Manuscript Title: Verbal fluency is affected by altered brain lateralisation in adults who were born very preterm

Abbreviated Title: Verbal fluency is affected by altered brain lateralisation in very preterm adults

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Abstract

Language difficulties have been reported in children and adolescents who were born very preterm (< 32 weeks' gestation) and associated with an atypical lateralisation of language processing, i.e. increased right-hemispheric engagement. This study used functional magnetic resonance imaging (fMRI) and spherical deconvolution tractography to study the hemodynamic responses associated with verbal fluency processing (easy and hard letter trials) and verbal fluency-related white matter fibre tracts in 64 very preterm born adults and 36 adult controls (mean age: 30 years). Tractography of the arcuate fasciculus (AF) and frontal aslant tract (FAT) was performed. Tracts were quantified in terms of mean volume, hindrance modulated orientational anisotropy, and lateralisation, assessed using a laterality index to indicate hemispheric dominance. During verbal fluency fMRI, very preterm participants displayed decreased hemodynamic response suppression in both the *Easy* > *Rest* and *Hard* > *Rest* conditions, compared to controls, in superior temporal gyrus, insula, thalamus and sensorimotor cortex, particularly in the right hemisphere. At the whole-group level, decreased hemodynamic response suppression in the right sensorimotor cortex was associated with worse on-line performance on the hard letter trials. Increased left-laterality in the AF was present alongside increased right hemispheric hemodynamic response suppression in controls. When only right-handed participants were considered, decreased hemodynamic response suppression in the right superior temporal gyrus during hard letter trials was related to weaker left and right FAT white matter integrity in the preterm group only. These results show that verbal fluency is affected by altered functional lateralisation in adults who were born very preterm.

Significance Statement

This is the first study to use both functional and structural magnetic resonance imaging to assess the neuro-anatomy of verbal fluency in very preterm born adults. Less suppression of brain activation was observed in very preterm adults compared to controls in several brain regions during completion of both easy and hard verbal fluency trials. Furthermore, across all subjects, decreased brain activity suppression in the right sensorimotor cortex was associated with worse on-line performance on the hard letter trials. Increased left-laterality in the arcuate fasciculus, a language-related white matter tract, was present alongside increased right hemispheric brain activity suppression in controls. These findings suggest that alterations in the typical development of left-lateralisation in very preterm individuals are still present in adulthood.

Introduction

During the third trimester of pregnancy, the fetal brain more than doubles in size and the volume of cortical grey matter increases approximately four-fold (Huppi et al., 1998). At the same time, thalamocortical axons are reaching the cortical plate and callosal white matter connections are spreading across the subplate zone (Kostovic and Jovanov-Milosevic, 2006). These processes establish the neural foundation for the development of cognitive and motor functions. Very preterm birth (< 32 weeks' gestation) can thus lead to a complex pattern of exogenous and endogenous insults (Volpe, 2009), which result in alterations to structural and functional brain development (Ball et al., 2015; Smyser et al., 2010).

In terms of cognitive outcomes, very preterm born individuals have shown poorer verbal fluency performance than controls (Aarnoudse-Moens et al., 2009; Nam et al., 2015). Verbal fluency involves strategic search and retrieval processes from lexicon and semantic memory (Sauzeon et al., 2004), which tests both verbal ability and executive control. Impairments in such domains are believed to affect academic achievement and may lead to poorer occupational prospects (Kroll et. al, 2017). While receptive language abilities have been shown to improve with age in very preterm children, deficits in expressive language functions seem to persist into adolescence (Luu et al., 2011). Using functional magnetic resonance imaging (fMRI), it was previously demonstrated that while completing a verbal fluency task with different cognitive loads, very preterm young adults showed differences in hemodynamic response compared to controls predominantly in frontal, parietal, temporal and subcortical regions (Kalpakidou et al., 2014; Nosarti et al., 2009).

Several studies described structural and functional brain asymmetries of language-related regions during typical development (Dehaene-Lambertz et al., 2006a; Dehaene-Lambertz et al., 2006b; Friederici et al., 2011; Kasprian et al., 2011; Sowell et al., 2002). A deeper right superior temporal sulcus and larger left temporal lobe was observed as early as 23 weeks' gestation (Kasprian et al., 2011). This asymmetry continues to develop postnatally, with perisylvian sulcal asymmetries being more prominent in adults than in children (Sowell et al., 2002). Functional MRI studies demonstrated dominant left-hemispheric responses during processing of language-related auditory stimuli in newborn infants (Dehaene-Lambertz et al., 2006a; Dehaene-Lambertz et al., 2006b). However, a lack of lateralisation in language related regions was observed in very preterm infants at term equivalent age compared to term control infants (Kwon et al., 2015).

Increased left-lateralisation in language homologs may reflect typical maturational processes from childhood to adulthood (Friederici et al., 2011). This process may be altered in very preterm individuals, as increased right-hemispheric engagement was found in very preterm adolescents during a verbal task (Gozzo et al., 2009; Myers et al., 2010), suggesting the use of alternate neural pathways for language processing. However, this alternative neural pathway could be suboptimal, given the finding that stronger right-lateralisation in very preterm adolescents was associated with poorer language performance (Scheinost et al., 2015).

Measures of language have also been related to microstructural integrity of white matter connections in preterm samples, and similarly to fMRI studies, show a bilateral language network (Feldman et al., 2012; Mullen et al., 2011). The arcuate fasciculus (AF) and the frontal aslant tract (FAT) are two white matter tracts that are involved in the verbal component of verbal fluency. The AF connects the superior temporal gyrus to the inferior frontal gyrus and has long been recognized for its involvement in language. The FAT is a recently identified pathway that connects the supplementary motor area to the inferior frontal gyrus (Catani et al., 2012). It has been shown to be involved in speech fluency in adults who stutter (Kronfeld-Duenias et al., 2016) and individuals with primary progressive aphasia (Catani et al., 2013).

This study tested these hypotheses: 1. during completion of verbal fluency, very preterm adults would display a greater recruitment of homologous language-related regions in the right hemisphere in comparison to controls; 2. very preterm adults would exhibit smaller volume and hindrance modulated orientational anisotropy (HMOA; a tract-specific characterization of white matter microstructure) and decreased left-lateralisation in the structural indices of the AF and FAT tracts compared to controls and 3. increased right hemispheric hemodynamic response in very preterm adults would be associated with worse verbal fluency performance and stronger right-lateralisation in white matter structural indices. We further explored possible between-group differences in the associations between fMRI data and task performance and white matter tract measurements to evaluate whether: a) they would show the same pattern in very preterm born adults and controls, or b) they would show different associations in the two participant groups.

Methods and Materials

Participants were part of a larger study that followed up a cohort of individuals born at less than 33 weeks of gestation who were admitted to the neonatal unit of University College Hospital, London, between 1979 and 1985. Term born control participants were recruited from the community and were matched in age to very preterm adults. Inclusion criteria were full-term birth (38-42 weeks), birth weight > 2500 grams, and age between 28 and 35 years. Exclusion criteria for the control group included birth complications (e.g. low birth weight defined as <2500 g, endotracheal mechanical ventilation), prolonged gestation (greater than 42 weeks), severe hearing and motor impairments, and mental retardation indicated by intelligence quotient (IQ) < 70. All study participants were native English speakers. Among these participants, 64 very preterm participants and 36 controls of either sex were assigned at random to complete a verbal fluency fMRI task.

IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), which consists of four subtests that estimate verbal IQ, performance and full-scale IQ. Participants' handedness was assessed using the Modified Annett Questionnaire (Annett, 1967). The threshold used was which hand participants reported using in more than 4 out of 6 questions. Participants gave full informed consent and the study was approved by the appropriate local ethics committees, and in compliance with national legislation and the code of ethical principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki).

Neonatal and socio-demographic information for all participants is shown in Table 1. Very preterm adults were slightly older and had lower verbal IQ scores than controls. Hence age was accounted for in all further analyses. Verbal IQ was not controlled for as it was assumed to share variance with the effect of interest. Performance IQ was not significantly different between the groups. There were no significant between-group differences in sex, socio-economic status, or handedness.

Table 1. Participants' neonatal and socio-demographic variables.

