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Gestational Age and Gender influence on Executive Control and its Related Neural Structures in Preterm Children at 6 Years of Age

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Abstract

Objective: Within preterm born children, being born male and at a lower gestational age (GA) have respectively been associated with a heightened risk for developmental difficulties. However, in this population little is known about the combined effect and the influence of these risk factors on cortical structures and executive control. **Method:** 58 preterm born children (GA ranging from 24.0 to 35.1 weeks) were administered the computerised Child Attention Network Task at 6 years of age. Brain magnetic resonance imaging was performed and analyzed using Voxel-Based Morphometry (VBM) in all children. **Results:** At a behavioral level, boys born < 28 weeks of GA had significantly less executive control than preterm girls born < 28 weeks (p =.001) and then preterm boys born ≥ 28 (p =.003). The reduced executive control in preterm born boys < 28 weeks gestation was related to lower cortical densities in the inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex (DLPFC). **Conclusions:** The current study links the higher incidence of reduced executive control in preterm boys to a higher degree of prematurity (low GA) and identifies brain structural abnormalities in the prefrontal cortex related to these deficits. The implication of these results are discussed.

Keywords: *executive control abilities, preterm children, gender differences, level of prematurity, brain structure*

1. Introduction

Studies show that children born prematurely (before 37 weeks of gestation) are at risk for long-term abnormal neurodevelopment (e.g. Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Kesler et al., 2008; Soria-Pastor et al., 2009). More specifically, many studies reported deficits in attentional abilities that seem to persist throughout childhood and adolescence in preterm born individuals (e.g. Jaekel, Baumann, & Wolke, 2013; Lindstrom, Lindblad, & Hjern, 2011; Mulder, Pitchford, Hagger, & Marlow, 2009; Wilson-Ching et al., 2013).

However, not all preterm children express these difficulties to a similar degree. Indeed, being born male has been associated with a heightened risk for general developmental delay (Stevenson et al., 2000). Furthermore, it has been shown that extreme preterm born (Gestational Age (GA) < 28 weeks) boys have significantly lower general cognitive scores than extreme preterm born girls, whereas no differences were found between boys and girls born at term (Marlow, Hennessy, Bracewell, Wolke, & Grp, 2007). Equally a recent study investigated cognitive outcome following late and moderate prematurity (late and moderate premature, LMPT; 32-36wks gestation) at 2 years of age (Johnson et al., 2015). This study indicated that among LMPT children, mean cognitive and language scores were 0.15 SD lower than among controls, which was equivalent to a 2.3-point deficit in standardised IQ scores. In this study the strongest risk factor for low cognitive scores was male sex: LMPT boys were at sevenfold increased risk compared with LMPT girls. Among males, LMPT birth conferred a greater risk of moderate/severe impairment compared to controls, while rates among female LMPT children and controls were similar and no significant gender difference were found in term born children. Earlier studies equally indicate longer term outcomes in preterm born children. McGrath et al. (2005) reported that boys born preterm have poorer sustained attention than girls at 4 years of age on specific problem solving tasks. However, other studies have shown that at later ages (7 years), although moderate preterm birth (32-36 weeks gestation) had influenced neuropsychological functioning at school age, moderately preterm born boys catch up whilst the moderately preterm born girls lagged (Cserjesi et al., 2012). Although gender differences are not addressed in all studies of attention and cognitive performance, gender is shown frequently in the literature to influence preterm neurodevelopmental outcome. Level of prematurity seems to equally be a determining factor of variable outcome, with extremely preterm children (GA < 28 weeks) having been reported to have a higher incidence of cognitive impairement (Larroque et al., 2008) and present greater attentional difficulties compared to moderately preterm born children (Mulder et al., 2009).

However, when discussing attention capabilities we need to be aware that attention is not a singular status. One of the conceptual models used in neuropsychological studies (Petersen & Posner, 2012; Posner & Petersen, 1990) divided attention abilities in three different components, namely alerting (maintaining vigilance capacities), orienting (selecting a modality or location in order to prioritize sensory input) and executive control (top-down controls allowing focal attention and the regulation of processing networks).

The child version of the Attention Network Task (ANT; Rueda et al., 2004), a task specifically designed to assess the three attention systems, has previously been used to assess preterm born and full-term born children at 6 years of age (Pizzo et al., 2009). The authors demonstrated that preterm children showed significantly lower performance on executive control than full-term born children. Similar findings were observed in preterm children aged 7-11 years (Leclercq, Jambaqué, Picard, Bricout, and Siéroff (2006). These studies imply that at school age, preterm born children have deficits mainly in the executive control task, using the ANT as assessment tool. From a neurological standpoint, the alerting network is sustained by a widely distributed network including parietal and frontal cortices (Petersen & Posner, 2012). Orienting abilities are sustained by the posterior attentional system composed of the dorsal attention network (top down visuospatial) and the ventral attention network (bottom-up reorienting). The dorsal attention network encompasses the frontal eyes fields (FEF) and the intraparietal sulcus /superior parietal lobe (ISP/SPL). The ventral attention network is composed of the temporo-parietal junction and the ventral frontal cortex (for a review see Petersen & Posner, 2012). Finally, the executive control network consists of the frontoparietal control system: the anterior cingulate cortex (ACC), the middle cingulate cortex (mCC), the dorsolateral prefrontal cortex (DLPFC), the anterior prefrontal cortex (including the inferior frontal gyrus), the thalamus, the intraparietal sulcus/superior parietal lobe (IPS/SPL) and the precuneus.

