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PERFORMANCE IN HAND COORDINATION TASKS AND CONCURRENT FUNCTIONAL MRI FINDINGS IN 13-YEAR-OLDS BORN VERY PRETERM

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Pikkukeskosilla CP-vamman ilmaantuvuus on laskenut viime vuosikymmeninä. Kuitenkin lievemmät hienomotoriikan ja koordinaation ongelmat vaikuttavat yleistyneen. Hienomotorisilla taidoilla tarkoitetaan pienillä lihaksilla aikaansaatuja tarkkuutta vaativia liikkeitä. Riittävät hienomotoriset taidot ovat mm. edellytys tavanomaiselle koulunkäynnille. Tämän työn tarkoituksena oli tutkia pikkukeskosina (syntymä ennen 32. raskausviikkoa ja/tai syntymäpaino on ≤ 1500 grammaa) syntyneiden ja täysaikaisena syntyneiden verrokkien hienomotorisia taitoja ja hienomotoristen tehtävien aikaisia toiminnallisia aivokuvantamislöydöksiä 13 vuoden iässä.

Tutkimus on osa PIPARI-seurantatutkimusta (Pienipainoisten riskilasten käyttäytyminen ja toimintakyky imeväisiästä kouluikään). Tutkimukseen osallistui 34 oikeakätistä pikkukeskosena syntynyttä nuorta ja 37 oikeakätistä täysiaikaisena syntynyttä verrokkinuorta. Kaikki tutkittavat olivat syntyneet Turun yliopistollisessa keskussairaalassa vuosina 2003-2006. Hienomotorisia taitoja arvioitiin Touwenin neurologiseen tutkimukseen kuuluvien sormien opponoinnin ja diadokokineesin avulla. Suoritukset videoitiin ja arvioitiin kokeneen lastenneurologin kanssa. Hienomotoriset tehtävät suoritettiin vielä uudelleen magneettikuvauksen aikana ja aivojen aktivaatiota mitattiin funktionaalisella magneettikuvauksella (fMRI).

Tutkimuksen perusteella pikkukeskosina syntyneet nuoret suoriutuvat hienomotorisista testeistä kliinisesti arvioituna verrokkien tavoin. Sen sijaan pikkukeskosilla todettiin täysaikaisia verrokkeja voimakkaampaa aktivaatiota ei-dominantin (vasemman) käden hienomotoristen tehtävien aikana tietyillä aivoalueilla. Löydös osoittaa, että fMRI-tutkimuksella voidaan havaita pitkäkestoisia neuraalisten mekanismien muutoksia hyvin ennenaikaisen syntymän jälkeen tilanteissa, joissa eroavaisuuksia täysaikaisena syntyneisiin ei kliinisin menetelmin ole todettavissa.

Asiasanat: pikkukeskonen, neurologia, hienomotoriikka, fMRI

Performance in hand coordination tasks and concurrent functional MRI findings in 13-year-olds born very preterm

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Short Title: Hand coordination and fMRI findings

Abbreviations:
CP – cerebral palsy
fMRI – functional magnetic resonance imaging
MRI – magnetic resonance imaging
ROI – region of interest
SPM12 – The Statistical Parametric Mapping
TFCE – Threshold-Free Cluster Enhancement

Highlights:

- Adolescents born very preterm had similar hand coordination compared to controls

- Very preterm group had stronger brain activation during left-hand coordination tasks

- Lower gestational age associated with stronger activation during left-hand tasks

Abstract

Objective: Fine motor and coordination problems are frequently reported among adolescents born preterm. We aimed to assess performance in hand coordination tasks and to compare concurrent brain activation between adolescents born very preterm and full-term at 13 years.

Method: 34 right-handed adolescents born very preterm (gestational age <32 weeks/birth weight ≤1500 grams) and 37 controls born full-term in 2003-2006 in Turku University Hospital, Finland, were recruited. At 13 years, finger opposition and diadochokinesis were assessed, and brain functional magnetic resonance imaging (fMRI) data was acquired while the adolescents performed unimanual, self-paced hand coordination tasks in response to visual cue.

Results: Adolescents born very preterm performed similar to controls in hand coordination tasks. The very preterm group evoked greater brain activation than the controls in the right precentral gyrus ($p=0.01$) and in the right postcentral gyrus ($p=0.02$) during left hand finger opposition, and in the right postcentral gyrus during left hand diadochokinesis ($p=0.03$). Within the very preterm group, lower gestational age was associated with reduced activation in the left superior parietal lobule during right hand diadochokinesis ($p=0.02$). Regarding left hand tasks, lower gestational age was associated with stronger activation in the right cerebellar lobule V ($p=0.03$) and left cerebellar lobule VI ($p=0.03$) during finger opposition, and stronger activation in the right superior parietal lobule ($p=0.03$) during diadochokinesis.

Conclusion: Very preterm birth affected hand coordination-related brain activation. Most of the effects were found for non-dominant hand. Clinical performance during the hand coordination tasks was similar in adolescents born very preterm and controls.

Keywords: Fine motor, fMRI, follow-up, prematurity

INTRODUCTION

Despite the decreased incidence of cerebral palsy (CP) (1,2) in children born preterm, motor impairments other than CP, including impairments of fine motor skills, are still more common in these children compared to peers born at term (3,4). Fine motor and hand coordination skills are an essential part of the cooperation between the hand and vision and thus required in e.g. manipulating objects, holding a pen, and drawing and writing. Dysfunctions in fine motor and coordination skills are of clinical importance since problems in these skills are associated with motor, learning and psychiatric disorders (5).

White matter abnormalities in neonatal MRI have shown to predict motor impairment in children born very preterm even when omitting children with CP (6). Decreased brain volumes in neonatal magnetic resonance imaging (MRI) at term age have shown to associate with poorer motor outcome (7). In children born extremely preterm, brain MRI findings at term age have shown to associate with fine motor skills at 6 years as these skills have shown to correlate positively with the volumes of precentral gyrus, cerebellum and brainstem, whereas a negative correlation between fine motor skills and cortical grey matter volume has been reported (8). However, structural MRI findings provide limited information on the underlying mechanisms of the motor impairments other than CP, and functional changes behind these impairments are largely unknown.

