

Case Report

Atypical representation of sensorimotor cortex in a patient with autism and epilepsy confirmed by direct electrocortical stimulation

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ABSTRACT

Prior studies have used functional neuroimaging to demonstrate that the organization of the autistic brain is different from that of the non-autistic brain. Similarly, patients with epilepsy have also shown cortical reorganization. We present a case study that provides direct confirmation of disorganized sensorimotor distribution in a patient with autism spectrum disorder and epilepsy. To our knowledge, this is the first time cortical mapping directly showing abnormal cortical organization in a patient with autism spectrum disorder and epilepsy has been reported in the literature.

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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with a prevalence of 7.6 per 1000 [1,2]. ASD is typically diagnosed between 38 and 120 months [3]. It affects a variety of brain regions including those involved in behavior, social interaction, communication, and motor functioning. Although not fully understood, it is believed that one mechanism by which ASD develops is through disruption of neural connectivity via synaptic dysfunction and dysregulation of axonal growth [4,5]. Deficits in fine and gross motor skills are present in both children and adults with ASD [6]. Abnormalities of movement can precede development of behavioral signs in children with ASD [7]. This could be due to atypical organization of motor system with a wider distribution compared to normal control subjects [8,9] and increased gray matter volume and surface area of sensorimotor regions [10].

Epilepsy occurs at an increased rate (1.8%) in ASD as compared to the general population and is further increased to 23.7% in those with intellectual disabilities in ASD [11]. Motor cortex reorganization has been noted in peri-rolandic epilepsy [12].

We present a case of an adult with ASD and drug-resistant focal epilepsy who underwent two-stage epilepsy surgery with implan-

tation of intracranial electrodes to define the epileptogenic zone and mapping of eloquent cortex. This case offers the unique opportunity to examine motor system organization of ASD and epilepsy in the same individual using intracranial cortical mapping.

2. Case study

This patient is a right-handed man with a diagnosis of ASD and drug-resistant epilepsy. He was first seen by our team in neurology clinic in 2003 at the age of 29. The procedures described below were performed in 2008 at age 33.

2.1. Early development

The patient was diagnosed with ASD in childhood by a pediatrician. History of motor and language developmental delay was noted. Onset of epilepsy was prior to 9 years of age. Otherwise, information on developmental history is limited. Medical records prior to 2003 could not be obtained, and the patient's parents, with whom he lived as a child, were not available. The patient lived with his grandparents at the time he was seen by our team, and they were unable to provide detailed information about his early development.

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2.2. Pre-surgical functioning and seizures

The patient's grandparents reported that he was not engaged socially. He preferred to stay in his room and listen to music. He sang in church choir although had minimal verbal communication otherwise. The patient had three focal to bilateral tonic-clonic seizures monthly, which was his only seizure type. The seizures were described as beginning with a behavioral arrest, followed by left head version, left facial clonic activity, and then evolve to a bilateral tonic-clonic seizure. He had failed phenytoin, lamotrigine and levetiracetam at appropriate doses.

2.3. Pre-surgical testing

Neuropsychological testing confirmed the diagnosis of ASD with limited language abilities and variable executive functioning. Testing showed low intellectual and cognitive functioning, particularly verbal skills (verbal IQ = 55; performance IQ = 96; and full-scale IQ = 74). Significant impairments in language and verbal skills are among the core characteristics of ASD, and individuals with ASD commonly obtain lower scores on tests of verbal ability relative to other measures of intellectual functioning [13]. As such, the above scores are consistent with a diagnosis of autism. Low verbal ability is also consistent with the patient's developmental history, family report of minimal verbal communication, and clinical presentation.

On neurologic exam, he answered questions with single word responses and avoided making eye contact. He had no focal neurological deficits.

Scalp video-EEG monitoring revealed right temporal seizure onset, but with a diffuse field and involving right central regions. MRI of the brain demonstrated a subtle area of FLAIR hyperintensity in the right anterior temporal lobe cortex. Interictal fluorodeoxyglucose PET scan showed an area of hypometabolism involving the right temporal lobe extending into the parietal and lateral occipital cortex. The patient was unable to complete a functional MRI study.

