Memory function and hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults

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Abstract

The hippocampi are regarded as core structures for learning and memory functions, which is important for daily functioning and educational achievements. Previous studies have linked reduction in hippocampal volume to working memory problems in very low birth weight (VLBW; ≤1500 g) children and reduced general cognitive ability in VLBW adolescents. However, the relationship between memory function and hippocampal volume has not been described in VLBW subjects reaching adulthood. The aim of the study was to investigate memory function and hippocampal volume in VLBW young adults, both in relation to perinatal risk factors and compared to term born controls, and to look for structure–function relationships. Using Wechsler Memory Scale–III and MRI, we included 42 non-disabled VLBW and 61 control individuals at age 19–20 years, and related our findings to perinatal risk factors in the VLBW-group. The VLBW young adults achieved lower scores on several subtests of the Wechsler Memory Scale–III, resulting in lower results in the immediate memory indices (visual and auditory), the working memory index, and in the visual delayed and general memory delayed indices, but not in the auditory delayed and auditory recognition delayed indices. The VLBW group had smaller absolute and relative hippocampal volumes than the controls. In the VLBW group inferior memory function, especially for the working memory index, was related to smaller hippocampal volume, and both correlated with lower birth weight and more days in the neonatal intensive care unit (NICU). Our results may indicate a structural–functional relationship in the VLBW group due to aberrant hippocampal development and functioning after preterm birth.

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Introduction

Children born preterm with very-low-birth-weight (VLBW) are at increased risk of perinatal brain injury and aberrant brain development that could have negative long-term cognitive consequences (Nosarti et al., 2012). In addition to general cognitive deficits (Løhaugen et al., 2010), VLBW individuals have an increased risk of neuropsychological deficits in attention/executive (Skranes et al., 2009; Bayless and Stevenson, 2007; Kulseng et al., 2006) and memory functions (Bohm et al., 2004; Woodward et al., 2005; Isaacs et al., 2000; Rose et al., 2001, 2005; de Haan et al., 2000) compared to term-born controls.

Memory is a complex process involving encoding, storage and retrieval of information, often divided into short-term or working memory and long-term memory. Long-term memory is further divided into implicit (priming and procedural) and explicit (semantic and episodic memory) (Schacter and Tulving, 1994). Episodic memory is “the conscious recollection of specific personal events (episodes), as well as the context (time and place) in which they occurred” (Strauss et al., 2006). Clinical measures of episodic memory involve free recall, cued recall and recognition of words, pictures, and faces (Strauss et al., 2006).

Memory deficits have been reported in preterm infants as young as 12 months old (Woodward et al., 2005; Rose et al., 2005; de Haan et al., 2000). de Haan et al. (2000) and Rose et al. (2005) demonstrated impaired recall in a deferred imitation task at 19 months and 12 months of age, respectively. However, Rose et al. described an improvement in memory function from 19 to 36 months of age in their preterm born study population, but the infants did not catch up with the full-term controls. In older preterm born children and adolescents, some studies have reported impairments in memory function (Isaacs et al., 2000; Taylor et al., 2000; Narberhaus et al., 2007) while others have not found any specific memory deficits (Rushe et al., 2001) and studies are lacking in adults born preterm.

Lesion studies have shown that the hippocampi are important brain structures for normal development of episodic memory (Gadian et al., 2000; Scoville and Milner, 1957; Bohbot et al., 2000). Individuals with developmental amnesia, due to a selective, bilateral injury to the hippocampi early in childhood, display impairments in memory and general cognitive abilities, which plausibly are related to hypoxic–ischemic injury (Gadian et al., 2000; Vargha-Khadem et al., 1997; Isaacs et al.,...
The hippocampi are vulnerable to ischemic episodes, and this form of injury is also seen in preterm born neonates (Volpe, 2012). Hippocampal volume is shown to be smaller in VLBW infants (Peterson et al., 2000), children (Isaacs et al., 2004; Abernethy et al., 2004), adolescents (Nosarti et al., 2002) and adults (Allin et al., 2004) compared to full-term controls, and some studies have also found a relationship between hippocampal volume and memory function in preterm children (Isaacs et al., 2000; Vargha-Khadem et al., 1997). However, studies conducted so far have examined memory function and its relation to hippocampal volume in preterm children and adolescents while knowledge is lacking about memory functions and their relationship to hippocampal morphology in adults born preterm.

