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Long-term brain structural and cognitive outcomes in a low-risk preterm-born sample

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Prematurity has been related to altered brain structure and cognition, and so our aim was to describe them in the absence of major structural brain injury following low-risk preterm birth during adolescence and young adulthood. The sample consisted of 250 participants, 132 of whom were low-risk preterm (30–36 weeks' gestational age) and 118 were full-term individuals (37–42 weeks' gestational age), aged between 16 and 38 years old. All participants underwent an extensive neuropsychological assessment. T1- and diffusion-weighted MRI images of 33 low-risk preterm and 31 full-term young adults (20–32 years old) were analyzed. No differences were found in terms of general cognitive functioning score or current socioeconomic status; however, the low-risk preterm group obtained lower scores in phonetic and semantic fluencies, and theory of mind. Significant reductions were identified in the thalamus volume as well as thicker cortex in the inferior temporal gyrus in the low-risk preterm group. Low-risk preterm young adults evidenced greater regional AD and MD compared to the full-term sample; while low-risk preterm group showed lower mean NDI and ODI (FWE-corrected, $p < 0.05$). Being born preterm is associated with poorer performance in various cognitive domains (i.e., phonetic and semantic fluencies, and theory of mind) later in life, along with differences in normative structural brain development in inferior temporal gyrus and regional white matter microstructure.

Keywords Low-risk preterm birth, Cognitive functioning, Current socioeconomic status, Brain macro and microstructure, Adolescence and young adulthood

Preterm birth, defined as any birth before 37 completed weeks of gestation, is described as a chronic condition, since it increases the risk of long-term neurological morbidity that can last a lifetime[1]. In low-risk prematurity [30–36 weeks' gestational age (GA)], neuropsychological abnormalities can be detected early in childhood, as well as brain changes that may constitute the basis for adverse long-term neurodevelopment with non-neonatal brain injury on cranial ultrasound[2,3]. In fact, in the absence of major structural brain injury, third-trimester global and regional brain growth may be disrupted by low-risk preterm birth[4].

Neuropsychological dysfunctions and poorer cognitive scores in preterm children are common in early life, showing a significant relationship between GA and cognition[5]. Low-risk preterm birth impairs certain domains and overall intellectual performance, which results in poorer cognitive functioning from infancy through to maturity[6–8]. The scant evidence collected among adolescents and young adults has revealed that the general cognition of individuals with very small GA did not catch up over time[9].

Atypical cortical development has been shown to be an outcome of prematurity in the first years of age, closely related to general and specific cognitive domains in preterm-born infants[10,11]. Furthermore, low-risk preterm children have altered regional thinning[12] and reduced volumes of several subcortical gray matter (GM) and white matter (WM) structures[6,8]. Additionally, lower fractional anisotropy (FA) and higher axial, mean, and radial diffusivity (AD, MD, and RD, respectively) in approximately 70% of the brain's major WM fiber tracts have also been found following low-risk preterm birth, related to poorer cognitive and language scores during childhood[13,14].

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With regard to adulthood, to our knowledge, there is scarce data that focuses on cognition and brain development in young adults born low-risk preterm and existing literature tends to focus largely on younger GAs or heterogeneous preterm samples. Very preterm birth is still closely linked to altered structural brain anatomy in early adulthood as well as in subcortical areas such as the thalamus, caudate nucleus, and putamen[15]. In fact, in terms of perinatal brain injury and medical complications, a number of structural alterations have tended to be related to a poorer intelligence quotient (IQ) and lower executive functioning scores in adolescence and adulthood following very preterm birth[16]. Additionally, FA reductions have been related to loss in GM as well as GA, and IQ scores in preterm-born adults[17]. Based on this, one could hypothesize that low-risk preterm infants might also evidence neurodevelopmental abnormalities even during adulthood, although as stated, there is limited literature on the subject. For this reason and owing to the above-mentioned, the aim of this study is to assess the long-term cognitive outcomes and brain macro- and microstructure that can be found following low-risk preterm birth in adolescents and young adults.

Methods

Participants

A total of 250 adolescents and young adults (age range from 16 to 38 years old) partook in this study: 132 low-risk preterm (M_{age} = 23.23 years; Md_{age} = 23.50; SD_{age} = 4.60) and 118 full-term (M_{age} = 23.97 years; Md_{age} = 24.00; SD_{age} = 4.79) subjects. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Deusto [ETK-22/17-18] and the Drug Research Ethics Committee of the Basque Country [CEIm-E, PI2018154]. All participants provided written informed consent, while underage participants gave written assent and their legal guardians provided informed consent prior to participation.

A group of preterm adolescents and young adults at lower risk of major disability was recruited at Cruces University Hospital (Barakaldo, Spain) and through chain-referral sampling (i.e., a non-probabilistic sampling strategy whereby existing participants refer new individuals for recruitment) from September 2018 to April 2021. This group consisted of 132 low-risk preterm subjects who met the following inclusion criteria: (1) GA of between ≥ 30 and 36 weeks (calculated from the last menstrual period and confirmed with the first echography, where necessary), (2) absence of brain pathology identified by neonatal cranial ultrasound, (3) lack of substantial neonatal morbidity (i.e., congenital neurological, cardiac, respiratory or digestive malformations, necrotizing enterocolitis, or septic shock), and (4) ranging in age at evaluation from 16 to 40 years. A full-term group of 118 participants was also recruited through chain-referral sampling on the same dates. Inclusion criteria were: (1) GA ≥ 37 weeks, and (2) ranging in age at evaluation from 16 to 40 years. The exclusion criteria for both low-risk preterm and full-term groups were: a history of brain injury [cystic periventricular leukomalacia, intraventricular hemorrhage, and periventricular hemorrhagic infarction (PVHI) diagnosed with cranial ultrasound during the neonatal period, and focal brain lesions], cerebral palsy or any other neurological impairment, congenital malformations, and chromosomal abnormalities.

