Cognitive impairment in Juvenile Absence Epilepsy: a neuropsychological investigation of patients and their unaffected siblings

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Rationale

Previous research has identified subtle profiles of cognitive impairment in mixed Idiopathic Generalised Epilepsy samples, which further studies have suggested not only vary between the specific syndromes, but share similar, endophenotypical underpinnings. Amongst those traits identified as at risk are those supporting visual and verbal executive functions, working memory, and processing speed.

The cognitive comorbidities of Juvenile Myoclonic Epilepsy are the most commonly studied, and it consequently has the most established profile. Whereas Juvenile Absence Epilepsy, until now, has represented a gap in the literature. This is primarily owed to the tendency of research into Absence Epilepsy to use mixed Juvenile/Childhood samples, considering the overlapping pathomechanisms.

The authors of this study therefore aimed to establish a homogenous JAE cognitive profile, focusing on traits previously linked to AEs. Through comparisons with unaffected first order siblings, genetic factors have been isolated and examined, whereas results from a historical JME cohort have been used to establish a firm basis of syndrome-specificity between the profiles.

Neuropsychological Battery

Cognitive Measure	Test/s
General Intelligence	NART
Working Memory	Digit Span (WAIS)
	Arithmetic (WAIS)
Visuo-Spatial Processing:	
Psychomotor Speed	Trail Making Time
Phonological Processing:	
Verbal Compreghension	Vocabulary (WAIS)
	Similarities (WAIS)
Verbal Fluency	Semantic
	Phonemic
Expressive Language	Graded Naming Test
Executive Functions:	
Cognitive Flexibility	Trail Making Task-Switch
Response Inhibition	Stroop Interference
Processing Speed	Trail Making Time
	Stroop Colour-Word
Memory and Learning:	
Verbal Recall/Learning	AMIPB - List
Non-verbal Recall/Learning	AMIPB - Design

Fig. 1. Table showing the tests administered to the participants in our four groups. The results of these tests formed the raw data for our comparison models.

JAE, Controls, Siblings

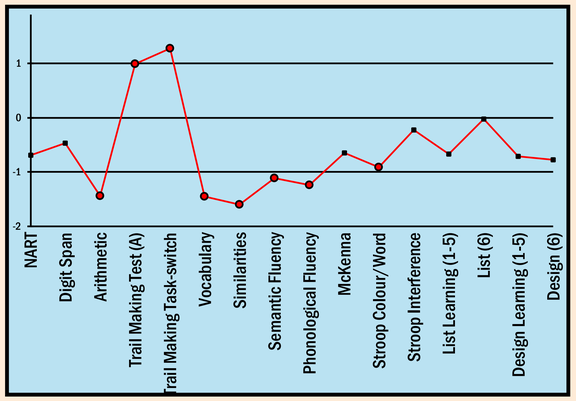

Fig. 2. Z-score comparison of JAE and Control group results, with controls as the baseline. Red markers indicate significant differences.

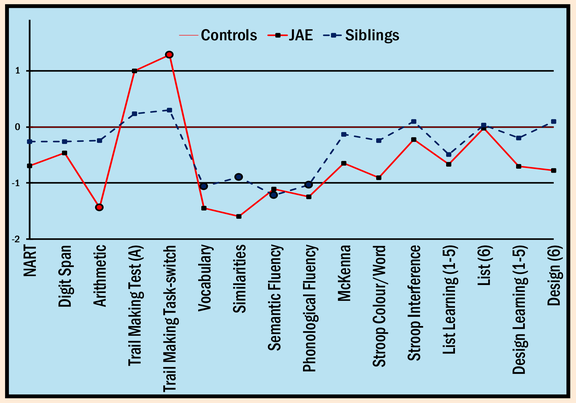

Fig. 3. Z-score comparison of JAE, Control, and JAE Sibling group results, with controls as the baseline. Blue markers indicate significant differences between siblings and controls, red markers between probands and siblings.