The first aim of our study was to compare memory functions in a group of VLBW young adults with term-born controls, applying the full Wechsler Memory Scale, 3rd edition (WMS-III). Secondly, we wanted to compare volumes of right and left hippocampi in the two study groups by cerebral MRI using an automated segmentation method. The third aim was to explore any associations between hippocampal volumes and the results in the memory tests, and finally to explore whether perinatal risk factors influenced the test results and MRI findings in the VLBW group. We hypothesized that the VLBW group would have reduced memory functions and smaller hippocampi compared to controls, and that perinatal risk factors would be associated with the results. We also hypothesized that there would be an association between performance on memory tests and hippocampal volumes in both groups, but most pronounced in the VLBW group based on expected increased hippocampal pathology and lower test results in this group.

Material and methods

This study is part of a hospital based, long term follow-up study of a 3-year cohort of VLBW children and term born controls born in 1986–88, investigating the clinical consequences of VLBW assessed by neuropsychological testing and brain development evaluated with structural cerebral MRI. The data collection for the study was carried out between October 2006 and December 2008 at age 19–20 years of the participants.

Participants

The original cohort has been described in detail previously (Løhaugen et al., 2010).

VLBW group

Inclusion criteria were those born preterm with very low birth weight (VLBW: birth weight ≤1500 g), who were admitted to the neonatal intensive care unit (NICU) at the St. Olav University Hospital in Trondheim, Norway in 1986–1988. Of 121 neonates, 88 survived the newborn period. One child with Down’s syndrome, nine children who were not reachable at follow-up, and two with severe cerebral palsy who were unable to perform the neuropsychological tests were excluded from long term follow-up, resulting in 76 VLBW children eligible for participation, of whom 55 (72%) consented to the examinations at 19 years of age. Fifty VLBW subjects consented to MRI examinations, but one did not consent to the cognitive assessment. Three MRI examinations had to be excluded due to overall poor image quality and two with mild CP were excluded from further analysis, leaving 44 non-CP VLBW participants that had a combined MRI and cognitive assessment.

Controls

The control group was recruited from a 10% random sample of term born (gestational age ≥37 completed weeks) children with birth weight >10th percentile to mothers who were enrolled for follow-up before week 20 of pregnancy in the Trondheim region as part of a multi-center study in 1986–88. In total, 122 children were included as controls. At the follow-up at age 19–20, ten individuals could not be traced and two were excluded due to congenital malformations, leaving 110 eligible for participation. Twenty-nine did not consent to participate due to lack of motivation or time, resulting in 81 (74%) controls that participated in the cognitive testing. Sixty-six consented to the MRI examination, and of these sixty-one also met for neuropsychological testing.

Non-participants

There were no significant differences between participants and non-participants regarding birth weight, gestational age at birth, maternal age and education at time of childbirth (data not shown).