Brain structure variations have been reported between preterm and full-term children at various ages from the newborn period to adulthood. For instance, smaller volumes of specific cerebral regions (e.g. premotor cortex, cerebellum, basal ganglia) and lower cortical density were measured in prematurely born children (Inder, Warfield, Wang, Huppi, & Volpe, 2005; Kesler et al., 2008; Ment, Hirtz, & Huppi, 2009; Mewes et al., 2006; Walhovd, Tamnes, & Fjell, 2014). In particular, preterm children at 12 years of age had significantly less gray matter volume specifically in the basal ganglia as well as cortically in the prefrontal cortex and the temporal lobe compared to children born at term (e.g. Kesler et al., 2008). Regarding the influence of GA on brain maturation, Davis et al. (2011) showed that longer duration of gestation was associated with increases in gray matter density in specific regions such as the temporal lobe, cerebellum and insula in children aged 6 to 10 years of age. Not only are differences noted as a function of level of prematurity but differences are also found across gender. Structural brain differences are observed between girls and boys with total brain volume being larger in boys than in girls (e.g. Allen, Damasio, Grabowski, Bruss, & Zhang, 2003; Luders et al., 2006). Although comparison of brain volumes in boys showed reduced volume for prematurely born boys compared to those born at term; preterm born girls' brain structures are generally not found to differ significantly from their term born counterparts (Kesler et al., 2008). In the same vein, Kapellou et al. (2006) reported that being born preterm and male has a negative impact on the brain gyrification expressed by the relationship of surface to volume of the brain. Some neurodevelopmental outcome studies in high risk preterm children have shown a clear disadvantage for boys compared to girls (Stevenson et al., 2000; Marlow et al., 2007; McGrath et al., 2005).

Taken together these studies suggest that preterm birth, as well as being born male differentially affects brain development. However, in line with the demonstrated structural and cognitive gender differences, differences in the development of the aforementioned attention network have not been evaluated, despite a high incidence of attention and learning difficulties in preterm children. In addition, to our knowledge, no studies have evaluated the combined effect of both gender and severity of prematurity on brain structure and attentional abilities. Hence, the current study specifically aims to extend reported findings of attention network deficits in preterm born children by examining whether this difference is influenced by gender and severity of prematurity, as well as examining the neural structures associated with the attention networks.

2.Material and Method

2.1.Population

Children were recruited from the Division of Child Development and Growth at the University Hospital of Geneva and the Child Development Unit at the University Hospital of Lausanne, and were examined at around 6 years of age. The study was presented to the parents in order to obtain informed consent. The procedure was approved by the ethics committee of both institutions.

All preterm children (n=136) born between September 2001 and August 2004 in Geneva or Lausanne, Switzerland were eligible to participate to the study. Children were part of a cohort recruited in previous projects. At that time, according to the hospital guidelines, all children born between 28 and 34 weeks of gestation received 1 or 2 courses of antenatal corticosteroids for lung maturation. None of the infants in this study received postnatal steroids. Inclusion criteria comprised being free of cerebral pathologies, i.e. intraventricular hemorrhage, ventriculomegaly or white matter injury assessed by early ultrasound and MRI at term equivalent age. Additionally, none of the children suffered from severe motor difficulties or cerebral palsy. Finally, children with central nervous system and spine malformations and children with chromosomal abnormalities were excluded from the study. Twenty children (from the 136 preterm birth) were excluded from the study because of these criteria. Additionally there were forty-seven refusals to participate. Of the remaining 68 children, 6 had moved away in the first year of life and 4 refused the MRI at 6 years of age (total N = 58). No differences were observed between children who participate in the study and who refused to participate with regards to neonatal (GA and brithweights) and sociodemographic characteristics (SES and gender). It needs to be noted that the sample is composed of 8 twins (n=16), which is consistent with epidemiological data from preterm populations (Goldenberg, Culhane, Iams, & Romero, 2008). The twins are equally distributed for GA and gender.

The sample was divided into four groups based on GA (extremely preterm vs. very preterm; $<$ 28 vs. $\geq 28 > 34.3$ weeks gestation respectively) and gender (girls versus boys). Neonatal variables were examined between groups with t-test analysis and chi-square analysis as appropriate (see table 1).

<<INSERT TABLE 1 ABOUT HERE>>

A significant difference between groups was found in the proportion of children born small for gestational age (SGA) with a birth weight below the 10^{th} percentile for gestational age and gender (see table 1). Additionally between group differences were found for chronic lung disease (CLD; defined as the need for supplemental oxygen for at least 28 days after birth and/or oxygen at 36 weeks postmenstrual age or at discharge (whichever comes first). As SGA and CLD were distributed heterogeneously between groups and the literature outlines an impact of these factors on developmental outcome (Böhm et al., 2002; Doyle & Anderson, 2009) these were entered as covariates in further analysis. Socio-economic status (SES) was evaluated for each of the groups using the Largo scale (Largo et al., 1989). This is a 6-point scale based on paternal occupation and maternal education; scores range from 2 to 12, with 2 being the highest and 12 the lowest. There were no group differences for SES (see table 1).

2.2. Magnetic Resonance Imaging (MRI)

2.2.1. Image acquisition

All images were acquired using a 3T whole-body MRI system (Siemens Tim-Trio, Erlangen, Germany). The images were obtained with a magnetization-prepared rapid acquisition gradient echo (MPRAGE 3-D) volume acquisition with repetition time of 2500 ms, echo time 2.91 ms, inversion time, 1100 ms, flip angle, 9°, matrix size 256 x 256, field of view 20 cm; slice thickness, 1.0 mm, acquisition time of 6,5 min.

