Intellectual functioning in clinically confirmed fetal valproate syndrome

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ABSTRACT

Background: An increased risk of impaired intelligence (IQ) has been documented in valproate-exposed children, but investigations have not previously focused on those with a clinical diagnosis of Fetal Valproate Syndrome (FVS).
Methods: This cross sectional observational study recruited individuals with a diagnosis of FVS and completed standardized assessments of intellectual abilities making comparisons to a normative comparison group. Both mean difference (MD) and prevalence of scores below the lower average range were analyzed.
Results: The mean full-scale IQ in 31 individuals with FVS (mean age 14.97; range 6–27 years) was 19 points lower (19.55, 95% CI −24.94 to 14.15), and IQ scores < 70 were present in 26%. The mean differences for verbal comprehension (21.07, 95% CI −25.84 to −16.29), working memory (19.77, 95% CI −25.00 to −14.55) and processing speed (16.87, 95% CI −22.24 to −11.50) performances were poorer than expected with the mean differences over one standard deviation from the comparison group. Sixty one percent of cases demonstrated disproportionately lower verbal comprehension ability. There were no significant group differences for IQ in high vs. moderate dose valproate or mono vs. polytherapy. There were no differences in IQ between those with and those without a major congenital malformation. The requirement for educational intervention was high at 74%.
Conclusion: Intellectual difficulties are a central feature of FVS and are more severe in their presentation in individuals with a diagnosis of valproate embryopathy. Individuals with FVS who present with the characteristic facial presentation should be considered at high risk of cognitive difficulties regardless of the dose of valproate exposure or the presence of a major congenital malformation.

1. Introduction

Prenatal exposure to valproate is associated with an increased risk of neurodevelopmental deficits (Bromley et al., 2014) in addition to the association with congenital malformations (Weston et al., 2016). Fetal valproate syndrome (FVS) is diagnosed when an individual has a recognizable pattern of facial features, specific malformations, medical or developmental problems in the context of in utero exposure to valproate and following exclusion of other conditions (Dean et al., 2000). Early reports specifically describing individuals with clinically confirmed FVS frequently documented neurodevelopmental deficits (Malm et al., 2002; Massa et al., 1987; Chevallier et al., 1989) but, to date, there has been only one cohort study of children with FVS (Moore et al., 2000). Thirty four children with FVS were reviewed, and elevated rates of developmental, speech and motor delay, along with a high rate of educational support requirements were found (Moore et al., 2000). However, reports of delay were based on parental report and no objective standardized intellectual assessment was undertaken in this cohort, so the sensitivity to detect intellectual impairment was limited.

There have been a number of studies aimed at investigating the risk to child cognitive functioning following exposure in the womb to valproate (Bromley et al., 2014), and such studies have clearly

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demonstrated that prenatal exposure to valproate is associated with an increased risk of poorer cognitive functioning; including poorer levels of early development (Bromley et al., 2010; Cummings et al., 2011; Meador et al., 2009), intellectual abilities (Adab et al., 2004; Baker et al., 2015; Bromley et al., 2016; Nadebaum et al., 2011; Meador et al., 2013), increased need for educational support (Baker et al., 2015; Adab et al., 2001), poorer educational examination results (Elkjaer et al., 2018), and increased rates of autistic spectrum disorder (Bromley et al., 2013; Christensen et al., 2013). These cohorts, however, include children with a general history of valproate exposure and are not confined to children with confirmed valproate embryopathy based on clinical review and following the exclusion of other likely causes of the child's difficulties. Individuals with FVS represent a specific group in whom a distinct cognitive profile may occur, and there remains then a lack of data pertaining to the intellectual abilities of individuals with clinically confirmed FVS. Considering that 30–40% of children with a history of valproate had an IQ one standard deviation below the mean (Bromley et al., 2014), individuals with FVS are undoubtedly at risk for intellectual difficulties, but the pattern, severity, and prevalence of such deficits remain unknown. Recently, the risks to the fetus associated with valproate have been the subject of a European regulatory review (PRAC Recommends New Measures to Avoid Valproate Exposure in Pregnancy, 2018) and are currently the subject of a government review in the UK (Review launched to respond to patient concerns about NHS treatments, 2018). It is therefore of paramount importance that information on the cognitive skills, including the intellectual abilities, of children with a clinical diagnosis of FVS is available.

