Intelligence in childhood epilepsy syndromes
Intellectual deficits are a significant cause of comorbidity in children with epilepsy.
Limitations of previous literature

- Studies lack well defined syndrome classification - based on seizure type.
- Frequently confined to school age
- Studies frequently restricted to children with intelligence in the normal range

- *Comparisons with our study* - biased to severe epilepsy
Seizure Classification

Generalised

Partial

Unclassifiable

Idiopathic

Symptomatic
Epileptic Syndrome

- Cluster of signs and symptoms regularly occurring together

- May include:
  - seizure type
  - time, circumstances of occurrence
  - neurological, EEG findings
TEMPORAL LOBE EPILEPSY
BITEMPORAL SHARP WAVES

<table>
<thead>
<tr>
<th>FP1  - F7</th>
<th>FP2  - F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>F7  - SP1</td>
<td>F8   - SP2</td>
</tr>
<tr>
<td>SP1 - T7</td>
<td>SP2 - T8</td>
</tr>
<tr>
<td>T7  - P7</td>
<td>T8   - P8</td>
</tr>
<tr>
<td>P7  - O1</td>
<td>P8   - O2</td>
</tr>
<tr>
<td>FP1 - SP1</td>
<td>SP1 - SP2</td>
</tr>
<tr>
<td>FT9-FT10</td>
<td>FT9-FT10</td>
</tr>
<tr>
<td>F3   - C3</td>
<td>F3   - C4</td>
</tr>
<tr>
<td>C3   - P3</td>
<td>C4   - P4</td>
</tr>
</tbody>
</table>

1 SEC.  100 μV
Approach

- Analysis of presenting seizure.
- Analysis of EEG.
- Above, with patient demography enables Syndrome Classification.
What is known?

Factors contributing to impaired intellectual function in childhood epilepsy:

- Onset of epilepsies in first years of life in focal and generalised epilepsies
  - Long duration of epilepsy
  - Frequent seizures
  - Polypharmacy

Need to allow for confounding factors to determine the primary intellectual characteristics of each syndrome
AIMS

- To classify childhood epilepsy syndromes accurately using clinical data, seizure semiology, ictal and interictal data.

- To analyse the intellectual function of a broad group of children with epilepsy, from infancy to adolescence, inclusive of all ranges of intellectual abilities, using age-normed and validated instruments.
AIMS

- To identify the impact of clinical epilepsy variables (age of onset, duration of active epilepsy, seizure frequency, polypharmacy) on intellectual function in childhood epilepsy.

- To compare the intellectual abilities of children with different childhood epilepsy syndromes.
Hypotheses

- Children with different syndromes have specific intellectual profiles.
- Children with generalised symptomatic epilepsy have the lowest intellectual ability.
- Children with generalised idiopathic epilepsy have only mild intellectual difficulties.
- Children with well-localised epilepsy have intellectual abilities similar to children with idiopathic epilepsy.
Methodology

- Recruitment
- Assignment of epilepsy syndrome
- Neuropsychological assessment

After adjusting for important epilepsy variables, 95% confidence intervals were generated for mean FSIQ using ANCOVA.
Methodology - Patients

● 0-18 years
● Referred to SCH and CHW for video EEG monitoring (consecutive series) July 1995-Dec 2001; exclusion criteria
● Data collection
  - age of epilepsy onset
  - duration of active epilepsy
  - seizure frequency
  - current medications
  - medical history and neurological exam
The four parameters of syndrome classification

- Parameter 1: History
- Parameter 2: Seizure semiology
- Parameter 3: Interictal EEG
- Parameter 4: Ictal EEG
Syndrome of Mesial Temporal Lobe Epilepsy

- History of prolonged febrile seizure, early encephalitis
- Seizure Semiology
  - Epigastric aura
  - Complex partial seizure: arrest and stare, orofacial automatisms, dystonic posturing of arm
  - Postictal phase: disorientation, recent memory deficit, dysphasia
**Epilepsy Syndrome**

<table>
<thead>
<tr>
<th>Generalised</th>
<th>Localisation-related (partial, focal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Symptomatic</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Symptomatic</td>
</tr>
</tbody>
</table>

**Examples of included syndromes**

- Childhood Absence epilepsy
- Juvenile Absence epilepsy
- Juvenile Myoclonic epilepsy
- Epileptic Spasm
- Lennox-Gastaut Syndrome
- Temporal lobe epilepsy
- Frontal lobe epilepsy
- Central epilepsy

