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Visual cortex hyperexcitability in idiopathic generalized epilepsies with photosensitivity: A TMS pilot study

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ABSTRACT

Background: The current understanding of the mechanisms underlying photosensitivity is still limited, although most studies point to a hyperexcitability of the visual cortex.
Methods: Using transcranial magnetic stimulation, we determined the resting motor threshold (rMT) and the phosphene threshold (PT) in 33 patients with IGEs (8 with photosensitivity) compared with 12 healthy controls.
Results: Eleven controls (92%) reported phosphenes compared with fifteen (46%) patients with idiopathic generalized epilepsy ($p = 0.015$). Phosphenes were reported more frequently among patients with epilepsy with photosensitivity (87.5%) than in patients with active epilepsy without photosensitivity (30.8%) ($p = 0.038$) and patients with epilepsy in remission without photosensitivity (33.3%) ($p = 0.054$); no differences were found between patients with epilepsy with photosensitivity and controls ($p = 0.648$). Resting motor threshold and phosphene threshold were significantly higher among patients with epilepsy (active epilepsy or epilepsy in remission without photosensitivity) compared to healthy controls ($p < 0.01$). Conversely, patients with active epilepsy and photosensitivity had significantly lower values than controls ($p = 0.03$).
Conclusions: The marked decrease in PT and the high phosphene prevalence in patients with IGE with photosensitivity indicate a regional hyperexcitability of the primary visual cortex.
Results of this study also suggest that the PT may serve as a biomarker for excitability in patients with IGE and photosensitivity.

1. Introduction

Idiopathic generalized epilepsies (IGEs) include many distinct epileptic syndromes and are thought to be the expression of a widespread hyperexcitability involving subcortical and cortical structures in both hemispheres, especially in thalamo-cortical circuitry. However, each seizure type characterizing an epileptic syndrome (typical absences, myoclonic jerks, and generalized tonic-clonic seizures, alone or in varying combinations and severity) involves a distinct hyperexcitable circuitry, which, in most instances, does not involve the whole brain [1]. The circuits involved may even change with age [1].

Photosensitivity is an abnormal sensitivity of the human brain in reaction to visual stimulation. It is a highly heritable electroencephalographic (EEG) trait characterized by the occurrence of spikes, spike–waves, and intermittent slow waves in response to visual stimulation [2]. Photosensitivity is a frequent feature of IGEs, with positive response to IPS reported to range from 7.5% in juvenile absence epilepsy to 100% in pure photosensitive epilepsy [3]. The current understanding of the mechanisms underlying photosensitivity is still limited, although most studies point to a hyperexcitability of the visual cortex [4–7].

Transcranial magnetic stimulation (TMS) has been used to noninvasively and directly assess cortical physiology and excitability *in vivo*, thus representing a fascinating method to study pathophysiological mechanisms underlying epilepsy in general and IGE in particular.

Transcranial magnetic stimulation of the motor cortex in epilepsy can assess cortical excitability by determining different parameters. Motor threshold (MT) represents the most easily recorded parameter. It reflects the excitability and the local density of a central core of excitatory interneurons and corticospinal neurons in the muscle representation at the primary motor cortex level, as well as the excitability of the target spinal motoneurons [8,9]. Resting MT (rMT) represents the physiological and methodological bases for more complex TMS assessments of cortical excitability, such as the evaluation of intra-cortical inhibition

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(ICI) or facilitation (ICF) patterns obtained by a paired-pulse paradigm [10]. Therefore, in addition to studies on ICI, ICF, and cortical silent period, the determination of rMT in patients with IGEs is essential for an overall assessment of motor excitability in this subgroup of epilepsy. Furthermore, the rMT can represent a parameter useful to test motor excitability in different conditions such as sleep or sleep deprivation both in healthy individuals and in patients with epilepsy [11].

More recently, TMS has been repeatedly used in patients with migraine to test occipital cortex excitability by measuring phosphene threshold (PT), which is inversely related to the overall level of visual cortex excitability [12].

In this study, we aimed to investigate further the cortical excitability levels in patients with IGEs with and without photosensitivity. We explored the corticospinal excitability and the excitability of the primary visual cortex by determining the rMT and the PT. Since it has been proven that PT and rMT do not correlate [13,14], an imbalance between these parameters (e.g., a marked decrease in PT compared to rMT) would indicate that in IGEs, cortical excitability is not homogeneously distributed but that some cortical areas have a higher intrinsic excitability level.

2. Methods

2.1. Participants

Thirty-four right-handed patients (24 women and 10 men; mean age 33 ± 6 years; range: 16–48 years) with IGE and twelve healthy age-matched right-handed control subjects (6 women and 6 men; mean age 35 ± 9 years; range: 25–48 years) were enrolled in the study. Statistical analyses showed no significant differences in age (two-tailed Mann–Whitney U test: p-value: 0.71) or gender ratio (two-tailed Fischer's exact test: p-value = 0.29) across the two groups.