Cognitive and neuropsychological assessments

The Wechsler Memory Scale, version 3 (WMS-III) (Tulsky, 2003) was used to assess auditory (verbal) and visual episodic memory, both immediate, delayed and recognition, in addition to working memory. The six primary subtests were used in this analysis: Logical Memory I & II, Verbal Paired Associates I & II, Faces I & II, Family Pictures I & II, Letter–Number Sequencing and Spatial Span (see supplemental material for description of subtests). The combined scores of the subtests produced eight index scores: Auditory Immediate (subtests Logical Memory I and Verbal Paired Associates I), Visual Immediate (subtests Faces I and Family Pictures I), Immediate Memory (sum of Auditory Immediate and Visual Immediate indices), Auditory Delayed (subtests Logical Memory II and Verbal Paired Associates II), Visual Delayed (subtests Faces II and Family Pictures II), Auditory Recognition Delayed (recognition scores from subtests Logical Memory II and Verbal Paired Associates II), General Memory Delayed (sum of Auditory Delayed, Visual Delayed and Auditory Recognition Delayed indices) and Working Memory (subtests Letter–Number Sequencing and Spatial Span) (Table S1). The auditory tasks require the participant to learn and remember language based material, and include remembering two different stories (Logic Memory I & II) and verbal pairs (Verbal Paired Associates I & II). Visual tasks include remembering faces (Faces I & II) and pictures of everyday situations (Family Pictures I & II) both immediately and delayed. In addition, a delayed recognition task from the stories in the Logic Memory and the Verbal Paired Associates (Auditory Recognition Delayed index) was included. The Wechsler Adult Intelligence Scale (WAIS-III) (Tulsky, 2003) was used to assess general cognitive ability and the results have been published previously (Løhaugen et al., 2010). US standardized norms were used for the WMS-III since Norwegian norms do not exist.

Perinatal variables

Perinatal variables included known risk factors for possible poor neurological outcome; birth weight, gestational age, Apgar score at 1 and 5 min, days on mechanical ventilator, and total days in the NICU.

Socioeconomic status

Socioeconomic status (SES) was calculated according to Hollingshead’s Two Factor index of Social Position, based on the education and occupation of one parent, or the mean index from both parents (Hollingshead, 1957).

MR imaging

Cerebral MRI was performed on a 1.5 T Siemens Magnetom Symphony with Quantum gradients (30 mT/m) and a quadrature head coil. A structural T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was acquired with the following specifications: TR = 7.1 ms, TE = 3.45 ms, TI = 1000 ms, flip angle 7°, FOV 256 × 256, slab thickness 170 mm, slice thickness 1.33 mm, acquisition matrix 256 × 192 × 128, reconstructed to 256 × 256 × 128,
giving a reconstructed voxel resolution of 1 × 1 × 1.33 mm, and acquisition duration of 8.5 min.

**Image analysis**

Two MPRAGE sequences acquired during each MRI scan were registered to correct for head motion and averaged into a single image. Volumetric segmentation and cortical surface reconstruction were performed with the freely available FreeSurfer image analysis suite version 5.1 ([https://surfer.nmr.mgh.harvard.edu/](https://surfer.nmr.mgh.harvard.edu/)) (Dale et al., 1999; Fischl et al., 1999a, 1999b). An automatic algorithm that included motion correction of multiple T1 image (Reuter et al., 2010), and removal of non-brain tissue (Segonne et al., 2004) was applied. The automated method would then perform Talairach transformation and segmentation of subcortical white matter and deep gray matter volumes (including hippocampus) (Fischl et al., 2002, 2004). In order to compare the volumes of cortical and subcortical structures, volumes were aligned and registered to a common space using the surface based method in FreeSurfer. These procedures register each subject to a spherical atlas based on individual cortical folding patterns, and match geometry across subjects with minimized metric distortions (Fischl et al., 1999b). All processed images were controlled with the following script: http://surfer.nmr.mgh.harvard.edu/fswiki/QATools and visually inspected for errors in the segmentation process by two trained technicians and a medical doctor. No manual segmentation was performed and scans with obvious errors due to motion or dental braces were discarded. Images with low signal-to-noise-ratio (SNR) and with significant hemispheric differences of the size of the two hippocampi were checked very carefully for segmentation errors. We rejected the specific volumes with segmentation errors from the data analysis resulting in the exclusion of two right hippocampal volumes in the VLBW group and volumes of one left and one right hippocampus in the control group.

