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Authors
Varcin, Kandice J
Nelson, Charles A
Ko, Jordan
et al.

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Visual Evoked Potentials as a Readout of Cortical Function in Infants With Tuberous Sclerosis Complex

Kandice J. Varcin, PhD¹, Charles A. Nelson III, PhD¹,², Jordan Ko, BA³, Mustafa Sahin, MD, PhD⁴, Joyce Y. Wu, MD⁵, and Shafali Spurling Jeste, MD²

Abstract
Tuberous sclerosis complex is an autosomal dominant genetic disorder that confers a high risk for neurodevelopmental disorders, such as autism spectrum disorder and intellectual disability. Studies have demonstrated specific delays in visual reception skills that may predict the development of autism spectrum disorder and intellectual disability. Based on evidence for alterations in the retinogeniculate pathway in animal models of tuberous sclerosis complex, we asked whether children with tuberous sclerosis complex demonstrate alterations in early visual processing that may undermine the development of higher-level visual behaviors. Pattern-reversal visual evoked potentials were recorded in infants with tuberous sclerosis complex (n = 16) and typically developing infants (n = 18) at 12 months of age. Infants with tuberous sclerosis complex demonstrated remarkably intact visual evoked potentials even within the context of intellectual disability and epilepsy. Infants with tuberous sclerosis complex show intact visual cortical processing, suggesting that delays in visually mediated behaviors in tuberous sclerosis complex may not be rooted in early visual processing deficits.

Keywords
tuberous sclerosis complex, visual evoked potentials, event-related potentials, visual processing, neurodevelopmental disorders

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tuberous sclerosis complex. In an electrophysiological study investigating face perception, we found that children with tuberous sclerosis complex had delayed latencies in their neural response to faces compared to typically developing, age-matched children.\(^2\) At the behavioral level, we found that infants with tuberous sclerosis complex demonstrated specific delays in visually mediated behaviors at 6 months of age that subsequently generalized to all developmental domains by 9 months.\(^1\) Moreover, infants with tuberous sclerosis complex who later developed autism spectrum disorder presented with specific delays in visually mediated skills (such as visual reception and fine motor skills) compared to those infants who did not develop autism spectrum disorder. Based on these findings, the group hypothesized that aberrations in the retinogeniculate pathway in tuberous sclerosis complex could lead to low-level visual processing abnormalities that destabilize the development of higher-level visually mediated behaviors. Yet, to our knowledge, the functional integrity of the visual pathway in patients with tuberous sclerosis complex has not been directly examined.

The functional integrity of the visual pathway can be noninvasively assayed by extracting visual evoked potentials, an index of low-level visual processing, from electroencephalographic (EEG) activity.\(^1\) Visual evoked potentials recorded in response to transient pattern-reversing stimuli (eg, checkerboards) reflect the arrival of visual information to the primary visual cortex (via the lateral geniculate nucleus) and are sensitive to alterations in the retinogeniculate visual pathway.\(^2\) Pattern-reversal visual evoked potentials reliably elicit a negative peak (N1) occurring approximately 75 milliseconds after stimulus onset followed by a positive peak (P1) at around 100 milliseconds and a later negative peak (N2) at approximately 150 milliseconds.\(^1\) The visual evoked potential is dependent on the integrity of structures along the entire visual pathway, from the retina to the visual cortex, and abnormalities in the visual evoked potential may arise from lesions at any point of this pathway. For this reason, the differential diagnostic accuracy of the visual evoked potential is limited in the absence of other electrodiagnostic tests (such as electroretinogram). Visual evoked potential recordings in young children are technically difficult because of the need to control for the influence of inattention and movement artifacts on the waveform.\(^2\) The clinical and research importance of this approach lies in its capacity to provide an objective and sensitive readout of the integrity of the visual pathway.\(^2\) Visual evoked potentials can be recorded from very early in life and have been used to study the development of the visual system from early infancy.\(^2\) Here, we draw upon the visual evoked potential as a research tool to inform our understanding of visual processing deficits in tuberous sclerosis complex.

In the current study, we examined pattern-reversal visual evoked potentials in infants with tuberous sclerosis complex in order to determine if deficits in higher-order visually mediated behaviors in this population may be grounded in alterations in low-level visual processing. We studied infants at 12 months chronological age because the morphology of the visual evoked potential has matured by that age and typically reflects the visual evoked potential that will then be preserved through adulthood.\(^18,28,29\) Based on the evidence for (1) disturbances in structural connectivity in the visual pathway in both animal and human studies of tuberous sclerosis complex, (2) delayed latencies in face processing in young children with tuberous sclerosis complex, and (3) atypical visually mediated behaviors in infants with tuberous sclerosis complex, we predicted that infants with tuberous sclerosis complex would demonstrate latency delays and morphologic alterations in the visual evoked potential relative to typically developing infants.

