

# Compromised approximate number system acuity in extremely preterm school-aged children

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## ABBREVIATIONS

w	Weber fraction
EPT	Extremely preterm children
TD	Typically developing children
ANS	Approximate number system acuity
WISC-IV	Wechsler Intelligence Scales for Children IV
MAR	Minimal angle of resolution

**AIM** The aim of this study was to compare the approximate number system acuity in children born extremely preterm aged 6 years 6 months and typically developing, age-matched peers.

**METHOD** This population-based follow-up study included 65 children born before 27 gestational weeks (35 males, 30 females; mean gestational age 25.4wks [SD 1.1wk]; mean birthweight 789g [SD 158g]) and 47 typically developing children (24 females, 23 males) at the age of 6 years 6 months. A battery of cognitive tests was administered, including a computerized test for measuring approximate number system acuity and tests for general cognition, working memory, processing speed, and visual attention. Approximate number system outcome measures were means of Weber fraction (*w*) values and response time in milliseconds.

**RESULTS** The 43 extremely preterm children in whom usable data were obtained performed significantly worse than the typically developing children on the approximate number system task ( $w=0.30$  [SD 0.23] vs. 0.17 [SD 0.13];  $p=0.003$ ) and were significantly slower (response time=2934ms [SD 1102ms] vs 2376ms [SD 310ms];  $p=0.002$ ). The differences remained when adjusting for differences in other cognitive functions ( $p=0.03$ ).

**INTERPRETATION** Preterm birth has a negative impact on an individual's ability to rapidly approximate and compare numbers of visually presented items. This deficiency is thought to be a consequence of dorsal stream dysfunction. Future studies will investigate whether this deficiency is correlated with lower mathematical proficiency in this group of children.

The survival rate of preterm children is increasing dramatically worldwide, particularly in the most immature infant groups, owing to advances in perinatal medicine.<sup>1</sup> The most immature infants are, however, also the most vulnerable, and concerns over mortality rates are now being replaced with concerns about morbidity and long-term sequelae.

Preterm birth places children at risk of impaired motor, cognitive, behavioural, and visual development.<sup>2</sup> Although there are well-established lines of research into the acute and long-term medical complications for which these children are at risk,<sup>3</sup> there is much to be learned about their more subtle and often later discovered cognitive and visual-perceptual deficiencies. These deficits range from lower general and specific cognitive functions to problems with attention and visual perception.<sup>4,5</sup>

The most commonly reported visual-spatial processing difficulties amongst preterm children include problems with the perception of motion, depth, and simultaneous perception, as well as the ability to survey a complex scene.<sup>6,7</sup> Problems with global and local processing are also

common.<sup>8</sup> These visual-spatial abilities are thought to be mediated by a dorsal stream network, connecting the primary visual cortex with the parietal lobes, and this hypothesis has been confirmed previously in a human neuroimaging study.<sup>9</sup> This pattern of visual problems is seen in developmental disorders such as Williams syndrome and autism, as well as in preterm populations, and has therefore led to the formation of the dorsal stream vulnerability hypothesis, which states that the dorsal stream is particularly vulnerable to disorder and insult during development.<sup>4,10</sup>

While most language deficits in preterm groups can be explained by the level of general IQ,<sup>11</sup> mathematical difficulties remain, even when taking general cognition into account, and are seen even when language abilities are relatively preserved.<sup>4</sup> This particular pattern of cognitive deficits fits well with the dorsal stream deficiency hypothesis, since both basic visual-spatial processes and more advanced mathematical processing are thought to rely heavily on areas of the dorsal posterior parietal cortex.<sup>12,13</sup>

One core numerical ability, the ability to quickly estimate and compare numbers of items, is known as the

approximate number system. All humans share the basic capacity to estimate numbers of items from input across all sensory modalities using imperfect ‘noisy’ mental magnitudes that are normally distributed around the number to be represented.<sup>14</sup> The noise in these numerical representations increases as the numbers get larger and this feature of the approximate number system yields an estimation performance that adheres to Weber’s law, whereby success at discriminating two estimated numbers depends on their ratio rather than their absolute difference.<sup>15</sup> The amount of noise associated with representing a particular number is not fixed over development and sharpens throughout infancy and childhood and well into adulthood.<sup>16–18</sup> However, there is also considerable variation in approximate number system acuity between individuals of all ages.<sup>18–20</sup>