	Very preterm (n=64)	**Control** (n=36)	**Test statistic**	**p-value**
Age (mean ± SD)	31.53 ± 2.44	30.47 ± 6.36	U = 806.0	**0.013**
Sex (M/F)	36/28	21/15	Chi-square = 0.041	1.000
Intelligence Quotient (IQ)				
Verbal IQ	97 ± 18.37	107.73 ± 16.33	U = 1159.5	**0.017**
Performance IQ	104.95 ± 14.90	109.72 ± 15.59	U = 1017.5	0.112
Gestational age	29.48 ± 1.98	--	--	--
Birthweight	1311.12 ± 376.41	--	--	--
Neonatal ultrasound (brain injury/normal)[a]	28/36	--	--	--
Handedness (L/R/A)[b^]	11/52/1	1/28/0	Fisher's exact = 3.838	0.12
Socio-economic status*[a]				
I-II (Professional & Intermediate)	27	15	Fisher's exact = 5.195	0.241
III (Skilled manual & Non-manual)	26	15		
IV-V (Semi-skilled & Unskilled manual)	2	0		
Students	1	4		
Unemployed	7	2		

* (Her Majesty's Stationary Office, 1991), missing information for one participant. [a] Neonatal brain injury includes uncomplicated periventricular haemorrhage without ventricular dilation

and periventricular haemorrhage with ventricular dilation (Stewart et al., 1983).[b] Fisher's exact test; ^ missing information for 7 control participants). P-values that remained significant after FDR correction are indicated in bold. SD = standard deviation.

Phonemic verbal fluency task

The fMRI task used in this study was a well-validated phonemic verbal fluency paradigm (Fu et al., 2002). Participants were required to overtly generate a word starting with the letter presented on a computer screen projected into the MRI scanner, but to not use proper names, grammatical variation of the previous word, or to repeat previous responses. If participants were unable to generate a response, they were asked to say "pass". Each letter was presented seven times within each block for a total of ten blocks, each block lasted 28 seconds (Figure 1). The "easy" letters were: T, C, B, P, S; and the "hard" letters were: I, N, F, E, G. The categorisation of easy and hard letters was based on the mean number of erroneous responses generated for each letter in a previous study (Fu et al., 2002). A 2-seconds "silent" period was set to allow for the participant to respond, coupled with a 2-seconds image volume acquisition period. During the "rest" blocks, participants were presented with the word "rest" and required to say "rest" out loud. The rest blocks were of the same duration as the task blocks. Verbal responses were recorded through a MRI-compatible microphone on Cool Edit 2000 (Syntrillium Software Corporation). Verbal fluency performance was assessed by the accuracy rate of participants' response (i.e. correctly producing a word starting with the indicated letter; not using proper names, grammatical variation of the previous word, or saying 'pass'). Participants were familiarised with the task prior to the fMRI experiment in an off-line training session in which they were asked to make responses to example trials using a different set of letters.

Figure 1. Verbal fluency fMRI task paradigm.

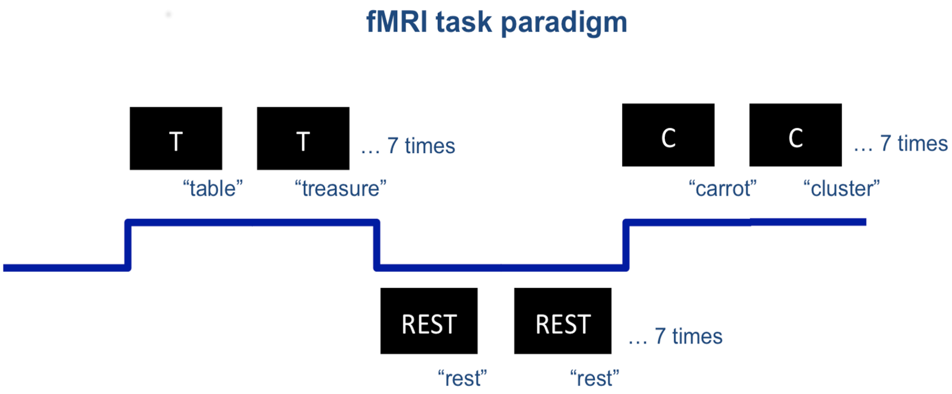


Image acquisition

Data were collected using a GE 3 tesla Signa MR scanner (GE Healthcare, USA). A gradient-echo EPI sequence (TR/TE = 2000/30ms) was used to collect data from 36 non-contiguous slices of 3.5mm thickness separated by a distance of 0.5 mm, and with in-plane voxel resolution of 3.75x3.75 mm^2. These were co-registered with T1-weighted anatomical image (TR/TE/TI: 7.1/2.8/450 ms, matrix: 256x256), allowing for 196 slices with no gap and an isotropic resolution of 1.1x1.1x1.1mm^3. Diffusion weighted images were acquired using a multi-slice spin echo EPI sequence (TE = 104.5 ms), obtaining 60 contiguous near-axial slice locations with isotropic (2.4×2.4×2.4mm^3) voxels. The b-value was 1300 s/mm^2, with 32 diffusion-weighted directions and 4 non-diffusion weighted volumes. Peripheral cardiac gating was applied with an effective TR of 20/30 RR interval.

Functional MRI analysis

Statistical analysis of fMRI data was performed using FEAT (http://www.fmrib.ox.ac.uk/fsl). The three initial volumes were removed to minimize the effects of magnetic saturation. Pre-processing steps included motion correction (FSL's FLIRT), time-slice correction, spatial smoothing (Gaussian, FWHM 5mm), and temporal high-pass filtering (sigma = 50 s). There were no statistically significant differences between very preterm and control participants in head motion during the fMRI task ($U = 1111$, $p = 0.59$). Denoising was performed using FSL's independent component analysis (ICA)-based Xnoiseifier (FIX) (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). The components of 20 participants (10 very preterms and 10 controls) were identified manually as noise or non-noise components according to established guidelines (Kelly et al., 2010). This information was used to train a classifier that can automatically classify the ICA components of each participant into noise or non-noise components. The time courses of the noise components were regressed out of the data. Regressors for each condition in the general linear model were convolved with a gamma hemodynamic response function. Only correct responses were used for the analyses. Individual participant data was then entered into a higher-level analysis using a mixed effects design (FLAME, http://www.fmrib.ox.ac.uk/fsl) whole-brain analysis and age was added as a covariate.

Three contrasts were studied: *Easy* > *Rest, Hard* > *Rest,* and *Hard* > *Easy*. Cluster-based thresholding was used to find significant clusters. Z-statistic maps were thresholded at $z = 2.3$. Voxels that pass the threshold formed clusters, and the spatial extent of each cluster was calculated. Then, random field theory was used to find the p-value of obtaining a cluster of a spatial extent given the chosen z-threshold and the spatial smoothness of the noise in the data under the null hypothesis. These p-values were corrected for family wise error across voxels and a threshold of $p < 0.05$ was used to obtain significant clusters. From the resulting cluster maps, we identified clusters of hemodynamic response that significantly differed between groups, after controlling for participants' age. No significant results were found when comparing very preterm adults with brain injury, very preterm adults with normal ultrasound classification (subgrouped according to neonatal ultrasound) and controls; therefore, we focused on comparisons between all very preterm individuals and controls. In addition to exploring between-group differences in hemodynamic response, we also investigated whether hemodynamic response in brain areas displaying significant between-group differences was associated with on-line task performance and white matter tract characteristics. This was done by obtaining cluster masks of regions displaying significant between-group differences in hemodynamic response and extracting the parameter estimates of each individual.

Normalisation

Each individual's functional data were registered to their structural scan using FSL's FLIRT (Jenkinson et al., 2002; Jenkinson and Smith, 2001) and boundary-based registration (BBR) cost function (Greve and Fischl, 2009). This technique extracts the surfaces from the T1-weighted image, and then aligns the fMRI data to the T1-weighted data by maximising the intensity gradient across tissue boundaries. This method has been shown to be more accurate and robust to signal inhomogeneities than traditional intra-subject registration algorithms. In order to map each individual's data into a common space, we used FSL-FNIRT (Andersson et al., 2010) to normalise each individual's structural data to a study-specific template, which is an average of 78 brain images from term-born and very preterm individuals as used in Froudist-Walsh et al., 2015 (available upon request).

