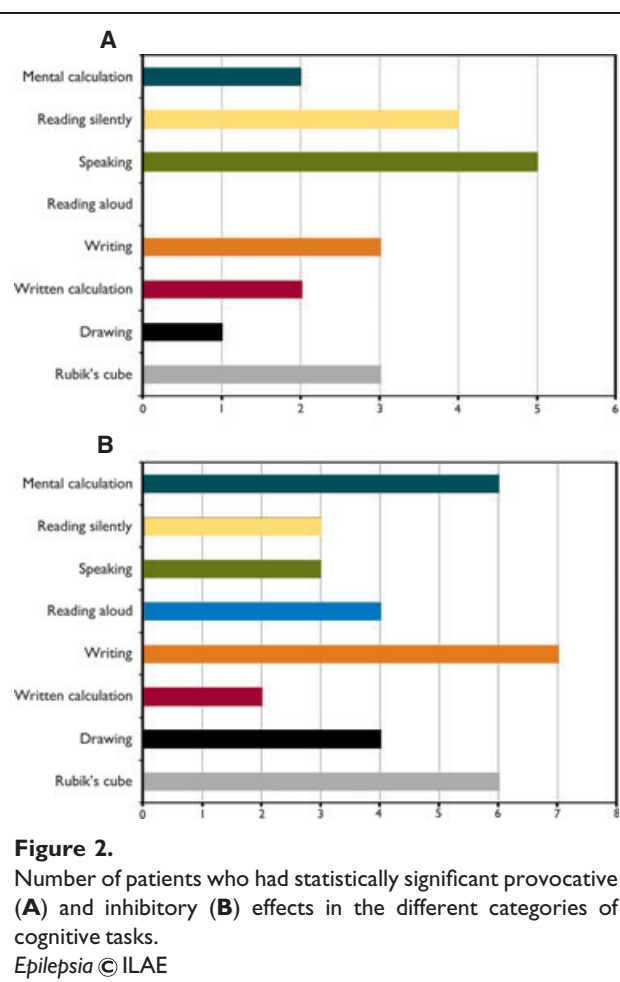lues from all epochs in the baseline period, for each patient. We found a significant increase in EDs for the whole period of cognitive tasks in one patient, while a significant decrease was found in six patients (66% of the patients who showed significant inhibition during the cognitive tasks). Seven of the nine subjects with statistically significant inhibition showed it during all types of cognitive tasks.

There was no significant difference between the rate of provocation among patients with (26%) and without (10%) EDs in the baseline period (p = 0.18). In the group of patients who had EDs in the baseline (n = 31), the number of patients with provocation (eight patients; 26%) and inhibition (nine patients; 29%) was very similar, when the spontaneous fluctuation was accounted for. *Photoparoxysmal response (PPR)* is the most well-known reflex epileptic trait common in JME. Twenty patients (33%) had PPR in the history. During the video-EEG recordings of this study, PPR (Kasteleijn-Nolst Trenité et al., 1999; Noachtar et al., 1999; Kasteleijn-Nolst Trenité et al., 2001) was observed in 14 patients (23%). When comparing the occurrence of EDs during IPS with the baseline period, IPS had a provocative effect in eight patients (13%) using the arbitrary method, and in six patients (10%) using the statistical approach

(p = 0.77). One patient without EDs in the baseline period had EDs reproducibly provoked by IPS. Decrease in the occurrence of EDs during IPS was concluded in 17 patients (55% of the patients with EDs in the baseline period) using the arbitrary method, and in two patients (6%) using the statistical approach (p = 0.0001).

Eye closure sensitivity

Nine patients (15%) had eye closure sensitivity.

Hyperventilation

Hyperventilation had a provocative effect on EDs in 15 patients (25%) based on the arbitrary method, and in 13 patients (22%) based on the statistical approach (p = 0.8). Hyperventilation had an inhibitory effect in nine patients (29% of the patients with EDs in the baseline period) using the arbitrary method, and in one patient (3%) using the statistical approach (p = 0.01).

