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Neuropsychological Deficits in Young Adults Born Small-for-Gestational Age (SGA) at Term

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Abstract

Reduced IQ, learning difficulties and poor school performance have been reported in small-for-gestational-age (SGA) subjects. However, few studies include a comprehensive neuropsychological assessment. Our aim was to study neuropsychological functioning in young adults born SGA at term. A comprehensive neuropsychological test battery was administered to 58 SGA subjects (birth weight <10th centile) born at term, and 81 term non-SGA controls (birth weight ≥10th centile). The SGA group obtained significantly ($p < .01$) lower scores on the attention, executive and memory domains compared to non-SGA controls and showed higher risk of obtaining scores below −1.5 *SD* on the memory domain (odds ratio = 13.3, 95% confidence interval: 1.57, 112.47). At a subtest level, the SGA group obtained lower scores on most neuropsychological tests, with significant differences on 6 of 46 measures: the Trail Making Test 3 (letter sequencing), the Wechsler Memory Scale mental control and the auditory immediate memory scale, the Design Fluency, the Stroop 3 (inhibition) and the Visual Motor Integration (VMI) motor coordination subtest. Young adults born SGA score more poorly on neuropsychological tests compared with non-SGA controls. Differences were modest, with more significant differences in the memory domain. (*JINS*, 2014, *20*, 313–323)

Keywords: Neuropsychological tests, Fetal growth restriction (FGR), Child development, Low birth weight, Follow-up study, Cognitive abilities

INTRODUCTION

It is well recognized that fetal growth restriction (FGR) resulting in low birth weight influences outcome later in life, even in children/adults born at term (Barker, 1995). FGR denotes normal fetal growth that has been inhibited during pregnancy, and may be caused by chronic hypoxemia and deprivation of nutrients (Wollmann, 1998). The lack of a clear definition of FGR has made research on this field problematic (Urquia & Ray, 2012; Wollmann, 1998) and the term small-for-gestational age (SGA) has been used as a proxy for FGR in epidemiological studies. This is a statistically set cutoff in birth weight, where the most commonly used is birth weight below the 10th percentile adjusted for gestational age (Pollack & Divon, 1992; Wollmann, 1998). A previous birth of a low birth weight baby, low pre-pregnancy maternal weight, and maternal smoking have all been related to SGA births, especially when several factors are combined (Bakketeig et al., 1993).

We have previously reported that one third of young adults born SGA at term have reduced full IQ scores compared to those born with normal birth weight, and lower scores on the Verbal Comprehension, the Working Memory, and the Perceptual Organization indices of the Wechsler Adult Intelligence Scale 3rd Edition (Lohaugen et al., 2013). As SGA applies to newborns that in most cases seem otherwise healthy, we believe that increased focus of attention should be given to the long-term cognitive and neuropsychological outcomes in this group of subjects.

Some studies on preterm SGA children have shown higher mortality, more executive function problems and ADHD symptoms compared with those born preterm with appropriate

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birth weight for gestational age. Several studies have argued that it is inadequate fetal growth that corresponds to poor outcome, not low birth weight and gestational age per se (De Jesus et al., 2013; Heinonen et al., 2013, 2010). Most studies on neurodevelopment and cognition in term SGA births have been conducted with preschoolers and school-age children, and few studies have included adults (Lohaugen et al., 2013; Lundgren, Cnattingius, Jonsson, & Tuvemo, 2001; Viggedal, Lundalv, Carlsson, & Kjellmer, 2004). Abnormal neurodevelopment in SGA children has been reported already at term age (Cruz-Martinez et al., 2009; Figueras et al., 2009), and also later in childhood, reflected in lower IQ scores and poorer school performance compared to controls with normal birth weight (Geva, Eshel, Leitner, Fattal-Valevski, & Harel, 2006; Leitner et al., 2012).

Viggedal et al. (2004) looked at long term cognitive consequences of being born SGA (at 21–28 years), and found that these young adults had lower IQ scores compared with healthy controls, especially verbal IQ, and specific neuropsychological problems to include reduced figurative learning, need for more trials in an auditory verbal learning task, lower scores on memory tests and slower visual scanning speed. However, they did not find that these deficits influenced academic achievement or the need for special education. Other studies have reported lower academic achievement, lower income and more mental health problems in term born SGA adults compared with controls born with normal birth weight for gestational age (Lund et al., 2012; Lund, Vik, Skranes, Brubakk, & Indredavik, 2011; Strauss, 2000). These results may have been confounded by parental socioeconomic status (SES) (Markestad et al., 1997).

In the current study, a neuropsychological test battery assessing attention, executive functions, memory, language, visual-spatial, and visual-motor functioning was administered to SGA and control subjects at age 19–20 years. Based on results from our evaluation of cognitive functioning in the SGA group at age 19–20 years (Lohaugen et al., 2013) and the results by Viggedal et al. (2004), we hypothesized that SGA subjects would be at disadvantage on tests assessing visual-spatial abilities, memory and language.

METHODS

Study Design

This study is part of a geographically based prospective follow-up study of the consequences of being born small-for-gestational-age at term. The participants were recruited from the Trondheim part of a multi-center study where 1200 pregnant women who had a singleton pregnancy and expected their 2nd or 3rd child, were enrolled before week 20 of pregnancy. These criteria were set because the intention of the original study was to investigate the implication of repeated SGA births *versus* SGA births of mothers who had previously delivered non-SGA infants. Recruitment was based on referrals from general practitioners and obstetricians in the Trondheim area (Bakketeig et al., 1993; Lohaugen et al., 2013).

