A Neurocognitive Endophenotype Associated with Rolandic Epilepsy

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Abstract

Purpose—Children with Rolandic Epilepsy (RE) experience difficulties in reading, language and attention. Their siblings are at high risk of dyslexia but are not otherwise known to have neurocognitive deficits. We therefore sought evidence for a RE-associated neurocognitive endophenotype.

Methods—Thirteen probands (male:female 9:4) and 11 epilepsy-free siblings (male:female 5:6) completed a neurocognitive evaluation within the domains of reading, language and attention. Frequencies of impairment were compared, and mean standardized scores of children with RE and their siblings were each compared against population means.

Key findings—Frequency of impairment in each domain was comparable for siblings and probands: 9% of siblings and 31% of probands were reading impaired; 36% of siblings and 54% of probands were language impaired; 70% of siblings and 67% of probands had attention impairments. Comparison of differences between sample and population means revealed evidence of a similar pattern of language deficits in both groups, specifically for picture naming and attention to competing words. For measures of attention, both groups made significantly higher omission errors and were impaired in their ability to sustain attention.

Significance—Children with RE and unaffected siblings demonstrate neurocognitive impairments in the domains of language and attention that are likely to remain undetected with general clinical protocols. Neurocognitively impaired probands and siblings showed a remarkably similar profile of deficits in language and attention that could explain poor academic performance. Early evaluation and intervention may benefit these children academically.

Keywords

Rolandic Epilepsy; Phenotype; Language; Attention; Auditory Processing

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Introduction

There is mounting evidence that Rolandic epilepsy (RE), the most common type of epilepsy (Shinnar et al., 1999), is a neurodevelopmental disorder with key neurocognitive impairments in speech, language, attention, executive and motor function (Baglietto et al., 2001, Boatman et al., 2008, Chaix et al., 2006, Chevalier et al., 2000, Croona et al., 1999, D'Alessandro et al., 1990, Deonna, 2000, Gündüz et al., 1999, Lindgren et al., 2004, Massa et al., 2001, Metz-Lutz et al., 1999, Monjauze et al., 2005, Northcott et al., 2005, Papavasiliou et al., 2005, Piccirilli et al., 1994, Staden et al., 1998, Weglage et al., 1997). Impairments in speech and language development lead to an increased risk of developmental and academic failures including speech sound disorder and reading disability (Clarke et al., 2007). Neurocognitive impairments remain even after seizure remission, suggesting a persistent course that does not correlate with the timecourse of either seizures or EEG abnormality in RE (Hommet et al., 2001); although the seizures and EEG abnormality may well complicate neurocognitive performance, as suggested by the association of attentional impairment and centrotemporal spikes (CTS) (Kavros et al., 2008).

We have demonstrated a familial pattern of risk for reading disability (RD), speech sound disorder (SSD), CTS and migraine in RE families (Bali et al., 2007, Clarke et al., 2009, Clarke et al., 2007). Some of these traits have been genetically mapped showing that the familial pattern of risk has a genetic basis (Pal et al., 2010, Pal et al., 2007, Strug et al., 2009). A closer look at the patterns of familial aggregation and co-aggregation also indicates evidence of overlapping and distinct genetic susceptibilities. For example, SSD co-aggregates in RE families, ie there is an increased risk of SSD in family members of RE probands whether or not the proband has comorbid SSD or not; whereas RD does not co-aggregate, ie the increased risk of RD in relatives is restricted to families in which the proband is comorbid with RD (Clarke et al., 2007). These inferences are supported by recent linkage evidence showing that a locus at 11p13 for CTS is pleiotropic for SSD in RE families (Pal et al., 2010); however, there is no evidence that RD shares susceptibility at the 11p13 locus, but rather maps to distinct loci (Pal et al., 2007). Most importantly, these results strongly suggest that susceptibility to the key comorbidities in RE is inherited and not the direct result of recurrent seizures – an insight that should guide approaches to intervention.

