A specific deficit of auditory processing in children with Rolandic Epilepsy and their relatives

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ABSTRACT

Previous research shows that children with Rolandic Epilepsy have deficits of auditory processing. We wanted to confirm the nature of this deficit and whether it aggregates in families.

We compared 40 children with Rolandic Epilepsy and 32 unaffected siblings with 99 typically developing children and 71 parents of RE children with 31 healthy adults on a battery of auditory processing tests. We also examined ear advantage in children with RE, their siblings and parents using population norms and measured non-word reading performance.

We found a specific deficit for competing words in patients, their siblings and their parents, suggesting that this particular impairment of auditory processing present in children with RE, is heritable and likely to be persistent. Importantly, scores on this subtest in patients and siblings were significantly correlated with non-word reading performance. We saw increased rates of atypical left ear advantage in patients and siblings but no evidence of this in parents.

We present these findings as evidence of familial incidence of dichotic listening and ear advantage abnormalities in relatives of children with Rolandic Epilepsy.

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1. Introduction

Rolandic Epilepsy (RE) is the most common childhood epilepsy, constituting 15% of all childhood epilepsies [1]. The International Classification of Epilepsies and Epileptic Syndromes (Commission Classification and Terminology of the International League Against Epilepsy 1989), defines RE as a syndrome of brief and simple partial, hemifacial motor and somatosensory seizures, often involving oropharyngeal muscles and which may evolve into secondarily generalized tonic–clonic seizures. Onset occurs between 3 and 13 years and seizures usually remit before the age of 16 [2]. Evidence suggests that inherited factors are important in RE: early studies show that siblings are more likely to present with seizures and identical EEG abnormalities to probands [3,4] while 11% of parents reported having seizures during their childhood [3]. Later EEG studies of unaffected siblings of children with RE have shown an autosomal dominant inheritance of abnormal Centro-Temporal Spikes (CTS) [5] localizing to chromosome 11p13 [6]. Other studies show that relatives of children with RE experience similar increases in neurological and neuropsychological abnormalities such as migraine [7], and cognitive difficulties [8–10].

These cognitive difficulties include literacy and language [11], and executive functions [12–15] as well as impairments of auditory processing, understood as the bottom-up processing of sounds by the brain in the central auditory system. Studies have shown deficits of auditory processing of either temporal information [16], filtered words [17], dichotic sounds [18–20], or dichotic words [8]. Remission of auditory deficits may occur contemporaneously with remission of spikes [18, 21], reflecting the pattern of other language related deficits [22], suggesting that auditory processing difficulties are associated with epileptiform activity. However, an alternative explanation is that these two phenomena co-occur due to linked genetic loci and family studies show that both patients with RE and their relatives have an elevated risk for developing co-occurring disorders such as migraine [7], Reading Disorder and Speech Sound Disorder [10]. An earlier study by our lab with a separate uncontrolled sample of RE patients and their unaffected siblings revealed a strikingly similar profile of impairments in language and attention as well as auditory processing across the two groups [8].

Auditory processing difficulties may underpin certain other higher order learning and behavioral problems in RE [23]. Children with dyslexia find dichotic listening tasks more challenging than controls [24] and demonstrate atypical left ear advantage [25]. Auditory processing

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deficits have been associated with non-word reading difficulties in children with dyslexia [26] and with RE [16].

This study aimed to define the nature of the auditory processing deficit in children with RE in a larger sample, hypothesizing deficits of auditory processing in this patient group compared with the comparison group, together with significantly greater rates of left ear advantage, indicative of shifts in language specialization. Since studies have shown siblings of children with RE are themselves more likely to present with abnormalities such as migraine [7], and cognitive difficulties [8–10], and that auditory processing difficulties may persist into adulthood [27] we also recruited siblings and parents of children with RE, examining auditory processing deficits and differences in ear advantage in family members of affected children. A final aim was to investigate associations between auditory processing and non-word reading as measured by the Graded Non-Word Reading Test (GNRT) [28] in a subgroup of the children with RE and their siblings.