**Statistical analysis**

IBM SPSS Statistics version 21 was used to perform the analysis. Differences in group means for variables that had a normal distribution were compared with the Student t test. Outcome measures that were not normally distributed were analyzed by the Mann–Whitney U test. To perform group comparisons of mean values of neuropsychological scaled scores we used a univariate general linear model with group as fixed factor, adjusted for sex and SES. To compare the hippocampal volumes in the two groups a univariate general linear model, with group as fixed factor, and sex and age at MRI was used. Both absolute hippocampal volumes and volumes adjusted for total intracranial volume were calculated. We explored the associations between perinatal variables and measures of memory outcome and absolute hippocampal volumes, respectively by using partial correlations. Clinical outcomes were adjusted for sex and SES, while sex and age were included as covarates in the morphometric analysis. We also controlled for degree of immaturity, i.e. gestational age at birth when looking at the relationship between outcome variables and days in NICU and days on mechanical ventilator, respectively. Partial correlations were also used to evaluate the relationship between memory function and hippocampal corrected volumes within the two groups. Two tailed p-values ≤ .05 were considered to be statistically significant.

**Ethics**

The Regional Committee for Medical Research Ethics (Health Region IV) approved the study protocol (Project number: 4.2005.2605). Written informed consent was obtained from each participant when they came for cognitive assessment.

**Results**

**Clinical characteristics**

Mean birth weight and gestational age for the VLBW adults were 1234 (SD 225) grams and 29.5 (SD 2.4) weeks, while the controls had mean birth weight of 3697 (SD 497) grams and mean gestational age of 39.7 (SD 1.3) weeks (Table 1). Sixteen of the 44 VLBW young adults were born small for gestational age (SGA). The VLBW group had lower head circumference at birth and lower Apgar scores than controls (p < .001). At the time of assessment the VLBW adults had received more special education, and fewer attended school or were employed. The VLBW group had lower mean full IQ than controls (89 versus 100, p < .001). No group differences were found regarding sex, maternal age at childbirth, socio-economic status (SES), participant’s dominant hand, or age at MRI (Table 1).

**Memory test results**

The VLBW adults had significantly lower scores than controls on most WMS-III indices (Table 2). There was no difference in memory function between the VLBW young adults born small for gestational age (AGA) (data not shown). Within immediate memory the VLBW group scored lower in both the Visual Immediate and the Auditory Immediate indices due to lower scores on the subtests Faces I, Family Pictures I, Logic Memory I and Verbal Paired Associates I, however only the latter subtest reached statistical significance. Of the delayed memory indices the VLBW group obtained inferior scores in the Visual Delayed index, scoring lower in both the Faces II and Family Pictures II subtests. There was a trend toward lower Auditory Delayed index, though this did not reach significance, while the Auditory Recognition Delayed index was similar in the two groups (Table 2). The VLBW group also obtained lower scores in the Working Memory index, reaching significance in the visual subtest (Spatial Span), but not in auditory/verbal subtest (Letter Number Sequencing). The memory profile depicting the subtest scores for the two groups is presented in Fig. 1, showing that the VLBW young adults had lower numeric scores than controls in all subtests, reaching significance in four subtests.

**Associations between perinatal variables and WMS-III indices**

When exploring the associations between perinatal variables and WMS-III indices in the VLBW group, there were significant negative correlations between number of days on ventilator and the Auditory Delayed and Working Memory indices, while days in NICU were negatively correlated with all memory indices (Table 3). Positive associations were found between birth weight and all WMS-III indices, except for the Visual Delayed and the Working Memory indices, while gestational age did not correlate to any of the WMS-III indices in the VLBW group.

**Hippocampal volumes**

The VLBW subjects had significantly lower total intracranial volume and absolute hippocampal volumes than controls when adjusting for sex and age at scan. The group differences in hippocampal volumes remained significant when corrected for total intracranial volume (Table 4). Scatterplots of all participant’s left and right hippocampal corrected volumes are included in Fig. 2. The AGA VLBW subgroup had smaller left hippocampi compared to the SGA subgroup (data not shown).

**Associations between perinatal variables and hippocampal volumes**

No significant correlation was found between the number of days on ventilator and hippocampal volumes. The number of days in NICU was negatively correlated with total [r = −.374, p = .021], left [r = −.377, p = .017] and right [r = −.341, p = .036] hippocampal
Table 1
Clinical characteristics of the two study groups.

