Brain volume and neuropsychological differences in extremely preterm adolescents

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Abstract. Although findings have revealed that preterm subjects are at higher risk of brain abnormalities and adverse cognitive outcome, very few studies have investigated the long-term effects of extreme prematurity on regional brain structures, especially in adolescence. The current study aims to investigate the volume of brain structures of 88 extremely preterm born 19-year old adolescents and 54 age- and socioeconomically-matched full-term born subjects. In addition, we examine the hypothesis that the volume of grey matter regions where a significant group or group-sex differences are found would be connected with the neurodevelopmental outcome. The results of the analysis show regional brain difference linked to extreme prematurity with reduced grey matter content in the subcortical regions and larger grey matter volumes distributed around the medial prefrontal cortex and anterior medial cortex. Premature birth and the volume of the left precuneus and the right posterior cingulate gyrus accounts for 34% of the variance in FSIQ. The outcome of this analysis reveals that structural brain differences persist into adolescence in extremely preterm subjects and that they correlate with cognitive functions.

Keywords: Prematurity · Brain volume · T1-weighted MRI · Grey matter

1 Introduction

The number of newborns surviving preterm birth is growing worldwide [8]; however, the outcome of their general health extends from physical impairments such as brain abnormality [14, 1, 9] and cardiovascular diseases [12] to psychological and cognitive function disabilities [6, 15]. While the normal period of gestation before birth is at least 37 weeks, preterm born subjects are born before this period [8]. Extremely preterm born subjects are born before 28 weeks of gestation [8].

Previous neuroimaging studies on preterm adolescents [13, 14, 9] have regularly reported developmental abnormalities throughout the brain volume and the grey matter in particular. The grey matter differences might have risen from premature exposure to the extra-uterine environment and the consequent interruption of normal cortical maturation, which takes place mainly after the 29^{th} week of gestation [17]. Differences in brain structural volume have been described in preterm newborns and adolescents, particularly in the prefrontal cortex, deep grey matter regions and cerebellum [14, 1]. Research has revealed that preterm subjects, across infancy and adolescence, are at higher risk of adverse neurodevelopmental outcome [12, 15]. Establishing links between regional brain volume and cognitive outcome could pave the way to better define specific risks in preterm subjects of enduring neurodevelopmental deficits [13, 14, 9].

Despite the researchers' efforts in investigating preterm infants cohorts [1], very few studies have investigated structural brain alteration in extremely preterm (EP) subjects, especially in adolescence. The long-term impact of extreme prematurity later in life is less examined, and the adolescent brain phenotype of extreme prematurity is not extensively explored. Neuroimaging data and neurodevelopmental measurements of EP adolescents are now available, and the measurement of brain structures can be linked with neurocognitive performance. This study aims to estimate the difference between the expected regional brain volume for EP subjects and full-term (FT) subjects once variation in regional brain volume linked to total brain volume has been regressed out. Besides, we test the hypothesis that the effect of premature birth on brain volume depends on whether one is male or female. Moreover, we investigate the hypothesis that the volume of grey matter regions where the significant group or sex-group differences are found would be connected with neurodevelopmental outcome.

2 Methods

2.1 Data

The Magnetic Resonance Imaging (MRI) data include a group of 88 (53/35 female/male) 19-year old adolescents born extremely preterm, and 54 (32/22 female/male) FT individuals matched for the socioeconomic status and the age at which the MRI scans were acquired. Table 1 reports further details about the cohort.

T1-weighted MRI acquisitions were performed on a 3T Philips Achieva system at a repetition time (TR) of 6.93 ms, an echo time (TE) of 3.14 ms and a 1 mm isotropic resolution. T1-weighted volumes were bias-corrected using the N4ITK algorithm [16]. Tissue parcellations were obtained using the Geodesic Information Flow method (GIF) [3]. GIF produces 144 brain regions, 121 of which are grey matter regions, cerebellum, and brainstem.

Overall cognitive ability was evaluated using the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) [11]. Full-scale IQ (FSIQ) was obtained by combining scores from block design, matrix reasoning, vocabulary, and similarities tasks [15].

Data-set features	EP females	EP males	FT females	FT males
Sample size	53	35	32	22
Age at scan [years]	19	19	19	19
GA [w] μ, (95% CI)	25.0 (23.3 − 25.9)	25.3 (25.9 − 23.4)	40 (36 − 42)	40 (36 − 42)

Table 1. Demographic features of the extremely preterm (EP) born females and males and the full-term (FT) females and males. The table reports the sample size, the age at which the MRI scans were acquired (Age at scan) in years, and the gestational age (GA) at birth in weeks (w).

