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Cognitive tasks as provocation methods in routine EEG: a multicentre field study

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ABSTRACT

Objective. This study aimed to analyse the effect of neuropsychological activation methods on interictal epileptiform discharges, compared to standard activation methods, for both focal and generalized epilepsies.

Methods. This was a multicentre, prospective study including 429 consecutive EEG recordings of individuals with confirmed or suspected diagnosis of epilepsy. Neuropsychological activation included reading aloud in foreign and native language, praxis and a letter cancelation task (each with a duration of three minutes). After counting interictal discharges in three-minute time windows, activation and inhibition were assessed for each procedure, accounting for spontaneous fluctuations (95% CI) and compared to the baseline condition with eyes closed. Differences between generalized and focal epilepsies were explored.

Results. Interictal epileptiform discharges were present in 59.4% of the recordings. Activation was seen during hyperventilation in 31%, in at least one neuropsychological activation method in 15.4%), during intermittent photic simulation in 13.1% and in the resting condition with eyes open in 9.9%. The most frequent single cognitive task eliciting activation was praxis (10.3%). Lasting activation responses were found in 18-25%. Significant inhibition was found in 88/98 patients with baseline interictal epileptiform discharges, and was not task-specific.

Significance. Adding a brief neuropsychological activation protocol to the standard EEG slightly increased its sensitivity in patients with either focal or generalized epilepsy. However, in unselected epilepsy patients, this effect seems only exceptionally to result in ultimate diagnostic gain, compared to standard procedures. From a diagnostic perspective, cognitive tasks should be reserved for patients with a suspicion of cognitive reflex epilepsy/seizures and probably require longer exposure times. Further research is needed to explore potential therapeutic applications of the observed inhibition of interictal epileptiform discharges by cognitive tasks in some patients.

Key words: epilepsy; electroencephalography; reflex seizures; neuropsychological activation; external modulation; interictal epileptiform discharges

Unpredictability is considered one of the most disabling characteristics of epileptic seizures. On the other hand, it is well-known that some intrinsic and extrinsic factors influence the individual seizure threshold [1, 2].

Most epilepsy patients describe different seizure facilitators: stress, sleep deprivation, fatigue, and poor adherence to antiseizure medication (ASM) being the most frequently reported [3]. Specific sensory precipitating factors, besides intermittent photic stimulation (IPS) in photosensitive generalized epilepsies, are less frequently identified. Moreover, seizures precipitated by other sensory stimuli such as aromas, music, or even just a slight touch have been described mostly in focal epilepsies [4].

Some patients reported seizures when they are exposed to specific complex cognitive tasks such as arithmetic, playing cards, drawing, writing, and finger manipulation [4]. Most of these activities have been included in the concept of praxis induction (PI) defined as seizure precipitation by complex, cognition-guided executive tasks [5, 6]. In addition, several cases of reflex seizures were reported by reading and speaking [7, 8]. Interestingly, the same factors may also have inhibitory effects [9].

Mixed effects (mostly inhibitory) of some cognitive tasks on interictal epileptiform discharges (IEDs) were described in a series of 91 unselected epilepsy patients with frequent IEDs at baseline recording [10], but restricted statistical analysis precluded a significant conclusion, and these results were considered not consistent. Applying a detailed neuropsychological activation (NPA) method, Matsuoka *et al.* [11] reported a provocative effect in 8% of patients with epilepsy, while an inhibitory effect was observed in 64% of patients with IEDs at baseline, awake EEG. Both provocative (22-38%) and inhibitory (90-94%) responses were consistently described in later studies in patients with juvenile myoclonic epilepsy (JME) [12, 13], although figures are lower (18% provocation and 29% inhibition) when applying a statistical method to ascertain significant variation [13]. In that multicentre study of JME, after controlling for spontaneous fluctuations of IEDs, we found that activation by NPA occurred as frequently as that with hyperventilation (HV) and IPS; moreover, for several patients, NPA was the most effective stimulation [13]. In consequence, we wondered whether cognitive stimuli should become a part of the standard EEG protocol in epilepsy or suspected epilepsy patients. Besides, the effect of cognitive stimuli on IEDs in focal epilepsies needs clarification, since most relevant studies on the topic dealt only with generalized epilepsies [14].