2. Material and methods

2.1. Participants

Children and adolescents with RE (n = 40), their siblings (n = 32) and their parents (n = 71) were recruited between 2010 and 2014 as part of a single large genetic study of RE in the South-East of England through consultant paediatricians from 28 hospitals. Children were considered eligible if they were aged 6–18, had a history of typical orofacial seizures with an age of onset between 3 and 12 years of age; normal developmental milestones; and neurologically normal examination. Handedness for these two samples was collected using the Edinburgh Inventory of Handedness [29]. We also recruited at least one biological parent (n = 71) for each proband. Additionally, we obtained data from two control groups consisting of children (n = 99) and adults (n = 31) recruited from local schools in Oxfordshire, UK. Handedness was not recorded for these latter samples.

2.2. Measures and procedures

We assessed audiometry, auditory processing, and phonological processing from RE cases and their families as part of a full day's assessment at the Institute of Psychiatry, Psychology & Neuroscience at King's College, London. All children with RE and their siblings and parents had normal hearing as assessed by a pure-tone audiometric threshold at 20 dB HL. A subgroup of children with RE (n = 35) and siblings (n = 26) completed the GNRT.

2.2.1. Auditory processing

The SCAN-C Test for Auditory Processing Disorders in Children revised [30] measures auditory processing in children aged between 5 and 11 years. Participants aged 12 and above were assessed by using the adult version of the measure, SCAN-A Test for Auditory Processing disorders in Adolescents and Adults [31], but the tasks are identical for each version and differ only in the normative data provided in the manual. Both the child and the adult version include four subtests: Filtered Words (FW), Figure Ground (FG), Competing Words (CW), and Competing Sentences (CS) and each subtest produces a standardized scaled score adjusted for age. The FW task presents monosyllabic words that have been low-pass filtered at 1000 Hz with a roll-off of 32 dB per octave to make them sound muffled and difficult to understand. This subtest assesses the ability of the participant to understand and repeat distorted speech. The FG subtest presents monosyllabic words that are presented with an accompanying quieter multi-talker speech babble background. This subtest asks the participant to identify words in the presence of background noise. The CW subtest is a test of dichotic listening and requires participants to repeat two monosyllabic words that are played simultaneously in each ear. In the first block of trials, the participant is required to repeat the word played in the right ear first and in the second block, the word played in the left ear first. Finally, during the CS subtest, two different sentences are presented to the right and left ears within 10 ms difference. The participant is asked to focus on and repeat the stimulus presented in one ear while ignoring the other.

Additionally, the CW subtest generates two ear advantage scores—one for the Right-Ear First Task and one for the Left-Ear First Task. The information presented on cumulative prevalence for ear advantage provides a means for measuring ear advantage since control data were unavailable for this measure. The more extreme or atypical the ear advantage score, the greater the possibility of an auditory-based disorder such as a language or learning disability and in particular, a left ear advantage may indicate reversed or absent dominance for language, a particular focus of this study.

2.2.2. Phonological processing

The Graded Nonword Reading Test (GNRT) [28] is administered individually and assesses children's ability to decode novel word-like graphemes. It is particularly useful in terms of assessing phonological skills and consists of 20 non-words, which increase from 1 to 2 syllables in length. Scores were converted into z scores using the means and standard deviations for each age group provided in the manual.

2.3. Statistical analysis

To compare gender distributions across the three groups we used a chi-squared test of proportions. We used independent t tests to compare continuous auditory processing performance variables across gender. We used a multivariate one-way ANOVA with group as a factor (children with RE, siblings and comparison group) to compare the three groups on each of the subtests of the SCAN-C.

Because ear advantage data were not available for our comparison groups, we tested the hypothesis that children with RE and their siblings would show increased rates of atypical left ear advantage scores, by comparing the proportion of children in the RE group and the sibling group who had atypical ear advantage as defined by scores expected by 10% of the population, using z tests to evaluate differences.

We also compared the mean scores of parents of patients and siblings with a group of typical adults described above using a multivariate ANOVA. Ear advantage data were also not available for our parent group so we again used population norms as described above.

