Chapter 8

School progress, neuropsychological functioning and behaviour in term small for gestational age children

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ABSTRACT

Disentangling the effect of being born small for gestational age (SGA) after term pregnancy on cognition and behaviour in young school aged children is difficult from previous literature. We contribute by neuropsychological investigation of a well- defined subset of children born after at least 34 weeks of gestation who meet strict criteria of SGA.

We examined the effect of being born SGA on school progress, cognition and behaviour in and evaluated whether bodily catch-up growth coincides with neuropsychological catch-up. Data were available from 40 term born SGA children (22 SGA+, 18 SGA-), and 31 children born appropriate for gestational age (AGA) (total sample aged 5.8 ± 1.0 years). Parents provided information on the family's home situation, parental educational level and on maternal smoking during pregnancy. Parents and teachers completed questionnaires on the children's behaviour. Children underwent neuropsychological investigation. Principal component analysis was carried out to reduce data into a set of uncorrelated components.

Subtle disadvantages in both SGA- and SGA+ children were observed in school progress and across components of cognition and behaviour. In SGA- children disadvantages mainly concerned measures of learning and retention (memory). In SGA+ children visuomotor integration and organization were poor. In our sample, differences between the groups could not be ascribed to psychosocial factors. Our data support the hypothesis that bodily catch-up growth in children born SGA does not implicate full catch-up of the brain.

INTRODUCTION

Children born 'small for gestational age' (SGA) are children whose birth weight or birth length is below a predefined cut-off as for instance 2 standard deviations (SD) below the mean (≤ -2SD) for the infant's particular gestational age (Lee *et al.*, 2003). In the majority of these children, the delay in body growth is spontaneously restored during the first two years of life (SGA+). Approximately 10% lack catch-up growth (SGA-) and exhibit persistent short stature (Hokken-Koelega *et al.*, 1995; Albertsson-Wikland *et al.*, 1998).

Being born SGA is associated with decreased levels of intelligence, cognitive sequelae and school difficulties (Van der Reijden-Lakeman *et al*. 1996, Van der Reijden-Lakeman *et al*. 1997, Strauss 2000; Frisk *et al.*, 2002; Geva *et al.*, 2006a; Geva *et al.*, 2006b; Lundgren *et al.*, 2001; Roza *et al.*, 2008). However, the nature and severity of these impairments differ widely and the overall outcome of each child is likely the result of a complex interaction between intrauterine and extra uterine factors (de Bie *et al.*, 2010). Interestingly, SGA+ is associated with better outcome than SGA-.

Recent work of ours in a rather homogeneous sample of 4 to 7-year-old SGA children demonstrated that SGA children differ on brain anatomy when compared with peers born appropriate for gestational age (AGA), relating to both global and regional anatomical differences (de Bie *et al.*, 2011). SGA children showed smaller cerebral and cerebellar white matter volumes, smaller volumes of basal ganglia together with a smaller overall cortical surface area. In addition, regional differences in prefrontal cortical thickness suggest a different development in cerebral cortex. SGA+ children constituted and intermediate between SGA- children and AGA controls. These results are in line with results from another study investigating brain anatomy in 15-year-old adolescents (Martinussen *et al.*, 2005; Martinussen *et al.*, 2009).

The present study was done to explore effects for cognition and behaviour in a group of SGA schoolchildren with documented different brain architecture (de Bie *et al.*, 2011).

METHODS

The study was approved by the Ethics Committee of the VU University Medical Center and was conducted according to the principles of the Helsinki Declaration. All children participated on the agreement of parents and of their written consent.

