Neonatal critical illness and development: white matter and hippocampus alterations in school-age neonatal ECMO survivors

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ABSTRACT

Aim Examine the neurobiology of long-term neuropsychological deficits following neonatal extracorporeal membrane oxygenation (ECMO).

Method This cross-sectional study assessed white matter integrity and hippocampal volume of ECMO survivors (8-15yrs) and healthy controls (8-17yrs) using Diffusion Tensor Imaging and structural MRI, respectively. Neuropsychological outcome was evaluated in patients. Included clinical predictors of white matter integrity: age start ECMO, ECMO duration, highest oxygenation index before ECMO, highest mean airway pressure and mechanical ventilation duration.

Results Patients (n=23) had lower global fractional anisotropy than controls (n=54)(patients=.368; controls=.381; p=.02), but similar global mean diffusivity (p=.41). Patients had lower fractional anisotropy in the left cingulum bundle (patients=.345; controls=.399; p<.001) and higher mean diffusivity in a region of the left parahippocampal cingulum (patients=.916; controls=.871; p<.001). Higher global mean diffusivity predicted worse verbal memory in patients (n=17)(β=-.74, p=.01). Patients (n=23) had smaller bilateral hippocampal volume than controls (n=43)(left: p< .001; right: p< .001). In patients, this was related to worse verbal memory (left: β=.65, p=.02; right: β=.71, p=.01).

Interpretation Neonatal ECMO survivors are at risk for long-term brain alterations, which may partly explain long-term neuropsychological impairments. Neuroimaging may contribute to better risk stratification of long-term impairments.

Running title: Brain alterations following neonatal ECMO

WHAT THIS PAPER ADDS

- School-age neonatal ECMO survivors are at risk for neuropsychological deficits.
- Neonatal ECMO survivors have white matter alterations and smaller hippocampal volume.
- Brain alterations may partly explain neuropsychological deficits in these children.

Extracorporeal membrane oxygenation (ECMO) has been used in over 28,000 neonates with severe respiratory failure, 74% of whom survived to discharge or transfer[1]. Previous studies found 10-59% of ECMO patients to have abnormalities on routine neuroimaging during treatment[2]. Furthermore, neurological complications such as hypoxia and cerebrovascular injury have been reported[3,4].

Neurodevelopmental follow-up of these children shows long-term (subtle) neuropsychological impairments that emerge in childhood and persist into adolescence[5-7]. Despite normal intelligence, these attention and memory deficits result in patients being at risk for school failure[5-7]. These results suggest a 'growing into deficit' phenomenon where subtle brain injuries acquired at a young age become functionally evident over time when demands on cognitive functioning increases[8]. This 'growing into deficit' is nested within different developmental processes that occur in the brain (i.e. myelination) during childhood and adolescence. Thus, it is important to study the underlying neurobiology of long-term neuropsychological impairments within a developmental framework.

Studies utilizing sophisticated neuroimaging methods to study neonatal ECMO survivors are scarce[9,10]. Structural MRI in school-age children who experienced neonatal hypoxia have shown bilateral lower hippocampal volume compared to healthy controls[9]. Furthermore, the lower hippocampal volume was associated with the extent of memory deficits. Our group previously found cortical thickness and global brain volumes in 8-to-15 year-old neonatal ECMO survivors to be similar to healthy controls, despite verbal memory problems in the patients[10]. These results suggest that the underlying brain injury in ECMO survivors is specific and/or subtle and therefore may not always be identifiable using high-resolution structural MRI . Alternative advanced imaging techniques may be better suited to identify subtle brain alterations in ECMO survivors.

Diffusion Tensor Imaging (DTI) is an imaging technique that can quantify microstructural characteristics of white matter. White matter has been shown to be especially vulnerable in the neonatal period, a time when it is undergoing rapid development[11]. Neonatal ECMO survivors may therefore be at an increased risk for white matter abnormalities. Moreover, white matter integrity has been associated with neuropsychological outcome[11]. Since white matter is important for high-speed transmission of neuronal signals between distant brain regions, aberrations in white matter development could affect the orchestration of specific cognitive functions. Thus, the long-term neuropsychological impairments observed in both 8-year-old and 17-year-old ECMO survivors could be due to underlying white matter alterations[5-7].

