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Jeste, SS
Hirsch, S
Vogel-Farley, V
et al.

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Atypical Face Processing in Children With Tuberous Sclerosis Complex

Shafali Spurling Jeste, MD1,2, Suzanna Hirsch3, Vanessa Vogel-Farley3, Amanda Norona1, Mary-Clare Navalta1, Matt C. Gregas, PhD2,4, Sanjay P. Prabhu, MD5, Mustafa Sahin, MD, PhD2,6, and Charles A. Nelson, PhD3

Abstract
There is a high incidence of autism in tuberous sclerosis complex. Given the evidence of impaired face processing in autism, the authors sought to investigate electrophysiological markers of face processing in children with tuberous sclerosis complex. The authors studied 19 children with tuberous sclerosis complex under age 4, and 20 age-matched controls, using a familiar–unfamiliar faces paradigm. Of the children, 6 with tuberous sclerosis complex (32%) had autism. Children with tuberous sclerosis complex showed a longer N290 latency than controls (276 ms vs 259 ms, \( P = .05 \)) and also failed to show the expected hemispheric differences in face processing. The longest N290 latency was seen in (1) children with autism and tuberous sclerosis complex and (2) children with temporal lobe tubers. This study is the first to quantify atypical face processing in children with tuberous sclerosis complex. This functional impairment may provide insight into a mechanism underlying a pathway to autism in tuberous sclerosis complex.

Keywords
tuberous sclerosis complex, autism, evoked potentials, cortical tubers

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Tuberous sclerosis complex is a very rare disorder, with an incidence of 1 in 10 000, and it is strongly associated with neurodevelopmental disabilities. As many as 80% of children have some form of cognitive impairment, and up to 60% are diagnosed with an autism spectrum disorder.1–6 Autism is a pervasive developmental disorder defined by impairments in social interaction and communication, and the presence of repetitive behaviors and restricted interests.

In this study, the authors investigated the neural correlates of face processing in children with tuberous sclerosis complex, using event-related potentials. The authors focused on face processing for two reasons. First, given the high prevalence of autism in tuberous sclerosis complex and the extensive literature on atypical face perception in individuals with autism, both in attention to faces and in neural markers of face processing using electrophysiology and neuroimaging, face processing could serve as a biomarker of autism in this population.7–12,13 The neural networks required for face processing include extrastriate visual cortex, superior temporal sulcus and lateral fusiform gyrus (for review, see Haxby et al14). It has been hypothesized that in children with autism, reduced attention to faces and, in turn, aberrant processing of faces may contribute to the social impairments characterizing the disorder, such as eye contact and joint attention.7–9,15–17

Second, face processing represents a construct that requires a combination of low-level visual processing (presence of stimuli on the screen) and higher order processing (categorization of identity), each of which could be impaired given the aberrant structural connectivity in visual projections shown in the tuberous sclerosis complex mouse model. In the neuron specific Tsc1 conditional knockout mouse, diffuse cortical and subcortical hypomyelination have been found.18

1 UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, USA
2 Department of Neurology, Children’s Hospital, Harvard Medical School, Boston, MA, USA
3 Laboratories of Cognitive Neuroscience, Children’s Hospital, Harvard Medical School, Boston, MA, USA
4 Clinical Research Program, Children’s Hospital, Boston, MA, USA
5 Department of Neuroradiology, Children’s Hospital, Harvard Medical School, Boston, MA, USA
6 F. M. Kirby Neurobiology Center, Children’s Hospital, Boston, MA, USA

Corresponding Author:
Shafali Spurling Jeste, MD, Semel Institute for Neuroscience and Human Behavior, UCLA Center for Autism Research and Treatment, 760 Westwood Plaza, Suite 68-237, Los Angeles, CA 90095, USA.
Email: sjeste@mednet.ucla.edu
In \( Tsc2 \) heterozygous mice, investigators have found abnormally exuberant axonal projections from retina to the lateral geniculate nucleus, suggesting defects in axon guidance. In addition, a recent study by Nie et al found abnormal axonal targeting in retinogeniculate projections in \( Tsc2 \) heterozygous mice, with visual projections appearing more diffuse and less organized. Thus, studies are now focusing on more advanced neuroimaging techniques, such as diffusion tensor imaging, to characterize neural circuitry in tuberous sclerosis complex. However, no studies have investigated the functional implications of this pathology.