Functional MRI (fMRI) has been used to assess regional changes in neural activation during motor tasks. Children, compared to adults, seem to exhibit different activation during motor tasks regarding both activation levels and areas activated (9,10). Compared with peers born at term, children born very preterm have shown at 12 years a reduced association between motor performance and subcortical-motor network connectivity, and in increased association between motor performance and a widespread set of cortical and subcortical networks in a resting-state fMRI

(11). In addition, 20-year-olds born very preterm, compared to controls, have displayed greater activation in fMRI during visually cued motor task of the right hand in right the cerebellum, extending into the lingual, parahippocampal and middle temporal gyri (12).

Our aim was to study the hand coordination skills of 13-year-old adolescents born very preterm and controls born full-term. The secondary aim was to examine brain activation during hand coordination tasks. We hypothesized that the adolescents born very preterm would have poorer hand coordination skills compared to the controls. Brain activation was hypothesized to differ between the adolescents born very preterm and the controls due to neurobiological risk associated with very preterm birth. In addition, we hypothesized that the hand coordination-related activations would depend on the gestational age in the very preterm group.

METHODS AND STATISTICS

Participants

This study is part of the prospective PIPARI study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age) of very preterm infants (13). The participants in the present study were born to Finnish- or Swedish-speaking families from April 2004 to December 2006 in Turku University Hospital, Finland. The inclusion criteria were gestational age <32 weeks or birth weight ≤ 1500 grams. The exclusion criteria were severe congenital anomalies or diagnosed syndrome affecting development. The control group included adolescents born full-term in Turku University Hospital from 2003 to 2004, and recruited to the PIPARI study as described by Munck et al (14). Only right-handed adolescents were included to minimize the effect of handedness. Adolescents with diagnosed severe neurodevelopmental impairment, i.e. cognitive impairment (full-scale intelligence quotient <70), CP, severe hearing impairment and/or visual impairment were excluded from the present study. Adolescents with major brain pathology in structural MRI in the year they became 13 were also excluded. The flow chart of the participants is shown in Figure 1.

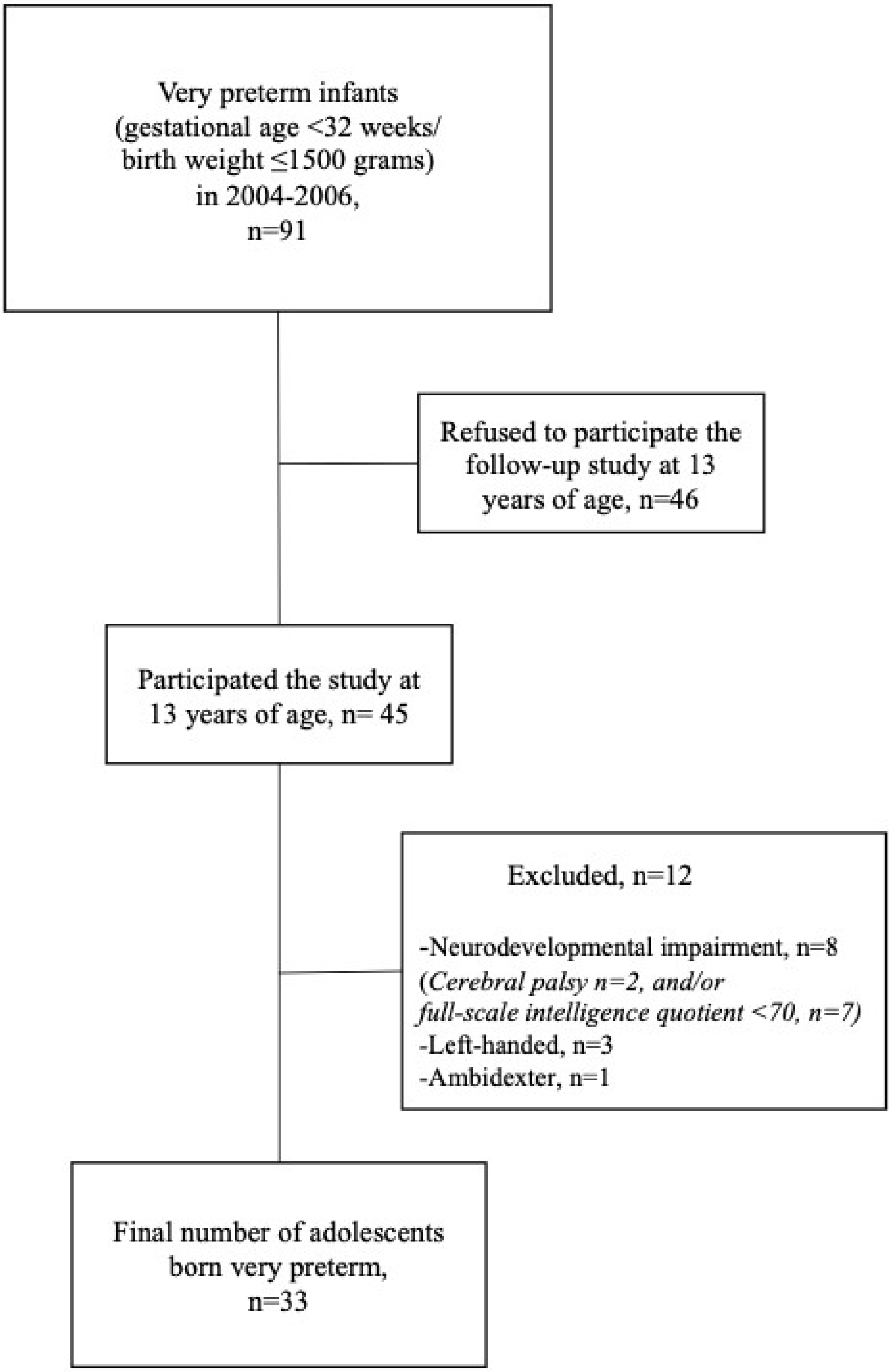


Figure 1. Flow chart of the participants born very preterm.

