Individual Variability of the Human Cerebral Cortex Identified Using Intraoperative Mapping

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BACKGROUND: Intraoperative functional cortical mapping using direct electrical stimulation may show a wider individual variability than suggested by noninvasive imaging data of healthy subjects.

METHODS: We assessed intraoperative variability of the frontal eye fields and the speech arrest sites in adult patients who underwent awake craniotomy with direct electrostimulation for treatment of diffuse gliomas located within eloquent regions, and we compared findings with human cortical parcellation of the Human Connectome Project.

RESULTS: The frontal eye fields were defined by intraoperative direct electrostimulations (14.3% of patients) projected on the superior subdivision of the premotor cortex covering the areas defined as frontal eye fields (parcel index 10), area 55b (parcel index 12), and premotor eye field (parcel index 11) and in the posterior part of the dorsolateral prefrontal cortex covering the areas defined as inferior 6–8 transitional area (parcel index 97), area 8Av (parcel index 67), and area 8C (parcel index 73). The speech arrest sites were defined by intraoperative direct electrostimulations (100% of patients) projected predominantly posteriorly to the inferior frontal gyrus in the inferior subdivision of the premotor cortex, that is, rostral area 6 (parcel index 78), ventral area 6 (parcel index 54), and area 43 (parcel index 99).

CONCLUSIONS: Intraoperative functional cortical mapping using direct electrostimulation highlights that actual individual variability is wider than suggested by analyses of healthy subjects and results in atypical patterns of functional organization and structural and functional changes of the human cerebral cortex under pathologic conditions.

INTRODUCTION

Accurate population-based human cortical parcellation comprising 180 distinct areas per hemisphere using noninvasive and multimodal structural and functional imaging data from hundreds of healthy subjects from the Human Connectome Project has recently been proposed. This new understanding of the human cerebral cortex sheds light on how the human brain is organized and has future clinical implications, providing neurosurgeons with detailed, individualized maps of the brains on which they operate. Neurosurgeons have the exciting task of transferring neuroscientific knowledge, including technologic and conceptual advances, into the operating room for the daily management of patients.

Diffuse gliomas induce vascular, anatomic, and functional changes in their vicinity as they proliferate and migrate, and functional organization is reshaped thanks to brain plasticity, limiting the applicability of functional magnetic resonance imaging (MRI) and noninvasive imaging investigations of cerebral connectivity. In addition, as a result of a hodotopical, dynamic, and operational approach of language processing, as constructed from findings provided by intraoperative brain mapping, the neural bases of cerebral function have evolved, and the subcortical connectivity is crucial in the networks subserving a given
function. As a practical consequence, safety during surgical resection of a primary brain tumor located within an eloquent area is achieved using intraoperative functional mapping. Functions of interest are monitored by using direct bipolar electrical stimulations in awake patients that mimic transient virtual lesions inducing functional negative or positive responses that allow recognition of the stimulated cerebral area as an essential part of a network subsuming a given function at both cortical and subcortical levels. As a clinical tool, the direct electrical stimulation technique allows maximal safe resection of primary brain tumors with optimized onco-functional balance and is currently implemented as a standard of care.5,6

The direct electrical stimulation technique is applicable only to patients undergoing surgical procedures for an underlying brain pathology; covers only the surgically exposed brain; and evokes a complex summation of electrophysiologic effects in the stimulated brain volume, which limits the interpretation of results beyond clinical purposes.3 During intraoperative mapping for primary brain tumor resection, neurosurgeons observe a variability in language functional organization from one patient to another, and noninvasive clinical investigations give a suboptimal prediction of the functional networks identified intraoperatively.3 With full knowledge of the limitations inherent to the comparison of these different techniques of cerebral mapping, the atypical topologic arrangements observed in the aforementioned recent cerebral cortex parcellation recall the common observation of variability in functional organization during brain surgery practice. We assessed the intraoperative variability of 2 examples of cortical organization, of frontal eye fields and of speech arrest, in a series of adult patients with diffuse gliomas located within eloquent regions treated with maximal resection according to functional boundaries using intraoperative corticosubcortical monitoring under awake conditions.