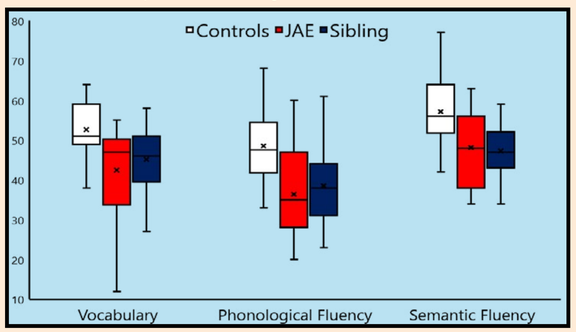

Fig. 4. Central tendency and spread of three measures of interest for the JAE, Control, and Sibling Group.

JAE, JME, Summary

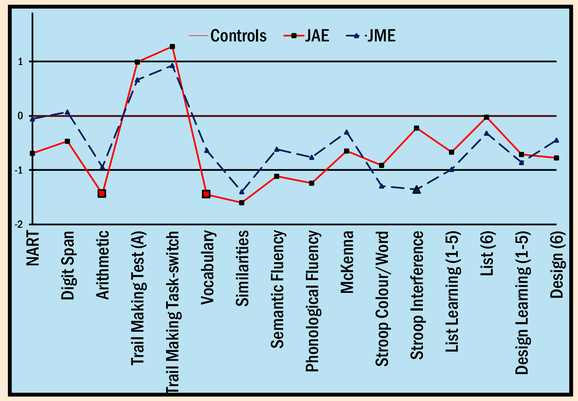

Fig. 5. Z-score comparison of JAE and JME group results, with controls as the baseline. The bold markers indicate significant differences between the two clnical groups.

Figures 2, 3, and 5 present the differences between the average group performances. The charts also provide a crude illustration of overall performance, wherein it can be seen that siblings tend to perform subtly worse than controls, although better than their proband siblings.

Of particular interest are the performances of the siblings and the probands on the phonological section of the battery. Aside from the Graded Naming test, the performances of both groups are close to/more than 1 S.D. from that of our controls, evidence for consistent disruption of linguistic abilities. This is present to a lesser degree in the JME patients, suggesting syndrome-specificity linked to genetic factors.

The two clinical groups do perform similarly to each other in several measures, however, hinting at the possibility of disruptions shared between IGE syndromes, or possibly the result of disease characteristics. Seizure frequency was also related to decreased processing speed, as well as phonological and semantic fluency.

Figure 4 has been included to illustrate that although the results we have found are significant in a clinical setting, the overall differences are not so profound as to be identifiable outside of testing conditions.

Many of the measures in which the JAE group underperformed in are reliant on neural correlates that have been shown to be affected in JAE.

Conclusions

The trends in performance exhibited by our groups are indicative of a syndrome-specific cognitive impairment profile in homogenous Juvenile Absence Epilepsy, with evidence of an endophenotype aetiology.

. Control comparisons show an impairment relative to a neurologically healthy sample, primarily in linguistic abilities, although diminished processing speed and working memory abilities were also found.

. Sibling comparisons evidence a component of this impairment (particularly for linguistic abilities) which cannot solely be the result of JAE development, also precluding a purely clinical explanation - AED usage and seizure activity were controlled for in our sibling sample. Instead, a genetic vulnerability in the families of JAE patients may interact with environmental factors.

. JME comparisons indicate that the profile of impairment can vary between IGE syndromes, with JAE patients demonstrating a greater vulnerability to disruptions of working memory, and JME patients performing worse on a task of cognitive inhibition. Similar performance trends in certain tasks does support the presence of IGE-general deficits, however, principally diminished processing speed and executive functioning.

. An important caveat that is often overlooked is that despite statistical - and in few cases clinical - significance, these differences are subtle. None of our results signify disability.

References

O'Muircheartaigh et al., 2011
Wandschneider et al., 2012
Jackson et al., 2013
Abarrategui et al., 2018
Caciagli et al., 2019
Guimaraes et al., 2019

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