Sleep

Fifty-four patients fell asleep (stages 1–3 non-REM sleep) during the recording (Iber et al., 2007). Sleep had provocative effect in 18 patients (33% of the 54 patients) based on the arbitrary method, and in 11 patients (18%) based on the statistical approach (p = 0.19). Twenty-six patients fell asleep of the 31 who had EDs in the baseline period. Inhibitory effect of sleep was concluded in 11 of these 26 patients (42%) based on the arbitrary method, and in three patients (12%) based on the statistical approach (p = 0.03).There was no statistically significant difference among the conventional provocation methods (hyperventilation, IPS), sleep, and the cognitive tasks (p > 0.2) concerning the number of patients with provocation of EDs.

Precipitation of seizures

EDs and seizures are different classes of epileptic events that do not necessarily occur in parallel. We therefore looked at recorded seizures separately.

Absence seizures were recorded in four patients: during baseline period in one and during hyperventilation in three.

Myoclonias (Fig. S1) were recorded in 12 patients (Fig. 3): during baseline period (3), hyperventilation (2), IPS (2), speaking (3), reading (2), playing with Rubik's cube (3), writing (2), mental calculation (1), and sleep (1). Seven patients had myoclonia during several test conditions/provocation methods.

Surprisingly, we found no consistent relation between type of task (manual vs. orofacial) and location of myoclonias. Orofacial myoclonia was observed in three patients: during language-related tests in one patient, during action-programming tests in the second patient, and during both types in the third patient. Upper limb myoclonia (recorded in six patients) was also observed during both of these test groups (language-related tasks: three patients; action-
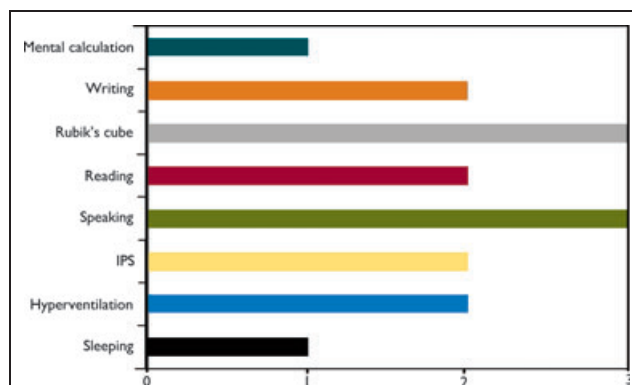

Figure 3.
Number of patients who had myoclonus during different provocation methods.
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programming tests: two patients). One patient had upper limb myoclonia during IPS.

There was no significant difference among the investigated reflex epileptic traits (groups of cognitive tasks) concerning the number of patients with myoclonia. Four patients had myoclonia during linguistic tasks, two patients during spatial tasks, and one patient during both of these categories. During the cognitive tasks myoclonia occurred in 10 patients. During the baseline period myoclonia were observed in only three patients (p = 0.07). This trend was not observed for the conventional provocation methods (two patients with myoclonia) (p = 1).

Myoclonia was seen more often among the patients with EDs in the baseline period (seven patients) than among patients without EDs in the baseline period (one patient; p = 0.05).

Influence of AEDs and of the therapeutic effect

Of the four patients who were not taking any AED, one had EDs triggered by cognitive tasks (writing). Conventional provocation methods have not modulated the EDs in these patients, and none of them had seizures during the recording. Of the seven patients who were taking inappropriate AEDs, six had EDs at baseline. Significant provocation during cognitive tasks was observed in only one of these patients, whereas five patients had provocative effect during the conventional methods. Inhibition during cognitive tasks was observed in three of these patients. Three of the seven patients had seizures during the recording: two patients had both absence (during hyperventilation) and myoclonia (during cognitive tasks); one patient had myoclonia during IPS. Although these numbers were too low to perform a statistical comparison, one could observe a trend for higher incidence of provocation during the conventional methods among the patients taking inappropriate AEDs as compared with the rest of the patients.

