

Relationship between hippocampal subfield volumes and memory function in adults born preterm with very low birth weight (VLBW)

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Abstract

Background: Being born preterm with very low birth weight (VLBW) is related to aberrant brain development. Hippocampus is a brain region particularly vulnerable to injury, for instance from consequences following preterm birth. The hippocampus is a complex structure with distinct subfields related to specific memory functions which are differently affected by neuropathological conditions. The relationship between deviations in hippocampal subfields and memory function has not been studied in adults born preterm with VLBW previously.

Aims: In this long-term follow-up study of a geographically based cohort (birth years 1986–88) of VLBW individuals and term born controls with normal birth weight, the main aim was to examine group differences in memory function and hippocampal volumes at age 26 years. We also explored hippocampal structure-function relationships in the VLBW group.

Methods: Fifty-two VLBW and 82 control individuals aged 26 years were examined clinically of whom 44 VLBW and 70 controls had high-quality structural cerebral MRI at 3T. The participants were assessed with subtests from Wechsler Memory Scale and Cambridge Neuropsychological Test Automated Battery on verbal, visual and working memory. From the T1 weighted 3D images, hippocampal subfield volumes were estimated in FreeSurfer 6.0. In addition to group comparisons, partial correlations were performed in the VLBW group between hippocampal subfields' volumes and neonatal risk factors, and between reduced hippocampal subfields' volumes and performance on the memory tests.

Results: Adults with VLBW had lower verbal, visual and working memory scores compared with term born control adults. Absolute hippocampal total and most subfield volumes were smaller in the VLBW group than in the control group, but with different findings in men and women. When adjusting for intracranial volume, left and right cornu ammonis fields and left dentate gyrus were smaller in VLBW women, while the right subiculum was smaller in VLBW men compared with control women and men, respectively. There was a negative correlation between days on mechanical ventilation and volume of the left subiculum in the VLBW group. Smaller left dentate gyrus volume was associated with lower visual memory performance in the VLBW group.

Conclusions: Adults born preterm with VLBW had lower performance on memory tests and smaller hippocampi compared with term born controls, and volume of dentate gyrus was associated with visual memory. Hippocampal subfield volumes seem to be differently affected following preterm birth in VLBW men and women.

Introduction

Being born preterm with a very low birth weight (VLBW <1500 gram) is related to an increased risk of aberrant brain development [1,2]. Even though there have been great improvements in perinatal medicine including medical treatment and care of very preterm born babies leading to increased survival and less severe brain damage, the incidence of more subtle diffuse brain injuries in grey and white matter is still high [3]. These injuries may have long-term consequences for early brain development resulting in different neuroimpairments, which include reduced general cognitive functioning [4], specific

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learning disabilities due to deficits in memory and executive functions [5-7], and attentional and mental health problems [3,8,9].

Brain structures have different vulnerability to injuries, and one of the more vulnerable structures is the hippocampus [10-13]. The hippocampus is a complex, heterogeneous structure situated bilaterally in the medial temporal lobe and responsible for normal development of learning and memory function [14-16]. The hippocampus is divided into different anatomically and functionally specialized, but highly interconnected subfields; the subiculum, presubiculum, parasubiculum, the cornu ammonis (CA) fields 1-4, and the dentate gyrus (DG) [17]. These subfields are considered to have distinct functions in short- and long-term memory with CA2/3 and CA4/DG more involved in short term memory while CA1 and subiculum more involved in retrieval and delayed episodic memory [18-21]. The CA1 and subiculum volumes have also been linked to delayed visual and verbal memory in older adults [20] and the left CA fields to verbal memory in healthy adults [21].

The hippocampus is sensitive to insults of hypoxia-ischemia [11-13] which are common complications following preterm birth [22]. Further, other complications of preterm birth such as hypoglycemia, stress, and undernutrition are factors that may have negative effects on normal hippocampal development [23,24].

Consequently, disturbances or damage to the developing hippocampus may contribute to neuroimpairments including memory deficits often reported in preterm born individuals [25,26]. We have previously reported reduced total hippocampal volumes (Bjuland, Rimol, Løhaugen, & Skranes, 2014) which was related to reduced memory function at age 19-20 years in the present geographical cohort of young VLBW adults (Aanes, Bjuland, Skranes, & Løhaugen, 2015). Although the role of the hippocampus in working memory is debated [27], we found a relationship between the volume of the right hippocampus and working memory ability in these VLBW young adults at age 19-20 years [6].

However, advances in MRI processing software [28,29] have made it possible to study hippocampal subfields in clinical studies. Examples are studies that have investigated hippocampal subfield development from 4-22 years of age [30], the relationship to learning and memory function in healthy children [31], examined survivors of pediatric brain tumors [32] and adults with subjective memory impairment [33]. The studies mentioned above demonstrate that MRI based subfield volumetry provides the opportunity to non-invasively study relationships between specific hippocampal subfields and different memory functions. To our knowledge, hippocampal subfields have not been investigated in preterm born individuals, except for our study of school-aged VLBW children born in the early 2000s [34]. Reduced volumes of the dentate gyrus, which were positively associated with spatial working memory, was found in these VLBW children. For older cohorts of preterm born individuals, who have not experienced advanced neonatal medicine, even more pronounced abnormal structure-function relationships related to injury to individual hippocampal subfields may exist and should be investigated.