The Ethics Review Committee of the Hospital District of South-West Finland approved the study protocol in 2000 and in 2016. Written informed consent for this study were provided by parents and adolescents.

Brain MRI at term age

The neonatal brain MRI of the adolescents born very preterm was performed at term age. The MRI equipment was a 1.5-T Philips Intera (Philips Medical Systems, Best Netherlands). The neonatal MRI findings were categorized into normal findings, minor pathologies and major pathologies. Normal findings consisted of normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum and posterior fossa structures), width of extracerebral space <5 mm, ventricular/ brain (V/B) ratio <0.35 and no ventriculitis. Minor pathologies consisted of consequences of intraventricular hemorrhage grades 1 and 2, caudothalamic cysts, width of the extracerebral space of 5 mm and V/B ratio of 0.35. Major pathologies consisted of consequences of intraventricular hemorrhage grades 3 and 4, injury in cortex, basal ganglia, thalamus or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5 mm, V/B ratio >0.35, ventriculitis or other major brain pathology (infarcts). (15)

Hand coordination tasks

Hand coordination was evaluated in the year the adolescents turned 13 by using the items of finger opposition and diadochokinesis in the Touwen examination (5) before the brain MRI. In the finger opposition, the adolescents were asked to place the fingers of one hand, starting with index finger, consecutively on the thumb of the same hand in following sequence: 2, 3, 4, 5, 4, 3, 2, 3, 4, 5 etc. (5). In the diadochokinesis, the adolescents were asked to hold one hand arm relaxed at his/her side, and hold the other at an angle of 90º at the elbow, the hand pointing forward and to quickly perform a pronation-supination of the hand and forearm (5). The examinations were performed by one of the three physicians (including KU) and the instructions for the tasks were given orally either in Finnish or Swedish according to the adolescent's native language. The hand coordination tasks were assessed separately for each hand. To guarantee the analogy between the assessments, all examinations were video recorded and scored as typical, mildly abnormal or definitely abnormal together with an experienced child neurologist (LH) according to the classification criteria of the Touwen examination manual (5). Finger opposition included scoring of finger-to-finger transition, smoothness of the movement, and associated movements of the contralateral hand. Scoring of diadochokinesis included the performance, and associated movements of the contralateral hand. A test result of typical or mildly abnormal was denoted as a normal performance i.e. performance within the normal range, and a result of definitely abnormal was denoted as an abnormal performance. Associated movements were scored as normal when absent and abnormal when present; children aged $\geq$10 years should show no or a minimum number of associated movements in the contralateral hand (5). The performance scoring of the finger opposition and diadochokinesis was done outside the scanner before the fMRI. During in-scanner performance, the accomplishment of the hand coordination task was observed, but the performance was not repeatedly scored.

Structural MRI

Each MRI experiment, performed on 3T Philips Ingenuity TF PET/MR (Philips, Amsterdam, Netherlands), started with structural scans: T1-weighted scan in sagittal planes with 8.1ms Repetition Time (TR), 3.7ms Echo Time (TE), and isotropic 1 mm voxel; T2-weighted set of axial slices with 4.82s TR, 80ms TE, and 3 mm slice thickness; a Coronal Fluid Attenuation Inversion Recovery sagittal images with 10 s TR, 2.8s Inversion Time, TE of 125ms, and slice thickness of 4mm. The structural MRI findings were categorized as described by Lind et al. (16). All structural magnetic resonance images were assessed by an experienced neuroradiologist (RP) who was blinded to the clinical and imaging data of the adolescents.

The T1-weighted images were used to create a group structural brain template and grey matter mask, both used in fMRI data processing and analysis. Considering potential systematic structural differences between 13-year-old and adult brains, a customized group-specific structural brain template was created with the Computational Anatomy Toolbox, CAT12 (17), Template-O-Matic, TOM8 software (18), and diffeomorphic algorithm (19). The resulting template included grey matter and white matter tissue segments registered to the Montreal Neurological Institute MNI152 standard brain space. The grey matter part of the template was also used to create a binary grey matter mask by an 8mm Gaussian smoothing of the grey matter segment of the template followed by an intensity thresholding with a value of 0.3.

Functional MRI

Blood-oxygenation-level dependent data for the entire brain volume (35 axial slices of 4 mm thickness) were gathered using a single-shot sequence for T2*-weighted echo planar imaging with 2.0s TR, 20ms TE, 75° flip angle, 80×80 matrix, and 3mm in-plane resolution. Each of 4 fMRI runs for each participant consisted of 80 scans including the first 4 dummy scans to allow for T1 equilibration. Visual stimulus delivery during fMRI sessions was controlled by the Presentation software (Neurobehavioral Systems, Inc., Albany CA, USA).

During the fMRI, adolescents performed the same self-paced, unimanual tasks of finger opposition and diadochokinesis as those performed during the out-of-scanner performance assessment. The instructions were explained before entering the fMRI scanner and repeated orally before each task run by the same physician who had performed the clinical examination of the hand coordination tasks. There were four runs: 1) finger opposition of the right hand, 2) finger opposition of the left hand, 3) diadochokinesis of the right hand, and 4) diadochokinesis of the left hand. Each fMRI run consisted of 4 sets, each set tasks included 19s of gaze fixation followed by 19s of hand coordination. Alternation of the gaze fixation and hand coordination task was guided visually by presenting a central cross for the gaze fixation periods and a hand image for task periods. During the gaze fixation periods participants were asked to keep their hand still and eyes on the cross. Participants could communicate with the physician using an in-scanner intercom and could stop the scan at any time by squeezing a ball on their stomach.

