Published in final edited form as:
*Brain Res*. 2012 January 18; 1433C: 85–97. doi:10.1016/j.brainres.2011.11.026.

# Left-Handedness and Language Lateralization in Children

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## Abstract

This fMRI study investigated the development of language lateralization in left- and right-handed children between 5 and 18 years of age. Twenty-seven left-handed children (17 boys, 10 girls) and 54 age- and gender-matched right-handed children were included. We used functional MRI at 3T and a verb generation task to measure hemispheric language dominance based on either frontal or temporo-parietal regions of interest (ROIs) defined for the entire group and applied on an individual basis. Based on the frontal ROI, in the left-handed group, 23 participants (85%) demonstrated left-hemispheric language lateralization, 3 (11%) demonstrated symmetric activation, and 1 (4%) demonstrated right-hemispheric lateralization. In contrast, 50 (93%) of the right-handed children showed left-hemisphere lateralization and 3 (6%) demonstrated a symmetric activation pattern, while one (2%) demonstrated a right- hemisphere lateralization. The corresponding values for the temporo-parietal ROI for the left-handed children were 18 (67%) left-dominant, 6 (22%) symmetric, 3 (11%) right-dominant and for the right-handed children 49 (91%), 4 (7%), 1 (2%). Left-hemispheric language lateralization increased with age in both groups but somewhat different lateralization trajectories were observed in girls when compared to boys. The incidence of atypical language lateralization in left-handed children in this study was similar to that reported in adults. We also found similar rates of increase in left-hemispheric language lateralization with age between groups (i.e., independent of handedness) indicating the presence of similar mechanisms for language lateralization in left- and right-handed children.

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**Keywords**

Language lateralization; language development; handedness; fMRI

## 1. INTRODUCTION

Handedness is a characteristic human trait. Even in our closest genetic relatives hand preference is not pronounced. In chimpanzees, 800 trials per participant of reaching for food revealed that 9/30 (30%) were using right hand ≥90% of the time, 9/30 (30%) were using left hand ≥90% of the time, and the remainder of the group was "ambidextrous" (Finch, 1941). The finding of equal distribution of handedness in chimpanzees has been recently questioned by others (e.g., (Corballis, 2009; Hopkins and Leavens, 1998; Hopkins et al., 2007; Hopkins and Nir, 2010)). Even so, the results of handedness evaluations appear to be consistent only in humans hence hand/extremity preference, while likely not an uniquely human feature, is consistently present only in the human race with approximately 90% of us reporting right hand preference (Gilbert and Wysocki, 1992) with this trait already present in 18 month old infants (Suzuki et al., 2009).

Genetically-determined and already present in chimpanzees (Hopkins and Nir, 2010) brain asymmetry may be the reason for language and auditory cortex asymmetries that emerge during prenatal and early postnatal human development (Chi et al., 1977; Hill et al., 2010) and that have been noted on the structural and functional levels in many adult studies published to date e.g., (Foundas et al., 1994; Penhune et al., 2003; Rademacher et al., 2001; Smith et al., 2010; Tzourio-Mazoyer et al., 2010b). Research provides evidence for the existence of a connection between familial sinistrality, personal handedness, cortical and subcortical asymmetries and language lateralization which could be linked by a common genetic factor or factors underlying the hemispheric organization of language and motor functions. Previous functional imaging studies have found a connection between familial left-handedness and hemispheric lateralization of language in adults (Hecaen et al., 1981; Szaflarski et al., 2002; Tzourio-Mazoyer et al., 2010a). However, while handedness appears to be at least partially mediated by genetic factors, a number of environmental, developmental and pathological factors have been shown to influence the presence and the degree of atypical handedness (Domellof et al., 2009; Francks et al., 2007; Hecaen and Sauguet, 1971; Hecaen et al., 1981; Lust et al., 2010; Springer et al., 1999; Staudt et al., 2002; Tillema et al., 2008; Yuan et al., 2006).

Handedness might be expected to provide an indicator of cerebral hemispheric language dominance (Geschwind and Galaburda, 1985). In general, two types of handedness are usually measured – personal and familial. Their effects on cortical and subcortical anatomy and function may be different (Tzourio-Mazoyer et al., 2010b). As discussed above, anatomical studies have shown that there are asymmetries in planum temporale and that these asymmetries are more pronounced in the right- when compared to the left-handed individuals (Foundas et al., 1995; Steinmetz et al., 1991). The extent of such asymmetries may be related to the presence or absence of familial handedness (Tzourio-Mazoyer et al., 2010b). As shown recently, these asymmetries may be, in part, related to "brain torque" (leftward frontal rightward occipital asymmetry) (Barrick et al., 2005). It has also been suggested that these anatomical asymmetries may be one of the reasons for left-hemispheric language dominance (Foundas et al., 1994; Steinmetz et al., 1991). Noninvasive fMRI studies of healthy adults (Pujol et al., 1999; Springer et al., 1999) have demonstrated that approximately 95% of right-handed adults have left hemispheric dominance for language. Similar findings were reported by authors using other non-invasive techniques to determine language lateralization e.g., transcranial Doppler ultrasonography (Knecht et al., 2000a;

Knecht et al., 2000b). A gradual decrease in the strength of left-hemispheric language lateralization with decreasing right-handedness (or increasing left-handedness) has also been noted with up to 27% of strong left-handers having right-hemispheric language representation (Knecht et al., 2000b). Similar findings of approximately 25% atypical language representation (symmetric or right-hemispheric) were reported in fMRI studies conducted in healthy left-handed adults (Pujol et al., 1999; Szaflarski et al., 2002). The strength of language lateralization may be further modulated by multiple factors including age (Holland et al., 2001; Szaflarski et al., 2006a; Szaflarski et al., 2006b), presence of familial sinistrality (Hecaen et al., 1981; Szaflarski et al., 2002; Tzourio-Mazoyer et al., 2010a), or brain/head size (Josse et al., 2006; Ringo et al., 1994; Tzourio-Mazoyer et al., 2010a).

