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Early onset of cortical thinning in children with rolandic epilepsy

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A B S T R A C T

Introduction: Rolandic epilepsy, a childhood epilepsy associated with language impairments, was investigated for language-related cortical abnormalities.

Methods: Twenty-four children with rolandic epilepsy and 24 controls (age 8–14 years) were recruited and underwent the Clinical Evaluation of Language Fundamentals test. Structural MRI was performed at 3 T (voxel size 1 × 1 × 1 mm3) for fully automated quantitative assessment of cortical thickness. Regression analysis was used to test for differences between patients and controls and to assess the effect of age and language indices on cortical thickness.

Results: For patients the core language score (mean ± SD: 92 ± 18) was lower than for controls (106 ± 11, p = 0.0026) and below the norm of 100 ± 15 (p = 0.047). Patients showed specific impairments in receptive language index (87 ± 18, p = 0.0016) and language content index (87 ± 18, p = 0.0016). Cortical thickness was reduced in patients (p < 0.05, multiple-comparisons corrected) in left perisylvian regions. Furthermore, extensive cortical thinning with age was found in predominantly left-lateralized frontal, centro-parietal and temporal regions. No associations were found between cortical thickness and language indices in the regions of aberrant cortex.

Conclusion: The cortical abnormalities described represent subtle but significant pathomorphology in this critical phase of brain development (8–14 years) and suggest that rolandic epilepsy should not be considered merely a benign condition. Future studies employing longitudinal designs are prompted for further investigations into cerebral abnormalities in RE and associations with cognitive impairment and development.

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1. Introduction

Rolandic epilepsy (RE) is an idiopathic focal epilepsy with most frequent onset at 7–10 years of age (Gomez and Klass, 1983; Panayiotopoulos et al., 2008). The epileptic focus is typically located in the lower motor and/or somatosensory cortex (rolandic area) (Koutroumanidis, 2007). RE is also known as benign (rolandic) epilepsy (of childhood) with centro-temporal spikes (BECTS), which reflects both the typical spontaneous remission of seizures during adolescence and the characteristic location of the epileptiform activity on the electroencephalogram (EEG) (Loiseau and Duché, 1989).

Although the seizure semiology of RE is relatively mild (Lerman and Kivity, 1975; Loiseau et al., 1992), recent evidence suggests serious comorbidities in selected cases and has put the assumed purely benign nature of RE under debate (Nicolai et al., 2006; Vinayan et al., 2005; Völkli-Kernstock et al., 2009; Weglage et al., 1997). An often reported comorbidity of RE is language impairment (Monjaou et al., 2005; Northcott et al., 2007; Overvliet et al., 2010; Papavasiliou et al., 2005). It has been suggested that the diagnosis of language impairment may even precede that of RE (Overvliet et al., 2011a).

Even though the sensorimotor and language system are mutually involved in for instance speech production (in which complex articulatory movement and auditory feedback are required), the link between RE and problems in purely cognitive aspects of language such as reading is less trivial (Carlsson et al., 2000; Clarke et al., 2007). The existence of such an association is suggested by that fact that a significant correlation has been demonstrated between problems in motor and problems in language development (Gündüz et al., 1999;
Overvliet et al., 2011b). This suggests the existence of a mechanism through which epileptiform activity originating from the sensorimotor cortex might enter and disturb the language system as a whole, the neuronal pathways of which are as yet unknown.

Structural imaging has been used in attempts to identify cerebral abnormalities in RE. Several authors concluded that distributed subtle structural abnormalities on clinical MRI are common in RE (Eeg-Olofsson et al., 2000; Gelisse et al., 2003; Lundberg et al., 1999), but not specific for this disorder (Boxerman et al., 2007). However, these studies did not include healthy controls, were of qualitative nature, and were not tailored for systematic abnormalities (i.e. consistent over subjects with respect to location). In this context, quantitative approaches might seem advantageous. In recent years, quantitative techniques to study cortical thickness have been developed (Fischl and Dale, 2000; Kim et al., 2005). These techniques allow local analysis of the entire cortex and are less influenced by inter-individual gyral variations than traditional voxel-based whole-brain methods, such as voxel-based-morphology (VBM) (Mueller et al., 2009). In a group of children with frontal lobe epilepsy, cortical thickness analysis has been successfully applied; in a study of Widjaja et al. (Widjaja et al., 2011), regions of thinner cortex were found both within and beyond the frontal lobe. Also in other types of epilepsy, such as temporal lobe epilepsy in adults, reduced cortical thickness has been reported beyond the lobe of the primary seizure focus (Mueller et al., 2009).

