# Contrast Gain Control Abnormalities in Idiopathic Generalized Epilepsy

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**Objective:** The origin of neural hyperexcitability underlying idiopathic generalized epilepsy (IGE) is not known. The objective of this study is to identify evidence of hyperexcitability in precisely measured visual evoked responses and to understand the nature of changes in excitation and inhibition that lead to altered responses in human patients with IGE.

**Methods:** Steady-state visual-evoked potentials (VEPs) to contrast reversing gratings were recorded over a wide range of stimulus contrast. VEPs were analyzed at the pattern reversal rate using spectral analysis. Ten patients with IGE and 13 healthy subjects participated. All subjects had normal visual acuity and had no history of photic-induced seizures or photoparoxysmal electroencephalograph (EEG) activity.

**Results:** At a group level, the amplitude of visual responses did not saturate at high stimulus contrast in patients, as it did in the control subjects. This reflects an abnormality in neuronal gain control. The VEPs did not have sufficient power to reliably distinguish patients from controls at an individual level. Parametric modeling using a standard gain control framework showed that the abnormality lay in reduced inhibition from neighboring neurons rather than increased excitatory response to the stimulus.

**Interpretation:** Visual evoked responses reveal changes in a fundamental mechanism regulating neuronal sensitivity. These changes may give rise to hyperexcitability underlying generalized epilepsy.

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Understanding the changes in neural excitation and inhibition that lead to hyperexcitability in epilepsy is important to elucidating the mechanism of disease. Here we further this endeavor by measuring visually evoked potentials (VEPs) in patients with idiopathic generalized epilepsy (IGE). IGE is a major class of epilepsy syndromes, accounting for 15% to 20%[1] and possibly as much as 40%,[2] of all epilepsies in the United States. Photosensitivity is much more common in generalized epilepsy than in localization-related epilepsy,[3] suggesting that visual stimulation can engage the mechanism underlying hyperexcitability in IGE patients.

The definition of IGE, according to the International League Against Epilepsy (ILAE) classification scheme,[4] includes generalized seizure types and electroencephalograph (EEG) abnormalities in association with normal neuroanatomy. In view of the absence of a well-defined seizure focus, the origin of hyperexcitability in this disorder remains a major question in epilepsy research. Studies in animal models have identified abnormal thalamocortical network interactions that lead to generalized spike and wave (GSW) discharges or seizures.[5–7] However, the pathophysiology of neural hyperexcitability in human IGE is incompletely understood. An early "centrencephalic" hypothesis proposed that the thalamus has a primary involvement in generalized absence seizures.[8] In rare cases of patients with GSWs who have undergone intracranial recordings, the evidence for a thalamic origin of GSWs was equivocal.[9,10] Concurrent functional magnetic resonance imaging (fMRI) and EEG recordings of GSWs in humans revealed symmetric and broad regions of blood oxygen-level dependent (BOLD) deactivation in the cortex coupled with BOLD activation in the thalamus,[11] confirming the involvement of both structures in these events. A further study showed BOLD signal changes in the cortical-thalamic-basal ganglia

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network a few seconds preceding the appearance of GSW discharges,[12] suggesting that changes in deep brain structures precede those in the cortex. However, the precise neural interactions that result in generalized epilepsies in humans remain unresolved. One question is how the balance between excitation and inhibition is changed, leading to hyperexcitability.[13]

Some clues come from identified genetic mutations in families with a strong pattern of disease inheritance[14–16]: $\gamma$-aminobutyric acid $(GABA)_A$ receptor subunits (GABRG2, GABRA1) in childhood absence epilepsy (CAE) and juvenile myoclonic epilepsy (JME), voltage-gated sodium channels (SCN1A) in generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). These genetic mutations suggest that an alteration of membrane excitability is important in epileptogenesis. Many (but not all, see eg, Meadows and colleagues[17]) of the mutations cause a defect in neuronal inhibition. For example, a loss-of-function mutation in a voltage-gated sodium channel (SCN1A) in a mouse model of SMEI produced selective decreased sodium currents in inhibitory interneurons, but not in excitatory pyramidal cells.[18] We hypothesize that abnormally weak inhibition causes hyperexcitability in patients with IGE.