Children

The sample under current analysis consisted of 40 children born SGA (22 SGA+ and 18 SGA-). Following the International Small for Gestational Age Advisory Board Consensus Development Conference Statement (2003), SGA was defined as a birth weight and/

or birth length ≤ -2SD, adjusted for gender and GA; SGA+ was defined as postnatal catch-up growth with an actual height of less than 2 SD below the mean; and SGA- as persistent postnatal growth failure based on an actual height below -2.5 SD, according to Dutch references (Fredriks *et al.*, 2000). Inclusion was mainly based on birth weight because data on birth length were not available in a substantial part of the children. Additional inclusion criteria were: 1) a neonatal period without signs of severe asphyxia, defined as an Apgar score ≥ 7 after 5 min, 2) single birth, and 3) calendar age between 4 and 8 years. Exclusion criteria were: 1) severe prematurity below 34 weeks, 2) growth failure caused by other somatic or chromosomal disorders or syndromes, 3) previous or present use of drugs that could interfere with growth, including GH-treatment, and 4) obvious learning disability or established intelligence quotient (IQ) below 70. Thirty-one healthy AGA children were assessed to control for effects of normal development. Most of the children were friends or classmates of the SGA children, some were siblings, and some were not at all related to the children. Parents of all children were asked to fill out a questionnaire on family situation, parental educational levels, and smoking during pregnancy. Parental educational levels were categorized according to the International Standard Classification of Education (ISCED 1997). Information on the child's school achievement was gathered through teachers' questionnaires.

Instrumentation

Intelligence

Children's IQ was estimated on the basis of a four-subtest short form of the Wechsler's scales, yielding an estimate of the Full Scale IQ (eIQ). Estimates of reliability and validity indicate the abbreviated forms of the Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R, Dutch Version), for children under 6 years, and the Wechsler Intelligence Scale for Children – Third Edition (WISC-III, Dutch Version) for children above 6 years, to approximate the Full Scale IQ when time limitations are a consideration (Wechsler 1989; Wechsler 2002; Kaufman *et al.*, 1996; LoBello SG. 1991).

Behaviour

Behavioural functioning of the children was measured by parents' ratings on the Child Behaviour Checklist (CBCL) (Achenbach and Edelbrock 1991) and by teachers' ratings on the Teacher Report Form (TRF) (Achenbach 1991). Two form types of the CBCL and of the TRF were applied, depending on the child's age: the C15 and T15 for children under 6 years of age, and the CBC and TRF for children aged 6 to 18 years. The C15/T15 consists of 100 behaviour problem items and the CBC/TRF consists of 113 behaviour problem items, on which parents/teachers rate the child's behaviour using 3-points scales, with a higher score reflecting more problems.

Neuropsychological functioning

We took advantage of the fact than children learn 'where' more easily than 'what' and administered a computerised memory task ('Learning Locations') (Schouten *et al.*, 2002) that required the children to memorise the locations of 16 coloured pictures of natural objects. The task was constructed similar to the much-used California Verbal Learning Test (Delis D.C. *et al.*, 1986). Dependent variables were 1. Total immediate recall: summed number of correctly recalled locations in each of five successive, identical learning trials (maximum = 5x16 = 80); 2. Within assessment retention: the percentage of correctly recalled locations after a delay of 30 minutes filled with other tasks, corrected for recall in trial 5 (recall trial 5 minus delayed recall)/ recall trial 5); 3. Retroactive interference: number of correctly recalled original locations after having recalled reordered locations, corrected for recall in trial 5 (recall trial 5 minus recall retroactive interference trial)/recall trial 5).

The 'Beery Developmental Test of Visual-Motor Integration' (VMI) is a well researched, commonly used and standardized test with an objective scoring system (Beery 2010).

