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Gray matter volumes and cognitive ability in the epileptogenic brain malformation of periventricular nodular heterotopia

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ABSTRACT

Periventricular nodular heterotopia (PNH) is a brain malformation clinically characterized by the triad of epilepsy, normal intelligence, and dyslexia. We investigated the structure–function relationship between cerebral volumes and cognitive ability in this disorder by studying 12 subjects with PNH and 6 controls using volumetric analysis of high-resolution anatomical MRI and neuropsychological testing. Total cerebral volumes and specific brain compartment volumes (gray matter, white matter, and cerebrospinal fluid) in subjects with PNH were comparable to those in controls. There was a negative correlation between heterotopic gray matter volume and cortical gray matter volume. Cerebral and cortical volumes in PNH did not correlate with Full Scale IQ, unlike in normal individuals. Our findings support the idea that heterotopic nodules contain misplaced neurons that would normally have migrated to the cortex, and suggest that structural correlates of normal cognitive ability may be different in the setting of neuronal migration failure.

1. Introduction

Neuronal migration disorders are developmental neurological conditions that commonly lead to cognitive impairment, motor disability, and epilepsy [1]. They arise from disruptions in the normal, complex process of migration of neuroblasts from progenitor zones toward the developing cortical plate, during fetal brain development [2,3]. Many migrational disorders are associated with the presence of gray matter heterotopia, located somewhere between the periventricular region and the overlying cerebral cortex [4,5]. In many cases, neurons within heterotopic regions appear to be normal in morphology, though their organization and synaptic connectivity may be highly abnormal [6–8]. These neurons are generally hypothesized to have failed to migrate properly to the cerebral cortex, because of either an arrest in or an absence of initiation of the usual migratory mechanisms.

Many of the clinical features associated with migrational defects are expressed with varying degrees of severity. Some patients can have quite significant neuropsychological deficits [9], whereas others, despite evidence of seemingly comparable widespread migration failure, exhibit a much more limited degree of cognitive impairment. Patients with bilateral periventricular nodular heterotopia (PNH), in which the ventricles are lined throughout with nodules of misplaced gray matter, typically demonstrate the clinical triad of localization-related epilepsy, normal intelligence, and an isolated form of dyslexia affecting reading fluency [10,11].

Through the use of functional neuroimaging such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), some investigators have demonstrated the ability of misplaced or malformed gray matter to retain aspects of physiologically important function [12,13]. Recordings from depth electrodes implanted within heterotopic tissue have revealed the potential for epileptogenesis in these regions [14,15]. However, a gap remains in our understanding of the structural relationships between heterotopic and cortical gray matter and the quantitative relationships, if any, between anatomical defects in these disorders and cognitive functioning. There are few methods, either in vivo in

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humans or in animal models, that allow us to study the relevant anatomical characteristics in detail.

Quantitative volumetric analysis of high-resolution structural brain MRI data is a powerful tool that allows for the investigation of total brain volume, the volumes of individual tissue compartments within the brain, and the volumes of other defined segments of gray and white matter [16,17]. Volumetric analyses have been widely used to demonstrate robust relationships between total cerebral volume or specific tissue compartment volumes and measures of intellectual ability such as Full Scale IQ in healthy subjects [18–20]. These findings have expanded our understanding of the influence of gray matter structure and volume on cognitive function in the normal population.

We sought to investigate the impact of neuronal migration failure on the brain–behavior relationships between gray matter and cognitive ability. To do this, we studied a cohort of subjects with PNH and healthy controls using a combination of quantitative volumetric techniques applied to high-resolution MRI data and neuropsychological testing.

2. Methods

2.1. Subjects

Subjects with PNH were identified through a database of patients with malformations of cortical development at our institution as well as through referrals from neurological clinicians. To be enrolled, subjects were required to be between ages 18 and 65 and to have at least one radiologically visible subependymal nodule of heterotopic gray matter in the brain, seen in more than one plane in conventional MRI scanning and on more than one consecutive slice in at least one of those planes. The presence of any additional region of dysplasia or malformation other than periventricular heterotopia was an exclusion criterion. Healthy adult controls with no history of neurological disorders were also identified. All subjects were enrolled after informed consent was obtained in accordance with protocols approved by the institutional review board of Beth Israel Deaconess Medical Center.