In addition, out of the total 250 adolescents and young adults, 64 participated in a neuroimaging study: 33 low-risk preterm (M_{age} = 25.33 years; Md_{age}: 26; SD_{age} = 2.92) and 31 full-term young adults (M_{age} = 26.35 years; Md_{age}: 26; SD_{age} = 2.18). As above, the same inclusion and exclusion criteria were followed, except in the case of an age ranging from 20 to 40 years.

Instruments

Neuropsychological assessment

Analogical reasoning was evaluated using the Raven's Advanced Progressive Matrices (RPM) test[18], whereas *receptive language* was measured by the Peabody Picture Vocabulary Test III (PPVT-III)[19]. Verbal Fluency was also assessed, which involved completing *phonetic* (P, M, R) and *semantic fluency* (category of animals) tasks (one minute for each trial)[20].

Working memory was assessed on the Wechsler Adult Intelligence Scale IV (WAIS-IV), using the digit span (forward, backward, and increasing) and arithmetic subscales[21]. Additionally, *cognitive flexibility* was measured using The Trail Making Test (TMT) part B[22], the Modified Wisconsin Card Classification Test (M-WCST)[23], and PC and interference measures from the Stroop Test[24]. Lastly, *processing speed* was assessed by means of the Stroop Test (i.e. P and C measures) and TMT part A[22,24].

Theory of mind was measured using four stories from the Happé's Strange Stories Test[25], while *moral competence* was evaluated by means of the Moral Judgment Test (MJT)[26], and the Delay Discounting Test (DDT), also referred to as the Monetary Choice Questionnaire, assessed *delayed gratification*[27].

With the exception of TMT and M-WCST perseverative errors, a higher score in all tests would imply better performance.

Socioeconomic status (SES)

The Hollingshead Index[28] was used to consider the occupation and education domains of participants and their parents independently. Thus, two different measures were obtained: participants' *current SES* (i.e., participants' ongoing occupation and highest level of education) and *familial SES* (i.e., the average of parents' ongoing occupation and highest level of education). For underage subjects, data on the education and occupation domains was obtained from a single parent, and so *familial SES* was the highest score obtained in the case of either the subject's father or mother.

Early life environmental factors

The parental bond was assessed using the Parental Bonding Instrument to appraise participants' parents' independent behavior toward them during childhood (i.e., mother's and father's care and overprotection domains)[29].

The data acquired were retrospective, but the following were evaluated at the time of MRI scanning. *Familial SES* was used as an early life environmental factor[28], and lastly, *adverse childhood experiences (ACEs)* were evaluated by the Adverse Childhood Experiences Questionnaire for Adults and Adverse Childhood Experiences Questionnaire for Teens designed by the WHO[30].

Emotional-behavioral assessment
The Child Behavior Checklist (CBCL) and The Adult Self Report (ASR) were employed as measures of *emotional-behavioral functioning*[31,32].

Life satisfaction, functionality, and resilience
The Satisfaction with Life Scale (SWLS) was used to measure participants' judgments of *satisfaction with their life*[33], while the WHODAS 2.0 subjects' report tool was employed to establish standardized *disability levels and profiles*[34]. Furthermore, *resilience* was assessed on the Connor-Davidson Resilience scale (CD-RISC), with higher scores reflecting greater resilience[35].

Personality data
The NEO Five-Factor Inventory was used to acquire a precise measure of the *five domains of personality* (neuroticism, extraversion, openness, agreeableness, and conscientiousness)[36].

Trained neuropsychologists conducted the overall assessment.

MRI images
3-dimensional MRI datasets were obtained from the Magnetic Resonance Imaging Unit "Osatek", Hospital Galdakao-Usansolo (Galdakao, Spain) for 64 participants, of whom 33 were low-risk preterm and 31 full-term young adults. Additionally, diffusion-weighted MRI images were obtained from a Philips 3 T Achieva dStream in an axial orientation with an anterior-to-posterior phase direction using a multiband EPI sequence (TR = 3820 ms and TE = 81 ms, matrix size = 128 mm × 112 mm; flip angle = 90◦, FOV = 224 × 224 × 120, slice thickness = 2 mm, no gap, 60 slices, acquisition time = 8 min 22.4 s, voxel size = 1.75 × 1.75 × 2.0) with multi-shell diffusion weighting in 128 uniformly distributed directions (b = 2,000 s/mm^2) and 8 b = 0 s/mm^2. T1-weighted images (axial orientation, TR/TE = 8.1/3.7 ms, 288 × 248 matrix, flip angle 8°, slice thickness 1 mm, no gap, 160 slices) were also acquired and they were checked for movement and scanner artifacts prior to processing.