While the above (and other) studies examined the relationship between handedness and language lateralization in right- and left-handed adults, normative neuroimaging data in the pediatric population are less readily available (Everts et al., 2009; Haag et al., 2009; Holland et al., 2001; Holland et al., 2007; Ressel et al., 2008). In 2011, we were not able to identify any studies that specifically focused on the neuroimaging of language lateralization in left-handed children and adolescents. Currently, there is evidence that left hemispheric dominance for language is present in 3 months old infants and that it continues to develop in pre-literate children (Dehaene-Lambertz et al., 2002; James, 2010). Studies such as these have also found that the left hemispheric contribution to language processing in right-handed individuals increases throughout childhood (Everts et al., 2009; Holland et al., 2001; Holland et al., 2007; Szaflarski et al., 2006a). Further, early studies of language development showed an association between language dominance and handedness and/or eye preference (Belmont and Birch, 1965; Benton and Kemble, 1960) and that non-right-handedness correlates with atypical language development, especially in patients with neurologic illness such as epilepsy (Binder et al., 1996; Kim et al., 2011; Woods et al., 1988; Yuan et al., 2006) or stroke (Jacola et al., 2006; Staudt et al., 2001; Tillema et al., 2008). But, to date, large-scale neuroimaging studies examining the left-hemispheric contributions to speech production taking into consideration the effects of personal and/or familial handedness and/or head size on cortical language distribution in left-handed children have not been conducted.

Therefore, the goal of this study was to establish the frequency of atypical language lateralization (symmetric or right-hemispheric) in a sample of left-handed children with familial history of left-handedness and compare them to age and gender matched right-handed children with or without family history of left-handedness. Based on previous studies of adults, we hypothesized that left-handed children (with family history of left-handedness) would have a higher proportion of bilateral and right-hemisphere dominant language function compared to right-handed children and that there should be an additive effect of familial left-handedness on language lateralization. We also hypothesized that lateralization would increase with age in both left- and right-handers. While sex differences and head size have been shown to exert influence on language lateralization (Plante et al., 2006; Tzourio-Mazoyer et al., 2010a), to avoid this possible confound in the present study of handedness, we controlled for sex and head size effects.

## 2. RESULTS

### 2.1. Composite activation map

Composite activation maps for all left handed subjects (N = 27) and all right handed subjects (N = 54) included in the study are shown in Figures 1A and 1B, respectively (threshold of $z \geq 4.5$, based on the random effects analysis). This nominal z-score value, combined with a cluster size of 30, resulted in a corrected p-value of $\leq 0.001$ as determined via Monte Carlo simulation (Forman et al., 1995). This activation pattern is very similar to the pattern seen in our previous studies that utilized similar methodology and will not be discussed here in detail (Holland et al., 2001; Szaflarski et al., 2006a; Szaflarski et al., 2006b) except that it is worth noting the strong similarity in the patterns of activation between the left and right handers.

### 2.2. Lateralization

The two right-handed groups were combined after finding no differences between them in the socio-demographic characteristics and after confirming the equivalence of the two regression coefficients resulting from fitting a model that relates lateralization index for the frontal and temporo-parietal ROIs with age. Further, to ascertain that there were no differences between the two groups, we ran the test of coincidence hypothesizing that the relationship between age and LI in the two groups is exactly the same. This implies that both the intercept and slope in the two groups are equal. This was achieved by fitting a single model which contains a dummy variable to identify group membership (i.e., Right-Right or Right-Left), age and the interaction between age and group given by:

$$Y=\beta_0+\beta_1 Age+\beta_2 Rgroup+\beta_3(Age*Rgroup)$$

where $\beta_0$ is the intercept, $\beta_1$, $\beta_2$, and $\beta_3$ are the coefficients for age, group, and the interaction between age and group. The test of coincidence is equivalent to testing the hypothesis that $\beta_2 = \beta_3 = 0$, in the above model, which implies that both the slope and the intercept for both groups are the same and can be fitted using the model:

$$H_0{:}\beta_2=\beta_3=0.$$

Finally, we used F-statistic to test simultaneously whether both, the slope and the intercept were the same using the following formula:

$$F=\frac{(SS(group)+SS(group*age))/2}{SS(error)/50}$$

where SS represents the sum of squares from the resulting regression fit. This resulted in F value of 0.4598 ($F_{2,\ 50}$, p=0.63), and 0.161 ($F_{2,\ 50}$, p=0.85) for the frontal and temporo-parietal ROIs, respectively. Of note is that some of the LI values represent outliers thus this model was run initially with and then without outliers; excluding the outliers resulted in minimal and non-significant changes. Hence, the results reported here are with the outliers included. In the frontal ROI, in left-handed group 23 participants (85%) demonstrated left-hemispheric language lateralization, three (11%) demonstrated a symmetric activation pattern, and one (4%) demonstrated right-hemisphere lateralization. In contrast, 50 (93%) of the right-handed children showed left-hemisphere lateralization and 3 (6%) demonstrated symmetric activation pattern, while one (2%) demonstrated a right- hemispheric language lateralization. The difference in the left hemispheric dominance between left- and right-handed groups is not significant (Fisher Exact test; p = 0.36). The corresponding values for the temporo-parietal ROI for the left-handed children are 18 (67%) left-dominant, 6 (22%) symmetric, 3 (11%) right-dominant. For the right-handed children the values were 49 (91%) left-dominant, 4 (7%) symmetric, 1 (2%) right-dominant. The difference in the left hemispheric dominance for temporo-parietal ROI is significant between the two groups (Fisher Exact test; p= 0.03).