The authors’ guiding hypothesis was that children with tuberous sclerosis complex would show impairments in neural markers of early visual processing and in face perception, and that these differences would be more prominent in children with comorbid tuberous sclerosis complex and autism. To best characterize face processing, the authors used a traditional event-related potential familiar–unfamiliar face paradigm. Event-related potential signatures of face processing include the P1 and N290/P400. The P1 is associated with low-level perception of a visual stimulus, and it is generated in striate and extrastriate cortex. The neural generators of the N290/P400 complex are localized in face-sensitive regions in ventral temporal cortex. It is important to note that several recent studies have shown that children with autism show atypical neural responses to faces.

This is the first electrophysiological study of face processing in children with tuberous sclerosis complex. Because tuberous sclerosis complex is a rare disorder, and thus children for this project were challenging to recruit, the authors’ goal in this preliminary study was to study as many children as possible, from infancy through preschool age. It is for this reason that the study sample varies so widely in age.

Methods and Materials

Participants

After obtaining Institutional Review Board approval, children with tuberous sclerosis complex under the age of 4 were recruited through the Children’s Hospital Boston Multidisciplinary Tuberous Sclerosis Program. A total of 28 children with tuberous sclerosis complex met age criteria for the study. 26 age matched controls were recruited through the Children’s Hospital Boston Laboratories of Cognitive Neuroscience Participant Recruitment Database. Informed consent was obtained from all subjects.

Review of Magnetic Resonance Imaging Data

As part of their clinical management, all children with tuberous sclerosis complex had at least one brain magnetic resonance image performed at Children’s Hospital, and the imaging sequence performed nearest to the date of the electrophysiological evaluation was chosen. A combination of sagittal T1, axial and coronal T2-weighted images, axial and coronal fluid-attenuation inversion recovery, T1-weighted 3-dimensional magnetization-prepared rapid gradient echo sequence, and post contrast axial and coronal T1 weighted images were reviewed by a pediatric neuroradiologist (SP) blinded to the clinical findings and electrophysiological data. Review was directed toward quantifying number, size, and distribution of tubers. A tuber was defined as a lesion of abnormal signal intensity located within a cortical gyrus.

Review of Clinical Data

All charts were systematically reviewed and data were extracted by a child neurologist (SSJ). Autism diagnoses of children above the age of 18 months and concerns for an autism diagnosis for children below 18 months were based on clinician/researcher report, using the Autism Diagnostic Observation Schedule (Lord 1999) or the Autism Observation Scale of Infancy (Bryson 2008).

Stimuli and Task Procedure

Children were either seated on their parents’ lap or in a chair. Event-related potentials were recorded while participants viewed alternating color pictures of a primary caregiver and a gender- and age-matched stranger. Each image was presented 50 times, with 100 total trials possible. The average number of trials presented was 68.

Electrophysiological Recording and Data Processing

Continuous electroencephalography was recorded using a Geodesic Sensor Net or Hydrocel Geodesic Sensor Net, with 64 or 128 electrodes (Electrical Geodesic Inc, Eugene, OR). Two different net sizes were used because of the large range of head circumferences in the authors’ population. Electrode groupings were chosen based on overlapping regions using the 10-20 system. The electrical signal was digitized to 250 Hz and amplified with a 0.1 to 100 band-pass filter. The data were analyzed offline using NetStation 4.4.2 analysis software (Electrical Geodesics Inc.). The continuous electroencephalographic signal was digitally filtered with a 30-Hz lowpass filter and then segmented to a 1600 millisecond period, with 100 millisecond baseline. After excluding segments with eye movements and blinks, the remaining segments were visually scanned for bad channels and other artifacts. Participants with fewer than 10 good trials per condition were excluded from further analysis. Finally, average waveforms for each individual participant were calculated and re-referenced to the average reference and baseline corrected.

Event-related Potential Data Extraction

Analysis focused on peak amplitude and latency for the occipital-temporal P1 (75-190 ms poststimulus onset), N290 (200-350 ms poststimulus onset), and P400 (350-550 ms poststimulus onset). Because different electrode densities and net types were used, the authors superimposed a 10-20 electrode distribution to select electrodes for each net type that covered approximately similar scalp regions for all subjects. Electrodes included PO7, PO3, O1, O2, PO4, PO8.