PARTIAL
### Assessment of intelligence according to age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Instrument</th>
<th>Low-functioning alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 3</td>
<td>Griffiths</td>
<td></td>
</tr>
<tr>
<td>3 - 6</td>
<td>DAS</td>
<td>Griffiths</td>
</tr>
<tr>
<td>6 - 16.9</td>
<td>WISC-III</td>
<td>Stanford-Binet IV</td>
</tr>
<tr>
<td>16.9 - 18</td>
<td>WAIS-R</td>
<td>Stanford-Binet IV</td>
</tr>
</tbody>
</table>

Handling of neuropsychological results

Results were recorded as standard deviations from the normed mean (z-scores). In a normal population the normed mean is zero, with 95% of the population having values within 2SDs of the mean. A score of -1 occurs in 16% of the population and a score of -2 occurs in the lowest 2.5% of the population
The population of 169 children, GIE (n=22, CAE:17), GSE (n=25), TLE (n=40), FLE (n=34), CE (n=16) PE (n=32).

Initial patient group: 208
Anti-epileptic drug (AED) use

No AED: 8 (5%)
1 AED: 62 (37%)
2 AED: 69 (41%)
3 AED: 27 (16%)
4 AED: 1
Anti-epileptic drug (AED) use

Sodium valproate: 40%
Lamotrigine: 36%
Carbamazepine: 35%
Vigabatrin: 12%
Topiramate: 12%
Clobazam: 11%
Results

Significant differences between epilepsy syndrome groups were found for:

- age of onset ($p < 0.001$)
- duration of active epilepsy ($p = 0.027$)
- seizure frequency ($p = 0.037$)
- polytherapy ($p = 0.024$)
Results

- Across all syndromes, the mean FSIQ was below the normed mean adjusted for age.

- PIQ and VIQ mirrored the FSIQ.
  \[(r = 0.94 \text{ and } p < 0.001)\]
  PIQ and VIQ were not influenced by lateralisation reflecting global dysfunction.

- Generalised Idiopathic Epilepsy had a negative impact on FSIQ.
Relationship of FSIQ* and Epilepsy Syndrome

- *covariates in model: age of onset, seizure frequency, number of AED;
- **z score = standard deviations from normed mean
Results

Analysing FSIQ: children with

- Generalised Idiopathic Epilepsy
- Central Epilepsy
- Temporal Lobe Epilepsy

performed best and did not differ significantly.
Results

Children with Generalised Symptomatic Epilepsy had a statistically lower FSIQ than other syndromes except Partial Epilepsy.
Results

Frontal Lobe Epilepsy functioned significantly better than Generalised Symptomatic Epilepsy but did not differ significantly from other groups.
Relationship of FSIQ* and Epilepsy Syndrome

- *covariates in model: age of onset, seizure frequency, number of AED;
- **z score = standard deviations from normed mean
Results

- On regression analysis clinical epilepsy variables (age of onset, seizure frequency and use of polytherapy) contributed to 26% of the variance in FSIQ.

- Epilepsy syndrome classification contributed a further 15% to the variance in FSIQ, independent of the clinical variables.
Lateralisation

- In children with FLE a right-sided focus was associated with a significantly higher FSIQ than a left sided focus (p=0.02) taking into account epilepsy variables.

- Other focal epilepsies did not have significant FSIQ discrepancies on lateralisation.
Conclusions

- In childhood epilepsy delineation of syndrome has important implications for prediction of intellectual ability.

- Across all syndromes the mean FSIQ was below the normal mean.

- This information is invaluable in planning education interventions and supporting the family.
Conclusions

Lower FSIQ levels were associated with younger age of onset, > 2 anticonvulsants and frequent seizures.

Our population does reflect referral bias for intractable epilepsy.
Conclusions

- Generalised idiopathic Epilepsy (CAE) had a negative impact on FSIQ

- Children with Generalised Symptomatic Epilepsy (GSE) have the worse performance. May reflect underlying pathology

- Children with Temporal or Central Lobe Epilepsies performed better than those with non-localised Partial Epilepsies

- Children with Frontal Lobe Epilepsy fell in the lower end of the spectrum of FSIQ in focal epilepsy.
  - Lateralisation effect
Conclusion

- FSIQ within the normal range does not negate the possibility of deficits in specific cognitive functions.