FMRIB Software Library (FSL) version 6.0.3 was utilized to preprocess and analyze the diffusion data[37], whereby each subject's pictures were first concatenated and radiologically oriented. The FSL Brain Extraction Tool (BET) was then used to remove nonbrain tissue[38], and Eddy was also utilized to spot any volumes with a considerable absolute or relative motion, as well as to compensate for any distortions or movement. TOPUP was also employed, as it is a robust and effective method that provides better performance in correcting distortions[39], which were rotated in order to adjust the diffusion gradients (bvecs). FA maps were then constructed by fitting a tensor model to the raw diffusion data using FDT (DTIFIT). In addition, we utilized MATLAB R2019b to generate NODDI images, including the NDI and ODI maps, using the NODDI Matlab toolbox. NODDI imaging yields NDI maps, which indicate neurite density, and ODI maps that show fiber orientation dispersion.

To examine group differences in FA, AD, MD, RD, NDI, and ODI data was prepared using tract-based spatial statistic (TBSS) in order to perform a nonlinear registration of all FA pictures in standard space[40], with the FMRIB58_FA standard-space image being utilized as the target in TBSS. Using the -T option, this requires just one registration per subject to provide appropriate alignment results. With a threshold of 0.2, the mean FA image was thinned to form a "mean FA skeleton," which reflected the centers of all tracts shared by the group. The "TBSS non-FA" script was used to evaluate AD, MD, and RD, NDI, and ODI data, and involved applying the original nonlinear registration to the data and integrating all participants' warped AD, MD, RD, NDI, and ODI data into a 4D file. To construct the 4D-projected data, this file was then projected onto the original mean FA skeleton.

Lastly, FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) (version v6.0.0) was used to extract cortical and subcortical volumes, as well as global and regional cortical thickness (CTh) from 3D T1-weighted structural MRI images[41]. To process T1 high-resolution scans, many methodologies contained in the software were employed. Errors in skull stripping, intensity normalization, WM segmentation, and surface extraction, on the other hand, were manually corrected as required. Each participant's cerebral cortex was divided into 68 subregions based on the Desikan-Killiany atlas[42].

Statistical analysis

Normal distribution of data was assessed using the Kolmogorov–Smirnov test (K-S). Missing values for neonatal data and environmental factors were imputed using the expectation maximization algorithm (i.e., the percentage of missing values was of 0.61%). The data that were imputed refer to the GA, birthweight (BW), familial SES, care measure, overprotection measure and ACEs. Cognitive or brain data, which are the main purpose of the study, were not imputed in any case. All tests were standardized in order to assess cognitive performance using a composite score (henceforth named general cognitive functioning score) obtained from: RPM analogical reasoning and PPVT-III receptive language total scores, M-WCST category and perseverative error scores, WAIS-IV digit span and working memory index, phonetic and semantic fluencies, Stroop Test P, C, PC and interference measures, TMT part A and B, Happé's Strange Stories Test total score, MJT moral competence final score, and DDT delay gratification ratio (reliability analysis of Cronbach's alpha = 0.80).

The Mann–Whitney U test was used to analyze differences in neonatal data (GA and BW), age at time of evaluation, familial SES, care measure, ACEs, emotional-behavioral problems, SWLS, WHODAS and personality data, with the exception of the openness measure. Furthermore, the Chi-squared test was required to assess

differences in two qualitative sociodemographic characteristics: gender and handedness. Student t-tests were also performed to compare overprotection, resilience and openness measures between both groups, while a multivariate analysis of covariance was conducted to compare different cognitive domains, the general cognitive functioning score and current SES (adjusted for age at evaluation). Furthermore, the Bonferroni corrected p-value for significance was calculated in the case of the different cognitive tests assessed ($p = 0.05/17 = 0.003$). Partial eta squared was employed to calculate effect sizes; around 0.01 is considered a small size effect, 0.06 is medium, and above 0.14 is considered to be large. For all preceding analyses, the SPSS version 26 was used, and the significance level was set at 0.05.

Neuroimaging study

A multivariate analysis of covariance (adjusted for age at evaluation) was used to establish the differences in cognitive domains, general cognitive functioning score and current SES between groups in the neuroimaging sample.

Based on the analysis of the neuroimaging data, multivariate analyses of covariance were used to compare global (left/right) and regional CTh (adjusted for age at evaluation), cortical and subcortical volumetric areas (adjusted for age at evaluation and eTIV), and global mean FA, AD, MD, and RD (adjusted for age at evaluation). The Bonferroni post-hoc test was employed to assess differences between groups, and the Bonferroni corrected p-value for significance was calculated for left and right regional CTh ($p = 0.05/34 = 0.001$), subcortical volumetric areas ($p = 0.05/23 = 0.002$) and global WM microstructure mean measures ($p = 0.05/4 = 0.0125$).

Regarding DTI and NODDI analyses, the "randomize" tool in FSL (5000 permutations) with threshold-free cluster enhancement (TFCE) correction for multiple comparisons was employed, including the—T2 option, in order to examine total WM integrity differences in FA, AD, MD, RD, NDI, and ODI. With an extent threshold of 100 voxels, the statistical threshold was set at $p < 0.05$, corrected for family wise error (FWE). The maximal coordinates contained in the clusters and other noteworthy regions were visually inspected with the MRI Atlas of Human White Matter[43], and labeled anatomically with JHU-ICBMDTI-81 WM Labels and JHU White-Matter Tractography Atlas implemented in FSL.

Results

Neonatal, sociodemographic, environmental, emotional-behavioral, life satisfaction, functionality, resilience, and personality variables are shown in detail in Table 1. As expected, there were significant differences in neonatal variables (GA and BW) between both groups. No differences were found in sociodemographic, environmental, emotional-behavioral, life satisfaction, functionality, resilience, or personality variables between both groups, except for the conscientiousness measure, with the full-term sample reporting lower scores.