The patient was deemed to be a candidate for two-stage epilepsy surgery due to diffuse scalp EEG onset and wide area of hypometabolism on PET scan.

2.4. Craniotomy and intracranial EEG recording

A right craniotomy was performed with implantation of subdural grid arrays overlying the right frontal, parietal, and temporal lobes (Fig. 1A–C). Three seizures were captured on extraoperative intracranial EEG. Two distinct areas of seizure onset were noted in the right orbitofrontal region and lateral temporal neocortex, with rapid spread to the inferior posterior frontal lobe anterior to the motor cortex (Fig. 1D). The seizure semiology of left head version and left facial clonic activity was consistent with spread to the supplementary motor area and (anterior to) motor cortex rather than associated with seizure onset foci in orbitofrontal and temporal neocortex. Mapping for motor cortex was performed by stimulating a pair of adjacent electrodes with a train of square wave electrical impulses of 300 μ sec duration at 10 Hz for 10 seconds using Grass S12 Isolated Biphasic Stimulator (Warwick, RI). The stimulus strength varied from 4.5 to 10.5 mA. The somatosensory cortex was systematically mapped by recording the evoked responses using an 8-channel montage (Nicolet Viking, Madison, WI) with consecutive electrodes of a single row connected in bipolar fashion in an anteroposterior direction. A referential recording was also obtained from the same electrodes by recording responses in a referential manner against a distant, relatively inactive electrode (AD1, depth electrode inserted in the right hippocampus). Traditionally, the central sulcus is identified as the

sulcus closest to the electrode showing phase reversal of N20 peak during bipolar recording in anterior-posterior fashion, while the highest amplitude of the N20 during referential recording defines the hand sensory area [14]. Motor cortex organization based on mapping is shown in Fig. 1D. Comparative motor cortex organization in our patient (Fig. 1E) and the classic description (Fig. 1F) is depicted. Similarly, the patient had an atypical representation of the primary sensory cortex (Fig. 1D). The sensory responses were recorded over much larger area from electrode just above the Sylvian fissure to the top most row of the FP grid (spanning at least 8 cm) and the amplitude of N20 changed variably instead of peaking in hand area and gradually tapering off in either directions. Similarly, electrical stimulation resulted in response from thumb from the electrode closest to Sylvian fissure while tongue and mouth were adjacent to the wrist area at least 6 cms superiorly, with interspread areas showing responses from face, mouth or eyelid.

2.5. Surgical resection

Based on the cortical mapping and epileptogenic zones, microsurgical resection of the right frontal and right temporal lobes was carried out with sparing of primary motor cortex. Medial temporal lobe was resected because of frequent interictal spiking and electrographic seizures noted during intraoperative electrocorticography. Pathology was unremarkable except for mild gliosis in end folium region of hippocampus and slightly increased number of neurons in other areas.

2.6. Post-surgical functioning and seizures

No immediate post-operative deficits were noted. At last follow-up (age 38 years), the patient was seizure-free for over 5 years post-operatively. ASD clinical features remained unchanged throughout.

3. Discussion

In this unique case, we demonstrated abnormal structure of the primary motor cortex in a patient with ASD and drug-resistant epilepsy via extraoperative intracranial EEG. We noted four distinct variations from the classic motor homunculus suggesting "variability" (different location) but absent "mosaicism" (overlapping), as follows: (a) location of the thumb was just superior to Sylvian fissure and lateral to mouth representations; (b) tongue and mouth representation was in a superior location; (c) mouth had multiple representative locations; and (d) there was a significant anteroposterior spread of motor representation extending to 3–4 cm posterior to sensory cortex in parietal lobe. We were not able to localize functional areas of arm and fingers (digits 1 through 4) despite extensive coverage of lateral frontoparietal cortex. The lack of localization of the leg and trunk areas was expected because of absent electrode coverage of medial frontoparietal cortex.