<table>
<thead>
<tr>
<th></th>
<th>VLBW (n = 44)</th>
<th>Controls (n = 61)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>1234 (225)</td>
<td>3697 (497)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>29.5 (2.4)</td>
<td>37.5 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>27.4 (2.0)</td>
<td>35.4 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex male (number, %)</td>
<td>18 (40.9)</td>
<td>26 (42.6)</td>
<td>.861</td>
</tr>
<tr>
<td>Maternal age at birth (years)</td>
<td>29.4 (6.6)</td>
<td>30.3 (4.1)</td>
<td>0.160</td>
</tr>
<tr>
<td>Socioeconomic status (SES)</td>
<td>3.4 (1.3)</td>
<td>3.7 (0.9)</td>
<td>0.131</td>
</tr>
<tr>
<td>Dominant right hand (number, %)</td>
<td>39 (88.6)</td>
<td>58 (95.1)</td>
<td>.219</td>
</tr>
</tbody>
</table>

Clinical data

APGAR 1 min | 7 | 9 | 7–9 | <0.001
APGAR 5 min | 9 | 10 | 1–10 | <0.001
Days in NICU | 66.6 (31.9) | 23–193 | – | –
Days on mechanical ventilator | 3.12 (7.5) | 0–44 | – | –
Small for gestational age (number) | 16 | 0 | – | –
Age at MRI (years) | 20.8 (0.8) | 18.9–22.1 | 20.3 (0.5) | 19.0–21.4 | 0.266
Received special education in school (number, %) | 9 (20.5) | – | 2 (3.3) | – | 0.005
In school or employed at time of study (number, %) | 37 (86.0) | – | 57 (93.4) | – | 0.050
WAIS-III Full IQ | 89 (13.0) | 50–110 | 100 (11.0) | 80–114 | <0.001

Subjects had lower performance in seven out of eight Wechsler Memory Scale (WMS-III) indices, indicating inferior memory functions compared to term born controls. The VLBW young adults also had higher scores on all corrected hippocampal volumes, indicating a learning disadvantage. The consequences may be that the VLBW group needs more repetitions during learning to be able to reproduce the information. This may result in learning problems, and contribute to inferior educational achievement, as already described by others (Løhauge et al., 2010; Hack, 2006).

The Visual Delayed and the General Memory Delayed indices were lower in the VLBW group than for controls, while the Auditory Delayed index revealed a tendency toward lower scores in the VLBW young adults (p = .081). A few other studies have reported impaired visual delayed memory in VLBW children (Thompson et al., 2013; Rickards et al., 1993), but none of these studies have used the Wechsler Memory Scale-III to assess this part of delayed memory and there is no agreement as to what extent the memory for verbal material is affected in VLBW groups. While some studies have shown reduced verbal memory in preterm born children (Taylor et al., 2000) and adolescents (Gimenez et al., 2004), others have not reported such difficulties (Narberhaus et al., 2007; Rushe et al., 2001) and studies are lacking in adult populations. The lower score in the Visual Delayed index than in the Auditory Delayed index among the VLBW young adults in our study may be related to increased vulnerability of the white matter in the visual system to hypoxic–ischemic injuries in preterm born subjects (Thompson et al., 2013). We have reported that reduced visual perceptual and visual–motor integration in the same VLBW study population at age 15 correlated to reduced white matter integrity in long association tracts evaluated with...
diffusion tensor imaging (Skranes et al., 2007). We speculate that reduced white matter connectivity in tracts transferring visual information, also may influence visual memory function.

Our finding of memory deficits in the VLBW group contradicts Rushe et al. (2001), who reported no significant difference in memory performance in preterm born adolescents compared to controls. Apart from age (14–15 years of age), the study population was similar to our cohort of VLBW young adults with respect to birth weight and gestational age. However, the tests to assess memory function used by Rushe et al. were different from ours, as they used only one subtest from the Wechsler Memory Scale, Paired Associate Learning, together with subtests from the Rivermead Behavioural Memory Test (RBMT) and the Rey–Osterrieth Complex Figure Test (ROCFT), to assess delayed verbal memory and visual memory, respectively. On the ROCFT, Rushe et al. found no difference between the groups, while we found significantly lower scores in visual memory. We speculate that this may be related to the ROCFT offering a prolonged exposure to the stimuli to be remembered as the participant is asked to copy a geometrical figure without a time limit, while the visual subtests from the WMS-III only allow for a short exposure, rendering more load on visual working memory that we also found to be inferior in the VLBW group.