Tractography analysis

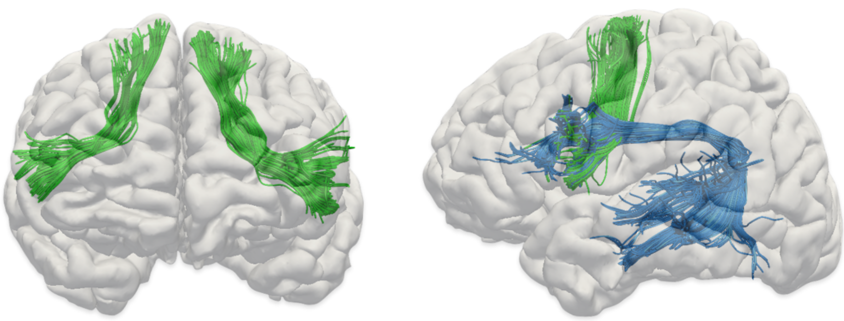
Preprocessing of diffusion MRI data followed the pipeline developed by Froudist-Walsh et al. (2015). Brain extraction was performed on the diffusion-weighted and b0 images using FSL's BET. Motion and eddy-current corrections was done on the brain-extracted data using ExploreDTI (Leemans et al., 2009). This motion correction step realigns the images and reorients the B-matrix so that the correct orientational information is preserved (Leemans and Jones, 2009). There were no statistically significant differences between very preterm and control participants in head motion in the diffusion data ($U = 1044$, $p = 0.84$). A constrained spherical deconvolution approach was chosen to differentiate multiple directions within one voxel (Tournier et al., 2004). We chose this approach as tractography using constrained spherical deconvolution outperforms tractography using other reconstruction methods when using data acquired with clinical b-values (Wilkins et al., 2015). Constrained spherical deconvolution was performed using a damped version of the Richardson-Lucy algorithm (Dell'acqua et al., 2010). Parameters were chosen based on recommendations from the StarTrack manual (https://www.mr-startrack.com) and by visual inspection of the reconstruction to find the best possible balance between resolving multiple fibre orientations and minimising false-positive fibre orientation distributions (FOD). The parameters used were: regularisation threshold $\eta = 0.02$, fibre response function (alpha) = 2, algorithm iterations = 300, and regularisation parameter $v = 20$; which is what was used in previous studies in the same cohort (Froudist-Walsh et al., 2015; Karolis et al., 2016; Tseng et al., 2017).

Visual inspection was performed in regions with known crossing fibres (e.g. between the corpus callosum, superior longitudinal fasciculus, and corticospinal tract) and without (e.g. middle of the corpus callosum).

Fibre orientation estimates were taken from the orientation of the peaks of the FOD profile. We used an absolute (equal to 4 times the amplitude of a spherical FOD obtained from a grey matter voxel) and a relative threshold (equal to 7% of the amplitude of the maximum amplitude of the FOD at that voxel) at each voxel to remove the general noise floor and surviving noise local maxima, respectively. Each FOD that survived the threshold were used as seeds to perform whole-brain tractography. Fibre orientation streamlines were propagated using Euler integration with a step-size of 1 mm. Propagation stopped if the angle between two successive steps exceeded 60°. As the AF is a curved bundle, a more lenient angular threshold was used to ensure the AF could be reconstructed in all participants. This threshold is also close to that used by Phillips et al., (55 degrees) to preclude the generation of fibres with biologically unrealistic curvature (i.e., "looping" fibres) (Phillips et al., 2012). Tractography reconstruction was performed using StarTrack (Dell'Acqua et al., 2013). The final reconstructed whole-brain tractography was visually assessed for all participants.

White matter dissection of the AF and FAT were performed in native diffusion space in TrackVis (trackvis.org) using a two-region method (Catani et al., 2012; Catani and Thiebaut de Schotten, 2008). In this study, we only considered the long segment of the AF, which is the only bundle that arches around the Sylvian fissure to connect posterior temporal regions to the inferior frontal gyrus (IFG). The AF was identified using region-of-interests (ROI) of the IFG and posterior superior temporal gyrus (STG) and middle temporal gyrus (MTG). Tracts that passed through these ROIs, but originated from the anterior temporal regions, were excluded in order not to include the middle longitudinal temporal parietal tracts. The FAT was identified using ROIs of the IFG (defined as BA45 and 44) and posterior superior frontal gyrus. All ROIs were hand drawn for each participant and all tracts were dissected in both hemispheres. Artefactual/non-anatomical fibres were removed using manually drawn region-of-avoidances based on the literature of brain anatomy and shape of the tract (Catani et al., 2012; Dick and Tremblay, 2012). An example of the dissected tracts is shown in Figure 2. White matter tracts were evaluated by HMOA and volume. White matter tract volumes were adjusted for intracranial volume by dividing tract volume by intracranial volume. Age was controlled for in all white matter variables using robust regression and a logistic weight function in MATLAB (MATLAB and Statistics Toolbox Release R2014b, The MathWorks, Inc., Natick, Massachusetts, United States), the residuals were then used for further statistical analysis described below.

Figure 2. The arcuate fasciculus (blue) and frontal aslant tract (green).



Lateralisation

Laterality index (LI) of the white matter tract measures (HMOA, volume, FA, RD) were obtained by LI = $(Q_{left}-Q_{right})/(Q_{left}+Q_{right})$ (Seghier, 2008).

Statistical analysis of demographic, behavioural, and IQ data and integration of imaging-derived measures

Statistical analyses were done in SPSS 21 (IBM SPSS Statistics for Macintosh, Version 21.0). The distributions of the imaging (fMRI and white matter tract measurements: left and right AF HMOA and volume, left and right FAT HMOA and volume, and LI of AF and FAT HMOA and volume), demographic (age, gestational age, birth weight), behavioural (verbal fluency task performance, head motion), and verbal and performance IQ data were tested for normality using a Shapiro-Wilk test. Not all variables were normally distributed; therefore, group comparisons were performed using Mann-Whitney U tests and correlation tests were performed using Spearman's correlation. To explore possible between-group differences in the associations between fMRI data and task performance and white matter tract measurements, all analyses were performed first across the whole sample, then within each group (control and very preterm). After identifying significant within group associations, interaction terms were included in a univariate linear regression analysis to test for between groups differences in such associations. Multiple comparison correction was performed using false discovery rate (FDR) (Benjamini and Hochberg, 1995). In order to investigate whether verbal fluency performance was driven by between-group differences in verbal IQ, additional analyses were performed to evaluate the relationship between verbal fluency and verbal IQ.

Results

Verbal fluency performance

Very preterm adults performed significantly worse than controls on the hard letter trials (U = 1449.5, $p < 0.001$) but not the easy letter trials of the on-line verbal fluency task (U = 1647.0, $p = 0.032$, non-significant after FDR correction). There were no statistically significant group differences in correct response times for both easy and hard letters (Table 2).

Table 2. Participants' on-line verbal fluency performance.

	Very preterm	**Control**	**Test statistic**	**p-value**
Task performance	Accuracy (mean ± SD)			
Easy letters	0.83 ± 0.15	0.89 ± 0.10	U = 1449.5	0.032
Hard letters	0.70 ± 0.17	0.83 ± 0.13	U = 1647.0	**< 0.001**
Correct response time	Milliseconds (mean ± SD)			
Easy letters	660.04 ± 159.11	640.83 ± 197.53	U = 875.0	0.759
Hard letters	636.73 ± 156.34	610.17 ± 180.78	U = 905.0	0.561

P-values that remained significant after FDR correction are indicated in bold. SD = standard deviation.

fMRI analysis

Group main effect on the *Easy* > *Rest* condition both showed positive hemodynamic responses in bilateral paracingulate gyrus, superior, middle, inferior frontal gyrus, anterior insula, caudate, intracalcarine cortex, cerebellum, left precentral gyrus, superior parietal lobule, supramarginal gyrus, putamen, thalamus, middle and inferior temporal gyrus, and lateral occipital cortex (LOC) in very preterm adults and controls. Very preterm adults also showed positive hemodynamic responses in right precentral gyrus, putamen, and thalamus. The *Hard* > *Rest* condition showed similar patterns of positive hemodynamic responses with additional involvement of bilateral superior temporal gyrus and right supramarginal gyrus and inferior temporal gyrus. When looking at group main effect on the *Hard* > *Easy* condition, the control group showed positive hemodynamic responses in the left LOC. The very preterm group did not show any regions of positive hemodynamic response (Table 3, Figure 3).

