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Variability in lateralised blood flow response to language is associated with language development in children aged 1–5 years

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ABSTRACT

The developmental trajectory of language lateralisation over the preschool years is unclear. We explored the relationship between lateralisation of cerebral blood flow velocity response to object naming and cognitive performance in children aged 1–5 years. Functional transcranial Doppler ultrasound was used to record blood flow velocity bilaterally from middle cerebral arteries during a naming task in 58 children (59% male). At group level, the Lateralisation Index (LI) revealed a greater relative increase in cerebral blood flow velocity within the left as compared to right middle cerebral artery. After controlling for maternal IQ, left-lateralised children displayed lower expressive language scores compared to right- and bi-lateralised children, and reduced variability in LI. Supporting this, greater variability in lateralised response, rather than mean response, was indicative of greater expressive language ability. Findings suggest that a delayed establishment of language specialisation is associated with better language ability in the preschool years.

1. Introduction

Studies in children show language is lateralised to the left hemisphere of the brain from six years of age (e.g. see Groen, Whitehouse, Badcock, & Bishop, 2012). Studies in clinical populations with reduced language skill suggest such functional specialisation is associated with greater cognitive performance (de Guibert et al., 2011; Everts et al., 2010; Flagg, Cardy, Roberts, & Roberts, 2005; Jacola et al., 2006; Johnson et al., 2013; Spironelli, Penolazzi, Vio, & Angrilli, 2006). When such lateralisation develops earlier in life and the trajectory of any such development is not clear. Traditionally, models have suggested underlying genetic risk by which weak laterality causes delayed or impaired language function, or which independently impairs both laterality and language (Annett, 1985; Bishop, 2013). However, such models have received limited support from studies investigating the heritability of functional brain asymmetry to language tasks, and those targeting candidate genetic variants (for review see Bishop, 2013).

Another view is that asymmetries to language reflect a maturational process, confined by genetic boundaries but largely defined by experience. Minagawa-Kawai, Cristia, and Dupoux (2011) proposed a model whereby lateralised language function begins very early in development as asymmetrical activation to different sounds, specifically rapid changing sounds yielding a left- or bi-lateral activation. After this, newly learned sounds are captured in the left-dominant phonetic and lexical circuits, typically giving rise to left-lateralised language networks. Consistent with this idea is the observed developmental trajectory of left lateralisation to phonological contrasts in an infant's native language (Arimitsu et al., 2011; Furuya, Mori, Minagawa-Kawai, & Hayashi, 2001; Minagawa-Kawai et al., 2009; Sato, Sogabe, & Mazuka, 2007; Sato et al., 2003). As well, studies in older children and adolescents demonstrating a left lateralisation to lexical–sematic tasks compared to more distributed or bilateral activation for syntactically-loaded tasks (Holland et al., 2007).

Studies in healthy populations of older children, typically from about school age onward, strongly support a left dominant activation in normal language development. fMRI paradigms in school aged children and adolescents typically show a predominant left hemisphere activation for silent word generation tasks (Norrelgen, Lilja, Ingvar, Gisselgard, & Fransson, 2012; Szaflarski

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et al., 2012; Wood et al., 2004), silent reading (Gaillard, Balsamo, Ibrahim, Sachs, & Xu, 2003) and an auditory categorisation task (Balsamo, Xu, & Gaillard, 2006) in areas of the frontal and temporal gyri as well as fusiform and supplementary motors area. In addition, a number of these studies have indicated a positive correlation between left activation and task performance (Balsamo et al., 2006; Wood et al., 2004). Magnetoencephalography (MEG) studies with children and adolescents aged 5–19 years have also shown a predominant left lateralisation to word generation tasks but, unlike in fMRI studies, one that increases in prominence with age between around 5–7 years and mid-late adolescence (Balsamo et al., 2006; Kadis et al., 2011; Ressel, Wilke, Lidzba, Lutzenberger, & Krageloh-Mann, 2008; Wood et al., 2004).