2.2 General linear model with interaction effects

The following linear model interprets the relationship between the volume of a brain region (RBV), the total brain volume (TBV), sex, and birth condition.

$$\log(\text{RBV}) = \alpha + \beta_1 * \text{group} + \beta_2 * \text{sex} + \beta_3 * \text{group} * \text{sex} + \beta_4 * \log(\text{TBV}) \quad (1)$$

The increase in TBV is linked to an increase in the volume of RBV. RBV and TBV are log-transformed to account for potential non-linearities. Dummy variables are used to moderate the effect of other explanatory variables such as sex and preterm birth. Specifically, α is the intercept, β_1 is the coefficient of the dummy variable group (EP=1, FT=0), β_2 the coefficient of the dummy variable for male/female (male=1, female=0), β_3 the coefficient for the interaction effect, and β_4 is the contribution of TBV.

The gap in expected regional brain volume between EP and FT females is estimated by β_1; while the gap in expected regional brain volume between EP and FT males is $\beta_1 + \beta_3$. The coefficient β_1 estimates the difference between the expected RBV for FT subjects and EP born subjects once variation in RBV caused by sex and TBV has been regressed out. The product variable group$*$sex is coded 1 if the respondent is both male and EP subject. Hence the increment or decrement to average regional brain volume estimated for group $*$ sex applies only to this distinct subset. Therefore, the coefficient β_3 for the interaction term estimates the extent to which the effect of being preterm born differs for male and female sample members.

For the sake of our analysis, we are interested in the gap between the groups and the interactions effect. By using the natural logarithmic transformation of the RBV, the relationship between the independent variables and the dummy variables from β_1 to β_3 is in proportional terms [7]. The difference in percentage associated with β_i is $100 * [\exp(\beta_i) - 1]$ [7]. The t test associated with the regression coefficients of the dummy variable β_1 tests the significance of the effect of being EP female rather than FT female (reference group). To assess the effect of being EP female rather than EP male, the t test associated with the difference in regression coefficients is [7]: $t = [(\beta_1 + \beta_3) - \beta_1]/[\text{var}((\beta_1 + \beta_3) - \beta_1)]^{1/2}$, using a *p-value* threshold of 0.05.

2.3 Cognitive outcome and grey matter volumes

The contribution of the regional brain volumes with significant between-group (or sex) differences to the neurodevelopmental outcome is analysed using stepwise linear regression. The FSIQ scores denote the dependent variable, while the grey matter volume and group (or sex) membership are the regressors.

3 Results

Overall the TBV of the EP born males ($1074.82\,\mathrm{cm}^3$) is significantly lower ($p = 1.96e^{-5}$) than the TBV of FT born males ($1198.74\,\mathrm{cm}^3$). Similarly the TBV of EP born females ($988.09\,\mathrm{cm}^3$) is significantly lower ($p = 7.26e^{-4}$) than the TBV of FT born females ($1054.24\,\mathrm{cm}^3$).

Group differences in grey matter regions are mostly bilaterally distributed. Figure 1 shows the amount by which the volume of each brain region has changed in the EP subjects (encoded in β_1) and the additional difference due to male sex (encoded in β_3). The values are in proportion to the reference group (FT born females). Figure 2 shows the statistics of the coefficients β_1 and β_3. Overall the subcortical structures, including bilateral thalamus, pallidum, caudate, amygdala, hippocampus, ententorhinal area, left parahippocampal gyrus, and right subcallosal area are significantly reduced by $8.23\% \pm 1.89\%$ on average. Bilateral central operculum is reduced by 8.17%, superior occipital gyrus by 6.75%, post-central gyrus medial segment by 19.99%, left posterior orbital gyrus by 6.95%, right gyrus rectus by 7.97%, right middle temporal gyrus by 8.36%, right superior parietal lobule by 7.27%, and brainstem by 3.77%.

The brain regions that are significantly increased in the EP are distributed in the medial prefrontal cortex with an average increase of $10.26\% \pm 3.55\%$, anterior medial cortex with mean rise of $10.25\% \pm 1.96\%$, bilateral middle frontal cortex a mean rise of 8.43%, and regions in the occipital lobe with an mean rise of $10.00\% \pm 5.88\%$.

The coefficient β_3 of the interaction effect shows that the bilateral temporal pole (L:-8.61%, R: -6.98%), cerebellum (L:-14.37%, R: -13.56%), cerebellar vermal lobules I-V (-15.71%), cerebellar vermal lobules VIII-X (-11.80%), and left fusiform gyrus (-6.34%) are significantly ($p < 0.05$) reduced in EP males. Left hippocampus (6.71%), left ententorhinal area (7.36%), and right parietal operculum (17.45%) are significantly ($p < 0.05$) increased in EP males.