One prediction of these two strands of epidemiological and genetic research is that probands and siblings should share a similar neurocognitive profile. The purpose of the current work is to seek evidence of a consistent pattern of impairment across reading, language and attentional domains that would support the concept of a neurocognitive phenotype in RE. Such a profile would be valuable both as a research model, and also for predicting areas for clinical and educational intervention. The aim of this study was to evaluate reading, expressive and receptive language including underlying auditory processing deficits, and attention in a group of rolandic epilepsy subjects and a sample of their epilepsy-unaffected siblings. We tested the hypothesis that siblings share the same pattern of neurocognitive impairment as RE probands, as predicted by familial aggregation studies (Clarke et al., 2007).

Methods

Subjects

The children of families enrolled in a RE genetic linkage study (Strug et al., 2009) were invited to participate in a neurocognitive research evaluation. Cases were enrolled into the genetic study if they met stringent eligibility criteria, including typical orofacial seizures, age of onset between 3–12 years, no previous epilepsy type, normal global developmental

milestones, normal neurological examination, an EEG abnormality demonstrating CTS and normal background, and absence of other structural abnormalities on routine brain magnetic resonance imaging (MRI) that could explain seizures (Clarke et al., 2007). All families approached agreed to participate. We obtained information from all subjects through a 125 item questionnaire addressing medical history and development, seizures, and treatment (Clarke et al., 2007). Details of ascertainment are published elsewhere (Clarke et al., 2007).

Two groups of children participated in the neurocognitive evaluations: 13 probands (M:F, 9:4); and 11 siblings (M:F,5:6). Thirteen families took part in the study (see Table 2 and 3): For most of these families, one proband and one sibling were recruited; for family 1 and 3, one proband and two siblings were recruited; for family 10–13 one proband was recruited but no sibling. There were no significant differences between the age of the probands (mean age: 10 years and 10 months (range 8–16) and the siblings (mean age: 11 years and 4 months (range 6–15 years)). There were no significant differences in their level of education (both groups: median sixth grade). The clinical characteristics of the probands and siblings are reported in Table 1 and 2.

Measures and Procedures

The neurocognitive test battery was composed of standard instruments used to assess general intelligence (Wechsler, 1999), and the following three domains: ***reading*** (Torgesen et al., 1999, Wiederholt & Bryant, 2001, Woodcock-Johnson, 2001b), ***language***, including receptive and expressive language (Kaplan et al., 2001, Semel et al., 2003) and underlying auditory processing (Keith, 2000, Woodcock-Johnson, 2001a) and ***attention*** (Sandford & Turner, 2002). See Appendix A for details of all measures. After the administration of the IQ tests, subtests were presented to the child in a randomized order. The neurocognitive evaluation was conducted by a licensed psychologist and two neurocognitive testers supervised by a board certified neuropsychologist. All evaluations and statistical analysis were conducted blind to the clinical data.

Scoring and statistical analysis

After eliminating scores that suggested that the participant had not performed a test properly, scores obtained from the neurocognitive evaluations were transformed to Standard Scores (SS), with the mean equal to 100 and a standard deviation (SD) of 15. For each case, we aimed to identify patterns associated with neurocognitive functioning: Two scores below one standard deviation (mean=<85) of the population mean (100) in the same domain for each participant were considered a marker of impairment, drawing upon earlier guidelines (Staden et al., 1998). We used these measures instead of customary cutoffs of clinical significance in order to detect patterns of relative weakness.

Given that frequencies are small and thus formal comparisons of rates of impairment based on the above criteria using chi square analyses are not possible, scores were also evaluated by using continuous data and comparing standardized group scores against a population mean of 100 for each measure using one-sample t tests.

Analyses were performed using Stata 8.2. The study was approved by the institutional review boards of the New York State Psychiatric Institute, Columbia University Medical Center, and all collaborating centers. Subjects gave written informed consent.

Results

Probands

All probands demonstrated a Full Scale IQ, Verbal and Non-Verbal IQ within normal range (see Table 3). There was some evidence of reading impairment in probands (30%) but impairments of attention (67%) and language were more marked (54%). One sample t tests for differences between proband means and population means for all reading measures revealed significant reading deficits, specifically reading accuracy and comprehension (see Table 3). This group also showed evidence of expressive language deficits including picture naming, attendance to competing words and sentence formulation. Measures of auditory and visual attention on the Continuous Performance Task (CPT) revealed significantly higher omission and commission errors as well as response variability and sustained attention (see Table 3). None of these differences survive adjustment for multiple testing.