Patients fulfilled the following inclusion criteria: diagnosis of IGE (according to Engel [15]); no metallic implants, electrical devices, or other contraindications for TMS; no pregnancy; no neurological deficits or other health problems; no developmental problems or learning disabilities; no drug abuse or alcoholism; and no migraine. Cerebral MRI was normal in all patients. Clinical information, EEG and MRI findings, as well as data on antiepileptic therapy at the time of TMS study were recorded on data collection forms.

To reduce clinical heterogeneity, patients were classified as having active epilepsy or epilepsy in remission. Patients were considered to be affected by active epilepsy if they had had at least one seizure in the previous 5 years, regardless of AED treatment [16,17]. Epilepsy in remission was considered a prevalent case of epilepsy with no seizures for ≥5 years regardless of AED treatment at the time of ascertainment [16,17]. Patients under AED therapy had a stable regimen in the last 3 months before TMS study. Photosensitivity was defined as the presence of an abnormal EEG response to IPS (photoparoxysmal response, PPR). Only patients with PPR consisting of generalized spike-and-wave discharges (PPR types III and IV, according to Waltz et al. [18]) were included.

The control subjects had no history of seizures, migraine, or alcoholism and did not take any drug with effect on cortical excitability.

To reduce clinical heterogeneity in the female subjects of both the group with epilepsy and the control group, TMS was performed 12–16 days after the first day of menses (at mid-cycle).

The study was approved by the local ethics committee, and all participants provided written informed consent.

We investigated the following three groups of patients: 13 subjects with active epilepsy without photosensitivity, 13 patients with epilepsy in remission without photosensitivity, and 8 patients with epilepsy with photosensitivity (7 with active epilepsy and 1 with epilepsy in remission).

Clinical details are given in Table 1.

Table 1
Clinical characteristics and PT and rMT values of patients with epilepsy and of controls enrolled in the study.

Participant number	Age (years), sex	Group	Medication	Syndromic diagnosis	PT	rMT
1	16, M	A	LEV	GTCA	76	58
2	32, F	A	VPA	JAE	NR	78
3	37, F	A	VPA	GTCA	80	70
4	30, M	A	VPA	GTCA	NR	84
5	32, F	A	LTG	JAE	76	60
6	25, F	A	VPA	JME	NR	73
7	29, M	A	CBZ, PB	JAE	NR	48
8	39, F	A	VPA	GTCA	NR	50
9	41, M	A	VPA	JME	NR	86
10	46, F	A	VPA	GTCA	NR	86
11	32, F	A	LTG	GTCA	NR	82
12	45, M	A	VPA, LTG, PHT	JAE	NR	87
13	17, M	A	None	GTCA	65	43
14	35, F	APS	VPA	JME	74	86
15	19, M	APS	VPA, TPM, PB	JAE	54	64
16	34, F	APS	CBZ	JME	68	76
17	26, F	APS	VPA	JME	46	68
18	25, F	APS	VPA	JME	48	72
19	25, F	APS	VPA	JAE	78	86
20	22, F	APS	VPA	JME	60	67
21	42, F	R	VPA, PB	JAE	NR	70
22	40, F	R	VPA, LTG	JAE	NR	55
23	38, F	R	VPA	JME	NR	75
24	48, F	R	VPA, PB	JAE	92	75
25	39, M	R	None	GTCA	56	48
26	36, F	R	VPA, PB	JAE	NR	74
27	55, F	R	VPA, PB	JAE	NR	90
28	28, M	R	VPA	GTCA	NR	89
29	44, F	R	VPA	PM	NR	84
30	27, F	R	VPA	JME	48	42
31	36, F	R	PB	JME	NR	60
32	29, F	R	VPA	JAE	67	54
33	25, M	R	None	GTCA	Not reliable	54
34	47, F	RPS	PB	JME	NR	47
35	25, F	C	None	–	100	50
36	28, M	C	None	–	59	45
37	27, F	C	None	–	70	45
38	30, M	C	None	–	71	52
39	25, M	C	None	–	72	45
40	48, F	C	None	–	68	56
41	37, M	C	None	–	66	54
42	52, F	C	None	–	72	48
43	42, M	C	None	–	70	50
44	45, F	C	None	–	74	46
45	32, F	C	None	–	76	58
46	30, M	C	None	–	74	56

A: active epilepsy without photosensitivity.
APS: active epilepsy with photosensitivity.
C: control.
CBZ: carbamazepine.
F: female.
GTCA: epilepsy with generalized tonic-clonic seizures only.
JAE: juvenile absence epilepsy.
JME: juvenile myoclonic epilepsy.
LTG: lamotrigine.
M: male.
NR: no response.
PB: phenobarbital.
PHT: phenytoin.
R: epilepsy in remission without photosensitivity.
RPS: epilepsy in remission with photosensitivity.
TPM: topiramate.
VPA: valproic acid.

2.2. EEG

In all participants (controls and patients), standard 19-channel digital electroencephalogram (EEG) was recorded prior to TMS administration. Intermittent photic stimulation (IPS) was performed according to internationally recommended guidelines [19]. The EEGs were independently analyzed by two experienced epileptologists who