In order to investigate correlations between child auditory processing performance and GNWR scores we used Pearson's correlation coefficient to examine the relationship between these scores and those scaled scores provided by the SCAN-C.

3. Results

3.1. Children

3.1.1. Age, gender and handedness

There were significant differences in age across all three groups: patients: (mean age of 10:4 (SD: 2:5)) siblings: (mean age 12:2 (SD: 3:11)) child comparison group: (mean age 8:6 (SD: 1:5)), (F = 30.9; df 2168); p < .0001).

There were significantly more boys in the proband group (65%) compared with the siblings (37%) and comparison group (51%), (χ^2 = 7.4; p = 0.024). We compared differences between males and females in auditory processing to determine whether gender should be included in the multivariate ANOVA model: there was no significant effect of gender on any of the auditory processing dependent variables (p > 0.17) but nevertheless gender was explored as a potential predictor variable.

Handedness did not differ between patients (81% were right handed) and siblings (80% were right handed) but was not measured in comparison children.

3.1.2. Auditory processing

Our one-way multivariate ANOVA model comparing children with RE, siblings and the comparison group was significant only for the CW subtest of the SCAN (F = 4.3; p = .015). Post-hoc t tests showed that compared with the comparison group, children with RE (p = .008) and siblings (p = .039) scored significantly lower on CW subtest. To test for possible gender effects on the CW subtest, a two-way univariate ANOVA was carried out adding gender as a factor. The effect of group remained significant (F = 3.3; p = .037).

3.1.3. Ear advantage

Ear advantage data were not available for the comparison group so we compared our children with RE and siblings with normative data reported in the SCAN-C manual for left ear advantage [30]. In children with RE, we found an atypical left ear advantage in 25% of the sample, a proportion significantly higher than the expected 10% described in the normative sample (z = 3.2; p = .001). A similar and significantly higher rate of 30% was observed in the sibling group compared with population rates (z = 3.6; p = .0003). Neither of these rates was associated with handedness and there were no differences in dichotic listening performance as measured by the CW subtest between those with and without atypical left ear advantage (t = −.275; df 68; p = .78).

3.2. Parents

3.2.1. Age, gender and handedness

The two adult groups were balanced for gender, but there were significant differences in age, with the comparison group being significantly younger (mean age 23:8 (SD: 10:1)) than the patients' parents (mean age 42:7 (SD: 7:0)), (t = 10.5; p < .0001). Because these standard scores were not normed using different age groups, age was included as a covariate.

Handedness was not measured in the adults.

3.2.2. Auditory processing

A multivariate ANCOVA comparing both adult groups on performance on all four subtests of the SCAN-A with age as a covariate showed that there were SCAN performance differences in parents of RE children compared with the comparison group; analyses showed a significant effect of group (F = 3.7; df 4, 85; p = 0.008), but no effect of age (F = 1.1; df 4, 85; p = ns). This significant difference was explained by performance on the CW subtest (F = 8.4; p = 0.005) (see Table 1) but no other subtests were significantly different across the two groups. Again we did not have ear advantage data available for our comparison group so we used population comparisons. 3.4% of the parents of patients had an atypical left ear advantage a rate which was less than but not significantly different to that of the normative rate of 10% [31].

3.3. Auditory processing and literacy

In order to explore the relevance of a deficit in CW to phonological processing, we correlated performance on the GNWR test in patients and siblings with all subtests of the SCAN-C. We found a significant correlation between GNWR performance and CW (r = .33; p = .02) but there were no other significant correlations between GNWR and other subtests (see Fig. 1).