Siblings

All except one sibling (who scored below) demonstrated a Full Scale IQ, Verbal and Non-Verbal IQ within normal ranges. There was evidence of reading impairment in 9% of the sibling sample and of language impairment in 36% of this sample. Attentional impairments were evident in 70% of the siblings.

One sample t tests for differences between sibling means and population means revealed no reading deficits (see Table 3). However, siblings showed evidence of expressive language and auditory processing deficits including picture naming, sentence formulation and attendance to competing words (see Table 3). None of these differences survive adjustment for multiple testing. Given the small sample sizes in this study, Table 3 shows effect sizes for each comparison with the population mean: Effect sizes can be informative in studies where samples are small, as although Type I probability levels may not be significant, effect sizes can provide information about potentially important differences, thus avoiding Type II errors.

Discussion

The above findings demonstrate that similar deficits occur in children with Rolandic Epilepsy and a group of siblings: Large effect sizes are observed in both groups on measures of dichotic listening (attendance to competing words), automatic naming and auditory attention. We interpret this as evidence for an endophenotype of RE-associated neurocognitive impairments, shared between probands and siblings, which may involve language, auditory processing and, to a lesser extent (since differences in the sibling group are just below significance level), attentional function. Our findings support and extend earlier work on language and attentional impairments in RE (Kavros et al., 2008, Staden et al., 1998).

Deficits of auditory processing in patients with RE are in line with a disruption of function within the perisylvian region, suggesting a consistent pattern of weakness predicted by the localization of focal sharp wave discharges over the perisylvian region (Staden et al., 1998). This auditory processing deficit may underlie language impairments also observed here in the patient group, given that research suggests that the neural correlates of auditory processing also include left inferior frontal cortex, a region also associated with semantic processing (Poldrack et al., 2001). The finding of significant impairments in attentional processing in this patient group suggests that the neural circuits disrupted by the underlying pathology extend beyond the perisylvian and left inferior frontal cortex (Kavros et al., 2008). We speculate that as well as disruption of left lateralised language and auditory processing in this patient group (Lillywhite et al., 2009), typically right-hemisphere

functions such as sustained attention may also be disrupted. The finding of sustained attention deficits in RE is highly relevant, given that this function is crucial for reading, a well established problem for patients with RE (Clarke et al., 2007, Kavros et al., 2008). Interestingly, neural substrates for reading include left inferior frontal gyrus and temporo-parietal cortex (Goswami, 2006) while neural correlates of sustained attention appear to involve right-sided homologues of this region: a meta-analysis of neuroimaging studies of sustained attention focussing upon similar paradigms to the one used in this study was able to demonstrate a consistently activated right-sided network involving right inferior and middle frontal gyrus and particularly the right temporo-parietal junction (TPJ) (Corbetta & Shulman, 2002), also supported by later studies (Bledowski et al., 2004, Mulert et al., 2004, Smith et al., 2011).

Comparison of patients and unaffected siblings

This pattern of neurocognitive disruption observed in children with RE was also seen in seizure-free siblings, within the domains of language (Boston naming), auditory processing (competing words) as well as auditory inattention measures (omissions and sustained attention) where large effect sizes were seen in both groups. This suggests that these specific impairments are unlikely to be a direct result of recurrent seizures. These findings support earlier work on the familial clustering of such deficits in RE families (Clarke et al., 2007) demonstrating a high degree of specificity in the nature of this inherited trait.

There is a similarity in neurocognitive profiles between probands and siblings that mirrors our previous finding of strong familial aggregation of speech sound disorder and reading disability in RE families (Clarke et al., 2007). The current findings elaborate on the domains in which siblings and probands share deficits, and suggest core neural impairments in language deficits and underlying auditory processing that may explain academic underperformance. This area of research may also be useful for future genetic analysis of proximate markers of vulnerability (endophenotypes), as has been suggested in sibling studies of neuropsychiatric disorders (Delawalla et al., 2006, Doyle et al., 2005, Francks et al., 2003, Haverkamp et al., 2002).