**Methods**

**Study Design**

The data reported here were collected as part of a multisite, longitudinal investigation mapping the development of infants with and without tuberous sclerosis complex over the first 3 years of life. Infants were recruited and tested at the University of California, Los Angeles, Center for Autism Research and Treatment and Boston Children’s Hospital, Laboratories of Cognitive Neuroscience. Infants with a diagnosis of tuberous sclerosis complex were recruited through tuberous sclerosis complex specialty clinics, newborn nurseries, neonatal intensive care units, high-risk obstetrics practices, and pediatrician offices and the Tuberous Sclerosis Alliance. Typically developing infants were recruited through institutional review board–approved infant databases in the greater Los Angeles and Boston areas. Exclusion criteria for typically developing infants included a history of prematurity (<37 weeks’ gestational age), birth trauma, developmental concerns, or immediate family history of autism spectrum disorder or intellectual disability.

Participating families received compensation for travel and lodging. Institutional review board approval was obtained at the 2 study sites (University of California, Los Angeles, IRB no. 11-002349, Boston Children’s Hospital IRB no. P00001144) and all families provided consent prior to their participation. Data reported in this study were collected as part of a multisite, longitudinal study. Participation is ongoing, and full data collection will be available in 2 years (November 2011 to January 2014).

**Participants**

Usable EEG data were recorded from 16 infants with tuberous sclerosis complex (9 at Boston Children’s Hospital, 7 at University of California, Los Angeles; 14 males) and 18 typically developing infants (14 at Boston Children’s Hospital, 4 at University of California, Los Angeles; 8 males). Six additional infants were tested (5 tuberous sclerosis complex, 1 typically developing), but their data were not usable because of technical error (n = 4) or insufficient number of trials (fewer than 20) for analysis (n = 2).

Age range was 11 to 16 months at the time of testing. There were no significant differences in median chronological ages between the tuberous sclerosis complex (median = 12.5 months) and typically developing (median = 12.2 months) groups, \(U = 199.50, z = 1.92, P = .055\). Infants with tuberous sclerosis complex demonstrated significantly lower IQ estimates compared to typically developing infants across both nonverbal (tuberous sclerosis complex median = 79.5, typically developing median = 124; \(U = 28.00, z = -4.00, P < .001\)) and verbal (tuberous sclerosis complex median = 69, typically developing median = 98; \(U = 28.50, z = -3.98, P < .001\)) domains.
as assessed via the Mullen Scales of Early Learning. Mental age equivalents for the tuberous sclerosis complex group were 10.25 months for nonverbal IQ and 8.5 months for verbal IQ compared to 15.25 and 11.75, respectively, for typically developing infants.

**Clinical Information**

Information regarding antiepileptic medications, seizure history, genetic testing, visual acuity, tubers, and any ophthalmologic manifestations of tuberous sclerosis complex was obtained from medical records and a standardized medical questionnaire at the time of the visit.

Results of genetic testing were available for 11 infants with tuberous sclerosis complex. Eight infants had mutations in the TSC2 gene, and 3 had mutations in the TSC1 gene. Eleven infants had experienced infantile spasms by 12 months of age; for 7 participants, these spasms remained unresolved at their 12-month assessment. Twelve infants had a history of seizures by 12 months, and 3 infants had no history of seizures (seizure history was missing for 1 infant). The average age of seizure onset was 3.21 months with a range of 1 day to 6 months; at the time of testing, 3 of 12 were controlled with medication, 5 of 12 had a partial response with medication, and 4 of 12 were experiencing refractory seizures.

There were no reported visual perception or ocular function problems in any infants with tuberous sclerosis complex at 12 months of age, with information missing for 1 infant. The presence or absence of hamartomas could be confirmed for 13 infants; 6 of 13 infants had retinal hamartomas at age 12 months (2 right eye, 3 left eye, 1 bilateral). The prevalence of retinal hamartomas (6/13 or 46%) in our sample was consistent with prevalence rates reported in large, population-based studies of tuberous sclerosis complex. Information on tuber location at 12 months was available for only a subgroup of infants (n = 5). Of these, 4 (80%) had confirmed occipital lobe tubers, ranging in number from 3 to 12.