4. Discussion

We have been able to confirm here that children with RE have a specific auditory processing impairment of dichotic listening of words. Intriguingly, this subtest alone subtest revealed significant deficits in parents and siblings of children with RE as well. The finding of deficits on the CW subtest of the SCAN-C in children with RE is consistent with earlier findings of dichotic listening in RE [18–20] and also supports work in our own lab with a different sample of children with RE and their siblings [8]. In our earlier work, we evaluated performance with population norms but here we have replicated our earlier findings with a larger, different sample of RE cases and made use of a large comparison group of typically developing UK children. An earlier study has shown this comparison sample to score almost one standard deviation lower than US school children in two of the SCAN subtests (filtered words and auditory figure ground) [32], illustrating the importance of using a comparison group. These population differences may be attributable to accent effects, as the SCAN is speech-based and performance is likely to be biased against children unfamiliar with American accents. By comparing our UK children with a comparable group of typically developing children we have reduced the likelihood of making a Type I error since differences are likely to be more, rather than less conservative. We also saw a significant deficit in the CW subtest in our sample of parents of patients, where we saw an effect size of approximately 1 standard deviation. Again, the deficit in this group was specific only to the CW subtest of the SCAN.

We have shown clearly here that epilepsy-free parents and siblings demonstrate a similar auditory processing impairment to children with RE, supporting established understanding that these impairments are unlikely to be directly attributable to epileptic seizures [33]. The finding that this deficit aggregates in families need to be explained: firstly, CTS waves may directly underlie this deficit. They have been shown to be directly related to cognitive measures of memory [34,35] but not necessarily for other types of cognitive performance [17,34, 35]: A detailed analysis of the association between CTS waves and cognition found no associations [36] and the cortical regions identified as abnormal in a recent structural MRI study of children with RE were shown to be far more extensive than the regions responsible for generating CTS waves [37].

An alternative explanation is that dichotic listening difficulties and CTS waves have a common genetic aetiology: they may be inherited together but have no causal relationship. PAX6 has been identified as one

Table 1
Gender, handedness, age, mean SCAN subtest scores and percentage with right and left ear advantage abnormality for typically developing children, children with RE, siblings of children with RE, typically developed adults and parents of children with RE. Standard scores are scaled with a mean of 10 and SD of 3.

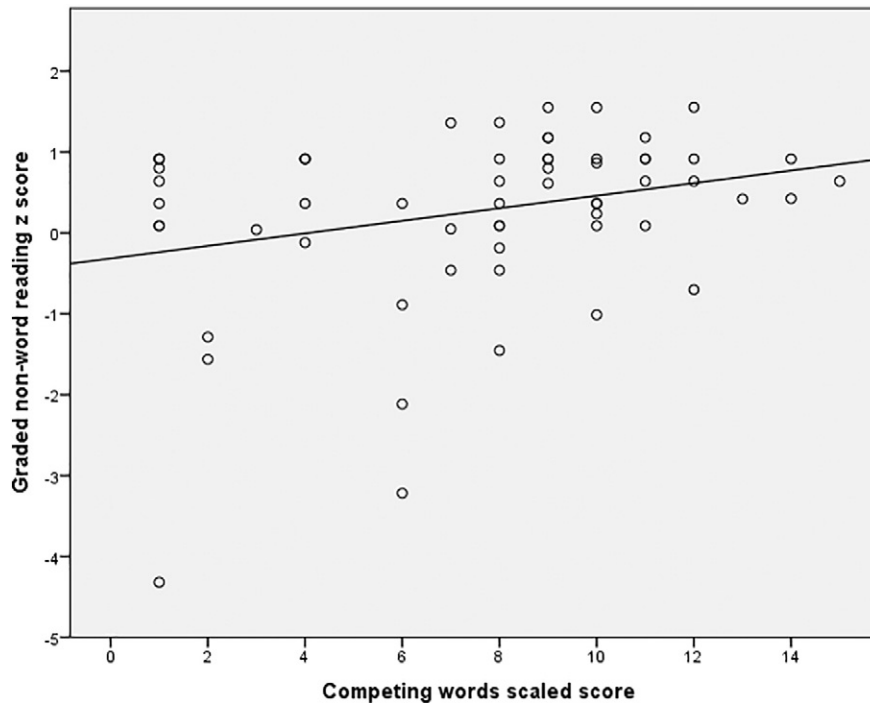|	RE children (n = 40)	Siblings (n = 32)	Comparison children (n = 99)	Parents of RE children (n = 64)	Comparison adults (n = 31)
Gender (% male)	67	35	51	43	32
Handedness (% right)	81	80	–	–	–
Age, y:m, mean (SD)	10:4 (2:6)	12:1 (3:9)	8:6 (1:5)	43:2 (7:0)	23:8 (10:1)
SCAN: FW, mean (SD)	6.6 (3.6)	7.3 (3.6)	6.7 (2.8)	8.5 (3.7)	7.2 (3.0)
SCAN: FG, mean (SD)	7.4 (3.4)	8.2 (3.2)	7.5 (2.5)	7.4 (4.1)	9.1 (2.9)
SCAN: CW, mean (SD)	7.3 (3.8)	7.6 (3.7)	8.9 (2.8)	4.8 (3.8)	8.6 (3.5)
SCAN: CS, mean (SD)	8.9 (4.0)	10.1 (4.0)	9.6 (2.6)	8.5 (3.6)	8.5 (4.0)
GNWR z score (SD)	.21 (1.2)	.34 (.87)	–	–	–
Left ear advantage abnormality (%)	25	30	–	3.4	–
Right ear advantage abnormality (%)	27.5	16			

