Cognitive and behavioural impulsivity in patients with Juvenile Myoclonic Epilepsy

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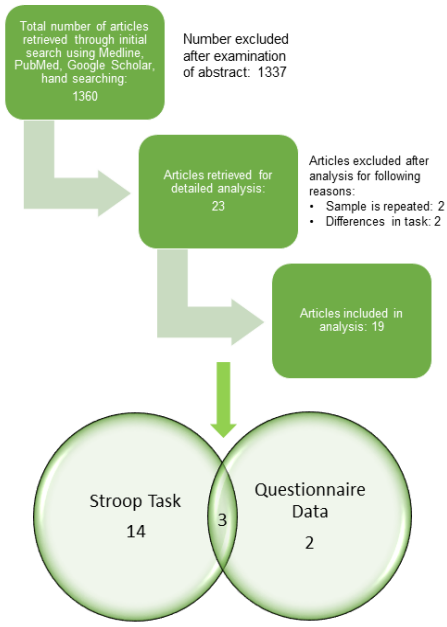
Purpose

When patients with juvenile myoclonic epilepsy (JME) present at clinic, the presence of impulsive behaviour and/or poor inhibitory control is often reported yet research findings are variable. The aim of this meta-analysis is to draw together existing research evidence to understand more about cognitive and behavioural impulsivity traits in this patient group.



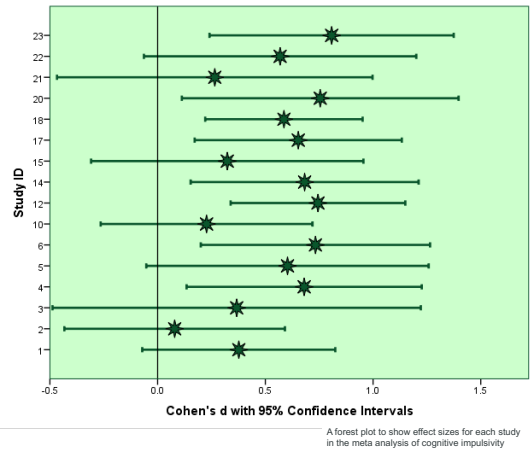
Methods

•Meta-analyses of 19 articles published between 2007 and 2016
•Studies of patients diagnosed with JME as defined by the International League against Epilepsy
•Overall effect sizes and heterogeneity were measured for
- the Stroop Task, a measure of **cognitive impulsivity** based on inhibition of interference (see above) (n=17)
- scores on questionnaires measuring **behavioural impulsivity** traits (n=5).

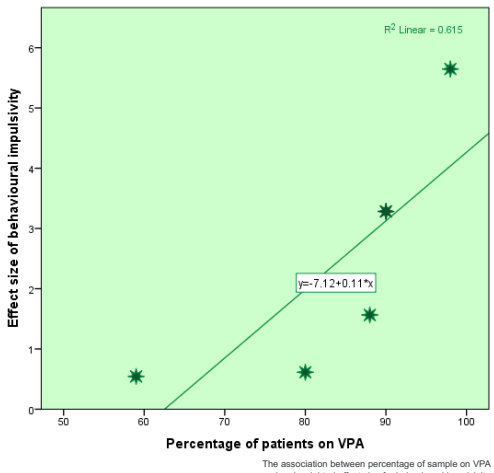
•Separate meta-analyses for the two measures of impulsivity were performed using SPSS scripts and mean effect sizes (ES) were calculated
•For both meta-analyses, homogeneity testing determined the extent to which there was variation in findings between studies using potential indicators.
•Heterogeneity was interpreted using a random effects weighted multiple regression (meta-regression) analysis: potential predictors of effect size were explored for their importance

Results

•Mean Cohen's *d* was d = .66 (95% CI 0.41–0.74; z = 8.00; p=<.0001) for cognitive impulsivity and d = 1.39 (95% CI .64–2.14; z = 9.47; p=<.0003) for behavioural impulsivity.
•Both sets of effect sizes were significantly variable (cognitive impulsivity: Q=25; p =.036; behavioural impulsivity: Q=111; p <.0001)
•The high variability of effect sizes associated with cognitive impulsivity was fully explained by an outlier which was removed resulting in homogeneity (Q=13; p = .72) and a slightly reduced but significant overall effect size of .56 (.44-.69) (z=8.8; p <.0001) (see below)
•Although for the behavioural data power was very limited we looked for potential associations and found that the higher the percentage of patients in sample who were medicated with sodium valproate (VPA) the larger the effect size (see below)



A forest plot to show effect sizes for each study in the meta analysis of cognitive impulsivity



The association between percentage of sample on VPA and and weighted effect size for behavioural impulsivity

Conclusion

We confirm that studies of patients with JME consistently find moderate effect sizes associated with cognitive impulsivity. Effect sizes for behavioural impulsivity are fewer, larger, more wide spread and correlate strongly with proportion of patients in each study taking VPA. This association could be due to a correspondingly a) higher number of male patients and b) higher number of severe cases of JME in those studies with higher effect sizes. Future studies should consider gender and severity effects in their analyses.