As we have shown previously in the right-handed children and adults (Szaflarski et al., 2006a), in this study, age was correlated with language lateralization for both, left-handed (as measured by the Spearman correlation coefficient; *r* = 0.43, p = 0.025 and *r* =0.41, p = 0.03 for the frontal and temporo-parietal ROIs, respectively) and right-handed (*r* = 0.26, p = 0.062 and r = 0.50, p = 0.0001 for the frontal and temporo-parietal ROIs, respectively) subjects (i.e., as the age increased, the leftward lateralization increased). Again, the reported values include the two data points detected as outliers; however, the impact of excluding these outliers from the analyses was only a slight increase in the correlation value. Further, in order to test for differential trajectory between the right- and left-handed children we fit a regression model that includes as a predictor both age and handedness as well as their interaction. The model is:

$$Y=\beta_0+\beta_1 Age+\beta_2 Hand+\beta_3(Age*Hand).$$

The interaction between handedness and age was not significant for either frontal (F=0.001, p=0.95) or temporo-parietal (F=1.24, p=0.27) ROIs. After removing the interaction term and refitting the model:

$$Y=\beta_0+\beta_1 Age+\beta_2 Hand,$$

the main effect of age approached significance for the frontal ROI (F=3.28, p=0.07) and was highly significant for the temporo-parietal ROI (F=18.08, p<0.001) indicating that for both handedness groups the slope was increasing with age at similar rate (Figure 2). We also investigated the potential for differential age slope across ROIs by fitting a model that includes the interaction between ROIs age and handedness group. The model for this interaction was:

$$Y=\beta_0+\beta_1 Age+\beta_2 Hand+\beta_3 ROI+\beta_4 Age*Hand+\beta_5 Age*ROI+\beta_6 Hand*ROI+\beta_7 Age*Hand*ROI.$$

In this model, we conducted hierarchical testing starting with the three way interaction followed by a test for the two way interactions depending on the strength of the coefficients. The three way interaction was not significant (F=0.57, p=0.45). After removing the three way interaction term, we fit the reduced model and tested for hand and age interaction which has the smallest contribution, which we found not to be significant (F=0.64, p=0.43). In a similar fashion, we tested the other two way interactions and found ROI by age interaction to be not significant (F=2.36, p=0.12) and the ROI by hand interaction to be marginally significant (F=4.17, p=0.04). The last finding is consistent with analyzing the data separately for the two ROIs in which we found an age effect in the temporo-parietal ROI (F=18.08, p<0.001) and a marginal age effect on the frontal ROI (F=3.28, p=0.07). Finally, since head size is indicated to intervene in language lateralization in adults (Josse et al., 2006; Tzourio-Mazoyer et al., 2010a), we investigated its impact on the relationship of age and LIs by including head circumference as a covariate in the above model. The simple correlation (Spearman) between head circumference and LI is significant, but much less so than the correlation of LIs with age. Thus, to explore the impact of including head circumference as a covariate in the model together with age we expanded the model as follows:

$$Y=\beta_0+\beta_1 Age+\beta_2 Hand+\beta_3 HeadCircumference$$

However the effect of head circumference on LIs in the presence of age and handedness was not significant and had very little effect on the slope.

We also investigated whether the pattern of the increasing LI trend was different between the two ROIs by fitting a regression model that included interaction terms of age, handedness group and ROI. None of the interaction terms, including the three way interaction, were significant. Although there was no age by group by sex interaction for either ROI (F=0.79, p=0.38 and F=3.6, p=0.06), as an exploratory analysis we evaluated the effects of sex on language lateralization. We tested the hypothesis of parallelism by first fitting a model that included the main effect of handedness group, age and their interaction for each gender group and tested the coefficient of the interaction term. A significant interaction term is an indicator that the slope (rate of change) for each handedness group might be different. Further, we did not find any differences between left- and right-handed girls with regard to lateralization in the frontal ROI (F=1.9, p=0.18) but left- and right-handed boys showed a significant difference in language lateralization indices (F=5.79, p=0.02) in this region. Finally, there were no differences in language lateralization between left- and right-handed girls or boys in the temporo-parietal ROI (all $p > 0.05$). There were no differences in the post-fMRI noun recognition accuracy quiz between the left- and right-handed groups. Mean and standard deviation were 13.87 (± 4.31) for the left-handed group and 13.40 (± 2.89) for the right-handed group ($p = 0.68$).

## 3. DISCUSSION

The finding that 15–33% of healthy left-handed children showed atypical language lateralization patterns (based on frontal or temporo-parietal ROI LIs, respectively) compared to 7–9% of right-handed children is consistent with our first hypothesis and with earlier fMRI studies of normal adults (Pujol et al., 1999; Szaflarski et al., 2002) as well as the traditional view of language lateralization (Code, 1997; Karunanayaka et al., 2010; Searleman, 1977). Semantic language function is typically lateralized to the left hemisphere in both right- and left-handed individuals. While it usually correlates with language lateralization, handedness is not a dependable predictor of hemispheric language dominance especially in left-handers. Symmetric representation of language is more common than right hemispheric lateralization in both the right- and left-handed groups. Not surprising but very interesting is the fact that these relationships are already present in childhood and that they are similar to the findings in adults (albeit the incidence of atypical language lateralization is somewhat lower when compared to adult studies which is likely related to a higher proportion of the youngest children having more symmetric language distribution – see Figure 2), especially in view of a recent study showing that the lateralization of language is a dynamic feature of human development that changes with age (Szaflarski et al., 2006a). These findings clearly suggest that there is a predisposition for particular lateralization of language in the human brain. Based on previous studies, it is likely an intrinsic predisposition (i.e., genetic) that may be modulated by environmental and other factors (Annett, 1998; Annett, 1999; Francks et al., 2002; Francks et al., 2007; Szaflarski et al., 2002; Tzourio-Mazoyer et al., 2010b). Thus, it is not surprising that these relationships already exist early in the brain development even though the process of brain maturation (synaptic pruning and myelination) continues for years, even into the late teens and twenties (Klingberg et al., 1999; Schmithorst et al., 2002; Yakovlev and Lecours, 1967).