The objective of this study was to collect information on the cognitive skills of individuals with a clinically confirmed diagnosis of FVS. It was hypothesized here that individuals with FVS would have a more severe level of intellectual difficulties than rates previously obtained from the cohorts of children with a history of valproate exposure whereby some in the group may exhibit morphological effects whilst others appear to be unaffected with respect to facial and other features.

2. Methodology

2.1. Recruitment

Children and adults with a diagnosis of FVS were recruited from one of two sources: the Manchester University NHS Foundation Trust's Genomic Medicine Department and from two UK based charities who support families post-diagnosis of FVS (Organization for Anti-convulsant Syndrome and The Fetal Anti-convulsant Trust). Letters were sent to patients of the Genomic Medicine department who were diagnosed with FVS inviting them to participate (46% recruitment rate). Those recruited through the charities were self-selecting following advertisements regarding the study. In the UK, the diagnosis of FVS is made based on previously published guidance whereby the following criteria should be met (Dean et al., 2000): 1) a history of in utero exposure, 2) presence of a characteristic facial appearance, 3) presence of at least one of the following: evidence of neonatal withdrawal, compatible congenital malformation, compatible medical problem, compatible developmental history, compatible behavioral problem, 4) normal relevant genetic investigations. Children and adults who were unable to provide written consent gave written assent with their parents providing written permission for participation. In families where there was more than one child with FVS, the oldest child was recruited into the study.

2.2. Assessment

Participants were assessed either in their home or at the University of Birmingham's Imaging Centre. Background history was from maternal report on medication type, dose and developmental and educational history. In the cases recruited from the hospital, medical notes

were consulted, where available, and in cases recruited through charities, available letters from medical specialists were reviewed to verify the diagnosis of FVS.

Individuals with FVS under the age of 16 years, 11 months and 30 days ($n = 18$) were assessed with the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) (Wechsler, 2004); with those older ($n = 13$) completing the Wechsler Adult Intelligence Scale, 4th Edition (WAIS-IV) (Wechsler, 2008). The test publishers reported an equivalence study on 157 examinees and reported high levels of correlation across the two measures (ranging from 0.77 to 0.91) (Wechsler, 2004; Wechsler, 2008).

Subtest scaled scores on the Wechsler Intelligence Scales were grouped into the domains of full-scale IQ, verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index. Where the same subtest was present on both the adult and child measure, results were pooled to give a single mean score. Discrepancies between the test index scores were calculated in line with the appropriate test manual by age of the participant and based on the overall sample (Wechsler, 2004; Wechsler, 2008). The significance level for discrepancies between the index scores was set at the 0.05 level. A discrepancy between two index scores may reach significance but may still be relatively frequent in the normative population, and therefore, the level of discrepancy was only classed as 'clinically significant' here if it exceeded the discrepancy amount obtained by equal or fewer than 5% of the normative comparison group. Classification of scores was undertaken in line with the published guidance (Wechsler, 2004; Wechsler, 2008): scores below 80 classified as below the lower average range. Additionally, the prevalence of individuals with scores over one standard deviation from the mean was also computed to allow for comparison to previous reports.

Data were collected on key covariates including maternal IQ, which was assessed using the two-subtest version of the Wechsler Abbreviated Intelligence Scale (WASI) (Wechsler, 1999). Information on gestational age at birth, presence of malformations, and dose of valproate were taken from maternal report and consultant letters, where available, and were included along with other covariates (gender, age at assessment and handedness). Assessments were completed by authors RB and AW, all assessments were double scored, and both verbal and written feedback was provided to the families. In a number of cases, feedback was provided to schools at the family's request.

2.3. Comparator group

We were unable to utilize an unexposed comparison group due to constraints of this study and instead, we used the normative data provided in the Wechsler IQ tests for comparison. Both the WISC-IV and WAIS-IV have large normative populations that are reported to be representative of the U.S English speaking population and are stratified by age, gender, ethnicity, education level, and geographical region (Wechsler, 2004; Wechsler, 2008). The normative population mean across both measures is 100 with a standard deviation of 15 for index scores and have a mean of 10 with a standard deviation of 3 at the subtest level.