In the initial part of the study, two groups were selected for follow-up. These were a 10% random sample of pregnant women selected by the sealed envelope method, serving as a population reference. They were found to be representative of the population (Bakketeig et al., 1993). The other group consisted of pregnant women with known risk factors for giving birth to an SGA infant. Risk factors included previous delivery of an SGA infant, cigarette smoking at the time of conception, low pre-pregnancy weight ($<$50 kg), previous perinatal death, chronic maternal disease, or essential hypertension. These yielded a sufficiently large sample of subjects born SGA. The SGA group in the long term follow-up comprised infants born of mothers in the 10% random sample, the high risk group, and also infants born SGA to women who consented and were eligible to participate, but not included in the 10% random sample or the high risk sample (i.e., the rest population). Details on the initial study population are provided by Bakketeig et al. (1993). Only those born from the 10% sample, or the high risk group had complete follow-up data from pregnancy. The control group comprised those born at term with birth weight $\geq$10th percentile, adjusted for GA and gender from the 10% random sample.

Our research group has published earlier reports on the same sample. At 12–13 months of age, cognitive scores (MDI) were lower in the SGA group, while motor scores (PDI) were comparable between the groups, assessed by the Bayley Scale of Infant Development (BSID) 1st edition (Markestad et al., 1997). At 5 years, significantly lower IQ scores were reported in the SGA group compared to the control group, but the difference was only modest (Sommerfelt et al., 2000). No significant group differences in IQ, attention, and executive functions were found at 14 years of age (Kulseng et al., 2006), but we reported significantly lower IQ in the SGA group compared to non-SGA controls at 19–20 years of age (Lohaugen et al., 2013). By young adulthood, the number of participants receiving special education was higher in the SGA group than among controls (Lohaugen et al., 2013).

Participants

Two subgroups of term born children (one SGA group and one non-SGA control group) born in the Trondheim area, Norway, in 1986–1988 were followed since early gestation, and were examined at age 19–20 years. The participants in the study group were small for gestational age at term [SGA, birth weight $<$10th percentile adjusted for gestational age (GA) at birth, and gender], based on data from the Norwegian Medical Birth Registry (Bakketeig et al., 1993).

SGA group

Of 104 young adults born SGA, we excluded one with a congenital syndrome. We were unable to get in touch with

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10 SGA subjects who were considered lost to follow-up, while another one was excluded due to severe disability at age 19. Of the remaining 92 young adults eligible for participation, 33 declined to participate, while 59 (64%) gave their consent to the cognitive evaluation. One participant with cerebral palsy was excluded from data analysis because of failure to perform many of the neuropsychological tests, leaving 58 SGA participants in the study.

Control group

The control group consisted of 122 young adults, but two with congenital malformations were excluded. We were unable to get in touch with 10 control subjects, and one young adult was excluded at the 19 years follow-up due to a severe medical condition. Of the remaining 109 subjects, 81 (74%) met for cognitive assessment, while 28 did not consent to participate.

Non-participants

There were no significant differences between participants and non-participants in any of the groups regarding SES (Hollingshead, 1958), gestational age, birth weight or maternal age at childbirth. IQ assessments at 6 (WPPSI-R), 10 (WISC-III), and 14 years (subtests from WISC-III) of age showed no difference in full IQ scores between those who participated both at an earlier age and at age 19–20, and those who were lost to follow-up before age 19–20 (data not shown).

The Regional Committee for Medical Research Ethics approved the study protocol (Project number: 4.2005.2605). Written, informed consent was obtained from each participant. All participants were offered a follow-up session about their test results with the neuropsychologist in the study.

Covariates

The SES was calculated according to Hollingshead's Two Factor index of Social Position, based on the education and occupation of both parents (Hollingshead, 1958). Information regarding occupational and educational attainment in the young adults was obtained through a short interview. SES data were missing in 12 SGA and 7 control participants, and for those SES values were imputed by the multiple imputation method. Gender, age at assessment, and SES were included as covariates in all analyses on group differences.

Measures

The neuropsychological testing was performed by a trained neuropsychologist who was blind to group affiliation and medical history. Testing took place during one session with a fixed order of tasks. A comprehensive neuropsychological test battery was administered, with 14 tests generating a total of 46 measures (Table 1). Five hours were set aside for cognitive and neuropsychological tests. Breaks were adjusted for each individual, and time for testing varied from 3.5 to 5 hr per person. Tests were conducted between October 2006 and December 2008. A detailed description of neuropsychological tests is given in Supplemental Material (S1). Information about tests is provided by Beery (1997), Strauss, Sherman, and Spreen (2006), and Tulsky et al. (2003). A Confirmatory Factor Analysis was applied to extract domain scores.

Low domain scores, that is, scores −1.5 *SD* or more from the control mean, were defined as deficits. Cognitive abilities were assessed by the Wechsler Adult Intelligence Scale-III (WAIS-III), and results from this test have been published earlier (Lohaugen et al., 2013). A few subjects had missing scores on some of the subtests, and the multiple imputation method was used to deal with missing neuropsychological data.

The following clinical variables were considered: birth weight, birth weight *Z*-score, gestational age, birth head circumference, birth length, maternal age at child birth, Apgar scores at 1 and 5 min, SES, and the participants' age at assessment. Birth weight *Z*-score is an individual standard deviation score for birth weight. This score indicates deviation from expected birth weight based on gestational age at birth, and adjusted for gender and parity; *Z*-score = (actual birth weight – mean expected birth weight)/*SD* for expected birth weight, with data from the Medical Birth Registry of Norway used in the equation (Skjaerven, Gjessing, & Bakketeig, 2000).