2.2.2. Images processing

Voxel-based morphometry (VBM) with diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL; Ashburner, 2007) was conducted using SPM5 (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) and implemented in Matlab 7.1.4. VBM with DARTEL. This method has been shown to be more sensitive than standard VBM (Klein et al., 2009) due to the more precise inter-subject alignment. Each participants' image was normalised with a 6 year old template created using "Template-O-Matic" toolbox (Wilke, Holland, Altaye, & Gaser, 2008). This toolbox allows creating an age-appropriate template, with MRI data from 404 healthy children. Thus, with this method, appropriate priors were generated in order to measure cerebral tissue volumes (cerebral grey matter, CGM; white matter, WM; and cerebrospinal fluid, CSF). Finally, for the statistical analyses, the images were smoothed with 6 mm full-width at a half-maximum (FWHM) kernel which is a relative conservative, but usual, smoothing for structural images.

2.3. Cognitive Assessment

2.3.1. Kaufmann Assessment Battery for Children (K-ABC)

In order to be able to control for potential cognitive variability between preterm groups, the K-ABC (Kaufman & Kaufman, 1993) was administered during the 6 year routine clinical evaluation. The K-ABC is a clinical instrument for assessing cognitive development yielding a general cognitive scaled score as found in tests of general intelligence (Mental Processing Composite: MPC, see table 1).

2.3.2. Child Attention Network Task (ANT)

In order to measure the three attentional networks proposed by Posner and Peterson (Posner & Petersen, 1990), i.e. alerting, orienting and executive control network, each child completed the computerized child ANT. The ANT was demonstrated to be a valid and reliable test and suitable for administration to children aged 6 years of age (Forns et al., 2014; Rueda et al., 2004).

The Child ANT was created with E-prime (Psychological Software Tools) and was obtained from the Sackler Institute for Developmental Psychobiology (http://www.sacklerinstitute.org). A yellow fish, which represents the target, was presented alone or in the middle of a horizontal row of five yellow fish (flanking fish). A fixation cross was always present, children were instructed to keep looking at this cross during the task. The target was presented either above or below this fixation cross. The children were asked to decide whether the central fish was facing left or right by pressing the left or right button on the mouse. On congruent trials, the flanking fish were all pointing in the same direction as the central fish. In contrast on incongruent trials the flanking fish were pointing in the opposite direction as the central fish. On neutral trials the central fish appeared alone (Fan et al., 2002). Furthermore, each target was preceded by one of the four cue (asterisk) conditions: (1) a center cue, presented at the location of the fixation cross; (2) a double cue, appearing above and below the fixation cross, with the target being presented at either one of these locations; (3) a spatial cue, appearing above or below the fixation cross at the location of the target; or (4) no cue. The task is composed of 24 practice trials and three experimental blocks of 48 trials each. Each block presents 12 conditions in equal proportions: three target types (congruent, incongruent, and neutral) and four cues (no cue, central cue, double cue, spatial cue). The task was administered individually in a quiet room by a qualified clinical psychologist and takes approximately 20 min to complete.

The reaction time and the success rate on this task were measured. More specifically, to compute the alerting network score the mean reaction time (MRT) was collapsed across the three flanker types (congruent, incongruent, and neutral) in the no cue condition and in the double cue condition. This collapsed no cue MRT was then subtracted from the collapsed double cue MRT to obtain the alerting network score. To measure the orienting network, the MRT was collapsed across the three different flankers in the center cue condition and in the spatial cue condition. This collapsed center cue MRT was then subtracted from the collapsed spatial cue MRT to obtain the orienting network score. Finally, to compute the executive control score, the MRT was collapsed across the four cue conditions (no cue, center cue, double cue, and spatial cue) in the incongruent condition and in the congruent condition. This collapsed incongruent condition MRT was then subtracted from the collapsed congruent condition MRT to obtain the executive control score. For all scores (except the mean success rate) higher scores represent poorer performances of the underlying attention network.

2.4. Procedures

The ANT was first performed in the psychology laboratory in Geneva and Lausanne prior to the MRI. The MRI was performed on average within 17 days after the ANT assessment.

No narcotics were used to keep the children still in the scanner, however, the purpose of the scan was explained to the children as well as the importance to remain still in the scanner. In addition, the children had the time to look at the scanner and to explore it, in order to be familiar with it and cartoons or music were offered during the scan. After the acquisition, the MR technician and the psychologist examined the images. If the quality was not good enough, the procedure was repeated until images were satisfactory for analysis.

2.5.Data analyses

2.5.1.Behavioural data

All analyses on behavioural data was computed with SPSS. The data was explored with boxplots revealing no outliers. In addition, the distribution of data was assessed with Kolmogorov-Smirnov tests, which indicated all data to suit a normal distribution enabling parametric analysis. A 2 x 2 (gender x gestational age group) MANCOVA was performed, where the five ANT scores (mean RT, mean success rate, alerting, orienting, and executive control scores) were entered as dependent variables and SGA and the CLD as covariates. By convention, the p-value was set at $p < 0.05$.

2.5.2.VBM analysis

In order to identify the cortical and subcortical areas which differ between the groups, a 2 x 2 (gender x gestational age group) VBM MANCOVA was performed, with the GM density maps as dependent variables and SGA and the CLD as covariates. This initial SPM analysis was done with $p < 0.001$ (uncorrected) and only clusters of 20 contiguous voxels were retained in order to avoid type II error. In order to explore whole brain volume differences, a 2 x 2 (gender x gestational age group) SPSS multivariate analyses of variance (MANOVA) was performed on the volume scores with the SGA and CLD as covariates (MANCOVA).

