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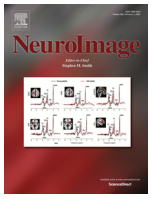

Atypical brain structure mediates reduced IQ in young adults born preterm with very low birth weight

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ABSTRACT

Preterm birth with very low birth weight (VLBW) confers heightened risk for perinatal brain injury and long-term cognitive deficits, including a reduction in IQ of up to one standard deviation. Persisting gray and white matter aberrations have been documented well into adolescence and adulthood in preterm born individuals. What has not been documented so far is a plausible causal link between reductions in cortical surface area or subcortical brain structure volumes, and the observed reduction in IQ.

The NTNU Low Birth Weight in a Lifetime Perspective study is a prospective longitudinal cohort study, including a preterm born VLBW group (birthweight ≤1500 g) and a term born control group. Structural magnetic resonance imaging data were obtained from 38 participants aged 19, born preterm with VLBW, and 59 term-born peers. The FreeSurfer software suite was used to obtain measures of cortical thickness, cortical surface area, and subcortical brain structure volumes. Cognitive ability was estimated using the Wechsler Adult Intelligence Scale, 3rd Edition, including four IQ-indices: Verbal comprehension, Working memory, Perceptual organization, and Processing speed. Statistical mediation analyses were employed to test for indirect effects of preterm birth with VLBW on IQ, mediated by atypical brain structure.

The mediation analyses revealed negative effects of preterm birth with VLBW on IQ that were partially mediated by reduced surface area in multiple regions of frontal, temporal, parietal and insular cortex, and by reductions in several subcortical brain structure volumes. The analyses did not yield sufficient evidence of mediation effects of cortical thickness on IQ. This is, to our knowledge, the first time a plausible causal relationship has been established between regional cortical area reductions, as well as reductions in specific subcortical and cerebellar structures, and general cognitive ability in preterm born survivors with VLBW.

1. Introduction

It is well-established that adolescents and young adults born preterm with very low birthweight (VLBW, <1500 g) underperform on tests of general intelligence (Breeman et al., 2015; 2015; Jaekel et al., 2019; Løhaugen et al., 2010; Nosarti et al., 2007; Pyhala et al., 2011; Twilhaar et al., 2018), as well as tests of executive functions and processing speed (Nosarti et al., 2007). Brain morphometry studies employing magnetic resonance imaging (MRI) show smaller regional surface area in adolescents (Grunewaldt et al., 2014; Rimol et al., 2016) and young adults (Rimol et al., 2016; Skranes et al., 2013) born preterm with VLBW. Furthermore, aberrant cortical thickness has consistently been observed in teenagers and young adults from Norway (Bjuland et al., 2013; Martinussen et al., 2005; Rimol et al., 2019) and the UK (Nam et al., 2015); and smaller subcortical brain structure volumes have been reported, along with ventricular enlargement, in multiple sam-

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ples of various nationalities (Allin et al., 2004, 2011; Ball et al., 2012; Bjuland et al., 2014; Gimenez et al., 2004; Parker et al., 2008). Taken together, these MRI-based morphometry findings establish a persisting pattern of gray matter deviation alongside a decline in general cognitive ability in this population. What is less clear, however, is whether the observed structural abnormalities are the cause of the reduction in cognitive ability.

Studies examining the neural basis for cognitive ability have documented a small but reliable association between overall brain size and general intelligence (McDaniel, 2005; Pietschnig et al., 2015). However, regional correlations with IQ vary (Colom et al., 2010) and global volumetric measures are not able to fully capture the complexity of the relationship between intelligence and brain structure. Jung and Haier (2007) proposed a "parieto-frontal integration theory" of intelligence (P-FIT) in which early visual and auditory sensory regions feed forward to the inferior (supramarginal and angular gyri) and superior parietal cortices, where "integration and abstraction" take place. The parietal regions further interact with lateral and medial frontal regions responsible for "hypothesis testing and problem solving." Once a solution has been found, the anterior cingulate constrains response selection and inhibits competing responses (Colom et al., 2009).

It is now commonly believed that cognitive function arises from the interaction between brain regions in large-scale distributed networks (Fuster, 2006), and recent theories propose cognitive control as a core process in human intelligence (Chen et al., 2019). Functional neuroimaging studies typically show increased activity in fronto-parietal networks during the performance of cognitively demanding tasks, especially active maintenance and manipulation of information in working memory (Dosenbach et al., 2006). In addition, the so-called "triple-network model" (Menon, 2011) ascribes control functions to a cingulo-insular network, consisting of the anterior cingulum and the anterior insula, with the crucial role of switching between distinct brain networks according to task demands.

Studies focusing specifically on associations between preterm brain structure and general cognitive ability have produced conflicting results. Volumetric MRI-based morphometry studies have reported positive associations with full-scale IQ in the temporal lobes of late childhood preterm survivors (7–9 years) (Peterson et al., 2000) and the parietal lobes of adolescents (15 years) born preterm (Isaacs et al., 2004). As opposed to surface-based representations of the cortex, however, volume-based methods are unable to distinguish between cortical area and cortical thickness (Winkler et al., 2018, 2010) and are notoriously unreliable in terms of spatial registration (Coalson et al., 2018; Van Essen et al., 1998). A longitudinal surface-based morphometry study of healthy children and adolescents (Shaw et al., 2006), using a selection of verbal and performance subtests from the Wechsler intelligence-scale for children (WISC), reported negative associations between intelligence and frontal and temporal cortical thickness in early childhood, and positive associations from late childhood, throughout adolescence, and into young adulthood. A study from the Bavarian Longitudinal Study by Schmitz-Koep et al. (2020) reported partial correlations between cortical thickness and full-scale IQ in multiple cortical regions. Using a different type of surface-based analysis, Skranes et al. (2013) reported positive partial correlations between IQ and cortical surface area in preterm-VLBW young adults, and especially the working memory and processing speed indices showed widespread regional association with cortical surface area. Nonetheless, despite multiple reports of correlations between brain structure and IQ in preterm-born populations, only one of the studies reviewed above directly addresses whether atypical brain structure acts as a statistical mediator on general cognitive ability. Schmitz-Koep et al. (2020) analyzed mean cortical thickness from the left and right hemisphere in 26-year-old survivors of preterm birth with VLBW and reported a modest mediation effect in the left cerebral hemisphere. However, regionally specific effects were not characterized in this study, and there was no investigation into possible mediation effects of reduced cortical area.

In addition to the cortical regions described above, Jung and Haier speculate that "regions identified in [functional neuroimaging] studies of discrete cognitive processes, such as the basal ganglia, thalamus, hippocampus, and cerebellum" are likely to be critical to human intelligence (Jung and Haier, 2007). Apart from a previous publication from our lab, reporting positive associations between IQ and multiple subcortical brain structure volumes in the present VLBW sample, including several limbic structures and the basal ganglia (Bjuland et al., 2014), there are few studies on IQ in relation to the morphometry of specific subcortical structures in the preterm literature. Nevertheless, a meta-analysis of children and adolescent survivors of preterm birth (de Kieviet et al., 2012) found that, along with smaller total brain volumes, smaller volumes of the cerebellum and the hippocampus were associated with lower IQ.