Statistical Analysis

The IBM SPSS statistics (Statistical Package for Social Sciences), version 19 (IBM, Armonk, New York) was used for statistical analysis. Clinical data were analyzed using non-parametric tests; Mann-Whitney *U* test for ordinal and interval data, and the χ^2 test for nominal data. The same analyses were used to look at differences between participants and non-participants.

Missing data (SES and neuropsychological test data) were dealt with by multiple imputations. Variables included in the model were SES, IQ, and all neuropsychological test scores. Pattern analysis was performed; showing that we had <5% missing data and that we could assume data was missing at random. Five imputed datasets were created, where pooled imputations were used in further analyses.

Log transformations were used to deal with variables with non-normally distributed values. Analyses on non-normally distributed data were initially performed on the original scales to ease interpretability. To correct for multiple comparisons, we considered an alpha level of 0.01 as significant for all analyses involving subtests. Tests were first categorized into five domains based on literature (Beery, 1997; Strauss et al., 2006; Tulsky et al., 2003): attention, executive, language, visual spatial/motor, and memory (Table 1). A confirmatory factor analysis (CFA) was then applied to examine the fit of our five-domain model using Mplus version 7 (Harrington, 2009; Muthén & Muthén, 1998). Only control subjects were included in the CFA, to assure generalizability. Before

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Table 1. Neuropsychological tests: Theory-driven categorization and results from the Confirmatory Factor Analysis (CFA)

Cognitive domain	Test	Subtests	CFA exclusion
Attention	Paced Auditory Serial Addition Test (PASAT)	Correct	Excl after 1st CFA (0.26, p = 0.097)
	The colour-word interference test (Stroop)	Naming colours (1)	
		Reading colour names (2)	
	Trail Making Test (TMT)	Visual Scanning (1)	Excl after 1st CFA (−0.39, p = 0.039)
		Numbers (2)	Excl after 1st CFA (−0.39, p = 0.025)
		Letters (3)	
	Conners' Continuous Performance Test (CPT)	Omissions	Excl after 1st CFA (−0.37, p = 0.015)
		Commissions	Excl after 1st CFA (−0.36, p = 0.006)
		Reaction time	Excl before 1st CFA
Executive	Wechsler Memory Scale-III (WMS-III)	Mental Control	
		Spatial Span forwards & backwards	
	Design Fluency (DF)	Total Score	
	The colour-word interference test (Stroop)	Inhibition (3)	
		Inhibition & Switching (4)	
	Trail Making Test (TMT)	Numbers & Letters (4)	
	Verbal Fluency (VF)	Total Correct	
	Wisconsin Card Sorting Test (WCST)	Number of categories,	Excl after 1st CFA (0.22, p = 0.129)
		Trials to complete first category	Excl before 1st CFA
		Failure to maintain set	Excl before 1st CFA
		Total Correct	Excl before 1st CFA
		% Perseverative responses	Excl before 1st CFA
		% Perseverative errors	
		% Non-perseverative errors	Excl before 1st CFA
	Tower test	Time to first move	Excl before 1st CFA
		Number of moves	Excl before 1st CFA
		Rule breaking	Excl before 1st CFA
		Total time	Excl after 1st CFA (−0.31, p = 0.018)
		Total Correct	Excl after 1st CFA (0.24, p = 0.067)
	Wechsler Adult Intelligence Scale-III (WAIS-III)	Letter-number sequencing	
Language	Boston Naming Test (BNT)	Correct	
	Wechsler Adult Intelligence Scale-III (WAIS-III)	Vocabulary	
		Similarities	
Visual-spatial/ motor	Rey Complex Figure Test	Copy	
	Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)	Copy	
		Visual Matching	
		Motor Coordination	
	The Grooved Peg Board (GPB)	Time both hands	Excl after 1st CFA (0.17, p = 0.396)
	Trail Making Test (TMT)	Motor Speed (5)	
	Wechsler Memory Scale-III (WMS-III)	Auditory Immediate Memory (scaled score)	
Memory		Auditory Delayed Memory (scaled score)	
		Auditory Recognition Delayed Memory (scaled score)	
		Visual Immediate memory (scaled score)	
		Visual Delayed memory (scaled score)	Excl after 1st CFA (0.27, p = 0.018)
	Rey Complex Figure Test	Immediate Recall	Excl after 1st CFA (0.39, p = 0.004)
		Delayed Recall	
		Recognition	Excl after 1st CFA (0.10, p = 0.363)

Note. A confirmatory factor analysis (CFA) was applied to test model fit with χ^2 test, Root Mean Squared Error of Approximation (RMSEA) and Comparative Fit Index (CFI) to assess goodness-of-fit. Exclusion prior to the CFA was based on poor correlation with other measures.

PASAT = Paced Auditory Serial Addition Test; TMT = Trail Making Test; CPT = Conners' Continuous Performance Test; WMS-III = Wechsler Memory Scale 3rd edition; DF = Design Fluency; VF = Verbal Fluency; WCST = Wisconsin Card Sorting Test; WAIS-III = Wechsler Adult Intelligence Scale 3rd edition; BNT = Boston Naming Test; VMI = Visual-Motor Integration; GPB = Grooved Peg Board; CFA = Confirmatory Factor Analysis; Excl = Excluded.

performing the CFA, we had to reduce the number of variables included in the theory-driven categorization. These were: Continuous Performance test (CPT) reaction time (excluded due to poor correlation with other attention measures); Wisconsin Card Sorting Test (WCST): trials to complete, failure to maintain set, total correct, perseverative responses, non-perseverative errors (excluded due to poor correlation with other executive functions measures); Tower: number of moves, time to first move, and rule-breaking (excluded due to poor correlation with other executive functions measures). We kept the CPT omission and commission subtest; the WCST: number of categories, perseverative errors; and the Tower test: time total and total correct. The χ^2 test, Root Mean Squared Error of Approximation (RMSEA), and Comparative Fit Index (CFI) were used to assess goodness-of-fit. An alpha level of 0.05 was considered significant for analyses on the domain level. The CFA model was applied to extract final domain scores.