Therefore, we carried out a prospective multicentre field study of an unselected cohort of epilepsy patients, in which a limited number of cognitive tasks were included in the standard EEG protocol. The primary aim of the study was to compare the effect of NPA and standard stimulation methods in generalized and focal epilepsies, through the modulation (including either activation or inhibition) of IEDs.

Methods

Study design and population

Participant centres included 10 EEG laboratories from Brazil, Denmark, Guatemala, Lithuania, Turkey, and Uruguay.

All consecutive individuals with established or suspected diagnosis of epilepsy, submitted for an EEG investigation during the study period, were prospectively assessed for inclusion.

Both patients on ASM and without pharmacological treatment were included.

Exclusion criteria were: age below eight years or any condition preventing the application of the predefined set of cognitive tasks during the EEG recording.

All participants signed informed consent before inclusion. In the case of children, at least one parent was requested to sign for informed consent for inclusion. The Ethics Committees of all participating centres approved the present study.

Procedures

Electrode placement was performed according to the international 10-20 system. Our EEG protocol is summarized in *table 1*, including the flow of the procedure and duration of each condition. All cognitive tasks (CT) were applied in 3-minute time windows while HV and IPS lasted 5 minutes and around 4 minutes, respectively, according to standard protocols. For the eyes open-eyes closed (EO-EC) condition, to investigate eye closure sensitivity (ECS), the number of trials was considered more relevant than duration, as this EEG response is time-locked to eye closure. Furthermore, as this can occur with a delay of 1-4 seconds and last up to 4 seconds, a minimum 10-second interval before a new EO/EC trial was pre-defined. Therefore, a total period of at least 60 seconds was recorded for this condition.

The reading task was performed both in a foreign language (English in most centres, and Portuguese in only one country, in which English was a widespread second language) and in the patients' native language, in 3-minute periods separately. The task consisted of reading aloud texts of previously standardized moderate difficulty. Silent reading was not additionally

Table 1. EEG protocol: sequence of conditions applied.

Condition	Duration
Baseline (rest, eyes closed)	15 min
Rest, eyes open	5 min *
Opening and closing eyes (≥10 sec) x 6 times	≥ 1 min
Hyperventilation	5 min *
Interval	2 min
Intermittent photic stimulation **	4 min #
Interval	2 min
Reading foreign language text aloud	3 min
Interval	2 min
Reading native language text aloud	3 min
Interval	2 min
Praxis task (Tangram / Rubik cube)	3 min
Interval	2 min
Letter cancellation task	3 min

*Interictal epileptiform discharges were counted during the last 3 minutes. **1,2,8,10,12,15,18,20,25,30,40,50 and 60 Hz –5 sec eyes open, 7 sec eyes closed, 5 sec intervals. Counting was stopped if photoparoxysmal response occurred, and restarted at the other end of the frequency range. #Interictal epileptiform discharges were counted during the first 3 minutes.

included, as we needed to ensure precise temporal delimitation of the effective task period in order to count spikes.

PI was evaluated either through the use of a Rubik's cube or a Tangram (type of Chinese geometrical puzzle consisting of a square cut into seven pieces which can be arranged to make various other shapes).

Although both reading and praxis tasks were performed by all patients, in three centres (54 patients), only the foreign language text was applied in the reading task, and one centre (10 patients) only used the text in their native language.

As any possible effects of CT could be caused by non-specific influences of increased attention [13], we included a letter cancellation task (letters A, I, B and W in this order were cancelled on a prepared sheet) as a condition assessing attention, outside the context of more specific CT.

Sleep recording was not part of the protocol.