Results of the Competing Word and Boston picture naming tasks show that auditory processing and language performance is significantly below normalized means in both probands and siblings, while impairments of auditory attention are significant in children with RE and approach significance in siblings. While some measures only reach trend level in the sibling group, frequently large effect sizes greater than 0.8 (Cohen, 1988) suggest this is attributable to small sample sizes. Although it is possible that these deficits may have occurred as a result of subclinical EEG activity, we speculate that they may represent an interaction between distinct genetic susceptibilities to CTS and language outcomes as suggested by linkage analysis (Pal et al., 2007). It is encouraging to observe similarities in the strengths of these two sibling groups, particularly in sound blending and incomplete words. We propose cautiously (given the small sample) that this similarity provides further support for our hypothesis that these two groups have similar profiles and also demonstrates that some features of language are not disrupted in either of these groups, specifically within phoneme manipulation. This suggests that in both groups, deficits may be associated with the acquisition of sounds and phonemes, but once sounds are acquired, there is no weakness in function.

Limitations

This work does not describe a comprehensive RE phenotype: here we have covered only some aspects of cognition while speech, oromotor and fine motor praxis impairments and some non-verbal deficits may also form part of a broader profile (Scabar et al., 2006). We

were not able to carry out proband-sibling paired analyses, since we included probands without siblings in our sample. We also had small sample sizes and so we compared each group's standardized scores to population means, which resulted in the detection of relatively large effect sizes. A larger sample would have allowed us to further validate and refine the phenotype using factor analysis or other data reduction techniques, preferably including appropriately matched unrelated controls in the design. We also acknowledge that it would have been useful to confirm the presence or absence of CTS in all sibling controls, thus establishing whether the cognitive endophenotype observed here was associated with CTS activity. Further, given that some anti-epileptic drugs (AEDs) have been shown to both enhance (Mintz et al., 2009) and impair cognition (Hirsch et al., 2003) we accept that this is a potential confounder in our study. Although our sample included a sub-group of patients who had received AEDs, given that there is no clear understanding of how AEDs affect specific cognitive functions, the power of this study is not adequate to consider a comparison of treated versus untreated patients, but could form the basis of future investigation.

Clinical implications

Siblings of RE patients are at risk of some of the same neurocognitive impairments as observed in RE. The clinician may be in a key position to plan early evaluation and intervention in presymptomatic siblings before teachers report symptoms of academic underachievement. The clinician may assess speech and language milestones in young siblings, or enquire about academic progress in school age siblings.

Acknowledgments

Appendix

A

Neurocognitive Study Instruments	Description of Task
General Intelligence	
Wechsler Abbreviated Scale of Intelligence (WASI)	Consists of four sub-tests of verbal (vocabulary and similarities) and performance (block design and matrixes) IQ
Reading	
Gray Oral Reading Tests 4 (GORT 4)	Assesses the ability to read orally, including: **Rate** – assesses the amound of time taken to read a story; **Accuracy** – assesses the ability to pronounce each word in the story correctly; **Fluency** – Rate and Accuracy Scores combined; **Comprehension** – assesses the appropriateness of the student's responses to questions about the content of each story read.

