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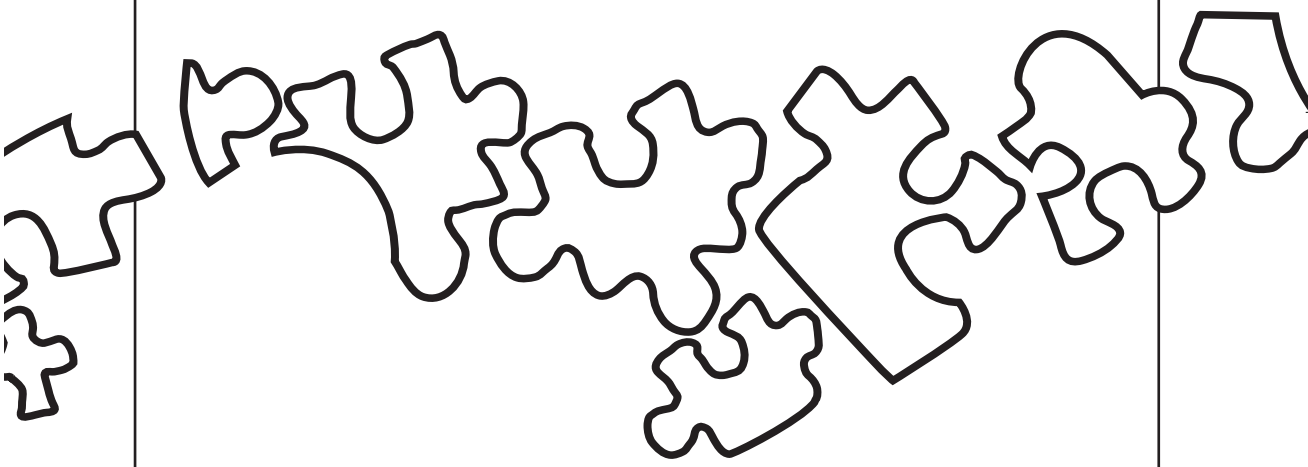
Intellectual functioning is related to brain volume in young children with developmental delay

Mijke Zeegers, Hilleke Hulshoff Pol, Sarah Durston, Claudine Dietz, Emma van Daalen, Hugo Schnack, Jan Buitelaar, Herman van Engeland.



Abstract

Objective

Brain size is a modest predictor of intellectual ability in adults and (pre-)adolescent children. This study investigated the relationship between intellectual functioning and brain volume in children with a developmental delay under the age of five years.

Methods

Intellectual functioning, intracranial volume, total brain volume, and ventricular volume were assessed in 13 children. Pearson correlation coefficients were calculated.

Results

There was a significant correlation of 0.74 between intellectual functioning and total brain volume, after controlling for intracranial volume. A significant negative correlation was found between intellectual functioning and total ventricular volume (r=-0.77). There was no correlation between intellectual functioning and total brain volume or intracranial volume.

Conclusions

These results suggest that there may be relative brain volume loss related to poor intellectual functioning in young children with idiopathic developmental delay.

Introduction

Several studies have shown that overall brain volume is associated with general cognitive functioning in humans. In adults, moderate correlations of 0.20 to 0.40 have been reported (Andreasen et al., 1993; Toulopoulou et al., 2004), and in (pre-)adolescent children reported correlations range between 0.20 and 0.28 (Reiss et al., 1996; Wilke et al., 2003). In a very recent study, it was demonstrated that the level of intelligence was related to the pattern of cortical growth in childhood and adolescence, indicating that the neuroanatomical expression of intelligence in children is dynamic (Shaw et al., 2006). The first years of life are thought to be pivotal in the development of both the brain and intellectual functioning. However, it is unclear whether cognitive functioning and brain volume are associated in children under the age of five. Some studies have taken head circumference as an indicator of brain size in young children (Bartholomeusz et al., 2002). In children small for gestational age, a small head circumference has been associated with lower intellectual functioning (Frisk et al., 2002). However, head circumference is a relatively crude measure of brain volume. Therefore, we used high-resolution magnetic resonance brain imaging to investigate the relationship between intellectual functioning and brain volume in children younger than five years of age.