When conducting functional imaging studies in young children, compliance with instruction to remain very still for extended periods without the possibility of close caregiver contact, and the limitations these restrictions place on task type (e.g., covert vs. explicit responses) and participant retention (Holland et al., 2007; Wood et al., 2004), limit application. Less invasive techniques with greater flexibility such as transcranial Doppler (TCD), which can measure cerebral blood flow velocity in the major cerebral arteries, are increasingly being used in the investigation of developmental origins and significance of language lateralisation (Bishop, Badcock, & Holt, 2010). So far in older children and adolescents, studies using a functional application of TCD recordings from the middle cerebral artery during picture or animation descriptions also show a predominant left lateralisation, and consistent with fMRI studies, no change in this pattern between the ages of 6–16 years (Groen et al., 2012; Haag et al., 2010). However, in the small number of studies available, there is disagreement as to whether such lateralised activation is associated with better language ability (Groen et al., 2012; Lohmann, Drager, Muller-Ehrenberg, Deppe, & Knecht, 2005).

In typically developing infants, near-infrared spectroscopy (NIRS), as well as TCD, have allowed for greater investigation of the developmental progression of language lateralisation. Using NIRS, Bortfeld, Fava, and Boas (2009) have shown greater hemodynamic activation in left temporal regions to an audio–visual presentation as opposed to visual only in 21 infants aged 6–9 months. Molavi et al. (2013) found a left-lateralised response to language in 19 newborn infants, and Peña et al. (2003) observed greater activation in left temporal areas in 12 newborns, 2–5 days post-birth, when exposed to normal speech compared to backward speech or silence, suggesting a lateralised response is already present at birth. FMRI data generally support these observations, showing that in 2-day-old newborns, language activation to speech is less lateralised compared to adults (Perani et al., 2011), but a left hemisphere advantage to speech over music is found in slightly older infants (Dehaene-Lambertz et al., 2010). To further test the idea of pre-birth development of lateralised response to language, bilateral brain response using NIRS to a familiar language (the primary language heard *in utero*) was greater compared to a decrease in activation to an unfamiliar language in 20 newborns within the first 3 days of birth (May, Byers-Heinlein, Gervain, & Werker, 2011). The neural processing of language therefore appears to be influenced by experience before birth.

Collectively, it appears that people are born with a preference for left lateralisation to language. However, this preference is strongly shaped by experience and begins to develop prior to birth and rapidly develops thereafter, remaining relatively stable throughout later childhood and possibly increasing further into adolescence and adulthood. What is missing from the literature and from a developmental perspective is analyses of lateralised response during the intermediary period between infancy and school-age. This is arguably the most difficult period in which to perform such studies from a compliance point of view, but is also the period of dramatic expressive language development. It would therefore seem a crucial period of life to examine lateralised response to language if we are to have a complete understanding of its origins and significance. Only a few studies have investigated such functions in preschool aged children, and all of these in clinical populations.

Sowman, Crain, Harrison, and Johnson (2014) investigated functional activation of brain regions using MEG to a picture naming task in 12 stuttering and 12 typically developing children aged 3–5 years. Their results show a predominant left activation in all children in language regions. In contrast to the more distributed or right language activation seen in adult stutterers (Brown, Ingham, Ingham, Laird, & Fox, 2005), these results suggest that at the time of pronounced expressive language development, and the typical emergence of stuttering, the pattern of brain activation is quite different and consistent with typically developing peers, supporting the maturational perspective on language and lateralisation development.

In contrast, Sato et al. (2011) used NIRS to assess lateralised responses to contrasts of phoneme (different vowels) and prosody (different vowel pitch) in a small group of 3- to 5-year-old children who stutter, and compared results to controls as well as to equivalent comparisons in 6- to 12-year-old children and adults. Consistent with the ideas put forward by Minagawa-Kawai et al. (2011), controls in each age group showed a predominant left side activation to phonemic contrasts compared to a more right side activation to prosodic contrasts. However, all stuttering groups showed a similar activation across both hemispheres for both conditions. While this result might seem at odds with Sowman et al. (2014), it is interesting to note that Sato et al. also showed a correlation between increased stuttering severity in adults and reduced lateralisation in the phonemic condition, an effect that was not found in either school- or preschool-aged children.