In order to address the issue of structure-function relationships in the preterm brain, we used a measurement-of-mediation design (Spencer et al., 2005) to test for indirect effects of preterm birth with VLBW on general cognitive ability (IQ). We included 19-year-old survivors of preterm birth with VLBW and a coetaneous term-born control group, from the NTNU Low Birth Weight in a Lifetime Perspective study, which is an on-going longterm follow-up study on the effects of preterm birth (Evensen et al., 2022). Average IQ, as measured with the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler et al., 2003), was reduced by one standard deviation in the preterm VLBW group (see Løhaugen et al., 2010). We have previously demonstrated reduced surface area in this sample, as well as significant correlations between IQ and cortical area (Skranes et al., 2013) and subcortical brain structure volumes (Bjuland et al., 2014) within the VLBW group. However, this leaves unanswered the important question whether there is a causal link between brain structural aberrations and cognitive deficits. Thus, the purpose of the present study was to test whether atypical cortical area and thickness, and/or atypical subcortical brain structure, statistically mediate the observed reduction in IQ. Furthermore, to ascertain which aspects of general cognitive ability are most affected by atypical brain development, we included all four indices from WAIS-III (Verbal comprehension, Working memory, Perceptual organization, and Processing speed).

Morphometric research on brain structure and cognitive ability has shown considerable variability across studies as well as imaging modalities (Colom, 2007; Colom et al., 2009) but based on the P-FIT model, we predicted that atypical cortical morphology in prefrontal and parietal regions, as well as in visual (extrastriate) and auditory (superior temporal) sensory regions, would statistically mediate the reduction in IQ and IQ-index scores seen in preterm-VLBW individuals. We also expected atypical cortical morphology in the cingulo-insular network to show mediation effects on IQ. And, finally, we predicted that IQ was mediated by reduced volumes in brain structures such as the thalamus, basal ganglia, hippocampus, and cerebellum in adult survivors of preterm birth.

2. Methods

2.1. Subjects

This is a hospital-based follow-up study of three-year cohorts (birth years 1986–88) of individuals born preterm (gestational age (GA) < 37 weeks) with VLBW (birth weight (BW) ≤1500 gs), and a term-born control group with normal birth weight (BW ≥10th percentile), at 19 years of age. Detailed inclusion criteria and results from multidisciplinary clinical assessments and cerebral MRI at ages 15 and 20 are reported in earlier publications (Bjuland et al., 2013; Martinussen et al., 2005; Olsen et al., 2018; Skranes et al., 2013, 2007).

2.1.1. VLBW group

Between 1986 and 1988, 121 VLBW children were admitted to the Neonatal Intensive Care Unit (NICU) at St. Olav's Hospital, Trondheim University Hospital, Norway. Of these, 33 died, nine had moved prior

Table 1
Demographical and clinical variables.

	n	VLBW	*n*	Controls	*p***
Age (years) at MRI*	38	19 (18-21)	59	19 (18-21)	
Sex (males)	38	18 (47 %)	59	25 (42 %)	
Birth weight (g)*	38	1234 (550-1500)	59	3711 (2670-5140)	
Gestational age (weeks)*	38	29.29 (24-35)	59	39.75 (37-43)	
Days in NICU§	37	74.49 (23-386)			
Days on ventilator§	36	3.03 (0-44)			
Intraventricular haemorrhage (grade 1 or higher)	*32*	3			
Socioeconomic status§,€	37	4(1-5)	53	4(1-5)	.15
Full-scale IQ£	38	89(12.8)	59	100(10.6)	10^{-5}
Verbal comprehension index£	38	90(12.3)	59	99(11.7)	.001
Working memory index£	38	84(13.0)	59	92(12.0)	.0.02
Perceptual org. index£	38	98(16.4)	59	108(12.8)	.001
Processing speed index£	38	93(15.4)	59	100(12.4)	.014

*Data presented as means with * = range, £ = standard deviation in parenthesis; or as § = median (range).*
€ Parent's SES, measured at time of birth.
*** Student's t-test was used to test for group differences in Socio-economic status, full-scale IQ and the four IQindices (Verbal comprehension, Working memory, Perceptual organization, Processing speed).*

to follow-up, and three were excluded due to severe cerebral palsy (quadriplegia with mental retardation) or Down's syndrome. Hence, 76 were eligible and invited to participate at 19 years of age. We obtained usable MRI and IQ-data from 38 of these participants (53% females).

2.1.2. Term-born control group

The control participants were recruited in Trondheim as part of a multi-center study, in which 1200 pregnant women with a singleton pregnancy and expecting their second or third child, were enrolled before the 20th week of pregnancy. A 10% random sample selected by the sealed envelope method was chosen for follow-up, serving as a population reference. The control group comprised 122 children born at term with birth weight ≥10th percentile, adjusted for GA and sex. At 19 years of age, ten children had moved and two were excluded due to congenital malformations, yielding an eligible control group for follow-up consisting of 110 children. The number of term-born participants with usable MRI-scans and IQ-data was 59 (58% females).

2.1.3. Ethics

The Regional Committee for Medical Research Ethics (Norwegian Health Region IV) approved the study protocols (project numbers: 78–00 May 2000; 4.2005.2605; 2013/636 REK midt), and all participants gave written informed consent.

2.1.4. Perinatal data

Descriptive statistics on birthweight (BW), gestational age (GA), and days in neonative intensive care, as well as frequencies of intraventricular hemorrhage (IVH) are reported in Table 1. For a detailed account of other perinatal risk factors, see Indredavik et al. (2010).

2.1.5. Cognitive and demographic variables

Intelligence Quotient (IQ) scores were obtained using the Wechsler Adult Intelligence Scale (WAIS), 3rd Edition, administered by a clinical neuropsychologist (Løhaugen et al., 2010). The full IQ score was based on the results from 11 subtests. In addition to full IQ, four indices were calculated: Verbal comprehension (Vocabulary, Similarities, Information, Comprehension), Working memory (Arithmetic, Digit Span, Letter-Number Sequencing), Perceptual organization (Picture Completion, Block Design, Matrix Reasoning), and Processing speed (Digit Symbol-Coding, Symbol Search).

Hollingshead's Two Factor index of Social Position was used to calculate socioeconomic status (SES) based on education and occupation (adapted to today's categories) of one parent, or the mean index of both parents (Hollingshead, 1957). Parental SES was collected when the participants were 14–15 years old (Indredavik et al., 2004), and supplemented at age 19 (Løhaugen et al., 2010).

2.2. MRI

2.2.1. Image acquisition

MRI scanning was performed on a 3 Tesla Siemens Skyra scanner, equipped with a 32 channel quadrature head coil. One sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) scans were acquired (echo time = 3.45 ms, repetition time = 2730 ms, inversion time = 1000 ms, flip angle = 7°; field of view = 256 mm, voxel size = 1 × 1 × 1.33 mm^3, acquisition matrix 256 × 192 × 128, reconstructed to 256 × 256 × 128).

