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Altered visual contrast gain control is sensitive for idiopathic generalized epilepsies

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HIGHLIGHTS

- Patients with idiopathic generalized epilepsy (IGE) manifest abnormal gain control to increasing contrast of visual stimuli.
- IGE patients were reliably classified from healthy controls based on the contrast responses.
- The most discriminating feature was patients' relative lack of gain control at high contrasts.

ABSTRACT

Objective: Visual hyperexcitability in the form of abnormal contrast gain control has been shown in photosensitive epilepsy and idiopathic generalized epilepsies. We assessed the accuracy and reliability of measures of visual contrast gain control in discerning individuals with idiopathic generalized epilepsies from healthy controls.
Methods: Twenty-four adult patients with idiopathic generalized epilepsy and 32 neurotypical control subjects from two study sites participated in a prospective, cross-sectional study. We recorded steady-state visual evoked potentials to a wide range of contrasts of a flickering grating stimulus. The resultant response magnitude vs. contrast curves were fitted to a standard model of contrast response function, and the model parameters were used as input features to a linear classifier to separate patients from controls. Additionally we compared the relative contribution of model parameters towards the classification using a sparse feature-selection approach.
Results: Classification accuracy was 80% or better. Sensitivity and specificity both were 80–85%. Cross validation confirmed robust classifier performance generalizable across the data from the two samples. Patients' relative lack of gain control at high contrasts was the most important information distinguishing patients from controls.
Conclusions: Individuals with idiopathic generalized epilepsy were distinguishable from the neurotypical with a high degree of accuracy and reliability by a reduction in gain control at high contrasts.
Significance: Gain control is an essential neural operation that regulates neuronal sensitivity to stimuli and may represent a novel biomarker of hyperexcitability.
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1. Introduction

Biomarkers are objective measurements reflecting a biological process and are a high priority in epilepsy research (Kelley et al., 2009). An ideal biomarker has high specificity and sensitivity, low costs and risks, and a potential to elucidate mechanism of disease. To date, however, no highly sensitive biomarker of epilepsy is available (Engel, 2011). In idiopathic (also termed primary or genetic) generalized epilepsies (IGE), the presence of bilateral syn-

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chronous epileptiform discharges is helpful to confirm the diagnosis (Koutroumanidis and Smith, 2005). Accordingly, electroencephalogram (EEG) is recommended following a first seizure (Krumholz et al., 2007). However, epileptiform discharges on EEG, being less sensitive (25–50%) than specific (79–98%) (Smith, 2005), are limited in diagnostic yield. The probability of identifying interictal epileptiform patterns on a first EEG is about 50% overall (King et al., 1998; Salinsky et al., 1987), somewhat higher in generalized epilepsies (King et al., 1998). While serial EEG (up to 4) can increase the diagnostic yield, around 10% of the patients do not have epileptiform discharges (Salinsky et al., 1987). Some patients require long-term monitoring to definitively characterize their epilepsy syndrome (Ghougassian et al., 2004). Therefore, a search for novel markers of IGE is warranted.

We have previously linked human IGE to alteration of contrast gain control (Tsai et al., 2011). Gain control refers to the dynamic adjustment of a system's sensitivity to its input and is essential to many sensory and cognitive functions (Carandini and Heeger, 2012). The relationship between the response magnitude and stimulus contrast, so-called contrast-response function (CRF), is well established in both humans and animals (Albrecht and Hamilton, 1982; Burr and Morrone, 1987; Ross and Speed, 1991). The typical CRF has an accelerating rising portion at low to medium contrasts and levels off at high contrasts (Carandini et al., 1997). This "contrast saturation" is shaped by mechanisms of contrast gain control, which reduces the system's sensitivity to stimulus contrasts under conditions of high prevailing contrast (Bonin et al., 2005; Carandini and Heeger, 1994, 2012; Heeger, 1992b; Ohzawa et al., 1981; Shapley and Victor, 1979). We identified a group effect of a lack of response saturation at high stimulus contrasts in IGE patients – that is, their CRF, *on average,* continued to increase at high contrasts. Moreover, by modeling the changes in contrast gain, we showed that reduced inhibitory modulation from surrounding neurons could account for the lack of response saturation (Tsai et al., 2011). These results suggest that the state of contrast gain control may be a potential novel marker of IGE. An important unanswered question is the power of this assay in resolving individual subjects. Here we address the accuracy and reliability of an assessment of visual contrast gain control in discerning individuals with IGE from the neurotypical. Our hypothesis is that a lack of response saturation is a marker of IGE.