The main aim of the present study was to investigate memory function and hippocampal subfields in adults born preterm with VLBW and term born controls at age 26 years. Secondly, we wanted to examine if hippocampal subfield volumes were associated with neonatal risk factors, such as birth weight, number of days in the neonatal intensive care unit (NICU) and days on mechanical ventilation in the VLBW group. Thirdly, we wanted to investigate if there were any structure-

function relationships between hippocampal subfields that were significantly reduced in the VLBW group compared to the control group and memory performance. We predicted reduced memory scores in the preterm born group. We also hypothesized that specific subfields of the hippocampus are vulnerable to injury or abnormal development after preterm birth, resulting in reduced hippocampal subfields in the VLBW group. Next, we expected an association between neonatal risk factors that may affect postnatal brain development, and hippocampal subfield volumes, and lastly; we predicted associations between reduced hippocampal subfield volumes and lower memory test performance suggesting possible brain structure-function relationships in the VLBW group.

Material and methods

Participants

The participants were part of a one of the first long-term follow-up studies of preterm born VLBW children where cerebral MRI was combined with multidisciplinary assessments at different ages. The study, headed by Professor Ann Mari Brubakk at the Norwegian University of Science and Technology, Trondheim, Norway consisted of three year-cohorts (born in 1986-1988) of VLBW children and term born controls examined clinically and with cerebral MRI at ages one [35], six [36], 14-15 [37-40], 19-20 [4,6,26] and 23 years of age [41,42]. Cortical thickness and white matter pathways have been reported in the same population at age 26 [43]. The study population investigated at the 26-year follow-up has previously been fully described [44] and only a brief summary is provided here.

VLBW group: Preterm born individuals with VLBW ($BW \leq 1500g$) who were admitted to the neonatal intensive care unit (NICU) at St. Olavs hospital, Trondheim University Hospital in Norway in 1986-1988 were included in the cohort. Thirty-three (27 %) of the 121 VLBW neonates died in the neonatal period, two were excluded at birth due to congenital syndromes or malformations while two were excluded for follow-up due to severe cerebral palsy (CP). Consequently, 84 VLBW were eligible and invited for follow-up at 26 years of age, and 55 agreed to participate (65 %). The results from three adults with mild CP were excluded from the present study leaving 52 (26 men) participants. Of these, 51 completed the cognitive assessment and 48 consented to cerebral MRI. T1 weighted scans from four participants were excluded due to inferior image quality, leaving 44 adults (24 men) with MRI scans of appropriate quality for hippocampal sub-segmentation.

Control group: The control participants were recruited from a 10 % random sample of term born (gestational age > 37 completed weeks) children born in 1986-1988 with a birth weight above the 10th percentile. The participants' mothers were enrolled in a multi-center study of 1200 multiparous women with singleton pregnancies before week 20 of pregnancy. In the original cohort, 120 newborns were included as term born controls. Two were excluded due to congenital malformations, and of 118 eligible, two could not be reached for the 26-year assessment. Eighty-two controls (69 %) agreed to participate, and of these 81 individuals (37 men) completed the cognitive assessment while 77 consented to cerebral MRI. Scans from five participants were excluded due to poor image quality leaving 72 controls (32 men) with MRI scans for hippocampal subsegmentation.

Non-participants: Of those eligible for assessment at age 26, 29 VLBW and 36 controls were lost to follow-up. In the VLBW group, participants did not differ from the non-participants with regards to birth weight, gestational age, and other neonatal variables, total IQ

or SES. However, there were more VLBW men ($n = 21$) who did not participate than VLBW women ($n = 8$).

In the control group the non-participants had lower gestational age (39.3 weeks versus 39.9 weeks; $p = .019$) and lower IQ (105 vs 91; $p < .0001$) than those who participated.

Neuropsychological assessment

The neuropsychological assessment was performed by three master students in psychology supervised by a trained neuropsychologist. All were blinded to group adherence and MRI findings. Memory function was assessed with the Logical Memory subtest from the Wechsler Memory Scale, 3rd edition (WMS-III) [45] for verbal memory and selected scores from the computerized tests Paired Associates Learning (PAL) and Spatial Working Memory (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) [46,47], assessing visual and working memory, respectively. The memory tests are described in Supplemental material. Full scale IQ scores (FSIQ) based on a full Wechsler Adult Intelligence Scale (WAIS-III) from the 19-year of age assessment [4] was used as a measure of general cognitive ability. The WAIS-III was administered during one session with a fixed subtest order by a trained neuropsychologist who was blinded to group adherence and neonatal history. The FSIQ, which is based on the results from 11 subtests, is considered the most reliable measurement of global intellectual functioning. For those who did not participate at the 19-year follow-up (about 20% of participants), estimated IQ was based on the Wechsler Abbreviated Scale of Intelligence (WASI, Norwegian version) assessed at age 26 years.

Neonatal variables

Neonatal variables associated with poor long-term neurological outcome after preterm birth were recorded. These included birth weight, gestational age at birth, Apgar scores, number of days on mechanical ventilator, total days of stay in the neonatal intensive care unit (NICU) and any presence of brain pathology on neonatal ultrasonography.