In terms of cognitive performance, as shown in Table 2, poorer performance was found in phonetic and semantic fluencies, as well as in theory of mind in low-risk preterm adolescents and young adults compared to their full-term peers. These differences remained significant after the Bonferroni correction was applied for multiple comparisons ($p = 0.003$) and small to medium effect sizes were obtained.

Neuroimaging study

As for the neuroimaging sample, significant differences remained in neonatal data. The differences evidenced in the cognitive domains were not maintained, with the exception of statistically significant differences in phonetic fluency without surviving Bonferroni correction. Moreover, statistically significant differences were found in current SES, with the low-risk preterm sample reporting lower values.

Statistically significant differences were not found in global left and right CTh in the neuroimaging study (see Tables S1 and S2). Moreover, no statistically significant differences were shown in regional CTh among groups. However, increased values in the right inferior temporal gyrus were displayed in low-risk preterm young adults compared to the full-term group surviving Bonferroni correction for the purpose of multiple comparisons ($p = 0.001$).

In global volumetric analyses, low-risk preterm young adults did not display any differences in cortex, total GM, and cerebral WM volumes compared to the full-term group. Nevertheless, low-risk preterm-born young adults obtained lower subcortical volumetric values compared to their full-term peers in the thalamus (see Table 3), without surviving Bonferroni correction (p-value = 0.002).

Lastly, no statistically significant differences were found in global mean FA, MD, and RD between both groups, whereas there were differences in global mean AD ($F = 4.24$ $p = 0.044$), with the low-risk preterm group reporting greater values. This difference did not survive Bonferroni correction (p-value = 0.0125). In addition, taking into account group-based regional analyses (see Tables 4 and 5), low-risk preterm young adults obtained greater mean AD and MD than their full-term peers (see Fig. 1); while low-risk preterm young adults obtained lower mean NDI and ODI (see Fig. 2) than the full-term group (FWE-corrected, $p < 0.05$). No significant differences were found regionally in the case of mean FA or RD.

Discussion

This study was conducted with both low-risk preterm and full-term groups and established a number of worse cognitive domains in adolescents and young adults born low-risk preterm. Even though cognitive performance was within normal thresholds, our findings indicate that preterm newborns in the absence of neonatal brain injury evidence lower cognitive performance during adolescence and young adulthood. Additionally, young adults born low-risk preterm evidenced thicker cortex in the right inferior temporal gyrus. Furthermore, regionally greater AD and MD were detected, as in low-risk preterm infants[13], across the frontal part of corpus callosum (CC) during young adulthood. However, contrary to what was found by Kelly et al.[44] in children born very

	Low-risk preterm n = 132 mean ± SD	Full-term n = 118 mean ± SD	Statistics (*p*)
Neonatal data			
GA. weeks [range]	34.15 ± 1.65 [30–36]	39.60 ± 0.91 [37–42]	U = 15,576.00 (< 0.001)
BW. g	2085.25 ± 453.49	3303.11 ± 415.65	t = − 22.05 (< 0.001)
Sociodemographic data			
Gender. male/female	55/77	47/71	X^2 = 0.87 (0.77)
Age. years [range]	23.23 ± 4.60 [16–38]	23.97 ± 4.79 [16–36]	*U* = 8414.50 (0.27)
Handedness right-handed/left-handed	117/15	111/7	X^2 = 2.29 (0.13)
Environmental factors			
Familial SES	39.95 ± 11.58	39.18 ± 14.53	*U* = 7515.50 (0.63)
Care measure	27.33 ± 5.43	27.02 ± 5.10	*U* = 7473.50 (0.58)
Overprotection measure	13.34 ± 5.49	13.81 ± 5.52	*t* = − 0.67 (0.50)
ACEs	3.22 ± 1.64	3.37 ± 1.45	*U* = 8436.50 (0.25)
Emotional-behavioral assessment			
Internalizing problems[¥]	15.39 ± 11.08	14.50 ± 8.17	*U* = 7344.50 (0.86)
Externalizing problems[¥]	9.36 ± 7.79	10.42 ± 6.55	*U* = 8278.50 (0.06)
Total behavioural problems[¥]	43.43 ± 27.46	45.78 ± 19.48	*U* = 8166.50 (0.09)
Life satisfaction, functionality and resilience			
SWLS[¤]	26.15 ± 5.28	25.62 ± 4.19	*U* = 4704.50 (0.16)
WHODAS[ƒ]	15.49 ± 4.46	15.53 ± 4.01	*U* = 5278.50 (0.75)
Resilience[≠]	70.60 ± 12.18	72.40 ± 8.74	*t* = − 1.19 (0.23)
Personality assessment			
Neuroticism[α]	20.24 ± 8.50	19.33 ± 7.56	*U* = 6987.00 (0.48)
Extraversion[α]	32.49 ± 7.31	32.37 ± 6.78	*U* = 7252.50 (0.83)
Openness[α]	29.82 ± 7.72	30.91 ± 7.57	*t* = − 1.12 (0.27)
Agreeableness[α]	31.97 ± 5.35	32.10 ± 5.43	*U* = − 7241.00 (0.81)
Conscientiousness[α]	33.05 ± 7.35	31.29 ± 6.25	U = 6168.50 (0.03)