All infants, except the 3 with no history of seizures, were taking antiepileptic drugs at the time of their visual evoked potential recording. Vigabatrin is considered a first-line treatment for infantile spasms in tuberous sclerosis complex. Eleven infants in our sample had vigabatrin exposure by 12 months of age (information on past vigabatrin exposure was missing for 1 infant); 10 infants were taking vigabatrin at the time of their visual evoked potential recording. This antiepileptic drug has been linked to bilateral visual field loss in approximately one third of children receiving this therapy. Alterations in visual evoked potentials have been reported in the context of retinal toxicity when the visual evoked potential paradigm is modified to assess the visual field; however, studies using a standard paradigm typically report visual evoked potentials within normal limits. Perimetry testing is used to assess for visual field loss rather than visual evoked potentials; however, because of the young age of our sample, such testing was not possible. There were no reports of retinal toxicity or vigabatrin-associated visual field loss in our sample. Other antiepileptic drugs included clobazam (n = 2), gabapentin (n = 1), levetiracetam (n = 2), oxcarbazepine (n = 2), phenobarbital (n = 1), topiramate (n = 3), and valproic acid (n = 2).

There were no reported seizures or exposure to antiepileptic medications in the typically developing group.

**Visual Evoked Potential Stimuli**

At both sites, stimuli consisted of black and white checkerboards that reversed their phase (ie, black to white and white to black) every 500 milliseconds (ie, 2 reversals per second). The checkerboards had a mean luminance of 80 cd/m² and a contrast of 99%. Although both sites used identical high-contrast stimuli, spatial frequency varied slightly between the sites. At the Boston Children’s Hospital site, infants were positioned approximately 60 cm in front of a 34.7-cm (width) screen; checker size was approximately 60 minutes of arc (side length of checker = 1.57 cm) and spatial frequency was 0.5 cycles/degree. At the University of California, Los Angeles site, infants were positioned approximately 65 cm in front of a 52-cm (width) screen; checker size was approximately 90 minutes of arc (side length of checker = 2.36 cm) and spatial frequency was 0.3 cycles/degree. Although stimuli at both sites were dominated by low spatial frequency, we accounted for and considered these differences in our analysis (see Results section).

**Visual Evoked Potential Procedure**

Visual evoked potential data acquisition occurred within the context of a larger test battery of EEG measures, acquired within a single study session as part of our longitudinal study of infants with tuberous sclerosis complex. Infants were seated on their caregiver’s lap in a sound-attenuated, electrically shielded, dimly lit room in front of a Tobii T60 monitor while binocular, pattern-reversal visual evoked potentials were recorded via EEG. Presentation of the stimuli on the monitor was managed by ePrime software (Psychology Software Tools, Pittsburgh, PA), whereas stimulus phase-reversal was driven by the infants’ visual fixation on the screen, as monitored by the Tobii Eye-Tracking system. In other words, stimuli continued to reverse only as long as the infants’ gaze was fixated on the screen (minimum fixation time 100 milliseconds) and paused when the infant looked away. Infants viewed 50 to 100 trials, dependent on their ability to attend to the paradigm and their overall tolerability of the testing setting. Most infants completed all trials on the first visual evoked potential recording attempt; only 3 infants with tuberous sclerosis complex and 4 typically developing infants required the paradigm to be stopped and then returned later in the recording session to complete all trials. There were no differences in the number of trials presented to the tuberous sclerosis complex (median = 88.5) versus typically developing infants (median = 100), U = 117.00, z = -1.05, P = .365. The duration of the visual evoked potential recordings (quantified as time elapsed from the first stimulus presentation through to the completion of all phase reversals) ranged from 25 to 234 seconds in the typically developing group (median = 107 seconds) and 25 to 256 seconds in the tuberous sclerosis complex group (median = 77.5 seconds); there were no differences in visual evoked potential recording duration between the groups, U = 119.00, z = -0.86, P = .403.