Socioeconomic status

Socioeconomic status (SES) ranging from 1 (low) to 5 (high) was calculated according to Hollingshead two factor index of social position (adapted to today's categories) based on the education and occupation of one parent or the mean index of both parents [48]. Parental SES was calculated at the 14-15-year assessment, and supplemented at 19-20 years for 3 participants in each group. SES scores were missing for 6 VLBW adults and 9 controls at the 26-year follow-up for whom SES scores were imputed using the mean SES score of the respective group.

Magnetic resonance imaging

Image acquisition: A 3T Siemens Skyra scanner with a 32 channel head coil was used to acquire the T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence with repetition time (TR) = 2730 ms, echo time (TE) = 3.45 ms, inversion time = 1000 ms, flip angle = 7°, voxel sizes of 1 x 1 x 1.33 mm³, and field of view (FOV) = 256 mm. All scans were visually inspected by trained personnel and only scans with sufficient quality were used in further processing.

Hippocampal subfield segmentation: The freely available FreeSurfer image analysis suit version 6.0 (<http://surfer.nmr.mgh.harvard.edu>) [49-51] with the hippocampal subfield segmentation module [28] was used to process the MRI scans. The scans are first motion corrected, non-brain tissue is removed, Talairach transformation and segmentation of subcortical white matter and deep gray matter

volumes are performed [51-54] before the subfield segmentation algorithm segments the hippocampus into subfields based on Bayesian inference from a high-resolution probabilistic atlas of *ex vivo* MRI data [28]. The module provides the following twelve hippocampal subfield labels for each hemisphere: CA1, CA2/3, CA4, the molecular layer (ML), the granule cell layer of the dentate gyrus (GC-DG), subiculum, presubiculum, parasubiculum, fimbria, the hippocampal-amygdaloid transition area (HATA), hippocampal tail, and hippocampal fissure. It also provides volume of the whole hippocampus, which includes all subfields except for the hippocampal fissure. This method shows moderate correlations with manual delineations [55,56]. In our study, a two-step quality control of subfield segmentations, as described in Cao et al. was performed for each individual [57]. The subfield segmentations were first manually inspected and volumes with obvious errors in location of the hippocampus or subfield assignments were excluded. This resulted in exclusion of two controls with bilateral segmentation errors and one control participant's left hippocampal subfields. Secondly, we performed outlier analyses according to Cao et al., where extreme subfield volumes were excluded. The latter step did not disclose any outliers.

To reduce the number of hippocampal subfield volumes, these were merged and regrouped into three combined subfields: the CA field, DG and Subiculum as suggested by Mueller *et al.* [58]. The rationale for doing this is that some of the smaller FreeSurfer subfields have shown to be less reliable when based solely on T1-weighted images as in this study [28,59,60]. The reclassification was done in the following way: CA field: CA1 + CA2/3 + Molecular layer + Subiculum; Dentate gyrus (DG): GC-DG + CA4; Subiculum = Presubiculum (see Figure 1. for illustration). This is a classification also more in line with other automated segmentation methods, such as the Automatic Segmentation of Hippocampal Subfields (ASHS) [29].

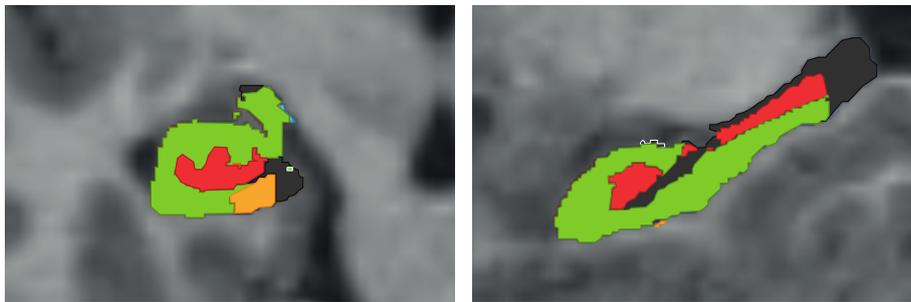
FreeSurfer also provides an estimated total intracranial volume (ICV) which we used for corrected volumes in the statistical analyses.

Statistical analysis

IBM SPSS Statistics version 25 was used to perform the statistical analyses. Differences in group variables were analyzed with the Student *t* test or Mann-Whitney U test depending on their distribution. Univariate general linear models were used for between-group comparisons of memory test scores and hippocampal subfield volumes. Group was added as a fixed factor and sex and age at assessment were added as covariates. For the memory tests, SES was also added as a covariate, while age was excluded as covariate when using scaled scores from the Wechsler Memory Scale. The hippocampal subfields were analyzed with and without intracranial volume as a covariate providing corrected and absolute volumes, respectively. We found a significant group*sex interaction for hippocampal volumes, and thus explored group differences in hippocampal volumes and memory performance for men and women separately. Effect size was calculated with Cohen's *d*. Cohen's $d \geq 0.4$ was considered a medium effect size and $d \geq 0.8$ a large effect size.