Building of a composite region of interest for analysis

The present study was focused on exploring neural activation during motor tasks within a region of interest (ROI) represented by a set of cortical and cerebellar regions known to relate to sensorimotor activity of fingers and wrist (Figure 2). A cortical part of the composite ROI included regions used in the studies of the neural basis of multi-finger sequences (20,21): bilateral primary sensory cortex, primary motor cortex, dorsal premotor cortex, medial premotor cortex, and superior parietal lobule. The Human Motor Area Template (22) was used to define the S1, M1, and premotor regions, The "Neuromorphometrics" Atlas available in the CAT12 software and based on data from the OASIS project (http://www.oasis-brains.org/) and the Neuromorphometrics, Inc. (http://neuromorphometrics.com/) was used to define the superior parietal lobule. Only a dorsolateral part of the primary sensorimotor cortex in the range of z coordinate from +40 to +75 was included in the composite ROI. This was done so as to reliably cover representations of the digits and wrist while minimizing the influence of the signal from irrelevant body parts like the mouth, trunk and legs (23,24).

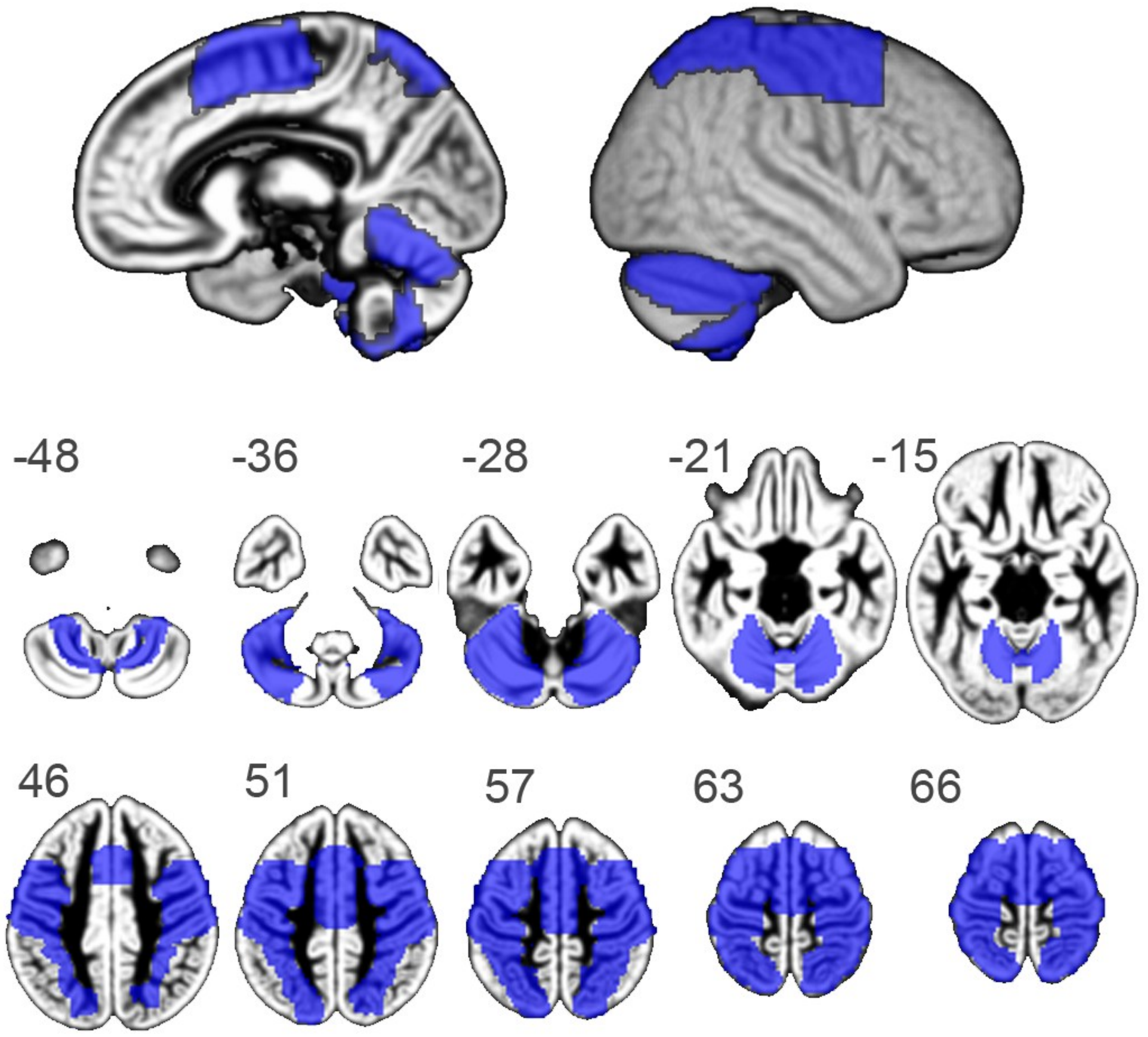


Figure 2. A combined region of interest (ROI) used to spatially constrain volume for between-group and regression analyses of effects of very preterm birth on brain activation. The ROI (in blue) is shown overlaid on a series of axial slices of the customized gray matter template. Numbers are z coordinates of the slices in the Montreal Neurological Institute brain space.

We included cerebellar lobules V, VI, VIII, and Cruse I that are most strongly associated with sensorimotor finger and hand representation according to studies on cerebellar somatotopy (25–27). The cerebellar areas were defined using the Spatially Unbiased Infratentorial Template (28). All these regions were combined into a single one and masked with the grey matter mask. The total volume of the resulting ROI was 9218 3-mm cubic voxels.

Functional MRI data processing and selection of participants

The Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (MathWorks Inc., Natick MA, USA) was used to process the fMRI data. Within each subject, fMRI data were corrected for head motion in a two-pass realignment procedure. Slice-timing difference was corrected by temporal interpolation using the acquisition time of the middle slice as a reference. Functional data were co-registered with the T1-weighed image for each subject. Finally, deformation fields, obtained during spatial normalization of individual structural images to the group template were applied to functional images, which were also resliced to the 3mm cubic voxel and smoothed with an 8mm Gaussian kernel.