**EEG Recording and Processing**

Continuous EEG was recorded using 128-channel HydroCel Geodesic Sensor Nets (Electrical Geodesics Inc, Eugene, OR) and amplified with a NetAmps 300 high-input amplifier. Data were sampled at 500 Hz and referenced to the vertex electrode (Cz) at acquisition. Electrical signal was recorded from 124 of the 128 channels on the nets as 4 electrooculographic electrodes (that are typically positioned on the face) were removed to enhance infants’ tolerability of the net. Signal processing occurred offline using NetStation 4.5 software. The signal was filtered with a 0.3- to 30-Hz finite impulse response (FIR) band-pass filter and segmented to 300-millisecond poststimulus-onset recording periods, with a 100-millisecond baseline. A temporal offset, specific to each site, was applied, at the point of segmentation, in order
to account for the delay between the stimulus trigger and appearance on the participant monitor. An additional 18-millisecond temporal offset was applied to account for the delay in EEG’s anti-aliasing filters for EEG sampled at 500 Hz with a NetAmps 300 amplifier, acquired with NetStation acquisition software 4.4 and above. Data were corrected to the mean voltage during the 100-millisecond period preceding a new phase reversal. Automated artifact detection was applied to detect channels, within each segment, that had a voltage change exceeding 200 μV. Trials were rejected if they contained more than 18 bad channels or if the electrode of interest (Oz) was marked bad. Trials were also rejected if they contained eye blinks, eye movements, artifact associated with body/eye movement or high-frequency noise, as determined by visual inspection of each segment. Of the remaining trials, channels marked for artifact were replaced using spherical spline interpolation. For each participant, an average waveform of all accepted trials was generated. Next, average waveforms for each participant were re-referenced to the average reference of all electrodes, excepting the 4 electrooculographic electrodes removed from the net (125, 126, 127, and 128) and the electrodes immediately proximal to these, that were not secured to the scalp because of the removal of the electrooculographic channels (1, 8, 14, 17, 21, 25, 32). To account for the recalibration of the data following referencing to the average of all channels, data were baseline corrected for a final time to the 100 milliseconds preceding stimulus onset. There were no significant differences in the median number of accepted trials for tuberous sclerosis complex (median = 46) and typically developing (median = 64) infants, \( U = 105.50, z = -1.33, P = .187. \)

**Visual Evoked Potential Data Extraction**

As per traditional visual evoked potential analysis approaches, we quantified activity over the midline occipital electrode, Oz. Specifically, we quantified peak amplitude and latency of the N1 (the first negative peak occurring between 40 and 100 milliseconds), the P1 (the positive peak immediately following the N1, occurring between 70 and 120 milliseconds), and the N2 (the negative peak following the P1, occurring between 100 and 170 milliseconds). Latencies were defined as latency to the peak of each component from stimulus onset. As per the International Society for Clinical Electrophysiology of Vision standard,\(^{19} \) amplitude of the P1 was measured from the preceding P1 peak (P1-N2 amplitude) and the amplitude of the N2 component was measured from the preceding P1 peak (P1-N2 amplitude).

**Statistical Analysis**

Distributions of amplitude and latency for each component, within each group, were nonnormal based on their respective histograms or Shapiro-Wilk tests. Mann-Whitney U nonparametric tests were performed to compare latencies of the N1, P1, and N2 between spatial frequency paradigms and groups and N1-P1 and P1-N2 amplitudes between spatial frequency paradigms and groups. All analyses were conducted using SPSS version 21.0 (IBM Corp, Armonk, NY).

**Results**

**Visual Evoked Potential Waveform**

As determined by visual inspection of the visual evoked potential waveforms for all participants, a typical N1-P1-N2 pattern of visual evoked potential responding was observed in both tuberous sclerosis complex and typically developing groups (see Figure 1), with a maximal distribution over the midline occipital region for both groups (see Figure 2). Specifically, for both groups, we observed an N1 occurring between 40 and 100 milliseconds, a P1 between 70 and 120 milliseconds, and an N2 between 100 and 170 milliseconds.

**Visual Evoked Potential: Spatial Frequency Comparisons (0.3 Versus 0.5 Cycles/Degree)**

**Latency.** For infants with tuberous sclerosis complex, there were no differences between the spatial frequency paradigms in latency to the N1 (\( U = 34.50, z = -0.32, P = .758 \)), P1 (\( U = 35.50, z = -0.42, P = .681 \)), or N2 (\( U = 40.50, z = 0.96, P = .351 \)). Similarly, there were no statistically discernible differences across the paradigms for typically developing infants in N1 (\( U = 34.50, z = 0.70, P = .505 \)), P1 (\( U = 44.00, z = 1.71, P = .101 \)), or N2 (\( U = 37.00, z = 0.96, P = .382 \)) latency.