Afterwards, in order to identify which brain regions are related to executive control, a multiple regression analysis was performed using SPM (with executive control score as predictor). Thus, the regression model of the SPM analysis comprised the executive control score of the ANT, GA, gender, SGA and CLD as explaining variables. Subsequently, the mean first eigenvariates for all brain clusters exhibiting significant correlation (at $p < 0.001$, uncorrected, to avoid type II error) with the ANT executive control score were extracted for each individual using a 5 mm radius sphere. With this design, the extraction of the eigenvariates from GM density values of the significant clusters was computed independently from the effects of gender and GA. Thus, one GM density value for each cluster (13 in total) for each child was obtained. Finally, in order to assess whether the variations in executive control between groups could be related to cortical density differences, a 2x2 (gender x gestational age groups) MANCOVA was performed on the detected regions where densities correlated with the ANT executive control score. In order to avoid a type I error, a Bonferroni correction for multiple comparisons was applied (adjusted $p < 0.05 / 13 = 0.004$).

3. Results

3.1. Brain volume differences at 6 years of age

3.1.1. Volume comparison

The first analysis assessed whether there were brain volume differences with regards to cortical grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) and intracranial volume (ICV) between preterm children born <28 weeks and those born ≥ 28 weeks of gestation. The analysis showed no significant difference in absolute brain volumes between GA groups for GM, WM, CSF or ICV. However, there were significant effects of gender (with GA groups collapsed) on brain volume in 6 year-old preterm born children. Boys in general had significantly larger GM volumes (Mean = 795.1, SD = 57.0) than girls (Mean = 738.1, SD = 62.8; $t(56) = 3.600$, $p < .001$, $\eta_p^2 = .197$), larger WM volumes (Mean=383.2, SD =

42.6) than girls (Mean = 359.6, SD = 38.8; $t(56)=2.208$, $p < .05$, $\eta_p^2 = .091$) and larger ICV volumes (Mean=1669.3, SD=139.9) than girls (Mean = 1554.6, SD = 166.2 ; $t(56)=2.821$, $p = \leq .01$, $\eta_p^2 = .134$). The CSF volume was similar between boys (Mean = 491.1, SD = 76.7) and girls (Mean = 457.0, SD = 85.3; *ns*). Table 2 shows the differences in brain volume by GA group and gender

<<INSERT TABLE 2 ABOUT HERE>>

3.1.2. VBM analysis: Cortical Density Comparison

The MANCOVA revealed significant main effects of gestational age and gender on the cortical densities map. Extremely preterm born children (below 28weeks) showed *less* cortical densities in the left superior occipital area, bilateral premotor cortex, and left insular cortex compared to the very preterm born children (above 28 weeks). Particularly larger densities were found bilaterally in the superior and medial area of the temporal lobe, superior frontal gyrus (frontal eye area), middle frontal gyrus (dorsolateral prefrontal cortex), inferior frontal area (triangularis), as well as the right inferior orbito-frontal area, right pre/postcentral area (premotor/primary motor) and the cerebellum. With regards to subcortical areas, the hippocampus, amygdala, putamen and pallidum differed bilaterally, where preterm boys exhibited greater densities than preterm girls (see figure 1).

<<INSERT FIGURE 1 ABOUT HERE>>

3.2. Cognitive Comparisons

MANCOVA on all measures of the ANT revealed neither GA nor gender differences on the general success rate and the mean reaction time. Additionally there was no main effect of gestational age (see table 3). A significant main effect of gender ($F(1, 42) = 5.33$, $p < .05$, $\eta_p^2 = .136$) was found for the alerting network, where boys (M = 82.21, SD = 61.39) are found to perform worse than girls (M = 24.18, SD = 82.87).

<<INSERT TABLE 3 ABOUT HERE>>

Furthermore, a significant interaction effect was found for gender by gestational age group on the ANT executive control score (F(1, 42) = 7.61, p <.01, η_p^2 =.162). Post-hoc independent t-tests indicate that boys born below 28 weeks of gestation had a significantly higher executive control score (poorer performance) in contrast to girls born below 28 weeks of gestation (p < .01), girls born above 28 weeks of gestation (p < .01), and boys born above 28 weeks of gestation (p < .01). This difference indicates a specific deficit in executive control in extremely preterm born boys.

3.3.VBM regression analysis: Cortical regions involved in executive control

This analysis revealed (see figure2 and table 4) that higher executive control scores were associated with lower densities in the associative visual cortex, occipitotemporal gyrus, medial temporal gyrus, precuneus, precentral gyrus, superior frontal gyrus, presupplementary motor area, inferior frontal gyrus (IFG, pars opercularis), dorsolateral prefrontal cortex (DLPFC), superior orbito-frontal cortex, superior medial frontal cortex and the hippocampus (see table 4 for details).