There was a trend for higher incidence of provocation by conventional methods among the patients who were not seizure free (13 of 25 patients; 52%) as compared with the seizure-free patients (9 of 35 patients; 26%) (p = 0.057). There was no significant difference concerning the modulation (provocation and inhibition) during CTs between the seizure-free patients and those who were not seizure-free.

DISCUSSION

Using the previously published, arbitrarily defined criteria for modulation of EDs by cognitive tasks (Matsuoka et al., 2000, 2005; Mayer et al., 2006; Guaranha et al., 2009) our data seem to indicate a similarly high (94%) occurrence of inhibition in patients with JME. However, when we accounted for spontaneous fluctuations by calculating the 95% CI in the baseline period, the occurrence of inhibition was much lower (29%). Our data indicate that although significant inhibition of EDs is demonstrable in patients with JME, most of the previously published high incidence of inhibitory effect is actually explained by spontaneous fluctuations of the EDs. Conversely, there was no significant difference between the incidences of provocation calculated using the arbitrary and the statistical method. This suggests that doubling of the rate (EDs/time) can indeed be considered a useful indicator of provocation in most cases of JME.

The arbitrary method calculates the rate of the EDs both from the long baseline period and from the much shorter time of exposure to the provocation method. This inequality makes the simple comparison (>200%; <50%) less reliable as it evens out the spontaneous fluctuation of the EDs in the baseline period. Especially inhibition is overestimated by the arbitrary method. A possible explanation of this comes from the "dynamics" of occurrence of EDs in the baseline period. We observed that EDs occur in "clusters," giving "values" in a baseline time-epoch and then stopping for a period of time (zero values in the following time-epochs; see Fig. 1). This pattern shows that cessation of EDs for a shorter period can occur spontaneously and does not necessarily mean an external suppression of the EDs. However, the arbitrary method calculates the rate of the EDs for a longer period, giving a relatively high "mean rate." This makes the arbitrary method biased toward more "false inhibition" than "false provocation" results.

Of course we cannot exclude that there was a fluctuation of the EDs also within the 5-min period (i.e., the time-epoch) of the test. We assessed the overall effect of a cognitive task (during the whole test period of 5 min) by comparing this with the normative range obtained from a baseline period 10 times the test period (i.e., 50 min).

The question remains open whether the observed inhibitory effects are specific to the various cognitive tests applied. That seven of nine subjects with inhibition showed it during all cognitive tests seems to indicate a mainly non-specific effect of the cognitive activation. It even cannot be excluded that inhibition of EDs is caused by increased attention or alertness only. To decide this question it would be necessary to introduce test periods with nonspecific increase of alertness, and this was not done here.

In our series, provocation by language-related tasks and by praxis was found in a similar number of patients, showing that these reflex epileptic traits were equally represented in our patient group. Therefore, our data further support the heterogeneity of JME. Defining patient-specific external triggers (modulators) of the EDs could contribute to further specifying clinical/electrographic endophenotypes, which in turn could yield more accurate diagnosis and possibly better, patient-tailored therapeutic options (Guaranha et al., 2011).

Myoclonia was observed more often among the patients with EDs in the baseline period than among patients without EDs in the baseline period. This could reflect the effect of medication in the group without EDs in the baseline period. Because the patients were sleep deprived before the recording, and the long baseline period (50 min) was recorded after awakening from sleep (if patients fell asleep during the start of the recording), it is reasonable to assume that only patients with a thorough effect of AED did not have EDs in the baseline period.

Given the well-established relation of photosensitivity to JME, it may be surprising that provocation of myoclonia by IPS was seen in only two patients, and of PPR in only 14 (23%) of 60 patients with this syndrome. However, the diagnosis of photosensitivity is rarely based on only one EEG investigation (Wolf & Goosses, 1986; Lu et al., 2008). Twenty (33%) of the patients with previous EEG investigations had been diagnosed as photosensitive. Not all photosensitive patients demonstrate a PPR in every EEG, and there are three reasons that the patients in this study are less likely to show PPR in the study investigation: (1) the average age of 28 is above the peak age for PPR; (2) 82% were treated with an adequate AED; and (3) 58% were seizure free. The absence of a PPR probably to a considerable extent reflects successful treatment.