Here we asked whether it was possible to identify abnormal inhibition in patients with IGE, specifically in the form of changes in gain control. Gain control is the machinery by which a system, biological or man-made, dynamically adjusts its sensitivity to the input. Gain control allows for a wide input range and keeps the output in an optimal regime. Modern digital cameras have automatic gain control that adjusts for ambient illumination, turning up the sensitivity in dimly lit settings to better record subtle shades and turning down the sensitivity in bright light to prevent overexposure. In biological vision, luminance differences between neighboring areas, or contrast, is an important perceptual feature. Accordingly, contrast gain control mechanisms have been identified in the retina,[19,20] lateral geniculate nucleus,[21] and cortex.[22,23] Not only does contrast gain control adjust the amplitude of the response as noted above,[23,24] it also affects the temporal aspects of the response, speeding up the response at high contrasts[20,25] and shifting the system's preference to faster stimuli.[20] Gain control is likely to be a generic cortical computation that operates throughout the brain to maintain optimal input-output relationships.[26] Finally, alterations in excitatory and inhibitory circuitry impact gain control.[27,28] For these reasons, we expect measures of gain control to inform the nature of hyperexcitability. Here we focus on cortical visual processing because it is easy to assay using noninvasive and direct measures such as the VEP. We do not address temporal aspects of gain control in this work.

Patients with photosensitive occipital lobe epilepsy, a *focal* epilepsy syndrome, have abnormal contrast gain control even during interictal periods.[29] This is characterized by an absence of response saturation to high stimulus contrast. This failure of gain control may contribute to reflex photic-induced seizures in these patients. However, the mechanism of abnormal contrast gain control was not addressed, as was its specificity to an occipital lobe origin of seizures. If neural hyperexcitability is reflected in widespread cortical gain control changes, we hypothesize that similar changes may be present in patients with IGE, and may be evident in their visual responses.

## Patients and Methods

### Subjects

IGE is an umbrella term encompassing several distinct but overlapping syndromes. Here we follow the approach of Berkovic and colleagues,[30] who proposed that IGE represents a biological continuum stemming from an interaction of genetic and acquired causes. We have therefore included patients with different seizure types and from an age range that is typical of IGE. Our patient population consisted of 1 male and 9 female subjects (mean age 35 years), who had been diagnosed with IGE at the University of California-San Francisco (UCSF) Epilepsy Center. We excluded patients who had a history of photic-induced seizures or photoparoxysmal responses (PPR) in order to minimize the risk of inducing seizures. Photoparoxysmal responses were evaluated using a standard clinical protocol in place at the UCSF Epilepsy Center. Thirteen healthy subjects (mean age 35 years) similar in sex and age to the patient cohort were recruited from a pool of subjects at the Smith-Kettlewell Eye Research Institute (SKERI). Control subjects did not have a history of neurological or psychiatric diagnoses such as migraine or schizophrenia. All subjects had normal or corrected-to-normal visual acuity. Acuity was measured using the Bailey-Lovie chart, which has 5 letters per line and equal log increments in the letter sizes across lines. Informed consent was obtained prior to study initiation under a protocol that was approved by the SKERI Institutional Review Board.

The patients' characteristics are detailed in the Table. Three patients, who did not receive a specific syndromic diagnosis, had primary generalized tonic-clonic seizures and EEG findings consistent with IGE. Two patients (Patients 2 and 5) were taking no or a negligible dose of antiepileptic drugs (AEDs). Three patients, who were taking AEDs, had well-controlled epilepsy having had no seizures in the preceding 2 years.

### Display System

Visual stimuli were presented on a 19-inch LaCie Electron Blue IV monitor at a resolution of 800 × 600 pixels, with a 72Hz

**TABLE: Characteristics of the Patients Included in This Study**

| Patient | Gender | Age (yr) | Age at onset (yr) | Dx | AEDs | Light Trigger | Seizure-Free > 2 yr |
|---|---|---|---|---|---|---|---|
| 1 | F | 70 | 20s | JME | VPA | No | Y |
| 2 | F | 29 | 10s | JME | None | No | N |
| 3 | F | 21 | 13 | IGE | ZNS | No | Y |
| 4 | F | 35 | 17 | JME | VPA | No | Y |
| 5 | F | 55 | <10 | IGE | LTG | No | N |
| 6 | F | 26 | 17 | JME | LEV | No | N |
| 7 | F | 21 | 19 | IGE | LEV | No | N |
| 8 | F | 22 | 15 | JAE | LTG, ZNS | No | N |
| 9 | F | 37 | 7 | CAE | VPA | No | N |
| 10 | M | 30 | 20 | JME | VPA | No | N |

AEDs = antiepileptic drugs; CAE = childhood absence epilepsy; Dx = diagnosis; IGE = idiopathic generalized epilepsy; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy; LEV = levetiracetam; LTG = lamotrigine; VPA = divalproex sodium; ZNS = zonisamide.

vertical refresh rate and a mean luminance of 34cd/m$^2$. The nonlinear voltage vs luminance response of the monitor was corrected in software. All stimuli were generated and presented using an in-house display system.