ASD has been extensively studied, but its etiology and pathogenesis remain incompletely understood. Evidence from multiple methodologies support abnormalities of the motor areas of the brain, and early deficits in motor skill acquisition suggest abnormal motor pathway development [7]. Imaging studies have shown early neuronal overgrowth concentrated in the frontal lobes possibly leading to abnormal connectivity in the motor area of the brain [15]. Functional MRI studies of simple movements have demonstrated significant variability in the organization of motor areas. During finger tapping paradigms, ASD patients had less activation along the motor strip and greater activation in the supplementary motor areas. Moreover, increased activation in prefrontal and parietal areas during motor learning tasks was demonstrated in ASD

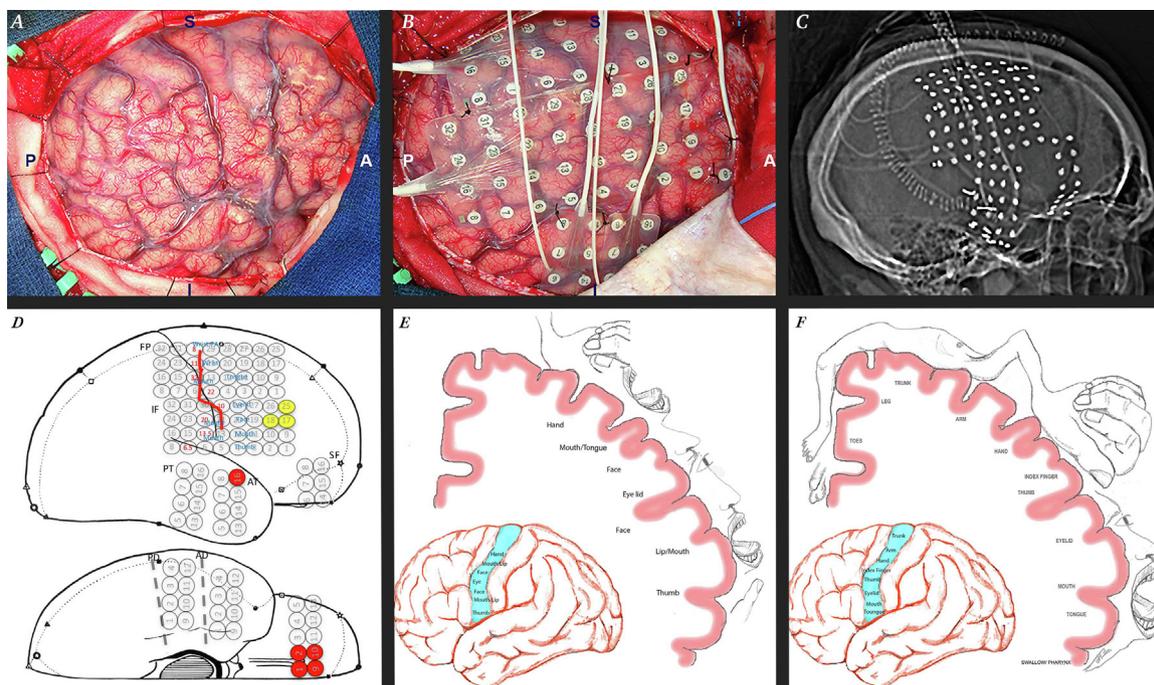


Fig. 1. Intraoperative photographs showing exposed cortical surface over the right hemisphere preimplantation (A) and following subdural grid implantation (B) where A = anterior, P = posterior, S = superior, I = inferior. A post-implant lateral skull x-ray shows location of the intracranial electrodes (C). Panel D summarizes the findings of extraoperative intracranial EEG monitoring with epileptogenic zone identified as filled circles (red circles = seizure onset, yellow circles = early seizure spread). The results of functional cortical mapping are also shown on the same diagram (SSEP in red letters and line, motor mapping in blue letters). 8-channels of SSEP were recorded from electrodes from both 4×8 subdural grids (FP and IF), obtaining separate trials for referential and bipolar recordings. The red line depicts electrodes where phase reversal of SSEP waveforms on bipolar recording was noted (identifying the central sulcus). The numbers in red letters in the circle depicts actual amplitude of SSEP during referential recording. The blue letters indicate positive motor response from the body part identified during motor mapping. As noted here, the sensory responses as well as motor responses show unusual organization with thumb responses recorded from inferior part of the sensorimotor cortex while tongue and mouth/lip responses recorded from the superior part of the homunculus. This superior part was at the same level and has the highest amplitude on median SSEP (third from the top). The classic motor homunculus (F) and the disorganized motor cortex in the patient (E) are also shown. FP = fronto-parietal grid; IF = inferior frontal grid; AT = anterior temporal grid; PT = posterior temporal grid; SF = subfrontal grid; AD = anterior depth electrode; PD = posterior depth electrode. Resection margins are noted with black broken lines in (B).

patients compared to non-autistic control subjects [9]. A navigated transcranial magnetic stimulation (nTMS) study in individuals with Asperger syndrome found less focused cortical organization of individual hand muscles as compared to healthy controls [16].