This study aimed to assess whether 8-to-15 year-old ECMO survivors have white matter alterations and whether these are partially responsible for the long-term neuropsychological deficits observed in these patients. We hypothesized to find white matter alterations in ECMO survivors, specifically in tracts associated with (working) memory and attention. Identification of neurobiological correlates of long-term neuropsychological impairments following neonatal ECMO may contribute to better risk stratification of these impairments in neonatal ECMO survivors.

METHOD

Patients

Children born between January 1997 and December 2003 treated with venoarterial neonatal ECMO in the Erasmus MC in Rotterdam, the Netherlands were included. ECMO support was given according to the entry criteria described by Stolar et al[12]. For each patient, cannulas were placed in the right cervical region by the same surgical team. Further recruitment details and in- and exclusion criteria are described elsewhere[10]. Of 60 eligible patients, six families were not traceable, 17 declined participation and one child had dental braces, leaving 36 participants. Of these, 23 had reliable DTI and structural data (8-15 years)(Supplementary Figure 1). Background characteristics retrieved from the medical records are presented in Table 1.

Controls

Healthy controls (8-18 years) were recruited through two different approaches. First, participating families were asked if their child had a friend who would be interested in participating. Second, we sent invitation letters to the parents of children attending a primary school in Rotterdam. In- and exclusion criteria are described elsewhere[10]. Eleven of 75 controls were excluded because of either preterm birth or because they were greater than six months younger/older than the youngest/oldest patient, leaving 64 eligible controls. Of these, 54 had reliable DTI data and 43 had reliable structural data (Supplementary Figure 1).

Study procedure

The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the Institutional Review Board at the Erasmus MC (MEC-2010-299). Informed consent was obtained prior to participation from the parents of each child and from children 12 years and older. All subjects had been administered subtests of the Dutch edition of the NEPSY-II-NL neuropsychological test battery (Pearson, Amsterdam)[13]. Only performance of the ECMO survivors was analyzed as the relationship between cognitive functioning and brain alterations is largely unknown following ECMO. Children between 8 and 12 years performed nine subtests, older children performed only six due to the age limit of three tests[13].

Neuroimaging

Participants first underwent a mock scanning session to become familiarized with the MR-environment[14]. MRI data were acquired on a 3 Tesla GE MR-750 system using an 8-channel head coil (General Electric, Milwaukee, WI). A full description of these methods is provided in Supplementary File 1. Briefly for the DTI data, after data processing, the voxel-wise scalar maps fractional anisotropy (FA) and mean diffusivity (MD) were computed. FA is the degree of directionality of diffusion and ranges from 0 to 1, where a higher FA generally represents a greater coherence of white matter fibers. MD is the rate of diffusion of hydrogen averaged in all directions. Lower MD is suggestive of increased integrity in axonal membranes, packing, or myelin. Fully automated probabilistic fiber tractography was performed using the FSL plugin "AutoPtx"[15] to create subject-specific, probabilistic representations of multiple white matter fiber bundles. Raw image quality was assessed using automated software[16] and visual inspection, leaving 77 datasets (patients=23, controls=54).

Statistical analysis

Age at MRI, gestational age and gender differences between groups were assessed using independent samples t-tests and a chi-squared test, respectively. As previous research showed congenital diaphragmatic hernia (CDH) patients tend to have lower IQ, we compared IQ between patients with meconium aspiration syndrome (MAS), CDH or other diagnoses using ANOVA[6].

Global white matter integrity of patients and controls was analyzed first. The association fibers and limbic system fibers (uncinate, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, cingulum bundle and parahippocampal part of cingulum) were used to

compute a measure of global FA and global MD. These fibers have been associated with neuropsychological functioning and in particular with attention and (working)memory – domains that have been shown to be affected in neonatal ECMO survivors[6,17]. The global measures were computed by multiplying the FA/MD values of each tract with the average volume of each tract, and then dividing this by the sum of the volumes of all tracts (Formula 1). This ensured that tracts of different size were appropriately weighted in their contribution to the global mean.

Formula 1:

$$\text{Global FA} = \frac{\sum_{i=1}^{6} FAtract_i Voltract_i}{\sum_{i=1}^{6} Voltract_i}$$

The same formula was used to compute global MD. Assumptions of normality were met for FA and MD.