Participants with excessive head motion, estimated as a mean frame wise displacement exceeding 2 SD of the sample mean were rejected from the analysis of the corresponding fMRI session data. Thus, 2 adolescents born very preterm and 2 controls were excluded from the right-hand finger opposition dataset; 3 adolescents born very preterm and 1 control from the left-hand finger opposition dataset; 2 adolescents born very preterm and 3 controls from the right-hand diadochokinesis dataset; and 2 adolescents born very preterm and 1 control from left-hand diadochokinesis dataset. One participant born very preterm was scanned only in the right hand finger opposition session. The final group sizes for fMRI analyses were 30/32 (very preterm/controls) for right-hand finger opposition, 29/31 for left-hand finger opposition, 28/32 for right-hand diadochokinesis, and 29/33 for left-hand diadochokinesis. The very preterm group and controls were not statistically significantly ($p<0.05$, two tailed t-test) different in mean frame wise displacement in any of these samples.

Statistical analysis of fMRI data

The fMRI data for each motor task and hand were analyzed separately. Statistical analysis was performed in SPM12 in two steps. First, a general linear model was built for each individual that included four 19s epochs of a motor task while the control condition was modelled implicitly. To account for the impact of head motion, the model included 6 realignment parameters, their Euclidian norm, and dummy regressors for scans with scan-to-scan changes in global mean $z>4$; translation >2 mm; rotation >1 degree (0.0175 rad) as provided by the Artifact Detection Tools software (https://www.nitrc.org/projects/artifact_detect). The condition regressor was convolved with the hemodynamic response function. A high-pass filter with a cut-off period of 128s was applied to account for a low frequency scanner drift. The model was estimated for each participant and individual contrast images of between-condition activation differences were fed into the second-level group analysis treating subjects as a random factor. All second level models included mean frame wise displacement as a nuisance covariate to account for individual difference in head movement.

Activation patterns for each task-hand combinations were obtained for the whole brain within each group with one-sample t-tests and a voxel threshold of $p<0.05$ after family-wise error correction for multiple comparisons. These were visually inspected to ensure the patterns met general expectation for the tasks used. Further analyses were performed within the ROI. Activation difference for each task-hand combination between the very preterm group and controls was analyzed with two-sample t-tests. The group differences were also explored when controlling for gender using full factorial ANCOVA models to obtain the main effects and interactions. A linear relationship between the fMRI signal and gestational age in each task-hand combination was analyzed within the very preterm group with and without adjusting for gender.

A permutation-based non-parametric Threshold-Free Cluster Enhancement method (TFCE) (29), as implemented in the TFCE Toolbox (Christian Gaser, Jena University Hospital, Germany), was applied to calculate a combined voxel-cluster statistic using 5000 permutations and family-wise error corrected significance threshold of $p<0.05$. To check and illustrate a direction and size of significant effects in the analyses, we calculated mean cluster values and 90% confidence intervals for significant clusters obtained in two-sample t-tests and ANCOVA analyses, as well as slope values and residuals obtained in regression analyses with the Marsbar software (30).

RESULTS

At the time of the fMRI experiment, the median age of adolescents born very preterm was 12.6 years (minimum 12.1, maximum 13.8) and 12.9 years (minimum 12.1, maximum 13.4) for the controls (p=0.8). Background characteristics of the 34 adolescents born very preterm and 37 controls are shown in Table 1. The background characteristics were also compared between the adolescents born very preterm participating the study and the eligible adolescents born very preterm who withdrew, and no differences were found.

Table 1.

	Adolescents born very preterm	Controls born full-term
Gestational age, mean (SD) [minimum, maximum], week	29.2 (2.8) [24.7, 34.0]	40.1 (1.2) [37.1, 42.1]
Birth weight, mean (SD) [minimum, maximum], grams	1180.6 (347.9) [620.0, 2120.0]	3611.6 (456.4) [2830.0, 4580.0]
Male, n (%)	20 (58.8)	20 (54.1)
Small for gestational age (<-2 SD), n (%)	12 (35.3)	
Multiple birth, n (%)	10 (29.4)	
Cesarean delivery, n (%)	21 (61.8)	
Bronchopulmonary dysplasia, n (%)	5 (14.7)	
Operated necrotizing enterocolitis, n (%)	2/31 (6.5)	
Sepsis, n (%)	2 (5.9)	
Laser-treated retinopathy of prematurity, n (%)	2/30 (6.5)	
Etiology of very preterm birth		
Spontaneous preterm contractions, n (%)	*8/24 (33.3)*	
Premature rupture of membranes, n (%)	*7/24 (29.2)*	
Indicated delivery due to preeclampsia and/or suspected placental insufficiency, n (%)	*8/24 (33.3)*	
Other pregnancy complications, n (%)	*1 (4.2)*	
Brain magnetic resonance imaging at term age		
Normal findings, n (%)	22/33 (66.7)	
Minor pathologies, n (%)	4/33 (12.1)	
Major pathologies, n (%)	7/33 (21.2)	
Mother’s education >12 years, n (%)	21/32 (65.6)	
Father’s education >12 years, n (%)	10/32 (31.3)	

Table 1. Background characteristics of the participants born very preterm and the controls born full-term.

Results of the hand coordination tasks including finger opposition and diadochokinesis are shown in Table 2. There were no statistically significant differences in the hand coordination tasks between adolescents born very preterm and the controls.

Table 2.