2.2.2. Brain morphometry image analysis

Cortical reconstruction and subcortical segmentation were performed with the FreeSurfer image analysis suite, version 5.3.0 (https://surfer.nmr.mgh.harvard.edu/). The technical details of cortical reconstruction with FreeSurfer are described elsewhere (Dale et al., 1999; Dale and Sereno, 1993; Fischl, 2004; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 1999a; Fischl et al., 1999b). Matching of cortical geometry across subjects is achieved by registration to a spherical atlas based on individual cortical folding patterns (Fischl et al., 1999b). Cortical thickness and surface area estimates were obtained as described in previous publications (Fischl and Dale, 2000; Winkler et al., 2018). Cortical area and mean cortical thickness were obtained for each of the 34 parcellations of the Desikan-Killiany parcellation scheme (Desikan et al., 2006), and these estimates served as morphometry variables in the ensuing statistical mediation analyses. Subcortical volumes were obtained from the automated procedure for volumetric measures of brain structures implemented in FreeSurfer (Fischl et al., 2002). Eighteen volumetric measures were investigated, including left and right thalamus, hippocampus, and amygdala, as well as the basal ganglia (left and right putamen, pallidum, caudate), cerebellar gray and white matter, and, finally, the left and right lateral ventricles (in FreeSurfer terminology, the 'lateral ventricle" and the 'inferior lateral ventricle' combined). For simplicity, we refer to these collectively as "subcortical structures" although, strictly speaking, hippocampus and cerebellum are not subcortical.

2.3. Statistical analysis

2.3.1. Demographic and clinical variables

Demographic and clinical variables were examined in IBM SPSS 20. Student's *t*-test was used for group comparisons of SES and IQ. Levene's test for homogeneity of variances was significant for SES, so two sample t-tests with unequal variances were used when comparing the groups on this variable. All other t-tests were conducted as two sample t-tests assuming equal variances.

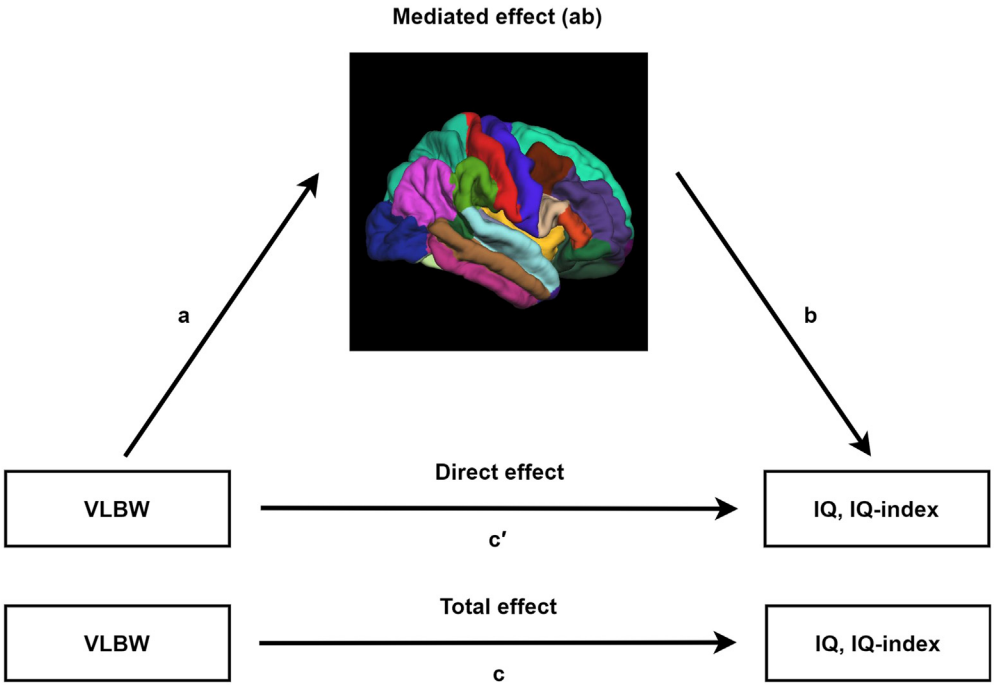

Fig. 1. Mediation analysis. The basic causal model for the mediation analyses: The effects of the exposure (causal) variable (VLBW) on the mediator (brain structure; a) and of the mediator on the outcome (IQ and IQ-index scores; b) were assessed in separate analyses and the coefficients entered into the mediation analysis. The mediation analysis estimated total effect (c), as well as direct (c´) and indirect (mediated) effects (ab), of the exposure variable on the outcome variable.

2.3.2. Mediation analyses

To test the hypothesis that atypical brain morphology mediates the effect of preterm birth with VLBW on general cognitive ability (IQ), we performed statistical analyses to assess indirect effects of an exposure variable (VLBW) on an outcome variable (IQ, IQ-indices) through the exposure variable's effect on a mediating variable (cortical area, cortical thickness, or subcortical brain structure volumes) (Fig. 1). The mediation analyses were performed within R-4.0.5 (R Core Team, 2018), using the R Package for Causal Mediation Analysis, version 4.5.0 (Dustin et al., 2014; Imai et al., 2011). Cortical area and cortical thickness data from the 34 parcellations of the Desikan-Killiany parcellation scheme (Desikan et al., 2006) served as mediator variables in the cortical analyses, and the 18 subcortical brain structure volumes described under 2.2.2 were mediators in the subcortical analyses. Two sets of general linear models were fitted with 1) area or thickness (from each parcellation, successively), or one of the subcortical brain structure volumes, as dependent variable, and group (control=0, VLBW=1) and sex as independent variables; and subsequently (2) with IQ or IQ-index score as dependent variable and group and sex, cortical area/thickness, or a subcortical brain structure volume, as covariates. Several of these analyses with IQ, or one of the IQ-indices, as dependent variable yielded significant interaction effects. Therefore, an interaction term (group*area/thickness/subcortical structure volume) was included in all these analyses, and the coefficients from these models were entered into the mediation analysis with group as exposure ("treatment") factor. This allowed for group-specific evaluation of the direct and *indirect* (mediation) effects of VLBW on the IQ(index) scores. We report the indirect (mediation) effects for the VLBW group here, which represent change in IQ(index)-score as a consequence of the change in brain morphology that results when the exposure variable is changed by one unit from control to VLBW. Thus, the indirect effect can be interpreted as "how many points does the IQ(index)-score change due to the changes in brain morphology associated with VLBW?" The mediation analyses were performed with 100 000 iterations, with one exception: The analysis of right thalamus volume on Perceptual organization index was performed with 1 million iterations to obtain extreme enough estimates to generate a specific p-value. Point estimates of the indirect effect for VLBW, 95% confidence intervals and proportion estimates, were obtained and the corresponding p-values were combined across the hemispheres to yield a brain-wide expected False Discovery Rate (FDR) of 5% (Benjamini et al., 2006) (The complete set of p-values, from all mediation analyses on cortical area and subcortical structures, is displayed in Supplementary tables S10-S15).