The only memory result that was similar in the two groups in our study was the Auditory Recognition Delayed index, indicating that recognition function seems relatively unaffected in the VLBW group. Recognition and recall memory may consist of different processes, where only some being dependent on the hippocampi. Recognition memory is theorized to consist of two processes: familiarity and recollection, i.e. if stimuli seem familiar or if you remember it. Recall on the other hand, is postulated to be purely based on recollection of the stimuli (Strauss et al., 2006). Rose et al. (2001) found that this model may also fit for subjects born preterm, and reported that prematurity, which increases the risk of hippocampal injury, affected recollection but not familiarity. The distinct impairment in recollection memory may reflect a deficit more related to retrieval of already stored information (Strauss et al., 2006). Our findings with lower score in the Auditory Delayed index, but not in the Auditory Recognition Delayed index in the VLBW group partly support this model.

Inferior working memory function has previously been described in several VLBW groups (Skranes et al., 2009; Kulseng et al., 2006; Grunewaldt et al., 2013), and has also been related to the increased rate of Attention Deficit Hyperactivity Disorder (ADHD) and Attention Deficit Disorder (ADD) symptoms reported in preterm born subjects (Indredavik et al., 2004). We found that the VLBW group achieved lower scores on both the visual (Spatial Span) and the verbal (Letter–Number Sequencing) working memory subtests, although only the Spatial Span subtest reached statistical significance. This is in line with other studies reporting that visual spatial working memory is especially vulnerable in preterm born infants (Woodward et al., 2005), children (Isaacs et al., 2000) and adolescents (Curtis et al., 2006), while verbal memory has been reported as adequate (Bohm et al., 2004; Sansavini et al., 2007).

### Hippocampal volumes

The hippocampal volumes were significantly smaller in the VLBW young adults compared to controls. This was also true after controlling for total intracranial volume. This is in agreement with Isaacs et al. (2000) who reported smaller volumes of the hippocampi in preterm born children at age 13.5 years (Isaacs et al., 2000). Fearon et al. (2004) investigated hippocampal volumes in a group of 23-year-old preterm born adults and compared the volume to term-born adult siblings. They reported smaller hippocampal volumes in the VLBW adults,

**Table 3**

<table>
<thead>
<tr>
<th>WMS-III indices (n = 44)</th>
<th>Days on ventilator (n = 42)</th>
<th>Days in NICU (n = 43)</th>
<th>Birth weight (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-Value</td>
<td>r</td>
</tr>
<tr>
<td>Visual Immediate</td>
<td>-.062</td>
<td>.706</td>
<td>-.435</td>
</tr>
<tr>
<td>Auditory Immediate</td>
<td>-.269</td>
<td>.098</td>
<td>-.459</td>
</tr>
<tr>
<td>Immediate Memory</td>
<td>-.163</td>
<td>.321</td>
<td>-.460</td>
</tr>
<tr>
<td>Visual Delayed</td>
<td>-.042</td>
<td>.802</td>
<td>-.441</td>
</tr>
<tr>
<td>Auditory Delayed</td>
<td>-.320</td>
<td>.047</td>
<td>-.619</td>
</tr>
<tr>
<td>Auditory Recognition</td>
<td>-.177</td>
<td>.380</td>
<td>-.575</td>
</tr>
<tr>
<td>Delayed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Memory (Delayed)</td>
<td>-.176</td>
<td>.290</td>
<td>-.600</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-.369</td>
<td>.021</td>
<td>-.592</td>
</tr>
</tbody>
</table>