A General Linear Model was applied to analyze the relationship between group (SGA *vs.* controls) and neuropsychological test scores and domain scores, with SES, gender, and age at assessment as covariates. Tests where a higher score represented poorer performance (i.e., errors or time) were transformed to negative scores. We compared raw scores on all tests, except for the auditory and visual memory measures of the WMS-III where we used scaled scores. *Z*-scores were calculated in the SGA group, based on mean value and *SD* in the control group, for each of the neuropsychological tests, and all scores were converted so that lower values were to be interpreted as negative. Domain scores were calculated by averaging the *Z*-scores from the individual tests within each domain. Correlation analyses (Spearman's rho and Pearson's r) were used to examine the relationship between clinical variables and domain scores in the SGA group. Secondary analyses were also performed to look at correlations between clinical variables and tests where the SGA group performed significantly more poorly than controls. All effect sizes (ES) were calculated by the Glass's delta (Δ). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to study the association between group adherence and having a deficit (score <-1.5 *SD*) in any of the neuropsychological domains.

To look at differences between participants and non-participants regarding IQ-scores, we applied a General Linear Model adjusting for gender and SES.

RESULTS

Clinical Characteristics

Table 2 shows the clinical characteristics of the study groups. Mean maternal age at birth was slightly lower in the SGA group than the control group, and a higher number of the SGA participants had received special education. Pregnancy complications such as hypertension or preeclampsia were not more common among mothers in the SGA than in the control group.

Confirmatory Factor Analysis

We first performed a CFA on all variables after the initial exclusions due to poor correlations with other measures. This model fitted the data poorly: χ^2 (619) = 1792.4, $p < .001$, RMSEA = 0.163 (0.155, 0.172), CFI = 0.413. Variables with poor fit (loading <0.40 and non-significant loading) were then excluded before performing a second CFA (see Table 1 for factor loadings and *p*-values).

Table 2. Clinical characteristics in the SGA and control group

	SGA ($n = 58$) Mean (*SD*)	Controls ($n = 81$) Mean (*SD*)
Birth weight (grams)	2918 (230.0)	3707 (473.2)
Gestational age (weeks)	39.7 (1.2)	39.7 (1,2)
Birth weight (z-score)*	−1.5 (0.4)	0.3 (1.0)
Apgar score 1 min**	9 (1–9) (n = 49)	9 (7–9) (n = 75)
Apgar score 5 min**	10 (9–10) (n = 49)	10 (9–10) (n = 76)
Gender (F/M)	35/23	48/33
Maternal age at child birth (years)	28.6 (3.7)	30.3 (4.4)
Socioeconomic status	3.6 (1.1)	3.6 (1.0)
Age at assessment (years)	19.7 (0.7)	19.6 (0.6)
Head circumference at birth (cm)	33.9 (1.2) (n = 49)	35.4 (1.2) (n = 75)
Length at birth (cm)	48.3 (2.2) (n = 50)	51.1 (1.9) (n = 76)
Special education yes/no	7/51	2/79
Unemployed or sickleave at time of assessment yes/no	6/51	2/77
Head cirumference at one year (cm)	46.6 (1.3) (n = 32)	47.4 (1.2) (n = 50)
Preeclampsia/Hypertension yes/no	1/57	7/74

Note. SGA = Small for gestational age; SD = standard deviation; Mann-Whitney U-test for two independent samples; Chi Square analysis for categorical data (gender, special education, and preeclampsia/hypertension).
*Birth weight z-score: compared to expected birth weight for gestational age, gender and parity.
**Apgar score 1 and 5 minutes presented as median and range.