	Normal performance, adolescents born very preterm	Normal performance, controls	p-value
Finger opposition, right hand			
Smoothness, n (%)	34 (100)	37 (100)	1.0
Transition, n (%)	33 (97.1)	36 (100)	0.5
Associated movements, n (%)	23 (67.6)	25 (67.6)	1.0
Finger opposition, left hand			
Smoothness, n (%)	34 (100)	37 (100)	1.0
Transition, n (%)	33 (97.1)	37 (100)	0.5
*Associated movements, n (%)**	24/33 (72.7)	19 (51.4)	0.07
Diadochokinesis, right hand*			
Performance, n (%)	31 (93.9)	37 (100)	0.2
Associated movements, n (%)	24 (72.7)	20 (54.1)	0.1
Diadochokinesis, left hand*			
Performance, n (%)	31 (93.9)	36 (97.3)	0.6
Associated movements, n (%)	19 (57.6)	15 (40.5)	0.2

*Data missing for one adolescent born very preterm

Table 2. Hand coordination skills at 13 years of age of adolescents born very preterm and controls born full-term.

Analysis for hand coordination task-induced acivation within each combination of task and hand in the entire grey matter volume showed a similarity in location of activated areas for the same hand within and across the tasks. In both groups, the areas most activated during finger opposition and diadochokinesis were in the contralateral primary sensorimotor cortex, the bilateral medial and lateral premotor areas, the occipital cortex, and in a part of the cerebellum.

Between-group comparisons during hand coordination tasks of the right hand showed no statistically significant differences in brain activation between the very preterm group and controls. During the left-hand tasks, adolescents born very preterm had stronger activation in right the precentral gyrus (p=0.01), and in the right postcentral gyrus (p=0.02) during finger opposition, and stronger activation in the right postcentral gyrus (p=0.03) during diadochokinesis compared to controls; even when adjusted with gender (Table 3A, Figure 3A and 3B).

Within-group regression analysis of the adolescents born very preterm showed that regarding finger opposition of the right hand, gestational age did not influence brain activation. Regarding diadochokinesis of the right hand, lower gestational age was associated with reduced activation in left the superior parietal lobule (p=0.02), also when adjusted with gender. Regarding left hand tasks, a lower gestational age was associated with stronger activation in the right cerebellar lobule V (p=0.03) and the left cerebellar lobule VI (p=0.03) during finger opposition, and with stronger activation in the right superior parietal lobule (p=0.03) during diadochokinesis (Table 3B, Figure 3C and 3D).

Table 3A.

Task	Group size, very preterm /control	T-contrast	Brain area	Cluster size, voxels	TFCE value	p-value, FEW-corrected	MNI coordinates		
							x	y	z
Finger opposition, right hand	n=30/32		No significant clusters						
Finger opposition, left hand	n=29/31	Very preterm > controls	Right precentral gyrus Right precentral gyrus Right postcentral gyrus	101	268.9 182.7 243.8	0.01[*] 0.04 0.02[*]	30 27 39	-18 -9 -27	57 51 57
Diadochokinesis, right hand	n=28/32		No significant clusters						
Diadochokinesis, left hand	n=29/33	Very preterm > controls	Right postcentral gyrus	23	193.3	0.03[***]	33	-30	57

fMRI; functional magnetic resonance imaging
TFCE; Threshold-Free Cluster Enhancement statistic
FEW; family-wise error
MNI; Montreal Neurological Institute
*Statistically significant also when adjusted with gender

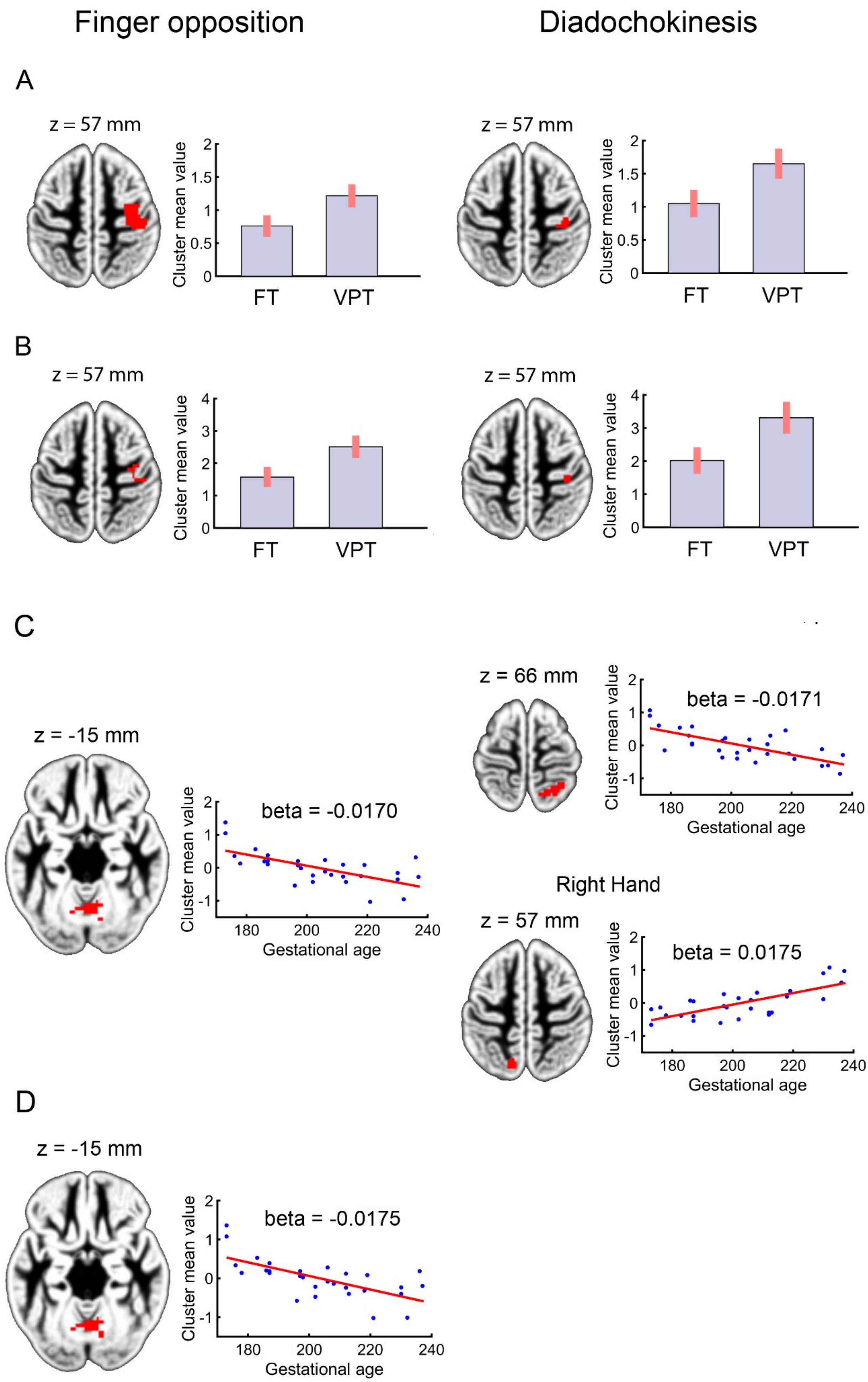
Table 3A. Activation differences in fMRI during hand coordination tasks between the adolescents born very preterm and the controls.