2.2. Structural image acquisition

All subjects were scanned using high-resolution three-dimensional T1-weighted anatomical magnetic resonance sequences, such as spoiled-gradient (SPGR) or magnetization-prepared rapid acquisition gradient echo (MPRAGE), dedicated to optimization of anatomical visualization and gray–white contrast. The most commonly used sequence for volumetric analysis was an axial T1-weighted three-dimensional MPRAGE sequence optimized for tissue compartment segmentation (TE1 = minimum, TI = 400 ms, flip angle = 10°, slice thickness = 1.5 mm with no gap, field of view = 24 cm, acquisition matrix = 256 × 256, number of excitations = 1) with images acquired on a 3-T GE VH/1 magnet using the product head coil.

2.3. Image processing and volumetric analysis

Anatomical images were visually inspected by investigators to ensure high quality and freedom from artifact. Removal of skull, scalp, and other nonbrain elements was performed with the automated Brain Extraction Tool (BET) [21], followed by further manual removal of nonbrain elements from anatomical images as needed. The anatomical images used for analysis extended from the axial slice that included the most superior piece of cerebral tissue, superiorly, to the axial slice just inferior to the last slice to include cerebellar tissue, inferiorly. To allow for comparability to existent analyses in the literature on gray matter–IQ relationships, which were generally performed on cerebral volumes alone, we manually removed the cerebellum and brainstem from the images above according to specific anatomical landmarks as described by other investigators [19]. Two investigators reached consensus on the optimally extracted images with nonbrain elements and cerebellum/brainstem removed.

Images were then processed in MRICroN using manually implemented local thresholding to segment the three brain tissue compartments of gray matter, white matter, and cerebrospinal fluid (CSF) [22]. This was performed independently by two investigators who set signal intensity thresholds for the gray–white boundary and the gray–CSF boundary between 0 and 255, such that all voxels were classified into one of these three compartments. Volumetric analysis then yielded a total number of voxels and metric volumes for each compartment. Interrater reliability was demonstrated by calculating an intraclass correlation coefficient for gray matter volumes between the two investigators, who were unaware of each other's intensity thresholds. To separate heterotopic gray matter from normal cortical and subcortical gray matter, a manual method of outlining these gray matter regions on axial images using MRICroN's region-of-interest drawing tools, slice by slice, was used. Volumes of heterotopic and cortical gray matter were then calculated (Fig. 1). Total cerebral volume was calculated as the sum of gray matter, white matter, and CSF compartment volumes. Fractional volumes were defined as the ratio of absolute compartment volume to total cerebral volume [16].

2.4. Cognitive testing

All subjects with PNH were tested using a battery of cognitive measures including intelligence screening (using the Wechsler

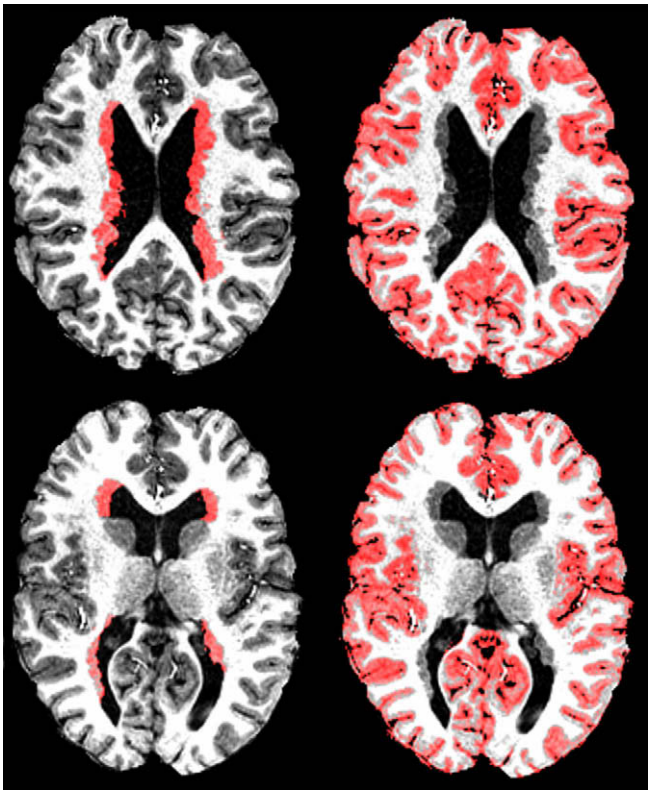

Fig. 1. Gray matter segmentation and parcellation in periventricular nodular heterotopia (PNH). For this representative subject with PNH, the two left images demonstrate parcellation of heterotopic gray matter, whereas the two right images demonstrate parcellation of normal cortical gray matter (all in red).