The 'Rey-Osterrieth Complex Figure' (ROCF) is a standardized procedure that has been extensively used and has been found to be a very sensitive measure both of perceptual organization and visual memory. The child is confronted with the ROCF stimulus card (Figure 8.1) and a response sheet. The child is asked to make a copy of the design. When

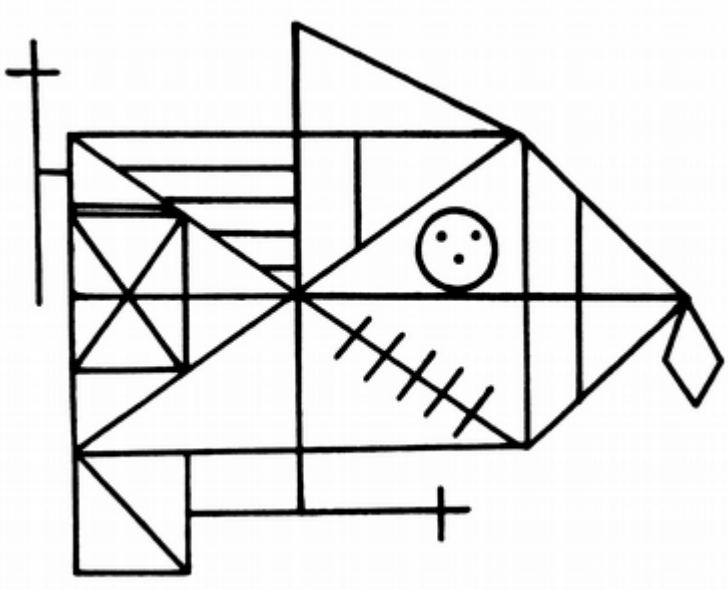

Figure 8.1: Rey Osterrieth Complex Figure (stimulus card).

the child has completed the copy condition, the ROCF stimulus card is removed, and the child is immediately presented with a new response sheet and asked to reproduce the design by heart (immediate recall). After several interpolated verbal tasks lasting 15- 20 minutes (delayed recall), and without warning the child, a new response card is presented asking the child to again reproduce the design by heart (Bernstein and Waber D.P. 1996). Dependent variables were scores derived with the ROCF developmental scoring system (DSS) (Bernstein & Waber, 1996) for each of the three productions (copy, immediate recall and delayed recall) 1. Organization: quantification of the child's appreciation for the organizational goodness of complex, visually represented materials; 2. Accuracy: the actual number of elements of the ROCF that are accurately reproduced, independent of how well they are organized or the style with which they are produced.

Statistical analysis

Analyses were carried out using SPSS 15.0 for Windows. Principal Component Analysis (PCA) with Varimax rotation was used for data reduction. Only components with eigenvalues greater than 1 were retained. A solution of 5 components that all matched clinically relevant cognitive constructs emerged (Table 8.1). The cumulative percentage of explained variance was 90.63%. The five components can be adequately characterized by the labels 1) Perceptual Organization, Visual Memory & Visuomotor Integration, 2) Behaviour as observed at School, 3) Behaviour as observed at Home, 4) Susceptibility for Interference, and 5) Learning & Retention (listed in decreasing percentages of explained variance). The five components were used as dependent variables in GLM multivariate ANOVA, with polynomial contrasts if appropriate. If relevant, eIQ and/or age were covariant(s).

Bonferroni correction was applied for multiple comparisons. Relationships between categorical data were analysed using Chi-square tests for independence of factors. When appropriate additional non-parametric tests were applied (Jonckheere-Terpstra test). Correlations between continuous data were calculated by Pearson correlations.

In all tests, p-values of less than .05 were deemed to be statistically significant. Values between .05 and .10 will be reported.

RESULTS

Sample descriptions

Anthropometry, demography, and information on school achievement, home situation, parental education and smoking during pregnancy, were summated in Tables 8.2 and 8.3. As expected, birth weight (F [df 1] = 99.55, p = 0.000) was significantly lower. Although head circumference was lower in both SGA groups compared to AGA this did

Table 8.1 Significant weights in the components yielded by the PCA Varimax Solution for the 20 cognitive and behavioural variables. Eigen values and the percentage of explained variance per component.