The goal of the current study is to investigate whether abnormalities in cortical thickness can be found in RE, both within and beyond the sensorimotor cortex. Furthermore, we investigated whether such abnormalities are localized in classical left perisylvian language areas and are associated with language impairment as assessed using neuropsychological testing.

2. Materials and methods

2.1. Study population

A total of 24 children (9 girls) with a clinical diagnosis of RE were selected as recently described (Overvliet et al., in press), see also the selection criteria below. The average age at testing was 11.3 years (range: 8–14 years) and the age at epilepsy onset (7.3 ± 2.2 years) was typical (Panayiotopoulos et al., 2008). An age and gender-matched healthy control population of 24 children (10 girls) was included. The average age of the controls at testing was 10.6 years (range: 8–14 years; t-test for group age difference: p = 0.15). Of the patients, 20/24 were right handed; of the controls 22/24. For further subject characteristics, see Table 1.

2.1.1. Selection criteria

Children with RE were selected based on EEG criteria and seizure semiology (Berroya et al., 2005; Panayiotopoulos et al., 2008). EEG criteria include the presence of spike and slow wave complexes occurring as individual paroxysms or in repetitive clusters with a maximum in the mid temporal and/or central electrodes and with a temporal-frontal dipole field. Additional independent central, mid temporal, parietal or occipital spike wave foci in the same or other hemisphere were allowed. To exclude severe cases (Landau–Kleffner syndrome (LKS) or LKS-like), interictal epileptiform activity was required to be present <85% of the time during non-REM sleep. With respect to seizure semiology, seizures with anarthria, hemiclonia involving the face and/or unilateral extremities, or secondarily generalized seizures were considered. In case of poorly observed nocturnal seizures, post-ictal signs of a generalized seizure or confirmation of post-ictal hemiparesis was sufficient for inclusion in case of otherwise typical EEG.

The children with RE were tested by the Wechsler Intelligence Score for Children, third edition (WISC-III), and all had a full-scale IQ > 70. None of the healthy controls had (a history of) dyslexia, learning disorders or psychiatric disorders, or attended special education. Children were excluded if they had dental braces (MRI quality) or were somewhat afraid in the scanner. Healthy controls were excluded in case of suspicion of language impairment (see language assessment).

A board certified neuroradiologist specialized in epilepsy (PH) reviewed all scans and no structural abnormalities were found.

All parents (or guardians) and children gave written informed consent prior to study participation. The study was approved by the ethical review boards of both participating institutions and has ClinicalTrials.gov identifier NCT01335425.

2.2. Language assessment

To assess language performance, the Clinical Evaluation of Language Fundamentals, Fourth edition (CELF-4), Dutch version, was used (Paslawski, 2005; Semel et al., 2010). The CELF-4 is considered the gold standard for the identification of language disorders or delays in children and yields several age-corrected indices. Among these are the core language score (norm value, mean ± standard deviation: 100 ± 15), which is a global measure for language performance and can serve as a screening measure (e.g. exclusion of language impaired controls). More specific language indices were obtained in the group of children with RE only, including receptive language index (listening and understanding), expressive language index (expressing oneself, speaking), and language content index (semantic development).

2.3. MRI acquisition

Structural T1-weighted MRI was performed at 3.0 T (Philips Achieva system; Philips Medical System, Best, The Netherlands) using an eight-element receive-only head coil. Acquisition settings were: 1 × 1 × 1 mm³ voxel size, 3D fast spoiled gradient echo sequence, echo time/repetition time/inversion time 3.8/8.3/1022 ms and acquisition time 8 min.

