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Sub-cortical brain morphometry and its relationship with cognition in rolandic epilepsy

Mahsa Shakeri[a,b,*], Alexandre N. Datta[c], Domitille Malfait[b,d], Nadine Oser[c], Laurent Létourneau-Guillon[e], Philippe Major[b,f], Myriam Srour[g], Alan Tucholka[b,h], Samuel Kadoury[a,b], Sarah Lippé[b,d]

[a] Polytechnique Montréal, Department of Computer and Software Engineering, Montreal, Quebec, Canada
[b] CHU Sainte-Justine, Montreal, Quebec, Canada
[c] University of Basel Children's Hospital, Basel, Switzerland
[d] University of Montreal, Department of Psychology, Montreal, Quebec, Canada
[e] Notre-Dame Hospital, Department of Radiology, Montreal, Quebec, Canada
[f] University of Montreal, Department of Neuroscience, Montreal, Quebec, Canada
[g] McGill University, Division of Paediatric Neurology, Montreal, Quebec, Canada
[h] Barcelona Beta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain

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ABSTRACT

Purpose: Rolandic epilepsy (RE), also called benign epilepsy with centrotemporal spikes (BECTS) is the most common childhood epilepsy syndrome. RE is associated with cognitive difficulties, which can affect children's quality of life. The underlying causes of these cognitive impairments are unclear. The objective of this prospective study is to investigate sub-cortical morphological alterations in RE children with left, right, or bilateral hemispheric focus and its association with cognition.
Methods: Participants include 41 children with rolandic epilepsy and 38 healthy controls (age 8–14 years), recruited from CHU Sainte-Justine Montreal Children Hospital ($N = 40$) and Basel's Children Hospital ($N = 39$). Quantitative volumetric assessment of putamen and caudate structures was performed on T1-weighted MR scans along with the morphological analysis to test for differences between patients and controls. These analyses were performed considering the side of epilepsy focus in all participants. Correlations were investigated between the sub-cortical morphometry and cognitive indices such as intelligence quotient (IQ), verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI).
Results: Children with bilateral BECTS showed statistically significant volume reduction in right caudate ($p < .05$), while no statistically significant putamen volumetric changes were detected in BECTS participants compared to normal controls. According to a spectral-based groupwise shape analysis, regional alterations were found in both putamen and caudate structures of children with BECTS. In particular, children with left BECTS showed significant outward local deformity in left putamen and individuals with bilateral BECTS showed inward local group differences in both right putamen and right caudate. The correlation assessment showed positive association between the volume of the left caudate and cognitive indices in the group containing all BECTS participants. Negative correlation was found between putamen sub-regional shape alterations and cognition in individuals with right BECTS and in all BECTS participants. Negative associations between caudate sub-regional morphologies and cognitive indices were detected in left cohort.
Significance: We have confirmed putamen and caudate shape alterations in children with BECTS. However, our results further suggest that variations in sub-cortical shape affect cognitive functions. Importantly, we have demonstrated that shape alterations and their relation with cognition depend on the side of epilepsy focus. Our results point to different syndromic entities in the BECTS population.

* Corresponding author at: Polytechnique Montréal, Department of Computer and Software Engineering, P.O. Box 6079, Montreal, Quebec, Canada H3C 3A7.
E-mail address: mahsa.shakeri@polymtl.ca (M. Shakeri).

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1. Introduction

Rolandic epilepsy (RE), also called benign epilepsy with centro-temporal spikes (BECTS), is the most common benign childhood focal epileptic syndrome (Kramer et al., 1998; Wirrell and Hamiwka, 2006), which occurs in children aged from 3 to 13 years old (Panayiotopoulos et al., 2008).

BECTS typically show cognitive deficits in language, verbal learning, attention, and executive function (Metz-Lutz and Filippini, 2006; Weglage et al., 1997), which affect children's quality of life (Malfait, 2011). Some studies on sub-cortical structures have shown atypical functional networks for language processes in BECTS (Datta et al., 2013; Malfait et al., 2015). Of special interest, the putamen and caudate have been shown to particularly engage in language cognitive tasks in BECTS, possibly reflecting a compensatory network (Malfait et al., 2015).

Recent studies on sub-cortical structures in BECTS have shown putamen volume enlargement (Garcia-Ramos et al., 2015; Lin et al., 2012). Furthermore, Lin et al. (2012) found shape changes in both putamen and caudate. They also reported a connection between putamen volume and cognitive performances on a complementary executive function test. Neither Garcia-Ramos et al. (2015) nor Lin et al. (2012) considered the side of epilepsy focus of the participants in their analysis, which could affect their findings. Among other available studies, few have considered the side of epileptic focus in detecting brain developmental impairment and finding the association between these morphological differences and cognition (Boxerman et al., 2007; Gelisse et al., 2003; Lundberg et al., 1999). These studies lacked a sufficient control group, due to including control participants with other pathologies, e.g., migraines (Boxerman et al., 2007) or not using any control cohort (Gelisse et al., 2003; Lundberg et al., 1999).