Table 1. Neonatal, sociodemographic, environmental, emotional-behavioral, life satisfaction, functionality, resilience and personality data. Significant values are in [bold]. Note: SD, standard deviation; GA, gestational age; wks, weeks; BW: birth weight; g, grams; yrs, years; *U*, Mann–Whitney U test; X^2, Chi-square test; *t*, Student-t; SES, socioeconomic status; ACEs, adverse childhood experiences; SWLS, satisfaction with life scale; WHODAS, WHO Disability Assessment Schedule. [¥]Available data for emotional-behavioural assessment: 125 low-risk preterm and 116 full-term adolescents and young adults. [¤]Available data for SWLS: 105 low-risk preterm and 101 full-term adolescents and young adults. [ƒ]Available data for WHODAS: 103 low-risk preterm and 100 full-term adolescents and young adults. [≠]Available data for Resilience: 109 low-risk preterm and 83 full-term adolescents and young adults. [α]Available data for personality assessment: 126 low-risk preterm and 117 full-term adolescents and young adults.

preterm, young adults born low-risk preterm evidenced lower NDI and ODI. These robust differences remain following very conservative statistical correction (i.e. Bonferroni and FWE corrections) was applied.

Compared to the full-term group, low-risk preterm adolescents and young adults performed worse in phonetic and semantic fluencies, and also theory of mind. Although no significant differences in the general cognitive functioning score were identified in this study, prematurity per se, along with neonatal and environmental factors, are thought to have a substantial effect on cognition throughout adulthood[7]. On the other hand, no differences were found in emotional-behavioral problems, life satisfaction, functionality, resilience, or personality data (with the exception of conscientiousness). However, adults born preterm with very low BW would seem to be at higher risk of internalizing problems and socially avoidant personality traits, pointing to BW as a key factor in the presence of these related adverse long-term outcomes[45].

The declines described in CTh from 15 to 20 years old follow a similar developmental trajectory in preterm and full-term adolescents[46], which might be in line with results obtained from this current study, since no differences were found in bilateral mean CTh values among groups. However, regional CTh increases were found in the right inferior temporal gyrus in the low-risk preterm group, as shown in the temporal region surface area following very preterm birth during childhood and thought to follow a delayed maturational trajectory[47]. According to Dimitrova et al.[48], anterior CTh increases had also been observed in heterogeneous preterm newborns at term equivalent age.

WM microstructure after preterm delivery follows a similar path to that of typically developing newborns from five to seven years of age[49]; and during young adulthood, as indicated in the present study, except for the global mean AD. Nevertheless, premature exposure to an extrauterine environment has been related to WM

	Low-risk preterm n = 132 mean ± SD	Full-term n = 118 mean ± SD	*F-Snedecor Statistic (p)*	η_p^2
Neuropsychological assessment (adjusted for age at evaluation)				
PPVT-III, receptive language	160.64 ± 15.26	163.82 ± 11.52	4.74 (0.03)	0.02
Phonetic Fluency	41.05 ± 11.09	46.00 ± 9.56	**14.60 (< 0.001)**	**0.06**
Semantic Fluency[¥]	22.44 ± 5.12	24.44 ± 4.66	**10.39 (0.001)**	**0.04**
RPM, analogical reasoning[¤]	22.83 ± 6.24	23.60 ± 4.66	1.18 (0.28)	0.01
M-WCST Categories, cognitive flexibility	6.50 ± 0.83	6.77 ± 0.61	8.20 (0.005)	0.03
M-WCST Perseverative Errors, cognitive flexibility	0.89 ± 1.08	0.70 ± 0.88	2.12 (0.15)	.01
Stroop Test (P), processing speed	112.35 ± 14.16	114.28 ± 13.26	1.29 (0.26)	0.01
Stroop Test (C), processing speed	75.77 ± 10.36	77.50 ± 10.54	1.69 (0.20)	0.01
Stroop Test (PC), cognitive flexibility	50.71 ± 9.52	52.63 ± 9.97	2.41 (0.12)	0.01
Stroop Test Interference, cognitive flexibility	5.98 ± 8.14	6.58 ± 6.95	0.40 (0.53)	0.00
WAIS-IV Digit Span, working memory	30.41 ± 6.25	29.83 ± 5.06	0.63 (0.43)	0.00
WAIS-IV WMI, working memory	106.36 ± 17.53	108.08 ± 13.61	0.73 (0.40)	0.00
TMT Part A, processing speed	27.64 ± 10.01	26.55 ± 7.62	0.93 (0.34)	0.00
TMT Part B, cognitive flexibility	56.61 ± 18.95	52.42 ± 15.83	3.53 (0.06)	0.01
Happe's Strange Stories Test, theory of mind	6.30 ± 1.38	6.79 ± 1.09	**9.56 (0.002)**	**0.04**
MJ, moral competence[♯]	15.81 ± 9.03	15.06 ± 9.18	0.41 (0.52)	0.00
Kirby DDT, delay discounting	0.62 ± 0.27	0.63 ± 0.28	0.05 (0.82)	0.00
Outcome data (adjusted for age at evaluation)				
General Cognitive Functioning Score	0.004 ± 0.51	− 0.005 ± 0.47	0.02 (0.89)	0.00
Current SES	33.24 ± 16.48	35.67 ± 16.23	2.54 (0.11)	0.01