In the VLBW group, partial correlation analysis corrected for sex, intracranial volume and age at scan were used to explore associations between hippocampal volumes and continuous neonatal variables, except for days on mechanical ventilation where we used Spearman's rho. For the number of days in NICU and birth weight the degree of immaturity, i.e. gestational age at birth, was added as a covariate. Partial correlations were also performed to evaluate possible structure-

Combined subfields



Original FS6.0 subfields

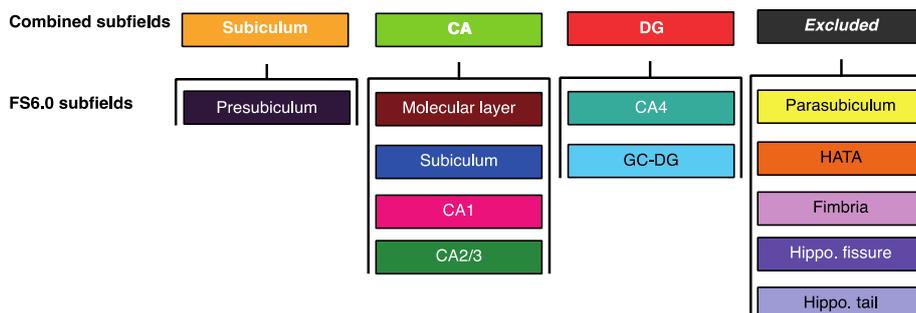
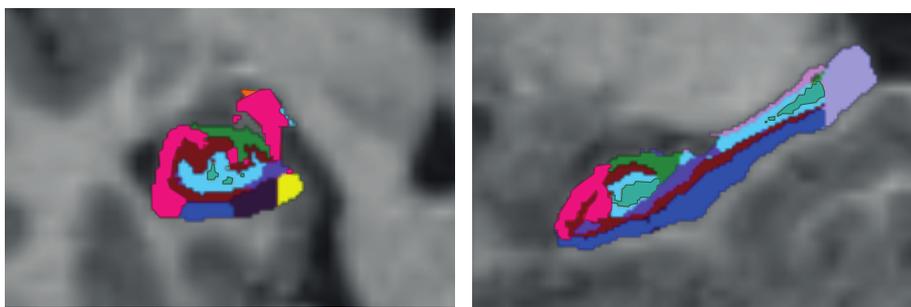


Figure 1. Combined hippocampal subfields based on original FreeSurfer (FS) 6.0 labels. The combined subfields used in the present analyses are shown in the upper row, while the original subfield labels from FreeSurfer are shown in the lower panel. Among the combined subfields the Subiculum is equal to the FreeSurfer label Presubiculum; The CA includes the FreeSurfer labels Molecular layer, Subiculum, CA1 and CA2/3; The DG consists of the FreeSurfer labels CA4 and GC-DG; while the HATA, fimbria, hippocampal fissure and hippocampal tail were all excluded from analyses

Abbreviations: CA = Cornu Ammonis; DG = Dentate gyrus; GC-DG = Granulate cells of the dentate gyrus; HATA = Hippocampal-Amygdaloid Transition Area.

function relationships between the reduced hippocampal subfields and memory test scores in the VLBW group.

We considered two sided p-values ≤ 0.05 as significant and corrected for multiple comparisons using the Bonferroni method. Bonferroni adjusted p-values of significance for the group comparisons of memory test scores were $(0.05 / 4) = 0.0125$, for the subfield volume analyses $(0.05 / 6) = 0.0083$ and for the possible structure-function relationships $(0.05 / 16) = 0.003125$. The Bonferroni corrected p-value for the correlation analyses between neonatal variables and hippocampal subfield volumes was $(0.05 / 24) = 0.002$.

Ethics

The Code of Ethics of the World Medical Association (Declaration of Helsinki) was followed when conducting this study. The Regional Committee for Medical Research and Ethics approved the study protocol (project number: 2013/636/REK midt) and the participants gave written, informed consent.

Results

Clinical characteristics

Clinical group characteristics are presented in Table 1. As expected, significant differences in mean birth weight, gestational age and Apgar scores were found between the two groups. The VLBW group had mean birth weight of 1227 (SD 240) grams and gestational age of 29 (SD 2.6) weeks, while the control group had mean birth weight of 3714 (SD 438) grams and gestational age of 40 (SD 1.2) weeks. The VLBW group had lower parental SES than the control group. Thirty-one VLBW participants were in need of mechanical ventilation with a mean period of 8 days on ventilator (median 3 days). Seven VLBW participants had intraventricular hemorrhage (IVH) in the neonatal period, four with grade 1, two with grade 2 and one with grade 4 IVH. The VLBW adults had lower mean IQ than controls (IQ score 91 vs 105, $p < 0.0001$), and four VLBW individuals had

IQ scores below 70, i.e. mental retardation. There were no significant group differences regarding sex or age at assessment.

Memory assessment

The results from the memory tests for the two groups are presented in Table 2. The VLBW adults had lower immediate and delayed verbal memory measured by the logical memory test compared with controls. They also had reduced visual and spatial working memory assessed by the two CANTAB tests. When we excluded four participants with IQ <70 in the VLBW group, the visual memory (p = .014) and spatial working memory (p <.0001) remained significantly lower in the VLBW group. When exploring group differences based on sex, the VLBW men performed worse than men in the control group on visual memory (p =.041), while both VLBW men and women performed worse than controls respectively on the spatial memory (p = .001 for women and p = .004 for men). The group difference in verbal memory performance did not survive Bonferroni correction for multiple comparisons; however the effect sizes were moderate (d = 0.41) for these subtests.