Differences between groups in global FA, MD and the diffusion metrics within individual white matter tracts were analyzed using ANCOVA, adjusted for age at MRI and gender[17]. The white matter tracts were assessed in the left and right hemispheres separately. Global FA/MD was added as a covariate to identify differences in the individual tracts only. The False Discovery Rate (FDR) correction[19] was used once to account for multiple testing in all analyses of FA/MD differences between groups. Results were considered statistically significant at the FDR-corrected $p < .05$.

Multivariable linear regression models were used to evaluate the effect of five clinical characteristics (age start ECMO, ECMO duration, highest oxygenation index prior to ECMO, highest mean airway pressure and mechanical ventilation duration) on global FA, global MD, and the altered white matter tracts. Age at MRI was adjusted for. For all clinical characteristics, log transformations were applied to satisfy parametric statistics assumptions.

In the ECMO survivors, white matter integrity and verbal memory were assessed to get a better understanding of the poor verbal memory performance in the ECMO survivors previously shown by our group[10]. Separate multivariable linear regression models were used to evaluate the effect of global FA, global MD and the altered tracts on verbal memory, adjusted for age at MRI. The effect of white matter integrity on the other eight NEPSY-II-NL subtests in the ECMO survivors was explored using multivariable linear regression analyses, as the relationship between cognition and white matter microstructure remains largely unknown in this group. FDR correction[19] was used to account for multiple testing for every set of analyses with the same NEPSY subtest. Results were considered statistically significant at the FDR-corrected $p < .05$.

Next, hippocampal volumes were compared between groups using ANCOVA. This was done separately for the right and left hippocampus, adjusted for age, gender and global brain volume. In patients, multivariable linear regression analyses were performed to analyze the relationship between hippocampal volume and verbal memory, adjusted for age, gender and global brain volume.

SPSS Statistics Version 22.0 (Armonk, NY: IBM Corp.) and the Stats package in R Statistical Software version 3.1.3 (R Core Team, 2014) were used for statistical analyses and the FDR correction, respectively. For all regression analyses, the regression coefficient beta (β) and p-values are reported. Multicollinearity was not found in the models (variance inflation factors < 2.5[18]). Effect sizes were calculated using partial eta squared (η_p^2). Results were considered statistically significant at $p < .05$.

RESULTS

Study population

The ECMO group consisted of 23 children (11 boys, 12 girls) with a mean age(SD) of 11.9(2.6) years. All patients attended regular education, but 35% (n=8) patients needed extra help in school. The control group consisted of 54 children (22 boys, 32 girls) with a mean age(SD) of 11.4(2.5) years. All controls attended regular education. Age at MRI, gestational age and gender did not differ between groups (p=.34; p=.57; p=.57, respectively).

None of the patients (n=23) had abnormal neonatal cranial ultrasounds or suffered cardiac arrests. Other clinical characteristics are reported in Table 1. Consistent with previous results, mean IQ(SD) did not differ between the diagnostic groups in the ECMO survivors (MAS: 100(23); CDH: 95(8); other diagnoses: 107(15)), p=.70[6].

DTI results

Patients had significantly lower global FA (n=23, global FA=.368) compared to controls (n=54, global FA=.381), p=.02, η_p^2=.07. Further analyses were performed on the individual tracts. Significantly lower FA was found in the left cingulum bundle(CB) of patients, p<.001, η_p^2=.13(Table 2, Figure 1A). Because the CB is a large bundle in which functional differences between the anterior and posterior parts have been demonstrated[20], we additionally analyzed the left anterior and posterior cingulate bundles(CBa, CBp) separately. We found significantly lower FA in patients in the left CBa and CBp(Table 2).

Global MD did not differ between patients (global MD=.803) and controls (global MD=.794), p=.41, η_p^2 =.01. Because DTI has not been used in neonatal ECMO survivors before, further analyses on MD in the individual tracts were conducted. Higher MD was found in the left parahippocampal cingulum(PHC) in patients, p<.001, η_p^2 =.12(Table 2, Figure 1B).