<< INSERT FIGURE 2 ABOUT HERE>>

<<INSERT TABLE 4 ABOUT HERE>>

The MANCOVA which was run on the detected cortical areas revealed no main effect of GA. However, a main effect of gender was found, with boys having a larger hippocampus density (F(1, 47) = 18.141, p <.001, η_p^2 = .302) than girls. Additionally, a significant interaction effect of gender by GA was found for the inferior frontal gyrus (IFG, F(1, 47) = 9.452, p <.01, η_p^2 = .184) and the DLPFC (F(1, 47) = 9.450, p <.01, η_p^2 = .184; see table 4). Post hoc independent t-tests were conducted between the 4 groups of interest (≤ weeks gestation/ > 28 weeks gestation and boys/girls). This revealed that, at 6 years of age, boys born below 28 weeks of gestation showed less cortical density in the DLPFC and the IFG (p < .05 respectively) compared to girls as well as boys born over 28 weeks of gestation. We observed a similar between-groups pattern of differences regarding DLPFC and IFG as well as executive control. Furthermore, we observe significant correlations between the densities in these brain regions and executive control scores (DLPFC: $r = -.354$, $p<.05$; IFG: $r = -.293$, $p<.05$).[1]

<<INSERT FIGURE 3 ABOUT HERE>>

4. Discussion

This study aimed to explore the effect of gender and different levels of prematurity on structural brain development as well as on attention network performance (in particular executive control) in preterm born children at 6 years of age. Firstly, the gender effect will be reviewed and secondly the most prominent finding of the study, namely, the interaction between gender and severity of preterm birth on executive control abilities and on the GM density in the IFG and the DLPFC.

4.1.Gender differences

The analysis examining overall gender differences revealed that at 6 years of age premature born boys in general present with poorer alerting abilities than girls of the same age. This result adds to the growing literature reporting a cognitive disadvantage of being male and born extremely preterm (for review see Pavlova & Krageloh-Mann, 2013).

Furthermore, when preterm born boys' and girls' brains were compared at 6 years of age it was not surprising that boys had larger brains than girls in addition to higher cortical densities in certain cortical (superior frontal gyrus, presupplementary motor area, IFG, DLPFC) and subcortical regions (hippocampus). These latter findings are consistent with previous studies in other preterm populations (Inder et al., 2005; Kesler et al., 2008; Mewes et al., 2006).

4.2. Executive control abilities

[1] As SES is often seen as an important contributing factor in these analysis, we controlled for SES influences on executive control score, IFG and DLPFC in our main analysis (MANCOVA). As the results were not found to be influenced by SES, we report the results of the un-corrected analysis

The current study shows that boys born extremely preterm have lower executive control abilities than girls born extremely preterm, as well as boys born moderately preterm. Similarly, previous studies reporting that preterm children (without segregation between gender and level of prematurity) have poorer executive control abilities than term born control children as measured with similar behavioral tasks (Doyle & Anderson, 2009; Leclercq et al., 2006; Marlow et al., 2007; Pizzo et al., 2009). More specifically, the present study emphasises that at 6 years of age extreme preterm birth and being male represents a supplementary risk factor and has a negative impact on the development of executive control abilities. Executive control is crucial for selecting specific and relevant information and ignoring information which is non-pertinent. This is essential for the fulfilment of many learning tasks as well as self-regulation which is the ability to control thoughts, feelings and behaviours (Böhm et al., 2002). As executive control enables us to look at a situation, identify a goal, create a sequence of steps, and initiate an action to accomplish the goal, it is clear that if these are lacking or poor, school learning becomes much more challenging. Therefore, executive control abilities could be related to learning difficulties often reported in children born preterm (Anderson & Doyle, 2004; Rickards, Kelly, Doyle, & Callanan, 2001). However, this study illustrates that not all preterm children have equivalent alterations of their executive control abilities. Indeed, extreme prematurity as well as being male predispose these children to poorer executive control abilities at an age when they would normally start primary school and when these skills become crucial.

Theoretically, this difference between extreme preterm and moderately preterm born children could be related to the disruption of the typical in-utero neurodevelopmental trajectory that takes place in the third trimester (Lax et al., 2013). Indeed, dendritic arborization and synaptogenesis accelerate in the third trimester producing a thickening of the developing cortex (Huttenlocher & Dabholkar, 1997). Further, during the third trimester the hippocampus, which plays a role in executive control and alerting abilities (Weible, 2013), begins to send projections through thalamic nuclear structures to the developing frontal cortex (Seress, 2001). A disruption of these events, in essence, could lead to a differential projection to the frontal cortex and hence an alteration in development. This alteration in development might affect boys differently than girls. In this perspective, the current study illustrates specific time windows of vulnerability for brain development in boys.

More globally, it has been proposed that sexual brain dimorphism is related to individual differences in fetal testosterone levels measured in amniotic fluid (Lombardo et al., 2012). However, the specific mechanisms underlying the brain differences in sex remains unclear, the influence specifically of androgen has recently been shown not to be the primary determinant of sexual dimorphism (Knickmeyer et al., 2013). Alternatively these gender differences could be related to differential temporal development between the male versus the female brain, thus shifting the window of susceptibility to environmental insults (McCarthy, 2009).

4.3.Brain structures

The observed cortical density differences in regions of the frontoparietal network, (which correlated with the ANT scores in our results), were in line with the literature on the structural substrate of executive functioning (Petersen & Posner, 2012; Posner & Petersen, 1990).

Advances in human lesion-mapping support the notion of the functional localization of response inhibition to right IFG predominantly (Aron, Robbins, & Poldrack, 2004). This area has been typically implicated in inhibition of manual motor responses related tasks such as the go/no–go (where the participant has to inhibit a prepotent response) and the stop signal (Aron & Poldrack, 2006; Aron et al., 2004). According to Petersen and Posner (2012) the IFG is part of the ventral attention system which allows the bottom-up reorienting ability. More specifically, this system is related to the active following of a target and was identified as part of the network responsive to sensory stimuli. Womelsdorf et al. (2007), further, proposed that the bottom up influence of sensory input involves synchronization between activity in the more dorsal attention areas and activity in the more ventral visual areas of the cortex. Thus, synchronization apparently leads to greater sensitivity in the visual system, allowing faster responses to visual stimuli and thus improving priority for processing the stimuli. Applied to the ANT, which is a visual task, executive control abilities require reorienting processes and synchronization of visual information. In particular, the participants had to select a non-dominant response after having inhibited the most prominent information leading to a wrong response. This is found to be more problematic for boys born extremely preterm and seems to be specifically related to brain structural alteration found in the IFG.