Event-related Potential Statistical Analysis

Peak amplitude and latency were calculated for each component in the chosen time windows. A repeated measures analysis of variance of hemisphere (right, left), condition (mother, stranger), and group (primary analysis included tuberous sclerosis complex, controls) was performed with both amplitude and latency as dependent variables. Several different groupings were analyzed in separate analyses of variance: (1) controls versus tuberous sclerosis complex, (2) tuberous...
### Table 1. Clinical summary of TSC sample.

#### TSC sample without autism

<table>
<thead>
<tr>
<th>Gender</th>
<th>Epilepsy</th>
<th>Spasms</th>
<th>Genetics</th>
<th>Tuber Burden</th>
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<tr>
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<td>N</td>
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</tr>
<tr>
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<td>N</td>
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<td>TSC2</td>
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</tr>
</tbody>
</table>

#### Tuber locations by lobe: F=frontal, P=parietal, O=occipital, T=temporal.

#### TSC sample with autism

<table>
<thead>
<tr>
<th>Gender</th>
<th>Epilepsy</th>
<th>Spasms</th>
<th>Genetics</th>
<th>Tuber Burden</th>
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<td></td>
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<td>Y</td>
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<tr>
<td>M</td>
<td>M</td>
<td>Y</td>
<td>not tested</td>
<td>10 9 9 4 31</td>
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</table>

Tuber locations by lobe: F=frontal, P=parietal, O=occipital, T=temporal.
sclerosis complex/autism versus tuberous sclerosis complex/no autism versus controls, (3) presence versus absence of temporal lobe tubers, and (4) presence versus absence of occipital lobe tubers. Greenhouse–Geisser correction was applied because the sphericity assumption was violated. When the analysis of variance yielded significant effects, pairwise comparisons including three or fewer means were carried out by using $t$ tests (Fisher’s least significant difference procedure).

**Results**

Of the 28 children with tuberous sclerosis complex, 19 (68%) provided adequate data for final analysis (three refused to wear the net, six had poor quality electrophysiological data due to movement artifact). Of the 26 controls, 20 (77%) provided adequate electrophysiological data (two refused to wear the net, four had poor quality data due to movement artifact). Within the subgroup with autism, 6/10 (60%) children with comorbid tuberous sclerosis complex provided adequate electrophysiological data, while 13/18 (72%) children with tuberous sclerosis complex/no autism provided acceptable electrophysiological data.

The age range was 3 to 46 months (average age 23.1 months in the tuberous sclerosis complex group, 22.9 months in controls). Males composed 12/19 (63%) of the tuberous sclerosis complex group and 6/20 (30%) of the control group. Additional clinical data recorded from the tuberous sclerosis complex group included genetic mutations, tuber count by location, history of infantile spasms, epilepsy, and diagnosis of autism. Mean tuber count was 20 (range 0–41). A summary of the clinical profiles of the tuberous sclerosis complex sample is provided in Table 1.

It should be noted that 15 of 19 children (79%) in the authors’ tuberous sclerosis complex sample had a diagnosis of epilepsy at the time of their event-related potential investigation, with all of these children being treated with at least one antiepileptic medication. No electrographic seizures were documented during the event-related potential recording. Moreover, due to the steps taken to generate an event-related potential from the raw electroencephalogram (viz, filtering, artifact detection and segmentation) any atypical background electrophysiological activity should not affect the time locked event-related potential. Several prior studies have successfully characterized event-related potentials in children with epilepsy.

**Event-related Potential Results**

**Tuberous sclerosis complex versus controls.** Despite their extensive cortical pathology, children with tuberous sclerosis complex showed robust electrophysiological evidence of face processing. There was a significant main effect of group in N290 latency, with tuberous sclerosis complex showing a longer N290 latency than controls ($F = 3.99, P = .05$). There was no significant difference between groups for the P1 peak amplitude or latency, N290 peak amplitude, or P400 peak amplitude or latency. In addition, there was a significant region by group interaction for the N290 latency ($F = 3.63, P = .04$; see Figure 1). Post hoc analysis showed that this interaction...
was driven by two factors. First, there was a significant difference for N290 latency between tuberous sclerosis complex and controls in the right hemisphere, \(t(33.2) = 2.68, P = .01\). Second, the control group showed an expected significant hemispheric difference for the N290, with N290 latency longer on the left compared to the right, \(t(19) = 2.98, P = .008\) see Figure 2. The tuberous sclerosis complex group did not demonstrate this hemispheric difference.