**Amplitude.** For tuberous sclerosis complex infants, there were no differences between the spatial frequency paradigms in N1-P1 amplitude (\( U = 32.00, z = 0.05, P > .999 \)) or P1-N2 amplitude (\( U = 39.00, z = 0.79, P = .470 \)). There were also no differences across the paradigms for typically developing infants in N1-P1 amplitude (\( U = 33.00, z = 0.53, P = .645 \)) or P1-N2 amplitude (\( U = 26.00, z = -0.21, P = .878 \)).

In the absence of discernible differences in visual evoked potential latencies and amplitudes across the spatial frequency paradigms, data from these paradigms were subsequently examined collectively.

**Visual Evoked Potential: Tuberous Sclerosis Complex Versus Typically Developing Infants**

**Latency.** There were no group differences in latency to the peak of the N1 (\( U = 118.00, z = -0.90, P = .384 \)), P1 (\( U = 185.50, z = 1.44, P = .154 \)), or N2 (\( U = 183.50, z = 1.37, P = .175 \)) of the visual evoked potential. Median latency values and interquartile ranges for each component are reported in Table 1.

**Amplitude.** There were no differences between the tuberous sclerosis complex and typically developing groups in N1-P1 amplitude (\( U = 146.00, z = 0.07, P = .959 \)) or P1-N2 amplitude (\( U = 108.00, z = -1.24, P = .224 \)). Median values for the N1-P1 and P1-N2 amplitudes, within each group, are reported in Table 1.

**Discussion**

The current study interrogated the functional integrity of the visual pathway in 12-month-old infants with tuberous sclerosis complex using binocular pattern-reversal visual evoked potentials. Based on evidence for aberrations in the retinogeniculo-oculuate pathway in animal models of TSC1/2\(^{14,15} \) and further supported by evidence of atypical visually mediated behaviors in infants with tuberous sclerosis complex\(^{16} \) and delays in face processing in older children with tuberous sclerosis.
complex, we posited whether infants with tuberous sclerosis complex might demonstrate functional disturbances in visual cortical processing, reflected in morphologic alterations to the visual evoked potential. Contrary to our hypothesis, we observed remarkably intact visual evoked potentials in infants with tuberous sclerosis complex, as quantified by comparable amplitudes and latencies of the primary components of the visual evoked potential—the N1, P1, and N2. These findings show that (1) pattern-reversal visual evoked potentials can be recorded in tuberous sclerosis complex, even in the setting of comorbid developmental delay, epilepsy, and antiepileptic drug exposure, and (2) the morphology of the visual evoked potential waveform is comparable to that of typically developing infants at 12 months of age, suggesting that the functional integrity of the visual pathway is preserved at a young age in tuberous sclerosis complex.

The absence of abnormalities in early visual cortical processing in tuberous sclerosis complex has important implications for our understanding of higher-level visual processing disturbances in this group. The robust visual evoked potentials found in this group suggest that the early processing of basic visual information is intact in tuberous sclerosis complex and, as a consequence, disturbances in more complex visual skills are unlikely to be a consequence of alterations in early visual processing in the first year of life. Therefore, the association between autism spectrum disorder and nonverbal cognitive impairment in tuberous sclerosis complex is not simply rooted in a low-level perceptual deficit and, instead, likely lies in circuits associated with the processing of more complex visual stimuli. In nonsyndromic autism spectrum disorder, it has been posited that impairments in the ability to attend to, and process faces, contribute to broader social impairments in autism spectrum disorder such as atypical modulation of eye contact and joint attention. Face processing is grounded in a complex neural network involving the superior temporal sulcus, fusiform gyrus, and extrastriate

Figure 1. (A) Grand-averaged VEP waveforms for TD and TSC groups; (B) individual VEP traces for 12-month-old TD infants, (C) individual VEP traces for 12-month-old infants with TSC. TD, typically developing; TSC, tuberous sclerosis complex; VEP, visual evoked potential.
visual cortex. In tuberous sclerosis complex, aberrations in this face-processing network from early in life may contribute to face-processing delays, which, in turn, undermine the development of other core social communication skills, such as eye contact and joint attention. In order to substantiate this contention more completely in tuberous sclerosis complex, future investigations will need to examine visual cortical processing across a wider range of developmental ages and more complex visual stimuli. Examinations of the visual evoked potential within the first year will affirm whether the visual evoked potential follows a typical maturational trajectory and whether there are individual differences in the trajectory of the visual evoked potential that may inform the specific delays in visually mediated behaviors observed at 6 months of age in tuberous sclerosis complex. Similarly, as most infants had antiepileptic drug exposure by 12 months, investigations within the first year will elucidate whether these medications served to normalize what would have otherwise been atypical visual evoked potentials. Future studies with larger sample sizes will also be of benefit in delineating any influence of medication exposure and seizure status on the processing of early visual information.