Table 3B.

Task	Activation /gestational age relationship, group size (n)	Brain area	Cluster size, voxels	TFCE value	p-value, FWE-corrected	MNI coordinates		
						x	y	z
Finger opposition, right hand	n=30	No significant clusters						
Finger opposition, left hand	Negative, n=29	Right cerebellar lobule V	67	265.1	0.03*	6	-63	-15
		Right cerebellar lobule V		228.2	0.04*	12	-72	-15
		Left cerebellar lobule VI		263.0	0.03*	-9	-66	-21
Diadochokinesis, right hand	Positive, n=28	Left superior parietal lobule	28	273.3	0.02*	-9	-69	57
		Left superior parietal lobule		234.2	0.03	-24	-66	51
		Left superior parietal lobule		225.7	0.04	-15	-63	51
Diadochokinesis, left hand	Negative, n=29	Right superior parietal lobule	31	239.7	0.03	18	-54	66
		Right superior parietal lobule		227.9	0.04	30	-48	63

fMRI; functional magnetic resonance imaging
TFCE; Threshold-Free Cluster Enhancement statistic
FWE; family-wise error
MNI; Montreal Neurological Institute
*Statistically significant also when adjusted with gender

Table 3B. Activation differences during hand coordination tasks in fMRI adjusted with gestational age in adolescents born very preterm.



Finger opposition
Diadochokinesis
A
z = 57 mm
Cluster mean value
FT
VPT
z = 57 mm
Cluster mean value
FT
VPT
B
z = 57 mm
Cluster mean value
FT
VPT
z = 57 mm
Cluster mean value
FT
VPT
C
z = 66 mm
Cluster mean value
beta = -0.0171
Gestational age
z = -15 mm
Cluster mean value
beta = -0.0170
Gestational age
Right Hand
z = 57 mm
Cluster mean value
beta = 0.0175
Gestational age
D
z = -15 mm
Cluster mean value
beta = -0.0175
Gestational age

Figures 3. Activation differences in fMRI during hand coordination tasks between the adolescents born very preterm and controls obtained without (A) and with (B) adjustment for gender; and areas of significant linear dependence of brain activation during hand coordination tasks adjusted with gestational age within the very preterm group obtained without (C) and with (D) adjustment for gender. The results are related to the left-hand usage (excepting one marked as “Right Hand”) for finger opposition (left column) and diadochokinesis (right column). Axial brain slices crossing main cluster maxima are shown according to neurological convention (right is right), with z coordinates in the Montreal Neurological Institute brain space indicated above them. The graphs illustrate effect sizes: mean cluster values with 90% confidence interval for the adolescents born full-term (FT) and very preterm (VPT) for A and B parts; scatterplots and regression lines along with mean slope (beta) value above the graphs for C and D parts. The clusters were thresholded at $p<0.05$ after family-wise error correction for the threshold-free cluster enhancement statistics.

DISCUSSION

This study reports performance and fMRI findings of hand coordination tasks in 13-year-old adolescents born very preterm and controls born full-term in a population cohort of infants born in 2003-2006 in Turku, Finland. Contrary to our hypothesis, 13-year-old adolescents born very preterm performed within the same level in hand coordination tasks compared to the controls. However, the fMRI showed that participants born very preterm had stronger activation in the contralateral primary sensorimotor cortex during left hand coordination tasks than controls born full-term. Moreover, within the very preterm group, the cerebellar and superior parietal activations were dependent on gestational age.

We found no difference in the rates of hand coordination dysfunction between adolescents born very preterm and controls. In this study, the performance of finger opposition (including finger-to-finger transition and smoothness of the movement) and the performance of diadochokinesis showed that only 6% of the very preterm group and 3% of the controls had dysfunctions in any of these domains. Interestingly, regarding associated movements of the contralateral hand, the maximum dysfunction rate was 40% in the very preterm group and up to 60% in the controls, although this difference was not statistically significant. This finding is divergent to the previously reported high rates of 20-40% fine motor impairments in individuals born very or moderately preterm compared to the reported rate of 7% in those born full-term (5,31). However, our findings are in line with the results of Husby et al. (32) who suggested that the fine motor performance of young adults born very preterm is accurate albeit slower than that of controls born full-term. Moreover, the prevalence of mild coordination problems, including diadochokinesis, has also increased in the general population (5). These findings, including our results, indicate that non-optimal performance in diadochokinesis and finger opposition, as well as hand coordination skills in general, are common not only in individuals born (very) preterm but also in those born full-term. This is supported by a previous study by Gaul and Issartel (33) which showed that after 7 years of age, fine motor skill proficiency seems to fall below the expected levels compared to normative data.