Neurocognitive Study Instruments	Description of Task
Test of Word Reading Efficiency (TOWRE)	Assesses the ability to read real and nonsense words thus testing Sight Reading and Phonetic Decoding Efficiency
Receptive Language (RL)	
Clinical Evaluation of Language Fundamentals, 4th Ed. (CELF)	**Concepts and directions** - assesses the ability to interpret, recall, and execute oral commands of increasing length and complexity
	Recalling sentences - assesses the ability to recall and reproduce sentences of varying length and syntactic complexity
	Understanding spoken paragraphs - assesses the ability to answer questions about a paragraph presented orally
Expressive Language (EL)	
CELF	**Rapid automatic naming** - tests the ability to name shapes colors and different color-shape combinations
	Formulated sentences - evaluates the ability to formulate compound and complex sentences when given grammatical (semantic and syntactic) constraints
Boston Naming Test, 2nd Edition	Assesses the ability to name objects from line drawings
Auditory Processing	
SCAN-C Auditory Processing Disorders in Children–Revised	**Filtered words** - assesses the ability to understand distorted speech
	Competing words - assesses the ability to understand competing speech signals (sometimes called binaural separation).
	Figure Ground - assesses ability to understand speech in the presence of background noise
Woodcock Johnson III (WJ III) (Incomplete Words, Sound Blending	**Incomplete words** - assesses the ability to recognize words dictated with some sounds omitted
	Sound Blending - assesses the ability to identify words dictated broken into separate sounds
Attention	
Integrated Visual & Auditory Continuous Performance Test (IVA CPT)	**Continuous Performance Task:** a combined auditory and visual target detection task lasting 13 minutes with a target to non-target ratio of either 5 to 1 (first block) or 1 to 5 (second block)
Woodcock Johnson III (WJ III)	**Auditory Working Memory** - assesses the ability to repeat randomly dictated words and numbers
	Numbers Reversed - assesses the ability to repeat increasingly long series of dictated digits in reversed order

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Table 1

Clinical Characteristics of RE Probands

Family No	Proband	Age	Sex	Handed	Grade	CTS	EEG Abn	Age at 1st Seizure	AEDs
1	P01	13	F	R	7	Present	L	9	CBZ
2	P03	12	M	L	7	Present	Bilat L>R	11	CBZ
3	P04	8	M	R	3	Present	Bilat L>R	5	CBZ
4	P05	12	F	R	6	Present	Bilat L>R	10	None
5	P07	8	M	R	2	Present	L	7	CBZ, LMG
6	P08	16	M	R	10	Present	R	4	CBZ
7	P09	8	M	R	2	Present	L	7	None
8	P12	8	M	R	3	Present	Bilat	3	None
9	P13	12	M	R	6	Present	Bilat L>R	9	None
10	P02	12	M	R	6	Present	Bilat	10	None
11	P06	13	M	R	7	Present	Bilat	10	CBZ
12	P10	8	F	R	3	Present	Bilat	5	None
13	P11	10	F	L	5	Present	Bilat	8	None

EEG abnormalities may be predominantly left-sided (L), right-sided (R) or bilateral Antiepileptic Drugs (AEDs): Carbamazepine (CBZ); Lamotrigine (LMG)

Table 2

Characteristics of siblings of RE probands

Family No	Sibling	Age	Sex	Handed	Grade	CTS
1	S01	11	M	R	4	Unknown
1	S02	9	M	R	4	Unknown
2	S03	11	F	R	6	CTS /R
3	S04	13	F	R	7	CTS /R
3	S05	11	F	R	5	CTS /R
4	S06	11	M	R	5	Unknown
5	S07	11	F	R	6	None
6	S08	15	F	L	10	Unknown
7	S09	6	M	R	1	Unknown
8	S10	13	M	L	7	Unknown
9	S11	13	F	R	8	None

Centrotemporal Spikes on EEG (CTS)

Table 3

Means and standard deviations, one-sample t and p values comparing probands and siblings with population norms on norm referenced tasks measuring IQ, reading, language and attention