	Components:		Perceptual Organization, Visual Memory & Visuomotor Integration	Behaviour at School	Behaviour at Home	Susceptibility to Interference	Learning & Retention
ROCF							
Organization		Copy	.697				
		Immediate Recall	.673				
		Delayed Recall	.711				
Accuracy	Incidental elements	Copy	.937				
		Immediate Recall	.885				
		Delayed Recall	.914				
	Structural elements	Copy	.912				
		Immediate Recall	.883				
		Delayed Recall	.891				
Learning Locations							
First registration	# correctly recalled locations after single trial						.521
Total immediate recall	total # correctly recalled locations after repeated (5) trials						.691
Within assessment retention	total # correctly recalled locations after 20 minute delay, controlled for total imm recall						.711
Retro active interference	total # correctly recalled original locations after interference (after reshuffle trial), controlled for total imm recall					.944	
Beery							
VMI			.651				
CBCL							
Internalizing					.703		
Externalizing					.706		
Total					.929		
TRF							
Internalizing				.841			
Externalizing				.664			
Total				.958			
Initial eigen values			692.62	412.09	386.97	223.53	131.038
% of explained variance			34.00	20.23	19.00	10.97	6.43

Table 8.2 Demography and anthropometry for the group of children born AGA and SGA (subdivided in SGA+ and SGA-)

		AGA	SGA+	SGA-	SGA total
Gender (n)					
	Boys	17	12	11	23
	Girls	14	10	7	17
Gestational age in weeks		39.9 ± 1.2	38.9 ± 2.0	39.3 ± 2.2	39.1 ± 2.1
At birth:					
Body length in SD*		0.49 (0.16)	-1.71 (0.34)	-2.74 (0.21)	-2.26 (0.21)
Body weight in SD		0.37 (0.19)	-2.63 (0.11)	-2.40 (0.11)	-2.50 (0.08)
Head circumference in SD*		0.03 (0.21)	-1.08 (0.13)	-1.12 (0.29)	-1.11 (0.17)
At assessment:					
Chronical age		5.8 ± 1.1	5.9 ± 0.3	5.6 ± 1.0	5.7 ± 0.9
Body length in SD		-0.09 (0.25)	-0.41 (0.23)	-2.99 (0.08)	-1.78 (0.26)
Body weight in SD**		0.02 (0.18)	-0.43 (0.27)	-0.80 (1.04)	-0.63 (0.56)
Head circumference in SD		0.41 (0.19)	-0.04 (0.16)	-1.33 (0.28)	-0.69 (0.20)

Legend: data are presented as mean (± standard deviation); *when birth length or head circumference were not available, measures from first visit at child health centre was taken, ** weight according to length

Table 8.3 Intelligence levels and information on school achievement, home situation and parental education for the total group of children born AGA and SGA, subdivided in SGA+ and SGA-.

	AGA	SGA			95% CI of diff	*p* (F[df 2]) #		
		SGA+	SGA-	SGA total			95% CI of diff	*p* (F[df 1]) ##
eIQ (WISC/WPPSI) (mean ± SD)	110 ± 15	106 ± 11	103 ± 11	105 ± 11	-14 to 7	ns	-12 to 1	ns
	AGA	SGA				*p* (Chi2; df 2)#		
		SGA+	*SGA-*	SGA total				*p* (Chi2; df 1)##
School achievement								
repeating grade(s) (%)	6.5	13.0	11.8	12.5		ns		ns
extra educational services (%)	9.7	13.0	17.6	15.0		ns		ns
special education (%)	0.0	4.3	0.0	2.5		ns		ns

Parental Education						
≥ post-secondary education (mothers) (%)	50.0	42.9	58.8	50.0	ns	ns
≥ post-secondary education (fathers) (%)	46.8	38.1	52.9	44.7	ns	ns
≥ post-secondary education (both)(%)	41.7	28.6	35.3	31.6	ns	ns
Smoking during pregnancy (yes)(%)	3.2	13.0	23.5	17.5	ns	ns
Home situation (troubled)(%)	12.9	4.3	29.4	15.0	ns	ns