Most recently, Bishop, Holt, Whitehouse, and Groen (2014) investigated lateralised function to silent animation descriptions using fTCD in 57 4-year-old children with or without impaired language development. Children with language difficulties did not show left-side lateralised activation, compared to a clear left lateralisation in children without language problems. However, consistent with the observation in older children, while those with language impairment showed reduced left-lateralised activation, many 4-year-olds with right-lateralised activation showed no language difficulty. Combined, these few results from preschool populations support the argument that a more bilateral or right-lateralised response to language reflects adaptive neuroplastic changes, rather than represent an underlying cause of impairment. To date no study of functional language lateralisation exists in a purely typically developing group of preschool aged children. The aim of this study was to explore lateralised response to language in a relatively large group of typically developing young children, and to assess the association of both mean lateralised response and variability in response to language and broader cognitive development.

2. Material and methods

2.1. Participants

Participants with known visual or auditory impairments, diagnosed learning problems, developmental delays or syndromes affecting cognitive development (e.g., autism or downs syndrome) were excluded from the study; as were those currently taking medication known to affect cardiovascular blood vessel function or neurocognitive performance (such as a stimulant or psychotropic drug) or who were suffering from any acute illness, such as a cold, were also excluded. Only children with English as the primary spoken language in the home were included in the study. Parents of 146 children initially responded to advertisements for the study, and after receiving study information 56 declined further participation. Seven children were excluded based on medical grounds, and 6 withdrew after enrolment but before completing testing. Functional transcranial Doppler ultrasound (fTCD) was attempted in the remaining 77 children and successfully recorded bilaterally in 68 children between 1 and 5 years of age. Data containing at least 6 clean trials were included for analyses ($n = 58$). Included children were aged 40.2 ± 12.9 months (59% male), and born between 35 and 42 weeks gestation. In addition to age and gender, child ethnicity (90% Caucasian) and socioeconomic status (1009.2 ± 47.9; using the Australian Bureau of Statistics Index of Relative Socio-economic Advantage/Disadvantage 2011 national census data (National mean = 1000, SD = 100) were recorded. Hand preference was determined by planned observation of each child using a number of age appropriate objects consistent with previous methods used in very young children (Michel, Ovrut, & Harkins, 1985).

2.2. Cognitive measures

Maternal intelligence (IQ) was measured due to its relationship with childhood development and cognition (e.g. Tong, Baghurst, Vimpani, & McMichael, 2007), using the Wechsler Abbreviated Scales of Intelligence (Wechsler, 1999). The WASI consists of four subtests that combine to produce a measure of full scale IQ. *T*-scores from a normative sample produce a mean of 100 (SD = 15) with higher scores indicating better performance.

Cognitive performance of children was assessed using the Mullen Scales of Early Learning (MSEL) and domains measuring visual reception, fine motor, expressive and receptive language skill were assessed (Mullen, 1995). *T*-scores are normally distributed ($M = 50$, SD = 10) with higher scores indicating better performance. Domain scores also combine to produce a Early Learning Composite Score, which is a proxy measure for general intelligence ($M = 100$, SD = 15). The MSEL is reported to have good internal reliability (.83–.95) and test-retest reliability (.70), and produces highly consistent results with equivalent measures across its domains (Mullen, 1995).

2.3. Functional transcranial Doppler recording

Bilateral cerebral blood flow velocity (CBFV) recordings were made using a DWL Doppler-BoxTM hardware and QL 2.8 software, a DiaMon® or elastic headband fixation, and 2 MHz ultrasound probes (Compumedics DWL, Singen, Germany). TCD velocity recordings were made in centimetres per second (cm/s) at 100 Hz. The left and right Middle Cerebral Artery (MCA) M1 segments were insonated from the transtemporal window, and confirmed by locating the anterior cerebral bifurcation. Insonation depths varied between 30 and 55 mm. TCD recordings were performed during the day, with the child sitting upright and awake, and attending to a computer screen. FTCD measures were taken during the ‘What Box’ item identification task (see Fig. 1) in order to assess language related activation. The What Box task included a series of up to 36 trials, each consisting of consecutive still frame images and accompanying sounds simulating animation. A schematic diagram of a single trial is presented in Fig. 1.