Table 2. Differences in Cognitive Domains, General Cognitive Functioning Score and Current SES between Low-Risk Preterm and Full-Term Adolescents and Young Adults. The cognitive domains in bold are those that remained significant after Bonferroni correction was applied for multiple comparisons ($p = 0.003$). Note: SD, standard deviation; PPVT-III, Peabody picture vocabulary test-III; RPM, Raven's Progressive Matrices; MWCST, Modified Wisconsin Card Sorting Test; WMI, working memory index; WAIS-IV, Wechsler Adult Intelligence Scale IV; TMT, Trail Making Test; MJT, Moral Judgement Test; DDT, Delay-Discounting Task score; SES, socioeconomic status; η_p^2, partial eta squared. [¥]Available data for semantic fluency: 132 low-risk preterm and 117 full-term adolescents and young adults. [¤]Available data for RPM: 131 low-risk preterm and 118 full-term adolescents and young adults. [♯]Available data for MJT: 127 low-risk preterm and 118 full-term adolescents and young adults.

abnormalities, which are found not only at term equivalent age but also in early maturity[50]. According to our DTI results, low-risk preterm young adults have greater regional AD and MD in widely diverse areas of the brain; a finding that has been previously reported in low-risk preterm-born infants[13]. However, very preterm birth showed lower FA and greater MD and RD within voxels in the approximate region of the CC, a significant region in current findings, when compared to moderate preterm newborns[51]. As per Dibble et al.[52], cellular substrates for our findings may entail altered axonal packing density and water content dependent to directionality, without proving FA and RD sensitivity to myelin damage or loss. Given a delay in brain development, it is also possible that WM microstructure is continuing to develop in the low-risk population too at a later age.

As for NODDI findings, regional group differences in NDI and ODI were lower after low-risk preterm birth; however, they could not resemble the lack of differences in directionality of molecular displacement (i.e., FA). The microstructural level of WM connectivity has been significantly altered, as seen by decreased NDI and ODI. This suggests that despite the upright spatial orientation of WM fibers, there are less WM fibers per voxel. According to Dimond et al.[53], NDI increases with age in all major WM tracts, but ODI remains stable within typical development. In fact, in adults with autism spectrum disorder found extensive reductions in NDI but no abnormalities in ODI[54]. Nevertheless, in line with our results, in those with a history of WM injury after very preterm delivery, lower ODI has been evidenced in the corona radiata during childhood[55]. Increased ODI along the peripheral sub-network, however, it has also been shown in adults born at less than 28 weeks[50].

Findings listed below do not meet the strict statistical criteria of the current study, but may guide future research with larger sample sizes. Firstly, GM volume was shown to be lower after preterm birth at school age, adolescence, and early adulthood, with no signs of catch-up growth, while WM is markedly low during adolescence[56]. Our findings identified the fact that cortex, GM and WM volumes were not diminished or increased in low-risk preterm young adults. Nevertheless, the low-risk preterm group obtained a higher WM mean which is thought to be caused by cortical dysgenesis resulting from the combination of normal brain development processes with perinatal brain lesions[57]. These lesions are found in the presence of extensive WM microstructural alterations following moderate and late preterm birth at term-equivalent age[13]; however, they were excluded from the current study sample. Lastly, low-risk preterm-born young adults obtained lower subcortical volumetric values only in the thalamus, in which at term-equivalent age and in the absence of severe WM

	Low-risk preterm n = 33 mean ± SD	Full-term n = 31 mean ± SD	*F-Snedecor Statistic (p)*	η_p^2
Subcortical volumetric areas mm^3 (adjusted for age at evaluation and eTIV)				
Left Cerebellum WM	14,137.74 ± 1745.15	14,300.25 ± 1747.35	019 (0.67)	0.00
Left Cerebellum Cortex	54,515.94 ± 6258.88	55,189.88 ± 6548.25	0.24 (0.63)	0.00
Left Thalamus Proper	6953.05 ± 721.37	7286.67 ± 933.03	4.67 (0.035)	0.07
Left Caudate	3481.57 ± 444.79	3678.39 ± 588.38	3.45 (0.07)	0.05
Left Putamen	5183.92 ± 683.77	5182.91 ± 558.32	0.00 (0.99)	0.00
Left Pallidum	1765.60 ± 209.62	1796.11 ± 249.52	0.45 (0.51)	0.01
Left Hippocampus	3849.81 ± 364.93	3913.21 ± 457.69	0.53 (0.47)	0.01
Left Amygdala	1493.56 ± 245.35	1473.82 ± 245.27	0.17 (0.68)	0.00
Left Accumbens Area	662.42 ± 103.23	706.69 ± 104.11	3.59 (0.06)	0.06
Right Cerebellum WM	13,553.62 ± 1663.64	13,647.49 ± 1666.66	0.07 (0.80)	0.00
Right Cerebellum Cortex	54,859.02 ± 6604.58	55,096.94 ± 6658.64	0.03 (0.87)	0.00
Right Thalamus Proper	6661.04 ± 662.58	6986.01 ± 795.72	5.65 (0.021)	0.09
Right Caudate	3609.67 ± 459.49	3789.79 ± 533.25	3.07 (0.09)	0.05
Right Putamen	5116.08 ± 569.30	5103.83 ± 522.68	0.01 (0.92)	0.00
Right Pallidum	1763.71 ± 208.14	1833.11 ± 242.61	2.05 (0.16)	0.03
Right Hippocampus	4007.44 ± 493.00	4008.45 ± 420.74	0.00 (0.99)	0.00
Right Amygdala	1716.93 ± 237.27	1731.83 ± 277.35	0.08 (0.78)	0.00
Right Accumbens Area	616.19 ± 95.30	644.13 ± 97.47	1.49 (0.23)	0.02
CC Posterior	906.10 ± 151.59	936.92 ± 151.07	0.78 (0.38)	0.01
CC Mid Posterior	512.25 ± 102.21	524.12 ± 92.44	0.23 (0.64)	0.00
CC Central	513.82 ± 74.24	515.44 ± 110.05	0.00 (0.95)	0.00
CC Mid Anterior	489.80 ± 76.80	528.24 ± 146.13	1.78 (0.19)	0.03
CC Anterior	896.36 ± 148.10	879.09 ± 162.57	0.22 (0.64)	0.00