### *Stimuli*

The stimuli consisted of horizontal sine gratings windowed by a circularly symmetric Gaussian envelope presented at fixation. The envelope was truncated at 4 degrees from the center. The spatial frequency of the grating was 2 cycles per degree. The mean luminance was kept constant throughout the experiments. Stimulus contrast was defined as the difference between the maximum and minimum luminance of the grating divided by their sum. The contrast of the stimulus was temporally modulated (contrast reversal) by a 7.2Hz sinusoid. The peak contrast during each trial was fixed and randomized to 1 of 5 values (conditions): 0.05, 0.1, 0.2, 0.4, and 0.8.

### *Electroencephalography*

We collected EEG signals using a 128-channel electrode array (Electrical Geodesics, Inc., Eugene, OR) while subjects fixated on a central marker in a dark and quiet room. Steady-state VEPs were acquired using an EGI NetStation 200 (Electrical Geodesics) and were processed via an in-house software package. Signals were recorded with a vertex physical reference, amplified at a gain of 1,000, bandpass filtered between 0.1Hz and 50Hz, and digitized at 432Hz. Each stimulus presentation lasted 10 seconds, and 5 conditions with 20 trials each were randomized in the experiment. A typical session lasted ~40 minutes allowing for brief breaks between trials.

### *Signal Processing*

Artifact rejection was done offline in 2 stages. In the first stage, raw data were evaluated sample by sample to determine those that exceeded a threshold (~25–50$\mu$V). Thresholds differed between subjects due to electromyogram, movement, and other artifacts. Noisy channels that had greater than 10% of the samples exceeding the threshold were replaced by the average of the 6 nearest neighbors. The discarded channels generally were located far from the occipital region and numbered less than 10% of the total. Second, individual channels were evaluated sample by sample, and epochs that contained samples that exceeded a threshold (~25–50$\mu$V) were rejected. Here an epoch was defined as a full stimulus cycle, 0.14 seconds.

After artifact rejection, the EEG was re-referenced to the common average of all the channels. Spectral analysis was performed via a discrete Fourier transform with 0.5Hz resolution. The contrast reversing stimuli we used generated VEPs whose spectra contained signals at even multiples of the stimulus frequency (2nd, 4th, and 6th harmonics). The combination of amplitude threshold and spectral analysis removed non–stimulus-locked signals such as eye blinks and epileptiform discharges from the resulting responses.

To obtain a summary measure of the each subject's data set, we concatenated the 2nd, 4th, and 6th harmonic responses over the 5 stimulus contrasts at each of the 128 sensors. From this data set and each subject, we computed a spatial principal component analysis (PCA). PCA is a simple means for capturing the variance of the data using a reduced number of variables. The first principal component explains as much of the variance in the data as possible. Each successive component explains as much of the residual variance as possible. The 2nd, 4th, and 6th harmonic responses were projected onto the first principal component and the Euclidian norm of these projected amplitudes was taken as an index of the magnitude of the VEP response. This quantity was averaged across subjects to obtain the group means. Statistical analysis was done using the package SPSS 18 (SPSS-IBM, Chicago, IL).

### Modeling

Contrast response functions are commonly fit to the hyperbolic ratio function.[22,31–33] We fitted contrast response measurements with the hyperbolic ratio function (Eq. 1) using a nonlinear least squares search, *lsqnonlin* in MATLAB (Mathworks, Natick MA).

$$y = R_m \frac{x^n}{x^n + \sigma^n} + R_0, \quad (1)$$

where $y$ is the VEP amplitude, $x$ is the stimulus contrast, $R_0$ is the EEG background amplitude, and $R_m$, $\sigma$, and $n$ are free parameters. The 3 free parameters of Equation 1 correspond to the maximal response ($R_m$), the semisaturation point ($\sigma$), and an output nonlinearity ($n$). The background amplitude ($R_0$) was estimated by averaging the magnitude of the EEG spectrum at the 2 frequency bins ($\pm$0.5Hz) adjacent to the stimulus harmonics. Significance testing of parameter values was based on a bootstrap procedure.[34]