Group main effect on the *Easy* > *Rest* condition showed hemodynamic response suppression (i.e. a less negative hemodynamic response) in bilateral precuneus/posterior cingulate cortex (PCC), inferior parietal lobule, occipital fusiform, lingual, superior and middle temporal gyri, insula, lateral occipital, sensorimotor, anterior cingulate cortices, superior frontal gyrus, thalamus, hippocampus, parahippocampus, amygdala, right putamen, and left cerebellum in both very preterm and control participants. Control participants also showed hemodynamic response suppression in the right frontal pole, while very preterm adults showed hemodynamic suppression in the left putamen. The *Hard* > *Rest* condition showed hemodynamic response suppression in similar regions as well as the right cerebellum. Very preterm adults had increased suppression in the left middle frontal gyrus. On the *Hard* > *Easy* condition, the control group showed no regions of hemodynamic response suppression. The very preterm group showed hemodynamic response suppression in bilateral precuneus, left PCC and LOC (Table 3, Figure 3).

Table 3. Hemodynamic responses in very preterm adults and controls during easy and hard letter trials.

Condition		Region	Peak MNI coordinate [x,y,z] (mm)[a]	Cluster size (voxels)*
Control ***Easy > Rest***	*Positive hemodynamic response*	Bilateral paracingulate gyrus, SFG, MFG, IFG, anterior insula, caudate, intra-calcarine cortex, cerebellum; left precentral gyrus, putamen, thalamus	[-50, 10, 30] [36, 10, 32] [-6, 10, 60] [-4, 16, 46] [8, 30, 34] [-42, 2, 26]	114161
		Left SPL, SMg, LOC	[-48, -38, 40]	8772
		Left STG, ITG	[-48, -50, -10]	3073
	Negative hemodynamic response	Bilateral precuneus/PCC, IPL, insula, LOC, sensorimotor cortex, ACC, SFG, thalamus, occipital fusiform gyrus, lingual gyrus, hippocampus, parahippocampus, amygdala; right frontal pole, MTG	[-1, -49, 27] [7, -53, 27] [6, -65, 28] [52, -56, 28] [57, -60,28] [-55, -60, 33]	257987
		Left cerebellum	[-27, -40, -52]	2701
		Left MTG	[-52, 3, -15]	2690
Very preterm ***Easy > Rest***	*Positive hemodynamic response*	Bilateral paracingulate gyrus, SFG, MFG, IFG, precentral gyrus, anterior insula, caudate, putamen, thalamus, intra-calcarine cortex, cerebellum; left STG, ITG	[-8, 18, 40] [2, 20, 46] [-46, 2, 26] [-52, 2, 22] [-6, 14, 52] [-4, 18, 48]	188520
		Left SPL, SMg, LOC	[-30, -68, 46]	12146
	Negative hemodynamic response	Right PCC, precuneus, sensorimotor cortex	[4, -50, 30]	79420
		Right LOC, SMg, AG, insula, MTG, putamen, thalamus	[49, -68, 34]	76944
		Left LOC, SMg, AG, insula, MTG	[-54, -62, 34]	46079
		Bilateral ACC, SFG	[-2, 52, 2]	30281
		Left occipital fusiform gyrus, lingual gyrus, parahippocampus, thalamus	[-14, -88, -12]	8467
		Left cerebellum	[-24, -75, -35]	1815
Control ***Hard > Rest***	*Positive hemodynamic response*	Bilateral paracingulate gyrus, SFG, MFG, IFG, precentral gyrus, anterior insula, caudate, putamen, intra-calcarine cortex, cerebellum	[-50, 6, 32] [-50, 14, 28] [-44, 24, 18] [-6, 12, 56] [-2, 16, 46]	125306
		Left SPL, SMg, LOC	[-46, -40, 38]	13728
		Left ITG	[-40, -60, -8]	4259

		Right MFG	[40, 40, 36]	2731
	Negative hemodynamic response	Bilateral PCC, precuneus, sensorimotor cortex; right LOC, SMg, AG, insula, MTG, hippocampus, parahippocampus, amygdala, occipital fusiform gyrus, lingual gyrus, putamen, thalamus	[10, -56, 28] [48, -60, 28] [48, -53, 20] [48, -60, 38] [52, -56, 32]	164196
		Bilateral ACC, SFG; right MFG	[4, 44, 4]	33368
		Left LOC, SMg, AG,	[-52, -61, 32]	15964
		Left insula	[-38, -20, 20]	15701
		Left cerebellum, occipital fusiform gyrus	[-30, -74, -36]	9585
		Left MTG	[-57, 0, -26]	6999
		Bilateral cerebellum	[6, -38, -52]	4063
		Left thalamus	[-15, -26, 3]	2301
		Right frontal pole	[44, 42, -15]	1818
Very preterm *Hard > Rest*	*Positive hemodynamic response*	Bilateral paracingulate gyrus, SFG, MFG, IFG, precentral gyrus, anterior insula, caudate, putamen, intra-calcarine cortex, STG, ITG, cerebellum; left SPL, SMg, LOC	[-6, 12, 52] [-42, 4, 28] [-8, 22, 40] [-6, 18, 48] [2, 18, 48]	215947
		Right SMg	[50, -34, 48]	2236
	Negative hemodynamic response	Bilateral PCC, precuneus, sensorimotor cortex; right frontal pole, LOC, SMg, AG, insula, MTG, occipital fusiform gyrus, lingual gyrus, parahippocampus, hippocampus, amygdala, putamen, thalamus	[12, -62, 28] [8, -64, 28] [8, -52, 29] [-10, -50, 39] [-5, -48, 38]	144407
		Left LOC, SMg, AG, insula, MTG, occipital fusiform gyrus, lingual gyrus, parahippocampus, hippocampus, amygdala, putamen, thalamus	[-49, -59, 38]	53775
		Bilateral ACC, SFG, MFG	[-5, 52, 18]	36855
		Bilateral cerebellum	[-9. -46, -46]	2930
Control *Hard > Easy*	*Positive hemodynamic response*	Left LOC	[-19, -72, 40]	2347
	Negative hemodynamic response	No significant clusters		
Very preterm *Hard > Easy*	*Positive hemodynamic response*	No significant clusters		
		Bilateral precuneus, left PCC	[-10, -48, 22]	8828

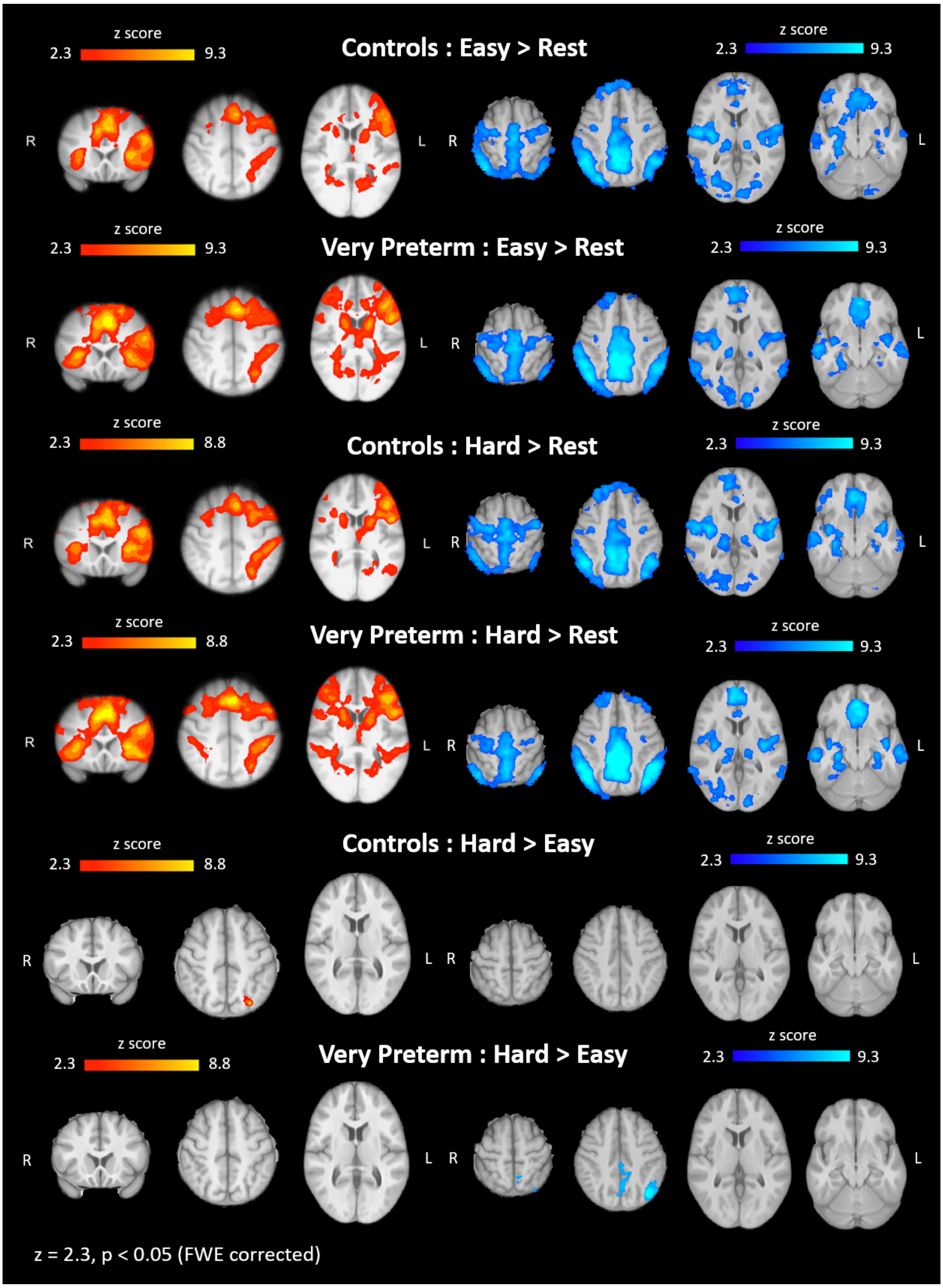
	Negative hemodynamic response	Left LOC	[-42, -70, 36]	3904