Given neurocognitive differences among children with BECTS and normal controls and the involvement of striatum in low and high order cognitive functions (MacDonald et al., 2014), the question is whether sub-cortical morphometric alterations explain variations in cognition. In fact, despite the various studies on neurodevelopmental etiology in BECTS, no research study has assessed the underlying structural shape alterations and its relation with cognition. Recent advancements in neuroimaging field have enabled subtle analysis of morphological differences between children with left, right, or bilateral BECTS and healthy controls. In this study, we use MR imaging and statistical morphological analysis to detect putamen and caudate changes in children with left, right, or bilateral BECTS compared to age and gender matched healthy individuals. In addition, we investigate the association of sub-cortical volumetric and shape differences with cognitive indices.

2. Methods

2.1. Participants

Demographic characteristics of participants are shown in Table 1. Forty-one patients with BECTS (mean age 10.34 ± 1.73 years; range 7.4–14 years; 13 girls) were recruited from CHU Sainte-Justine Montreal Children Hospital (N = 20) and Basel's Children Hospital (N = 21). All epileptic participants underwent both EEG and MRI scans. A routine classical waking EEG was performed on all children with duration of about half an hour to locate the seizure focus. EEG characteristics of patients were according to the latest abnormal EEG. The time distance between the EEG scans and MRI acquisitions was around 4.8 ± 8.7 months and all children were in active epilepsy phase. The epileptic focus was located in the left hemisphere for 13 patients and in the right centro-temporal areas for 18 patients. Nine children showed bilateral activation in both hemispheres. For one subject the information about the side of epilepsy focus was not available.

Thirty-eight healthy children (mean age 11.18 ± 1.72 years; range 8.1–14.8 years; 13 girls) were included as healthy controls (N = 20 from CHU Sainte-Justine Montreal Children Hospital and N = 18 from Basel's Children Hospital). EEG analysis was not performed on healthy participants and children with any personal or family history of any epileptiform discharges were excluded from the study. All participants and their parents gave written informed consent prior to study participation. The ethics, scientific, and administrative committee of CHU Sainte-Justine Montreal Children Hospital and Basel's Children Hospital approved this study.

We created an age, gender, and IQ matched control cohort corresponding to each epileptic group (i.e., 13 L-BECTS, 18 R-BECTS, 9 B-BECTS, 41 BECTS) and used these matched control groups in all analysis.

Table 1
Demographic characteristics of participants.

	NC	BECTS
N	38	41
Age (years)	11.18 ± 1.72	10.34 ± 1.73
Gender (F/M)	13/25	13/28
Age at onset	–	7.59 ± 1.77
AED (yes/no)[a]	–	26/15

[a] AED, antiepileptic drug(s); including: sultiam, levetiracetam, valproic acid, clobazam, carbamazepine, lamotrigine.

2.2. Neuropsychological tests

To test cognitive performance, all participants underwent a comprehensive neuropsychological examination. Intelligence was assessed with the Wechsler Intelligence Scale (WISC IV (Wechsler, 2005)), which includes four scales: verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI).

2.3. MRI acquisition

MR data from CHU Sainte-Justine Montreal Children Hospital were obtained on a 3.0-T Philips Achieva (Philips Healthcare, Best, The Netherlands). The participants (N = 40) underwent a T1-weighted structural scan (voxels = 1 mm isotropic, TR = 8.1 ms, TE = 3.7 ms, flip angle = 8°, FOV = 248 mm, slice thickness = 1 mm, slices = 160, direction = sagittal, in-plane resolution = 256 × 256). Data from Basel's Children Hospital were acquired using a 3.0-T Siemens MagnetomVERIO (Siemens Healthcare, Erlangen, Germany) MRI system. The imaging protocol of the participants (N = 39) included T1-weighted MRI scan (voxels = 1 mm isotropic, TR = 2000 ms, TE = 3.37 ms, flip angle = 8°, FOV = 256 mm, slice thickness = 1 mm, slices = 176, direction = sagittal, in-plane resolution = 256 × 256).

2.4. MRI processing

Putamen and caudate sub-cortical structures are automatically extracted using FSL-FIRST segmentation tool from FMRI Software Library (FSL) (Patenaude et al., 2011). FIRST is a model-based tool, which uses a template created from manually segmented images, with sub-cortical labels parameterized as surface meshes. A Bayesian Active Appearance Model (AAM) is also utilized to define the boundary of each sub-cortical mesh precisely (Patenaude et al., 2011). Recent studies have shown that the accuracy of the FIRST segmentation tool can reach up to 88% (Bruce Fischl, 2000). The output of the FIRST segmentation framework is a 3D binary mask, that will later be converted to 3D triangulated mesh model for volumetric and morphometry analysis.