2.4. Cortical thickness analysis

Cortical thickness analysis was performed using the Freesurfer image analysis software package (Dale and Sereno, 1993; Dale et al., 1999; Fischl and Dale, 2000). Freesurfer tessellates the interface between gray and white matter and between gray matter and cerebrospinal fluid (CSF) based on image intensity (gradients) in a highly robust and fully automated fashion. The shortest distance between the two surfaces represents an estimate of the cortical thickness (at approximately 300,000 nodes). Freesurfer was also used to spatially register the cortical thickness maps to Freesurfer standard space, and to perform general linear model (GLM) analysis for group comparisons and to find predictors for cortical thickness variations. To account for residual registration errors and to strengthen the assumption of Gaussian distribution of the data, the thickness maps were smoothed using a Gaussian kernel (full-with-at-half-maximum 10 mm). As on average males have a somewhat
thicker cortex than females (Raznahan et al., 2011), all analyses were
gender corrected.

Matlab (R2008a, The MathWorks, Natick, MA) was used to per-
form additional data visualizations. Additionally, Matlab was used to
perform robust quadratic fits for cortical thickness–age relationships
(Fig. 2).

2.5. Statistical analysis

Group comparisons of core language score and comparisons of pa-
tient specific indices to the CELF-4 norm values were performed using
two-sided Student’s t-tests (SPSS, version 17); p-values below 0.05
were considered significant. The cortical thickness group comparison
and associations of cortical thickness with age and language indices
were investigated using FreeSurfer’s build-in GLM tool, Qdec. All Qdec results (at approximately 300,000 nodes) were corrected for
multiple comparisons using the built-in tool for assessment of the
cluster size p-values. These multiple-comparisons corrected results
were considered significant for p < 0.05.

3. Results

3.1. Neuropsychological assessment (CELF-4)

The core language score of the patients (92 ± 18) was under the
norm score of 100 (p = 0.047) and lower than that of the healthy
controls (106 ± 10.5, p = 0.0026). The patients scored below norm
on all subtests. The deficits were significant in receptive language
index (87 ± 19, p = 0.002) and language content index (87 ± 18,
p = .0016) and a trend of reduced expressive language index was
found (92 ± 18, p = .054).

3.2. Thinner cortex in rolandic epilepsy

In the left hemisphere, a perisylvian region was identified in which
patients had a thinner cortex than controls (Fig. 1A, age corrected).
This region was located predominantly in the supramarginal gyrus and
partly covered the bank of the superior temporal sulcus, the supe-
rior temporal gyrus and the lower postcentral gyrus.

No aberrant regions were found in the right hemisphere and no
regions were found in which the patients had a thicker cortex than the
controls.

3.3. Cortical thinning with age in rolandic epilepsy

The effect of age on cortical thickness was subsequently investiga-
gated for both groups separately. The patients exhibited widespread
cortical thinning with age in predominantly the left hemisphere
(Fig. 1E, G). The left frontal region covered superior and rostral mid-
dle frontal areas and parts of the pars triangularis and opercularis
of the inferior frontal gyrus and the insula (Fig. 1E). The left parietal re-
region partly covered the supramarginal gyrus and also the lower part
of the postcentral gyrus. The left temporal region largely covered
the middle temporal gyrus and a part of the bank of the superior tem-
poral sulcus, whereas the posterior region covered parts of the inferi-
or parietal and lateral occipital areas. This region extended medially
(Fig. 1G) to cover parts of the cuneus and precuneus, the pericalcarine
and lingual cortex, and the cingulate cortex. In the right hemisphere
(Fig. 1F, H), several smaller regions were found in the rostral middle
frontal and lateral orbitofrontal cortex, the lateral temporal, the supe-
rior parietal and the lateral occipital cortex.

No regions were found showing cortical thickening with age and
also no (linear) age effect was found in the controls. In fact, whereas
the patients show consistent cortical thinning, the controls seem to
be in the transition from cortical thickening to cortical thinning
(Fig. 2).

3.4. Correlations between cortical thickness and language indices

The association between cortical thickness and language indices
was investigated per group (age corrected). No associations were
found within the regions of abnormal cortical thickness and/or aber-
rant age effect described above. Instead, in the patients, higher core
language scores were associated with lower cortical thickness in the
left inferior occipital lobe, more specifically the lingual and lateral oc-
cipital cortex (Pearson correlation r = −0.65, p < 0.001). Similar ef-
fects were found for the receptive language index, the expressive
language index and the language content index, while no effects
were found in the controls.