[a] Sub-peaks are only reported for clusters larger than 100,000 voxels.

*All clusters were obtained with z = 2.3, p < 0.05 (corrected for family wise error across voxels).

SFG = superior frontal gyrus; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; SPL = superior parietal lobule; SMg = supramarginal gyrus; AG = angular gyrus; PCC = posterior cingulate cortex; MTG = middle temporal gyrus; ITG = inferior temporal gyrus, LOC = lateral occipital cortex.

Figure 3. Hemodynamic responses in very preterm adults and controls during easy and hard letter trials. Positive hemodynamic response clusters are shown in red-yellow, negative hemodynamic response clusters are shown in blue-light blue.



FWE = family wise error.

When comparing the hemodynamic responses between groups, very preterm participants showed decreased hemodynamic response suppression in both the *Easy* > *Rest* and *Hard* > *Rest* conditions compared to controls. In the *Easy* > *Rest* condition, this was observed in a region that extended from the right STG to the posterior insula and thalamus. In the *Hard* > *Rest* condition, very preterm participants showed decreased negative hemodynamic response compared to controls in the left and right STG (also extending to the insula) as well as the right sensorimotor cortex. In the *Hard* > *Easy* condition, very preterm adults showed greater hemodynamic response suppression compared to controls in bilateral LOC (Table 4, Figure 4).

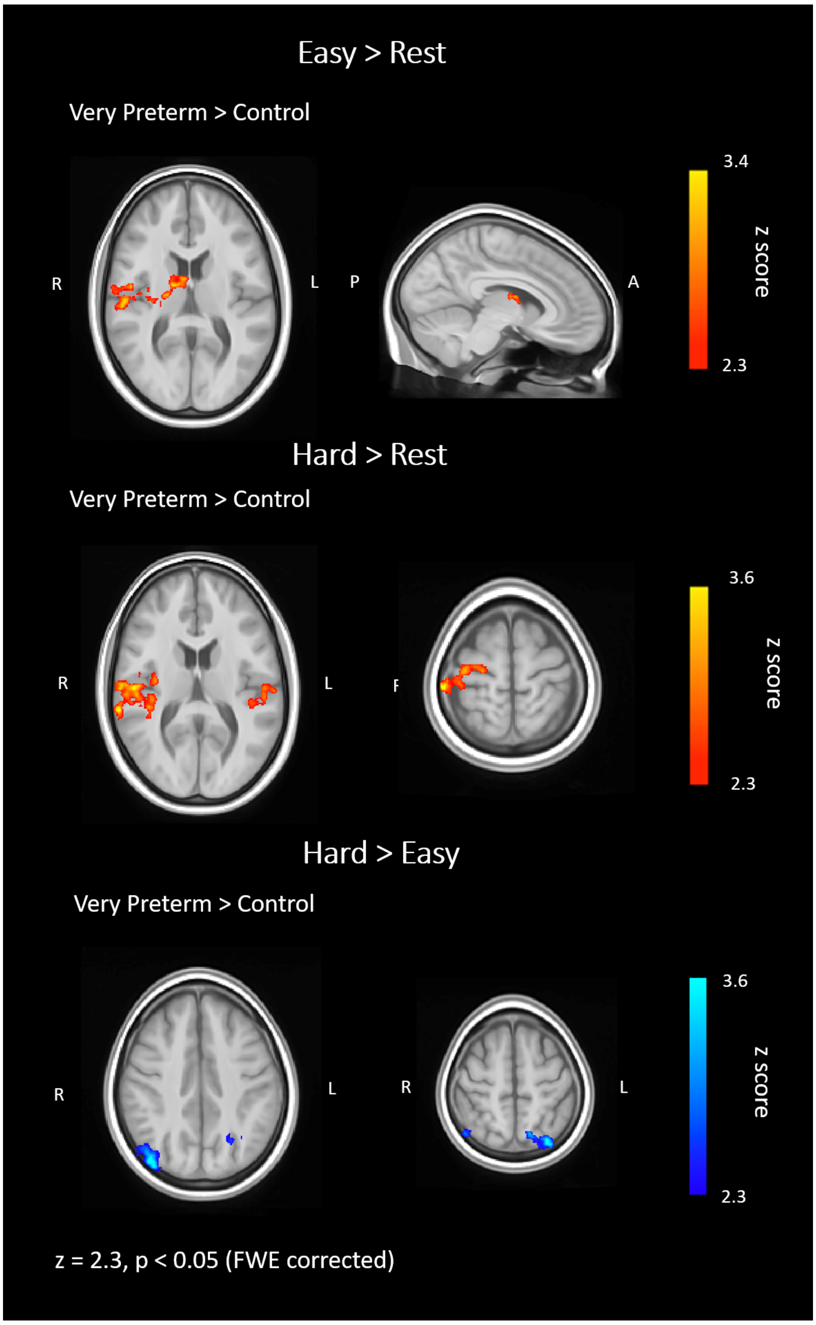
Table 4. Differences in hemodynamic responses between very preterm adults and controls during easy and hard letter trials.

Condition	Region	Peak MNI coordinate [x,y,z] (mm)	Cluster size (voxels)	p-value*	Contrast of parameter estimate (mean±SD) (very preterm; control)
Easy > Rest					
Very preterm > Control	Right STG, insula, thalamus	[68, -2, 4]	3838	**< 0.001**	-2.65±11.71; -12.39±11.21
Hard > Rest					
Very preterm > Control	Right STG, insula	[62, -18, -6]	8492	**< 0.001**	0.02±10.12; -11.56±10.27
	Left STG, insula	[-54, -4, 2]	2079	**0.02**	-3.52±13.56; -15.34±10.86
	Right sensorimotor cortex	[48, -40, 68]	2013	**0.02**	-1.54±14.16; -12.71±13.99
Hard > Easy					
Very preterm < Control	Left LOC	[-30, -76, 45]	2356	**0.00567**	-3.01±19.21; 9.84±16.43
	Right LOC	[43, -82, 30]	1944	**0.0185**	-2.33±26.59; 6.34±12.06

*Cluster p-values were obtained with $z = 2.3$, $p < 0.05$ (corrected for family wise error rate across voxels).

STG = superior temporal gyrus; LOC = lateral occipital cortex.

Figure 4. Differences in hemodynamic response between very preterm adults and controls during *Easy* > *Rest*, *Hard* > *Rest*, and *Hard* > *Easy* conditions. Red-yellow indicates relatively increased hemodynamic response in the very preterm group compared to controls, while blue indicates relatively decreased hemodynamic response in the very preterm group compared to controls.



FWE = family wise error.

The regions which displayed between-group differences in hemodynamic responses were also those that showed negative hemodynamic responses in both groups, with the exception of the thalamus, where positive hemodynamic response was found in the very preterm group. The hemodynamic responses in these regions ranges across negative and positive values in very preterm adults (Table 4).