White matter integrity and clinical characteristics in ECMO survivors

None of the clinical characteristics significantly predicted global FA or MD. Higher oxygenation indices prior to ECMO predicted higher FA in the right CB, β=.50, p=.03. Longer duration of mechanical ventilation, β=.36, p=.03, and younger age at the start of ECMO predicted higher MD in the left PHC, β=-.62, p=.002.

White matter integrity and neuropsychological outcome in ECMO survivors

Global MD significantly predicted cued and free recall verbal memory, β=-.74, p=.01 (n=17) (Figure 2). Global FA (p=.20), FA in the left CB (p=.97), and MD in the left PHC (p=.21) were not related to verbal memory. None of the other subtests of the NEPSY-II were related to the white matter alterations(Supplementary Table 1).

Hippocampal volume

Patients had significantly smaller mean hippocampal volume(SD) than controls, in the left, p< .001, η_p^2=.41 (patients=3597(407), n=23; controls=4245(398), n=43), and right hemispheres, p< .001, η_p^2=.22 (patients=3646(515); controls=4111(490)).

Left, β=.65, p=.02, and right, β=.71, p=.01, hippocampal volumes were associated with verbal memory performance in ECMO survivors (n=17).

DISCUSSION

We found global white matter alterations and smaller bilateral hippocampal volume in school-age neonatal ECMO survivors compared to healthy controls, as well as specific white matter alterations in the CB and PHC. Lower verbal memory performance in ECMO survivors was related to altered white matter integrity and smaller bilateral hippocampal volume. These results suggest long-term brain alterations that persist through childhood and into adolescence.

Global FA was significantly lower in patients. FA is a measure of coherence of hydrogen diffusion within microstructures (i.e. axons, microtubules) and is lower in disorganized white matter tracts[21]. Lower global FA may indicate long-term injury to neural tracts. This is in line with earlier results showing brain alterations following neonatal hypoxia and ECMO treatment[9]. Interestingly, global MD did not differ between patients and controls. This may be because the white matter alterations are specific (i.e. disorganization of axon fibers), leaving other structures (i.e. cellular structures) relatively intact[11]. However, this remains speculative as FA and MD are summary parameters that cannot give detailed histological information.

We recently demonstrated verbal memory deficits in both 17-year-old ECMO survivors as well as in the patients that are part of this study[5,10]. In the latter group, we found that higher global MD predicted lower verbal memory. It is unclear why MD rather than FA predicted verbal memory, as only global FA differed between ECMO survivors and controls. Nonetheless, our findings are in line with a previous neuroimaging study showing lower white matter volume and memory deficits in 11-to-13 year-old neonatal ECMO survivors[9].

Lower FA was found in the entire left CB in neonatal ECMO survivors, indicating aberrations along the entire tract. Even though global MD did not differ, ECMO survivors had significantly higher MD in the left PHC. The limbic system fibers (i.e. CB and PHC) have been found to develop rapidly in the first six months of life, causing FA to increase and MD to decrease[11]. As our subjects were critically ill in the first weeks of life, the development of these fibers may be at risk.

We found white matter alterations only in the left hemisphere. Left side predominance of brain injury following neonatal ECMO has been previously reported using cranial ultrasound[4]. Of note, before correcting for multiple comparisons, right hemisphere differences in the CB and PHC were also found. Furthermore, unlike the small effect sizes found for the rest of the tract comparisons, differences in the right CB and PHC showed medium effect sizes[22]. The lack of right hemisphere differences may thus due to a small sample size rather than being indicative of an increased left hemisphere vulnerability.

CB or PHC alterations in the ECMO survivors were not associated with verbal memory. The CB is a large bundle involved in various cognitive functions, including working- and visuospatial memory and attention[23]. The CB alterations may thus be specific to other neuropsychological deficits that have been observed following neonatal ECMO[5-7]. Furthermore, the verbal memory task used focused on episodic memory, whereas the parahippocampal region seems involved in semantic memory[24]. As episodic memory has been associated with the hippocampus, a structure vulnerable to hypoxic injuries, hippocampal rather than CB or PHC alterations may partly explain the verbal memory deficits observed[9]. Indeed, we found smaller bilateral hippocampal volume in ECMO survivors compared to controls. Moreover, smaller hippocampal volume was associated with worse verbal memory in ECMO survivors.