- Disparities between academic progress and FSIQ should indicate need for detailed neuropsychological testing including assessment of memory, attention and executive function.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Group</th>
<th>GIE</th>
<th>GSE</th>
<th>CE</th>
<th>TLE</th>
<th>FLE</th>
<th>PE</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. cases</td>
<td>169</td>
<td>22</td>
<td>25</td>
<td>16</td>
<td>40</td>
<td>34</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>53</td>
<td>45</td>
<td>64</td>
<td>47</td>
<td>48</td>
<td>62</td>
<td>48</td>
<td>0.587⁺</td>
</tr>
<tr>
<td>Mean age at exam in years (95% CI)</td>
<td>9.6</td>
<td>9.3</td>
<td>5.8</td>
<td>8.4</td>
<td>10.7</td>
<td>10.9</td>
<td>10.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median age at onset in years (IQR)⁴</td>
<td>3.0</td>
<td>6.0</td>
<td>0.6</td>
<td>4.0</td>
<td>3.5</td>
<td>5.5</td>
<td>2.8</td>
<td>&lt;0.001#</td>
</tr>
<tr>
<td>Median seizure duration in years (IQR)⁴</td>
<td>3</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
<td>5.0</td>
<td>3.0</td>
<td>6.0</td>
<td>0.027⁹</td>
</tr>
<tr>
<td>Daily seizures (%)</td>
<td>45</td>
<td>45</td>
<td>68</td>
<td>31</td>
<td>28</td>
<td>51</td>
<td>50</td>
<td>0.037⁺</td>
</tr>
<tr>
<td>AEDb (median)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.024⁺</td>
</tr>
</tbody>
</table>

³IQR=interquartile range (25%-75%); ⁴AED= number of anti-epileptic drugs per patient; ⁵ANOVA; ⁶Kruskal Wallis; ⁷Chi square analysis.
## Intelligence Quotient Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total group</th>
<th>GIE (95%CI)</th>
<th>GSE (95%CI)</th>
<th>CE (95%CI)</th>
<th>TLE (95%CI)</th>
<th>FLE (95%CI)</th>
<th>PE (95%CI)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Full Scale IQ</td>
<td>-1.41</td>
<td>-0.39</td>
<td>-3.44</td>
<td>-0.62</td>
<td>-0.85</td>
<td>-1.09</td>
<td>-2.06</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(-1.68– -1.14)</td>
<td>(-1.08– 0.30)</td>
<td>(-4.21– -2.66)</td>
<td>(-1.30– -0.06)</td>
<td>(-1.22– -0.48)</td>
<td>(-1.56– -0.61)</td>
<td>(-2.74– -1.39)</td>
<td></td>
</tr>
<tr>
<td>Mean Verbal IQ</td>
<td>-1.33</td>
<td>-0.49</td>
<td>-3.27</td>
<td>-0.45</td>
<td>-0.82</td>
<td>-1.06</td>
<td>-1.90</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(-1.60– -1.06)</td>
<td>(-1.16– 0.18)</td>
<td>(-4.17– -2.36)</td>
<td>(-1.17– 0.28)</td>
<td>(-1.20– -0.44)</td>
<td>(-1.59– -0.53)</td>
<td>(-2.50– -1.29)</td>
<td></td>
</tr>
<tr>
<td>Mean Non-verbal IQ</td>
<td>-1.28</td>
<td>-0.22</td>
<td>-3.24</td>
<td>-0.55</td>
<td>-0.75</td>
<td>-1.05</td>
<td>-1.89</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>(95%CI)</td>
<td>(-1.55– -1.00)</td>
<td>(-0.94– 0.50)</td>
<td>(-4.10– -2.38)</td>
<td>(-1.16– -0.06)</td>
<td>(-1.16– -0.35)</td>
<td>(-1.42– -0.67)</td>
<td>(-2.60– -1.18)</td>
<td></td>
</tr>
</tbody>
</table>

*Z scores before adjusting for covariates; *ANOVA
Acknowledgments

Melinda Nolan
Antoinette Redoblado
Sunica Lah
Mark Sabaz
John Lawson
Anne Cunningham
Andrew Bleasel
The Neuropsychological and Language Profile of Benign Rolandic Epilepsy
Why Study Benign Rolandic Epilepsy

- Ideal to study impact of epilepsy itself as comorbidities of other epilepsy syndromes are not present. Provides a model to study cognition and impact of paroxysmal activity.
- Onset: 3 years and above
- Infrequent seizures.
- Child may not be on medication
- Not associated with motor handicap or previous global delay. Underlying brain structure normal.