Fig. 1. Cortical abnormalities in rolandic epilepsy. Inflated brain visualizations of the regions showing abnormal cortical morphology in RE. Subfigures A–D display reduced cortical thickness in RE (age and gender corrected), subfigures E–H depict regions showing cortical thinning for increasing age, an effect which was only found in the patients (gender corrected). Reduced cortical thickness was found predominantly in the supramarginal gyrus and partly covered the bank of the superior temporal sulcus, the superior temporal gyrus and the lower postcentral gyrus (A). Cortical thinning with age was predominantly found in the left hemisphere and involved the inferior frontal gyrus, the inferior postcentral and the supramarginal gyrus and the middle temporal gyri at the lateral side (E), and the cuneus, precuneus and cingulate cortex medially (G).
4. Discussion

In this study, we set out to detect cortical abnormalities in children with RE and potential associations with language performance.

4.1. Main findings

We found reduced cortical thickness in patients compared to controls, not only within the seizure onset zone (rolandic cortex), but also beyond, in peri-rolandic regions of the left hemisphere. More extensive and distributed cortical abnormalities were observed when taking into account the effect of age, which demonstrated cortical thinning as a function of age, predominantly in the left hemisphere and in patients only. Language impairment in RE was confirmed for multiple language domains, particularly concerning receptive language and language content.

4.2. Reduced cortical thickness

Reduced cortical thickness in epilepsy is not specific for RE and has been demonstrated before in both adult and paediatric patients (Mueller et al., 2009; Widjaja et al., 2011). In this study, we found reduced cortical thickness not only in the rolandic cortex, but also in the supramarginal and superior temporal gyrus of the left hemisphere. We speculate that this is secondary pathology (i.e. not coinciding with the epileptic zone) and, given its location (Wernicke’s area), might be related to language impairment. To explain reduced cortical thickness outside the seizure onset zone, previously the existence of an underlying network has been suggested to propagate epileptiform activity to other cortical regions and to induce distal atrophy (Mueller et al., 2009; Widjaja et al., 2011). An alternative explanation is that both cortical abnormalities and seizures are symptoms of an underlying pathology (benign childhood seizure susceptibility syndrome; BCSSS (Panayiotopoulos, 1993; Panayiotopoulos et al., 2008)).

4.3. Cortical thinning with age in RE

Widely distributed morphological abnormalities were found when studying cortical thickness as a function of age. Gradual cortical thinning for increasing age was found predominantly in the left hemisphere in several frontal, centroparietal, temporal, and medial regions in the patients only. Again, not only the laterality of these abnormalities (left
No image provided.
demonstrates the relevance of the effect of age in RE and proposes to adopt the view that RE represents a deviation from the normal developmental trajectory of the brain in a critical period of brain maturation. The earlier this deviation occurs, the more severe the consequences, with children of age at seizure onset below 6 years being having the lowest language performance (Jürkeviciene et al., 2012). This warrants further research into whether it is possibly to exploit the increased brain plasticity in this critical period as a window of opportunity to redirect aberrant development onto a normal trajectory (Andersen, 2003). A possible approach is to stimulate language network formation by speech therapy, however this has not systematically been studied yet (Besag, 2006). Alternatively, improper neuronal signaling might be reduced by suppression of seizures and/or epileptiform activity using anti epileptic drugs (Porrats-Kattz et al., 2011), although in clinical practice this is controversial in RE as it is difficult to differentiate adverse effects of medication from disease effects (Hughes, 2010).

In conclusion, for the first time specific cortical abnormalities consistent over subjects were observed in children with RE. The abnormalities were localized predominantly in language mediating brain regions of the left hemisphere and involve areas of reduced cortical thickness and of early onset of cortical thinning of patients compared to controls. Future longitudinal research is prompted to further investigate developmental abnormalities in RE, e.g. investigating whether the cortical abnormalities represent a predictive cerebral marker for language impairment risk during and potentially after the active seizure period.

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