2.4. Analysis

Data was entered and statistics produced in SPSS version 22. Due to the number of comparisons made at both the index and subtest levels, a Bonferroni correction was applied, and significance was set at < 0.003 (0.05/18). Univariate linear regression was used to investigate the influence on the IQ indexes of the following variables: gender, polytherapy, valproate dose, maternal IQ, age at assessment, handedness, and IQ test. Variables with a p value of < 0.2 were entered into multiple regression analysis. To investigate dose of valproate, the group was split into doses ≤1500 mg/d (moderate dose group) or > 1500 mg/d (high dose group), which was the dose closest to the median for the group

(1650 mg/d). When the mother reported increasing dose during gestation, the highest dose was utilized in the dose assessments reported below.

2.5. Ethical approval

Ethical approval was provided by North West Regional Ethics Committee- Manchester Central (Reference 12/NW/0221) and Central Manchester University Hospitals NHS Foundation Trust.

3. Results

Recruitment totaled 34 participants, however one child was unable to be assessed due to significant challenging behavior, one participant was excluded due to a diagnosis of spina bifida with hydrocephalus, and in one case a definite diagnosis of FVS could not be ascertained.

In all cases, use of valproate was for the treatment of epilepsy, and in all cases exposure lasted for the entire gestational period. The valproate exposure was monotherapy in 22 cases (71%), with eight additional cases exposed to one additional AED concurrently (carbamazepine $n = 3$, lamotrigine $n = 2$, phenytoin $n = 1$ and clobazam $n = 2$) and in one case to two additional AEDs (carbamazepine and vigabatrin). The mean dose of valproate for maternal treatment was 1650 mg/d (1676 mg/d for monotherapy exposures and 1711 mg/d for polytherapy). Further details regarding cohort characteristics are displayed in Table 1.

3.1. Intellectual function: index scores

Analysis of the neuropsychological data was therefore conducted on IQ data for 31 individuals with FVS (aged 6 to 27 years). No significant differences in terms of intellectual outcome were found between those completing the adult or child IQ assessments (mean difference −5.45 95% CI −16.3 to 5.4, $p = 0.317$), and therefore, the cohort was treated as a single group. Across all the assessed skill areas, there were no significant differences between monotherapy and polytherapy cases or

Table 1
Fetal valproate syndrome ($n = 31$) cohort characteristics.

	N	Percentage	Mean	Range
Valproate exposure				
Monotherapy	22	71		
Polytherapy	9	29		
Dose[a]	30		1687	800–4500 mg/d
Education				
Mainstream school – no support required	8	26		
Statement of specialist educational needs	23	74		
Gender				
Male	18	58		
Female	13	42		
Handedness				
Right	25	81		
Left	6	19		
Maternal IQ (points)[c]	21		103	70–127
Malformations[b]	11	36		
Age at assessment (years)	31		15	6–27
Mean FVS group FSIQ	31		80	56–108

Key: N = number; mg/d = milligrams per day.
  [a] Dose information was missing in 1 case.
  [b] Malformation information was missing in 2 cases. Malformations included: Undescended testes (surgically corrected) 3 cases; Inguinal hernia (surgically corrected) 1 case; Right fibula and right toe missing; Cleft hand; High palate; Squint (surgical correction); Hypospadias (3 cases); Limb malformation; Narrow airway; Shoulder blade rotation; Radial ray defect; Congenital heart defect; Skeletal malformation (2 cases); Spina Bifida with Hydrocephalus.
  [c] Maternal IQ was missing in 10 cases.

between those who were attributed to the high dose group and those in the moderate dose group (Table 2).

The mean full-scale IQ score was 19 points lower for those with FVS (−19.55, 95% CI −24.94 to −14.15) (Table 3), with 15/31 (52%) falling below the average range (Fig. 1). The rate of individuals with a IQ < 70 was 8/31 (26%). Individuals with FVS scored significantly lower on the verbal comprehension index with a mean difference (MD) of −21.07 points (95% CI −25.84 to −16.29). Of note, 7/31 of the FVS sample scored < 70 (23%) (Fig. 1) and the rate of performance one standard deviation below the mean was 19/31 (61%). The FVS group also performed poorer on the working memory index (−19.77, 95% CI −25.00 to −14.55) and the processing speed index (−16.87, 95% CI −22.24 to −11.50), with elevated scores below the lower average ranges (Fig. 1). The perceptual reasoning index was the only index in which the FVS group means did not differ (Table 3), and where there were more comparable rates of performance falling within the extremely low range (3/31, 7%).