This simple equation describes an important neural computation—divisive normalization (Fig 1). In this model,[35,36] the neuron's receptive field acts as a spatiotemporal filter, shaping excitatory postsynaptic currents in response to the stimulus. The stimulus also drives a large number of surrounding visual neurons (labeled the "gain pool") tuned to various orientation, frequency, and size. The gain pool modulates the neuron's response via inhibitory synapses such that the neuronal output is divided by the combined activity of the gain pool. Thus the response of a single neuron is normalized against its peers. Note that since this divisive operation typically reduces response magnitude, it is also termed divisive inhibition. Finally, a rectification stage generates action potentials from membrane currents. Normalization is an attractive framework because it has been used to model contrast response functions[22] and accounts well for contrast response saturation and gain control.[21,35,36] Moreover, because it incorporates a simple and explicit model of the interaction between excitation and inhibition as described above, we expect that the model could capture the changes in excitation and inhibition in epilepsy. As an illustration, the 2 main parameters of the normalization model (Eq. 1) have different effects on the contrast response function. First, the parameter $R_m$ scales the overall response function by a constant (see Fig 1B). The greatest difference between the 2 functions occurs at the highest contrast. Changes of this type are known as response gain.[37] Second, the parameter $\sigma$ shifts the function laterally (on linear-log axes) without changing the shape of the function. This is known as contrast gain change. It is worth noting that both parameters may change at the same time.

## Results

As a group, patients exhibit less response saturation at high stimulus contrasts than controls. Group mean response amplitude is plotted against stimulus contrast in Figure 2. Repeated measures multivariate analysis of variance (MANOVA) shows a significant interaction between group and stimulus contrast [$F(4,18) = 3.223$, $p = 0.037$], indicating that the shape of the contrast response function differs between the 2 groups. There is a trend toward significance in the main effect of group [$F(1,21) = 3.042$, $p = 0.096$]. Individual data are shown in Figure 3. The patients are in the left panel and the controls in the right panel. In a majority of control subjects, responses saturate at high contrasts, while in most of the patients they do not. While the VEP responses shown here cannot reliably classify an individual subject as control vs patient, the group difference is strong and robust. A separate paradigm using a "sweep VEP" method that sampled the contrast values more finely led to the same results (Supporting Information). Some of the variability in the response pattern is undoubtedly driven by heterogeneous characteristics present in our patient group. Among these factors, factors such as seizure control and medication might be expected to correlate with the degree of hyperexcitability. We denote a number of these factors including AED treatment, degree of seizure control, and specific type of epilepsy using different line styles. There is no obvious relationship between these factors and the response. While these are factors that might potentially be relevant to the responses, our sample size precludes drawing meaningful correlations.

Fig. 2 show that unlike controls, patients' responses do not saturate above some contrast, but rather continue to increase. This suggests that contrast gain control is abnormal in patients, particularly at high contrasts. Then we fit the normalization model (Eq. 1) to the contrast response data to determine whether the difference between patients and controls could be explained by changes in the model parameters, and if so, how these changes might relate to excitation and inhibition in the gain control circuitry (see Fig 1). We tried fitting the model to individual subjects (data not shown). A number of subjects were poorly fit by the model, probably because of the intrinsic variability in the measurements and the limited sampling of the contrast response function in our data. A similar level of variability was found in another VEP study of contrast response function (Porciatti and colleagues[29]; see their Fig. 3). To proceed with the analysis, we fit the model to the group means.

Dashed lines depict the model fits to the data in Figure 2. Here we have fixed the exponent $n$ (Eq. 1) to a value of 1.4, which was found to describe well human contrast response functions measured by VEP.[31] For the controls, the best fitting parameter values are: semisaturation constant ($\sigma$) of 0.15 (95% confidence interval [CI], 0.05–0.41), consistent with reported values in the literature (eg, Zemon and Gordon[38]); $R_m$ of 3.4 (95% CI,