fMRI can be clinically used for sensorimotor localization for isolated epilepsy-related resection. However, it is more commonly used for eloquent cortex mapping for tumor resection with or without epilepsy. Limited data suggests that hand area can be most consistently mapped in both task-based and resting-state fMRI [17,18]. In a case series, Liu et al. demonstrated that hand and tongue motor areas can be reliably distinguished and fMRI localization was confirmed by direct cortical stimulation in one case [17]. Similarly magnetoencephalogram and transcranial magnetic stimulation has been found to have accurate motor cortex localization as compared to cortical brain mapping [19]. fMRI could not be completed in our patient.

It was initially thought that human motor cortex (M1) has a rigid one-to-one representation of different body parts. However, functional imaging studies later reported normal variations in this motor somatotopy [20]. Patients with peri-rolandic epilepsy have been found to have variations in motor organization in 20% of cases as demonstrated by direct cortical mapping [12]. In addition, mosaicism (overlapping) and variability (different location) were noted in multiple epilepsy patients who underwent direct cortical mapping and had seizure-onset focus distant from the peri-rolandic area [21].

In contrast to the more localized recording of somatosensory evoked potential (SSEP) responses, in this case, the SSEP was obtained from a wide area of the central region of the cerebral cortex. It also showed variability with the amplitude of SSEP response

increasing from inferior row to superior and then decreasing before increasing again. In a magnetoencephalogram (MEG) study of ASD patients without seizures, increased distance between sensory cortex representation of thumb and lips was noted [22]. Typically, thumb and lips sensory areas are adjacent. Thus, sensory reorganization typical of ASD with thumb and mouth areas less focused was seen in this patient.

The major limitation of our case report is that the recorded sensori-motor variability might not be due to interplay between epilepsy and autism. It could very well be physiological as a pattern of normal variation seen in some humans. However, we believe that in this case the reorganization is most likely due to a combination of ASD and epilepsy. As suggested by previous studies [23,24], migrational deficits of the cortex are common in ASD. In the study of peri-rolandic epilepsy with direct cortical mapping, 28% of patients with motor cortex variation had cortical dysplasia [12]. However, cortical dysplasia was not seen in this patient. Neither of the two studies with peri-rolandic epilepsy and direct cortical mapping report autism as a comorbidity [12,21]. The retrospective nature and a single case presentation of this report are further limitations.

4. Conclusion

In summary, as epilepsy is frequently seen in ASD, careful brain mapping is imperative to detect functional reorganization and to avoid functional deficits in drug-resistant patients undergoing surgical evaluation. Findings from this case study are consistent with previous functional and imaging studies that demonstrated

abnormal motor and sensory patterns in ASD and functional radiographic and electrocorticographic studies in epilepsy. To our knowledge, this is the first demonstration of cortical abnormalities using direct cortical mapping in a patient with autism with or without epilepsy, and as such contributes new information to the overall understanding of the autistic brain.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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