A somewhat unexpected finding is the lack of the effect of familial left-handedness on language lateralization in right-handed children. The intercept (initial value of LI) and the slope of LI with age did not differ significantly between right-handed children with and without 1st degree left handed relatives. Since such effect was observed in some of the previously mentioned adult studies, we expected the Right-Left group to exhibit a degree of language lateralization between that found in left-handed and Right-Right children. This effect was not found in our cohort despite previous reports of such relationship observed in adults by e.g., Hecaen et al. (Hecaen et al., 1981). Failure to observe this effect may be related to the relatively small sample of children in the Right-Right and Right-Left groups, having only immediate family history of handedness (no history on more distant family members other than parents and siblings which may have led to inclusion of children with remote family history of left-handedness in the Right-Right group), or lack of the effect of familial handedness on language lateralization in children with this effect emerging later, after the maximum left-lateralization of language functions is observed in the early 20’s (Szaflarski et al., 2006a).

The language lateralization index used to parameterize language-related brain activity in our analysis is a non-dimensional ratio that is designed to be robust to differences in the level of activation between subjects. As such, it includes contributions from the mirrored ROIs in frontal lobe and temporal lobe in both the right and the left hemisphere. This means that an atypical value of LI ($LI<0.1$) reflects a greater contribution from the right hemisphere region. Recent studies (Staudt et al., 2001; Thiel et al., 2005), including several by our group (Tillema et al., 2008; Wilke et al., 2011; Yuan et al., 2006) have demonstrated right-hemispheric involvement in typically left-lateralizing language production tasks in pathological conditions such as stroke or epilepsy but the efficacy of such a non-dominant switch has been questioned (Anderson et al., 2011; Saur et al., 2010; Winhuisen et al., 2007). Therefore, we believe that atypical language representation in subjects with normal language skills (data points in Figure 2 represented by the triangles in the range of $LI<0.1$) and no history of underlying neurological condition (e.g., epilepsy, stroke or trauma) is genetically mediated as suggested by the recent discoveries of correlations between certain genes and handedness. In case of an insult (focal or global), there may be remodeling of cortical language representation akin to insult-related changes in handedness (Domellof et al., 2009), but such a process is not efficient and its success may be age-dependent with earlier insults of longer duration (i.e., years as in brain tumors or epilepsy vs. minutes as in trauma or stroke) resulting in more efficient neuroplasticity, and therefore, better and more complete recovery. Targeted interventions can also modulate pathologic neuroplasticity and recovery of language function (Baker et al., 2010; Hamilton et al., 2011; Szaflarski et al., 2011).

The correlation of age with leftward lateralization in the right-handed group is consistent with our previous findings in a larger group that included both right-handed groups of children and showed increasing language lateralization with increasing age (Szaflarski et al., 2006a). This correlation likely reflects an increasing specialization of the left hemisphere for language, although a trend toward left-hemispheric specialization may be present from very early in life (Dehaene-Lambertz et al., 2002). According to the “neural constructivism manifesto,” we can speculate that right-handers (and left-handers with typical language dominance) have developmentally earlier relegation of language to the left cerebral hemisphere (Quartz and Sejnowski, 1997) that may be related to or preceded by the already prenatally present anatomical asymmetries between the left and the right temporal areas (Chi et al., 1977; Hill et al., 2010; Wada et al., 1975). Indeed, the intercepts of the graphs in Figure 2 suggest that right-handed subjects express stronger left lateralized language function in temporo-parietal regions earlier than left handers while this process is not as apparent in the frontal regions. The other, more plausible explanation is that this process is related to the degree of brain maturation and inhibition of the right hemispheric language homologues by the left dominant circuitry (i.e., the more the white matter tracts are myelinated the more inhibition is exerted by the left hemisphere) (Vigneau et al., 2011). This is supported by the evidence from childhood and adolescent studies that showed an increase of white matter tract integrity with increases in age (Fields, 2005; Yakovlev and Lecours, 1967). Overall, studies of language lateralization in right-handed children and adolescents demonstrate similar rates for left hemispheric language lateralization as reported in adults. However, the effect of age on language lateralization depends on the characteristics of language tasks utilized, the task presentation modality (auditory vs. visual), regions of interest examined, and the age span examined. For example, our group and others have previously noted age-dependent increasing language lateralization to the left hemisphere for the verb generation task (Everts et al., 2009; Haag et al., 2009; Holland et al., 2001; Szaflarski et al., 2006a), while other studies did not confirm that finding (Gaillard et al., 2003; Wood et al., 2004). Notably, the trajectories of increasing language lateralization with age for the left- and right-handers are parallel in the temporo-parietal ROI but intersect in the frontal regions (Figure 2). Increasing left lateralization with age in both the left- and right-handed children in both ROIs indicates a similar developmental process that is independent of handedness. These age-related changes could be related to myelination, synaptic pruning, changes in brain/head size (and concomitant differences in the length of white matter tracts) and other, thus far undiscovered factors (Huttenlocher, 1979; Ringo et al., 1994; Schmithorst et al., 2002). While there is no evidence that the processes of myelination or synaptic pruning are handedness-dependent, there certainly is evidence for anatomical asymmetries between left- and right handers (Foundas et al., 1998), for the effect of handedness on cortical language representation (Pujol et al., 1999; Szaflarski et al., 2002) and for the effect of familial handedness on brain symmetry (Tzourio-Mazoyer et al., 2010b).