2. Methods

Data were collected at two sites, University of California San Francisco (SF) and the University of Washington (UW). The SF sample was published in a previous report (Tsai et al., 2011) and re-analyzed here. Experimental procedures were as previously published (Tsai et al., 2011) except for minor differences noted below. Local ethics review boards approved the recruitment and experiment procedures.

2.1. Participants

The SF data comprised of ten patients (mean age 35 years) and thirteen neurotypical controls (mean age 35 years). The UW data comprised of 14 patients (mean and median age 33 years) and 19 neurotypical controls (mean age 29 years, median 21 years). Patients were diagnosed with IGE at tertiary epilepsy centers. Here we consider idiopathic generalized epilepsies as a neurobiological continuum (Berkovic et al., 1987) wherein syndromes share overlapping features, including genetic loci (Sander et al., 2000), seizure types, diurnal pattern of seizures, and response to treatment (Reutens and Berkovic, 1995). Medications and other clinical information of the UW patients are summarized in Table 1. Excluded were those with other neurological disorders. All subjects had normal or corrected-to-normal visual acuity.

2.2. Display and stimuli

Stimuli were shown in a darkened room using in-house software (powerDIVA) on cathode-ray tube monitors calibrated for nonlinear voltage vs. luminance response: a 19" LaCie Electron Blue monitor with 72 Hz vertical refresh rate and a mean luminance of 34 cd/m^2 (SF), and a 19" SONY 75 Hz refresh rate and mean luminance of 57 cd/m^2 (UW). Subjects viewed the display binocularly at a distance of 127 cm.

Briefly, stimuli were horizontal sine gratings (2 cycles/degree) windowed by a circularly symmetric Gaussian envelope (4 degrees radius) presented at fixation. 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-reversals) by a 7.2 Hz and 7.5 Hz sinusoid for SF and UW, respectively. For the SF experiments, the peak contrast was held fixed to one of the following: 0.05, 0.1, 0.2, 0.4, and 0.8, during each trial (10 s). For the UW experiments, the peak contrast was swept from 0.013 to 0.94 in 10 equal log-steps over each 10-s trial. The fixed-contrast and swept steady-state visual evoked potentials (SSVEP) paradigms have been shown to yield comparable contrast response functions (Tsai et al., 2011). Twenty trials of each condition were obtained with a short 3–5 s break in between trials.

2.3. SSVEP recording and preprocessing

EEG was recorded using 128-electrode HydroCel Sensor Nets on an Electrical Geodesic Inc. (Eugene, OR) NetStation 200 (SF) or NetStation 300 system (UW). Signals were recorded with a vertex physical reference, amplified with a gain of 1,000, band-pass filtered at 0.1–50 Hz, and digitized at 432 Hz (SF) or 450 Hz (UW). Artifact rejection, re-referencing, and spectral analysis were as described in Tsai et al. (2011). The frequency resolution of the spectral analysis was 0.93 Hz and 0.5 Hz for the UW and the SF data, respectively. The data-processing pipeline is illustrated in Fig. 1 using data from a typical subject.

We followed the approach outlined by Appelbaum et al. (2006) in calculating a "total amplitude" index of SSVEPs. The rationale for this approach is to maximize the power of the index by capturing as much of the SSVEP response as possible without a priori knowledge of which harmonics are important to distinguish epilepsy subjects. As illustrated in Fig. 1B, the SSVEPs consist of even harmonic components since two contrast reversals occur in each cycle of the stimulus (Regan, 1989). Therefore, we pooled the largest three even harmonics to represent the total activity. From the collated responses at each stimulus contrast and each channel for each subject, we computed the first spatial principal component, which represented a weighted sum of the channels so as to account for the largest proportion of the variance in the data. The even harmonic responses were projected onto the first principal component (Fig. 1C) and the Euclidian norm of the projections was computed as a measure of the response magnitude.

2.4. Modeling

Contrast response functions were fitted to a standard model (Albrecht and Hamilton, 1982; Heeger, 1992b; Peirce, 2007),

$$R = R_{max}\frac{c^2}{v^{2s}+c^{2s}} + b \quad (1)$$