In addition, the executive control abilities in extremely preterm boys seem to be related to lower cortical densities in DLPFC. From the adult literature, we know that lesions of DLPFC cause deficits in executive control, such as inhibiting responses, but can also impair decision-making or judgment regarding relevant or irrelevant responses (Aron et al., 2004). Furthermore, according to Petersen and Posner (2012), the DLPFC is part of the frontoparietal control system which enables a moment-to-moment control, which is responsible for resolving conflict. Thus, it could be postulated that when completing the ANT task a weaker conflict monitoring system, in extremely preterm born boys, did not allow proper identification of the conflict imposed by the incongruent condition of the ANT task, thus resulting in a higher executive control score (i.e. lower performance). More generally, it has been reported that the frontoparietal control system is highly connected to the dorsal attention system (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). As such, this system plays an important role for the communication and the integration of information between these regions, and for monitoring complex tasks. Furthermore, the DLPFC is found to play a role in not only monitoring but also preparing tasks. Studies using repetitive Transcranial

Magnetic Stimulation (rTMS) have been used to interfere with neural processing in order to determine whether a specific brain area is required in task performance (Vanderhasselt, De Raedt, Leyman, & Baeken, 2010). This process highlighted a specific role of the left DLPFC in actively preparing for a specific task in the presence of a distracting task. Thus, lower cortical density in DLPFC, observed in extreme preterm born boys, could have a negative impact on the development of connectivity in this network, which has been shown to be imperative to attention and executive control abilities.

Our results imply that boys and girls are neurologically differentially impacted by level of prematurity. Likewise, studies report that only preterm boys exhibit significantly reduced white matter compared with term born boys, while no differences between preterm and term-born girls were observed (for review see Pavlova & Krageloh-Mann, 2013). Gender also seems to play a role in genetic conditions, in 22q11.2 deletion syndrome, reductions in frontal lobe as well as DLPFC volume reduction has been shown in boys but not girls (Kates et al., 2005). It seems that boys are impacted differently than girls on early developmental insult and that this difference carries through their development, implicating the importance of severity of prematurity in different genders.

In the context of the current findings, the potential benefits of cognitive training reported to enhance executive attention function and to produce changes in attention-related brain areas need to be considered (Klingberg, 2012; Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005). This training may be particularly beneficial for this subpopulation of preterm children (see also Wass, 2014).

The current findings do shed light on a gender specific vulnerability in cortical development, which so far has been sparsely studied in preterm infants. It equally indicates the potential importance of gender differences in executive function difficulties. Nevertheless, what needs to be kept in mind is that even though the current study indicates volumetric variability between boys and girls and between extreme and very premature children, volumetric studies do not measure the level of activation in these areas of the brain. As such further studies combining structural and functional imaging designs are warranted in order to link brain activation during specific tasks to brain structural changes.

4.4. Limitations

There are certain limitations in this current study. The selection criteria, excluding children with severe brain lesions, makes generalization of the results to all the preterm children difficult. However, this procedure is consistent with the majority of studies in preterm populations and necessary to avoid outliers as well as allowing 3D analysis of imaging data. Additionally, our findings are based on a single measure of executive control revealing large variation in terms of performances in some subgroup (which are composed of small number of participant). This might have influenced our results. Furthermore, the aim of the study was to examin the impact of pretmaturity severity rather than comparison with fullterm development, however, including a term-born control group would make possibly make the findings more generalizable. Finally, as acquiring a large representative sample of this type of population is rather difficult our study suffered from a low of power. We were able to observe larger effect sizes (with potential clinical relevance), however, perhaps we could have missed a smaller effect size. Thus, our study represents a first step towards a better understanding of the relationships between brain and behavior in a preterm population, but further studies are warranted with larger samples in order to confirm and expand the current results.

4.5. Summary

This study highlights that boys are significantly more affected by their level of prematurity than girls. In fact, the reduced executive control in extremely preterm born boys (< 28 weeks gestation) is related to lower cortical densities in specific brain regions, namely the inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex (DLPFC). These findings imply that being born both male and extremely preterm carries a supplementary risk; diminishing executive control and hence decreasing the ability to focus strictly on pertinent information. These risk factors are found to be present at the age where children start school, a time where such skills are highly recruited, hence potentially affecting their learning abilities and school performance. In sum, the specific brain structural differentiation associated with executive control difficulties found in extremely preterm born boys might express a specific brain vulnerability associated explicitly with both gender and extreme prematurity.

5.References

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Table 1. Groups descriptive

Measures	< 28wks		≥ 28wks		Main effect of GA[1]	Main effect of gender (girls > boy)[1]
	Boys	Girls	Boys	Girls		
N	13	17	13	15	*Ns*	*Ns*
Age (years) at testing	6.7 (0.6)	6.7 (0.4)	6.5 (0.3)	6.7 (0.7)	*Ns*	*Ns*
GA (wks)	26.0 (0.9 ; 24.3-27.4)	26.7 (0.9 ; 24.0 -27.7	30.9 (2.9 ; 28.0-35.1)	31.2 (2.4; 28.0-34.3)	.001	*Ns*
BW (gr)	810.0 (234.7; 510-1320)	877.1 (217.7; 550-1320)	1298.5 (502.6; 600-2170)	1233.3 (410.9; 590-1970)	.001	*Ns*
BW <P 10^{th} (%)	23.1	23.5	53.8	53.3	.022	*Ns*
HC birth (cm)	23.2 (2.0)	24.4 (1.8)	28.2 (4.1)	26.2 (2.8)	.001	*Ns*
HC < P 10^{th} (%)	30.8	23.5	23.1	33.3	*Ns*	*Ns*
SES	5.8 (1.9)	7.0 (2.9)	4.7 (2.7)	5.7 (3.4)	*Ns*	*Ns*
CLD (%)	61.5	52.9	7.7	13.3	.001	*Ns*
K-ABC MPC	91.9 (11.0)	102.5 (13.0)	96.1 (13.0)	96.3 (15.0)	*Ns*	*Ns*