Hippocampal total and subfield volumes

The VLBW adults had significantly reduced hippocampal total volumes bilaterally compared with term born controls. Also, the absolute volumes of the right and left CA field, and left DG and right subiculum were lower in the VLBW group (Supplemental material, Table S1). However, total intracranial volume was also significantly lower in the VLBW group compared to controls. After correcting

for intracranial volume, total hippocampal volumes were no longer significantly reduced in the VLBW group, while the left CA field was still reduced (Table 3A), although it did not survive Bonferroni correction (d = 0.40).

We found a significant group versus sex interaction for several hippocampal subfields which necessitated subgroup analyses split on sex. The VLBW women had smaller total hippocampal volumes and reduced absolute volumes of CA fields and DG bilaterally compared with control women. Among men, only the absolute volume of the right subiculum was smaller in the VLBW group (Table S1). After adjusting for ICV, all group differences in hippocampal subfields, except the right DG in women, remained significant, indicating reduction in specific hippocampal subfield volumes in the VLBW group (Tables 3B & 3C). When adjusting for multiple comparisons with Bonferroni no group differences were significant, although several subfield volumes in women had moderate effect sizes.

The absolute volumes of all the twelve hippocampal subfields segmented by FreeSurfer for the two study groups are shown in Supplemental material Table S2.

Associations between neonatal variables and hippocampal subfield volumes in the VLBW group

There was a significant negative correlation between days on mechanical ventilation and volume of the left subiculum (r = -.427, p

Table 1. Clinical characteristics of the two study groups

	VLBW group			Control group			p-value
	n	Mean (SD)	Range	n	Mean (SD)	Range	
Birth weight (grams)	52	1227 (240)	645 – 1500	82	3714 (438)	2670 – 5140	<.0001
Gestational age (weeks)	52	29 (2.6)	25 – 35	70	40 (1.2)	37 – 43	<.0001
Sex male n (%)	52	26 (50 %)	-	70	37 (45 %)	-	.581
Socioeconomic status (SES) ^a	52	3.4 (1.2)	1 – 5	82	3.9 (1.0)	2 – 5	.006
APGAR 1 minute	51	6.5 (2.3)	0 – 9	77	8.9 (0.4)	7 – 9	<.0001
APGAR 5 minute	51	8.3 (1.4)	1 – 10	78	9.8 (1.1)	1 – 10	<.0001
Days in NICU n	51	73 (57)	23 – 386				
Days on mechanical ventilator n ^b	31	8 (6)	1 – 44				
IVH n (%)	52	7 (13 %)	-				
Age at clinical assessment (years)	51	26.4 (0.5)	25.5 – 27.5	81	25.5 (0.3)	25.8 – 27.5	.116
Age at MRI (years)	44	26.3 (0.7)	25.2 – 28.4	70	26.4 (0.4)	25.6 – 27.3	.322
Full scale IQ ^c	52	91 (15)	62 – 127	82	105 (13)	82 – 145	<.0001

Participant characteristics; Student’s T-test was used for parametric data, Mann-Whitney U test for non-parametric data, Pearson’s Chi-Square for categorical data. *Abbreviations:* VLBW = very low birth weight; NICU = neonatal intensive care unit; IVH = intraventricular hemorrhage; IQ = intelligence quotient.

^aSES was calculated according to Hollingshead’s two factor index of social position, based on education and occupation of one parent, or the mean index of both parents. ^b31 (60%) of the 52 VLBW were in need of mechanical ventilation in the neonatal period. ^cFull scale IQ scores from WAIS-III assessment at 19 years of age supplemented with estimated Full IQ (WASI) from 26 years for those (20%) who did not participate at age 19.

Table 2. Memory test results in the VLBW and control groups

Memory test	VLBW group (n = 51)		Control group (n = 81)		Cohen’s d	p-value
	Mean	95 % CI	Mean	95 % CI		
Verbal Memory						
- Immediate (Logical Memory I)	9.5	8.7 – 10.2	10.6	10.0 – 11.3	0.41	.019
- Delayed (Logical Memory II)	10.4	9.6 – 11.1	11.5	10.9 – 12.1	0.41	.016
Visual Memory^a						
- PAL total errors	9.2	7.1 – 11.3	5.1	3.7 – 6.5	0.64	.002
Working Memory^b						
- SWM errors	29.4	24.0 – 34.7	13.6	9.4 – 17.9	0.87	<.0001

General linear model with group as fixed factor and socioeconomic status and sex as covariates for the scaled scores in verbal memory tests, and group as fixed factor and socioeconomic status, sex and age at assessment as covariates for visual and working memory tests. Cohen’s d ≥ 0.4 is indicated in bold. *Abbreviations:* VLBW: very low birth weight; CI: Confidence Interval; PAL = Paired Associates Learning; SWM = Spatial Working Memory. ^an = 48 VLBW, 78 controls, ^bn = 49 VLBW, 77 controls.