The differences in the lateralization growth trajectories between the frontal ROI and the temporo-parietal ROI between left- and right-handers, as shown in Figure 2, lead to some interesting speculations. First, the intersection of the growth curves for lateralization in the frontal ROI at approximately the age of 13 may be responsible for the lack of statistical significance in the difference between left- and right-handers in the lateralization of language function in this ROI. As noted in the Results section, left-handers and right-handers do exhibit a statistically significant difference in lateralization in the temporo-parietal ROI. In this ROI the LI growth curves are parallel but offset by approximately LI = 0.3. Therefore, it is not clear why the lateralization growth trajectories between left- and right-handers in the frontal ROI converge at the age of 13 years around the time of puberty especially that this finding is mainly driven by the LIs in girls and not boys (see below). What we know is that gray matter volume continues to increase in this region during adolescence (Wilke et al., 2007) and that there are subtle differences in verbal and non-verbal abilities and language lateralization between sexes (Allendorfer et al., 2011; Plante et al., 2005; Shaywitz et al., 1995; Waber, 1976). Perhaps, we are observing an interaction of brain growth and sex hormones released during puberty and handedness in continued frontal lobe language development. Further, a careful inspection of Figure 2 for the frontal ROI also yields another interpretation of the intersecting trajectories for the left- and right- handed groups. It is possible that the left frontal lobe is necessary for efficient verbal fluency and that the left-handers are “catching-up” with the right-handers with left lateralization in this region until the age of 13 (Waber, 1976). Our data beyond this age is sparse for the left-handed group, so it is possible that with additional right-hemispheric dominant left-handers in the age range from 14 and up, the lateralization trend could decline to match that of the right-handed groups. With only 4 left-handed subjects in this age-range in the present data set, it is not possible to test this hypothesis.

There were no differences in language lateralization between left- and right-handed girls based on the frontal ROI. In contrast to girls, left- and right-handed boys showed a significant difference in language lateralization indices. These differences need to be placed in the context of several previous studies focusing on the evaluation of sex differences in language localization and lateralization. These studies have found various differences in language and white matter characteristics between sexes (e.g., (Allendorfer et al., 2011; Schmithorst and Holland, 2006)) which are relatively easy to explain because of the sex differences in e.g., brain size in children (Lynn et al., 2000) or adults (Davison Ankney, 1992; Gur et al., 1999), familiar sinistrality (Szaflarski et al., 2002; Tzourio-Mazoyer et al., 2010b), hormonal exposure during pregnancy (especially testosterone) (Lust et al., 2010), or using the psychometrically defined “extreme male brain” theory that postulates that the “male brain” is much better at systemizing (i.e., analyzing) than the “female brain” that is much better at empathizing (Baron-Cohen, 2002). In our data, the impact of head size on the interaction of LI with handedness and age was not significant. This differs somewhat from the results presented by Josse et al., and Tzourio-Mazoyer et al., who found positive interaction between skull perimeter and language lateralization for speech comprehension but not spatial attention fMRI tasks (Tzourio-Mazoyer et al., 2010a) and between brain volume inferred from MRI data and story comprehension but not verb generation PET tasks (Josse et al., 2006). The results of the second study, especially the lack of correlation between brain volume and language lateralization with verb generation PET task are in agreement with our results obtained with fMRI task of verb generation. Thus, the underlying reasons for the observed discrepancies between these studies may be the differences between enrolled subjects (children vs. adults), cohort sizes, or differences in language tasks utilized to study language lateralization.

The differences we found between right- and left-handed boys are more difficult to explain. One possible explanation is based on Geschwind’s theory that the left-hand dominance is related (at least in part) to differences in sex hormones levels before birth (Geschwind and Galaburda, 1985; Lust et al., 2010) and the dimorphism in certain steroid receptors e.g., within the diagonal band of Broca or mamillary nuclei (Fernandez-Guasti et al., 2000). We have known for a long time that the levels of sex hormones during prenatal development are different between boys and girls, i.e., testosterone level is up to 10 times higher in males than females in the latter part of the third trimester of the prenatal development (Swaab et al., 1997) and that this may affect handedness and brain development (for detailed review see (Halpern, 2000)). The gestational hormonal milieu can affect both, handedness and language lateralization. Correspondingly, sex differences are observed not only on the anatomical (Zhou and Swaab, 1999) but also on the connectivity (Schmithorst and Holland, 2007) and functional (Schmithorst and Holland, 2006) levels. So, it is possible that the combined effect of handedness and hormones on brains is different between left- and right-handers, especially left-handed boys. Another possibility is that this trend is related to some thus far undiscovered factor(s). This could also be a spurious result related to the small number of left-handed boys (n=17) or left-handed girls (n=10) enrolled; one of the weaknesses of this study. Other weaknesses include reliance on a covert version of a verb generation fMRI task that does not permit intra-scanner performance monitoring which could be used to co-vary for performance-related effects. Finally, collecting more detailed developmental histories could have detected minor prenatal or postnatal insults that may have been missed but which could have an effect on language lateralization and localization (Code, 1997; Searleman, 1977).

## 4. EXPERIMENTAL PROCEDURE

### 4.1. Subjects

Twenty-seven left-handed children, all with family history of sinistrality, were selected for the current analysis from a larger study of normal language development involving approximately 340 children between the ages of 5 and 18 (Holland et al., 2001; Holland et al., 2007; Karunanayaka et al., 2010; Karunanayaka et al., 2007). While some of the above mentioned and other studies of this cohort have also included these left-handed children, specific analyses contrasting language lateralization in the left- and right-handers have not been performed. Thus, to contrast the left-handers vis-à-vis right-handers, a group of 54 right-handed children was obtained by selecting two children of the same gender closest in age to each left-handed child from the larger group of participants. Two comparison right-handed subjects (one Right-Right and one Right-Left) for each left-handed subject were included in order to examine possible effects of familial handedness on language lateralization in left-handed children. For the first control group (the Right-Right group) we selected children with no history of familial sinistrality in a first degree relative; the selected children were the same sex and closest in birth date to each left-handed subject. In addition, a second age-matched group of 27 right-handed children with at least one left-handed first-degree relative (the Right-Left group) was selected from the larger group of participants. The age range in all three groups was from 5 to 18 years with an average age of 10.5 ± 3.4. There were 17 boys and 10 girls in each group. The children identified themselves as Caucasian (n = 72), African-American (n =5), Multi-Ethnic (2), Asian (n = 1), and Asian/European (n = 1). The mean Full Scale IQ (from the Wechsler Intelligence Scale for Children, Third Edition, Wechsler, 1994) for all groups was in the high average range and did not differ between the groups ($F(2,78) = 0.68$; $p > 0.05$). The left-handers had a mean Full Scale IQ of 111 (range 90–134); the Right-Right group had a mean Full Scale IQ of 115 (range 86 – 146) and the Right-Left group had a mean Full Scale IQ of 113 (range 87–147).