To date, there are only a few studies that have looked at the development of the approximate number system in atypically developing populations. Piazza et al.<sup>18</sup> and Mazzocco et al.<sup>20</sup> demonstrated that children with dyscalculia (a severe learning disability specific to mathematics) have significantly worse approximate number system acuity than age-matched peers without dyscalculia. This suggests that less accurate approximate number system representations may be related to difficulty in mathematics for children from the lowest end of the mathematics achievement scale. In addition, children with dyscalculia do not show a modulation in their parietal cortex activation when engaging in a numerical comparison task and have less grey matter density in these regions compared with children without dyscalculia.<sup>21,22</sup> Furthermore, people with Williams syndrome, a rare genetic disorder that is characterized by strong social and linguistic skills but poor visual-spatial processing, have severe numerical estimation deficits.<sup>23</sup>

Decreased mathematical abilities in preterm children coupled with their other dorsal stream-mediated vulnerabilities lead us to believe that even the fundamental ability of approximating and comparing visually presented numbers of items may be compromised in school-aged children born extremely preterm. We also hypothesize that this impairment is specific and not a consequence of a general cognitive deficit, poor working memory, poor attention, or slow processing speed.

## METHOD

The regional ethics committee in Stockholm approved the study and written informed consent was obtained from all parents of the participating children.

### Participants

The participants, representing a Stockholm cohort, were drawn from a national, population-based follow-up study and consisted of a group of children born extremely preterm and a comparison group of typically developing term-born children. The extremely preterm group, which comprised all surviving infants born before gestational week 27 ( $\leq 26$  wks+6d) in the Stockholm area between January 2004 and November 2005, were recruited at birth.

## What this paper adds

- Extremely preterm-born school-aged children showed impaired approximate number system acuity.
- Approximate number system deficiency persisted when controlling for other cognitive functions.
- Results support the dorsal stream deficiency hypothesis in preterm children.

Cognitive outcome at 30 months and neonatal brain imaging on almost the same group has been presented previously.<sup>24</sup> The frequency and stages of retinopathy of prematurity in the larger but similar national study group have also been presented.<sup>25</sup> The typically developing children were recruited either at the time of the 30-month follow-up study or during the present study and were matched by birth date, sex, hospital, mother’s nationality, parental education, and parity. For every extremely preterm child, up to 10 eligible typically developing children were chosen and contacted one by one until a willing participant was found. All children were 6 years 6 months (SD 2mo) of age at examination.

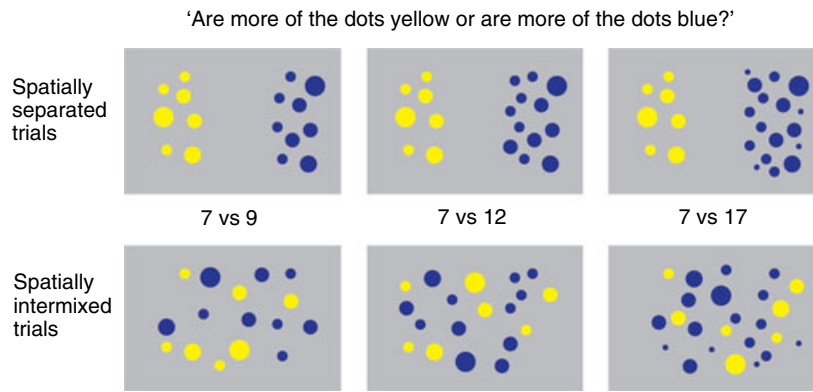
### Approximate number system acuity task

Participants sat at a table approximately 60cm from a computer screen. The study began with a careful description of the task and practice trials until the child understood the procedure. Participants were shown two arrays of blue and yellow dots simultaneously displayed on the screen for 200 ms, displayed too quickly to count, and asked to say which array was more numerous by naming the appropriate colour (Fig. 1). The responses were registered promptly by one of two examiners, who pressed a colour-coded key on the keyboard.