Fig. 1. Scattergraph to show relationship between SCAN-C CW scaled scores and GNWR z scores in patients and siblings.

of the top candidate genes for epilepsy [38] and in support of this, very recent research has shown that a variant locus residing in PAX6 is associated with presence of CTS waves [39]. Highly heritable dichotic listening deficits [40] are thought also to be attributable to the PAX6 gene: Mutations of this gene are thought to impact upon the function of the anterior commissure and corpus callosum, leading to difficulties in hemispheric transfer, auditory processing and phonological processing [41]. These latter two processes are likely to be related and indeed, some describe the function of dichotic listening as verbal rather sensory [42,43]. Importantly, we observed a significant correlation uniquely between phonological processing and CW performance but not for the other SCAN subtests for patients and their siblings: since this deficit was specific to words rather than sentences we assume that in the competing sentence task the opportunity may have been greater for potential compensatory comprehension strategies. The association seen here between dichotic listening and non-word reading suggests that the processes involved in dichotic listening may be associated with phonological processing, thought to underpin literacy skills. Our lab has shown in a meta-analysis that individuals with RE demonstrate difficulties with phonological processing and decoding [11]. Asking these patients and their siblings to perform a simple dichotic listening task at a young age may serve as a useful screening measure of later literacy difficulties.

We also found unusually elevated left ear advantage rates in our patients with RE and their siblings, which appears unrelated to dichotic listening deficits as demonstrated by very similar performances between the children with and without abnormal left ear advantage. While typical right ear advantage is reflective of the direct auditory pathway that runs from right ear to left hemisphere, confirming that language function is lateralized to the left [44], an atypical left ear advantage is thought to be an indicator that the neural substrates for language are not located in the left hemisphere [45]. Unexpected symmetrical EEG activation has been observed in RE patients during listening activities, suggesting that language organization may be less lateralized [20,46]. Although a recent case study has shown changes in lateralization during a language task in a patient with RE using functional imaging techniques [47] this needs to be confirmed with a larger sample.

Although it is highly advantageous to make use of a comparison group rather than rely on normative data based on children of a

different nationality, this aspect of our study does present some limitations: firstly, there were significant age differences across all three groups, although this is mitigated to some degree by the standardization of the SCAN scores using normative data stratified by age. We felt it was important to include older children in our RE and sibling samples, as it is at this developmental stage that language related deficits may become more marked [11]. Another limitation is that the comparison participants were recruited in a different region of the UK so there is a possibility that they differ in terms of socio-economic status, culture and social background to the patients and siblings. Finally, the comparison children were not screened for neurological impairments and so we cannot be sure that they represent typically developing children.

5. Conclusion

We observed a specific deficit of dichotic listening in patients with RE and their siblings and parents, suggesting that there is a biological risk underlying auditory processing. This finding has important clinical implications, since even in the absence of seizures, difficulties with dichotic listening may be present in family members of those with RE and may serve as an indicator of future literacy difficulties. We also observed increased rates of atypical left ear advantage in children with RE and their siblings, suggestive of differences in language lateralization.

Disclosure

None of the authors has any conflict of interest to disclose

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