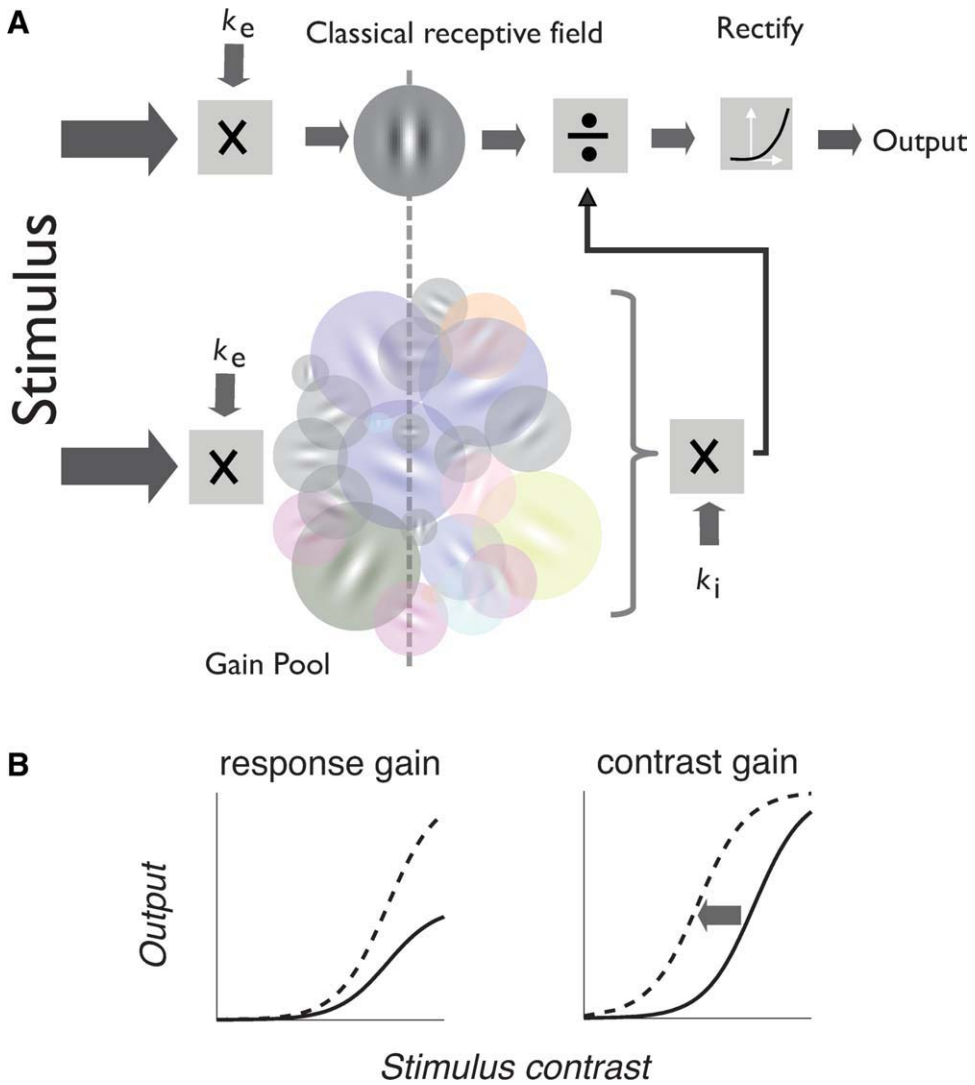


**FIGURE 1: (A) Schematic diagram of the "normalization model" of gain control. A neuron produces output (action potentials) in response to an input stimulus. The sensitivity of the output to a change in the input is modulated by the gain control circuitry. The circuitry consists of 2 components: an excitatory drive shaped by the classical receptive field, and an inhibitory signal from a pool of neurons, which, in turn, respond to the stimulus through their own receptive fields. The classical receptive field acts as a linear spatiotemporal filter. The inhibitory signal provides context-dependent modulation and underlies nonlinear phenomena such as response saturation. The labels $k_e$ and $k_i$ indicate 2 sites in the circuitry where the strength of excitation and inhibition, respectively, may be altered. See Results section for detailed explanation of the model. (B) The 2 main parameters of the normalization model, $R_m$ and $\sigma$ (Eq. 1) produce different effects on the contrast response function (neuronal output plotted against stimulus contrast). Response gain (left) refers to a change in the scaling constant, $R_m$ (positive in this example shown by the dashed line). Contrast gain (right) refers to a change in the semisaturation constant, $\sigma$, resulting in a shift in the contrast axis (negative in this example, as shown by the dashed line). [Color figure can be viewed in the online issue, which is available at www.annalsofneurology.org.]**

2.6–5.1). For patients, there is a trend for both parameters to be greater than in controls: $\sigma$ of 0.23 (95% CI, 0.10–0.49), and $R_m$ of 5.3 (95% CI, 3.4–8.3). Graphically (see Fig 2), the best-fit curve for patients is shifted rightward and scaled upward compared to the controls. These results suggest that the difference between patients' and controls' contrast response function results from a combination of contrast gain and response gain (cf. Fig 1B). While the group difference in the parameters, considered separately, did not reach statistical significance, some combination of the parameters may better discriminate between the 2 groups.