Note. Data are expressed if not specified in Mean (SD; range), P10^{th} : 10^{th} percentile; GA : Gestational age; BW: Birth Weight; HC: head circumference; SES : socio-economic status, CLD: chronic lung disease ; K-ABC MPC: K-ABC Mental Processing Composite.

[1] results of independent sample *t*-tests and chi-square analysis, as appropriate.

Table 2. Brain volumes by GA group and gender

	Boys		Girls	
	< 28 wks GA	≥ 28 wks GA	< 28 wks GA	≥ 28 wks GA
GM	805.1 (51.5)	796.2 (66.2)	745.9 (63.2)	733.0 (60.5)
WM	381.5 (40.1)	407.1 (49.8)	372.2 (45.8)	367.5 (36.1)
CSF	406.0 (76.3)	448.4 (72.3)	415.4 (73.3)	371.1 (46.9)
ICV	1592.6 (112.7)	1651.7 (123.7)	1533.5 (160.0)	1471.7 (113.9)

Note. GM: gray matter; WM : white matter; CSF: cerebro-spinal fluid; ICV: intracranial volume expressed as Mean (Standard Deviation) in cc.

Table 3. Descriptive data of the Attentional Network Test

	Boys		Girls				
	< 28 wks GA	≥ 28 wks GA	< 28 wks GA	≥ 28 wks GA	Main effect of GA	Main effect of gender (girls > boy)	Interaction effect (GA x gender)
Mean success rate	.84 (.10)	.88 (.07)	.87 (.15)	.76 (.14)	*Ns*	*Ns*	*Ns*
Mean RT	894.4 (91.4)	902.0 (145.1)	973.5 (153.1)	980.9 (103.1)	*Ns*	*Ns*	*Ns*
Alerting	79.4 (70.6)	85.3 (53.0)	34.9 (62.4)	14.2 (99.6)	*Ns*	.027	*Ns*
Orienting	22.6 (79.3)	44.0 (70.8)	55.0 (101.4)	36.2 (134.9)	*Ns*	*Ns*	*Ns*
Executive Control	202.5 (88.3)	74.5 (85.8)	93.0 (52.2)	97.0 (82.7)	*Ns*	*Ns*	.009

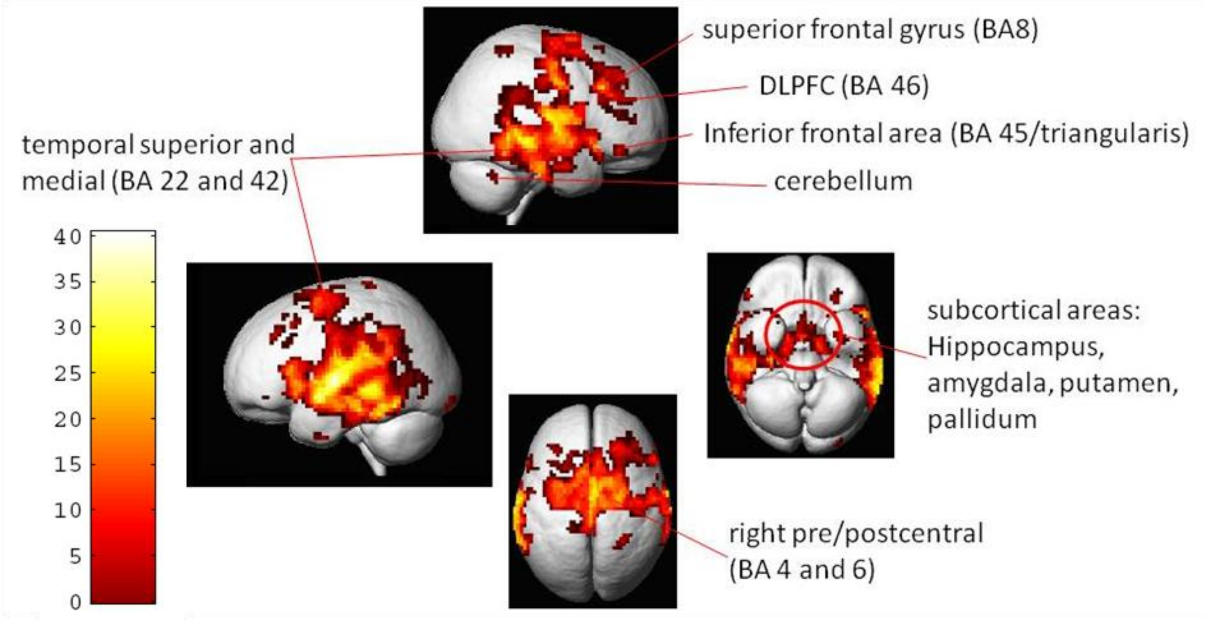
Note. The data expressed in ms are presented as Mean and (standard deviation).