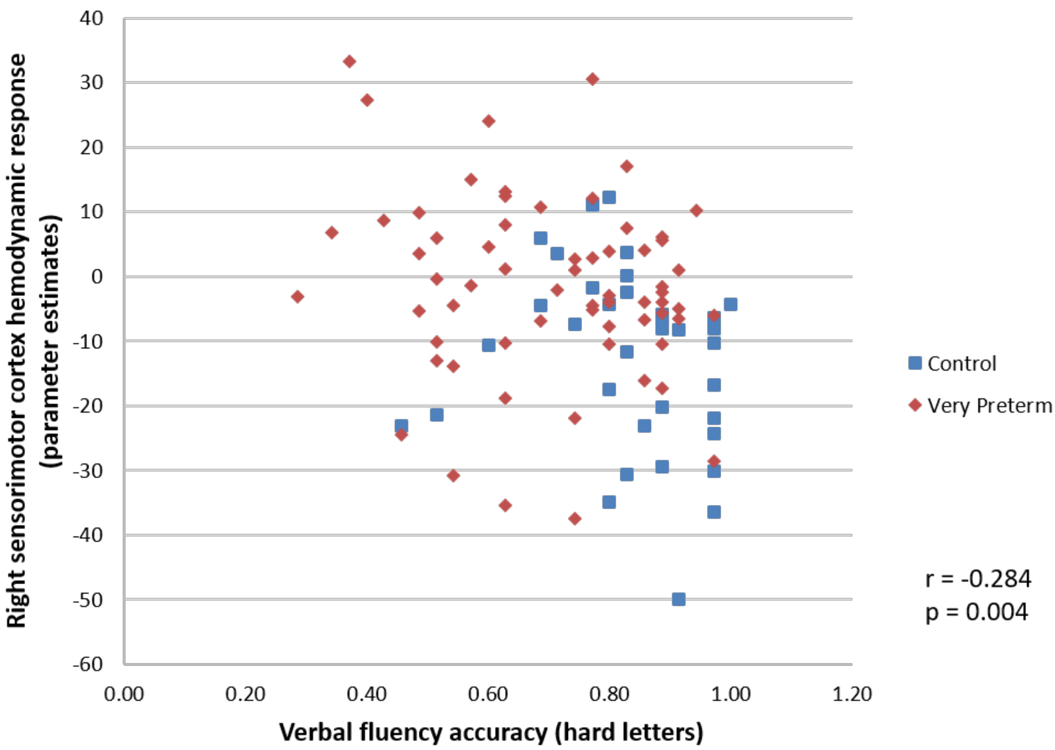
Tractography analysis

The AF and FAT did not differ between groups in terms of volume or HMOA in either hemisphere, nor did they differ in terms of LI.

Functional-behavioural associations

The contrast of parameter estimates in regions where between-group differences in hemodynamic response where found (*Easy* > *Rest*: right STG; *Hard* > *Rest*: left STG, right STG, and right sensorimotor cortex, *Hard* > *Easy*: left and right LOC) was correlated with participants' online task performance and head motion. Only increased hemodynamic response in the right sensorimotor cortex in the *Hard* > *Rest* condition in the whole sample was significantly negatively correlated with performance on the hard letter trials of the on-line verbal fluency task ($r = -0.284$, $p = 0.004$), i.e. the greater the hemodynamic response the worse the performance (Figure 5). All the correlation tests were corrected for multiple comparisons. Within group analyses did not reveal any significant group-specific association between hemodynamic response and verbal fluency performance. Head motion during the fMRI task was not associated with any of the fMRI findings.

Figure 5. Verbal fluency accuracy and right sensorimotor cortex hemodynamic response during hard letter trials in the whole sample.



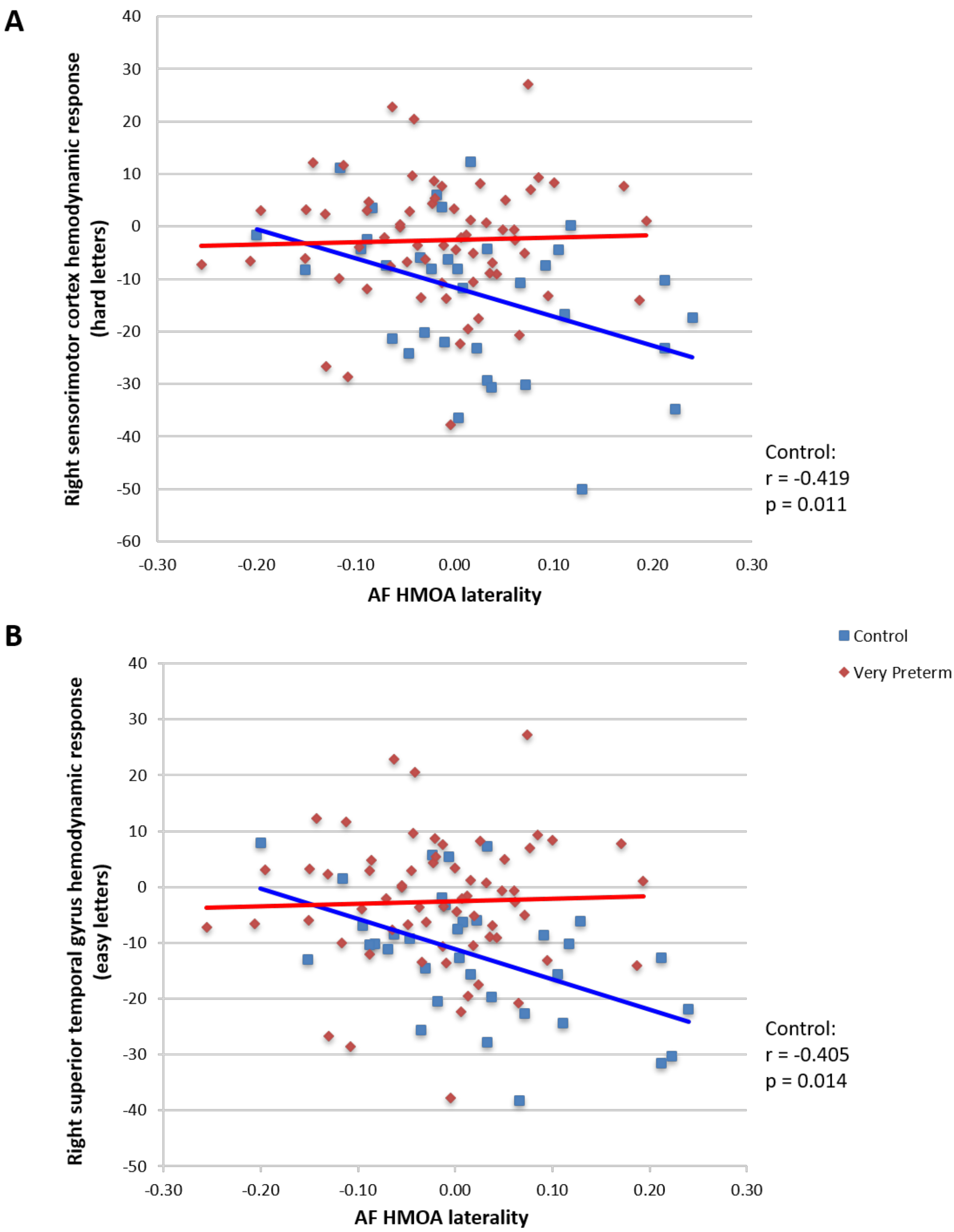
Structural-behavioural associations

As no significant between-group differences in white matter tract indices were observed, associations between white matter tract indices and behaviour were not further explored.

Functional-structural associations

Correlation tests across the whole sample did not show any significant functional-structural associations. Within-group analyses revealed group-specific patterns of association between hemodynamic response and white matter characteristics. Hemodynamic response in right sensorimotor cortex in the *Hard > Rest* condition significantly negatively correlated with the laterality of AF HMOA in controls (r = -0.419, p = 0.011), but not in very preterm individuals (r = 0.003, p = 0.981); i.e. the more hemodynamic response suppression the more left-lateralised the AF HMOA. This association was significantly different between groups (lateralisation*group interaction: F = 7.446, p = 0.008) (Figure 6A). Hemodynamic response in the right STG in the *Easy* > *Rest* condition also significantly negatively correlated with AF HMOA laterality in controls (r = -0.405, p = 0.014), but not in very preterm individuals (r = 0.14, p = 0.269) and this significantly differed between groups (lateralisation*group interaction: F = 5.494, p = 0.021) (Figure 6B). Hemodynamic response in the left STG in the *Hard* > *Rest* condition negatively correlated with the left FAT volume in the very preterm group and not in the control group, but this association was not significantly different between groups (volume*group interaction: F = 3.326, p = 0.071). All the correlation tests were corrected for multiple comparison correction.