[#] SGA- *vs.* SGA+ vs. AGA; [##] SGA *vs.* AGA

not reach statistical significance. The SGA- and SGA+ groups did not differ with respect to birth weight and head circumference at birth. Mean eIQ's were in the normal range, with a tendency to more favourable eIQ's in AGA compared to SGA (F [df 1] = 3.056, p = 0.085). Nearly 13% (n = 5) of SGA children had repeated a grade at school, substantially but not statistically significantly more than nearly 7% (n = 2) in the AGA sample but only slightly more than usual in The Netherlands (11%). Extra educational services or special schools were more often granted in (subgroups) of SGA but differences did not reach statistical significance.

Parental education levels were distributed equally across groups. Although not statistically significant, a relevant overrepresentation of troubled homes and smoking during pregnancy was seen in the SGA-sample.

Component scores

No significant differences between SGA and AGA were found for any of the components. Differentiating SGA- from SGA+ and comparing both to AGA revealed a tendency to difference between subgroups of SGA and AGA for Perceptual Organization, Visual Memory and Visuomotor Integration (F[df 2] = 3.16, p = 0.06) and for Learning and Retention (F[df 2] = 3.30, p = 0.05). For Perceptual Organization, Visual Memory and Visuomotor Integration, significant differences tended to occur between SGA+ and AGA to the disadvantage of SGA+; for Learning and Retention differences tended to occur between SGA- and AGA to the disadvantage of SGA-. Polynomial trend analyses showed significances for Perceptual Organization, Visual Memory and Visuomotor Integration (p = 0.02) with poorest performances in SGA+, then SGA-, then AGA; for Behaviour at School (p = 0.08) with most problems in SGA+, then SGA-, then AGA; and for Behaviour at Home (p = 0.05) with most problems in SGA+, then SGA-, the AGA. Component z-scores are illustrated in figure 8.2.

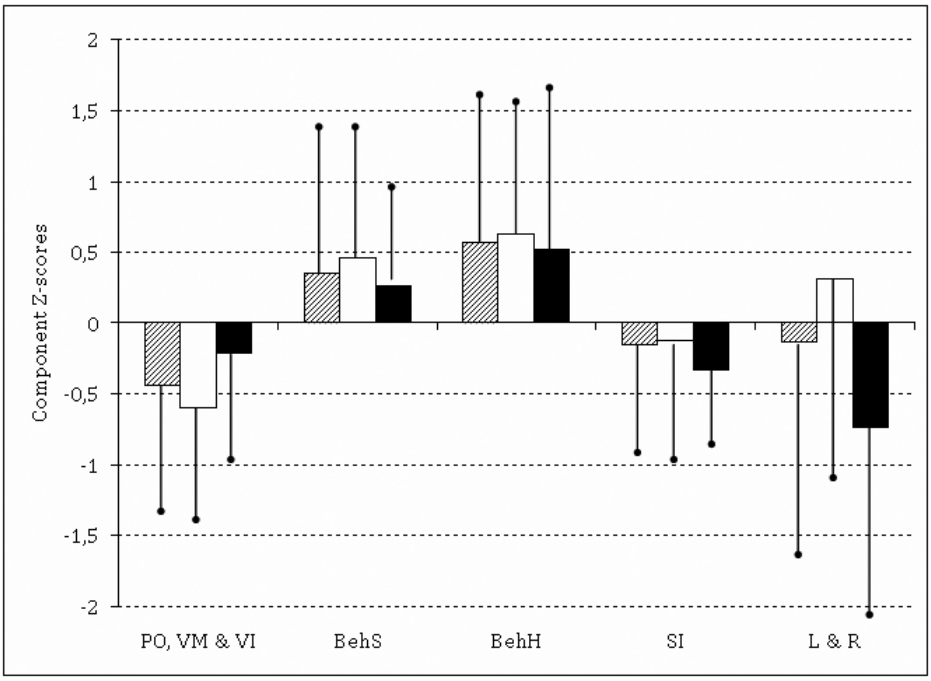

Figure 8.2 Mean deviation (with standard deviations) from mean component z-score in AGA (=0), in the total sample of SGA (shaded) in SGA+ (white), and SGA- (black). PO, VM & VI = Perceptual Organization, Visual Memory & Visuomotor Integration; BehS = Behaviour at School (the higher the more problems); BehH = Behaviour at Home (the higher the more problems); SI = Susceptibility to Interference; and L&R = Learning & Retention.