Both the blue and the yellow arrays contained 5 to 16 dots. The ratio between the arrays varied randomly among three ratio bins (1.25, 1.67, 2.4). After a careful description of the task and some practice trials, there were 16 trials of each ratio, for a total of 48 test trials. In half of the trials, the two arrays were spatially intermixed, and in the other half the two arrays were spatially separated to the left and the right side of the screen. A random half of the trials involved displays that equated the total blue and yellow surface area to avoid participants’ use of surface area as a cue for determining which array was more numerous. In addition, half of the trials contained more yellow dots and the other half contained more blue dots. In all trials, individual dot sizes varied in order to disrupt the stability of area or dot size as a cue to number (for further details on controls for non-numerical dimensions, see Halberda and Feigenson,<sup>16</sup> and Halberda et al.<sup>19</sup>). The test–retest reliability of this measure, assessed by Cronbach’s alpha, is approximately 0.65.<sup>17</sup>

### Cognitive abilities

All cognitive tests were administered on the same day in a quiet testing room. Block Design, a subtest in the standardized Wechsler Intelligence Scales for Children IV (WISC-IV) battery that is highly correlated with Full-scale IQ, was used as a proxy for general cognitive ability.



**Figure 1:** Sample of approximate number system acuity task stimulus.

Processing speed and working memory were measured with WISC-IV indexes: Processing Speed Index and Working Memory Index. Visual attention was measured with a Developmental Neuropsychological Assessment subtest for visual attention.

### Statistical analysis

We calculated two different measures of approximate number system acuity for each participant: the average response time across all trials and the Weber fraction ( $w$ ). To find each individual child’s  $w$  value, we fit each child’s responses over all trials with a commonly used psychophysical model:<sup>16,19</sup>

$$\frac{1}{2} \operatorname{erfc} \left( \frac{n_1 - n_2}{\sqrt{2w} \sqrt{n_1^2 + n_2^2}} \right) * 100$$

where  $n_1$  is the number of the larger set,  $n_2$  is the number of the smaller set, and  $\operatorname{erfc}$  is the complementary error function. This model has only a single free parameter ( $w$ ), which indexes the amount of imprecision in the underlying Gaussian representations (i.e. the standard deviation of the Gaussian number representations, such that  $SD_n = n \times w$ ). Larger  $w$  values indicate larger SDs and thereby poorer discrimination of the system across all ratios and numbers. The best fitting  $w$  value was determined for each child using the least-squares method, which minimizes the sum of the squares of the residuals of the data from the curve (for further details on the model and fitting procedures, see Halberda et al.<sup>19</sup>).

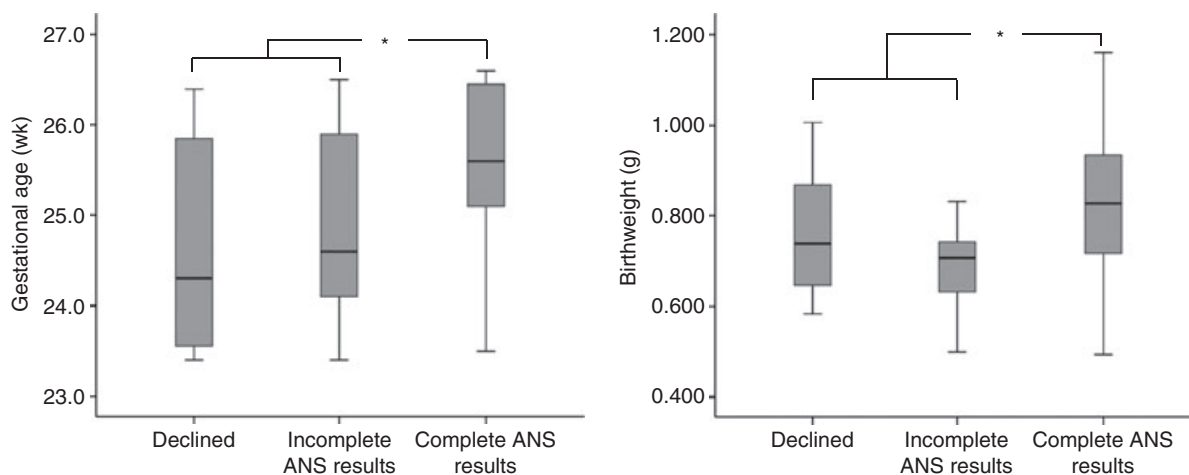
All data were collected and encoded for computerized analysis with the use of SPSS for Windows software version 19 (IBM Corporation, New York, NY, USA). Differences between groups on continuous variables were analysed with independent Student’s  $t$ -tests. Statistical tests of associations between the approximate number system acuity measures and covariates were examined using a general linear model, where the dependent/outcome variable was a com-