The sequence of each trial included the face ‘moving’ down and then up the screen ‘searching’ for something. A box then appears and opens, a “look” verbal cue is presented, an object is presented (e.g., biscuit, bottle, and animals) and the “what’s this?” verbal cue is presented with time for object naming. The object label is then played followed by a smiling face and randomised celebratory sound (e.g., crowd cheers, “yahoo”, “yay”, and laughing) to reinforce attention. Each trial lasted 35 seconds, and participants were encouraged to complete as many of the 36 trials for a total assessment time of 21 min. A randomly selected background image was presented during each trial up until the “look” cue in order to sustain attention, and after which the background was black. Coloured background images included houses, rooms (e.g., kitchen, bedroom), and natural scenes (e.g., gardens, landscapes). Background images were blurred and mirrored. Blurring reduced the presence of sharp features that may have captured attention and mirroring (down the vertical centre) controlled for any bias in the lateralisation of visual attention. The horizontal positions of other images were at random distances left or right of centre within a corridor 20% of the screen width. This was done to avoid any bias in the lateralisation of visual attention. Vertical positions included the horizontally central, vertically top-third position, and horizontally offset, vertically offset positions. The vertical offset was randomly selected to be within the middle or bottom third of the screen. The position of the eyes also varied randomly at each position

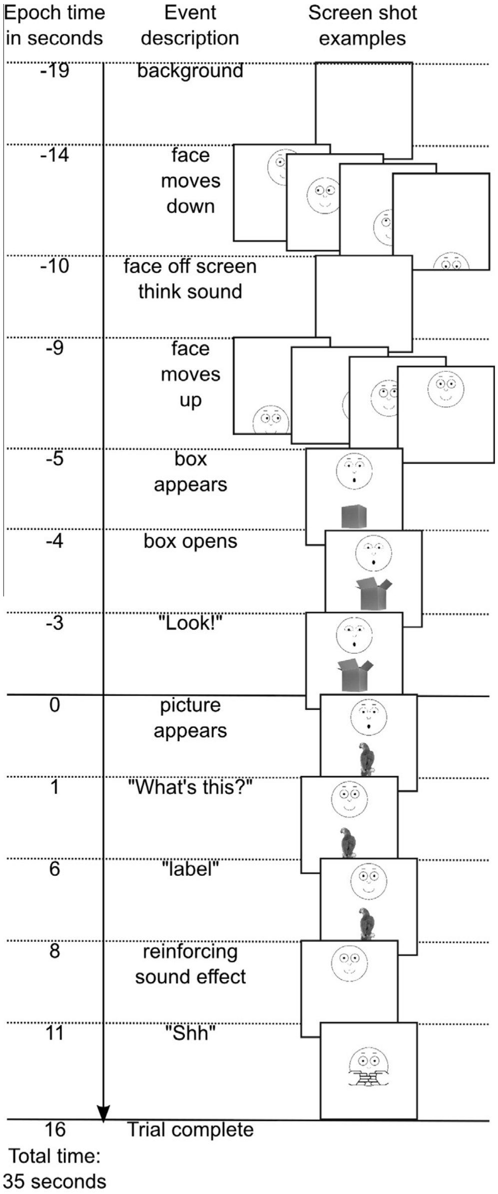

Fig. 1. Schematic diagram of WhatBox paradigm schedule.

except for the top position when they were set to straight ahead (i.e., looking at the participant).

2.4. Functional transcranial Doppler processing

The fTCD data was analysed using dopOSCCI (Badcock, Holt, Holden, & Bishop, 2012), a MATLAB-based summary-suite. The data were normalised across hemispheres to remove measurement differences due to probe angle. Velocity variation due to heart cycle was removed and the data were epoched at −14 to 15 s surrounding each event marker: the onset of the target object, time 0 in Fig. 1. Epochs with activation ±50% of mean activation or left-minus-right difference >20% were automatically excluded, and manually excluded if the participant was observed to be disengaged from the task, exhibited large gross motor movement, or was talking during the baseline period. Epochs were then baseline-corrected and averaged to produce an evoked-flow response plot. Laterality Indices (LIs) were calculated as the average left minus right signal over a 2 s period surrounding the peak left-right difference within a task specific period of interest (5–15 s post-presentation of the target object). Positive LI values indicate left lateralisation and negative LI values indicate right lateralisation. Time to peak difference was also recorded.