Table 3. Hippocampal total and subfield relative volumes (mm³) in the two study groups (3A), and stratified analyses by sex (3B and C)

Table 3A		VLBW group			Control group			Cohen's d	p-value
		n	Mean	95 % CI	n	Mean	95 % CI		
Hippocampal total volumes									
Left hippocampal volume		44	3641	3560 – 3722	69	3704	3640 – 3767	0.23	.242
Right hippocampal volume		44	3752	3676 – 3828	70	3796	3736 – 3855	0.17	.384
Hippocampal subfields									
Left CA-field		44	1950	1900 – 1999	69	2017	1978 – 2056	0.40	.040
Right CA-field		44	2004	1957 – 2052	70	2059	2022 – 2096	0.35	.083
Left DG		44	592	576 – 608	69	610	597 – 622	0.35	.097
Right DG		44	624	607 – 640	70	623	611 – 636	0.02	.955
Left Subiculum		44	323	313 – 333	69	325	317 – 332	0.06	.772
Right Subiculum		44	307	299 – 316	70	315	308 – 322	0.31	.199
Total intracranial volume (cm³)		44	1627	1590 – 1664	70	1711	1682 – 1740	0.67	.001

Table 3B - WOMEN		VLBW group			Control group			Cohen's d	p-value
		n	Mean	95 % CI	n	Mean	95 % CI		
Hippocampal volumes									
Left hippocampal volume		20	3443	3319 – 3567	39	3559	3476 – 3643	0.37	.151
Right hippocampal volume		20	3539	3416 – 3662	39	3669	3585 – 3752	0.41	.110
Hippocampal subfields									
Left CA-field		20	1822	1748 – 1896	39	1945	1895 – 1995	0.65	.013
Right CA-field		20	1868	1792 – 1944	39	2001	1949 – 2052	0.68	.009
Left DG		20	560	535 – 586	39	594	577 – 611	0.51	.049
Right DG		20	581	555 – 606	39	609	591 – 626	0.42	.097
Left Subiculum		20	306	293 – 320	39	305	296 – 315	0.03	.962
Right Subiculum		20	300	286 – 315	39	301	291 – 311	0.03	.977
Total intracranial volume (cm³)		20	1505	1436 – 1574	39	1596	1548 – 1643	0.51	.044

Table 3C - MEN		VLBW group			Control group			Cohen's d	p-value
		n	Mean	95 % CI	n	Mean	95 % CI		
Hippocampal volumes									
Left hippocampal volume		24	3830	3711 – 3949	30	3873	3767 – 3978	0.11	.602
Right hippocampal volume		24	3926	3824 – 4028	31	3958	3868 – 4047	0.10	.652
Hippocampal subfields									
Left CA-field		24	2066	1993 – 2139	30	2103	2037 – 2168	0.16	.469
Right CA-field		24	2112	2048 – 2176	31	2137	2081 – 2192	0.13	.571
Left DG		24	620	598 – 642	30	629	610 – 649	0.13	.549
Right DG		24	657	635 – 679	31	643	624 – 662	0.20	.332
Left Subiculum		24	343	327 – 358	30	345	332 – 359	0.04	.795
Right Subiculum		24	315	304 – 326	31	331	322 – 341	0.47	.034
Total intracranial volume (cm³)		24	1758	1711 – 1804	31	1828	1787 – 1868	0.49	.027

General linear model with group as fixed factor and age at MRI and intracranial volume as covariates. Cohen's $d \geq 0.4$ is indicated in bold. *Abbreviations:* VLBW= very low birth weight; CI = confidence interval; CA = Cornu Ammonis; DG = dentate gyrus.

= .030) indicating that more days on ventilator were associated with lower subicular volume in the VLBW group. This finding remained significant when removing an outlier with 35 days on ventilator ($r = -.444, p = .026$) (the participant with 44 days on ventilator mentioned in Table 1 did not have MRI). However, the correlation did not survive Bonferroni correction. There were no associations between the other neonatal variables (i.e. gestational age, birth weight and days in NICU) and hippocampal subfield volumes.

Associations between reduced hippocampal subfield volumes and memory function in the VLBW group

Volume of the left DG was negatively correlated with visual memory assessed by PAL total errors from CANTAB ($r = -.374, p = .022$). This means that smaller volumes were associated with more errors on the visual memory test in the VLBW group. The correlation did not survive Bonferroni correction.

Discussion

The VLBW adults had reduced immediate and delayed verbal memory as well as reduced visual and spatial working memory compared with controls. Smaller absolute hippocampal total volumes and smaller absolute and relative subfield volumes of the bilateral CA fields, dentate gyrus and the right subiculum were uncovered in the VLBW adults compared with term-born adult controls. The subfield volume reductions were mainly found in VLBW women. Furthermore, there was a negative correlation between days in need of mechanical ventilation and volume of the left subiculum in the VLBW group. Reduced volume of the left dentate gyrus was associated with lower visual memory in the VLBW adults.

Strength and limitations

A major strength of this study is the prospective design where the study participants have been examined with cerebral MRI and clinical

assessments at regular intervals from childhood. We used quantitative MRI and a rather novel and recently improved algorithm for automatic hippocampal subfield segmentation. To our knowledge, this is the first study to explore hippocampal subfield volumes in adults born preterm with VLBW. Standardized tests were used to assess different aspects of memory function.

However, there are some limitations that need to be considered. First, the rather small sample size may have resulted in too little power to detect group differences of clinical importance that did not reach statistical significance, especially after Bonferroni correction for multiple comparisons. The likelihood of type II errors (false negative) is increased by the use of the rather conservative Bonferroni method on such a sample size so that real differences between groups may appear non-significant [61]. However, presenting uncorrected p-values only may increase the risk of type I errors or false positive results. In our study uncorrected p-values revealed consistently lower volumes and performance in the VLBW group compared with controls, which are biological plausible results and probably not due to chance. This was also supported by group differences of medium effect size when using Cohen's *d*, indicating that they may be of clinical importance.