3. Results

3.1. Demographic and clinical variables

Demographic and clinical variables are presented in Table 1. The preterm-VLBW group had lower full-scale IQ (M = 89, SD=13) than the control group (M = 102, SD=13); t89=4.73, p < .001, as well as lower average scores on all four IQ-indices (See Table 1). The difference in average raw scores on the IQ-indices were (Cohen's d in parenthesis): Verbal 11.33 (0.9); Working memory: 5.25 (0.4); Perceptual organization: 13.24 (0.9); Processing speed: 7.36 (0.5).

3.2. Statistical mediation analyses of cortical data

The statistical mediation analyses yielded significant effects of cortical area on Full-scale IQ (FSIQ) in multiple regions in both hemispheres (see Table 2 and Fig. 2), including the lateral orbitofrontal cortex and the precentral gyrus, the superior and inferior parietal gyri (SPG and IPG) and the middle temporal gyrus (MTG), as well as the fusiform gyrus and the insula. In addition, there were unilateral mediation effects in the right medial orbitofrontal cortex, the opercular and triangular parts of the right inferior frontal gyrus (IFG), the posterior cingulate gyrus, and the right superior (STG) and transverse temporal gyri, as well as the left inferior temporal gyrus (ITG). Thirteen of 21 (62%) significant mediation findings were in the right hemisphere. There were also nominally significant mediation effects, which did not survive the 5% FDR correction for multiple comparisons, in an additional 14 regions across the left and right hemispheres (Table 2). It is notable that the confidence intervals around several of the significant estimates in Table 2 are wide, reflecting uncertainty as to the true size of the effects.

The findings for the four IQ-indices are displayed in Supplementary tables S1-S4 (see also Supplementary figures S1-S4). The Perceptual Organization index showed evidence of mediation in most of the same

Table 2
Indirect (mediated) effect of cortical area on Full-scale IQ, Bold: significant at the 0.05 level; *: still significant after 5% FDR correction, £ Prop. (or, proportion) is the indirect, or mediated, effect as a proportion of the total effect of VLBW on IQ.

	Left hemisphere				Right hemisphere			
	Indirect effect	95% CI	P	Prop.£	Indirect effect	95% CI	P	Prop.
Frontal pole	0.2	(−1.8, 2.3)	n.s.	−0.01	−0.1	(−2.3, 1.9)	n.s.	.01
SFG	−1.2	(−3.5, 0.6)	n.s.	.10	−0.8	(−2.8, 1.0)	n.s.	.06
Lateral OFG	**−5.9**	**(−10.1, −2.5)**	**.0003***	**.51**	**−4.9**	**(−8.8, −1.9)**	**.001***	**.42**
Medial OFG	−1.0	(−3.7, 1.3)	n.s.	.08	**−2.3**	**(−4.9, −0.4)**	**.011***	**.19**
IFG opercular	**−2.2**	**(−5.3, 0.03)**	**.046**	**.18**	**−5.2**	**(−9.4, −1.9)**	**.0002***	**.45**
IFG orbital	−1.5	(−3.9, 0.1)	n.s.	.12	−1.9	(−4.6, 0.2)	n.s.	.15
IFG triangular	**−1.6**	**(−4.0, 0.001)**	**.05**	**.13**	**−4.9**	**(−9.1, −1.6)**	**.0008***	**.42**
Caudal MFG	−0.9	(−3.3, 1.0)	n.s.	.07	−0.5	(−2.9, 1.7)	n.s.	.04
Rostral MFG	−0.8	(−3.2, 1.3)	n.s.	.06	−0.2	(−2.0, 1.4)	n.s.	.02
Precentral gyrus	**−3.5**	**(−6.8, −1.0)**	**.001***	**.30**	**−4.8**	**(−8.8, −1.8)**	**.0003***	**.41**
Rostral ant. cing.	−1.8	(−4.9, 0.7)	n.s.	.15	**−2.3**	**(−5.6, −0.1)**	**.03**	**.19**
Caudal ant. cing.	−0.3	(−3.1, 2.4)	n.s.	.02	**−1.9**	**(−4.9, 0.0)**	**.05**	**.15**
Posterior cing.	−1.3	(−3.5, 0.2)	n.s.	.10	**−3.4**	**(−7.0, −0.8)**	**.004***	**.29**
Isthmus cing.	−2.4	(−5.5, 0.0)	n.s.	.20	**−2.3**	**(−5.3, −0.2)**	**.02**	**.18**
Insula	**−3.6**	**(−6.9, −1.1)**	**.003***	**.31**	**−2.3**	**(−5.0, −0.4)**	**.01***	**.19**
Postcentral gyrus	−2.2	(−5.3, 0.4)	n.s.	.18	−2.0	(−5.5, 1.1)	n.s.	.17
Paracentral gyrus	−1.1	(−3.6, 0.7)	n.s.	.09	−0.2	(−1.9, 1.5)	n.s.	.01
SPG	**−3.5**	**(−6.8, −1.0)**	**.002***	**.30**	**−4.6**	**(−8.4, −1.6)**	**.0004***	**.39**
IPG	**−3.0**	**(−6.1, −0.7)**	**.005***	**.25**	**−3.9**	**(−7.5, −1.2)**	**.002***	**.34**
SMG	−2.0	(−5.2, 0.4)	n.s.	.17	**−2.8**	**(−6.1, −0.4)**	**.02**	**.23**
Precuneus	**−1.7**	**(−4.2, 0.0)**	**.048**	**.14**	−1.6	(−4.0, 0.2)	n.s.	.13
Lateral occipital g.	0.5	(−1.5, 2.7)	n.s.	−0.04	−1.5	(−4.0, 0.5)	n.s.	.12
Cuneus	−1.7	(−4.4, 0.2)	n.s.	.14	−1.4	(−4.0, 0.6)	n.s.	.11
Pericalcarine s.	−2.3	(−5.5, 0.4)	n.s.	.19	−1.8	(−4.9, 0.6)	n.s.	.15
Fusiform gyrus	**−2.7**	**(−6.1, −0.4)**	**.015***	**.23**	**−2.8**	**(−6.0, −0.5)**	**.01***	**.24**
Lingual gyrus	**−3.0**	**(−6.4, −0.2)**	**.032**	**.25**	−1.8	(−4.5, 0.1)	n.s.	.15
Temporal pole	0.2	(−1.9, 2.3)	n.s.	−0.01	1.1	(−0.5, 3.6)	n.s.	−0.08
STG	**−2.5**	**(−5.5, −0.4)**	**.014**	**.21**	**−3.6**	**(−6.9, −1.2)**	**.001***	**.31**
Heschl's gyrus	−1.4	(−4.0, 0.3)	n.s.	.11	**−4.9**	**(−9.3, −1.4)**	**.01***	**.42**
STS	−1.4	(−4.0, 0.6)	n.s.	.12	**−2.7**	**(−5.9, −0.4)**	**.02**	**.22**
MTG	**−4.1**	**(−7.5, −1.4)**	**.0005***	**.35**	**−6.4**	**(−11, −2.7)**	**.0003***	**.55**
ITG	**−2.6**	**(−5.6, −0.4)**	**.01***	**.21**	−1.5	(−4.4, 0.8)	n.s.	.12
PHG	**−2.6**	**(−6.0, −0.1)**	**.04**	**.21**	−2.1	(−6.6, 0.9)	n.s.	.17
Entorhinal cortex	−0.3	(−2.5, 1.7)	n.s.	.02	−0.2	(−1.7, 0.9)	n.s.	.01