*however increasingly realised maybe cognitive difficulties and it is hypothesised spike burden may impact on cognition*
Benign Rolandic Epilepsy

- Most common school age epilepsy
- Age of onset is between 3 and 13 years
- Simple partial seizures
- Spike focus in the centrotegmental area with normal background activity
- Seizures infrequent
- Spontaneous remission during adolescence
Morphology: Centrotemporal Spikes

Fp2-F8
F8-T4
T4-T6
T6-O2
Fp2-F4
F4-C4
C4-P4
P4-O2
Fz-Cz
Cz-Pz
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
8-year old child – trains in wakefulness, drowsiness and sleep
BRE cognitive profile

- Early studies found normal levels on intelligence testing
- Current debate on what deficits may exist
- Verbal, visuomotor, non-verbal, attention, language, memory, executive functioning and global IQ deficits have been documented

- Methodological problems:
  - Small sample sizes
  - Patient selection
  - Often minimal assessments conducted
Current Research: Aims

1. To define the neuropsychological and language profile of a group of patients with BRE

2. To study these deficits in relation to specific EEG features
Hypotheses

- Children with BRE show consistent differences in neuropsychological function compared with normative data.

- Children with BRE show consistent differences in language compared to normative data.

- There is a correlation between specific EEG features and cognitive functions.
Method

- Subjects recruited from six EEG laboratories across Sydney
- EEG features typical of BRE
- Confirmation of syndromal diagnosis from doctor and parent by telephone interview
- Exclusion criteria:
  - developmental delay
  - neurological insult
  - other systemic diagnosis that could affect performance on testing
  - abnormal imaging
Neuropsychological Assessment

- Intellectual Functioning
- Memory and Learning Ability
- Academic Achievement
- Executive Functioning
- Speed of Information Processing
Language Assessment

- Receptive, Expressive and Total Language
- Receptive Vocabulary
- Expressive Vocabulary
- Phonological Awareness and Analysis
- Speech Motor Production
- Oral/Verbal Dyspraxia
Phonological Awareness

- Ability to analyse spoken language into small sound units
- It is a general appreciation of the sounds of speech as distinct from their meaning
- A crucial transition from preliterate to literate state requires control of phonemic units of language.
- Predicts reading and spelling acquisition
- It is amenable to intervention
Methodology: Analysis of EEG features

- Spike morphology
- Spike location
- Spike frequency (quantitated, trains)

*analysis in wakefulness, drowsiness, and sleep*
Results: Patient demography

- Patients: 42, 16F, 26M, mean 8.5 years
- Duration of epilepsy < 5 years for all and 55% < 1 year
- Number of seizures: 1-40
  - <5: 23
  - 5-20: 15
  - >20: 4
- Medication: 27
  - carbamazepine: 12
  - sulthiame: 6
Results: Cognitive function

- Average FSIQ - 105.28
- Average Total Language - 105.53
- Receptive language - 106.77
- Expressive language - 104.26

42 recruited, ages 5-12 years (mean 8.5)
Significant neuropsychological difficulties (grouped means) compared to normative data

Wide Range Assessment of Memory and Learning (WRAML)

- Verbal Memory Index: p<0.0005
  91.95
- Visual Memory Index: p=0.01
  93.85
- General Memory Index: p=0.007
  93.37
Significant **language** results compared to normative data

Queensland University Inventory of Literacy (QUIL)

*(Testing of phonological awareness)*

- Non-Word Spelling: $p=0.01$
- Non-Word Reading: $p=0.003$
- Visual Rhyme Recognition: $p<0.0005$
- Phoneme Manipulation: $p=0.034$
Medication did not account for the significant differences found in memory and phonological awareness.
<table>
<thead>
<tr>
<th>TEST</th>
<th>&gt;1 SD</th>
<th>&gt; 2 SDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory Index</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(18/40)*</td>
<td>(4/40)</td>
</tr>
<tr>
<td>Visual Memory Index</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(12/38)</td>
<td>(2/38)</td>
</tr>
<tr>
<td>General Memory Index</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(12/37)</td>
<td>(3/37)</td>
</tr>
</tbody>
</table>

*Number of children
### Percentage of QUIL language test scores below full-scale IQ

<table>
<thead>
<tr>
<th>TEST</th>
<th>&gt; 1SD</th>
<th>&gt; 2SDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Word spelling</td>
<td>41</td>
<td>24</td>
</tr>
<tr>
<td>(15/37)*</td>
<td>(9/37)</td>
<td></td>
</tr>
<tr>
<td>Non-Word Reading</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>(13/37)</td>
<td>(9/37)</td>
<td></td>
</tr>
<tr>
<td>Visual Rhyme Detection</td>
<td>65</td>
<td>26</td>
</tr>
<tr>
<td>(22/34)</td>
<td>(9/34)</td>
<td></td>
</tr>
<tr>
<td>Phoneme Manipulation</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>(14/37)</td>
<td>(5/37)</td>
<td></td>
</tr>
</tbody>
</table>