PPR is only defined based on qualitative features of the EDs during (and following immediately) the stimulus (Waltz et al., 1992; Noachtar et al., 1999). This definition does not consider the possible occurrence of the EDs during the baseline, thus not taking care of the possibility that an ED occurring during IPS is actually not caused by it (i.e., it is coincidental). In our study only half of the patients with PPR showed a significant increase in the occurrence of EDs during IPS as compared with the baseline. Interpreting as PPR those cases in which occurrence of EDs during IPS is coincidental might contribute to the poor association between PPR and the clinical photosensitivity. The recently proposed nomenclature and classification for EEG phenomena during IPS introduced the term "activation of preexisting epileptogenic area," mentioning that it is questionable

whether this should be considered a PPR (Kasteleijn-Nolst Trenité et al., 2001). However, the authors do not specify the precise criteria for using the term in this situation. Our findings advocate for adding a quantitative criterion for defining the PPR in cases with EDs in the baseline EEG: an increase of at least 2 times compared with the baseline, when ''spontaneous'' EDs are also present in the ''unprovoked'' period.

Divergent findings in the literature about the efficacy of various CTs, and the types of myoclonia precipitated seem to be due mostly to differences in the test protocols. The protocol of Matsuoka et al. (2000) was highly effective to detect the responses that are subsumed under the term of praxis induction (Inoue et al., 1994), precipitating myoclonia usually in the upper limbs, whereas it seemed to be much less able to detect perioral reflex myoclonia. Mayer et al. (2006) revised the protocol, introducing more extensive linguistic testing and found perioral reflex myoclonia precipitated by language tasks in nine (35%) of their patients with JME. However, they studied an enriched population of patients with JME who in a questionnaire had indicated the possible occurrence of reflex myoclonia by praxis and language. Guaranha et al. (2009) using the same protocol with an unselected group of 76 patients with JME observed cognitive task–provoked myoclonia in 13 patients (17%), five of whom had perioral reflex myoclonia (two with praxis-induced brachial myoclonias in addition). Like in the present study, cognitive tasks were more provocative of myoclonia than any other provocation method.

Conclusion

In conclusion our data indicate that spontaneous fluctuation of EDs accounts for most of the previously described inhibitory effect of cognitive tasks. The remaining observed inhibitory effects are not necessarily task-specific but seem rather to be related to cognitive activation as such. Even a completely nonspecific effect of increased alertness seems possible. In contrast, the provocative effect of CTs seems to be task-specific. The previously defined arbitrary criterion for the provocative effect (i.e., a >2 times increase compared with the baseline) gives results similar to those of the statistical approach. This can be relatively easily implemented also in standard recordings, and the criterion of quantitative increase of EDs should be considered also when interpreting the consequence of conventional provocation methods and should be included in the definition of the PPR for the cases where ''spontaneous'' EDs are also present in the recording. Cognitive tasks were as effective as the conventional methods in provoking EDs but more effective in precipitating myoclonia. The investigated reflex epileptic traits were similarly effective in provoking EDs/precipitating myoclonia. As a practical consequence, extension of the standard EEG protocol with a series of cognitive tasks should be considered in cases where the differential diagno-

sis of JME is difficult. Several data indicate that in JME, the susceptibility to show EDs and cortical excitability are highest in the morning (Labate et al., 2007). Therefore, we have performed all the recordings in the morning, following sleep deprivation.

Our findings yield further knowledge on the mechanism of ictogenesis in patients with JME, and have potential clinical significance concerning the more precise, quantitative criteria for interpreting the results of provocation methods also in a standard, clinical setting.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Myoclonus during a cognitive task (Rubik's cube).

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