Abbreviations: Prop.: Proportion; g.: gyrus; s.: sulcus; c.: cortex; ant.: anterior; cing: cingulate gyrus; SFG: superior frontal gyrus; OFG orbitofrontal gyrus; IFG: inferior frontal gyrus; MFG: medial frontal gyrus; SPG: superior parietal gyrus; IPG: inferior parietal gyrus; SMG: supramarginal gyrus; STG: superior temporal gyrus; STS: superior temporal sulcus; MTG: middle temporal gyrus; IFG: inferior temporal gyrus; PHG: parahippocampal gyrus.

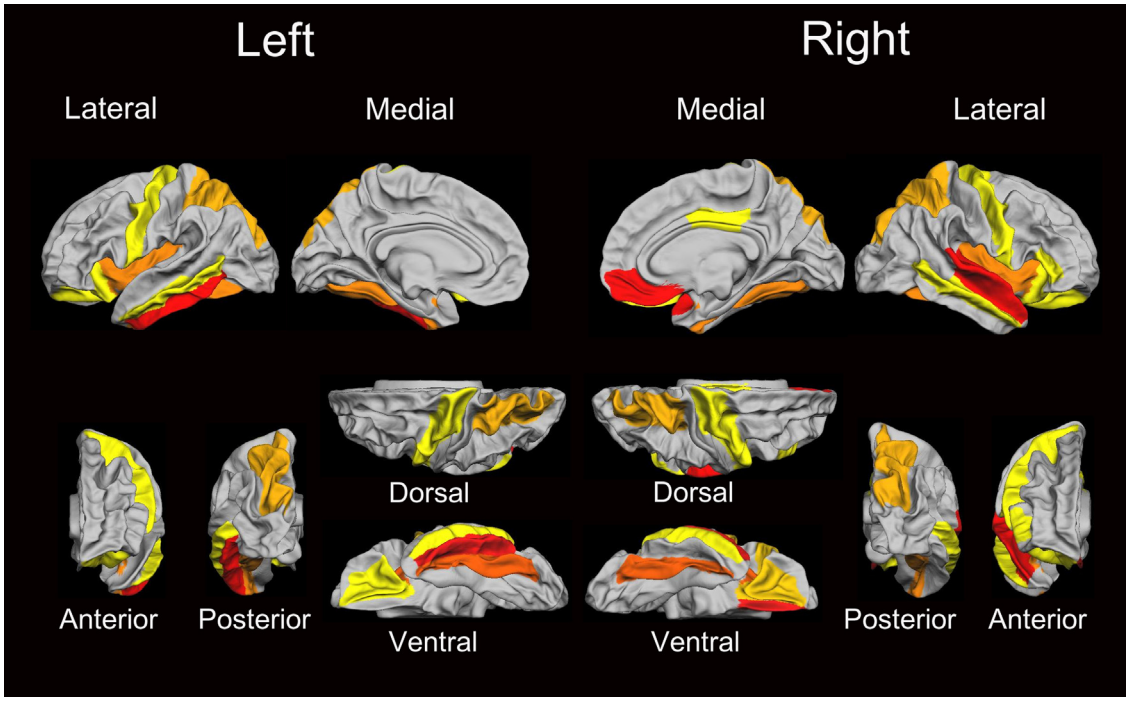

Fig. 2. Cortical regions showing significant mediator effect of cortical area on IQ, Red: $P < .05$; Orange: $P < .01$; Yellow: $P < .001$, The figure displays cortical regions that yielded a significant indirect (mediation) effect after correction with 5% FDR, as presented in Table 2. The figure was generated by overlaying the regional p-values on the fsaverage cortical template in the tksurfer program (FreeSurfer).

Table 3
Indirect effect of subcortical brain structure volumes on full-scale IQ and IQ-indices*.

	Full-scale IQ			
	Indirect effect	95% CI	P	Proportion$
Left-TH	−7.8	(−12.8, −3.6)	$6*10^{-5}$	0.68
Right-TH	−8.2	(−13.2, −3.8)	.0001	0.72
Left-HC	−3.5	(−6.8, −1.0)	.002	0.31
Right-HC	−5.0	(−8.8, −2.0)	.0001	0.43
Left-Amygdala	−2.1	(−4.9, −0.1)	.03	0.18
Right-Amygdala	−2.8	(−5.8, −0.6)	.005	0.24
Left-Caudate	−4.0	(−7.5, −1.2)	.002	0.35
Right-Caudate	−4.0	(−7.7, −1.2)	.002	0.35
Right-Putamen	−3.1	(−6.4, −0.6)	.011	0.27
Left-Pallidum	−3.4	(−6.8, −0.8)	.005	0.30
Right-Pallidum	−5.3	(−9.5, −1.9)	.001	0.46
Left-Cereb-WM	−5.2	(−9.1, −2.1)	.0001	0.45
Left-Cereb-C	−3.3	(−6.5, −0.9)	.002	0.28
Right-Cereb-WM	−4.5	(−8.2, −1.6)	.0005	0.38
Right-Cereb-C	−3.6	(−6.9, −1.1)	.001	0.30
	Perceptual Organization			
	Indirect effect	95% CI	P	Proportion
Left-TH	−10.4	(−16.5, −5.2)	$4*10^{-5}$	0.95
Right-TH	−11.5	(−17.7, −6.0)	$4*10^{-6}$	1.05
Left-HC	−4.9	(−9.1, −1.6)	.002	0.45
Right-HC	−6.8	(−11.7, −2.9)	$2*10^{-5}$	0.62
Left-Amygdala	−3.0	(−6.8, −0.4)	.02	0.28
Right-Amygdala	−4.2	(−8.2, −1.2)	.003	0.39
Left-Caudate	−4.2	(−8.4, −1.0)	.006	0.39
Right-Caudate	−4.6	(−9.0, −1.2)	.004	0.42
Right-Putamen	−4.1	(−8.1, −0.9)	.011	0.37
Left-Pallidum	−4.4	(−8.7, −1.1)	.006	0.41
Right-Pallidum	−6.3	(−11.3, −2.1)	.002	0.57
	Processing Speed			
	Indirect effect	95% CI	P	Proportion
Left-TH	−9.4	(−15.4, −4.3)	.0001	1.31
Right-TH	−9.7	(−15.8, −4.3)	.0002	1.35
Left-HC	−3.7	(−7.4, −0.9)	.003	0.51
Right-HC	−5.2	(−9.7, −1.7)	.0008	0.72
Left-Pallidum	−3.7	(−7.6, −0.8)	.006	0.51
Right-Pallidum	−7.9	(−13.1, −3.6)	$2*10^{-5}$	1.10
	Verbal Comprehension			
	Indirect effect	95% CI	P	Proportion
Left-TH	−5.9	(−10.9, −1.6)	.007	0.68
Right-TH	−5.7	(−10.9, −1.1)	.016	0.66
Left-HC	−2.5	(−5.4, −0.4)	.015	0.28
Right-HC	−3.6	(−7.3, −0.8)	.008	0.42
Left-Caudate	−3.7	(−3.8, 0.5)	.006	0.14
Right-Caudate	−3.5	(−4.4, 0.3)	.01	0.20
Right-Putamen	−2.4	(−7.3, −0.9)	.014	0.42
Left-Pallidum	−2.5	(−5.5, −0.3)	.014	0.40