Demographic and clinical data were obtained from the patients themselves and their clinical charts; in the case of children, from the parent or the relative in charge during the study. Clinical diagnosis was based on the clinical history, including previous and current EEG recordings, and neuroimaging when available.

Data analysis

IEDs and ictal EEG activity were visually identified by trained clinical neurophysiologists, and marked in the record following predefined criteria. IEDs were defined according to the criteria of Gloor (spike, sharp wave, polyspike, spike/sharp wave-slow-wave complexes and polyspike-and-wave complexes). Seizures were identified through electroclinical correlation; recognition of ictal EEG patterns included rhythmic activity with evolution in time, space or morphology, or an electrodecremental pattern. In the case of bursts of spikes or sharp waves, each graphoelement was separately considered for counting, to provide useful data for comparison among conditions and patients, as previously described [13]. IED counting was then performed in a predefined time window, lasting for 3 minutes for each study condition (*table 1*), with the exception of the EO-EC condition. Since, in most cases, this was less than 3 minutes (at least 1 minute), definition of IED activation was more demanding. Similar considerations apply to the analysis of potential IED activation during inter-task periods (lasting 2 minutes).

As in previous studies [13, 15], baseline frequency of IEDs was calculated as the mean and 95% confidence interval (CI) of the five, consecutive, 3-minute-duration time windows during standard baseline conditions, with the patient awake and resting with closed eyes. Additionally, to improve the accuracy of the 95% CI estimation, a bootstrapping method was applied (random model, 5,000 repetitions). Bootstrapping pools the data to simulate different possible combinations (resampling) and provides a more accurate estimation of the original sample distribution. Whenever not otherwise specified, data is presented and discussed based on these statistical estimates.

Significant activation or inhibition of IEDs under a certain condition was defined to be present when the number of IEDs during that 3-minute period was above or below the individual 95% CI for baseline IEDs, respectively. Seizures or subclinical ictal EEG patterns (ictal EEG patterns as described above, but without overt clinical signs or symptoms), arising during a particular condition were also considered as activation. For those standard activation procedures lasting more than 3 minutes (HV, IPS), an operational definition of counting IEDs in a 3-minute time window was stated (first 3 minutes for IPS, last 3 minutes for HV and the resting period with eyes open) (*table 1*).

Inhibition of IEDs under any condition compared to baseline can only be evaluated in the subset of patients with baseline IEDs. Statistically significant inhibition was explored for conditions lasting at least 3 minutes, and in patients with baseline IEDs and a lower limit of their 95% CI of at least 1.0. Thus, inhibition was not assessed for inter-task periods and the EO-EC condition.
To investigate associations among the different variables under study, Pearson´s chi-square test, Student´s t-test, or Cox-regression analysis (a=0.05) were applied when appropriate. Statistical analysis was performed with the *Statistical Package for Social Sciences* (SPSS Version 21.0).

Results

The main demographic and clinical data of the 429 participants are summarized in *table 2*. Individuals not receiving ASM at the time of the study accounted for 11% of the study sample, while 46% were under monotherapy.