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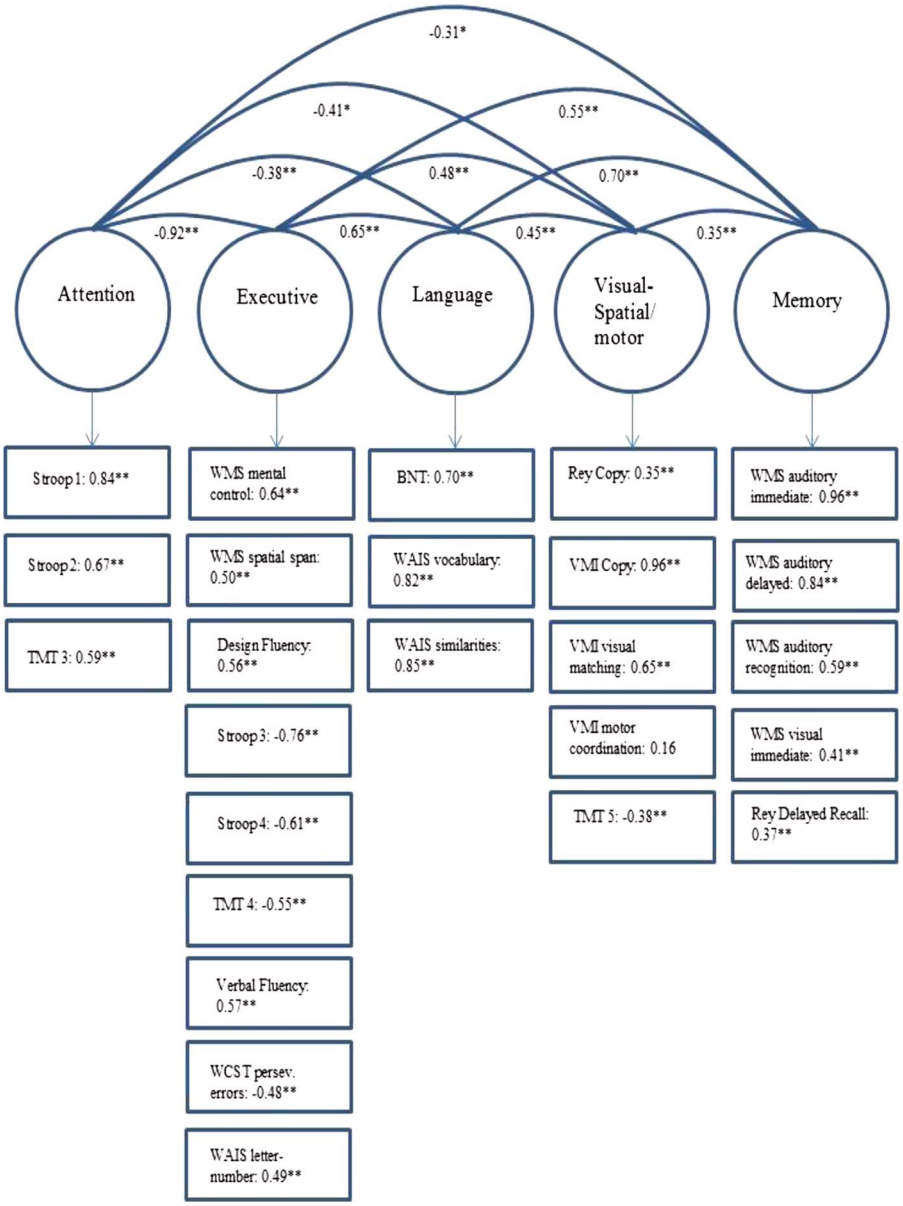

Fig. 1. Confirmatory factor analysis – final model, showing inter-factor correlations and factor loadings for all items. The CFA was performed in the non-SGA control group. Only items with significant factor loadings >0.400 were included in the extraction of domain scores for further analyses. The Visual-Spatial/Motor domain was excluded from further analyses as only two items fulfilled these criteria. TMT: Trail Making Test; WMS: Wechsler Memory Scale; WCST: Wisconsin Card Sorting Test; BNT: Boston Naming Test; WAIS: Wechsler Adult Intelligence Scale.

A second CFA was performed, including only variables that had a significant loading <0.40 in the initial CFA. This model fitted the data moderately: χ^2 (300) = 1127.07, $p < .001$, RMSEA = 0.093 (0.078, 0.107), CFI = 0.778. The final model consisted of five domains: attention, executive functions, language visual-spatial/motor, and memory (Figure 1). However, the visual-spatial/motor domain was excluded from further analyses as only two subtests loaded on this domain. Only tests with a significant factor loading >0.400 were included when we extracted domain scores for each subject.

Individual Neuropsychological Test Scores

The SGA group had lower raw scores than controls on 35 of the 46 neuropsychological tests, after adjustment for SES, gender, and age at assessment. Differences reached significance ($p < .01$) for 6 of the 46 measures. These were the Trail Making Test (TMT) 3 (letter sequencing) (ES = −0.61), the Wechsler Memory Scale (WMS) mental control subtest (ES = −0.56), the auditory immediate memory (ES = −0.48), Design Fluency (DF total score) (ES = −0.53), the Stroop 3 (inhibition) (ES = −0.48), and

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the Visual Motor Integration (VMI) motor coordination subtest (ES = −0.66) (see Table 3).

Cognitive Domain Scores and Neuropsychological Subtest Profile

The SGA group obtained lower scores than controls on all cognitive domains (Table 4), and differences reached significance ($p < .05$) on the attention (ES = −0.35), executive (ES = −0.27), and memory (ES = −0.35) domains after controlling for SES, gender, and age at assessment. There was an increased risk for deficits in the memory domain (OR = 13.3, 95% CI [1.57, 112.47]) in the SGA group. Forty-five (77.6%) SGA subjects had scores above −1.5 *SD* on any of the domain scores compared with 76 (93.8%) of controls (OR = 0.23 95% CI [0.07, 0.70]). Thirteen (22.4%) SGA subjects and five (6.2%) controls had low scores on one or more domains ($p = .188$).

Associations of Clinical Variables with Neuropsychological Outcome in the SGA Group

Of the clinical risk factors that were investigated looking for associations with domain scores in the SGA group, SES correlated with two of the scores, that is, language ($r = 0.318$; $p < .01$) and memory ($r = 0.220$; $p < .01$). No other clinical variable, including the birth weight *Z*-score, correlated with any of the domain scores. Secondary analyses of clinical variables and subtests that were significantly poorer in the SGA group, showed that Design Fluency correlated significantly with birth weight ($r = 0.343$; $p < .01$) and the WMS Auditory Immediate score correlated with SES ($r = 0.346$; $p < .01$).

DISCUSSION

Our main finding was that the SGA young adult group obtained inferior results on most neuropsychological measures, and within all cognitive domains, as compared with the non-SGA control group. However, differences reached significance in only 6 (13%) of the 46 subtests ($p < .01$), and three of the four domains (attention, executive functions and memory) ($p < .05$). Differences were generally small, and effect sizes only modest. Approximately 1 in 5 of the SGA subjects showed deficits (score <−1.5 *SD* from control mean) on one or more of the domains, while this was the case for less than 1 in 13 controls. The risk for low scores in the SGA group was highest for memory functions.