Handedness was determined by self-report (i.e., asking the child, “Are you right- or left-handed”) as well as by administering the Edinburgh Handedness Inventory (EHI; (Oldfield, 1971)). The mean EHI score for the Left group was −59; for the Right-Left group, it was 84; and for the Right-Right group, it was 86. There were no differences in personal handedness between left-handed boys EHI = −56.8 (SD = ±34.0; N = 15) and girls EHI = −61.3 (SD = ±37.0; N = 10); P = 0.76. History of familial handedness was obtained from parent (and/or child) at the time of the study visit; binary responses (Yes/No) were requested. Because of the non-significant difference between the EHI score for the two right-handed groups ($F(1,52) = 0.82$, NS) and the similarity in pattern and distribution on other measured variables including the fMRI measures (see Results section) we combined them for subsequent analysis. The EHI and self-report methods produced the same handedness classification in all cases. This analysis suggests that a simple dichotomous classification of handedness is adequate for the purpose of assigning subjects to two groups: left- and right-handers. However, for the purpose of examining correlations between handedness and other variables (e.g., language lateralization) the continuous data provided by EHI is preferred. Maximal occipito-frontal head circumference was measured manually in each subject using a flexible tape measure, encompassing the areas above the eyebrows, above the ears and around the back of the head. Mean and standard deviation of the head circumference did not differ between right and left handed groups (right-handers mean head circumference = 53.88 cm, SD = 2.3 cm, left-handers = 53.71 cm, SD = 2.0 cm; there is no difference between the two groups with p = 0.74).

All children were recruited via advertisement throughout the medical center as well as local television news programs (Byars et al., 2002; Holland et al., 2001) and flyers distributed throughout the Cincinnati community. Parents of potential participants underwent a brief screening interview over the telephone. Children who had a history of language or motor delay, neurologic or psychiatric illness, special education, or speech therapy were excluded from the study. All children spoke English as a first language. A five-category index of socioeconomic status (SES) was constructed based on median family income for the participant's 2000 US census tract (---, 2000). The majority of participants fell in the middle SES category; all five categories were equally represented in all handedness groups. All parents signed an informed consent form previously approved by the Institutional Review Board of the Cincinnati Children’s Hospital Medical Center; where appropriate, children gave assent.

### 4.2. Functional MRI Task

The verb generation task used in this study has been widely used to assess hemispheric dominance for language with PET and fMRI studies of children and adults (Petersen et al., 1988; Szaflarski et al., 2006b). We have used it extensively in our own investigations of trends in language development (Karunanayaka et al., 2007; Szaflarski et al., 2006a; Szaflarski et al., 2006b). This task involves the auditory presentation of a series of nouns. The subjects are required to silently generate as many verbs as possible associated with each noun, during a 5 second interval, similar to the implementation of the paradigm by Wise, et al. (Wise et al., 1991). For example, if the noun "ball" is presented, the participant might generate the verbs "throw," "kick," and "hit." The subjects are instructed to generate the verbs covertly in order to minimize the motion artifact associated with speech. Five 30-second blocks of nouns are interspersed with 30-second blocks of bilateral finger tapping. Children are instructed to touch each finger sequentially to the thumb of the same hand each time they hear a tone. Finger tapping rate is paced by a tone cue that occurs at a rate of once every five seconds. This task is used as a control for the auditory stimulation present in the verb generation task and for distracting the child from continuing to generate verbs during the control period. Furthermore, it creates a reference area of activation within the motor strip as an independent method of validating compliance with the task in the MRI scanner by providing motor activation as reference data for each child. Finger tapping typically produces discrete areas of activation in pre- and post-central sulcus and the motor homunculus and, therefore, is unlikely to overlap with those known to occur with verb generation tasks (Schapiro et al., 2004). Switching to an alternate, motor task effectively prevents children from continuing the verb task during these periods; motor activity is known to provide distraction during which continuous verbal processing is unlikely (Friedman et al., 1982; Kemper et al., 2003).

We began our data collection in 1999. At that time, our program and others beginning to use fMRI with children, designed tasks to minimize motion artifacts (Byars et al., 2002; Gaillard et al., 2000). Overt oral responses and button presses were initially thought to be too demanding for children as young as 5 years. Consequently, we chose to perform verb generation covertly and not to require response recording. The finger tapping sequences were monitored by closed circuit video and scans were terminated and repeated if subjects failed to perform the task consistently. This monitoring provided some assurance of task compliance. Although no in-scanner behavioral data were collected, verb generation performance was tested using a post-hoc test of memory for the nouns presented. This quiz consisted of a yes/no recognition test involving the 25 nouns and 25 distracters. Excellent age-independent performance on this post-scan recall task was previously reported elsewhere by our group (Chiu et al., 2006). The verb generation and finger tapping tasks were rehearsed prior to scanning to ensure that the child understood the requirements and children were not admitted to the scanner unless they were able to generate at least one verb per noun in the practice condition.