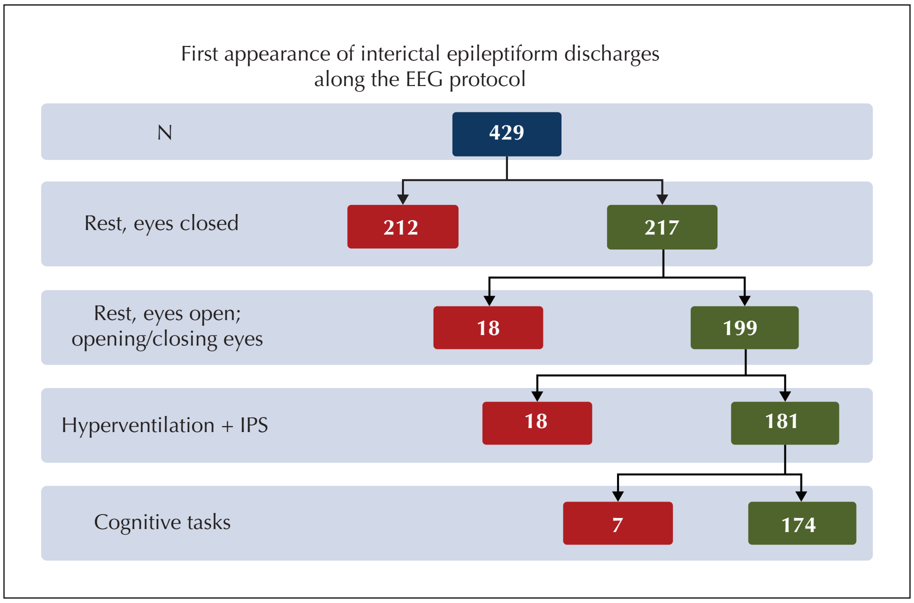
EEG recording

IEDs were present during the EEG protocol in 255 recordings (59.4%): 148/249 focal epilepsies, 96/152 generalized epilepsies, and 11/28 patients with epilepsy of unknown type. Seizures were recorded in six patients: three during IPS (one with JME, one right frontal lobe and one right temporal lobe epilepsy), one at the end of HV (focal epilepsy with mesial temporal sclerosis), one immediately after the praxis task (JME patient) and another patient with focal epilepsy and right MTS after the reading task in her native language. Recorded seizures mostly occurred in young adults (patients aged from 16 to 37 years).
The temporal sequence of the first appearance of IEDs/ictal patterns in all EEG recordings, according to the study protocol, is summarized in *figure 1*. Seven patients presented IEDs exclusively during NPA, meaning that in only 1.6% of the total sample, NPA effectively increased the EEG diagnostic yield. No association was found with age at the time of the study (9-50 years old), or epilepsy type (three generalized, three focal, one unknown).
Provocative and inhibitory responses to the different tasks or conditions are shown in *table 3*. In the present study, bootstrapping had the effect of narrowing confidence intervals, allowing to identify significant differences in more test conditions and cases than standard 95% CI calculation. Regarding standard EEG activations, HV was the condition most frequently eliciting IED activation (31.0%). On the other hand, inhibition could be assessed in 98 EEG recordings according the

▼ **Table 2.** Demographic and clinical features of the individuals included in the study.

n	429					
Age (years)	32.4+15.5 (8-83)					
Sex ratio	191 M: 238 F					
Epilepsy Type	**Etiology**					
	Genetic		**Structural**		**Unknown**	**All**
Focal	14		139		96	249
	CECTS	13	MTS	29		
	COE (GT)	1	Tumors	13		
			TBI	10		
			Vascular	9		
			MCD	9		
			Other	69		
Generalized	132		0		20	152
	JME	52				
	JAE	22				
	CAE	11				
	Other	47				
Unknown epilepsy type or suspected epilepsy	0		0		28	28

CECTS: childhood epilepsy with centrotemporal spikes; COE(GT): childhood occipital epilepsy (Gastaut-type); JME: juvenile myoclonic epilepsy; JAE: juvenile absence epilepsy; CAE: childhood absence epilepsy; MTS: mesial temporal sclerosis; TBI: traumatic brain injury; MCD: malformation of cortical development.



■ **Figure 1.** Suppression of interictal epileptiform discharges (IEDs) during the sequence of tests. EEG recordings without IEDs are depicted in green and those with IEDs are depicted in red.

aforementioned methodological criteria, and corresponding to 71 patients with focal epilepsy, 25 with generalized and two with epilepsy of unknown type. Statistically significant inhibition of IEDs was observed in 88/98 patients. Standard activation methods were the less likely conditions to unveil inhibitory phenomena.

Modulation of IEDs by cognitive tasks

A provocative effect of at least one cognitive task was seen in 67 cases (15.6%): 20/132 IGE and 47/249 focal epilepsy patients. The most frequent single cognitive task eliciting activation was praxis. Specific or exclusive activation by a single cognitive task was exceptionally found in three cases.