Using SGA as a proxy for FGR is problematic. Regardless of definition or algorithm used to identify children as SGA, a certain proportion of newborns below a statistical defined birth weight cutoff will be constitutionally small, while some significantly growth restricted newborns may have birth weight above the cutoff (Urquia & Ray, 2012). Such misclassification will most likely dilute the differences between children exposed to FGR and those who are unexposed. Thus, our findings of lower scores in the SGA than in the control group, using the 10th percentile as cutoff, are probably an underestimate of the true effect sizes of fetal growth restriction. SGA mothers in our study had no more pregnancy complications (preeclampsia, hypertension, diabetes, infections) than the mothers of controls, an unsuspected finding. In accordance with our findings, neurocognitive development was found to be similar in 9- to 10-year-old children whether their mothers' pregnancies were complicated by hypertension/preeclampsia or not (Leitner et al., 2012).

Pyhälä et al. (2011) found no difference between preterm SGA or appropriate-for-gestational-age births at young adult age, using a large neuropsychological test battery, and these authors suggested the detrimental effects of being born preterm were irrespective of intrauterine growth. Still, the etiology of being born preterm SGA and term SGA is different, as the preterm infant is more vulnerable and more susceptible to adverse events such as respiratory distress syndrome due to immature lungs, infection, inflammation, hypoglycemia and neonatal encephalopathy, increasing the risk of perinatal brain injury (Volpe, 1995).

The current study is a geographically based, 3-year cohort study. The prospective longitudinal design and the use of a comprehensive standardized neuropsychological test battery are some of the strengths of this study. We had a participation rate that is regarded acceptable in epidemiologic cohort studies, that is, 64% of the SGA subjects and 74% of the controls met for neuropsychological assessment (Fewtrell et al., 2008), although higher retention would have been preferable. Also, there were no significant differences in clinical characteristics between participants and non-participants, making selection bias less likely.

There are some limitations to our study; one is the rather low number of subjects compared to the number of tests. To balance the risk of type I and II errors, we adopted a conservative alpha ($p < .01$) to all analyses on subtest level. Because of the original intentions of this long-term follow-up study, we had strict inclusion/exclusion criteria, and excluding mothers expecting their first child and multiple pregnancies is a limitation. As we also excluded subjects with malformations, serious medical conditions and cerebral palsy, this may further underestimate the true difference in outcome between the SGA and non-SGA group. We also acknowledge that health care standards in the middle of the 1980s differ from today's standards, which may be a restriction on generalizability of the results. We did not obtain good fit of our model after performing the CFA, and analyses on the domain level must be interpreted with caution. We, therefore, chose to discuss results on both subtest and domain levels.

In our study, the SGA group obtained significantly lower scores on one of the nine attention tests: the TMT 3 (letter sequencing), and three of the 20 executive tests: the WMS mental control, the Stroop 3 (inhibition), and the Design Fluency test. The SGA group obtained significantly lower scores on tasks requiring processing speed, working memory, inhibition of a more pre-potent response, and mental flexibility. Even though differences were small and effect-sizes

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Table 3. Neuropsychological test scores in the SGA ($n = 58$) and the control group ($n = 81$)