We reparameterized the model with aims (1) to increase the power to differentiate between patients and controls and (2) to interpret findings in terms of excitation and inhibition in the gain control circuitry.[39] We designate 2 sites where excitation and inhibition may be modulated (see Fig 1). First, the strength of excitatory postsynaptic currents is modulated by the parameter $k_e$. This parameter applies to all neurons in the model,

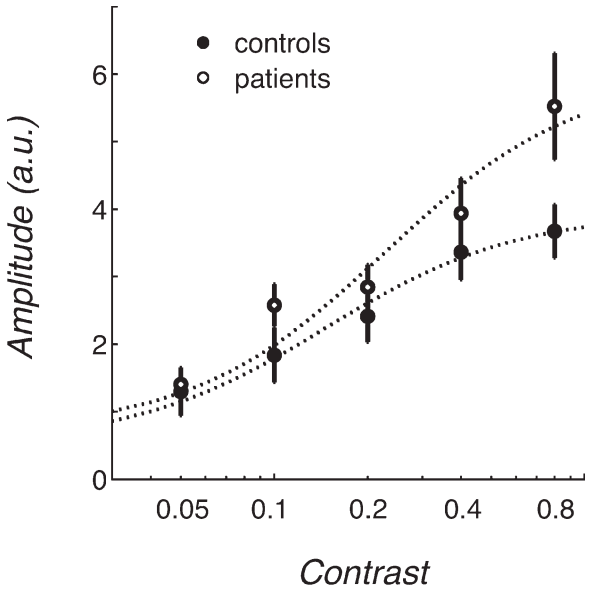


**FIGURE 2: Group mean contrast response functions of patients (*open circles*) and controls (*filled circles*). Error bars are standard errors of the mean. Controls manifest response saturation at high contrasts; patients do not. Dotted lines represent the model fit as per Eq. 1. The model produces good fits to the data: $R^2$ = 0.98 (controls) and 0.93 (patients). The values of the parameters are: $R_m$ = 3.4, $\sigma$ = 0.15 for controls; $R_m$ = 5.3, $\sigma$ = 0.23 for patients.**

including those in the gain pool. Second, the strength of inhibition from the gain pool is controlled by the parameter $k_i$. The parameters $k_e$ and $k_i$ may be thought of as modulating the effectiveness of excitatory and inhibitory input, respectively. We assume that the response difference between patients and controls can be attributed to changes in effective excitation and inhibition. The new model is formulated in Equation 2.

$$y = R'_m \frac{(k_e x)^{n'}}{k_i (k_e x)^{n'} + (\sigma')^{n'}} + R_0, \qquad (2)$$

where $n'$, $\sigma'$ and $R_m'$ are constants obtained from fitting the standard model (Eq. 1) to the controls. This reparameterization amounts to a coordinate transformation of the parameter space, from ($\sigma$, $R_m$) to ($k_e$, $k_i$). It can be shown that there is a nonlinear relationship between the original parameters and $k_i$:

$$\sigma = \frac{\sigma'}{k_e \sqrt[n]{k_i}}; \quad R_m = \frac{R'_m}{k_i}.$$

Note that $\sigma$ and $R_m$ both depend on $k_i$, and that when $k_e$ and $k_i$ equal 1 (which we assume for controls), Equation 2 reduces to Equation 1.

Using this model (Eq. 2), we find that relative changes in excitation and inhibition can account for the difference between patients and controls. First, as shown above, the model fits the mean contrast responses of the controls very well (Fig 4, gray line, $R^2 = 0.99$, $\chi^2 = 0.27$, df = 2). Next, in fitting the patients' data, we consider 3 cases (see Fig 4): allowing the excitatory modulation $k_e$ to vary (Model 1), the inhibitory modulation $k_i$ (Model 2), or both (Model 3). Model 1 (dashed line) is

