Functional connectivity in tuberous sclerosis complex with autistic spectrum disorder preliminary findings

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Abstract. Despite the frequent occurrence of autism spectrum disorder (ASD) in tuberous sclerosis complex (TSC), the neurophysiological factors that distinguish children with TSC from children with TSC presenting with ASD symptoms remain unspecified. Growing evidence suggests that ASD may be characterized by atypical structural and functional connectivity between specific cortical regions. In this exploratory study, we utilized magnetoencephalography to derive resting brain connectivity patterns, in an attempt to identify neurophysiological markers that may differentiate TSC children with ASD (n = 2) from TSC children without ASD (n = 2) and typically developing children (n = 2). Connectivity pattern analysis revealed that TSC children presenting with ASD symptoms can be distinguished from TSC and typically developing children by the presence of long-range, medial, anterior-posterior connections previously observed in adolescents with ASD. While preliminary in nature, our findings support the notion that altered functional connectivity may be a constituent characteristic of ASD and may enable prediction of which TSC children are likely to develop ASD and facilitate early behavioral and medical intervention.

Keywords: Tuberous sclerosis complex, autism spectrum disorder, magnetoencephalography, functional connectivity

1. Introduction

Autism spectrum disorder (ASD) is one of the more common co-morbidities associated with tuberous sclerosis complex (TSC) (incidence of 17–63%) [1], though the neurological factors that may account for this overlap remain unclear. For instance, there is some indication that clinically, the prevalence of ASD in TSC may be related to infantile spasms [1]. Furthermore, differentiation of individuals with TSC from those presented with TSC and ASD, based on neuro-anatomical and physiological features, has been
Table 1

Tuberous sclerosis complex patient clinical characteristics

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Gender</th>
<th>TSC genotype</th>
<th>Age seizure onset (yr)</th>
<th>Infantile spasms (yes/no)</th>
<th>Current age (yr)</th>
<th>Current seizure type</th>
<th>Current seizure frequency</th>
<th>Current developmental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>TSC2 and polycystic kidney disease</td>
<td>0.25</td>
<td>Yes</td>
<td>4.5</td>
<td>Generalized myoclonic</td>
<td>Every other day to weekly</td>
<td>Global delay, autism spectrum disorder</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>TSC1 and TSC 2</td>
<td>Birth</td>
<td>Yes</td>
<td>4.7</td>
<td>Complex partial</td>
<td>Rare (up to 3–4 mo seizure free between seizures)</td>
<td>Global delay, left hemi paresis, autism spectrum disorder</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>TSC2</td>
<td>3.5</td>
<td>No</td>
<td>8.8</td>
<td>Complex partial</td>
<td>One every 2–3 wk</td>
<td>Borderline cognitive functioning, Attention deficit-hyperactivity disorder combined type</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>Negative for TSC1 and TSC2</td>
<td>1</td>
<td>No</td>
<td>8.8</td>
<td>Complex partial</td>
<td>Seizure-free</td>
<td>Borderline cognitive functioning</td>
</tr>
</tbody>
</table>

TSC = Tuberous sclerosis complex.

attempted only in a handful of studies that seem to suggest that the prevalence of temporal lobe tubers [2, 3], as well as aberrant temporal lobe function [1,3], may underlie the manifestation of ASD symptoms among individuals with TSC. More recently, diffusion tensor imaging (DTI) studies have enhanced understanding of the neural correlates of ASD in TSC, suggesting that TSC individuals with ASD can be distinguished from those without ASD and neurologically intact controls on the basis of aberrant inter- and intra-hemispheric connectivity, exemplified by reductions in the integrity of callosal fibers [4] and of the arcuate fasciculus [5].

Similarly, while the pathophysiology of ASD itself remains unknown, a model of the autistic brain is beginning to emerge, characterized by atypical structural and functional connectivity between specific brain regions posited to underlie the integration of information at the cognitive level [6]. Specifically, alterations in patterns of regional connectivity in ASD have been demonstrated using diffusion tensor imaging and hemodynamic imaging [7], a claim also supported by electroencephalography and magnetoencephalography (MEG) studies which have differentiated between individuals with ASD and neurologically intact controls, on the basis of altered neural connectivity patterns derived from baseline (resting) brain activity recordings [8,9].

If aberrant network organization is a constituent characteristic of ASD, this feature may also enable prediction of which individuals with TSC, early in development, are likely to develop ASD, thus facilitating early intervention. In this exploratory study, we utilized resting MEG to derive brain connectivity patterns, in an attempt to identify neurophysiological markers that could potentially differentiate reliably children with TSC presenting with ASD from TSC children without ASD and typically developing (TD) controls. In our earlier studies of connectivity pattern analysis in adolescents with ASD, we have found that the feature extraction and classification methods we have developed are most accurate when they are based on resting connectivity patterns derived with the method known as Granger causality [8,9]. Accordingly, we adopted an identical approach to derive connectivity patterns based on resting MEG recordings in two TD controls, two TSC children without ASD, and two TSC children with ASD (TSC/ASD).