		SGA		Controls			
Domain	Individual test	Adj mean	95% CI	Adj mean	95% CI	Effect-size	*p*-Value
Attention	Pasat Correct*	42.4	39.0, 45.8	45.5	42.6, 48.4	0.05	0.175
	Stroop 1 Naming colours	30.5	29.0, 32.0	28.6	27.3, 29.8	−0.34	0.058
	Stroop 2 Reading colour names	23.2	21.9, 24.4	22.5	21.5, 23.6	−0.11	0.433
	TMT 1 Visual scanning*	20.2	18.9, 21.5	18.0	16.9, 19.1	−0.44	0.016
	TMT 2 Numbers*	34.6	31.8, 37.4	30.8	28.5, 33.2	−0.40	0.046
	TMT 3 Letters	33.9	31.6, 36.3	28.6	26.6, 30.7	−0.61	*0.001*
	CPT Omissions*	3.5	2.5, 4.5	2.7	1.8, 3.5	−0.35	0.217
	CPT Commissions*	17.0	15.3, 18.7	17.8	16.4, 19.2	0.15	0.462
	CPT reaction time*	315.4	305.1, 317.8	317.8	309.1, 326.4	0.02	0.724
Executive	WMS-III Mental Control	24.2	22.8, 25.5	26.8	25.7, 27.9	−0.56	*0.004*
	WMS-III Spatial Span	16.7	15.9, 17.5	17.6	16.9, 18.3	−0.29	0.091
	Design Fluency Total Score	29.0	27.3, 30.6	32.3	30.9, 33.7	−0.53	*0.003*
	Stroop 3 Inhibition	55.3	52.2, 58.4	49.7	47.0, 52.3	−0.48	*0.007*
	Stroop 4 Inhibition and Switching	63.0	58.9, 67.1	58.3	54.8, 61.7	−0.31	0.082
	TMT 4 Numbers and Letters	71.1	65.2, 77.0	65.7	60.7, 70.7	−0.29	0.167
	Verbal Fluency Total Correct	36.9	34.1, 39.8	37.7	35.3, 40.1	−0.11	0.619
	WCST Number of categories*	5.9	5.6, 6.1	5.7	5.5, 5.9	0.18	0.227
	WCST Trials to complete first*	11.8	9.2, 14.4	15.8	13.6, 18.0	0.33	0.023
	WCST Failure to maintain set*	0.5	0.3, 0.7	0.5	0.3, 0.7	−0.06	1.000
	WCST Total correct*	70.0	68.0, 72.0	70.0	68.3, 71.7	−0.02	0.985
	WCST % perseverative responses*	8.5	7.2, 9.8	10.3	9.2, 11.4	0.38	0.035
	WCST % perseverative errors	8.5	7.3, 9.6	9.7	8.8, 10.7	0.33	0.092
	WCST % non-perseverative errors*	9.5	7.8, 11.3	10.1	8.6, 11.6	0.01	0.645
	Tower Time to first move*	41.6	36.3, 46.9	35.1	30.6, 39.6	−0.31	0.069
	Tower Number of moves*	137.9	127.7, 148.1	144.0	135.4, 152.6	0.17	0.365
	Tower Rule breaking*	0.52	0.3, 0.8	0.44	0.2, 0.6	−0.12	0.604
	Tower Total time*	437.8	403.8, 471.8	422.3	393.5, 451.0	−0.15	0.493
	Tower Total Correct*	18.1	17.2, 19.0	17.7	16.9, 18.4	0.15	0.487
	WAIS-III Letter-number sequencing	8.4	7.8, 9.0	8.9	8.4, 9.4	−0.22	0.152
Language	Boston Naming Test Correct	49.6	48.6, 50.6	50.1	49.2, 50.1	−0.16	0.478
	WAIS-III Vocabulary	31.8	29.9, 33.7	34.8	33.2, 36.5	−0.37	0.019
	WAIS-III Similarities	17.7	16.2, 19.1	20.1	18.8, 21.3	−0.38	0.015
Visual-spatial/motor*	Rey Copy*	33.1	32.6, 33.7	33.7	33.2, 34.1	−0.28	0.160
	VMI Copy*	26.4	25.8, 27.0	27.0	26.5, 27.5	−0.31	0.099
	VMI Visual Matching*	28.5	28.0, 28.9	28.2	27.9, 28.6	0.08	0.516
	VMI Motor coordination*	28.3	27.8, 28.7	29.2	28.8, 29.5	−0.66	*0.004*
	GPB Time total*	67.6	65.5, 69.7	64.0	62.2, 65.8	−0.36	0.012
	TMT 5 Motor speed*	23.3	21.4, 25.1	21.7	20.1, 23.3	−0.22	0.194
Memory	WMS-III Auditory Immediate Memory	93.1	89.5, 96.7	99.3	96.3, 102.4	−0.48	0.010
	WMS-III Auditory Delayed Memory	95.9	92.8, 99.0	99.5	96.8, 102.1	−0.35	0.087
	WMS-III Auditory Recognition	94.1	90.4, 97.8	100.0	96.9, 103.1	−0.47	0.018
	WMS-III Visual Immediate Memory	90.3	87.0, 93.6	92.0	89.2, 94.7	−0.15	0.443
	WMS-III Visual Delayed Memory*	87.7	84.4, 91.0	88.7	85.9, 91.4	−0.09	0.658
	REY Immediate Recall*	18.6	16.9, 20.2	21.2	19.8, 22.6	−0.48	0.016
	REY Delayed Recall*	18.1	11.4, 24.8	26.6	21.0, 32.3	−0.22	0.057
	REY Recognition*	20.7	20.2, 21.2	21.1	20.7, 21.5	−0.26	0.201

Note. A General Linear Model was used to compare groups, with SES, age at assessment and gender as covariates. Scores are presented as raw score in most tests, except the WMS-III: auditory immediate memory, auditory delayed memory, auditory recognition, visual immediate memory and visual memory, which are presented as scaled scores (population mean = 100, $SD = 15$). Log transformations were made for non-normally distributed data, but these are presented as raw data in the table to simplify interpretation of scores. Multiple imputations were applied for missing data. Adjusted means are presented. Effect sizes were calculated by the Glass' delta (Δ).

SGA = Small for gestational age; WMS-III = Wechsler Memory Scale-III; WAIS-III = Wechsler Adult Intelligence Scale-III; DF = Design Fluency; WCST = Wisconsin Card Sorting Test; VF = Verbal Fluency; TMT = Trail Making Test; CPT = Conner's Continuous Performance Test; VMI = Visual Motor Integration; GPB = Grooved Pegboard.

*Not included in final extraction of domain scores (see Fig. 1; Table 1)

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Table 4. Cognitive domain scores in the SGA group ($n = 58$), measured as effect size (difference from control mean).

Domain	Effect size	95% CI for effect size	*p*-Value
Attention	−0.35	−0.57, −0.13	0.017
Executive	−0.27	−0.44, −0.10	0.022
Language	−0.27	−0.54, −0.01	0.058
Memory	−0.35	−0.56, −0.14	0.018

Note. Domain scores were calculated by averaging z-scores from individual neuropsychological tests in each category. Categorization was based on theory and confirmatory factor analysis. A General Linear Model was used to compare groups with socioeconomic status (SES), gender, and age at testing as covariates. Log transformations were used for non-normally distributed data. Multiple imputations were applied for missing neuropsychological test data. Effect sizes were calculated by the Glass' delta (mean and *SD* from the control group).
SGA = Small for gestational age; CI = Confidence interval.

modest, we speculate that the lower attention- and executive scores seen in the SGA group in the present study may be related to functional problems as seen in ADD (attention deficit disorder) and ADHD. Lund et al. (2011) and Lund et al. (2012) found higher psychiatric morbidity compared to non-SGA controls in the same SGA group at age 19, with anxiety (13%) and ADHD (7%) as the most prevalent diagnoses. In the control group, the frequency of these diagnoses was 3% and 0%, respectively. The SGA group had higher inattention, hyperactivity and total scores on the self-report ADHD rating scale compared with controls (Lund et al., 2011), and they also reported more attention problems than controls on the Achenbach System of Empirically Based Assessment (ASEBA) (Lund et al., 2012).