Other than verbal memory, no relationships were found between performance on the NEPSY-II and white matter integrity. This suggests specificity between the verbal memory deficit and white matter microstructure in ECMO survivors. Nonetheless, ECMO survivors have been shown to be at risk for working-memory, visuospatial memory and attention impairments, as well as school failure[5]. Subtle neuropsychological deficits have been shown to be difficult to detect with the NEPSY-II[25], which could explain the lack of findings with some of the subtests. In future studies it is therefore critical to use tests specifically designed to measure these types of deficits. Such outcomes should be combined with neuroimaging to improve our understanding of brain alterations and their clinical impact following neonatal ECMO.

No clinical predictors of global white matter were found, but longer duration of mechanical ventilation and younger age at the start of ECMO negatively influenced MD in the left PHC. These

findings provide some support that severity of illness negatively influences outcome[6,9]. However, we found that a higher OI prior to ECMO was associated with higher FA in the right CB. As higher FA is generally associated with better organization of white matter, these analyses should be replicated by future studies before any firm conclusions can be drawn.

Our study has some limitations. First, the small size of the patient group restricts our findings to those with moderate to large effect sizes and limits the interpretability of the multivariable regression analyses. Second, more elaborate neuropsychological assessment offering finer details of specific neuropsychological domains is better suited to assess white matter alterations in ECMO survivors. Third, while we do have age, gender and NEPSY outcomes of the healthy controls, we do not have IQ scores of this group. However, because all children performed within normal ranges on the NEPSY and attended regular education, they are likely to have average intelligence[13]. Fourth, all patients had been treated with VA ECMO. However, while the application of VV ECMO has increased, VA ECMO remains the most frequently used modality for neonatal respiratory or cardiac failure[1]. Lastly, we have limited clinical information of the patients due to lack of a digital patient management system (introduced in our unit in 2003) at the time of treatment.

Despite the limitations, this study is the first to use DTI to study white matter microstructure in school-age neonatal ECMO survivors and show long-term global and specific white matter alterations in neonatal ECMO survivors. Global MD alterations and lower hippocampal volume were associated with worse verbal memory performance in patients. These results help define the underlying neurobiology involved in the long-term neuropsychological deficits following ECMO. Furthermore, severity of illness may have partly influence white matter development. The use of advanced neuroimaging techniques such as DTI may contribute to better risk stratification and earlier identification of long-term neurodevelopmental impairments in critically ill infants.

AKNOWLEDGMENT SECTION

Conflict of Interest Disclosures: The authors declare that they have no conflict of interest.

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Table 1. Clinical characteristics of the ECMO survivors

	Patients (n = 23)
IQ, mean (SD)	100 (19)
Gestational age (weeks), median (IQR)	40 (2)
Birth weight (grams), median (IQR)	3530 (810)
Diagnosis, n (%)	
MAS	15 (66)
CDH	4 (17)
Other	4 (17)
Age start ECMO (hours), median (IQR)	20 (24)
ECMO duration (hours), median (IQR)	124 (100)
Highest oxygenation index prior to ECMO, median (IQR)	46 (27)
Highest mean airway pressure, median (IQR)	20 (5)
Mechanical ventilation (days), median (IQR)	11 (9)
O2 post-ECMO, n (%)	
1 day – 1 week	11 (48)
>1 week - <1 month	11 (48)
>1 month	1 (4)
BPD presence, n (%)	
Yes	2 (9)
No	21 (91)
Nitric Oxide pre-ECMO, n (%)	
Yes	16 (69)
No	5 (22)
Unknown	2 (9)
Inotropic use, n (%)	
Yes	21 (92)
No	1 (4)
Unknown	1 (4)
Morphine use, n (%)	
<1 week	4 (18)
1 week – 1 month	15 (65)
>1 month	3 (13)
Unknown	1 (4)
Muscle relaxant use, n (%)	
No	2 (8)
Perioperative only, n (%)	3 (13)
1 day – week	12 (53)
>1 week	5 (22)
Unknown	1 (4)
Corticosteroids use, n (%)	
Yes	2 (8)
No	21 (91)

Other diagnoses consist of persistent pulmonary hypertension of the newborn (PPHN) (n = 1), pneumonia (n = 2), and sepsis (n = 1).
abbreviations: IQ, intelligence quotient; IQR, interquartile range; MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane

oxygenation; O2 post-ECMO, extra oxygenation need post-ECMO; BPD, bronchopulmonary dysplasia.