Methods

Thirteen children with developmental delay were included; five children had a diagnosis of mental retardation and eight children were diagnosed with language disorder according to the definitions of DSM-IV (mean age 41 months, SD=12, range 26-62 months). Intellectual functioning was operationalised as the non-verbal intelligence measure (the fine motor and visual acuity subtests) of the Mullen Scales of Early learning (Mullen, 1995). Verbal measures were not taken into account as eight children had been diagnosed with language disorder and non-verbal tests are considered more suitable for children with mental retardation (Skovgaard et al., 2004). The developmental quotient was calculated as the mean of the age equivalents of the two non-verbal subtests divided by chronological age times 100, representing a position in a normal distribution with a given mean of

100 and a given standard deviation of 15 (Mullen, 1995). In one case, a Dutch non-verbal intelligence test, the SON-R (Tellegen et al., 1996), comparable to the Mullen scales, was used. All statistical analyses were repeated without this child.
All participants completed an extensive medical assessment. A developmental paediatrician performed a physical examination and medical history, including assessment of perinatal circumstances and maternal illness during pregnancy. An audiologist and speech and language therapist evaluated hearing and language. All subjects were admitted to the neuropaediatric ward of the UMC Utrecht for an extensive blood screening, including amino acids, thyroid function, a karyogram, Fragile X testing and screening for metabolic disorders. The admission included consults by a paediatrician, child neurologist, and clinical geneticist. A lumbar puncture procedure was performed to assess the presence of metabolic abnormalities (van Daalen et al., in preparation). No metabolic or genetic abnormalities were reported for any of the children included in the current sample. All children had a karyogram as expected according to gender. Two children were born prematurely at thirty-three and thirty-four weeks of gestation with accordingly lower birth weights. All children were born with a birth weight above fifteen hundred grams. One boy diagnosed with mental retardation had been previously treated with valproic acid for symptoms of epilepsy. No birth complications were reported for any of the subjects. As such, the sample included in the current report is representative of children with idiopathic developmental disability not due to an detected biological cause. A control group of typically developing children could not be included as the children were below the allowed age for inclusion in MR studies for research purposes, as stated by the Dutch Central Committee on Research involving Human Subjects.

T1-weighted three-dimensional fast field echo scans with 1.5-mm contiguous coronal slices of the whole head and T2-weighted dual echo turbo spin-echo scans with 3.0-mm contiguous coronal slices were acquired on a Philips Gyroscan (Philips Medical Systems, Best, The Netherlands) at 1.5 Tesla. The MRI procedure was planned after the lumbar puncture procedure, while patients were still under full anaesthesia. The study design was approved by the Medical Ethical Review Board of the University Medical Center Utrecht. All parents gave written informed consent after

full explanation of the study. Post-processing included semi-automatic histogram intensity analyses to obtain estimates of cranium and total brain and total ventricular volume. Intrarater reliabilities were estimated using intraclass correlation coefficients and were > 0.98 for all measures (for more details, see Durston et al., 2004). After radiological evaluation, three children were found to have a left temporal cyst (which was not included in the total brain volume). One boy with mental retardation had a subcortical band heterotopia, which has no known implications for brain volume. All statistical analyses were repeated without these children.

Analyses were conducted using the SPSS statistical package (version 11.5). Bivariate and partial Pearson correlation coefficients were calculated. Significant correlations were followed up with linear regression analysis.

Results

Mean developmental quotient was 81 (SD=18, range 39-107). There was a strong correlation between intracranial and total brain volume ($r=0.96$; $p<0.01$). There were no significant correlations between intellectual functioning and intracranial volume ($r=0.10$; $p>0.1$) or between intellectual functioning and total brain volume ($r=0.30$; $p>0.1$). There was a significant correlation of 0.74 between total brain volume and intellectual functioning after partialling out intracranial volume ($p<0.01$). The model predicted by the linear regression analysis explained 56 % of the variance in intellectual functioning ($F=6.24$; $p=0.017$), see figure 1.

Significant negative correlations were found between intellectual functioning and total ventricular volume ($r=-0.77$; $p<0.01$). Findings were not significantly altered by partialling out age, gender, weight, height, or level of parental education, or after exclusion of the child with the SON-R or the children with radiological abnormalities. Findings did not alter when raw scores were used instead of age equivalent measures of the Mullen.

