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DTI-based tractography of the arcuate fasciculus in patients with polymicrogyria and language disorders☆

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ABSTRACT

Objectives: To assess the integrity of the arcuate fasciculus (AF) with diffusion tensor imaging (DTI) and tractography in patients with congenital polymicrogyria (PMG) and language disorders.
Methods: Twelve patients with PMG and 12 matched controls were prospectively evaluated with DTI (32 gradient encoding directions, *b*-value = 1000 s/mm^2) at 3.0 T. The AF was virtually dissected with a deterministic streamline approach. DTI metrics included FA (fractional anisotropy), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). A subset of patients ($n = 4$) was evaluated to assess cognitive performance and language skills.
Results: Qualitative evaluation revealed several abnormalities in tracts size and architecture in nearly all PMG patients. Remarkably, in 3 patients with bilateral PMG, the AF was not delineated on both hemispheres. In comparison to controls, patients exhibited significant decrease of FA ($p = 0.003$) in addition to increase of RD ($p = 0.03$) in the right AF, whereas there was significant increase of MD in the left AF ($p = 0.04$). All 4 patients with language evaluation had suboptimal performance on lexical fluency and prosodic linguistic.
Conclusions: DTI and tractography suggest that the AF is severely disrupted in patients with PMG, providing an anatomical in vivo substrate for the language disorders commonly associated with these cortical malformations.

1. Introduction

Congenital polymicrogyria (PMG) is a malformation of cortical development (MCD) resultant from abnormal postmigrational corticogenesis and commonly manifested with epilepsy and language disorders. Magnetic resonance imaging (MRI) exhibits abnormal overfolding of too many small gyri with shallow sulci that produce an irregular cortical surface. It may affect one or both cerebral hemispheres and is commonly seen around widened or verticalized Sylvian fissures [1]. High-resolution MRI is able to accurately identify the limits of the affected cortex and to demonstrate the extension of the superficial lesions on curvilinear and three-dimensional (3D) surface-rendered reformats, but conventional MRI is limited to point the underlying abnormalities in the white matter (WM).

Although PMG primarily affects the cortical gray matter (GM), it is largely known that the development of the WM is strictly dependent on the former. The normal-appearing WM in MCD patients shows several metabolic and functional changes, as demonstrated by previous works with magnetic resonance spectroscopy [2] and nuclear medicine tests [3]. On the other hand, diffusion tensor imaging (DTI), by taking advantage of the directionality of water molecules in cerebral tissues, may advance further to characterize the associated abnormalities in brain parenchyma, providing additional insights into WM microstructure and architecture [4].

Few DTI studies with heterogeneous methodologies have demonstrated qualitative and quantitative changes of brain WM in MCD patients. Eriksson et al. described increased diffusivity and

Abbreviations: AD, axial diffusivity; AF, arcuate fasciculus; BNT, Boston naming test; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; MAC, montreal communication evaluation battery; MRI, magnetic resonance imaging; MD, mean diffusivity; PMG, polymicrogyria; RD, radial diffusivity; ROI, region-of-interest; SLF, superior longitudinal fasciculus.

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reduced anisotropy in areas coincidental to and beyond the visible lesions by using statistical parametric mapping [5]. Other authors detected decreased fiber connectivity with region-of-interest (ROI) analyses subjacent to focal cortical dysplasias [6].

DTI-tractography allows evaluation of more specific white matter tracts, providing biomarkers that may be linked to impairment of particular cognitive domains. It has been demonstrated changes in several WM tracts – e.g., cingulum, fornix, uncinate fasciculus, superior and inferior longitudinal fasciculi – in distinct epilepsy syndromes, such as mesial temporal sclerosis and juvenile myoclonic epilepsy [7]. Recently, diffusion abnormalities of the corpus callosum have also been demonstrated in MCD patients, including individuals diagnosed with PMG [8].

It is well known that one of the most prominent features of PMG is its association with language disorders [9]. Although the mechanisms underlying human language processing are complex and not completely elucidated so far, it is recognized that the arcuate fasciculus (AF) plays an important role. The AF represents the dorsal language pathway and is a major association tract that connects the Broca's area in the frontal lobe (speech production) with Geschwind's area in the parietal lobe (semantic processing) and Wernicke's territory in the temporal lobe (speech comprehension) [10].

Bernal et al. first reported two PMG patients with delayed speech development, poor prosody and impaired articulation who showed bilateral agenetic or rudimentary AF [11]. Another group has retrospectively reviewed DTI examinations in a small group of PMG patients that were evaluated with distinct scanners and protocols. They were not able to track the AF in three patients with more severe impairment, but there were no quantitative changes in the superior longitudinal fasciculus (SLF) in other three individuals who had developed normal speech [12]. Later on, another patient with bilateral PMG with delayed language development was reported to have preserved motor tracts but absent left AF [13].