Possible selection bias with regard to participants and non-participants cannot be excluded in our study. Although neonatal variables did not differ in VLBW participants and non-participants, VLBW non-participating men had lower IQ than those who participated (IQ 88 versus 96, $p = .108$). Previous studies of clinical groups have shown that participants with more school problems, lower education and SES are more likely to decline participation [62-64], making it possible that individuals with the lowest performance are lost to follow-up. This could indicate that the true group differences were underestimated in our study. However, since the same trend was observed among the participating controls, i.e. they also had higher IQ than non-participants in our study, the group differences could also be driven in the opposite direction.

The automated segmentation method has some advantages compared to manual segmentation which is more laborious, less reproducible and has potential bias (Mueller et al., 2018). However, automated segmentation also has some important limitations that need consideration. Although, the method has been proven appropriate and reliable in datasets with different resolution and contrast [28,65] and has shown decent correlations with manual methods (de Flores et al., 2015; Schmidt et al., 2018) as well as high test-retest reliability for all subfields except for the hippocampal fissure [65], it is recommended to use a combination of T1 and T2-weighted high resolution data. In our study, only T1 images were available unfortunately. The accuracy on lower resolution structural MRI data of automated methods has been questioned [66]. There is also an ongoing debate on definitions of subfields and placement of boundaries [67]. We have tried to overcome these limitations by using well-defined composite subfields that are more in line with other automated protocols such as ASHS [29] as suggested by Mueller et al. (Mueller et al., 2018), and thereby excluding smaller, less reliable subfields such as the hippocampal fissure, parasubiculum, HATA and fimbria. Nevertheless, it is still a rather novel method and more studies are needed for validation of the subfield segmentation methods particularly in relevant clinical groups such as larger cohorts of preterm born individuals.

Memory function

We found lower verbal, visual and working memory performance in the VLBW adults compared with controls. This is in accordance

with our results from assessment of these groups at 19-20 years of age [6]. At age 19, a full Wechsler Memory Scale (WMS) was performed, while at age 26 only the logical memory test for verbal memory from the WMS was performed and showed similar group differences. Visual and working memory was assessed with subtests from the automated CANTAB-test battery. The reason for this change in assessment tools was a focus on other aspects of neuropsychological functioning which were evaluated with CANTAB, leading to assessment of memory functions not being prioritized. Previous studies in the preterm population have also used the CANTAB test battery to assess spatial working memory function and found more errors and reduced memory function in preterm born children [68-70]. However, a study by Lenehan et al. (2016) which investigated if the different CANTAB tests distinguished between cognitive domains in healthy older adults found that the spatial working memory test did not load on to any of the assessed domains, including working memory. The paired associate learning (PAL) test was the only CANTAB test that strongly loaded on the memory domain and was confirmed to measure episodic memory [71]. The PAL test has been shown to be associated with bilateral hippocampal activation in a load-dependent manner, confirmed to assess object-location memory and recognized as a good test of hippocampal function and connectivity [72]. We were unable to find other studies that had used PAL from CANTAB to assess memory function in preterm born individuals; however at age 19 our VLBW adults scored lower than controls on the quite similar visual paired associate test from the Wechsler Memory Scale [6].

Hippocampal volumes in adults with VLBW

Reduced hippocampal volume in children and adolescents following very preterm birth has been reported by others [73]. We found reduced hippocampal total absolute and relative volumes in the same geographically based cohort at ages 19-20 years (Aanes et al., 2015; Bjuland et al., 2014). Although the hippocampal total absolute volumes were still smaller in the VLBW group at age 26, this group difference did not survive ICV correction. This may be explained by a slightly different group of participating adults at age 26 than earlier, since only 30 of the 44 (68 %) VLBW adults and 38 of the 70 (54%) controls aged 26 participated in the study at 19-20 years. Still, we found significant group differences in absolute and relative volumes of hippocampal subfields between the groups, with lower volumes of the CA-fields and DG in VLBW women and smaller left subiculum in VLBW men compared with controls. This relative reduction of specific hippocampal subfields may indicate increased vulnerability of these structures related to preterm birth (see section 4.5.), but the findings have to be confirmed in larger studies.

Sex differences in brain and hippocampal development

Sexual differentiation of the brain seem to occur early during brain development and is present in preterm born children scanned with MRI at 35 weeks of gestation with larger cerebral tissue volume in boys and larger folding area in girls [74]. The hippocampus is larger in men than women; however this difference disappears when correcting for total intracranial volume [75]. In addition, the development of the hippocampus follows different trajectories in boys and girls from adolescence with a continued increase in boys and a slight decrease in girls [76,77]. Sex differences are also seen in hippocampal functions, however, the mechanisms underlying the observed effects of sex are not fully understood [78]. For instance, sex differences in the DG seem to be take place early in development and this may explain the

sex differences seen in memory function with better spatial memory abilities in men and better object memory in women [78].

The male brain seems particularly vulnerable to preterm birth with increased morbidity, mortality, neurodevelopmental-cognitive deficits and lower academic achievement and social functioning [8,79]. Studies indicate that the sex of very preterm born individuals influence mechanisms by which the developing brain is affected. Preterm born boys appear to be particularly vulnerable to adverse effects on white matter development and preterm born girls show strong correlations between neuro-anatomical variables and cognitive outcome [80]. Although a study on preterm born individuals found no sex differences in hippocampal asymmetry at birth [81], no studies, as far as we know, have investigated possible sex effects on hippocampal volumes in preterm born VLBW adults.