In the present study, the task-induced activation patterns obtained within the adolescents born very preterm and the controls demonstrated similarity in the location of the activated areas for the same hand within and across the tasks. Both tasks in either group mostly activated the contralateral primary sensorimotor cortex, the bilateral medial and lateral premotor areas, and a part of the cerebellum. There was also activation in the occipital cortex, which may have occurred due to visual difference between cues used in the task and control conditions. The between-group comparisons within the ROI, both when unadjusted and adjusted with gender, only found significant activation difference during the left-hand tasks. The activation difference was always located in the contralateral primary sensorimotor hand area where activation was stronger in adolescents born very preterm compared to the controls.

The finding of group activation difference only for left-hand coordination tasks in our right-handed participants could be explained by decreased efficiency of motor control and related excessive neural activation for the non-dominant hand in adolescents born very preterm, while for dominant right hand such difference could have already diminished by the age of 13. As the activation difference was found only in the primary sensorimotor cortex but not in the premotor areas, one may hypothesize that the most affected neural mechanisms are mostly related to low-level motion attributes, such as strength and velocity. Assumingly, this excessive activation may be thought of as compensatory and employed to maintain the desired level of task performance, which was similar in both groups.

Lawrence et al. (12), who studied a cohort of 20-year-olds performing joystick movement with the dominant hand, have reported a similar presence of greater activation in individuals born very preterm in the absence of performance difference in comparison to controls born full-term; however, the authors found group differences in activation outside the primary sensorimotor cortex presumably due to differences in experimental design and brain areas covered between their and our studies. Aside from motor coordination, Lind et al. (16) also observed a similar situation with excessive neural activation without performance difference during visual perception tasks in adolescents born very preterm compared to term born controls.

Unlike the results of Lawrence et al. (12), we did not find group activation differences in the cerebellum. However, we observed a negative dependence between anterior cerebellar activation and gestational age within the group of adolescents born very preterm, although it is notable that this dependence was only found for the finger opposition of the left hand. This supports the idea that motor control of the non-dominant left hand in right-handed individuals may require more resources compared to motor control of the dominant, i.e. the right hand, and appears to be particularly affected by very preterm birth. Nevertheless, dependences between local activations and gestational age were also found for the diadochokinesis task: for the right hand diadochokinesis the contralateral superior parietal lobule demonstrated activation that was positively dependent on gestational age, whereas for the left hand the relation was negative. This was an unexpected finding, hypothetically caused by a difference in the pace of development between neural systems for dominant and non-dominant hands. There are known functional hemispheric distinctions in motor control including areas beyond the primary sensorimotor cortex (34). Such differences could be further enhanced or otherwise affected by very preterm birth. A more solid interpretation of this observation would require contribution from further research.

Studies of placental bed have shown that pathophysiology of the placental spiral arteries is linked with perinatal complications such as preeclampsia, preterm premature rupture of membranes, intra-uterine growth restriction and abruptio placentae (35). Placental pathological findings have shown to predict neonatal survival and subsequent neurodevelopmental outcomes at 2 years in very-low-birth-weight children (36). Specific diagnosis of the placental histopathological alterations requires placental biopsies (37). Moreover, it has been shown that intra-amniotic infection/inflammation is associated with the subsequent development of white matter lesions of the neonatal brain and that fetal inflammatory response increases the risk of periventricular leukomalacia and cerebral palsy (38). Therefore, pathophysiological mechanisms such as oxidative stress and exaggerated inflammatory responses may contribute to the brain activation and neurodevelopmental outcome of individuals born very preterm. In our study, when classified according to the etiology of prematurity, the numbers of adolescents born very preterm in each group were limited, which would restrict the power of the statistical analysis concerning these perinatal etiological factors and therefore restrain the generalizability of the results regarding the association between the histopathological etiology of prematurity and the fMRI findings at 13 years of age. In future studies, the effect of maternal/placental/fetal triad factors as well as gene-environment interactions should be taken into account when assessing the significance of preterm birth to the subsequent neurodevelopment and neural activation.

A major strength of this study was that both in-scanner fMRI data during the hand coordination tasks and the concurrent clinical examination of hand coordination tasks were available. To minimize the effect of handedness, only right-handed adolescents were included. A potential limitation was that the handedness was based on self-reported information instead of performance measures. The evaluation of hand coordination skills was based on a qualitative assessment instead of a quantitative one. Scoring of the hand coordination tasks was done outside the scanner before the fMRI and although the accomplishment of these tasks was monitored during the in-scanner session, the performance was not repeatedly scored. Tasks were always presented in a fixed order and no quantitative estimation of hand movement pace was controlled for the analysis.

In conclusion, this study demonstrates that hand coordination skills were equal in adolescents born very preterm and full-term. This may reflect a compensatory neural mechanism that enables appropriate hand coordination performance compared to those born full-term. These results show the potential of fMRI in the detection of long-lasting neural mechanisms after very preterm birth even in cases where they cannot be determined by clinical/behavioral assessment methods.

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FIGURE LEGENDS

Figure 1. Flow chart of the participants born very preterm.

Figure 2. A combined region of interest (ROI) used to spatially constrain volume for between-group and regression analyses of effects of very preterm birth on brain activation. The ROI (in blue) is shown overlaid on a series of axial slices of the customized gray matter template. Numbers are z coordinates of the slices in the Montreal Neurological Institute brain space.

Figures 3. Activation differences in fMRI during hand coordination tasks between the adolescents born very preterm and controls obtained without (A) and with (B) adjustment for gender; and areas of significant linear dependence of brain activation during hand coordination tasks adjusted with gestational age within the very preterm group obtained without (C) and with (D) adjustment for gender. The results are related to the left-hand usage (excepting one marked as “Right Hand”) for finger opposition (left column) and diadochokinesis (right column). Axial brain slices crossing main cluster maxima are shown according to neurological convention (right is right), with z coordinates in the Montreal Neurological Institute brain space indicated above them. The graphs illustrate effect sizes: mean cluster values with 90% confidence interval for the adolescents born full-term (FT) and very preterm (VPT) for A and B parts; scatterplots and regression lines along with mean slope (beta) value above the graphs for C and D parts. The clusters were thresholded at $p<0.05$ after family-wise error correction for the threshold-free cluster enhancement statistics.