2.5. Procedure

Data collection occurred over a single 2–3 h session at the University of South Australia Cognitive Neuroscience Laboratory in Adelaide, Australia. Where possible the MSEL was administered to each child in a separate room and at the same time that the WASI was administered to the mother. Afterwards, the child was familiarised with the TCD headset by allowing them to play with it, try it on and decorate it with stickers. The headset was then fixed in place and probes were attached whilst the child watched an age-appropriate television program. Upon the accurate detection of the M1 segment of the MCA on the left and right side, the probes were fixated in place after which acquisition began.

2.6. Analysis

Statistical analyses were performed using IBM SPSS Statistic version 21.0 (IBM Corp, Armonk, NY). Associations between TCD indices, demographic and cognitive measures were determined using Pearson correlation. The contribution of LI and standard deviation of LI to cognitive performance domain scores (controlling for any co-varying factors identified in correlations in a first step) were determined using linear regression. Given the dependence of tests, and to help control the likelihood of type 1 error in correlation and regression analyses, bootstrap resampling (1000 iterations) was used. Comparisons of demographic, cognitive and TCD indices between lateralised groups were made using independent samples t-test or univariate ANOVA. Values are displayed as mean ± standard deviation unless otherwise indicated, and significance was determined at $\alpha = 0.05$.

3. Results

Number of trials completed by participants ranged from 6 to 32 (mean = 15.1 ± 6.3). Number of completed trials was not significantly associated with age, cognitive test scores or LI values. Maternal IQ ($M = 115.9$, SD = 10.5, range = 93–140) and child cognitive performance (Table 1) was in the average to above average range. Fifty (86%) of the children were classified as right-handed, 6 (10%) as left-handed, and 2 (4%) as both. The mean activation plot across the group for the task is presented in Fig. 2. The Lateralisation Index (LI) related to the naming task was positive ($M = 0.80$, SD = 3.0, range = −4.45 to 7.45) and significantly different from zero; $t(57) = 2.05$, $p < .05$, Cohen's $d = 0.54$; indicating lateralisation to the left at the group level. Overall, standard deviation in LI (indicating variance in response between trials) was $M = 5.26$, SD = 2.13, and mean time to peak activation was $M = 10.39$, SD = 3.5 seconds. There were no differences in demographic or TCD indices between males and females (all difference $p > .05$).

Table 1
Cognitive performance results from Mullen Scales of Early Learning.

	Mean	SD	Range
Visual reception	62.3	9.2	39–80
Fine motor	67.6	11.0	42–80
Receptive language	60.8	10.0	35–78
Expressive language	64.7	10.0	44–80
Early learning composite	127.2	13.6	100–153

Correlations between TCD indices and child demographic characteristics show no significant associations other than variation in LI (i.e., standard deviation of LI) being negatively associated with child age, $r = -0.29$ (95% CI = 0.00, −0.57), $p < .05$. Regression analyses show LI was not predictive of performance on any cognitive domain. However, after controlling for child age, the SD of LI was predictive of expressive language ability; $B = 1.43$ (95% CI = 0.33, 2.50), $p < .01$, explaining 8.4% of the unique variance in test scores and indicating greater variability being predictive of higher test score (Fig. 3).

Based on LI values and corresponding 95% confidence intervals, children were classified as right- ($n = 7$; negative LI value with CIs less than zero), left- ($n = 21$; positive LI values with CIs greater than zero), or bi-lateralised ($n = 30$; LI value with CIs that crossed zero). No differences on demographic or cognitive measure were found between right- and bi-lateralised children. These two groups were combined and compared to left-lateralised children. Left-lateralised children had mothers with slightly lower IQ (112.3 ± 10.2 vs. 118.0 ± 10.0, $t = 2.1$, $p < 05$) and reduced variability in LI results (i.e., SD of LI; 4.4 ± 1.8 vs. 5.8 ± 2.1, $t = 2.5$, $p < 05$). After controlling for maternal IQ, left-lateralised children displayed lower expressive language scores ($F = 4.17$, $p < .05$), but did not differ from other children for remaining cognitive domains (Table 2).