In our study, the hippocampal subfields were differently affected by VLBW in men and women with significant reduction in the volumes of CA fields and left DG among VLBW women and reduced volume of right subiculum in VLBW men. Tamnes et al. reported larger hippocampal subfield volumes in boys than girls aged 8-21 years [31]. In our study, we also found larger absolute subfield volumes in men compared to women in both groups, but these differences were no longer significant after adding ICV as a covariate (data not shown). Nevertheless, we found differences in absolute and relative volumes of several hippocampal subfields between VLBW women and control women, with far fewer group differences among men. This may be due to selection bias having lost more VLBW men with low IQ to follow-up. However, one could speculate that our finding is due to sex dependent vulnerability to preterm brain injury among VLBW men and women. Larger studies with preterm born survivors have to be performed to either confirm or reject our findings of sex-specific deviations in hippocampal subfields among VLBW individuals.

Hippocampal subfields vulnerability related to preterm birth

The hippocampal subfields have different functional roles and vulnerability to cerebral insults. The *CA fields* are particularly vulnerable to ischemia [10] which is a common complication of preterm birth that may cause injury to and/or harm further development, growth and maturation of white matter and subcortical structures leading to neuroimpairments in individuals born preterm with VLBW [22,82]. However, in our study the reduced CA field was only found in the VLBW women. There was no significant difference in neonatal risk factors between men and women in the VLBW group. The *DG* is susceptible to injury following preterm birth since hypoglycemia [83,84] and stress [85] have been reported to lead to loss of neurons through apoptosis, impaired neurogenesis and neuronal necrosis in this hippocampal subfield. We found smaller DG bilaterally in a cohort of school-aged children born preterm with VLBW in the 2000s (Aanes et al., 2019). In the present study both left and right DG were significantly smaller among VLBW women compared to control women, but only the left DG remained significantly smaller after correcting for ICV. However, when looking at effect sizes with Cohen's *d* moderate effect sizes were found for CA fields and DG bilaterally. The *subiculum* is reported to be susceptible to hypoxic-ischemic episodes [86] and stress related to its role in regulation of the hypothalamic-pituitary-adrenal (HPA)-axis [87]. The right subiculum was reduced in VLBW men compared with control men with an effect size of 0.47. We did find smaller right subiculum in the study of school-aged VLBW children as well, but we did not explore sex differences in that study (Aanes et al., 2019). We found a negative association between days in

need of mechanical ventilation and the left subiculum in VLBW group at age 26 years, reflecting that more days on mechanical ventilation (as a sign of immaturity and/or morbidity) were associated with smaller volume of the subiculum. A relationship between days on ventilator and the volume of subiculum was also found in the school-aged VLBW children study (Aanes et al., 2019). We therefore speculate that the individuals with more immature lung function and in need of mechanical ventilation may have more episodes with hypoxia-ischemia and stress during the neonatal period, which may affect the developing hippocampus, and especially the subiculum. However, more and larger studies are needed to confirm these findings.

Structure-function relationships

We found a possible hippocampal structure-function relationship in the VLBW group where larger volume of the left DG was associated with better visual memory. Similarly, we found a positive association between the left hippocampal volume and visual memory measured in the young adults at age 19 years [6]. Similar results have been reported in patients with schizophrenia in whom the extent of impairment on the CANTAB PAL test correlated with observed lower hippocampal volume [88], and a relationship between visuospatial associative memory and DG [89].

In the cohort of school-aged VLBW children born in the 2000s, we found a positive association between spatial working memory and the right DG [34], while the working memory index was highly correlated to the right total hippocampal volume in the young VLBW adult study at age 19 [6]. The lack of a similar structure-function relationship between the spatial working memory index and hippocampal subfield volumes in the present study could have several possible explanations. It may be due to the nature of the CANTAB test used – the Spatial Working Memory, that has been reported not to load well on to the working memory index [71]. Another CANTAB test, Spatial Span, would have been more similar to the working memory tests included in our previous studies but was unfortunately not included in this study. Also, working memory is shown to be less dependent on the hippocampi in adulthood (Nosarti & Froudust-Walsh, 2016) and it is possible that the VLBW adults at age 26 have gained a more mature working memory network that is less dependent on hippocampal structure and functioning. We argued in our paper on school-aged VLBW children that the association between spatial working memory and the right DG could be due to the spatial nature of the test and not working memory per se [34]. Nevertheless, these findings may indicate that deviations in DG following preterm birth may have consequences for memory functions even in adulthood. However, larger studies of VLBW individuals using more extensive memory test batteries have to be performed to explore further any structure-function relationship between memory function and hippocampal subfield volumes.

Conclusions

Adults born preterm with VLBW had reduced memory scores and smaller hippocampi compared with term born controls at age 26 years. When adjusting for ICV, total hippocampal volumes did not differ between groups, but left and right CA fields and left DG were smaller in VLBW women, while the right subiculum was smaller in VLBW men compared with control women and men, respectively. This may indicate sex differences in vulnerability of hippocampal subfields in early brain development following preterm birth. Reduced volume of the left DG was correlated to lower visual memory performance in

the VLBW group, indicating a possible structure-function relationship that may be affected by preterm birth. Larger studies are needed before generalization of the findings from our study.

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