bined measure of approximate number system acuity as defined below (see ‘Results’, second paragraph). The fixed factor in the model was group (extremely preterm vs typically developing children) and the covariates were Block Design, Working Memory Index, Processing Speed Index (WISC-IV), and visual attention scores on the Developmental Neuropsychological Assessment. All statistical tests were two sided.  $p$  values of  $<0.05$  were considered statistically significant.

### RESULTS

Sixty-five extremely preterm children were eligible for the present study. Fifty-four of them participated and 11 extremely preterm children, who previously participated in earlier testing waves, declined to participate or did not answer the invitation for this testing wave. Forty-three of those 54 children (80%; 21 males, 22 females) provided usable data. Eleven children failed to complete the test: two because of insufficient visual acuity and nine for behavioural or cognitive reasons (i.e. they could not pay attention long enough to complete the task or did not understand the instructions). In the group of typically developing children, 43 out of 47 children provided usable data. Data from two children were lost as a result of equipment problems, one child did not understand the task, and one child declined to participate. All of the participants with usable data had a binocular visual acuity above 0.4 logMAR (20/50 Snellen acuity) and a Full-scale IQ above 70. Gestational ages and birthweights of the 65 eligible extremely preterm children are shown in Figure 2.

Extremely preterm children were significantly slower and had significantly greater  $w$  values than typically developing children (Table I; see also Fig. 3). Thus, for all further analyses, we combined response time and  $w$  value into a single measure of approximate number system acuity, equal to the mean of the  $z$  score values of  $w$  value and response time. As expected, extremely preterm and typically developing children differed significantly on this combined measure of approximate number system acuity



**Figure 2:** Gestational age and birthweight of all 65 eligible extremely preterm children. Bold lines represent medians and boxes represent interquartile ranges. Declined refers to the 11 extremely preterm children who declined participation. Incomplete ANS results refers to the 11 extremely preterm children who failed in completing ANS task. Complete ANS results refers to the 43 extremely preterm children who produced usable ANS results. The extremely preterm children who produced usable ANS results had significantly (\*) higher gestational age and birthweight than the other extremely preterm children. ANS, approximate number system.

**Table 1:** Approximate number system acuity measures for the two study groups

	Extremely preterm children, <i>n</i> =43; mean (SD)	Typically developing children, <i>n</i> =43; mean (SD)	<i>t</i> statistic (degrees of freedom)	<i>p</i>
Weber fraction	0.30 (0.23)	0.17 (0.13)	3.12 (67)	0.003
Response time, ms	2934 (1102)	2376 (310)	3.2 (48.6 <sup>a</sup> )	0.002

<sup>a</sup>The fact that degrees of freedom is not a whole number reflects an unequal distribution of variance in response times.

( $t=4.31$  [degrees of freedom 53.1],  $p<0.001$ ). The differences in both approximate number system measures remained significant even when excluding the six outliers in the group of extremely preterm children. No associations were found between gestational age, birthweight, retinopathy of prematurity stage, ocular motor dysfunction, or sex and approximate number system acuity in either group (not shown).