4. Discussion

In this study we examined the lateralisation of object naming and its relationship to cognitive development in children between 1 and 5 years of age. The results suggest that while lateralisation of language ability is evident during the preschool years, it is not as prominent as typically shown for older children and adults (Groen et al., 2012; Gutierrez-Sigut, Payne, & MacSweeney, 2015). These findings fill a developmental gap in the literature with regard to lateralised response to language, and highlight an aspect of lateralised response that has not been fully appreciated by focus on mean-brain measures exclusively. Greater variability in lateralised response was indicative of greater cognitive performance on a measure of expressive language ability. To our knowledge, variability of responsiveness has not been considered in this light previously and may provide new insight into the mechanisms linking lateralisation and language in both typically and atypically developing groups.

In older children, language is predominantly lateralised to the left hemisphere (Balsamo et al., 2006; Groen et al., 2012; Haag et al., 2010; Kadis et al., 2011; Lohmann et al., 2005; Wood et al., 2004). In contrast, when language is impaired, the degree of left lateralisation is more commonly reduced, or displays a bi- or right-lateralised response (de Guibert et al., 2011; Everts et al.,

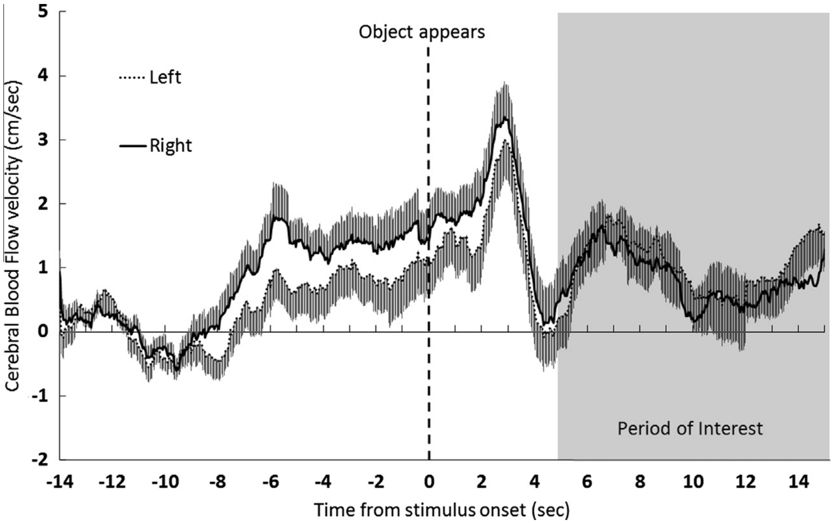

Fig. 2. Left (dotted line) and right (solid line) channel, baseline-corrected, mean Doppler velocity (cm/s) with SEM averaged across all accepted epochs. Children where cued to name a visual stimulus appearing 14 s after commencement of each trial. The period of interest during which laterality indices were determine is depicted by the shaded area.

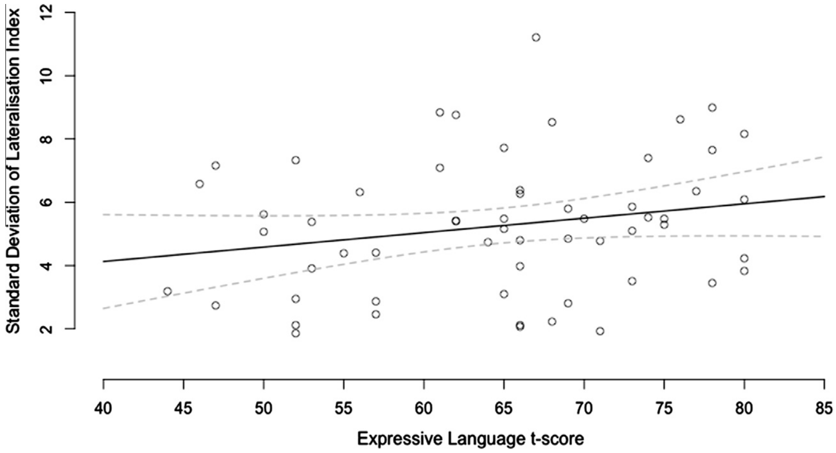

Fig. 3. Scatterplot of standard deviation of lateralisation index against expressive language performance in children. After controlling for child age the association was statistically significant, $R = .35$, $p < .05$.