3.2. Intellectual function: subtest performance

Reductions in performance on verbal tasks were seen across nearly all verbal subtests and therefore the verbal comprehension index weakness was not being driven by one isolated deficit (Table 3).

3.3. Index discrepancies

Significant levels of individual performance discrepancy were noted between the verbal comprehension index and the perceptual reasoning index; with 19 cases (61%) demonstrating a significantly poorer verbal comprehension index. Two additional cases showed levels of discrepancy within one point of the threshold required for a classification of a significant discrepancy. Only 1 case (3%) demonstrated a significant discrepancy in the other direction (perceptual reasoning < verbal comprehension) but not to a clinically significant level. Within those with significantly poorer verbal comprehension score, 12/31 (38%) had a clinically significant level of discrepancy; the level found in only 5% of the comparison group. Other discrepancy comparisons are reported in eTable/supplementary 1.

3.4. Factors associated with an increase in reduced IQ

Subsidiary analyses were used to examine factors associated with IQ. Univariate regression analysis failed to find an association between polytherapy valproate exposure and dose of valproate (as a continuous variable) with any of the index scores, even when the influence of maternal IQ was adjusted for. The IQs of 21 of the mothers (68%, mean = 103) were available; none scored below < 70; 15/31 (48%) and 4/31 (13%) were in the average and above average range, respectively. There were no differences in offspring IQ for families in which we did/not have maternal IQ data (FSIQ, U = 87.50, Z −1.112, $p = 2.71$). The variables of gender, age at assessment, IQ test type, and handedness were all found to have p values < 0.2 in their respective univariate analyses for one or more of the indexes; however the multiple linear regression models found no significant association between these variables and the index scores (eTable 2).

3.5. Educational outcome

Seventy four percent of participants were reported to require formal learning support either within a mainstream educational setting or in a special school environment. Of those who required educational support 14/31 (61%) had a full scale IQ and a verbal comprehension index below the average range (IQ < 80).

Table 2

Mean IQ index scores by valproate exposure type, dose, malformation and assessment battery type.

Index	Verbal comprehension	Perceptual reasoning	Working memory	Processing speed	Full scale IQ
Valproate monotherapy (mean, SD)[a] N = 22	77.68 (12.4)	91.82 (17.3)	79.32 (14.2)	84.91 (15.5)	79.64 (14.9)
Valproate polytherapy (mean, SD) N = 9	82.0 (14.7)	98.44 (18.2)	82.44 (14.8)	78.78 (12.0)	82.44 (15.0)
High valproate dose (mean, SD) N = 17	80.12 (11.6)	92.12 (15.1)	76.94 (13.43)	81.29 (13.9)	79.00 (12.2)
Moderate valproate dose (mean, SD) N = 13	77.23 (15.5)	94.54 (20.9)	83.23 (14.8)	86.08 (16.1)	81.62 (18.2)
Major congenital malformation N = 11	76.45 (12.1)	92.18 (17.4)	78.00 (12.3)	82.00 (13.6)	78.36 (13.0)
No Major congenital malformation N = 18[b]	79.00 (13.8)	93.50 (18.5)	80.17 (15.6)	83.28 (15.8)	80.33 (16.0)

Key: SD standard deviation.

[a] Equal variances not assumed due to sample difference between groups.

[b] Malformation information was missing in two cases.

4. Discussion

Formal assessment of intellectual abilities in individuals with FVS revealed high rates of poorer performance and increased rates of IQ < 70, which were driven by poor verbal comprehension/reasoning, auditory working memory, and processing speed deficits. This is the first study to report on a cohort of individuals with clinically diagnosed FVS. The findings are concordant with the larger observational studies of children with a history of valproate exposure but highlight the more severe presentation of the intellectual difficulties in children diagnosed with FVS.