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Developmental coordination disorder in children with Rolandic epilepsy and their siblings

Stuart D. W. Smith, Anna B. Smith and Deb K. Pal

KING'S College LONDON

Introduction

- Cognitive problems in Rolandic epilepsy (RE) may involve speech, language and literacy (Pal et al., 2010, Smith et al., 2015, Vega et al., 2015).
- These problems are prevalent within families of children with RE and may represent an endophenotype.
- New evidence suggests motor problems or developmental coordination disorder (DCD) may also be present in children with RE (Brindley et al., 2016, Kirby et al 2017).
- It is unknown whether DCD is detectable in siblings of children with RE.

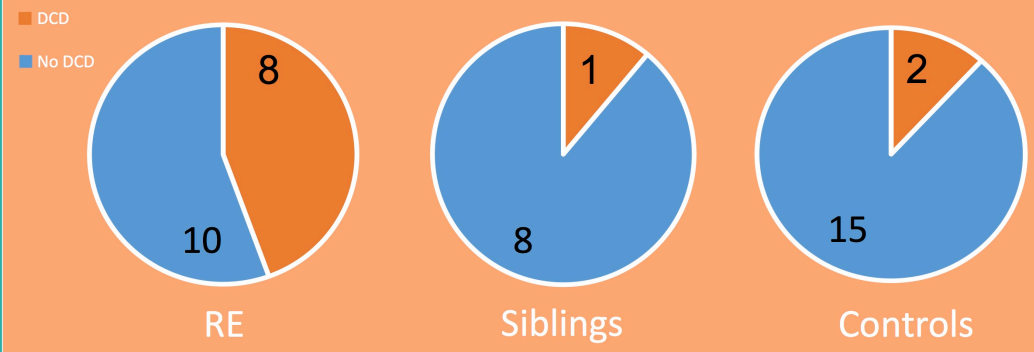
Methods

- Age 7-17, IQ>80
- RE N=18, Sibs N=9 and Con N=17
- % male: RE 66, Sibs 22 and Con 58
- Chi-squared testing
- MANOVA analysis of subscores: Control during movement, fine motor and coordination.

Goals

1. Using the DCDQ'07 to detect DCD symptoms in children with RE, their siblings and controls.
2. Identify the key problems in motor abilities from subscores.

Overall scores



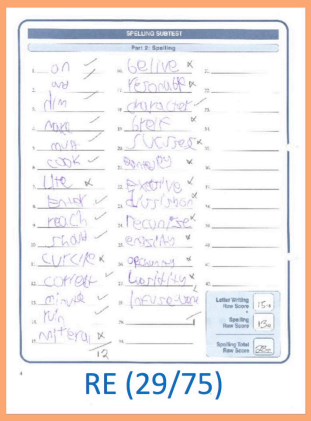
- **Forty-four percent** of children with RE had an indication of DCD.
- This was larger than the controls (χ^2=4.58, p= .032) and siblings (χ^2=3, p= .08).

Subscores

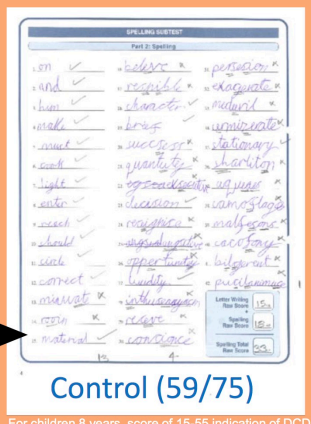
MANOVA analysis of subsection scores was not significant (F=1.8, df=6, 80, p=.109)

However, post hoc, Bonferroni testing between RE and controls was significant for fine motor control (p=.01) and coordination (p=.04).

Hand writing examples of 8 year old children (DCDQ scores)

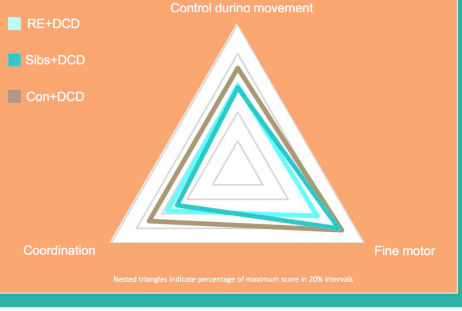

RE (29/75)


Sibling (75/75)


Control (59/75)

For children 8 years, score of 15-55 indication of DCD. 56-75 probably not DCD

Key problems



Conclusions

- There is a high prevalence for the indication of DCD in children with RE compared to controls.
- There appears to be an apparent association with coordination and fine motor skills.
- Indication of DCDQ was less prevalent in siblings.
- Further investigation is needed to see if DCD is related to the RE seizure disorder rather than a component of the endophenotype.