We speculate as to why being born SGA may affect some areas of attention and executive functioning, whereas other areas are unaffected. Our results showed no difference between the groups on the PASAT test, which is a potent measure of attention, but also puts demands on working memory. The SGA group also obtained lower scores compared with controls on other working memory tests used in this study, but only the mental control subtest of the WMS-III was significantly lower. The SGA group actually obtained higher scores than controls on some attention- and executive tests, such as the CPT commission and reaction time, the WCST and the Tower tests. This result suggests that impulse-inhibition, problem solving and rule learning seem to be equal, and maybe even better, in the SGA group compared to controls. Still, all attention and executive tests where the SGA group performed more poorly than controls also put demands on performance speed. It may be that their disadvantage is caused by slower performance on an attention-demanding task.

Viggedal et al. (2004) also looked at neuropsychological functioning in young adults who were born SGA, but did not find any differences between SGA and control participants on attention. That finding was based only on the results from one test, the Conner's CPT, where there also were no difference between the groups in our study. Our results showed the most pronounced difference between the groups on the Trail Making Test (TMT), which Viggedal et al. did not use. This test assesses different aspects of attention than the CPT, with fewer demands on sustained attention, and more on processing- and performance speed and the ability to inhibit distracting items. Several studies of adolescents born SGA failed to identify more attention problems in SGA subjects relative to controls based on neuropsychological tests or self- and parent-reported questionnaires (Kulseng et al., 2006; O'Keeffe, O'Callaghan, Williams, Najman, & Bor, 2003). In our study, we were able to demonstrate such differences, albeit small and only in a few of the attention tests. Our findings should be interpreted in light of the already described misclassification of using SGA as a proxy for FGR.

The Design Fluency test demands initiation and flexibility in creating a strategy to successfully produce different designs without perseveration. In fact, Geva et al. (2006) reported that 9-year-old SGA subjects showed problems with similar executive function tasks in addition to attention, visual/spatial-motor-, and verbal skills relative to controls. However, the Design Fluency task also puts demands on visual-spatial abilities and especially visual-constructive abilities. Sommerfelt et al. (2002) found that five year old SGA children obtained lower scores than age-matched controls on visual-spatial and manual dexterity tasks, but not on any other neuropsychological tests. Our SGA group obtained lower scores relative to non-SGA controls on most subtests assessing visual-spatial, visual-constructive abilities, and fine motor skills, with the most severe problems on the VMI motor coordination subtest. However, the SGA group actually obtained marginally higher scores than controls on the VMI visual matching task, not statistically significant. One explanation for this finding is that the visual matching task places less demand on eye-hand coordination and visual-constructive skills than do the other VMI subtests. To our knowledge, no other study has reported results on this specific function in an adult SGA population, but several studies have shown poorer performance among preterm born children and adolescents on the VMI, in addition to a relationship between birth weight and VMI scores in preterm born individuals (Foulder-Hughes & Cooke, 2003; Taylor, Minich, Bangert, Filipek, & Hack, 2004).

Memory functions were also affected in our SGA group compared to controls. These results are consistent with Viggedal et al. (2004) who report that SGA participants needed more trials to remember a wordlist than the control group, with both short-term and long-term verbal memory affected. In our study, group difference only reached significance on the auditory immediate memory scale. The SGA group did not perform significantly more poorly on the visual memory subtests, but the SGA group obtained lower scores on all tests assessing memory compared to controls. Viggedal et al. (2004) reported that their SGA young adults had problems with figurative learning (i.e., Rey Complex Figure) relative to controls. In our study, the SGA group performed poorer than controls on all subtests of the Rey Complex Figure, but differences did not reach significance. The study by Viggedal et al. (2004) differed from ours as they had a more

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conservative definition of SGA (birth weight <-2 *SD* for gestational age (i.e., 2.28%ile), the mean birth weight was lower in the SGA group and their sample was smaller than ours (17 SGAs and 18 controls). Geva et al. (2006) and Geva, Eshel, Leitner, Fattal-Valevski, and Harel (2008) also found that SGA children exhibited memory problems. In their study, these problems seemed to be restricted to verbal short-term memory, especially the encoding of auditory information (verbal working memory), consistent with our results.

Young adults born SGA have an increased risk of neuropsychological deficits, especially within the memory domain. Our results indicate that the effect of fetal growth restriction on the brain may be comprehensive and have a functional impact on cognition that lasts into young adulthood. As our results showed no significant relationships between birth weight and neuropsychological functioning within any of the groups, we speculate that it may not be birth weight in itself that accounts for these cognitive differences, but being born after fetal growth restriction. Although the differences in scores are small, the inferior results on several tests may affect school performance, as our results indicate that more SGA subjects than controls needed special education in school (Lohaugen et al., 2013).

CONCLUSION

We have found that being born SGA at term was associated with lower scores on several neuropsychological tests at a young adult age, especially on tests assessing attention, executive functions, auditory memory, performance speed and fine motor function. These findings suggest that fetal growth restriction may have long lasting effects on brain development and cognitive functioning.

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Supplementary Materials

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1355617714000034

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