DISCUSSION

The data described here indicate subtle disadvantages in cognition in children born SGA already in the earliest stages of their academic career. Twice as many SGA children repeated a grade at school, and slightly more extra educational services or special education was granted to SGA than to AGA children. These figures on school performance may not be extremely alarming but caution against an at risk school career in both SGA+ and SGA-. Our data demonstrate that bodily catch-up growth in children born SGA does not implicate full catch-up of neuropsychological functioning.

The explanation of somewhat hampered school progress in SGA may lie in the high average level of general intelligence in our AGA sample, or in psychosocial factors such as coming from a troubled home situation. On the other hand, because of the general level of intelligence in the SGA-sample being rather high itself, together with the relative high parental educational levels and relative low numbers of smoking during pregnancy, we find it hard to avoid the impression that the composition of our patient sample is

somewhat biased positively. That we none the less find indications for hampered school careers justifies careful follow-up.

Our data describe cognitive vulnerabilities. Groupwise, SGA children do not have statistically significant poorer scores in principal components of cognition than AGA controls. However, standardized performances are nearly all to the disadvantage of the former (figure 8.2). For subgroups of SGA, disadvantages reach statistical significance in different components of cognition: SGA- children remain behind on measures of learning and retention, whereas SGA+ children lack behind on measures of perceptual organization, visual memory and visuomotor integration. Although not statistically significant, raw data show more behavioural problems in SGA than in AGA, with problems that reach clinical significance in 22%, as against 17.5 % of behavioural deviancy in a large sample of 4- to 16-year-olds in the Netherlands (Reef *et al*., 2009). Trend analyses show most behavioural problems in SGA+.

From the time the first studies related to cognition in SGA were published until present, no one has been able to unify conclusions and conflicting views remain. The discrepancies regarding the effects of being born SGA are probably the result of different methodology applied and different sample composition in both age and gestational characteristics.

Most studies are AGA controlled studies that use a combination of neuropsychological measures to assess cognitive functioning. Viggedal et al. (Viggedal *et al.*, 2004) administered a comprehensive neuropsychological battery covering main aspects of cognition in young adults. Lower IQs, specifically reduced verbal comprehension and deficits in figurative learning and memory functions were found, but no difference in educational achievement. Studies in adolescence (Kulseng *et al.*, 2006; O'Keeffe *et al.*, 2003; Westwood *et al.*, 1983) reported that full term nonasphyxiated SGA infants might have an impaired potential for physical growth but a good prognosis for cognitive development. Paz et al. (Paz *et al.*, 1995; Paz *et al.*, 2001) limited assessment to IQ testing and found term born SGA adolescents to be not at increased risk for low IQ scores. Van der Reijden-Lakeman investigated intelligence and attention in a group of short statured SGA children in The Netherlands (Van der Reijden-Lakeman *et al*., 1996; Van der Reijden-Lakeman *et al*., 1997). Total IQ as well as the verbal IQ and performance IQ was significantly lower than that of the general population. In addition, SGA children exhibited significant deficits in divided, focused and sustained attention and suffered from impulsiveness.