Verbal comprehension ability was the weakest skill for the individuals with FVS, and analysis of the subtests demonstrated wide ranging verbal cognition deficits. Weaker verbal reasoning/IQ skills have been frequently reported within cohorts of children exposed to valproate (Bromley et al., 2014; Adab et al., 2004; Baker et al., 2015; Bromley et al., 2016; Nadebaum et al., 2011; Meador et al., 2013) but not to the level reported here. Deficits in purer language functioning have also been reported (Nadebaum et al., 2011) and, neuroarchitecture in eloquent cortex has been reported to be abnormal in children with a history of valproate exposure (Wood et al., 2014). The results here are consistent with previous findings but suggest that the severity of the cognitive difficulties is increased in those with diagnosed FVS. Fifty two percent of those with FVS had a verbal comprehension score below the lower average range which is only present in 9% of the normative sample of the Wechsler measure. High levels of discrepancy between individual performances on the verbal comprehension index and the perceptual reasoning index suggest that this discrepancy is a frequent feature within the FVS phenotype. The question as to why verbally mediated skills are disproportionally affected by valproate exposure requires further investigation.

The cohort also displayed reduced performance in their auditory working memory abilities, and 38% demonstrated impairment in both their verbal comprehension and auditory working memory ability. Difficulties with processing of visual information were also noted to significant levels with over half falling below the lower average range. Observations of this cohort during completion of the assessments supported these findings with assessments taking longer than is standard to complete. The substantial need for educational support (74%) was identical to that reported previously (Moore et al., 2000) and demonstrates the real life implications of the reported IQ deficits and the cost not only to the individual but also to society.

The presence of a major congenital malformation has been associated with a significantly increased chance of lower IQ in the context of valproate exposure (Baker et al., 2015); however, we demonstrated here that intellectual difficulties were not confind to those with a major congenital malformation. This has been highlighted by others (Nadebaum et al., 2011; Kasradze et al., 2017), and suggests that intellectual difficulties are not simply predicted by the presence of a major congenital malformation following valproate exposure. All participants in this study demonstrated more subtle physical markers of exposure (i.e. dysmorphic facial features) as these are required to be present to reach the diagnostic criteria for FVS (Dean et al., 2000). Previous work highlighted a relationship between dysmorphic facial features consistent with valproate exposure and child IQ (Kini et al., 2006). This study provides additional evidence to support the diagnostic criteria of Dean et al. (2000) that a diagnosis of fetal valproate syndrome should be considered, even in the absence of a major congenital malformation, should the typical facial and neurodevelopmental features be present.

Rates of IQ one standard deviation below the mean were higher at 61% and 54% for the verbal comprehension index and the FSIQ respectively, than the 30–40% figures reported from groups of children with valproate exposure (Bromley et al., 2014) but without confirmed FVS. Further, the effect sizes noted for the FSIQ and verbal comprehension index are substantially higher than those reported from general valproate exposure cohorts (Bromley et al., 2014; Weston et al., 2016; Dean et al., 2000; Malm et al., 2002; Massa et al., 1987; Chevallier et al., 1989; Moore et al., 2000; Bromley et al., 2010; Cummings et al., 2011; Meador et al., 2009; Adab et al., 2004; Baker et al., 2015; Bromley et al., 2016; Nadebaum et al., 2011; Meador et al., 2013; Adab et al., 2001). This is hypothesized to be due to two co-existing factors. The mean dose in this cohort was higher. Secondly, this group, through their physical symptoms, had been demonstrated to be susceptible to the associated effects of the valproate exposure. This highlights the likelihood that there exists a spectrum of deficits associated with prenatal valproate exposure, and that there is a need to accurately characterize the breadth of this spectrum, but also the specific features of different presentations as we have begun to do here. This study has demonstrated that extrapolating rates of intellectual difficulties from a cohort of children with a history of valproate exposure (Baker et al., 2015; Nadebaum et al., 2011; Meador et al., 2013) to summarise the intellectual difficulties of children with confirmed valproate embryopathy would not reliable. More research attention should be directed to a better understanding of the full impact of valproate exposure, and the specific characteristics of children with confirmed valproate embryopathy.