Figure 6. Associations between hemodynamic response and white matter characteristics in each group: A) Right sensorimotor cortex hemodynamic response (hard letter trials) and AF HMOA laterality. B) Right superior temporal gyrus hemodynamic response (easy letter trials) and AF HMOA laterality.



Analyses including only right-handed participants

As handedness may be associated with laterality (Knecht et al., 2000), all analyses were repeated for right-handed participants only (very preterm adults n=52; controls n=28). In these analyses, all significant results reported above remained unaltered, except for the association between left STG hemodynamic response during the hard letter trials and the left FAT volume in the very preterm group, which was no longer significant.

However, other significant structure-function associations became evident: in the very preterm group, but not in controls, higher left and right FAT HMOA were associated with increased right STG hemodynamic response suppression during hard letter trials ($r = -0.411$, $p = 0.002$; $r = -0.315$, $p = 0.023$). The association of the left FAT HMOA and right STG hemodynamic response was significantly different between groups (lateralisation*group interaction: $F = 4.44$, $p = 0.038$).

Association between verbal fluency and verbal IQ

In the whole sample, verbal IQ was significantly associated with verbal fluency performance on the easy and hard letter trials ($r = 0.321$, $p = 0.002$; $r = 0.413$, $p < 0.001$). Within group analyses showed that verbal IQ was only significantly associated with verbal fluency on hard letter trials in very preterm adults ($r = 0.42$, $p = 0.001$) but not in controls ($r = 0.296$, $p = 0.113$). However, the difference between the correlation coefficients in the two groups was not statistically significant.

Sex differences within the very preterm group

Very preterm males performed better than very preterm females on the easy letter trials ($U = 301.0$, $p = 0.015$); no sex difference was found on the hard letter trials (U = 389.0, $p = 0.235$). Very preterm males also had higher verbal IQ and performance IQ than very preterm females (verbal IQ: U = 214.5, $p = 0.003$, performance IQ: U = 239.0, $p = 0.014$). There was however no evidence of sex differences in regions where group differences in hemodynamic response were observed during verbal fluency processing.

Discussion

This study investigated the functional and structural brain correlates of verbal fluency in adulthood following very preterm birth. At a functional level, results showed decreased hemodynamic response suppression in very preterm adults compared to controls in several brain regions, which seemed to be suboptimal for completion of hard letter verbal fluency trials. At a structural level, increased left-laterality in the arcuate fasciculus was demonstrated in controls compared to very preterm adults and this was associated with increased right hemispheric functional deactivation. These findings suggest that alterations in the typical development of left-lateralisation in very preterm individuals are still present in adulthood.

Functional MRI results and verbal fluency performance

Very preterm adults compared to controls showed decreased hemodynamic response suppression in the right STG, posterior insula and thalamus during completion of both easy and hard letters of a verbal fluency task. During processing of hard letters, altered hemodynamic responses in the very preterm group were more extensive and included left STG and insula and right sensorimotor cortex. Hemodynamic responses in these regions showed a more dynamic range of both positive *and* negative measures in very preterm adults. This could reflect individual differences when performing verbal fluency, with some participants engaging regions that are not typically required for the specific tasks or some participants failing to suppress a region. Taken together with the findings that very preterm adults performed worse on the hard letters but not the easy letters compared to term-born controls, these results suggest that hemodynamic responses are particularly affected when a task presents high-cognitive demands. In the following paragraphs we will discuss findings with regards to each region.

The STG has been recognized to play a role in speech recognition and comprehension. The left and right hemisphere, however, process speech differently. Hickok and Poeppel proposed that integration of information over longer timescales predominantly occurs in the right hemisphere, while integration over shorter timescales may be more bilateral (Hickok and Poeppel, 2007). Another view is that the left hemisphere may be associated with phonemic perception and process information more categorically than the right hemisphere (Liebenthal et al., 2005). Other than differences in speech processing, the left and right STG also differ in their involvement in speech production. Specifically, the left posterior STG is suggested to be involved in the phonological processing of both speech input and output (Hickok et al., 2003; Hickok et al., 2009). In regards to verbal fluency, a previous PET study revealed a decrease in relative cerebral blood flow in bilateral STG during a letter verbal fluency task in controls (Frith et al., 1991). Similarly, decreased hemodynamic response was found in the right superior temporal gyrus when comparing hemodynamic response during verbal fluency to an automatic speech control condition in healthy participants (Birn et al., 2010). These differences could be due to differences in auditory processing and STG suppression may be needed to perform the task.

The insula has a known role in language processing due to its strong connections to the inferior frontal gyrus and temporal cortex. In particular, the posterior insula has been found to be involved in word retrieval and lexical knowledge (Ardila et al., 2014), which is utilised during verbal fluency tasks. Based on a model proposed by Just and Varma (2007), when a task is sufficiently difficult, resource demands on the typical brain network engaged by such task will exceed resource supplies, and additional brain regions with spare resources and relevant functional specializations will be recruited to aid task performance (Just and Varma, 2007). When an individual's resource supply is reduced as a result of neurodevelopmental alterations, recruitment of additional brain regions to aid task performance may occur. It was previously shown that individuals born very preterm who sustained perinatal brain injury displayed increased hemodynamic response in bilateral insula and associated perisylvian areas, and this correlated with performance on a verbal working memory task (Froudist-Walsh et al., 2015). The insula is also involved in a wide range of other functions, such as auditory, motor, affective and gustatory processing (Chang et al., 2013). Very preterm adults may have showed decreased hemodynamic response suppression in the insula during completion of a verbal fluency task because they may have required the support of a wider range of cognitive functions than those employed by control participants. The 'extra' recruitment of hemodynamic resources during language processing has been previously observed in preterm adolescents during performance of a sentence comprehension task (Barde et al., 2012).

Increased hemodynamic response in the very preterm compared to the control group was also found in the thalamus. The thalamus is activated during letter fluency in healthy controls (Ravnkilde et al., 2002), and thalamic lesions lead to impairment in verbal fluency (Annoni et al., 2003). The thalamus is vulnerable to very preterm birth and volumetric deficits are often described in very preterm individuals (Boardman et al., 2006; Nosarti et al., 2014). Volumetric reductions of the thalamic nuclei have been related with worse letter verbal fluency in very preterm adolescents (Gimenez et al., 2006). The thalamus may represent a central monitor for language-related cortical activities, controlling and adapting the connectivity between cortical regions and bandwidth the exchange of information (Klostermann et al., 2013). The increased hemodynamic response in the thalamus we see in our results may indicate the increased effort very preterm adults need to complete a letter fluency task, although we only noticed this during the easy and not the hard letters. It is therefore possible that increased thalamic response is reflective of more effective information processing to facilitate task performance.

The sensorimotor cortex was the only region that showed decreased hemodynamic response suppression during completion of hard letter trials in the preterm group compared to controls that is not typically involved in language processing. The cortical systems for action control and language were traditionally thought to be independent systems, although more recent theoretical views suggest these may be served by interactive functional systems (Pulvermuller, 2005). Evidence of white matter connections between motor and language regions and somatotopic activation in the motor cortex in response to action-related words supports this notion (Pulvermuller, 2005; Pulvermuller and Fadiga, 2010). Schafer and colleagues (2009) found that in preterm adolescents, hemodynamic response in the left sensorimotor cortex during a lexical semantic association fMRI task was correlated with better task performance (Schafer et al., 2009). In the same study, functional connectivity between typical language-related temporal and sensorimotor areas was only present in preterm adolescents, suggesting that the sensorimotor cortex may mediate connections between language areas in the preterm brain.

Using a verbal fluency task, we found that at the whole group level decreased hemodynamic response suppression in right sensorimotor cortex during completion of the hard letter trials was associated with participants' poorer task performance, supporting the idea that increased neural recruitment does not necessarily lead to better cognitive performance (Tseng et al., 2017; Turkeltaub et al., 2012). This finding may be expected given that significant group differences in verbal fluency (hard letters) and right sensorimotor cortex hemodynamic response were found. Nonetheless, other regions that also exhibited differences in hemodynamic response did not show an association with verbal fluency performance. Previous research suggested that recruitment of right hemispheric mechanisms for language may occur when left hemispheric specialisation is disrupted, though it is unclear whether this leads to the successful acquisition of typical language skills (Holland et al., 2007). Contrasting findings between the current and Schafer's study could be due to the use of different tasks assessing different language processes.