A significant decrease of IEDs by at least one cognitive task was found in 82 cases: 23 patients with generalized epilepsy, and 59 patients with focal epilepsy. Inhibition under all cognitive tasks applied (reading, praxis and cancellation) was observed in 38% of patients, and most of them also showed an inhibitory response during the resting state with eyes open.

In 13 cases, both activation and inhibition were elicited in the same patient by different tasks. Opposite effects of praxis and language tasks accounted for the three IGE cases with mixed effects. In focal epilepsies, whenever the cancellation task had an inhibitory effect, the only cognitive task for which an opposite activation effect on IED was observed was praxis, which occurred in six cases.

From a global perspective, in a third of unselected epilepsy patients, cognitive tasks may have a modulatory effect on IEDs.

Delayed responses

Activation responses persisted after cessation of the stimuli or task in 22% of cases with IED activation by HV, in 18% by IPS, 27% by praxis, 24% and 18% by reading in foreign and native language texts, respectively, and 25% by the cancellation test.

An additional set of patients showed a delayed increase in IEDs, arising during the inter-task periods. This late activation was found in five cases after HV, in four after IPS, in 19 after reading aloud, in 13 patients after the praxis task, and in six after the letter cancellation task (end of the whole protocol). Furthermore, in three of these EEG recordings, IEDs were exclusively present during a post-stimulation period: after IPS (1), praxis (1), and the letter cancellation task (1). As described above, two out of the six seizures recorded occurred in the 2-minute time lapse after the end of a cognitive stimulation task in patients with IEDs at baseline.

Either a sustained or a delayed increase in IEDs during at least one inter-task period was seen in 38 cases, and this response was not associated with epilepsy type.

No information on a prolonged or delayed inhibitory effect can be derived from this study, as inter-task periods were shorter than the 3-minute time interval established for statistical analysis.

▼ Table 3. Statistically significant activation and inhibition of interictal epileptiform discharges (IEDs) in different conditions, based on the two statistical methods applied.

Method of comparison		INHIBITION of IEDs					CONDITION		ACTIVATION of IEDs				Method of comparison	
Relat diff*	Abs diff	95% CI standard		[0,5-6]95% CI Bootstrap					95% CI Bootstrap		95% CI standard		Abs diff	Relat diff
%	n	%	n	%	n	N [1]		N [2]	n	%	n	%	n	%
175	42	24.7	24	68.0	66	97	**Resting state with eyes open**	426	42	9.9	30	7.0	12	40
							Opening and closing eyes x6	424	26	6.1	17	4.0	9	53
280	14	5.1	5	19.4	19	98	**Hyperventilation**	429	133	31.0	114	26.6	19	17
320	32	10.3	10	43.3	42	97	**Intermittent photic stimulation**	428	56	13.1	46	10.7	10	22
235	40	17.3	17	58.2	57	98	**Praxis**	429	44	10.3	36	8.4	8	22
175	42	25.3	24	69.5	66	95	**Reading, foreign language**	419	21	5.0	14	3.3	7	50
292	38	16.7	13	65.4	51	78	**Reading, native language**	375	23	6.1	20	5.3	3	15
200	42	21.7	21	64.9	63	97	**Letter cancellation task**	428	32	7.5	23	5.4	9	39

Abs diff: absolute difference (difference in number of cases with significant activation/inhibition according to the statistical method applied). Relat diff: relative difference (percentage increase of significant activation/inhibition applying Bootstrap, compared to standard 95% CI). N[1]: number of individuals exposed to the task among those with IEDs at baseline.N[2]: number of individuals exposed to the task.

Modulation of IEDs in the clinical context

Modulation of IEDs following different commands or tasks was seen in 57% and 52% of patients with generalized and focal epilepsies, respectively. Activation by any condition included in the protocol was elicited in 54% of generalized and 41% of focal epilepsy patients. Activation of IEDs by IPS was more frequently seen in patients with a diagnosis of generalized epilepsy (*table 4*).