Table 2
Comparison of cognitive performance between children right/bi-lateralised and left-lateralised to a language task.

	Right/bi-lateralised		Left lateralised		*F*-value	Effect size (partial η^2)[a]
	M	SD	*M*	SD		
Visual reception	62.5	8.2	61.2	11.0	0.2	0.03
Fine motor	66.5	11.8	69.6	9.5	3.0	0.05
Receptive language	61.2	10.2	60.2	9.8	0.9	<0.01
Expressive language	67.4	8.9	59.9	10.2	4.2[*]	0.07
Early learning composite	128.4	13.9	125.1	13.1	<.01	<0.01

[*] $p < .05$.
[a] Effect size of 0.01, 0.06 and 0.14 = small, medium and large respectively.

2010; Flagg et al., 2005; Jacola et al., 2006; Johnson et al., 2013; Spironelli et al., 2006). A number of studies in older children have also shown that left lateralisation to language is associated with better language ability (Balsamo et al., 2006; Groen et al., 2012; Wood et al., 2004), but not all studies support this finding (Lohmann et al., 2005). In newborns, it appears that receptive language function is already somewhat lateralised to the left (Bortfeld et al., 2009; Dehaene-Lambertz et al., 2010; Molavi et al., 2013; Peña et al., 2003) and this asymmetry likely influenced by early exposure to language, even before birth (May et al., 2011). What is typical in the intermediate period, when expressive language becomes evident and develops rapidly, is less clear. Previous studies comparing typically developed 3- to 5-year-old children to clinical groups suggest left activation in children without language problems. However, findings from this age range also suggest that the reduction or reversal of left-lateralised response to language in clinical groups is not predictive of impairment at an individual level (Bishop et al., 2014). Furthermore, a typical left side activation to phonemic contrasts compared to right side activation to prosodic contrasts (Sato et al., 2011) fits nicely with the proposition by Minagawa-Kawai et al. (2011) that newly learned sounds are captured in the left-dominant phonetic and lexical circuits, as opposed to a bilateral activation for syntax, with which prosody heavily interfaces. The results of our study, in a relatively large group of typically developing children aged between 1 and 5 years, confirm a left activation to spoken words and show for the first time that the lateralised effect at this young age is not predictive of language ability. These results help to complete the developmental picture of lateralised response to language and combined with other studies suggest a more "neuroplastic" model as proposed by Bishop (2013), where language impairment or delay influences brain development and lateralisation of activity.

The focus in previous child-based studies has been on absolute degree of language lateralisation (i.e., LI mean) and based on the assumption that degree of lateralisation may be predictive of development and/or ability, and therefore also represent part of the mechanism in language disorders. The finding here that variance in the lateralised response to language is a stronger predictor of expressive language performance is novel and consistent with recent MRI work in adults (Grady & Garrett, 2014). Studies in younger and older adults show that the variability in BOLD signal, representing relative change in blood oxygenation and due to metabolic demand, was higher in younger and better performers on various tasks. In addition, measures of BOLD variability did not covary strongly with mean BOLD measures, and were a stronger predictor of performance. The finding that variability differences predict group behavioural differences in adults suggest this would also be worth investigating in young children with delayed language development or impairment. As with adults, longitudinal data may help to clarify whether individuals who maintain higher levels of variability across different levels of cognitive demand may have better cognitive function generally (Grady & Garrett, 2014). The observation that variability in response was associated with age is also novel and, consistent with BOLD comparisons between older and younger adults, suggests that as young children develop the variability of response diminishes. Combined with the associations shown with expressive language function, it also suggests a protracted period of greater variability benefits language function. Investigation of the relationship between changes in response variability and language over a larger age range, and the implications of different trajectories of response variability change, are needed to fully investigate developmental origins and patterns.