Partial correlations, adjusted for sex, gestational age and socioeconomic status. Abbreviations: VLBW = very low birth weight; WMS-III: Wechsler Memory Scale 3rd edition. Correlations with p-values ≤ .05 are in bold font.
although this difference did not reach significance, which may be due to
the rather small sample size in their study (n = 33 preterms and 18 con-
trol siblings). When looking at perinatal risk factors’ influence on hippo-
campal volumes in adulthood we found relationships between
hippocampal volume and birth weight and number of days spent in
NICU, but not with gestational age. The lower the birth weight and the
longer the stay in the NICU, the smaller the hippocampal volume, even
after correcting for degree of prematurity. These correlations may indi-
cate that both intrauterine growth restriction and perinatal morbidity in-
terfere with normal maturation and growth of the hippocampi in preterm
born subjects. Thompson et al. (2008) have reported that the hippocampi
are particularly vulnerable to white matter injury (Thompson et al.,
2008). We have previously reported reduced fractional anisotropy (FA)
values in association tracts in the external capsule and inferior and middle
superior fascicles in the same cohort of VLBW young adults at age 14–
15 years (Skranes et al., 2007), in addition to entorhinal cortical thinning
(Skranes et al., 2012). The entorhinal cortex has important cortical projec-
tions to and from the hippocampi, and impaired microstructure in the
white matter networks of these areas may influence connectivity and
processing of information leading to cortical thinning and hippocampal
volume reduction due to the loss of afferent input to the hippocampi
through the hippocampal–entorhinal–neocortical network.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>VLBW</th>
<th>Controls</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SE)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Total intracranial volume</td>
<td>44</td>
<td>1506.14 (19.62)</td>
<td>1467.19–1545.01</td>
</tr>
<tr>
<td>Total absolute hippocampal volume</td>
<td>42</td>
<td>7.33 (0.11)</td>
<td>7.10–7.55</td>
</tr>
<tr>
<td>Left absolute hippocampal volume</td>
<td>44</td>
<td>3.66 (0.06)</td>
<td>3.54–3.77</td>
</tr>
<tr>
<td>Right absolute hippocampal volume</td>
<td>42</td>
<td>3.67 (0.06)</td>
<td>3.55–3.79</td>
</tr>
<tr>
<td>Volumes corrected for ICV:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hippocampal volume</td>
<td>42</td>
<td>7.49 (0.10)</td>
<td>7.30–7.68</td>
</tr>
<tr>
<td>Left hippocampal volume</td>
<td>44</td>
<td>3.75 (0.05)</td>
<td>3.65–3.84</td>
</tr>
<tr>
<td>Right hippocampal volume</td>
<td>42</td>
<td>3.75 (0.05)</td>
<td>3.64–3.85</td>
</tr>
</tbody>
</table>

Univariate general linear model with group as fixed factor and sex and age at MRI as covariates for the absolute volumes. The volumes were then corrected for total intracranial volume, sex and age at MRI in another GLM-analysis. Abbreviations: VLBW = very low birth weight group. Controls; control group. ICV = intracranial volume.

Relationship between volumes of the hippocampi and memory profile

The majority of significant associations between hippocampal volumes and memory functions were found in the VLBW young adults, although we did find some correlations in the control group. The VLBW adults with the largest hippocampi had the highest scores in all indices of the WMS-III. This is in agreement with a study by Thompson et al. (2013) who investigated volume and shape variations of the hippocam-
pi measured at term-equivalent age (TEA) and memory function at age 7
in very preterm born children (Fearon et al., 2004). They also reported a
positive association between hippocampal volume and memory. In our
study the strongest correlation was found between hippocampal volume and memory. In our study the strongest correlation was found between hippocampal volumes and the Working Memory index. This is in line with
Beauchamp et al. (2008), who reported similar correlations between
volume of hippocampi at TEA and working memory in 2-year-old
VLBW-children.

Our study shows that similar relationships between hippocampal
volumes at term equivalent age and later memory function in very
preterm born children, also apply to hippocampal volumes measured
in early adult life in the same patient group. We will argue that this
may indicate permanent trophic changes to and reduced hippocampal
growth resulting in reduced memory functions.