Herein, our purpose is to prospectively assess the integrity of the AF with high-resolution DTI and tractography in a series of patients with PMG in comparison to healthy matched controls. Secondarily, evaluation of cognitive performance and language skills will also be held in a smaller subset of patients.

2. Materials and methods

2.1. Participants

The institutional review board approved this investigation, and all study participants provided written informed consent. Patients followed at an outpatient epilepsy facility were consecutively recruited during 1-year period to join the study. Inclusion criteria were a previous MRI-confirmed diagnosis of PMG and clinical records of language disorders. Exclusion criteria were brain lesions other than cortical malformations in the patients group, and incidental findings in the control group. Twelve patients were prospectively included the study, as well as 12 healthy volunteers with no neurological deficits from the same community. Two experienced neuroradiologists (C.S.A., C.C.L.) examined all structural images in consensus.

Patients and controls were matched for age (patients: mean age $\pm$ SD = 29.9 $\pm$ 6.1 years, range = 21–42 years; controls: 30.3 $\pm$ 7.4 years, range = 19–38 years, *t*-test, *p*-value = 0.88), gender (6 female and 6 male individuals in each group) and educational level (patients: mean studied years $\pm$ SD = 10.9 $\pm$ 3 years; controls: 11.1 $\pm$ 2.5 years, *t*-test, *p*-value = 0.88). One subject of the control group (8.3%) and six of the patients group (50%) were left-handed (chi-square test, *p*-value < 0.001).

2.2. MRI acquisition

All subjects were evaluated with identical MRI protocols at 3.0 T (Intera Achieva, Philips Healthcare, Best, The Netherlands) by using an eight-channel head coil (Philips Healthcare, Best, The Netherlands). Anatomic images consisted of a sagittal 3D T1 fast-field echo sequence (TR/TE/TI = 7/3.2/900 ms, flip angle = 8°, resolution = isotropic 1 mm^3) and an axial FLAIR sequence (TR/TE/TI = 11,000/130/2,800 ms, slice thickness = 4.5 mm).

DTI was a single-shot echo planar imaging (EPI) obtained in the axial plane with 70 slices covering the whole brain and the following parameters: 32 noncollinear encoding directions, *b*-values = 0 and 1000 s/mm^2, TR/TE = 8500/61 ms, number of excitations = 2, field of view 256 $\times$ 256 mm^2, matrix size = 128 $\times$ 128, resolution = isotropic 2 mm^3 with no inter-slice gap. Total duration for the DTI-scan was 14 min.

2.3. Data processing

DTI preprocessing was performed using the Functional MRI Brain Software Library (FSL), version 5.0 (Analysis Group, Oxford Centre, Oxford, United Kingdom). First, potential eddy-current induced geometrical distortions were corrected and a brain mask was applied with the brain extraction tool (BET) available at FSL. Subject motion correction was applied with a B-matrix rotation to correctly preserve the orientational information with the freely available toolbox ExploreDTI, version 4.8.3 (A. Leemans, University Medical Center, Utretch, The Netherlands). Quality assessment of DTI images, tensor estimation and fiber tracking were performed in all subjects by the same rater (C.S.A.). The DTI datasets were evaluated in the native space to avoid potential misregistration and incorrect alignment of images, which are critical in patients with large distortions of brain anatomy.

First, whole-brain tractography was automatically obtained with a brute-force approach. The AF was then virtually dissected with a deterministic streamline approach and the fiber assignment by continuous tracking (FACT) algorithm [14]. A specific set of predefined rules based upon a priori anatomical knowledge was adopted in the same way on both cerebral hemispheres to ensure accurate tracking, as previously described [14]. Placement of regions-of-interest (ROIs) was made on fractional anisotropy (FA) conventional color-encoded maps (left–right direction in red; superior-inferior direction in blue; anteroposterior direction in green). One "AND" ROI, large enough to include the whole frontoparietal transition above the lateral fissure, was placed on the coronal plane where the AF appears as a green triangle. One "SEED" ROI was placed in the axial plane encompassing the green bulk of the SLF lateral to the blue corticospinal tract (CST), and another one was drawn in a lower slice where the AF turns down to the temporal lobe and is identified as a blue structure lateral to the green sagittal stratum. The "SEED" ROIs are used to initiate tracking, while the "AND" ROIs ensure that only fibers passing through the area are selected. "NOT" ROIs were placed to exclude fibers from other main WM tracts, specifically on the coronal plane to exclude the anteroposterior cingulum bundles, and on the midsagittal plane to avoid the interhemispheric fibers of the corpus callosum. The minimal FA to start and keep fiber tracking was thresholded at 0.25 in order to avoid contamination with voxels containing GM or cerebrospinal fluid. The minimum fiber length was set at 50 mm, and the maximal tract angle was 60° (Fig. 1). The AF was chosen because it is the major intrahemispheric tract involved in human language and it is well characterized with DTI-based tractography (Fig. 2) [15].