Table 3. Differences in Subcortical volumetric areas between low-risk preterm and full-term young adults. Significant values are in [bold]. Note: SD, standard deviation; η_p^2, partial eta squared; mm^3, cubic millimeter; eTIV, total intracranial volume; WM, white matter; CC, corpus callosum.

	Brain regions	Cluster size (voxels)	*x*	*y*	*z*	*t*	*p*
Whole brain differences in mean AD between low-risk preterm and full-term young adults							
Cluster 1	**Frontal part of the CC (forceps minor)**, inferior fronto-occipital gyrus, middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, anterior corona radiate, anterior and posterior limb of the internal capsule, external capsule, fornix, left cingulum, left transverse temporal gyrus, left cerebral peduncle, right superior longitudinal fasciculus, right gyrus rectus	33,852	103	159	71	3.943	0.002
Whole brain differences in mean MD between low-risk preterm and full-term young adults							
Cluster 1	**Optic tract**, corticospinal tract, anterior thalamic radiation, CC (forceps major and minor), left gyrus rectus, left medial orbital gyrus, left inferior fronto-occipital fasciculus	12,463	95	130	54	3.134	0.033

Table 4. Cluster characteristics of the DTI whole brain differences between low-risk preterm and full-term young adults. Cluster size denotes the extent of the cluster of significant voxels. FMRIB Software Library (FSL) coordinates indicate: x increases from left to right; y increases from posterior to anterior; and z increases from inferior to superior. Regions represent the maximum significant difference coordinate encompassed in the given cluster. AD, axial diffusivity; CC, corpus callosum; MD, medial diffusivity. Region in bold represents the maximum coordinate encompassed in the given cluster.

injury a disrupted development of the thalamocortical system has been observed[58]. Nonetheless, our results do not resemble adults born preterm with a wide range of GA (25–36 weeks) smaller volumes in putamen, caudate or hippocampus[17].

To our knowledge, this is the first study that has assessed long-term neuropsychological performance with low-risk preterm and full-term groups. In other words, unlike previous studies that used heterogeneous preterm samples, this study employed neonatal and sociodemographic data to reach comparable groups, thus supporting the generalizability of results. However, the methodological strategy (i.e., non-probabilistic sampling) the sample was recruited is very likely to bias our results. Moreover, neonatal CUS screening might fail to detect WM gliosis in participants born low-risk preterm. Another drawback is the sample size, particularly in the neuroimaging study, which limits the interpretation of these findings. A large age range (16–38 years old) was also represented, even though our analyses were age-controlled. Additionally, in our study population, the mean GA at birth falls in the late preterm range (between 35 and < 37 weeks). When it comes to adulthood, there are minimal differences

	Brain regions	Cluster size (voxels)	*x*	*y*	*z*	*t*	*p*
Whole brain differences in mean NDI between low-risk preterm and full-term young adults							
Cluster 1	**Frontal part of the CC (forceps minor)**, anterior thalamic radiation, cingulum, left superior and inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left uncinate fasciculus, left corticospinal tract	19,806	120	158	95	3.393	0.019
Whole brain differences in mean ODI between low-risk preterm and full-term young adults							
Cluster 1	**Frontal part of the CC (forceps minor)**, anterior thalamic radiation, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus	24,830	100	127	60	3.936	0.006

Table 5. Cluster characteristics of the NODDI whole brain differences between low-risk preterm and full-term young adults. Cluster size denotes the extent of the cluster of significant voxels. FMRIB Software Library (FSL) coordinates indicate: x increases from left to right; y increases from posterior to anterior; and z increases from inferior to superior. Regions represent the maximum significant difference coordinate encompassed in the given cluster. NDI, neurite density; CC, corpus callosum; ODI, fiber orientation dispersion. Region in bold represents the maximum coordinate encompassed in the given cluster.