*Only findings significant after 5% FDR correction are included in the table.
$ Proportion of the total effect estimated to be represented by the indirect effect, **Abbreviations:** TH: Thalamus; HC: Hippocampus.

regions as full-scale IQ, and mostly with larger effect sizes. The Working memory (see Supplementary table S2) and Verbal comprehension (S1) indices showed less widespread effects, and the Processing speed index (S4) showed the least effects of the four IQ-indices. With regard to cortical thickness, there were no significant mediation effects on IQ or any IQ-index in either hemisphere (Supplementary tables S5-S9).

3.3. Statistical mediation analyses of subcortical data

The statistical mediation analyses yielded significant effects of subcortical brain structure volumes on FSIQ in multiple regions in both hemispheres (Table 3). As in the cortical analyses, the Perceptual organization index displayed a pattern of findings similar to FSIQ . The Verbal comprehension and Processing speed indices showed mediation effects by several subcortical brain structures, albeit fewer than for Perceptual organization, while no mediation effects survived correction for the Working memory index. The findings were almost without exception bilateral. As is evident from Table 3, the estimated mediation effects for FSIQ were strongest for left and right thalamus (7.8 and 8.2, respectively), which also had the widest confidence intervals, spanning 9 and 11 points. For Perceptual organization, the estimates for left and right thalamus were even higher, with confidence intervals from 5.2 to 16.5 and 6.0 to 17.7 points. Thus, the data show strong evidence of an indirect effect on IQ for multiple subcortical brain structures, but the width of the confidence intervals indicate a high degree of uncertainty regarding the size of the effects.

4. Discussion

We demonstrate statistical evidence indicating a causal link between observed gray matter aberrations in the brain and reduced general cognitive ability in a Norwegian cohort of 19-year-old adults born preterm with VLBW. Statistical mediation analyses yielded evidence of an indirect effect of preterm birth with VLBW on IQ as measured with WAIS-III, mediated by smaller surface area in the lateral frontal lobes and the orbitofrontal cortex, the insula, fusiform gyrus, and the lateral parietal and temporal lobes. In addition, there were mediation effects of several subcortical brain structure volumes on IQ. Although persistent abnormalities in cortical gray matter are well-documented in the preterm brain (Bjuland et al., 2013, 2014; de Kieviet et al., 2012; Nam et al., 2015; Rimol et al., 2019; Skranes et al., 2013; Sripada et al., 2018), the functional correlates of these structural aberrations have not yet been established. A German study conducted by Schmitz-Koep et al. (2020) reported a modest indirect (mediated) effect of mean cortical thickness in the left hemisphere on full-scale IQ in adults born preterm with VLBW but did not investigate cortical surface area. Thus, the present study is, to our knowledge, the first to demonstrate a plausible causal effect of reduced cortical area on general cognitive ability in survivors of preterm birth.

We were unable to replicate the cortical thickness findings of Schmitz-Koep et al. (2020), as our analyses showed no indirect effect of cortical thickness on full-scale IQ or any of the IQ-indices. The German sample was approximately twice as large as ours but since our effect sizes for mean cortical thickness in the left and right hemispheres were small and did not even show a trend toward statistical significance, the difference in mediation findings cannot likely be reduced to a matter of statistical power. The German preterm-VLBW sample had a higher mean IQ than the Norwegian sample (94 vs. 89) with similar standard deviations, which means that at least some of the German subjects were high functioning, and there were fewer low functioning subjects than in the Norwegian sample. The surface-based method used in the German study is different from the one applied here, and we are not aware of any direct comparison of the sensitivity and specificity of the two methods. Nonetheless, our failure to find a mediation effect of cortical thickness on IQ is consistent with previous studies reporting an absence of correlation between cortical thickness and IQ in a Norwegian (Sølsnes et al., 2015) and a Spanish (Zubiaurre-Elorza et al., 2012) late-childhood cohort, both using the same surface-based method as the present study.

4.1. Cortical surface area

The parieto-frontal integration theory (P-FIT) suggests the most important regions for general intelligence are found in the frontal and parietal lobes, including the lateral prefrontal cortex (PFC) and the angular and supramarginal gyri (Jung and Haier, 2007). We observed that reduced IQ in preterm-VLBW was partly mediated by reduced surface area in the frontal lobe of each hemisphere, including the lateral orbitofrontal cortices and the precentral frontal gyrus, as well as the right inferior

frontal and medial orbitofrontal gyrus. Contrary to expectation, neither hemisphere showed evidence of mediation in the middle frontal gyrus (Brodmann area 46) or superior frontal gyrus (Brodmann area 6,8–10). The orbitofrontal cortices are not included in the P-FIT, but a voxel-based morphometry study designed to test the P-FIT found correlations with general intelligence in these regions (Colom et al., 2009). Moreover, we found mediation effects in the superior and inferior parietal lobes of both hemispheres, consistent with our preditions. It should be noted, however, that in the Desikan-Killiany parcellation scheme used here (Desikan et al., 2006), the 'inferior parietal lobe' includes the angular gyrus but not the supramarginal gyrus. We also found mediation effects in the right STG, consistent with our predictions based on the P-FIT model, as well as in the bilateral middle and left inferior temporal gyri, which also associated with general intelligence in Colom et al. (2009). Contrary to our predictions, the occipital "extrastriate regions" did not show clear evidence of mediation effects. In the Desikan-Killiany parcellation scheme, the 'cuneus' label roughly corresponds to the medial part of the extrastriate cortex, although superior aspects of the lingual region may also be part of it (Killiany, 2022, January 20). We found only nominally significant effects in the left lingual gyrus and failed to find evidence of mediation in the cuneus. Furthermore, lateral "extrastriate regions" (Brodmann areas 18 and 19) are located within the 'lateral occipital lobe' in the present scheme (Killiany, 2022, January 20), and there was no evidence of mediation effects there in either hemisphere. We found substantial mediation effects bilaterally in the insula. This is not predicted by the P-FIT but is consistent with meta-analyses of neuroimaging data indicating a central role for the anterior insula in domain-general attention and control processes, together with the frontal operculum and the anterior cingulate (Gratton et al., 2018; Nelson et al., 2010). Finally,the right frontal inferior gyrus (opercular and triangular parts) and posterior cingulate showed mediation effects in our data, whereas there were only trend-level (nominally significant) findings in the right anterior cingulate.