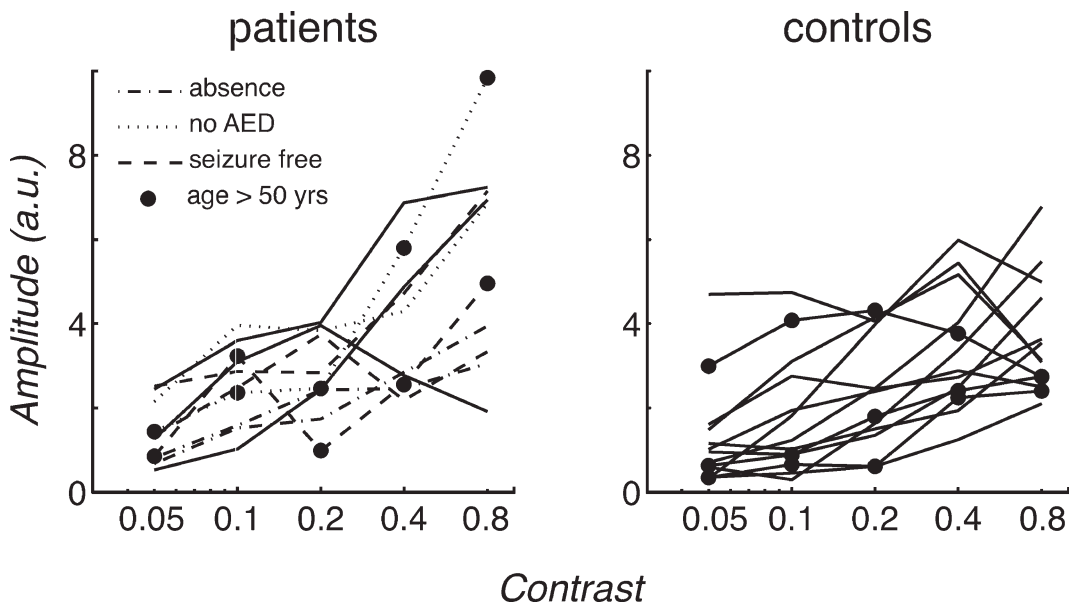


**FIGURE 3: Contrast response function of individual subjects. Patients generally show a lack of response saturation, in contradistinction to controls. Within-group heterogeneity is similar to VEP measurements reported in the literature, but bears no obvious relationship to subject characteristics: seizure freedom greater than 2 years (*long dashed lines*), no treatment with AEDs (*short dashed lines*), absence epilepsy (*dash-dot lines*), and age greater than 50 years (*circles*). AEDs = antiepileptic drugs; VEP = visual-evoked potentials.**

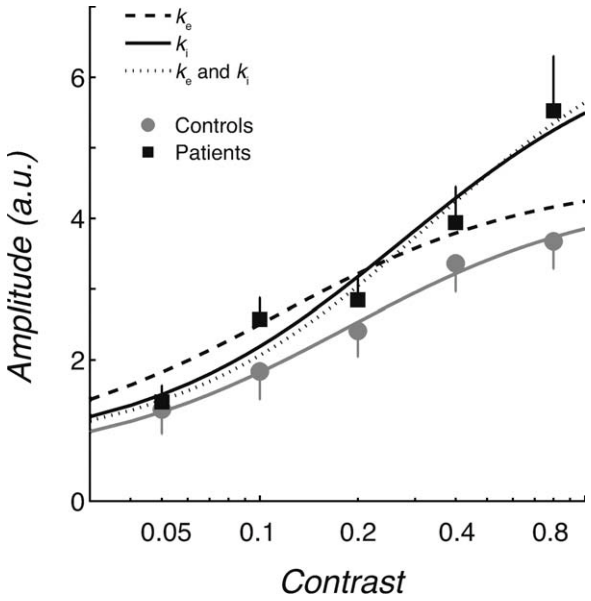


**FIGURE 4: Modeling of contrast response functions. Group mean data for patients and controls are fitted to a normalization model of gain control (Eq. 2). Three cases are shown which differ in the parameters that are allowed vary: $k_e$, $k_i$, or both (see Results section for details). Decreased inhibition ($k_i$), without a change in excitation ($k_e$), is necessary and sufficient to account for the difference between patients and controls.**

a poor fit ($R^2 = 0.77$, $\chi^2 = 7.78$, df = 4), particularly at the highest contrast where the model deviates widely from the data. Model 1 fails because changing $k_e$ shifts the contrast response function along the contrast axis, but does not change the shape of the function; thus it does not predict a lack of response saturation. Model 2 (solid black line) fits the data well ($R^2 = 0.95$, $\chi^2 = 3.42$, df = 4), as does Model 3 (dotted line; $R^2 = 0.96$, $\chi^2 = 3.6$, df = 3). Model 2 shows that patients have significantly decreased inhibition compared to controls ($k_i = 0.65$; 95% CI, 0.44–0.95), similarly for Model 3 ($k_i = 0.60$; 95% CI, 0.30–0.98). Furthermore, Model 3 shows that excitation is not significantly altered in patients ($k_e = 0.88$; 95% CI, 0.54–1.57). Indeed, though Model 3 has 1 more parameter than Model 2, it produces no better fit. Taken together, these results indicate that a decreased inhibition from surrounding neurons in the gain control circuitry is necessary and sufficient to account for the patients' contrast responses.

## Discussion

We report 2 novel results in this work. First, we find decreased response saturation at high contrasts in patients with IGE. This finding closely mirrors that identified in a group of 11 patients with idiopathic photosensitive occipital lobe epilepsy.[29] Our group of patients with IGE had neither occipital seizure foci nor photoparoxysmal EEG activity. Nevertheless, they showed evidence of abnormal visual contrast gain control. This suggests that abnormalities in visual contrast gain control may be more prevalent in epilepsy than previously suspected. We have identified a VEP correlate of visual hyperexcitability in a broad group of patients with IGE.