Around half of all participants (and the majority of controls) had a negative contrast of parameter estimate in the right sensorimotor cortex, indicating that suppression of this region compared to the baseline is needed to perform well on a verbal fluency task. Intra-subject comparisons of fMRI deactivation during visual attention and working memory processing suggest that deactivation may be an inhibition mechanism to reduce distracting neural processes, rather than a local reduction of relative cerebral blood flow in less active brain regions due to increased relative cerebral blood flow in activated brain regions (Tomasi et al., 2006). Better visual attention performance has in fact been associated with stronger disconnection of task-irrelevant brain regions (Tomasi et al., 2014).

Greater LOC hemodynamic response suppression in very preterm adults compared to controls in the *Hard* > *Easy* condition could be related to differences in word form processing. The LOC is connected to the visual word form area through the vertical occipital fasciculus (Yeatman et al., 2013). Damage to the anterior vertical occipital fasciculus has been found to impair reading abilities (Yeatman et al., 2014). It is possible that this region is more engaged during the REST control condition when reading a word and dependent on successful word retrieval during the task conditions. However, white matter properties and task performance were not associated with this difference.

Structural MRI results

Contrary to our prediction, very preterm adults did not have smaller volume and HMOA and decreased-left lateralization in both structural indices of the AF and FAT compared to term-born controls. One possible explanation could be that the primary site of perinatal injury (i.e. periventricular hemorrhage) involves periventricular regions, therefore affecting subcortical regions and its connections (e.g. the dorsal and ventral cingulum and the fornix) to a greater extent than structures that lie more laterally in the brain (Froudist-Walsh et al., 2015). In previous studies, it was also shown that the superior longitudinal fasciculus, which is distant from the ventricles, did not exhibit between-group volumetric differences, suggesting that there may be a medial-lateral gradient of risk for structural injury following very preterm birth (Caldinelli et al., 2017; Froudist-Walsh et al., 2015). A lack of significant group differences in AF and FAT, which connect to or within the frontal lobe, could be also interpreted using a neurodevelopmental perspective: the frontal lobe displays protracted maturation compared to other brain areas (Petanjek et al., 2011), possibly resulting in decreased vulnerability of its white matter connections to early brain insults.

Functional-structural associations

We expected that increased right hemispheric hemodynamic response in very preterm adults would be associated with increased right-lateralisation of AF or FAT white matter indices. Instead, only in controls we found an association between increased right-lateralisation of AF HMOA and decreased hemodynamic response suppression in right STG in the *Easy* > *Rest* condition and in right sensorimotor cortex in the *Hard* > *Rest* condition. As decreased hemodynamic response suppression in right sensorimotor cortex was associated with worse verbal fluency performance on hard letter trials, these findings highlight the importance of left-lateralisation for language-related functions. Part of the left AF is considered as a direct phonologic pathway and may be particularly important to aid children's language acquisition (Glasser and Rilling, 2008), and early leftward AF asymmetry is seen in term-born infants (Dubois et al., 2009). The fact that this was not found in very preterm adults may indicate a lateralisation alteration, considering that the asymmetry of the cerebral hemispheres (most prominently in perisylvian cortex) emerges during the late second and third trimester of gestation, when very preterm birth occurs (Habas et al., 2012).

Neuroimaging studies investigating language functions in preterm individuals have highlighted the importance of interhemispheric connections and lateralisation in language development (Salvan and Nosarti, 2018). An increased right-hemispheric engagement found in this study has been previously reported during language tasks in preterm individuals (Gozzo et al., 2009; Myers et al., 2010; Scheinost et al., 2015) and may reflect deviations in typical cortical language network development, when functional specialization increases (Skeide and Friederici, 2016). Atypical lateralisation of language networks has also been shown in disorders such as autism spectrum disorder and schizophrenia (Mitchell and Crow, 2005; Preslar et al., 2014). We speculate that the atypical functional lateralisation of verbal fluency networks seen here could contribute to the increased psychiatric risk in very preterm samples (Nosarti et al., 2012).

While not demonstrating a significant association between right STG and right sensorimotor cortex hemodynamic response and the AF seen in controls, very preterm adults instead showed a distinct relationship between increased right STG hemodynamic response suppression during hard letter trials and higher left FAT HMOA. This finding is consistent with other studies proposing that the FAT plays a role in verbal fluency processing in clinical populations (Catani et al., 2013; Kronfeld-Duenias et al., 2016). Together with the previously discussed findings, our results suggest a remapping of the neuroanatomical underpinnings of verbal fluency to prioritise the left FAT in very preterm adults. However, as neither left FAT HMOA nor right STG hemodynamic response showed a significant association with on-line task performance, with the current results we are unable to determine whether this observed structural-functional association may be adaptive or maladaptive. Another interpretation for our unique within-group results could be that the two tracts we investigated, the AF and the FAT, which are differentially involved in various aspects of language (Catani and Bambini, 2014), may be supporting distinct linguistic operations in controls and very preterm adults. It was not within the scope of this study to carry out an extensive assessment of language processing and further studies are needed to pinpoint the specific functions of each tract in typically and atypically developing samples.

Brain lateralization and language

So far in the reviewed literature, left-lateralisation of the brain has been associated with better language skills. However, previous studies have also reported no relationship between functional brain lateralization and language skills in healthy subjects (Knecht et al., 2001), but in those with developmental difficulties (Illingworth and Bishop, 2009). It is possible that atypical cerebral lateralisation is a potential risk factor for language impairment and the addition of or interaction with other factors (e.g. genetic) may be the cause of language difficulties (Bishop, 2013). It is worth highlighting that cerebral lateralisation can change throughout development and may be a consequence rather than a cause of poor language abilities (Bishop, 2013).

Sex differences within the very preterm group

Contrary to previous findings that preterm girls outperform boys on language skills (Eriksson et al., 2012), this study found that very preterm men performed better than women on the easy letters during the verbal fluency task and had higher verbal IQ. However, in the larger sample the current participants were drawn from (Kroll et al., 2017), there were no sex differences in verbal IQ. Future studies with larger sample sizes are needed to confirm whether there are sex differences on language abilities in very preterm adults.

Limitations

We acknowledge that there are several limitations to this study. The nature of verbal fluency, being a combined measure of verbal and executive function abilities, makes it difficult to tease out which cognitive component may be affected in a specific population sample. This study selectively focused on the language component of the task. The executive function component of verbal fluency and corresponding white matter connections, which may explain other aspects of the long-term sequelae of very preterm birth, remains an area to explore further.

Very preterm adults in this study only showed lower verbal and not performance IQ compared to controls, although in the larger sample they were drawn from, they had lower verbal and performance IQ (Kroll et al, 2017). In this study, we found that poorer verbal IQ was associated with worse verbal fluency on the hard letter trials in the very preterm group only, suggesting that verbal fluency may represent one of the various aspects of language processing that may be affected by very preterm birth, although not assessed here.

There are a number of potential methodological limitations. First, is the exclusive consideration of white matter fibre tracts that we thought to be involved in verbal fluency. Therefore, we did not investigate other tracts, such the uncinate fasciculus, which enables the mapping of sound to meaning and is viewed as a critical component of the language network (Friederici and Gierhan, 2013), yet has not been directly implicated in letter fluency (Catani et al., 2013; Kljajevic et al., 2016).

Second, there is the concern that false positive rates of fMRI findings using parametric statistical methods with cluster-based inference is higher than anticipated (Eklund et al., 2016). There is currently no non-parametric equivalent of FEAT's FLAME to assess differences in findings between parametric and nonparametric methods. Therefore, the results reported in this study should be interpreted with caution and future work to validate these findings with non-parametric methods is needed.

Conclusion

Very preterm adults exhibited worse verbal fluency performance than controls when a high cognitive demand was required. The results of this study suggest that this may be due to deviations in typical development, resulting in a less left-lateralised network underlying verbal fluency. Verbal fluency processing in very preterm adults may be supported by a potential remapping of structural-functional brain associations, involving the FAT. Based on this study, future work is warranted to explore the development of brain lateralisation in very preterm individuals at different stages of development.

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