Table 4. Areas related to executive control in the whole sample and results of the MANCOVA (age by gender)

	Brodmann Area (BA)	Hemi-sphere	Number of voxels	Stereotaxic coordinates (MNI-pace)[1] x	y	z	z-value	Main effect of GA *p*	Main effect of Gender (boy > girl) *p*	GA x Gender Effect *p*
Occipital lobe										
associative visual cortex	19	left	144	-40	-75	30	3.47	ns	ns	ns
occipitotemporal gyrus	37	left	68	-51	-66	-17	3.90	ns	.018	.037
Temporal lobe										
medial temporal gyrus	39	left	148	-40	-58	23	3.58	ns	ns	ns
medial temporal gyrus	39	right	572	42	-55	20	5.00	ns	.042	ns
precuneus		left	136	-6	-45	51	3.71	ns	ns	ns
Frontal lobe										
precentral gyrus	6	right	122	27	-33	62	3.79	ns	ns	ns
superior frontal gyrus	8	left	321	-10	9	63	4.01	ns	.028	ns
presupplementary motor area	6	left	109	-24	2	59	3.94	ns	.042	ns
inferior frontal gyrus (IFG)(opercularis)	**44**	**right**	80	51	18	33	3.79	ns	.030	**.004**
dorsolateral prefrontal cortex(DLPFC)	**46**	**right**	130	26	41	12	3.67	ns	.030	**.004**
superior orbito-frontal	10/11	right	689	17	60	-9	4.18	ns	.039	ns
superior medial frontal	10	left	160	-4	59	20	3.83	ns	ns	ns
Subcortical										
hippocampus		**left**	49	-18	-14	-15	3.48	ns	**<.001**	.023

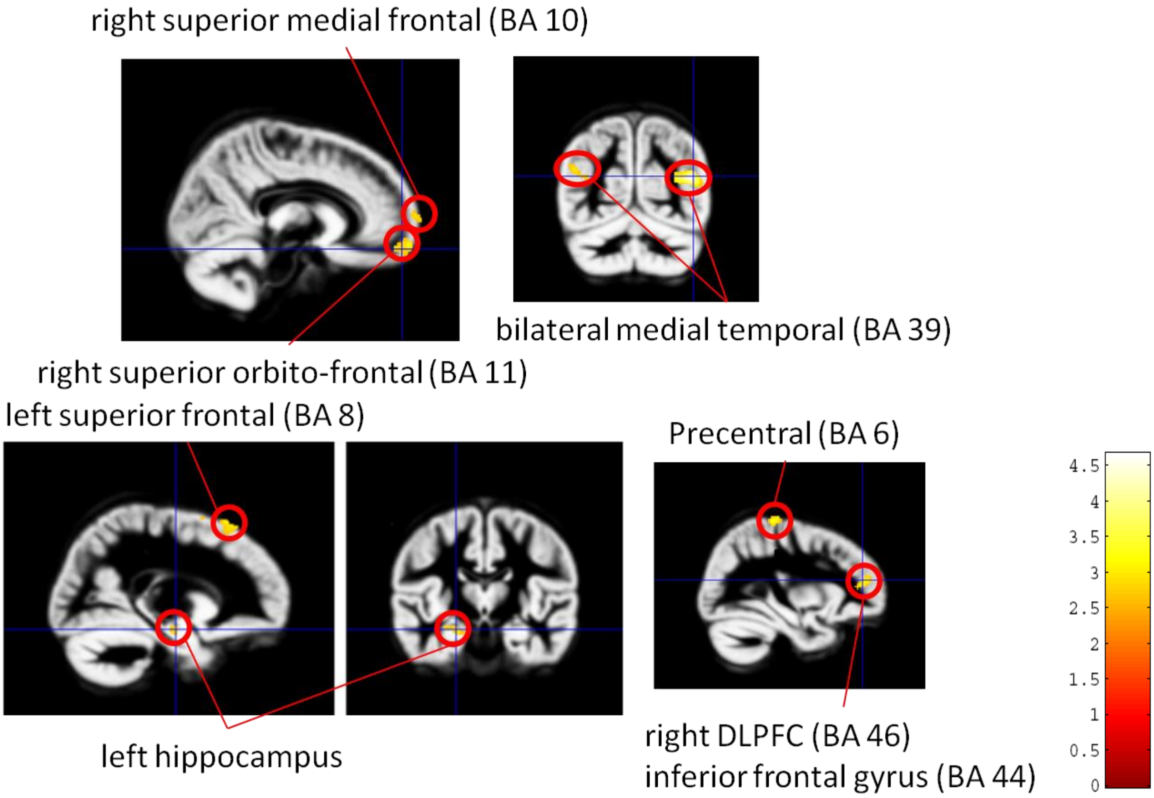
[1] the MNI coordinates are issued from a pediatric template. See Method section for details.

Figure 1. Gender differences in gray matter densities maps



Note. Results of the VBM analysis exploring the main effect of gender on gray matter densities (boys > girls). The different regions showing significant differences ($p < .001$, without correction, $k > 20$) were reported. The red-yellow scale (on the left) represents the value of z (from t-test).

Figure 2. VBM analysis: cortical regions involved in the ANT executive control task



Note. Correlation between (VBM analysis) the cortical regions and the executive control score (ANT task). The different regions showing significant differences (p <.001, without correction, k >20) were reported. The red-yellow scale (on the left) represents the value of z (from regression).

Figure 3. Gender by gestational age interaction effect on executive control (Panel A) and on cortical densities in the dorsolateral prefrontal cortex (DLPFC, Panel B) and the in inferior frontal gyrus (IFG, Panel C)