![Fig. 2. Scatterplots of left and right hippocampal volumes for all the participants (VLBW in blue, controls in red). The volumes are corrected for total intracranial volume, sex and age at MRI by a univariate general linear model.](image-url)
When correcting for intracranial volume we demonstrate more significant correlations for the left hippocampus, which correlated with all memory indices except for the Auditory Recognition Delayed and the Working Memory indices, than for the right, which only correlated with the Working Memory index. This could be due to a functional lateralization of the hippocampus where the left hippocampus seems more involved with episodic memory and the right with spatial memory (Spatial Span subtest). This is in accordance with previous studies, which have demonstrated similar lateralization of the hippocampi in London taxi drivers (Fewtrell et al., 2008) and patients with Alzheimer’s disease (Han et al., 2006), and also in a review paper (Reuter et al., 2012).

### Strength and limitations

The strength of the present study is the comprehensive assessment of memory function with the full Wechsler Memory Scale 3rd edition test battery performed by a trained neuropsychologist blinded to group status and medical history. The study was conducted on a well-defined cohort of VLBW young adults who had been followed prospectively since birth. The relatively small sample size may be a limitation, which makes it less likely that results are due to chance. Nevertheless, a consistent difference between the study groups were found, which makes it less likely that results are due to chance. The study has a follow-up rate comparable to other reports of long-term follow-up (Fewtrell et al., 2008), and there was no signficant difference in existing background information between participants and non-participants in the study. Parental cognitive function and sex are unlikely confounding factors as there was no difference in level of maternal education, SES and sex between the two study groups. The neuroimaging volume measurements were calculated with the well-known and freely available FreeSurfer 5.1 software package using an automated algorithm for cortical and subcortical segmentation (Fischl et al., 2002, 2004). The FreeSurfer’s automated algorithms have shown satisfactory test–retest reproducibility over different MRI scanners and field strength (Han et al., 2006; Reuter et al., 2012), and the subcortical segmentation algorithms have shown intermediate accuracy in hippocampal segmentation (Morey et al., 2010). However, all hippocampal segmentations were quality controlled by inspection, and instead of manual correction of imperfect automated segmentations and thereby introducing bias, such hippocampal volumes were rejected from further analyses.

### Conclusions

In our study young adults born preterm with VLBW have inferior memory skills compared with term-born controls. The memory profile indicated deficits especially in the Visual Delayed and the Working Memory indices in the VLBW group. The relationship between reduced memory skills and smaller hippocampal volumes may indicate a structure–function relationship based on aberrant hippocampal development and functioning due to preterm birth with perinatal morbidity.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2014.10.023.

### References


### Table 5

Associations between hippocampal volumes (total, left and right) corrected for total intracranial volume and memory functions assessed by the eight WMS-III indices in VLBW young adults at 20 years of age.

| WMS-III Indices (n = 44) | VLBW group | | Left hippocampal volume (n = 44) | | Right hippocampal volume (n = 44) | |
|-------------------------|------------|-------------------------------|----------------|-------------------------------|----------------|
|                         | Total hippocampal volume | |                         | Left hippocampal volume | | Right hippocampal volume |
|                         | r p-Value | |                         | r p-Value | | r p-Value |
| Visual Immediate        | .399 .013 | | .411 .009 | | .308 .060 |
| Auditory Immediate      | .228 .168 | | .308 .053 | | .173 .299 |
| Immediate Memory        | .376 .020 | | .433 .005 | | .298 .070 |
| Visual Delayed          | .323 .051 | | .338 .035 | | .241 .151 |
| Auditory Delayed        | .231 .164 | | .317 .046 | | .147 .379 |
| Auditory Recognition Delayed | .277 .093 | | .276 .084 | | .268 .104 |
| General Memory (Delayed) | .327 .049 | | .367 .021 | | .256 .127 |
| Working Memory          | .336 .039 | | .250 .120 | | .374 .021 |

Partial correlations, adjusted for sex, socioeconomic status and age at MRI. Abbreviations: VLBW = very low birth weight; WMS-III: Wechsler Memory Scale 3rd edition. Correlations with p-values ≤ .05 are in bold font.

* n = 43.