Among patients with focal epilepsies, a strong localization hypothesis could be provided in 178 cases: 117 had temporal, 41 frontal, four parietal, and five occipital lobe epilepsies; in the remaining 20 patients, more than one lobe was involved. In these patients with focal epilepsies, activation of IEDs during either baseline recording with eyes open or IPS was marginally associated with a frontal lobe origin. No significant differences were found for inhibitory responses among different epilepsy locations (*table 5*), although a marginal association could be postulated between temporal lobe epilepsies and inhibition through a reading task in the native language.

Based on multivariate analysis for prediction of the epilepsy type based on these EEG modulation patterns, performed in the subset of 255 patients with abnormal EEG recordings, the model (logistic regression, Cox-Snell R^2=0.20) only retained IED activation by IPS (p=0.001) in association with generalized epilepsy. With marginal significance, activation by reading a text in the native language (p=0.034) and IED inhibition during the letter cancellation test (p=0.046) predicted focal epilepsy. These EEG data allowed a correct allocation of epilepsy type in 81.7% of focal epilepsies and 57.3% of generalized epilepsies.

Discussion

It has been largely agreed that routine EEG should include a baseline recording of at least 20 minutes, followed by activation procedures, usually HV and IPS, in order to improve epilepsy diagnosis [16]. Other potentially activating procedures are defined on an individual basis.

Applying this standard EEG protocol, the sensitivity of the first EEG to detect IEDs in a given patient with a history of seizures lies at around 50% (25-56%) [17]. We examined only one EEG recording per patient, including NPA, and the overall sensitivity was 59.4%.

Our study confirmed that HV is the most effective method to activate IEDs and that IPS is particularly effective in generalized epilepsies.

▼ **Table 4.** Activation and inhibition (bootstrap) of interictal epileptiform discharges (IEDs) in different conditions during the EEG recording, according to epilepsy type.

IED ACTIVATION						CONDITION	IED INHIBITION					
Focal (*n*=249)		Generalized (*n*=152)			Total #		Total #	Focal (*n*=71)		Generalized (*n*=25)		
n	%	n	%	p *	n		n	n	%	n	%	p *
24	9.6	14	9.2	0.134	42	**Rest, eyes open**	66	47	66.2	19	76	0.46
11	4.4	15	9.9	0.067	26	**Opening and closing eyes x6**						
75	30.1	55	36.2	0.14	133	**Hyperventilation**	19	15	21.1	4	16	0.77
21	8.4	35	**23.0**	**0.000**	56	**Intermittent photic stimuli**	42	33	46.5	9	36	0.48
32	12.9	12	7.9	0.055	44	**Praxis**	57	40	56.3	17	68	0.35
13	5.2	8	5.3	0.602	21	**Reading foreign language**	66	48	67.6	18	72	0.80
18	7.2	5	3.3	0.12	23	**Reading native language**	51	35	49.3	16	64	0.25
23	9.2	8	5.3	0.245	32	**Letter cancellation task**	63	47	66.2	16	64	1.00

Statistically significant associations are highlighted. *Pearson chi-square test, including as epilepsy type the three categories: focal, generalized, unknown. #Total number of cases showing activation/inhibition, including epilepsies with unknown type.

▼ **Table 5.** Response of interictal epileptiform discharge to different conditions in frontal and temporal lobe epilepsies.