This study has many strengths. It is the first study to systematically measure the profile of intellectual function in this particular condition and highlights the significant burden on the individuals and their

Table 3

Differences in outcome mean IQ scores in comparison to the normative comparison mean.

Index/subtest[a]	FVS mean[c]	FVS mean adjusted[b]	Mean difference (95% CI)[b]	p-Value
Verbal comprehension	78.94	79.44	−21.07 (−25.84 to −16.29) t(30) = −9.004	< 0.0001
Similarities	6.61		−3.39 (−4.27 to −2.50)	
Vocabulary	5.90		−4.10 (−5.08 to −3.11)	
Comprehension	5.50		−4.500 (−6.08 to −2.92)	
Information	7.69		−2.31 (−3.82 to −0.80)	
Perceptual reasoning	93.74	94.54	−6.26 (−12.69 to 0.17) t(30) = −1.987	0.056
Block design	9.45		−0.55 (−1.98 to 0.88)	
Matrix reasoning	8.23		−1.77 (−2.94 to 0.60)	
Picture concepts	7.67		−2.33 (−3.84 to −0.83)	
Visual puzzles	11.69		1.69 (−0.27 to 3.66)	
Working memory	80.23	80.09	−19.77 (−25.00 to −14.55) t(30) = −7.730	< 0.0001
Digit span	6.19		−3.81 (−4.85 to −2.77)	
Letter number sequences	6.78		−3.22 (−4.73 to −1.71)	
Arithmetic	7.23		−2.769 (−4.63 to −0.90)	
Processing speed	83.13	82.90	−16.87 (−22.24 to −11.50) t(30) = −6.413	< 0.0001
Coding	6.45		−3.55 (−4.69 to −2.40)	
Symbol search	7.35		−2.65 (−3.75 to −1.54)	
Full scale IQ	80.45	80.89	−19.55 (−24.94 to −14.15) t(30) = −7.398	< 0.0001

Key: 95% CI = 95% confidence interval.

[a] Indexes have a mean of 100 and a standard deviation of 15; subtests have a mean of 10 and standard deviation of 3. Subtests of Similarities, Vocabulary, Block Design, Matrix Reasoning, Digit Span, Coding, Symbol Search are present on both measures and therefore the mean score reflects the total cohort. Visual Puzzles, Arithmetic and Information are from the WAIS-IV only whilst the Letter Number Sequencing and Comprehension task are from those who completed the WISC only.

[b] Mean adjusted for assessment type completed.

[c] FVS unadjusted mean in comparison to normative mean (100, standard deviation 15).

families and the cost to society. Unlike previously published cohorts of valproate exposed children, this group was limited to individuals with a confirmed diagnosis of FVS, other possible causes of their difficulties had been discounted and they presented with the physical symptoms of valproate exposure. The use of standardized intelligence assessments provided increased rigor in the measurement of cognitive functioning. The inclusion of one child per family removed the risk of sibling confounding/bias, and the exclusion of cases with a condition with a known association with neurodevelopmental difficulties removed further possible biases. Finally, the inclusion of adults with the condition provided the first evidence that the cognitive deficits associated with FVS do not diminish over time. These important data will allow for accurate counseling of families at diagnosis and for the planning of future needs.

The study had some limitations. The measurement of maternal IQ was only completed in 68% of cases where the mother was in attendance at the appointment. Although incomplete, the spread of maternal IQ results indicated that the IQ results presented here for the individuals with FVS are not simply due to lower maternal IQ; a lack of relationship between maternal and child IQ following exposure to valproate is consistent with the findings of others (Meador et al., 2009). Weaker aspects of this study design include its opportunistic sampling method which may have introduced bias towards the more severely affected individuals with FVS; however, the pattern of intellectual difficulty reflects that reported from prospectively ascertained cohort studies of children with a history of valproate exposure. Further, the authors have significant experience with FVS, and these results reflect anecdotal clinical experience. History of the mother and the individual with FVS was taken from maternal report and the medical notes or specialist clinic letters provided by the families and therefore may be influenced by recall bias. Data pertaining to consumption of other teratogens (such as alcohol or nicotine) was not documented in the current protocol as this cohort had been *clinically* diagnosed with valproate embryopathy, and there were substantial concerns regarding recall bias due to the length of time passed. Nevertheless, their clinical diagnosis supports the contention that the intellectual features described cannot be attributed to other teratogen exposures, and we have included in our analysis other potential confounds. Future studies should extend the finding with sequential case ascertainment, with increased amounts of prospectively ascertained information, additional details about the family background and with a control group recruited in the same manner.