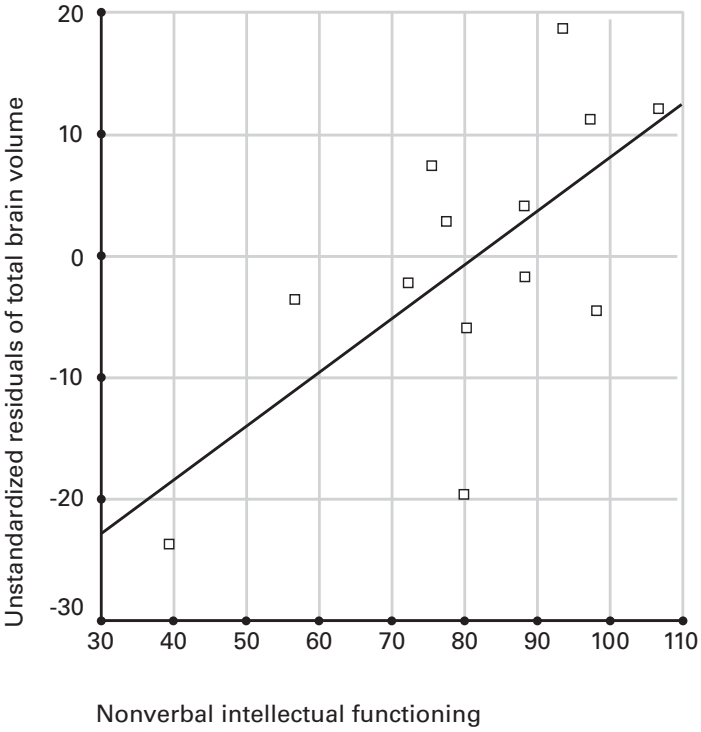


Figure 1 *The relationship between non-verbal intellectual functioning and the unstandardised residuals of total brain volume while controlling for intracranial volume in 13 children with a developmental delay below the age of five years.*

Discussion

The relationship between intellectual functioning and brain volume was investigated in children under five years of age. There was a strong correlation between brain volume and intellectual functioning after partialling out intracranial volume, where brain size relative to head size accounted for 56% of the variance in intellectual functioning at this age in developmentally delayed children.

Previous studies have reported associations between cerebral volume and intellectual functioning in (pre-)adolescent children (Wilke et al., 2003; Reiss et al., 1996). We did not find a relationship between intracranial or total brain volume with intellectual functioning by itself, but rather a relationship of brain volume with intellectual functioning when correcting for intracranial volume. This difference

may be related to our sample of developmentally delayed children.
In the first few years of life, intracranial volume increases partially under the influence of total brain volume growth (Dyke et al., 1933). Brain growth may or may not have been abnormal in early development, but the finding of a relationship between intellectual functioning and total brain volume only when controlling for intracranial volume suggests that there are later effects on total brain volume. This is in keeping with our finding of negative correlations between intellectual functioning and ventricular volume, which may be interpreted to indicate atrophy. As such, these results implicate the relevance of subtle regressive events in brain development in children with a developmental delay.
In this sample, three children were found to have intracranial cysts. Soto-Ares and colleagues (Soto-Ares et al., 2003) reviewed MR images of children with non-specific mental retardation. They reported cysts in 10% of their population, similar to the findings in this report. Our findings are based on a small sample of very young children with idiopathic developmental delay not related to a biological cause, as established by our extensive medical assessment. Taken together with the results from Soto-Ares and colleagues, this leads us to believe that, although our sample is small, it is representative of children with developmental delay.
Although we included a unique sample of very young children, with data on intellectual functioning and brain volumetric measures, this study was limited by small sample size. It took several years to acquire a group of young developmentally delayed children with no underlying biological substrate. As such, these results should be considered preliminary and need to be replicated in larger samples. Furthermore, as this sample was limited to children with subnormal to normal intellectual functioning, inferences regarding children with a higher level of intellectual functioning are precluded.

In sum, we report a correlation between total brain volume and intellectual functioning in a group of very young children with idiopathic developmental delay, when intracranial volume is controlled for, whereas there was no correlation between intellectual functioning and total brain volume or intracranial volume. These results suggest that there may be relative brain volume loss related to poor intellectual functioning in young children with idiopathic developmental delay.

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