	ACTIVATION					INHIBITION				
	Frontal (*n*=41)		Temporal (*n*=117)			Frontal (*n*=41)		Temporal (*n*=117)		
CONDITION	*n*	%	*n*	%	*p**	*n*	%	*n*	%	*p**
Rest, eyes open	9	21.9	11	9.4	**0.054**	7	17.1	35	29.9	0.15
Opening and closing eyes x6	3	7.3	6	5.1	0.70	9	21.9	30	25.6	0.68
Hyperventilation	18	43.9	47	40.2	0.72	5	12.2	7	6.0	0.31
Intermittent photic stimulation	9	21.9	10	8.5	**0.047**	6	14.6	23	19.6	0.64
Reading in foreign language	2	4.9	8	6.8	1.0	10	24.4	33	28.2	0.69
Reading in native language	5	17.8	10	9.1	0.54	4	14.3	28	25.4	0.07
Praxis	10	24.4	15	12.8	0.09	7	17.1	28	23.9	0.51
Letter cancellation task	5	12.2	13	11.1	0.78	11	26.8	30	25.6	1.0

*Pearson's chi square test.

Neuropsychological activation

Cognitive stimulation could be considered as the second most effective method if all three modalities are included (15.6% of patients).

Most studies evaluating the activation of ictal or interictal epileptiform activity by NPA were performed in patients with IGE, and particularly JME. The majority of these studies included a large subset of neuropsychological tasks in highly selected, small samples of patients with [18-20] or without [12, 21] clinically evident precipitant factors associated with cognitive or perceptual domains as inclusion criteria. Compared to HV sensitivity for the provocation of IEDs, some NPA protocols were found to be similarly effective, however, none of the single tasks were sensitive enough to make a difference in the whole EEG diagnostic yield [13, 22]. Accordingly, in the present study, either exclusive activation or inhibition by a cognitive task was seldom found.

From a different perspective, we observed that in some patients, the duration of the activation effect surpassed the duration of the stimuli or task; such a prolonged effect was more frequent for NPA. We can speculate that the complexity of the task, implying the recruitment of more extended brain networks and even the putative addition of emotional factors, could explain a lasting activation. In the case of a delayed increase in IEDs, a rebound effect due to post-task relaxation can be alternatively hypothesized. Although there is persistent or delayed modulation of IEDs following other interventions (olfactory stimulation) in patients with both focal and generalized epilepsy [15], a clear explanation is still lacking.

Praxis induction

Undoubtedly the most frequently effective NPA method, PI is the conceptual umbrella under which many different tasks involving visuospatial processing, motor planning, and usually a fine motor action as final output, in different combinations and complexity, are clustered. PI has been extensively described in JME patients [6, 12, 18, 23]. In terms of prevalence, our results are similar to those found in a previous study on unselected epilepsy patients [11]. On the other hand, the high prevalence in JME patients in earlier studies, including our own series, was not replicated, probably due to the much shorter exposure time in the present study, restricted to exposure times suitable for routine clinical EEG investigations.

The observation that PI was the most effective cognitive trigger of IEDs in our study should be considered with caution, as an additive effect of previous activations cannot be excluded, especially in view of the unexpected delayed responses observed in our study.

Reading

Most communications are focused on primary reading epilepsy, accounting for ictal recordings during prolonged exposure to reading in highly selected patients. Subclinical EEG activation may also appear without a significant delay from the reading task onset [24]. Although activation by language tasks has been clearly correlated with temporal or temporo-parietal lesions, some cases in generalized epilepsies have also been reported. Besides the reference of increased mean frequency of IEDs while reading or performing arithmetic tasks in 20 children with epilepsy, selected only on the basis of the frequency of EEG discharges at rest [25], systematic data on IEDs or seizure provocation by reading in otherwise unselected patients are lacking.

In the present study, modulation of IEDs by reading tasks was more frequently found in focal epilepsies. Interestingly, reading in the native language was associated with IED activation, while reading a text in a foreign language induced mostly inhibition of IEDs. Duration, difficulty, and emotional component of the reading task have been postulated as the main factors influencing the provocative effect in patients with primary reading epilepsy [1, 7, 8, 25]. Both texts were of a similar, moderate level of difficulty regarding the content and syntax; a better understanding and more personal experience regarding the content of the story could have explained the more provocative properties of reading in native language, while the stressful situation of trying to read aloud a text in a foreign language in public may have acted as an IED suppressor.