5. Conclusions

Intellectual difficulties within the FVS population are frequent, and it is therefore proposed that intellectual difficulties, particularly when there is a significant impact on verbal/auditory cognitive skills, should be considered a central feature of the FVS phenotype. The intellectual difficulties are likely lifelong. The dose of the valproate exposure and the absence of a major congenital malformation may not predict impact on IQ in a clinical population and if the individual has the facial characteristics of FVS a referral to an appropriate specialist for a neuropsychological assessment should be made.

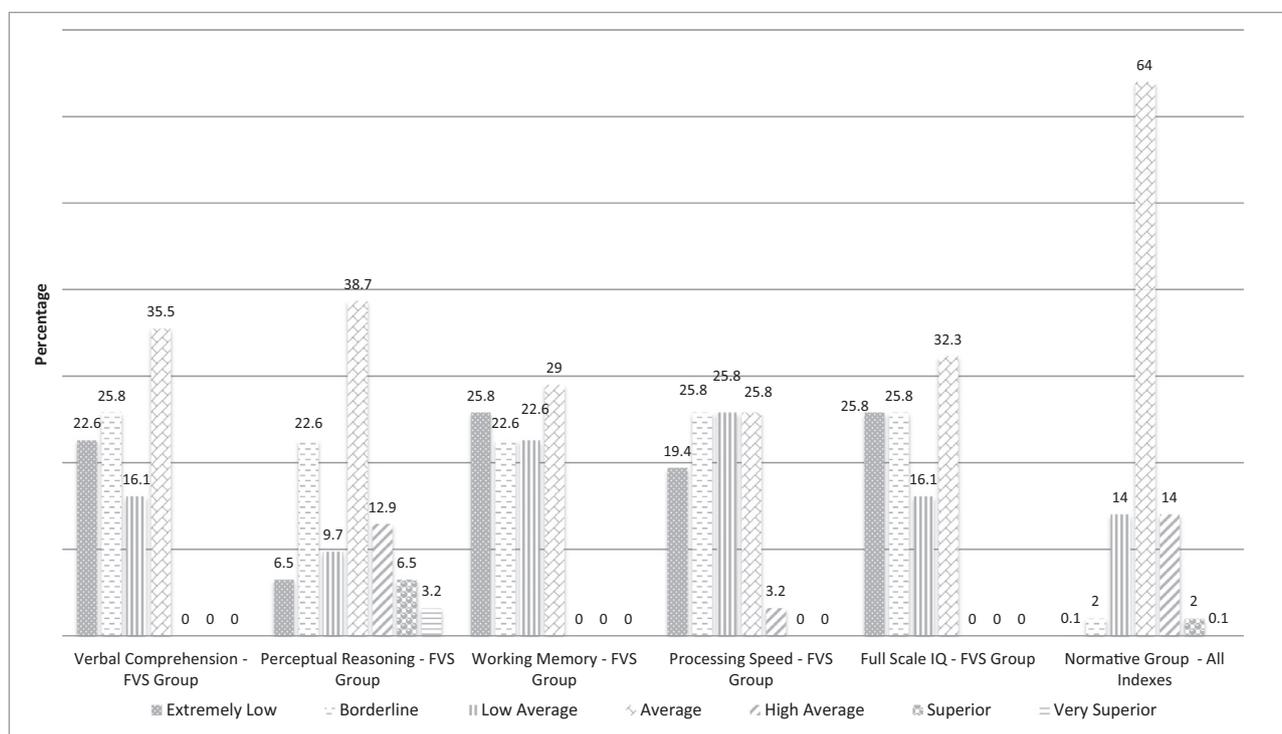## Transparency document

Acknowledgements

Fig. 1. IQ index score classifications for the FVS and normative comparison group*.
*Normative comparison group distribution taken from Wechsler manual and applies to all indexes (Wechsler, 2004; Wechsler, 2008).

not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ntt.2018.11.003.

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