Table 2. FA and MD group differences in white matter tracts.

Tract	Hemisphere	Mean FA Controls	Mean FA Patients	$p_{uncor.}$	p	η_p^2	Mean MD Controls	Mean MD Patients	$p_{uncor.}$	p	η_p^2
UNC	Left	.347 (.03)	.334 (.03)	.69	.83	.00	.819 (.03)	.826 (.03)	.92	.93	.00
	Right	.361 (.03)	.346 (.02)	.46	.71	.01	.813 (.03)	.817(.02)	.57	.80	.01
IFO	Left	.415 (.03)	.401 (.02)	.81	.93	.00	.808 (.03)	.815 (.03)	.93	.93	.00
	Right	.422 (.03)	.407 (.03)	.66	.83	.00	.808 (.03)	.813 (.02)	.42	.71	.01
SLF	Left	.367 (.03)	.357 (.03)	.32	.71	.01	.769 (.03)	.779 (.03)	.40	.71	.01
	Right	.367 (.03)	.361 (.02)	.07	.28	.04	.769 (.03)	.775 (.03)	.48	.71	.01
ILF	Left	.401 (.02)	.388 (.02)	.40	.71	.01	.822 (.03)	.829 (.03)	.68	.83	.00
	Right	.407 (.02)	.397 (.02)	.89	.93	.00	.833 (.03)	.836 (.03)	.22	.60	.02
CB	**Left**	**.399 (.05)**	**.345 (.04)**	.002	**.02**	**.13**	.761 (.04)	.782 (.04)	.06	.28	.05
	Anterior	**.376 (.05)**	**.321 (.04)**	**.00**		**.13**					
	Posterior	**.429 (.06)**	**.381 (.04)**	**.02**		**.07**					
	Right	.368 (.05)	.323 (.04)	.01	.10	.08	.762 (.03)	.778 (.03)	.12	.35	.03
PHC	Left	.271 (.03)	.249 (.03)	.11	.35	.04	**.871 (.05)**	**.916 (.06)**	.002	**.02**	**.12**
	Right	.275 (.03)	.259 (.03)	.39	.71	.01	.897 (.05)	.932 (.06)	.03	.20	.06

Results of ANCOVA's showing differences between patients (n = 23) and controls (n = 57) on all association and limbic system fiber tracts. Additional analyses on the anterior and posterior parts of the cingulum were done only for FA in the left cingulum bundle as differences between patients and controls were found in this specific tract. Mean weighted average FA (SD) is given for each tract per group. The partial eta squared (η_p^2) is given as an effect size. The size of the effect is interpreted according to Cohen's guidelines[23] which states 0.01 to be a small effect size, 0.06 to be a medium effect size, and 0.14 to be large. Age, gender and global FA or MD were added as covariates in the ANCOVA's. **FDR-corrected *p*-values** <.05 were considered statistically significant. $P_{uncor.}$ gives the uncorrected *p*-value. Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; UNC, uncinate fasciculus; ILF, inferior longitudinal fasciculus; IFO, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; CB, cingulum bundle; PHC, parahippocampal cingulum bundle.

FIGURE LEGENDS

Figure 1. FA/MD differences between ECMO patients and healthy controls

Figures 1a and 1b show FA and MD (10^{-3} mm^2/s) for the individual white matter tracts of patients and controls. Effect sizes (partial eta squared) are used to show the magnitude of the difference between groups. Effect sizes of 0.01 are considered to be small, 0.06 to be medium, and 0.14 to be large(23). In Figure 1a, FA in the left CB differs significantly between patients and controls. In Figure 1b, MD in the left parahippocampal cingulum differs significantly between patients and controls. Abbreviations: -l, left; -r, right; FA, fractional anisotropy; UNC, uncinate fasciculus; ILF, inferior longitudinal fasciculus; IFO, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; CB, cingulum bundle; PHC, parahippocampal cingulum bundle.

Figure 2. Verbal memory and white matter integrity

Scatterplot showing the relationship between global Mean Diffusivity (MD) and cued and free recall verbal memory in neonatal ECMO patients. Verbal memory minimum and maximum scores: 0-34.