2. Materials and methods

2.1. Participants

Individuals with TSC were identified through a retrospective chart review of patients admitted to the epilepsy monitoring unit of the comprehensive epilepsy program at Le Bonheur Children’s Hospital, having undergone inter-ictal electroencephalography/MEG, magnetic resonance imaging, genetic and formal neuropsychological testing as part of their routine clinical evaluation (see Tables 1 and 2 for patient clinical features and evaluation summary, respectively). The TD children consisted of one male and female,
Table 2
Tuberous sclerosis complex patient evaluation summary

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age at evaluation (yr)</th>
<th>Magnetic resonance imaging findings</th>
<th>Interictal electroencephalography</th>
<th>Interictal magnetoencephalography (localization of activity sources)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.2</td>
<td>Typical tuberous sclerosis complex findings, no focality</td>
<td>Generalized and multifocal epileptiform discharges, diffuse background slowing</td>
<td>Left frontal and right temporal</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>Typical tuberous sclerosis complex findings and right parietotemporal pachygyria</td>
<td>Right frontotemporal central focal slowing and epileptiform discharges, diffuse background slowing</td>
<td>No activity sources noted</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Left parietal and occipital hamartomas, right occipital hamartomas</td>
<td>Left occipital epileptiform discharges and focal slowing</td>
<td>Multifocal</td>
</tr>
<tr>
<td>4</td>
<td>5.4</td>
<td>Right frontal calcified hamartoma</td>
<td>Right frontal epileptiform discharges and focal slowing; generalized epileptiform discharges</td>
<td>Right frontal</td>
</tr>
</tbody>
</table>

Fig. 1. Resting magnetoencephalography group-based connectivity profiles of (A) typically developing, (B) tuberous sclerosis complex, and (C) tuberous sclerosis complex/autism spectrum disorder children. (Colours are visible in the online version of the article; http://dx.doi.org/10.3233/JPN-130599)

4.3 and 4.6 yr of age, respectively. These individuals were considered as typically developing on the basis of normal developmental milestones, including: 1) no preterm birth (i.e., < 37 wk of gestation) as determined by medical history; 2) no history of frank neurological damage or diagnosed seizure disorder; 3) and no history of serious psychopathology resulting in psychiatric hospitalization (e.g., for psychotic episode).

The study was performed in accordance with the declaration of Helsinki and approved by the institutional review board of the university of Tennessee health science center.

2.2. MEG and resting connectivity pattern analysis

Causal relationships among all brain areas were assessed by analyzing all channels $X_1, X_2, \ldots, X_N$ of the MEG data simultaneously (detailed in [10]). The principle of Granger causality is based on modeling the data as a system of autoregressive time series and on the model’s ability to predict future values of each signal from past values of itself and of all other signals. For each subject, approximately ten minutes of resting MEG data was recorded using a 248-channel whole-head Magnes WH3600 system (4D Neuroimaging, San Diego, CA) with a sampling rate of 1 kHz. Band pass filtering between 0.1–80 Hz and decimation by a factor of six gave an effective sampling rate of 166 Hz. A noise-removal and artifact-rejection procedure was also applied before granger causality analysis. In addition, in TSC patients (with and without ASD), epochs containing epileptic-form activity (e.g., spikes, sharp waves, and spike-wave complexes) were removed from the time series. A connectivity matrix was computed for each subject individually and then group templates were estimated by averaging all matrices in each group. The density of the computerized networks was reduced using a common threshold on the strength of the links. Finally, a spatial filtering procedure based on the physical distance among the MEG sensors was used to separate local from long-range connections.
3. Results

Consistent with findings from our earlier resting MEG study of ASD and normal adolescents [9], TD children in the present study exhibited a dense network of long-range anterior/posterior connections, especially in the left hemisphere (Fig. 1A). Furthermore, similar to adolescent ASD individuals, TSC/ASD children in the present study displayed the characteristic more medial long-range anterior/posterior connections (Fig. 1C). In contrast however, TSC children (Fig. 1B) exhibited a reduction in long-range connectivity, most notably left anterior/posterior connections, present in TD children, but also lacked the medial anterior/posterior connections characteristic of TSC/ASD children.

4. Discussion

Despite the small sample size, findings from this exploratory study support the growing notion that functional deficits, which characterize individuals with ASD may be reflective of abnormal functional connectivity, resulting in a deficit in integration of information at the neural and cognitive levels. More importantly, these preliminary results demonstrate that patterns of resting brain activation, in the form of connectivity networks, may possess the characteristics of neurophysiological markers of sufficient specificity and sensitivity that reliably differentiate between TD, TSC, and TSC/ASD children. In addition to providing an objective means of disambiguating the presently difficult behavioral diagnosis of ASD, early identification of the neurological factors, which may account for the co-morbidity between TSC and ASD could facilitate early behavioral and medical intervention.

References