It is also possible that early visual processing abnormalities may manifest later in development in tuberous sclerosis complex, as the studies of structural abnormalities in visual cortex in both the mouse model and humans were performed after 1 year of age, and our study demonstrating atypical face processing was performed in preschool-age children with tuberous sclerosis complex. Finally, the examination of early visual processing across a wider range of spatial frequencies and to more complex stimuli (such as examination of the P1 component to faces or other objects) may reveal more subtle alterations in visual cortical processing in tuberous sclerosis complex than are detectable from a low spatial frequency, checkerboard stimulus. For example, in children with nonsyndromic autism spectrum disorder, alterations in steady-state visual evoked potential responses (marked by reductions in signal amplitude) to vertical gratings manifest only within a specific range of spatial frequencies.

The visual evoked potential represents a promising powerful translational biomarker of cortical function that can be studied in both animal and human models of tuberous sclerosis complex. Studies from animal models of TSC1/2 have significantly advanced our understanding of the consequences of a tuberous sclerosis complex mutation to the structural integrity of the retinogeniculate pathway. However, the functional consequences of aberrations in the visual pathway in these animal models have yet to be examined. Given the cortical pathology found in tuberous sclerosis complex mouse models, measurement of the visual evoked potential in these models would directly address the question of whether structural abnormalities translate to functional impairments in visual processing. The relationship between structure and function in visual systems could, in turn, also be studied in patients with tuberous sclerosis complex by relating structural imaging methods, such

Table 1. Median Values (and Interquartile Range) for Peak Latencies and Amplitudes of the N1, P1, and N2 for TSC (n = 16) and Typically Developing (TD; n = 18) Groups.

<table>
<thead>
<tr>
<th>Latency (ms)</th>
<th>N1</th>
<th>P1</th>
<th>N2</th>
<th>N1-P1</th>
<th>P1-N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC</td>
<td>60 (10)</td>
<td>99 (12)</td>
<td>141 (16)</td>
<td>13.52 (12.88)</td>
<td>14.04 (11.07)</td>
</tr>
<tr>
<td>TD</td>
<td>63 (8)</td>
<td>94 (11)</td>
<td>138 (14)</td>
<td>14.40 (13.22)</td>
<td>18.62 (16.83)</td>
</tr>
</tbody>
</table>

Abbreviation: TD, typically developing; TSC, tuberous sclerosis complex.
as diffusion tensor imaging, with the visual evoked potential characteristics.

In summary, we have shown that a clinically heterogeneous group of infants with tuberous sclerosis complex, most with infantile spasms, intellectual delay, antiepileptic drug exposure, and some with retinal hamartomas and occipital tubers demonstrate remarkably robust visual evoked potentials in response to high-contrast, low spatial frequency pattern-reversal stimuli. We did not find any evidence to suggest that the arrival of visual information to the primary visual cortex and subsequent early processing of visual information is altered in infants with tuberous sclerosis complex at 12 months of age. These findings support the utility of phase reversal visual evoked potentials as readouts of visual cortical processing in tuberous sclerosis complex and suggest that delays in more complex visual skills in tuberous sclerosis complex may not be rooted in deficits in the processing of basic visual information.

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Author Contributions
KV was involved in data acquisition, data analysis, and data interpretation and drafted the manuscript. CN substantially contributed to study design, conception, and implementation; was responsible for supervision of data acquisition at the University of California, Los Angeles site; and critically revised the manuscript for important intellectual content. JK contributed to data acquisition and analysis and critically revised the manuscript for important intellectual content. MS and JW were involved in study design and critically revised the manuscript for important intellectual content. SJ substantially contributed to study design, conception, and implementation; was responsible for supervision of data acquisition at the University of California, Los Angeles site; and critically revised the manuscript for important intellectual content. All authors gave their final approval and agree to be accountable for all aspects of this work.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval
Institutional Review Board approval was obtained from the University of California, Los Angeles, Institutional Review Board (no. 11-002349) and Boston Children’s Hospital Institutional Review Board (no. P00001144). Informed consent was obtained from all families prior to their participation in the study.

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