* Number of children
### Percentage of QUIL Language test scores below CELF-3 Total Language

<table>
<thead>
<tr>
<th>TEST</th>
<th>&gt; 1SD</th>
<th>&gt; 2SDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Word Spelling</td>
<td>45</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(17/38)*</td>
<td>(6/38)</td>
</tr>
<tr>
<td>Non-Word Reading</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>(15/38)</td>
<td>(8/38)</td>
</tr>
<tr>
<td>Visual Rhyme Detection</td>
<td>47</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>(16/34)</td>
<td>(11/34)</td>
</tr>
<tr>
<td>Phoneme Manipulation</td>
<td>41</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>(15/37)</td>
<td>(6/37)</td>
</tr>
</tbody>
</table>

* Number of children
## Phonological Awareness and Academic Achievement

<table>
<thead>
<tr>
<th></th>
<th>WIAT Reading</th>
<th>WIAT Spelling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Word Spelling</strong></td>
<td>r=0.741</td>
<td>r=0.485</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0005</td>
<td>p=0.004</td>
</tr>
<tr>
<td><strong>Non-Word Reading</strong></td>
<td>r=0.609</td>
<td>r=0.451</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0005</td>
<td>p=0.008</td>
</tr>
<tr>
<td><strong>Phoneme Manipulation</strong></td>
<td>r=0.481</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>p=0.004</td>
<td></td>
</tr>
</tbody>
</table>
EEG Features correlated with Neuropsychology and Language

- Particular EEG features were correlated with specific neuropsychological and language measures but association was minimal (5/61)

HOWEVER...

- Specific EEG features were not associated with pattern of difficulties in memory and phonological awareness
Cognition and EEG laterality

Children with bilateral spikes in drowsiness performed at lower level on WRAML verbal memory index than children with left spikes.

\[ p=0.64 \]
Conclusions

- Children with BRE have normal overall IQ and language scores

- General memory difficulties for both verbal and visual material are common

- Language difficulties in phonological awareness are also common and are associated with achievement in reading and spelling -- this has implications for literacy skills and exceeds the level of reading disability in the population (10%)
Conclusions

- There is a minimal relationship between EEG features and specific cognitive findings.
- Previous authors have not quantitated spike frequency and laterality and correlated it with specific neuropsychological and language functions.
- Specific EEG features are not associated with memory indices and tests of phonological awareness.
Conclusion- Recommendations

- Parental interview specifically in areas of academic performance related to pre-reading, reading, spelling, memory and mathematics

- Continued monitoring as difficulties may not be apparent early
Conclusion - Recommendations

● Assessment by school counsellor to target memory and phonological awareness. Overall intellectual and language ability may not reflect difficulties.

● Interventions: training in phonemic awareness (beneficial to reading success) and memory strategies.
Statistical Analysis

- Separate analysis for wake, drowsy and sleep states
- Correlations to determine degree of agreement between EEG and cognitive functioning
- Linear regression of significant correlations to determine if EEG adds anything over and above IQ in predicting the result
Neuropsychological Assessment

- WISC-3 (IQ, speed processing, freedom from distractibility)
- WRAML (verbal, visual, general indices)
- WIAT (Academic achievement)
- Rey Complex Figure (executive)
- Trail Making Test (attention, visuomotor speed)
- COWAT and animals (verbal fluency)
Language Assessment

- CELF-3 (receptive, expressive, total)
- VMPAC (motor speech production)
- QUIL (phonological awareness)
- Boston Naming Test (expressive vocabulary)
- PPVT-3 (Receptive vocabulary)
- TLC (language competence)
Phonological awareness testing

- Nonword spelling: eg dorf
- Nonword reading: eg didderent
- Visual rhyme recognition: which word is different?
  log, let, sip, lap
- Phoneme manipulation: belt without saying “t” sound - sounds like bell
Acknowledgments

Ellen Northcott  Anne Connolly
Dr Anna Berroya  Dr Mark Sabaz
Jenny McIntyre  Jane Christie
Dr Alan Taylor  Dr Jennifer Batchelor
Dr Andrew Bleasel  Dr John Lawson

Sydney Children’s Hospital Foundation
The Financial Markets for Children
The Australian Brain Foundation
National Health and Medical Research Council (NHMRC)