**Autism grouping.** Of the sample with tuberous sclerosis complex, ten children had a diagnosis of autism, with 6 providing adequate electrophysiological data. Of the children, 18 did not meet criteria for autism, with 13 providing adequate electrophysiological data. No significant differences were found for the P1 or P400 peak amplitude or latency. There was no significant group by region interaction, thus regions were collapsed and analyzed together. With regions collapsed, there was a marginally significant group difference for N290 latency, such that the children with both tuberous sclerosis complex and autism showed a longer N290 latency compared to the children with tuberous sclerosis complex and no autism \(F = 2.43, P = .09\).

**Tuber groupings.** To better characterize the relationship between cortical pathology and face processing, the authors created subgroups within the tuberous sclerosis complex sample based on presence of tubers in (1) temporal cortex and (2) occipital cortex. The authors focused on these two regions because of the known neural origins of the P1, N290 and P400. Imaging data were not available on one child with tuberous sclerosis complex, thus the total was reduced to 18 for the tuber analysis, with control group remaining at 20. Of 18 children, 14 had temporal lobe tubers (ranging from 1 to 8 tubers). There were no group differences in the P1 or P400 amplitude or latency, or N290 amplitude. However, there was a significant main effect of group for N290 latency, with the temporal lobe tuber group displaying a longer N290 latency \(F = 3.2, P = .05;\) see Figure 3). Of 18 children, 11 had occipital lobe tubers (ranging from 1 to 8). No significant group differences, based on presence or absence of occipital lobe tubers, were found in the P1, N290, or P400 peak amplitudes or latencies.

**Discussion**
In this study, the authors sought to characterize low-level visual processing and face processing using event-related potentials in young children with tuberous sclerosis complex. The authors’ sample was drawn from a large multidisciplinary tuberous sclerosis complex clinic, with a representative range in phenotypes. Given the rarity of this disorder, the number of subjects from which the authors have gathered high-quality data is unprecedented.

In these results, children with tuberous sclerosis complex demonstrated slowed face processing, most prominent in the subgroup with autism. This difference was not driven by a deficit in low-level visual processing, as there were no group differences in the P1. The authors also found that children with tuberous sclerosis complex lacked a hemispheric difference in
face processing speed. Compared to controls and children without temporal lobe tubers, children with temporal lobe tubers showed the slowest face processing based on N290 latency. There also was a trend toward the slowest face processing in children with both tuberous sclerosis complex and autism. These findings hold great promise in future studies focused on the identification of biomarkers of autism in tuberous sclerosis complex.

First, with regard to the difference in N290 latency, several studies have demonstrated a difference in the N290 component between children with autism and controls. The fact that low-level visual processing did not differ between groups supports a specificity to prolonged processing of faces and not a global deficit in visual processing.

The lack of hemispheric asymmetry, as seen in the tuberous sclerosis complex group, has been documented both structurally using volumetric magnetic resonance imaging and also functionally using electroencephalography, single photon emission computed tomography, and functional magnetic resonance imaging, in resting state and in response to a variety of perceptual and cognitive tasks in children and adults with a known diagnosis of autism, as well as in parents of children with autism. More specific to face processing, McCleery et al recently investigated face and object perception in 10-month-old infants at high risk for autism. The group identified a lack of asymmetry in face-sensitive components only in the high-risk group. This lack of asymmetry may reflect abnormal functional organization of brain regions over development and, in turn, a failure to develop cortical specialization in networks and domains critical for typical social and cognitive development.