The results of the cortical mediation analyses differed between the four IQ-indices. The Perceptual Organization index showed the most widespread effects, followed by the Working Memory index; both indices displaying bilateral mediation effects in frontal and temporal cortical regions. The Perceptual Organization index showed a pattern of mediation similar to FSIQ, with bilateral findings in frontal, parietal and temporal regions, as well as the insula and the fusiform gyrus. The effect sizes were larger for the Perceptual organization index, whereas the confidence intervals were a little tighter for FSIQ. It is notable that the confidence intervals for the significant findings in Table 2 tend to be wide, spanning from 4 to 8 IQ-points (average = 6), with the lower bounds in several cases close to zero. This limitation underscores the need for replication with larger samples before firm conclusions are drawn about the magnitudes of the effects presented here.

The Verbal comprehension index (VCI) and the Working memory index comprise the "verbal IQ" score, and verbal IQ-tasks have been associated with left hemisphere function, in particular the left lateral temporal cortex (Gingras and Braun, 2018). However, our strongest findings for the Working memory index and the VCI were in the right frontal and temporal lobes, The Working memory index in WAIS-III contains several complex arithmetic tasks with a significant verbal comprehension component, which have been found to correlate highly with verbal tasks (Arnau and Thompson, 2000). Working memory functions also depend substantially on attentional control, which is associated with the brain's executive control networks and is weakened in many clinical groups. Based on recent neuroimaging evidence suggestive of functional distinctions within the fronto-parietal network (Gratton et al., 2018), tasks that load heavily on executive functions may be expected to be especially dependent on right frontal and parietal regions involved in post-response processing associated with subsequent top-down control, whereas the left hemisphere may be more involved in early, stimulus-driven or bottom-up processing (Gratton et al., 2017; Neta et al., 2015). This might explain why we found mediation effects in the right frontal cortex, and to a lesser degree in the left, for the Working memory index. The VCI to a large extent reflects "crystallized" abilities, i.e., learned procedures and knowledge acquired through experience or education, which are likely to rely heavily on cognitive representations in long term memory. However, it seems reasonable to assume that executive functions are necessary for problem solving also in the context of verbal tasks (Alexander, 2002). We can only speculate regarding the executive load on the verbal comprehension tasks, but it is possible that especially the Similarities subtest loads on several executive components (Cabrera et al., 2018), and clinical experience indicates that executive dysfunction is associated with problems on the Similarities and Comprehension verbal tests. The fact that also the VCI findings were lateralized to the right might reflect a top-down component in these verbal tasks.

4.2. Subcortical brain structures

The statistical analyses yielded evidence of an indirect effect of preterm birth with VLBW on full-scale IQ, as well as three of the four IQ-indices, mediated by smaller volumes in the thalamus, hippocampus, basal ganglia, amygdala, and cerebellar white and gray matter. Connectivity between subcortical gray matter and the cerebral cortex is likely disrupted in the preterm brain (Salvan et al., 2014), and disruption specifically of the thalamocortical system is probably a key component in preterm brain injury (Volpe, 2009b). The thalamus acts as a relay station for almost all incoming sensory information to the cerebral cortex, and has a key role in perception, learning (Jaepel et al., 2017), and consciousness (Lagercrantz and Changeux, 2009). A recent resting-state functional MRI study identified the thalamus as common locus for IQ, as well as domain-specific cognitive skills such as reading and arithmetic (Koyama et al., 2020).

The time between very preterm birth and term-equivalent age is a critical period for the establishment of functional thalamocortical connections. Early in the second trimester of gestation, thalamic fibers project toward the cortex and form synapses in a transient cortical compartment - the subplate zone –, before penetrating into the cortical plate by the beginning of the third trimester (Kostovic and Judas, 2010). Major neurogenetic events such as proliferation and migration, cortical differentiation, and synaptogenesis are to a large extent genetically controlled, but early (prenatal) thalamocortical input is believed to be vital for cortical differentiation (Bourgeois et al., 1989; Lagercrantz and Changeux, 2009). Throughout this process subplate neurons, thalamic neurons, and pre-myelinating oligodendrocytes are susceptible to injury caused by hypoxia, infection/inflammation, or any number of pre- and perinatal risk factors (Ball et al., 2015; Ligam et al., 2009). Damage to any of these cell populations, whether pre- or peri-/postnatal, may disrupt the microstructural development of the cortex, the thalamus, and associated white matter tissue (Dean et al., 2013; Volpe, 2009a).

The reductions in cortical surface area and smaller thalamic volumes observed in our cohort (Bjuland et al., 2014; Skranes et al., 2013) may be a reflection of thalamocortical pathology, which may ultimately result in poor cognitive performance. Bjuland et al. (2014) reported positive partial correlations between IQ and several subcortical brain structure volumes that included the thalamus, hippocampus, and amygdala, as well as the basal ganglia and cerebellum. Here, we demonstrate evidence of meditation by all the aforementioned structures (see Table 3), and the data show strong evidence of indirect effects of several subcortical brain structure volumes on IQ. However, as indicated by the wide confidence intervals around several of the estimates (see Table 3), it is highly uncertain how large the real effect is. For thalamus, the confidence intervals start more or less at a clinically significant level, at least in the full-scale IQ and Perceptual organization analyses, where the lower bounds are at 5–6 IQ-points, but for several analyses it is unclear whether the mediation effects carry any real practical or clinical significance.

Our mediation findings in the amygdala are intriguing. The amygdala is traditionally considered to have a role in regulating emotion and

encoding emotionally salient memories, and has not received nearly as much attention as a putative node in a network subserving general intelligence. However, it has recently been found to play a role in forming non-emotional memories in humans (Inman et al., 2018), and a functional MRI study demonstrated that the amygdala is involved in a medial temporal lobe network pivotal to cognitive processing of visual stimuli (Evensmoen et al., 2021). It is possible that several of the subcortical brain structures mentioned here, and the cerebellum as well, participate in networks supporting general, multipurpose cognitive operations. There is evidence, from resting-state functional MRI, of reduced connectivity between multiple brain structures in neonates born very preterm (< 32 weeks gestation and 500 to 1500 gs), including the amygdala and thalamus, hypothalamus, brainstem, and insula (Scheinost et al., 2016). According to Ball et al. (2015), "preterm birth impacts on the development of the whole-brain structural connectome, resulting in reduced cortico-subcortical connectivity."