Second, we extend a canonical model of neural gain control to the study of epilepsy. We believe this is the first time an epilepsy syndrome has been characterized in this way. Other investigators have examined suppressive and facilitatory interactions present in VEPs in patients with epilepsy.[40] Here we show how specific changes in excitation and inhibition in a gain control model could lead to abnormal responses. This model predicts specific changes in the contrast response function. For example, increasing the $R_m$ parameter in Equation 1 would lead to larger responses at high contrast levels (response gain); however, this manipulation would only scale the contrast response function by a multiplicative factor but would not change its semisaturation point. Alternatively, increased excitatory currents would cause hyperexcitability, which would be described by a decreased $\sigma$ and would correspond to a shift of the contrast response function (contrast gain). Finally, we find that the observed effect is best characterized by changes in both response gain *and* contrast gain and is consistent with a diminished inhibition from surrounding neurons (ie, the gain pool) in patients.

We speculate that the change in gain control in IGE may be related to reduced GABAergic inhibition. Decreased intracortical inhibition has been reported in the motor cortex of patients with JME[41,42] and in a rodent model of absence epilepsy.[43] The alteration of GABAergic inhibition may result from a channelopathy; eg, a sodium channel mutation causes reduced activity of GABAergic inhibitory interneurons in a mouse model of SMEI,[18] possibly resulting in an abnormal gain pool response. On the other hand, not all monogenic mutations linked to IGE are associated with a channelopathy. Mutations of the EFHC1 gene on chromosome 6 is linked to JME in some Latino and Japanese families.[44] EFHC1 is involved in neuronal mitosis and migration during development.[45] Microscopic abnormal cortical development including heterotopic neurons and abnormal cortical architecture, termed microdysgenesis, has been reported in a number of autopsies of patients with JME.[46] The pathogenesis of microdysgenesis in epilepsy is unclear; however, discrete dysplastic cortical lesions have been associated with fewer and abnormal GABAergic neurons.[47] Abnormal cortical development therefore may lead to hyperexcitability[45] via abnormal inhibitory component in the gain control circuitry. We did not

perform genetic analysis of the patients included in this study and thus could not draw conclusions on the relationship of abnormal gain control and specific genetic mutations. Nevertheless, one might speculate that abnormal gain control may be a common manifestation of the heterogeneous and multi-factorial causes of epilepsy.

The model described in this work addresses the nature of computations performed by the gain control circuitry rather than the details of its biophysical substrate. In this way, the model glosses over complex interactions of cell types and neurotransmitter mechanisms in the neural network.[48] Nevertheless, our results are in keeping with more detailed biophysical models of thalamocortical circuitry.[49] Experimental[6] and modeling[49] studies have shown that GSW discharges can evolve from a normal corticothalamic rhythm – decreased intracortical GABA-mediated inhibition gives rise to a strong excitatory feedback to the thalamus and drives $GABA_B$-mediated ~3Hz oscillations in the thalamus. Of note, while enhanced $GABA_B$-mediated inhibition is present in local thalamic circuitry, the generation of GSW discharges is critically dependent on a cortical hyperexcitability, caused by reduced $GABA_A$-mediated inhibition.[49] The reduced inhibition we observed in VEP may reflect this cortical component.

The limitations of the study include small sample size and heterogeneity of IGE patients. The small sample size precludes meaningful subgroup analysis. Correlating to specific syndrome diagnosis, degree of seizure control, and other variables requires a larger study. On the other hand, a repeated measure design increased the power of the current study. Despite the heterogeneous syndromic diagnosis, the group difference is robust. Finally, it should be emphasized that the lack of VEP amplitude saturation at high stimulus contrast cannot be attributed to treatment with AEDs as these drugs are known to reduce, not increase, photosensitivity[50]; indeed, reduction of photosensitivity has been as used a screening test for drug development.[50]

In summary, we found that adult patients with IGE have impaired contrast gain control. This is likely a result of reduced inhibitory modulation in the gain control circuitry. These findings suggest additional questions for study. There may be a behavioral correlate to the VEP findings, for example, abnormal perception of high-contrast stimuli. Gain control abnormalities may be present in other functional domains in patients with IGE, such as audition, motor control, and executive function. Abnormal gain control could be present in other disorders of neural excitability. Finally, gain control abnormalities could, potentially, serve as biomarkers for hyperexcitability in clinical practice.

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## Potential Conflicts of Interest

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