There is a significant difference (p=$7.57e^{-11}$) between EP subjects (mean= 88.11, SD= 14.18) and FT participants (mean= 103.98, SD= 10.03) on FSIQ. Although, there is no statistically significant ($p > 0.05$) difference between males and females in each group, the EP males (mean= 85.94, SD= 14.04) achieved lower mean score than the EP female individuals (mean= 89.70, SD= 14.07).

Results of the stepwise linear regression comparing EP and FT revealed that the premature birth and the volume of the left precuneus and the right posterior cingulate gyrus (in which EP showed greater regional volume than FT) accounts for 34% of the variance of FSIQ (F= 22.96 $p = 4.67e^{-12}$). Group membership

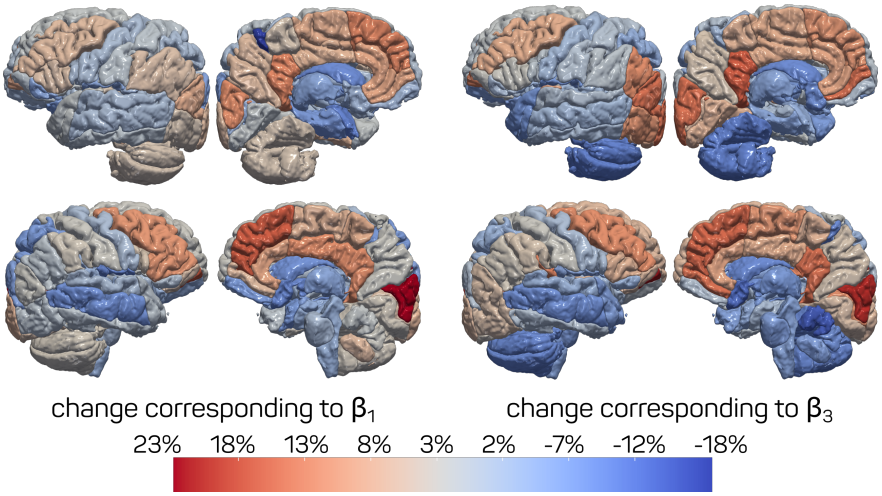

Fig. 1. The left side shows the change in the volume of being EP subject regardless of sex, while the right side illustrates the additional effect of being a male subject born extremely premature. The regions in blue colours are reduced and the regions in red are increased. The darker the colour, the greater the change.

($p = 1.76e^{-7}$) accounted for most of the variance (21.8%) and the volume of the right posterior cingulate gyrus accounted for the least (2.5%). The stepwise linear regression comparing EP males and females showed that the sex differences in the EP subjects and the volume of the cerebellar vermal lobules IV and right temporal pole account for 23.5% of the variance in FSIQ (F= 8.27 $p = 7.26e^{-5}$).

4 Discussion

We examined regional brain volume differences in a cohort of extremely preterm adolescents compared to their age- and socioeconomically-matched peers. We controlled for total brain volume and sex and investigated the impact of extremely preterm birth on the volume of grey matter structures. We further examined the hypotheses that differences in regional brain volume associated with extreme prematurity would be more substantial for male than female individuals, and that there is an association between the volume of grey matter regions where significant between-group (or sex) differences are found and neurodevelopmental outcome.

The findings of the present analysis suggest that EP adolescents lag behind their peers as the brain differences and poor cognitive outcome persist at adolescence. Similar to other studies on very preterm individuals in mid-adolescence [13], our analysis showed both smaller and larger brain structures. The decrease in the volume of subcortical regions observed in the present analysis has been reported by many preterm studies on newborns [1] and mid-adolescents [14].