Inhibition and the role of attention

While task complexity, including decision-making and/or emotional involvement, have been related to IED activation, arousal and attention were hypothesized to underlie IED inhibition [13]. In the present study, we, therefore, included the letter cancellation test as a control condition that involves attention and executive function with minor language and motor components. This task produced inhibitory effects at the same magnitude as with other cognitive tasks.

Unexpectedly, the letter cancellation task also resulted in IED activation in 7.5% of our patients. Three possible explanations for this are: i) the cancellation test acted as true cognitive activation; ii) the effect of other cognitive tasks is non-specific itself, at least in patients without reflex epilepsies; and iii) this reflects a carry-over effect from previous tasks.

Through the present approach and from a global perspective, all cognitive tasks were more prone to inhibit than provoke IEDs. Inhibition was also frequently

observed when just recording the resting period with eyes open. Extended, mostly inhibitory brain responses to eye opening have already been described both in EEG and connectivity studies [26-29], favouring the hypothesis of a major role of attention.
To add even more complexity, mixed provocative and inhibitory effects in the same patient have been previously recognized [12, 22]. Opposite effects found on language and praxis tasks in some of our patients support a specific effect which may not be explained by simply using attention resources.

Limitations of the study

Methods to assess activation or inhibition of IEDs are debatable, and no consensus has been achieved. From the pivotal studies on the topic [11, 18], in which doubling the baseline IED frequency was considered as activation, to the recent statistical approach developed by our group [13], similar results were found regarding IED activation, while inhibitory responses were less frequent when spontaneous fluctuations of IEDs were taken into account. In the present study, we added a resampling method to increase the likelihood of identifying a truly significant difference, given that the number of individual sampling periods was low. This bootstrapping method proved to be more sensitive in identifying both activation and inhibition. In any case, both statistical approaches showed similar quantitative trends and qualitative associations.
A potentially relevant limitation of the study refers to task duration. Previous NPA studies on series of unselected or IGE cases describe a total duration of NPA between 10 and 35 minutes, while including 7-31 tasks (around one minute per task) [11, 21, 22]. In contrast, while our NPA lasted only 9 minutes, specific responses to specific tasks could have been better assessed through homogeneous 3-minute time lapses. In any case, in individual patients with clinically recognizable cognitive precipitation, it would be wise to test this relationship through more detailed, individualized and prolonged NPA protocols.
Another limitation that merits discussion is the potential influence of the chosen sequence of tests. The modulation of IEDs during one particular task may have been contaminated by carry-over effects from the preceding tasks. Given our findings, it would be interesting to develop further studies to explore in detail the lasting effects of each individual task on IEDs.
Finally, in our NPA protocol, all selected tasks required the patient to be alert and have eyes open. It might be interesting to consider the baseline condition with eyes open, rather than the resting state with eyes closed. In any case, this remains a question to be answered in future studies, as the 5-minute recording in the condition with eyes open is insufficient to derive statistical conclusions.

Conclusion

Adding a brief NPA protocol to the standard EEG, testing reading and visuomotor coordination, slightly increased its sensitivity in patients with either focal or generalized epilepsy. However, in unselected epilepsy patients, this effect seems to only exceptionally result in ultimate diagnostic gain, beyond that for standard procedures. From a diagnostic perspective, we would, therefore, recommend that cognitive stimulation is reserved for patients with a suspicion of cognitive reflex epilepsy, or with a history of seizures precipitated by different types of cognitive processes, using longer exposure times than those in the present study. Further research is needed to explore potential therapeutic applications of IED inhibition by cognitive tasks in some patients. In the era of precision medicine, individual patterns of IED activation and inhibition by different tasks and stimuli could be of use to design tailored strategies to avoid or abort seizures. ■

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Is activation of interictal epileptiform discharges specific to generalized epilepsies?

(2) What type of procedure may have an inhibitory effect on EEG epileptiform activity?

(3) Should we include cognitive tasks as a routine activation procedure in standard EEG recordings?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".