Studies carried out at school age fail to differentiate SGA from intrauterine growth restriction (IUGR) (Geva *et al.*, 2006a; Geva *et al.*, 2006b; Geva *et al.*, 2008; Leitner *et al.*, 2007; Strauss and Dietz 1998). Several authors ((Frisk *et al.*, 2002; Hollo *et al.*, 2002) strictly defined SGA but included both preterm and term born children. Dating from the early 70's, Fitzhardinge & Steven (Fitzhardinge and Steven 1972) reported on a higher

incidence of school failure in SGA, despite normal IQs. They alluded on mild maturation defects of the brain featured by EEG abnormalities of mild, diffuse nature as well as by mild speech defects in SGA. One decade later, Harvey et al. (Harvey *et al.*, 1982) enforced this hypothesis by using ultrasound information to measure the time of onset of slow head growth by comparing biparietal diameters with normal curves. Not birth weight itself but rather an early onset of IUGR was the best indicator of an infant's later poor perceptual performance subscores. More recently, Sommerfelt et al. (Sommerfelt *et al.*, 2000; Sommerfelt *et al.*, 2002) reinterpreted differences between term SGA and AGA preschoolers and found parental factors rather than growth restriction itself to be associated with itself marginal neurocognitive, disadvantages in SGA. Theodore et al. (Theodore *et al.*, 2009) could not find any long-term effects of SGA birth on intelligence in middle childhood, and stressed the importance of modifiable post-natal and demographic factors in understanding vulnerabilities in SGA.

Studies on behavioural functioning in SGA are less extensive. Van der Reijden-Lakeman demonstrated significantly higher problem scores on the CBCL in a group of 83 SGA- children (mean age 7.3 years). Higher scores were obtained on social problems, attention problems, delinquent behaviour and the aggressive behaviour syndromes. In contrast, other studies in childhood failed to find behavioural disadvantages or differences in emotional skills in SGA children (Hadders-Algra and Touwen 1990; Sommerfelt *et al.*, 2001). Van Lieshout & Boylan (Van Lieshout and Boylan 2010) included preterm and term born SGA adolescents, covariate for gestational age and used CBCL-based questionnaires. They found SGA to be associated with increased levels of depressive symptoms in females but not in males, and that this first emerged in early adolescence. Indredavik et al. (Indredavik *et al.*, 2010) used a combination of scales to assess psychiatric outcome and found socioeconomic status to be the main risk factor for psychiatric symptoms in term born SGA adolescents.

Our results demonstrate that it seems important to distinguish SGA- from SGA+ when studying cognitive functioning and behaviour. That especially learning and retention (memory) is at stake in SGA- is relevant with respect to, for instance, acquiring scholastic skills. Further investigation on this finding should be focussed on whether memory problems can be explained by deviances in brain development (de Bie *et al.*, 2011). That perceptual organization, visual memory and visuomotor integration seem important in SGA+ also impedes further study. Especially the combination of these organization and integration problems and the elevated level of behavioural problems in SGA+ (as shown by the polynomial contrasts) question the efficiency of children's self-regulation capacities. This hypothesis is supported by our recent findings on reduced cerebral and cerebellar white matter volumes in the SGA sample (de Bie *et al.*, 2011) suggesting deviant of altered maturation of white brain matter. Maturation of the brain is synonymous with the development of neurotransmitter systems that are critical because of their

role in regulating early neurobehavioral processes (Berger *et al.*, 2007). Figueras et al. (Figueras *et al.*, 2009) observed poor self-regulation and organization of state in SGA term newborns (Ben-Sasson *et al.*, 2010).

Not unlike the majority of similar studies, the one presented here would have benefited from a longitudinal design in enlarged samples. The small group sizes impeded in-depth analysis and interpretation of possible parental and psychosocial factors influencing intrauterine growth, but also early neurobehaviour including regulation (Dejin-Karlsson *et al.*, 2000). A research focus on differences in self-regulation is recommended. Assessments should enable one to study executive aspects of responses in addition to established levels of skill or attainment, and apart from the clinical surroundings of test laboratories. A process approach might be envisaged that evaluates the effect of individually tailored interventions that pertain to strategies aimed at improving learning, retention and self-regulation in SGA.

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