References:

Brindley, Lisa M., et al. "Ipsilateral cortical motor desynchronisation is reduced in Benign Epilepsy with Centro-Temporal Spikes." Clinical Neurophysiology 127.2 (2016): 1147-1156.

Kirby, Amanda, et al. "Benign childhood epilepsy with centrotemporal spikes (BECTS) and developmental co-ordination disorder." Epilepsy & Behavior 72 (2017): 122-126.

Pal, Deb K., et al. "Idiopathic focal epilepsies: the "lost tribe"." Epileptic Disorders 18.3 (2016): 252-288.

Smith, Anna B., et al. "A neurocognitive endophenotype associated with rolandic epilepsy." Epilepsia 53.4 (2012): 705-711.

Vega, Yaiza Hernández, et al. "Risk factors for reading disability in families with rolandic epilepsy." Epilepsy & Behavior 53 (2015): 174-179.

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Incorporating epilepsy genetics into clinical practice: utility and cost saving

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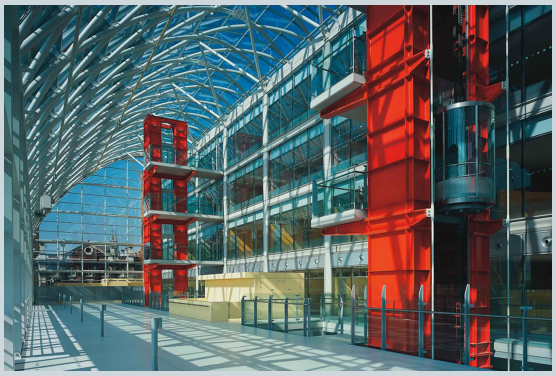
Introduction

We established a regional epilepsy genetics service:
- southeast **England**
- serving a population of **3.5 million**.

The service has two components:
- a specialist outpatient **clinic**
- a **molecular diagnostic** service.

We evaluated:
- the **effectiveness** and **utility** of NGS
- investigation **costs**
- the patient/referrer **experience**



Evelina London Children's Hospital

Methods

- **Prospective** observational design over 18 months
- **N=96 consecutive** patients with primary Dx suspected genetic epilepsy
- Educational workshop for paediatricians

We used:
- Amplexa epilepsy **NGS gene panels**: 46 – 102 genes
- **ACMG** variant classification
- MDT clinical interpretation
- ILAE definition of AED resistance

We assessed:
- **Diagnostic yield** by age group
- Family and referrer **satisfaction** survey
- Investigational **costs** in neonatal epilepsy (n=16)
  - video EEG, MRI, metabolic, single genes

Results

Effectiveness and Utility

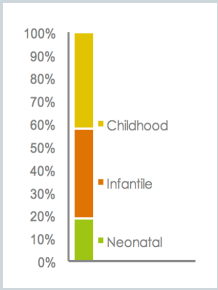


Figure 1. Demographic breakdown of tested patients

- 60% of patients had ≥ 1 variants
  - 19 benign
  - 16 VUS
  - **23 likely pathogenic**

Pathogenic variants: *SCN8A, SCN2A, SCN1A, KCNQ2, HNRNPU, GRIN2A, SYNGAP1, STXBP1, STX1B, CDKL5, CHRNA4, PCDH19, PIGT*

- **SCN8a** (n =4) and **SCN2a** (n=3) most common
- **Turnaround Time: 21 DAYS**
- Overall diagnostic **yield 29%** amongst **AED resistant** cases
- Treatment **implications for 63%** with pathogenic variants

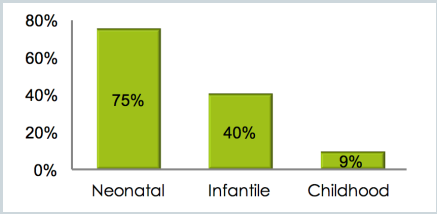


Figure 2. Diagnostic yield by age of seizure onset

Cost

- Actual investigation costs neonatal epilepsy **€10,171** (range: €5,534 – €16,972).
- Theoretical costs if gene panel first line**: €3,083**

Patient/Referrer Experience

- **100%** families would **recommend** to friends and family
- **50%** referrers think gene panel **reduces investigations**