### 4.3. MRI Parameters

The scans were performed on a Bruker Biospec 30/60 MRI scanner based on a 60 cm, 3.0 Tesla magnet (Bruker Medizintechnik, Karlsruhe, Germany). A T2*-weighted, gradient-echo, EPI sequence was used for fMRI scans with the following parameters: TR/TE= 3000/38 msec, FOV = 25.6 × 25.6 cm, matrix = 64 × 64, slice thickness = 5mm. Twenty-four slices were acquired at 110 time points during the alternating 30 second periods of control and language stimulation for a total imaging time of 5 min. 30 sec. The initial 10 time points were discarded during post-processing to allow the protons to reach T1 relaxation equilibrium. In addition, a 3D MDEFT (Modified Driven Equilibrium Fourier Transform) whole brain scan was performed in an axial plane (Duewell et al., 1996; Ugurbil et al., 1999). Parameters for this scan are as follows: TR/TE/TI = 15.7/4.3/550 msec, FOV=19.2 × 25.6 × 16.0 cm, matrix = 256 × 192 × 128, total imaging time = 7 min. 20 sec, with a voxel size of 1×1.5×1.5 mm. A three-dimensional phase reference image was obtained prior to the EPI functional scans (Schmithorst et al., 2001). This phase map was used during reconstruction to correct simultaneously for Nyquist artifacts and geometrical distortion.

### 4.4. Data Analysis

Details of our fMRI processing methods have been previously reported (Holland et al., 2001; Holland et al., 2007; Karunanayaka et al., 2010). All fMRI data processing was done using Cincinnati Children's Hospital Image Processing Software (CCHIPS) developed in the IDL software environment (ITT Visual Information Solutions, Boulder, CO). A Hamming filter was applied to the raw EPI data prior to reconstruction to reduce the truncation artifacts at the edges of k-space and reduce high frequency noise in the images (Lowe and Sorenson, 1997).

**4.4.1. Motion Correction—**Functional MRI data from children are especially vulnerable to the effects of motion. In order to eliminate motion-contaminated frames we recently implemented an objective measure of motion during the functional task. The first step in this algorithm is co-registration of all frames to a reference frame generated based on median motion parameters (see below) using the pyramid co-registration algorithm (Thevenaz and Unser, 1998). This co-registration algorithm does not require external landmarks in our implementation in CCHIPS. In order to accomplish this, we computed an intensity-based cost function for every co-registered frame as follows:

$$\mathrm{Cost}_{\mathrm{ref},i}=\left(\sum(\mathrm{frame}_{\mathrm{ref}}-\mathrm{frame}_{i})^{2}\right)/\sum(\mathrm{frame}_{\mathrm{ref}})^{2}$$

where $\mathrm{frame}_{\mathrm{ref}}$ and $\mathrm{frame}_{i}$ are the signal intensity for the reference and the $i^{th}$ frame considered for co-registration. The frame with the lowest median cost value across all of the co-registered frames was chosen as the ideal frame for alignment. This cost function, which is the mean square deviation in signal intensity from that of the ideal frame, was used as an objective measure of motion for each subject. After co-registration with the optimal reference frame as described above, the value of the cost-function was below the set threshold of 0.005 (Szaflarski et al., 2006b), hence all frames from all subjects were retained for subsequent analyses.

Next, an affine spatial transformation was used with the brain rotated into AC–PC coordinate frame and then linearly scaled into the Talairach reference frame prior to statistical analyses (Talairach and Tournoux, 1988). We have previously shown that the Talairach coordinate frame provides an adequate reference frame for the co-registration of pediatric brain image data from multiple subjects over the age of 5 years (Wilke et al., 2002). Individual subject data were analyzed using the general linear model to identify voxels with a time course similar to the time course of stimulus presentation. Signal drift and respiratory and cardiac signals were accounted for by using a set of cosine basis functions as covariates. Z-score maps were computed from the results of this analysis.

**4.4.2. Regions of Interest used for Language Lateralization—**In order to generate frontal and temporo-parietal regions of interest (ROIs) related to language functions underlying the verb generation task, we performed independent component analysis (ICA) on the entire dataset (right and left-handed subjects combined; n = 81) using methods previously described (Karunanayaka et al., 2011a; Karunanayaka et al., 2011b). ICA is a data-driven method capable of investigating the spatial and temporal behavior of the network without *a priori* assumptions (McKeown et al., 1998). With this analysis, we generated multiple components of the language circuitry including one that corresponded to “component D”, previously described by us (Karunanayaka et al., 2010). This component encompasses left frontal (inferior and middle frontal gyri) and left temporo-parietal (left middle temporal and angular gyri and the left parietal lobule) regions and is highly left lateralized with a lateralization index of 1 (Figure 3). This independent component is thought to be responsible for semantic representation of the heard nouns, their mental manipulation in working memory and later generation of verbs associated with them (Karunanayaka et al., 2010). This component was selected for construction of two ROIs related to semantic language function supporting the covert verb generation used in this study.

The two ROIs constructed from the left lateralized language component described above are shown in Figure 3. The frontal ROI, anterior to the dashed line in Figure 3, included a large region that encompassed Broca’s area in the frontal lobe (spatial coordinates of the left frontal centroid are −36, 13, 24). The temporo-parietal ROI, posterior to the dashed line in Figure 3 encompassed the anterior and medio-lateral aspects of Wernicke’s area in the temporal lobe (spatial coordinates of the left temporal centroid are −38, −50, 23). These areas are considered critical for language in the classic models of language representation in cerebral cortex. Because we retained all active voxels within these areas, the frontal ROI included the entire inferior frontal gyrus (BA 44, 45, 47) and extended into additional dorsolateral prefrontal regions, including portions of the middle frontal gyrus (BA 46, 48, 49) and precentral gyrus (BA 46). The temporo-parietal ROI extended from the temporal plane (BA 41, 42) inferiorly through middle temporal gyrus to the margin of the inferior temporal gyrus (including portions of BA 22, 21, 37) but did not include posterior aspects of Wernicke’s area (BA 22, 39). ROIs for the right hemisphere homologues were established by reflecting the coordinates about the Y-axis (interhemispheric fissure). Figure 3 shows these two ROIs overlaid on the composite T1 grey-scale images in the axial plane with a dashed line demarcating the frontal and temporo-parietal ROIs.