Measure	Proband					Siblings				
IQ	**n**	**Mean (sd)**	**t value**	**Effect size (d)**	**P (1-tailed)**	**n**	**Mean (sd)**	**t value**	**Effect size (d) ***	**P (1-tailed)**
Full Scale	10	104 (11)	1.10	.64	.15	11	104 (13)	.935	.59	.16
Verbal	12	101 (13)	.21	.12	.42	11	104 (14)	1.038	.65	.18
Performance	10	103 (13)	.86	.50	.21	11	103 (13)	.906	.58	.19
Reading		**Mean (sd)**	**t value**	**Effect size (d)**	**p (1-tailed)**		**Mean (sd)**	**t value**	**Effect size (d)**	**P (1-tailed)**
GORT: Rate	13	98 (15)	−.45	.26	.33	10	105 (17)	.94	.31	.17
GORT: Accuracy	13	93 (15)	−1.76	1.02	.05*	10	99 (18)	−.17	.06	.44
GORT: Fluency	13	92 (18)	−1.62	.94	.06	10	103 (20)	.48	.17	.32
GORT: Comprehension	13	91 (19)	−1.76	1.01	.05*	10	99 (20)	−.52	.06	.31
TOWRE: Sight	7	103 (15)	.55	.32	.30	9	106 (15)	1.30	.82	.11
TOWRE: Phono	7	100 (14)	.08	.05	.45	9	105 (13)	1.14	.72	.14
Language	**N**	**Mean (sd)**	**t value**	**Effect size (d)**	**p (1-tailed)**	**n**	**Mean (sd)**	**t value**	**Effect size (d) ***	**P (1-tailed)**
CELF: Following Directions (RL)	10	99 (21)	−.08	.05	.47	7	101 (14)	.26	.16	.40
CELF: Sentence recall (RL)	13	95 (11)	−1.45	.83	.09	11	94 (15)	−1.42	.90	.09
CELF: Understanding (RL)	13	100 (18)	.08	.05	.47	11	105 (14)	1.26	.80	.12
CELF: Rapid automatic naming (EL)	13	93 (13)	−1.93	1.11	.04*	11	98 (18)	−.31	.20	.38
CELF: Sentence form (EL)	13	91 (16)	−1.90	1.10	.04*	11	104 (17)	.81	.51	.21
Boston naming (EL)	12	89 (16)	−2.50	1.44	.01*	11	91 (16)	−1.95	1.23	.04*
SCAN:filtered words (AP)	12	95 (17)	−1.10	.64	.15	9	94 (16)	−1.08	.68	.16
SCAN:figure ground (AP)	12	93 (18)	−1.48	.85	.08	9	103 (9)	1.07	.68	.16
SCAN competing words (AP)	12	77 (19)	−4.22	2.44	.0005*	9	77 (18)	−3.83	2.42	.002*
WJ III: Incomplete words	13	105 (13)	1.39	.80	.09	11	106 (11)	1.71	1.08	.06
WJ III: Sound blending	13	105 (19)	.89	.51	.20	11	107 (16)	1.37	.87	.20
Attention	**n**	**Mean (sd)**	**t value**	**Effect size (d)**	**p (1-tailed)**	**n**	**Mean (sd)**	**t value**	**Effect size (d) ***	**P (1-tailed)**

Measure	Proband					Siblings				
Auditory: omissions	12	90 (17)	−1.92	1.11	.041*	9	82 (33)	−1.70	1.07	.06
Auditory:variability	12	89 (12)	−3.24	1.87	.004*	10	101 (21)	.22	.14	.41
Auditory: commissions	12	85 (21)	−2.49	1.44	.015*	10	94 (16)	−1.20	.76	.14
Auditory:sustained	12	89 (19)	−1.98	1.14	.037*	9	78 (39)	−1.70	1.07	.06
Auditory:reaction time	12	102 (13)	.47	.27	.33	10	101 (20)	.11	.07	.45
Visual:omissions	12	93 (30)	−.80	.46	.22	8	92 (17)	−1.30	.83	.23
Visual: variability	12	89 (22)	−1.70	.98	.06	8	97 (16)	−.52	.33	.30
Visual commissions	12	89 (18)	−2.05	1.18	.03*	8	98 (18)	−.33	.21	.32
Visual: sustained	11	103 (18)	−.59	.34	.25	8	88 (28)	−1.19	.75	.14
Visual: reaction time	12	104 (6)	1.95	1.13	.04*	8	103 (11)	.67	.42	.25

IQ: Weschler Abbreviated Scale of Intelligence (WASI); **Reading**: Gray Oral Reading Tests 4 (GORT 4), Test of Word Reading Efficiency (TOWRE); **Receptive Language (RL)**: Clinical Evaluation of Language Fundamentals (CELF); **Expressive language (EL)**: CELF; Boston Naming Test, **Auditory processing (AP)**: Auditory Processing Disorders in Children-Revised (SCAN): Woodcock Johnson III (WJ), **Attention**: Integrated Visual & Auditory Continuous Performance Test (IVA CPT) (see Appendix A for more details of measures)

*
Effect sizes (d) have been described in the following way by Cohen (1988): .2 = small; .5 = medium; .8 = large