The idea that variability in response is cognitively beneficial is also consistent with work showing more intelligent children demonstrate greater cortical plasticity, with a prolonged phase of cortical development. In a study of over 300 children aged 7–16 years assessed longitudinally, Shaw et al. (2006) showed that the trajectory of change in cortical thickness, rather than cortical thickness itself, is a better predictor of intellectual performance. Initially, children with highest intelligence had a relatively thinner cortex, but a more rapid increase in cortical thickness, thicker cortex by late childhood, and accelerated cortical pruning by late adolescence. The authors suggest that the prolonged phase of cortical gain in the most intelligent children might extend a 'critical' period for cognitive development. As such, it was not the mean thickness that ultimately was the best predictor of performance, but the variation in cortical maturation throughout development. The cross-sectional nature and age range confined to the preschool years of the current study limit the ability to form robust conclusions about developmental trajectories of lateralised response to language. Consequently, it will be interesting to follow the children longitudinally to establish whether a more definite but protracted lateralised response becomes evident later in development, and whether this pattern is predictive of greater language and cognitive performance.

The use of fTCD presents a number of advantages in this age group. Namely, quick set-up and noiseless operation, non-invasiveness and flexible administration environment. However, the poor spatial resolution limits analyses to measures of gross activation or lateralised response. Hopefully, data such as presented here will help justify more targeted analyses (such as with fMRI) with fewer required participants to explore more precisely the brain structures and patterns of activation between such structures important in the trajectory of lateralised response to language over age. This will provide important comparative data to clinical samples, with the further aim to better define mechanisms leading to language disorders in children and adults. Working with children of this young age invariably presents challenges in maintaining sufficient quality recordings. While the advantages of fTCD methods helps maximise data retention, reliability of data should always be carefully considered. In the present study split-half reliabilities for 6 consecutive trials were 0.4 for Mean LI and 0.5 for SD of LI, and Cronbach's alpha coefficients were 0.4 for mean LI and 0.7 for SD of LI. While only the coefficient for SD of LI would be considered good by conventional standards, the values also indicate the still variable nature of lateralised response at this age, and even supports the idea put forward that a lateralised language response is a consequence and not cause of developmental factors. A potential limitation of this study is the assumption that trials evoke a language response. While the number of participants and included trials, in combination with the time locked-to-stimulus recording and good temporal resolution of the TCD signal should ensure responses are to the language stimuli, not all stimulus presentations evoked an expressive response. An attempt was made to quantify the ratio of expressive to receptive trials in all participants, but was not achieved for all children. Of the data recorded, the vast majority of trials did evoke an expressive response, and this may help explain the association with expressive but not receptive language performance more broadly. Correlations between number of completed trials, ages and cognitive scores are presented as a supplement to this manuscript. Furthermore, studies in adults have shown that the number of words produced in a word generation task did not affect the LI (Badcock, Nye, & Bishop, 2012), and more recently in children that the LI was left lateralised and no different in strength between overt and covert speech production (Gutierrez-Sigut et al., 2015). Further analysis and future studies may selectively target specific aspects of language to help characterise mechanisms underlying impairment of those same aspects. Finally, while not effecting the direction of change to a large degree, visual inspection of raw performance scores from the Mullen across age suggests a greater degree of ceiling effect was evident amongst children from around 48 months of age. Standardisation of raw scores by age can otherwise obscure such effects. While the Mullen provided an assessment of the domains targeted, future studies may incorporate measures with better norms and therefore limit any influence such performance effects may have on the results.

4.1. Conclusion

Our data present the first examination of lateralised cerebrovascular activation to language in a healthy sample of preschool children. In combination with studies in older and younger samples, as well as clinical populations of a similar age, the results help complete a developmental picture of the lateralised language response and add weight to the growing opinion that such a response develops very early, but is largely guided by experience and other environmental factors. This helps explain why a predominant left activation in typically developing children compared to reduced left activation seen in many clinical populations does not predict language skill at an individual level (Bishop et al., 2014). The results also highlight a novel predictor of ability, namely the variability in lateralised response during this age, previously shown using fMRI data in older adults (Grady & Garrett, 2014). Whether this feature of response represents greater plasticity and subsequently facilitates neural processing of language, and language performance, remains to be confirmed with longitudinal data.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandl.2015.04.004.

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