Finally, to determine whether the differences in approximate number system acuity between extremely preterm and typically developing children are the result of group differences in general cognitive function, working memory, information processing speed, or visual attention, we used a general linear model, with the combined measure of approximate number system acuity as the dependent variable, group (extremely preterm vs typically developing) as the fixed factor, and Block Design, Working Memory Index, Processing Speed Index (WISC-IV), and visual attention scores on the Developmental Neuropsychological Assessment as covariates. We found significant approximate number system acuity differences between extremely

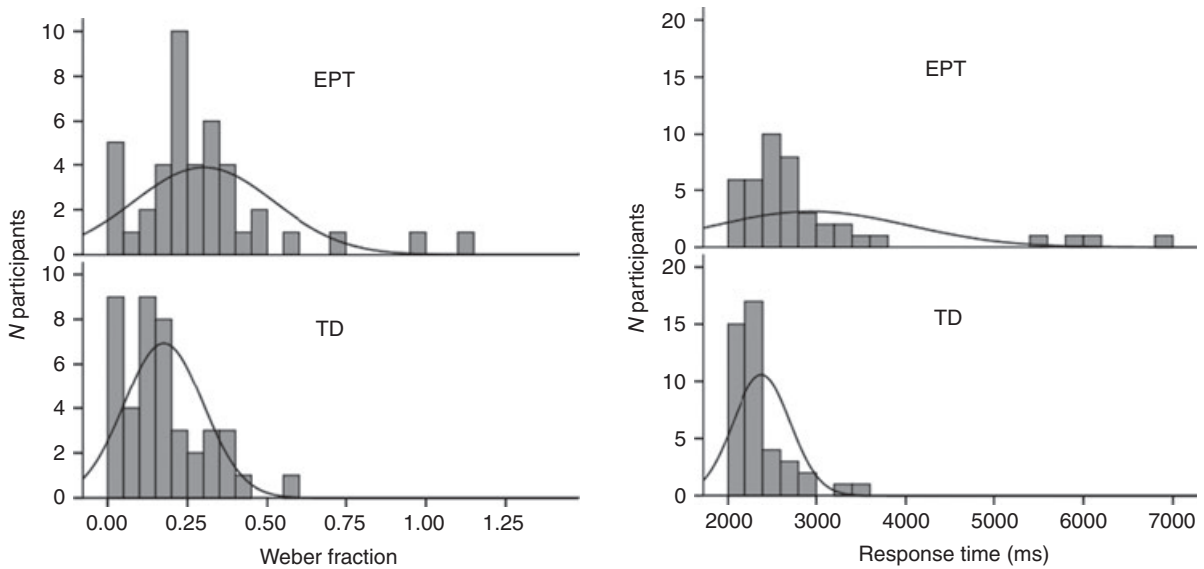
preterm and typically developing children, even when adjusting for these general cognitive abilities ( $F_{1,78}=4.92$ ,  $p=0.03$ ). The  $R^2$  value for the general linear model was 0.312 compared with 0.181 when the other cognitive abilities were not included in the analysis, indicating that half of the variance in approximate number system acuity could be accounted for by the other cognitive abilities.

## DISCUSSION

The aim of the current study was to compare children born extremely preterm with typically developing children on their basic numerical approximation and comparison abilities. The results confirmed our hypothesis that extremely preterm school-aged children have specific deficiencies in this ability compared with typically developing peers, even when accounting for differences in general cognitive function, visual attention, working memory, or processing speed. Given that approximate number system acuity appears to be a dorsal stream-mediated ability,<sup>12</sup> our findings add to the growing number of dorsal stream-mediated deficits that are frequently documented to be impaired in this population.<sup>4,5</sup>

This was a population-based follow-up study of all survivors aged 6 years 6 months born extremely preterm in the Stockholm area from January 2004 to November 2005. Although 83% of the extremely preterm group participated, one-fifth of them failed to complete the task. All participants who succeeded in completing the task had a total IQ above 70 and an attention span that allowed them to complete the task. Furthermore, these participants had higher birthweights and gestational ages than those who failed to produce usable data or did not participate (Fig. 2). Our results, therefore, most probably represent the performance of only the higher-functioning individuals in this extremely preterm