There have been several clinical studies exploring the possible association between temporal lobe pathology and neurodevelopmental disorders in tuberous sclerosis complex. Bolton et al first described the association between bilateral temporal lobe epileptiform discharges and autism in tuberous sclerosis complex. More recently, Numis et al studied a cohort of 103 patients with tuberous sclerosis complex, 40% of whom held a diagnosis of autism. Patients with autism were more likely to have interictal epileptiform abnormalities in the left temporal lobe. Finally, in a study correlating neuroimaging with “neurological severity,” defined by seizures, developmental delay and autism, Chou et al found that left temporal lobe tuber burden was significantly associated with severity scores.

The authors recognize that there is much more complexity to the neuropathology in tuberous sclerosis than simply tuber burden. Increasing evidence from animal models of tuberous sclerosis complex points to the presence of aberrant structural connectivity, with the tuberous sclerosis complex/mTOR signaling regulating synaptogenesis and synaptic function, growth of axons and dendrites, and myelination. The authors’ grouping by temporal lobe tubers was driven by their understanding of the importance of temporal lobe circuits for face processing. The differences found between groups may be driven by aberrant connectivity or hypomyelination in the temporal cortex, with tuber burden serving as an associated variable rather than the driving force.
There are several possible reasons why the N290 latency difference seen between autism groupings approached, but did not reach, significance. First, the small sample size limits the power of the analysis. Second, there is inherent phenotypic heterogeneity in children with autism, not only in core deficits but also in cognitive and perceptual processing. With a larger sample size, the authors will be able to correlate event-related potential characteristics with specific clinical characteristics within the autism sample. Third, given the understanding that the pathway to autism in tuberous sclerosis complex is mediated by the interaction of several factors, possibly with slowed face processing being one element, it is likely that differences in face processing suggested by the current findings may predispose these children to develop autism, but may not necessitate it. Nevertheless, the current findings demonstrate that face possessing is a promising and crucial area of future tuberous sclerosis complex research.

In addition to the small sample size, another limitation to this study is the age range. The authors are well aware that face processing changes over early development, thus leading to age effects in the authors’ sample. The authors chose not to divide the sample by age to best characterize their sample and retain statistical power. Of note, the authors’ group has data on this paradigm in infants at risk for autism, from ages 6 to 36 months, and no age effects are seen (manuscript in preparation). The fact that the authors found no differences in event-related potentials between the familiar and unfamiliar condition may, in fact, be rooted in the age range of the participants. Typically developing children show larger responses to mother in early infancy followed by larger differences seen between autism groupings approached, but did not reach, significance. First, the small sample size limits the power of the analysis. Second, there is inherent phenotypic heterogeneity in children with autism, not only in core deficits but also in cognitive and perceptual processing. With a larger sample size, the authors will be able to correlate event-related potential characteristics with specific clinical characteristics within the autism sample. Third, given the understanding that the pathway to autism in tuberous sclerosis complex is mediated by the interaction of several factors, possibly with slowed face processing being one element, it is likely that differences in face processing suggested by the current findings may predispose these children to develop autism, but may not necessitate it. Nevertheless, the current findings demonstrate that face possessing is a promising and crucial area of future tuberous sclerosis complex research.

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This is the first study to explore the neural markers of face processing in children with tuberous sclerosis complex. These promising results demonstrate that children with tuberous sclerosis complex are slower to process faces, and that they lack the hemispheric specialization for face processing seen in typically developing children. The authors also characterize a trend toward slower face processing in children with temporal lobe tubers and in children with tuberous sclerosis complex/autism. Through this work, the authors have begun to define an electrophysiological biomarker of a perceptual domain critical for normative social development, with the ultimate goal of defining functional pathways to autism in tuberous sclerosis complex.

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Author Contributions
SSJ designed the study and took primary responsibility for manuscript preparation. SH contributed to data acquisition and analysis and manuscript preparation. VVF was involved with data collection and manuscript preparation. AN and MN contributed to manuscript preparation. MCG was responsible for statistical analysis. SPP was responsible for analysis of the imaging data. MS was the lead clinician in the Children’s Hospital, Boston tuberous sclerosis complex program and was involved in study design and manuscript preparation. CAN was the principal investigator of the study, and therefore he advised on study design, data collection, analysis, and manuscript preparation. All authors agreed with the conception, analysis, and drafting and approved the manuscript, and all contributing authors are indicated.

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
The study was performed with Institutional Review Board approval at Children’s Hospital, Boston (IRB # 06110518). Parental informed consent was obtained for all subjects.

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