Conclusions

1. NGS panel has high utility and effectiveness if seizure **onset <2 years**
2. Earlier diagnostic use of gene panel could **cut** investigation **costs by 70% or €7,000**
3. Turnaround time is **world leading** 21 days vs. median diagnostic delay 3 years
4. Enthusiastic **acceptance of genomic medicine** by referrers and families

High prevalence of intellectual disability, autism, ADHD and diminished adaptive functioning in Doose syndrome (MAE)

Tang S[1,2], Smith A[2], Parker A[3], Agrawal S[4], Hughes E[1], Lascelles K[1], Williams R[1], Fallon P[5], Robinson R[6], Cross J H[6], Hedderly T[1], Eltze C[6], Ferrie C[7], Kerr T[5], Desurkar A[8], Hussain N[9], Kinali M[10], Vassallo G[11], Whitehouse W[12], Goyal S[1], Absoud M[1], Pal D K[1,2]

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Introduction and Purpose

- Myoclonic astatic epilepsy accounts for 1 to 5% of childhood epilepsy.
- The epilepsy prognosis is variable and about 1/3 go into remission.
- The neurodevelopmental outcome is unclear and poorly reported.
- We therefore deeply phenotyped MAE cases for neurodevelopmental symptoms of cognitive ability, adaptive behaviour, autism and ADHD symptoms.

Methods

- MAE cases were recruited across UK paediatric neurology centers. Ref : 09/H0713/76
- MAE case definition was based on ILAE 1989 classification:
  1. Usually normal development before onset of epilepsy.
  2. Onset of myoclonic, myoclonic-atonic or atonic seizures between 6 months and 6 years.
  3. Generalised spike wave and/or polyspike wave discharges on EEG.
  4. Absence of related structural cerebral abnormalities on MRI.
- Phenotyping protocol Table 1:

Symptoms	Assessment Tool
Epilepsy	Clinical history and examination
Cognitive ability	WPPSI III, Bayleys III
Adaptive Behaviour	Adaptive Behaviour Assessment system
Autism spectrum disorder	Social communication questionnaire (SCQ), Developmental Diagnostic interview (3di)
ADHD	Conner's Comprehensive Behavioral Rating Scale – Parent and Teacher DSM IV ADHD subscale, T score > 70
Behavioral screening	Strength and Difficulties questionnaire

Results

- 67 UK MAE cases (49 Male, 18 Females) were recruited.
- Median age of onset 35 months (range 6 to 65), 23 (34%) cases had febrile seizures. Family history of epilepsy in 32 cases (47%).
- Seizures: 100% myoclonic-atonic or atonic, 82% GTCS, 83% myoclonic, 64% absence, 22% tonic and 9% focal seizures.
- Seizure remission of > 2 years was seen in 20 (30%) of cases.
- Low cognitive ability (Figure 2) and adaptive behavior (Figure 3).

Figure 2. Cognitive ability in 25 MAE cases

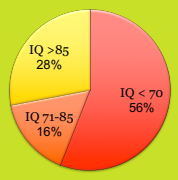
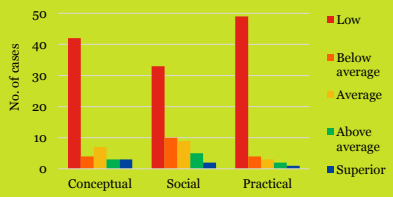
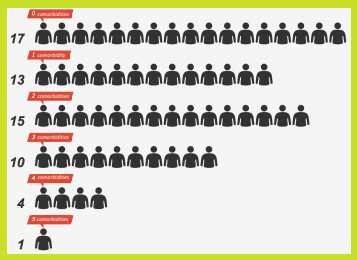


Figure 3. Adaptive behaviour domain scores



- Autism spectrum disorder symptoms were elicited in 20/64 (31%) through the 3di (9/22) and SCQ (16/61).
- ADHD: 21/42 (41%) parents report ADHD with both parent and teacher in 7/52 (13%).
- High scores in behavioural symptoms: emotional symptoms 10/60 (16%), conduct problems 19/60 (31%), hyperactivity/inattention 22/60 (36%), peer relationship problems 29/60 (48%), prosocial behaviour 35/60 (58%). Figure 4 demonstrates multi-morbidity of behavioural symptoms.

Figure 4. No. of behavioural symptoms in 60 MAE cases



Summary:

- One third of MAE patients achieve seizure remission > 2 years.
- MAE patients have significant neurodevelopmental difficulties:
  - 56% have moderate to severe intellectual disability
  - 70% have low adaptive function scores, worst with practical skills
  - 31% have Autism spectrum disorder symptoms
  - 41% have Attention deficit hypertensive disorder symptoms
  - 58% of parents report these difficulties to significant impact on the child and family

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