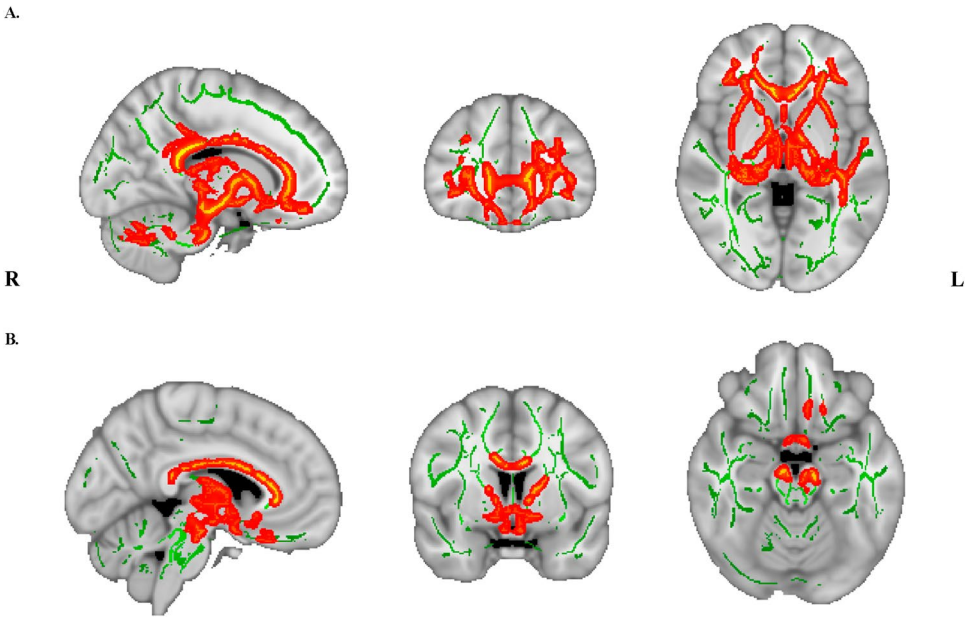

Figure 1. (**A**, **B**) Whole brain AD and MD differences between low-risk preterm and full-term young adults. Differences are significant at $p < 0.05$ corrected for family-wise error (FWE). WM regions in which low-risk preterm young adults showed a higher mean AD and MD compared to their full-term peers are displayed in red-yellow; the WM skeleton is shown in green. R, right; and L, left.

between individuals born late preterm and full-term[59]. However, although the risk of severe neonatal morbidities is low, late prematurity still led to a higher risk of adverse outcomes in comparison to typically developing infants[60]. There were also significant differences in conscientiousness and current SES (only in the neuroimaging sample) between both groups, and so caution would be required regarding the actual findings.

In conclusion and as discussed in this study, low-risk preterm birth has an impact on phonetic and semantic fluencies, and also theory of mind, together with deviations from normative structural brain development in right inferior temporal gyrus and regional WM microstructure during young adulthood, when statistically rigorous standards are applied. Our results support the idea that any degree of preterm delivery will have something of an impact on cognition, resulting in adverse neurodevelopment over time[5]. Understanding the brain scheme by which long-term performance outcomes arise following low-risk preterm birth increases the chances of identifying children who are at a higher risk early on. In fact, low-risk preterm newborns may be at a social disadvantage compared to those with a lower GA, who are more likely to receive more extensive developmental follow-up and early interventions. Thus, the availability of appropriate resources, mainly for those with atypical development in areas related to right inferior temporal gyrus and the frontal part of CC, might lead to an improved preterm neuropsychological profile later in life. However, additional research is needed in order to provide further data concerning macro- and microstructural brain development and its associations with possible adverse future outcomes in larger low-risk preterm samples.

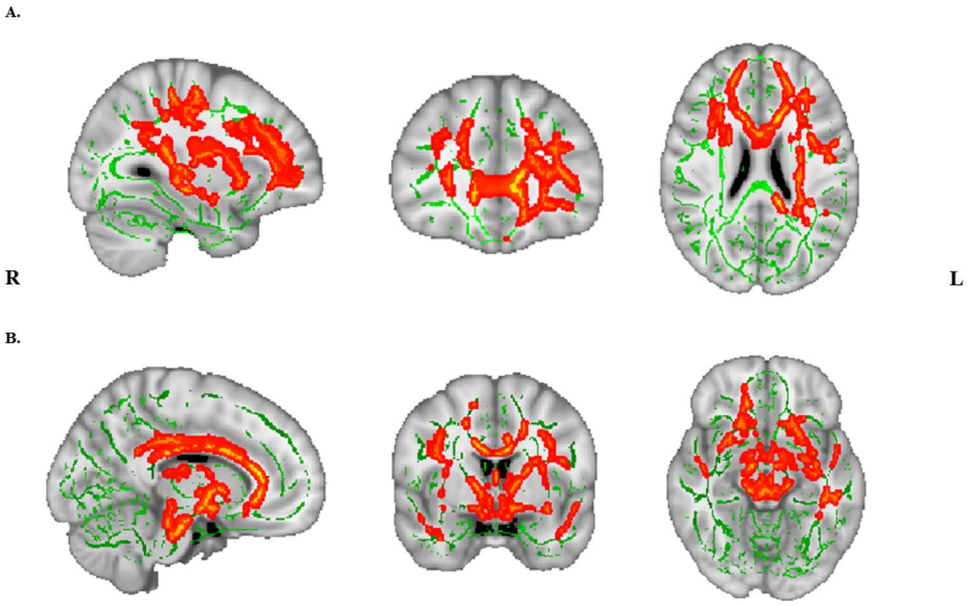

Figure 2. (**A**, **B**) Whole brain NDI and ODI differences between low-risk preterm and full-term young adults. Differences are significant at $p < 0.05$ corrected for family-wise error (FWE). WM regions in which low-risk preterm young adults showed a lower mean NDI and ODI compared to their full-term peers are displayed in red-yellow; the WM skeleton is shown in green. R, right; and L, left.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

L.Z.-E., N.O., B.L.-G. and J.M.O. conceived and designed the study, including participant selection, recruitment, and data collection. L.Z.-E., A.G.-G. and L.F.G.-O. carried out the statistical analysis and interpretation of the data. All authors collaborated in drafting the manuscript and critically revised and edited the initial manuscript as well as read and approved the final manuscript as submitted.

Competing interests

The authors declare no competing interests.

Additional information

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