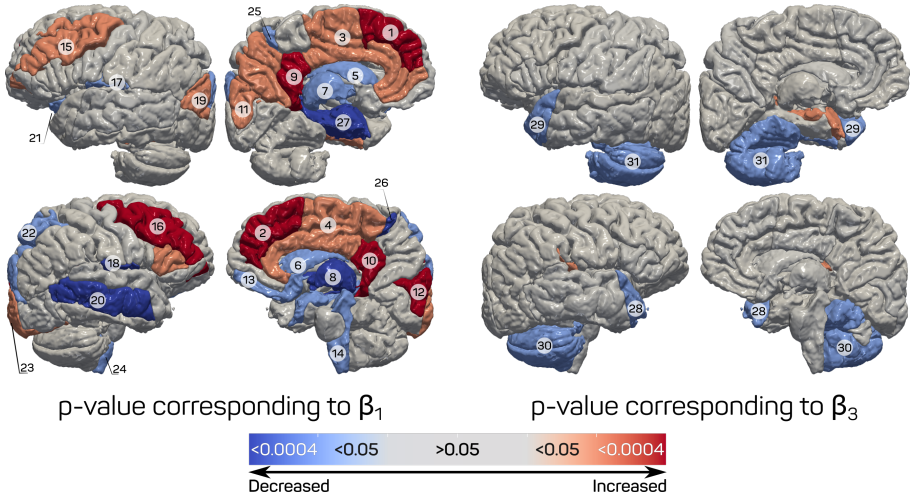

Fig. 2. Statistics of the difference in regional brain volume in EP born subjects. The regions in grey colour do not exhibit a significant difference ($p > 0.05$). Darker colour indicates that the region is significantly different after Bonferroni correction ($\alpha = 0.0004$) and lighter colour shows that the region is lower than the standard threshold $p = 0.05$ but above the critical Bonferroni threshold. Red colours indicate increased volume in EP subjects and blue colours display decreased volume in EP subjects. The significant regions are: 1 : 2 R-L superior frontal gyrus medial segment, 3 : 4 L-R supplementary motor cortex, 5 : 6 R-L caudate ,7 : 8 R-L thalamus, 9 : 10 R-L posterior cingulate gyrus, 11 : 12 R-L cuncuneus, 13 R gyrus rectus, 14 brainstem, 15 : 16 R-L middle frontal gyrus, 17 : 18 R-L hippocampus, 19 L middle occipital gyrus, 20 middle temporal gyrus,28 : 29 R-L temporal pole ,30 : 31 R-L cerebellum.

The consistency of these findings suggests that these regions might be especially vulnerable to damage and that the EP subjects would endure long-lasting or permanent brain alterations. The loss in grey matter content in the deep grey matter might be a secondary effect of white matter injury, as white matter damage is linked to grey matter growth failure [2]. Larger grey matter volumes in EP subjects are distributed around the medial prefrontal cortex and anterior medial cortex. Such a result might reflect a paucity of white matter content; alternatively, as proposed by some authors [14], this might indicate a delayed pruning process specific to these regions.

The interaction term investigates whether the effect of being extremely preterm born differed for males and females. The results showed that the status of being male and born extremely preterm results in a significant reduction in the bilateral cerebellum and temporal pole. Although this result did not persist after adjustment for multiple comparisons was made, it is worth considering for further analysis in view of other studies describing sex-specific brain alterations [13] and sex-specific cognitive impairments [15]. As the incidence of cerebellar haemorrhage [10] and white matter injury [5] is higher in preterm born males, it is plausible that the reduced volume in the cerebellum and temporal pole is due to grey matter loss attributable to complex pathophysiological mechanisms triggered by either cerebellar haemorrhage [4] or white matter injury [2].

In line with previous findings [14, 15], EP subjects achieved lower scores than FT subjects on Full-scale IQ measurements. Our results suggest involvement of the precuneus and posterior cingulate gyrus in explaining the variance in the IQ scores although this does not rule out important influences from other connected brain regions.

The assumption of homogeneity of variance might not hold due to either the *a priori* variable impact of prematurity on EP subjects or the unequal sample sizes of the groups. The change in brain structures in the EP cohort is variable with EP subjects reporting from normal to very divergent brain volume. Besides, the dataset contains more EP than FT individuals and more females than males subjects. Although Levene's test suggests that all input samples are from populations with equal variances ($p = 0.1$), the factors as mentioned earlier might present a limitation in the present analysis. The linear model presented here can capture the average group effect; however, it is clear that there is an individual variability that this kind of analysis ignores. As mentioned above, since the extreme prematurity has a variable effect on EP subjects, an analysis targeted to tackle this might lead to richer findings. Future work on this dataset will develop a framework to investigate this opportunity.

The present analysis has been carried out on a unique dataset of EP 19-year old adolescents with no differences in gestational age, age at which the MRI scans were acquired, and socio-economic status; moreover, the control group are matched with EP in age at MRI scan and socio-economic status. These characteristics of the data allow the analysis to rule out some hidden factors that affect other studies. Furthermore, the volume of brain structures has been measured

in the subjects space, removing from the workflow additional uncertainty due to registration error.

The grey matter of the EP adolescent brain shows long-term developmental differences, especially in subcortical structures, medial prefrontal, and anterior medial cortex. The variations in the regional brain volume are linked with neurodevelopmental outcome. The main outcome of this analysis is that the extremely preterm brain at adolescence remains affected by early-life injuries; however, it is hard to conclude if the observed volume abnormalities are growth lag or permanent changes. To investigate this further, future investigations on this cohort or similar cohorts need to take place at later stages of life of the subjects.

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