**Figure 3:** Histogram of Weber fraction and response time (ms) in the two study groups. EPT, extremely preterm children; TD, typically developing children.

cohort, because it is known that the more immature individuals and those who weighed less at birth are often those with the lowest function and poorest outcomes.<sup>2,26</sup> There is, however, every reason to place confidence in our findings, despite the fact that they probably represent a best-case scenario for the extremely preterm group. The performance of the typically developing group was very similar to that of previously reported groups around 6 years 6 months of age ( $w=0.17$  in the present study and 0.18 in Halberda and Feigenson<sup>16</sup>). In contrast, the extremely preterm children were both significantly slower and less accurate on the approximate number system task than the typically developing children. The preterm birth disadvantage remained on a group level, even when outliers were excluded, which shows that the results can be generalized to the extremely preterm group as a whole, and are not the result of a subgroup of a few low-performing individuals.

It is interesting to note that there was no correlation between any of the approximate number system measures and gestational age at birth or birthweight, which suggests a more complex causality. Indeed, previous studies indicate that the correlations between neonatal events and long-term neurological and visual outcome are complex and multifaceted, and probably include the level of maturity at birth, neonatal morbidity, and postnatal growth impairment.<sup>3,27</sup> Another explanation of the lack of correlation might be the narrow span of gestational age in the group of participants that managed to complete the task (23+4d to 26+6d). The ones who failed to complete the approximate number system task were born at a significantly lower gestational age, and therefore failure to complete the task can be considered a result in and of itself. With this in mind, there was a significant difference in the approximate number system acuity task completion with regards to gestational age and birthweight.

The differences between the extremely preterm and the typically developing groups were significant regardless of the approximate number system measure used ( $w$  value, response time, and combined  $w$  value and response time). Many perceptual and cognitive tasks are subject to a certain degree of speed-accuracy trade-off (i.e. slower response times are associated with greater accuracy and vice versa). However, previous work using the approximate number system acuity task has shown that both speed and accuracy are meaningful estimates of approximate number system acuity (i.e. the worst-performing participants tend to be both slower and less accurate than the better-performing participants).<sup>17,28</sup> For this reason, we sought to combine our measures of reaction time and accuracy into a single estimate of approximate number system acuity in the present study. When the performance of the extremely preterm group was examined at the individual level, before combining the  $w$  value and response time, some interesting patterns emerged. Some individuals were slow and accurate while others were quick but inaccurate. Both response types are considered to be problematic in a pedagogical environment, and this provided further justification for our decision to combine the two measurements into one, measuring overall approximate number system acuity.

Although children born extremely preterm invariably display a worse outcome in terms of general cognition and often score between a half to a whole standard deviation lower on tests of general cognition,<sup>26</sup> studies have demonstrated that mathematics problems persist even when adjusting for general IQ.<sup>4,27</sup> Although approximate number system acuity is a much more fundamental numerical ability than mathematical ability, previous studies have found a small but consistent link between approximate number system acuity and school mathematics ability.<sup>19,20,28</sup> Therefore, it is possible that some of the deficits in mathematics that have been

reported in extremely preterm children can be accounted for by differences in approximate number system acuity rather than differences in general cognition.

Performance on the approximate number system task has not yet, to our knowledge, been evaluated in groups of preterm children born at later gestational ages. However, there is reason to believe that they might also be at risk of deficits on this task, as they are at risk of other cognitive deficits.

### Limitations

The limitation of this study is the relatively small number of observations, most likely limited to the highest functioning individuals in the extremely preterm group. Therefore, non-significant results must be interpreted with caution. The significant differences found between extremely preterm children and typically developing peers, however, are clear.

### CONCLUSION

In summary, children born extremely preterm had more difficulty approximating and comparing visually presented numbers of items than term-born children, even when controlling for general cognitive level, visual attention, working memory, and processing speed. The difficulties that

extremely preterm children have on this dorsal stream-mediated task supports the dorsal stream vulnerability hypothesis: that the dorsal stream is especially vulnerable to early insult. Future studies will reveal whether these difficulties can be related to higher-level mathematical abilities and other neonatal data.

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