MATERIALS AND METHODS

Patients
We prospectively collected a consecutive series of all patients who underwent functional-based surgical resection under awake conditions for a supratentorial hemispheric diffuse glioma located within eloquent brain areas at Sainte-Anne Hospital—Paris Descartes University in Paris, France, between March 2010 and March 2016. Inclusion criteria were the following: 1) adult patients ≥16 years old at the time of radiologic diagnosis; 2) glioma supratentorial location within or close to eloquent cortical and subcortical regions; 3) surgical resection according to functional boundaries under intraoperative functional corticosubcortical monitoring under awake conditions; and 4) histopathologic diagnosis of World Health Organization (WHO) grade II, III, or IV diffuse glioma. The institutional review board approved the study protocol (A01933-48, 2016-A01933-48), and informed consent was obtained from all patients before enrollment.

Intraoperative Functional Mapping
In all cases, intraoperative functional mapping was performed through cortical and subcortical direct electrostimulation using the “asleep-awake-asleep” protocol. Cerebral sulci and gyri were first identified using intraoperative neuronavigation with ultrasound and MRI. Functional mapping used a bipolar electrode with a 5-mm space between tips delivering a biphasic current with a pulse frequency of 60 Hz and pulse phase duration of 1 ms (Osiris NeuroStimulator; inomed North America, Madison, Wisconsin, USA). The entire exposed brain was stimulated, and all responsive and nonresponsive sites were restimulated 3 times for confirmation. The current intensity was determined individually by progressively increasing the amplitude in 0.5-mA increments until a functional response was elicited (baseline 1 mA, maximum 6 mA). In all cases in which the central region was exposed, sensorimotor mapping was first performed to confirm positive responses.

The patient was then asked to perform language tasks, including counting (regular rhythm, from 1 to 10, repetitively) and the DO (dénomination orale) 80 picture-naming task, with a goal to identify the essential cortical sites known to be inhibited by stimulation. Simultaneously, the patient was asked to continuously perform movements of the upper limb comprising repetitive and alternating flexion and extension of the arm, hand, and fingers at a gross frequency of 0.5 Hz. Before naming each picture, the patient was asked to read a short phrase (“this is a …”) to verify that there were no seizures generating complete speech arrest if the patient was not able to name the picture. The patient was never informed when the brain was stimulated. The stimulation duration was approximately 4 seconds. At least 1 picture was presented without stimulation in between each actual stimulation, and no site was stimulated twice in succession. The types of language disturbances (speech arrest; anomia; phonetic, phonemic, or semantic paraphasia; slowness with initiation disturbances; and perseverations) were classified by a senior speech therapist and differentiated from dysarthria and motor arrest. The concomitant picture-naming task and upper limb movement task allowed the identification of true speech arrest, also called anarthria (when direct electrical stimulation stopped the picture-naming task or the counting task but not the movement task with the exclusion of positive and negative motor pharyngeal and tongue response), and its discrimination from anomia (when the patient continued the movement task and could read the test phrase “This is a …” during direct electrical stimulation but was unable to find and correctly name the object shown in the picture), from dysarthria (when direct electrical stimulation stopped the picture-naming task or the counting task but not the movement task owing to motor pharyngeal and/or tongue response), and from motor arrest (when direct electrical stimulation stopped both the picture naming task or the counting task and the movement task of the upper limb). Each eloquent area was noted and marked with a sterile numbered tag (0.25 cm²) on the brain surface.

The glioma was then removed by alternating resection and electrostimulation for subcortical functional mapping. Using the same stimulation parameters, the functional pathways were followed progressively from the cortical eloquent areas through the depth of the resection. The patient was asked to continuously perform the required tasks throughout the glioma resection. All resections were continued until eloquent subcortical structures were encountered within the surgical cavity or until the patient felt too tired to work efficiently.
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