4.3. Structure-function relationships in the preterm brain

A note of caution should be offered on the generalizability of the findings discussed here. Most studies of the relationship between brain structure and IQ are based on samples from the general population, and discrepancies between our findings and models based on general population data can perhaps be attributed to an altered relationship between structure and function in the preterm brain, possibly caused by early brain damage and subsequent disruption of normal brain development. Indeed, the fact that the IQ-index regression analyses yielded significant interactions between 'group' and 'area' in several cortical regions, suggests there is an altered relationship in at least some parts of the brain. Furthermore, data from our lab (Olsen et al., 2018) suggest that executive control may be organized differently in the preterm brain, as indicated by lower levels of activation in the anterior cingulate related to task-set maintenance. The pediatric brain appears highly adaptable in response to early neuronal insults (Krageloh-Mann, 2004). For instance, brain plasticity is well established for language functions after early left-sided lesions (Staudt et al., 2001), and some evidence exists for compensatory potential within in the motor system after prenatal white matter injury (Krageloh-Mann, 2004). However, visual deficits after even mild cases of mostly bilateral periventricular leukomalacia (PVL) acquired early in brain development, appear not to be easily compensated (Pavlova et al., 2003). It is possible that relocation of function is more difficult in the very premature brain, which typically shows diffuse bilateral damage that also affects white matter pathways, compared to an immature brain with unilateral cortical damage, where a healthy contralateral hemisphere can compensate for loss of function. Thus, while PVL may disrupt cortical development in e.g., the supramarginal gyrus, where we failed to find strong evidence of statistical mediation in the VLBW group, it is unclear whether such disruption can lead to a relocation of function to adjacent or more distal regions of the cerebral cortex.

4.4. Comparison of cortical area between preterm-VLBW and control group

In a previous publication (Skranes et al., 2013), we showed reduced surface area bilaterally across the cortical mantle in the preterm-VLBW group. Although the most prominent findings were in temporal regions and the insula, there were also reductions in frontal, parietal, occipital, and cingulate regions. While primary cortical gray matter maldevelopment probably occurs in preterm birth, perinatal gray matter injury may to a large extent be secondary to focal or diffuse PVL (Rimol et al., 2019; Volpe, 2011). The incidence of PVL in this cohort is unknown (see Rimol et al., 2019), but neuroimaging studies of VLBW survivors suggest that cognitive and behavioral deficits are related to diffuse cerebral white matter injury (Dyet et al., 2006; Haynes et al., 2008; Woodward et al., 2006, 2012). The cause of diffuse axonal injury in PVL is "likely complex with no one single mechanism" (Haynes et al., 2008), but the role of hypoxic-ischemic injury in the pathogenesis of PVL is well-documented. The putative mechanism behind secondary gray matter loss is axonal degeneration with retrograde and anterograde transsynaptic (Wallerian) effects, resulting in degeneration of the overlying cortex (Back, 2014; Volpe, 2009a), including loss of cortical thickness (Bjuland et al., 2013). It is not known to what extent this may affect cortical surface area. According to the radial unit hypothesis, cortical area is determined by the number of cortical columns at birth (Rakic, 1988), but the cortical surface appears to continue to expand throughout childhood and into adolescence, most likely primarily due to myelination (Brown and Jernigan, 2012). It is unclear whether reduction of neuropil and neuronal death, secondary to white matter damage, can cause cortical columns to shrink and hence reduce surface area or limit its growth, and on what time scale such a process might take place.

4.5. Strengths and limitations

This is an observational study, and as such it does not prove biological causation, but a measurement-of-mediation design is a well-established method for causal inference from observational data. An underlying assumption is that the mediator is not a confounding variable, which means that reduced cortical area cannot be a cause of both preterm birth/VLBW (the exposure variable) and decreased IQ (the outcome) (MacKinnon and Dwyer, 1993). We would argue that the most plausible casual model is one where preterm birth leads to aberrant cortical development with reduced surface area in the adult brain as the result. It is, however, unclear exactly how consequential pre- and perinatal damage to the preterm brain is, and to what extent interventions and other environmental factors throughout early childhood can alter the course of brain development. Thus, a limitation of this study is that preterm birth with VLBW is a proxy for several pre- and perinatal events that influence subsequent brain development, and it is not known exactly which factors are causative of reductions in cortical area and, ultimately, reduced cognitive ability. This also means that there are potentially multiple unmeasured confounding factors that may increase the risk of preterm birth as well as influence brain cortical development, such as genotype in combination with various socioeconomic factors, as well as other prenatal confounding factors that include legal (alcohol, nicotine) and illegal drugs. Moreover, since our inclusion criterion is birthweight under 1500 g, most of our participants were born before 32 weeks of gestation, and among participants born with a higher gestational age there is likely to be an overrepresentation of individuals with fetal growth restriction. Finally, because we have investigated a predetermined set of cortical regions individually, using univariate models, we are essentially blind to possible non-linear relationships between cortical morphology and IQ, and to global trends in the structure-function relationship that can only be discovered with a multivariate approach.

A strength of our study is that we use a surface-based approach to cortical morphometry that includes both cortical thickness and cortical area. By separating the two constituent components of cortical volume, we achieve a higher degree of specificity than volumetric studies, while at the same time allowing for a fuller account of cortical development than previous studies which investigated only cortical thickness. Another strength is the comprehensive assessment of cognitive ability, performed by an experienced clinical neuropsychologist using the complete WAIS-III test with scores for the four index abilities. A final strength is that the present study includes a well-defined patient cohort with low attrition rate (Fewtrell et al., 2008).

5. Conclusions

We report indirect effects of preterm birth with VLBW on general cognitive ability, mediated by reductions in regionalcortical surface area and subcortical brain structure volumes, in a Norwegian sample of 19-year-olds born in the late 1980s. Multiple regions in frontal, parietal

and temporal cortices, and to lesser extent the occipital lobe and cingulate cortex, showed mediation effects on IQ as measured with WAIS-III. In addition, several subcortical brain and cerebellar structures showed mediation effects on IQ, including the thalamus, suggesting dysfunctional thalamocortical connectivity, and possibly also in networks involving the basal ganglia and other subcortical and cortico-cerebellar structures. Due to uncertainty in several of the mediation estimates, the present findings require replication in a larger sample. There was no relationship between cortical thickness and IQ.

5.2. Data and code availability statement

The datasets generated and/or analyzed during the current study are not publicly available because permission has not been applied for from neither the participants nor the Ethical Committee but are available from the corresponding author upon reasonable request.

Data availability

The authors do not have permission to share data.

Credit authorship contribution statement

Lars M. Rimol: Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Henning Hoel Rise:** Writing – review & editing, Visualization. **Kari Anne I. Evensen:** Funding acquisition, Project administration, Supervision, Writing – review & editing. **Anastasia Yendiki:** Writing – review & editing. **Gro C. Løhaugen:** Investigation, Writing – review & editing. **Marit S. Indredavik:** Funding acquisition, Project administration, Writing – review & editing. **Ann-Mari Brubakk:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. **Knut Jørgen Bjuland:** Formal analysis, Writing – review & editing. **Live Eikenes:** Writing – review & editing. **Siri Weider:** Writing – review & editing. **Asta Håberg:** Funding acquisition, Project administration, Writing – review & editing. **Jon Skranes:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119816.

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