**4.4.3. Lateralization Index—**A lateralization index (LI) was calculated for each subject based on the individual Z score maps. Only voxels with Z scores greater than or equal to the mean Z score within an ROI (left or right hemispheric) for each individual subject were used in the calculation of LIs (Szaflarski et al., 2006a; Szaflarski et al., 2006b). Counting activated voxels above a global threshold yields the least variability and most robust LI with immunity to outlying voxels with high statistical values (Wilke and Schmithorst, 2006). Pixels above this median z-score threshold were counted and a LI was defined as the difference in the number of activated voxels, summed independently for the left and right regions of interest, divided by the summed total of active voxels in the left and right regions of interest. This z-score threshold for the inclusion of voxels in the LI calculation typically falls between 2 and 2.5 which corresponds to the flat portion of the iterative curve in in the method proposed by Wilke and Lidzba in Figure 2 (left bottom panel) (Wilke and Lidzba, 2007). Laterality Index values close to “0” (i.e., $-0.1 \leq LI \leq 0.1$) define symmetric language distribution (Holland et al., 2001). A subject with $LI > 0.1$ is categorized as left dominant, while a subject with $LI < -0.1$ is categorized as right-side dominant (Eaton et al., 2008; Jacola et al., 2006; Karunanayaka et al., 2010; Szaflarski et al., 2011; Szaflarski et al., 2006a; Szaflarski et al., 2006b; Szaflarski et al., 2008; Tillema et al., 2008; Vannest et al., 2009; Yuan et al., 2006).

## Highlights

- 15% of left-handed children showed atypical language lateralization in the frontal regions
- 33% showed atypical language lateralization in the temporo-parietal regions
- left-hemispheric language lateralization increased with age
- increase in language lateralization with age was similar in left- and right-handed children

## Acknowledgments

This research was supported by R01 HD38578 to SKH and K23 NS45019 to AWB). Further support included K23 NS052468 and R01 NS048281 to JPS.

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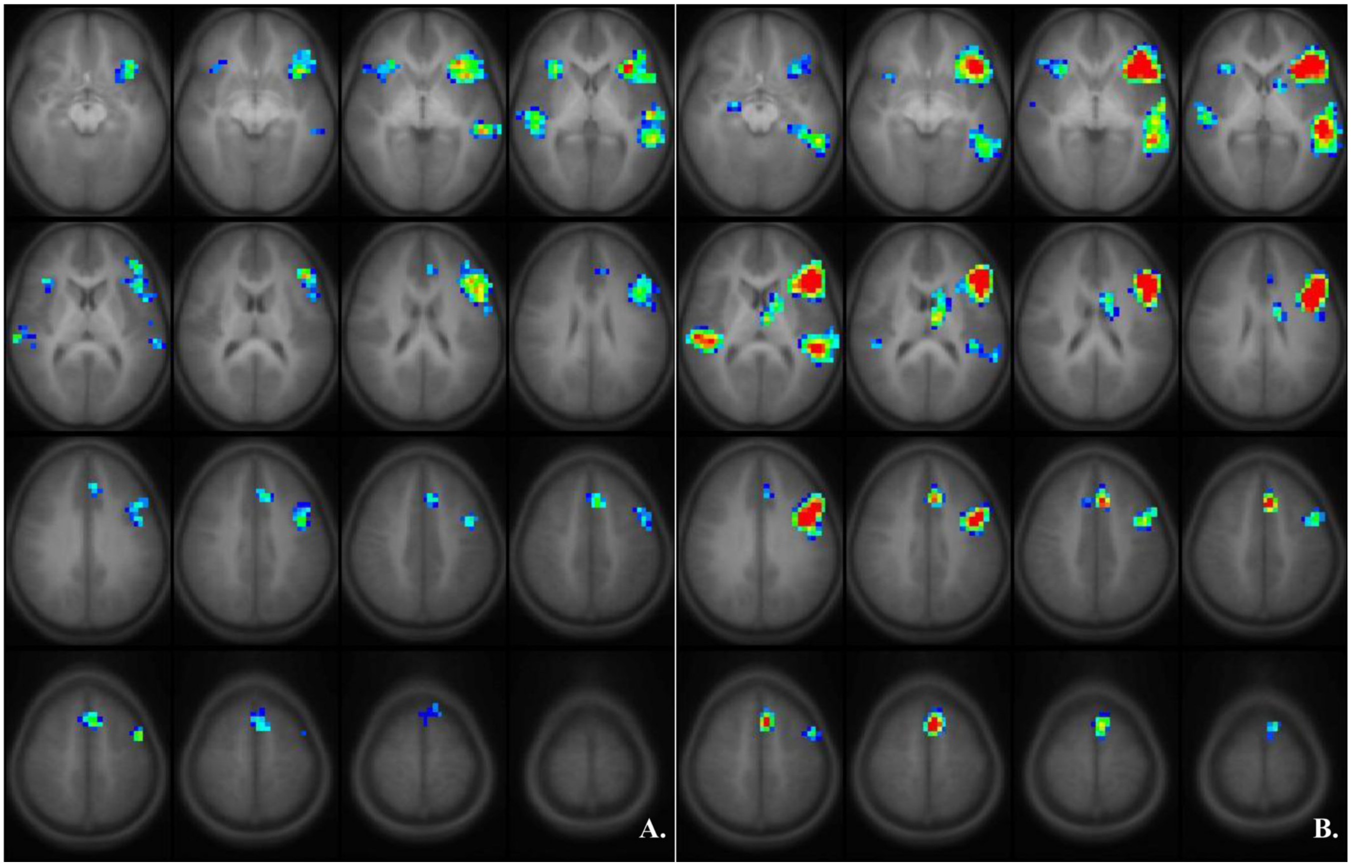

**Figure 1.**

Composite activation map for the verb generation task based on random effects analysis for all left-handed (A; N = 27) and right-handed (B; N = 54) subjects. Images are in radiologic convention with left in the brain corresponding to the right in the figure. These activation maps were generated using cluster size = 30; smoothing filter = 2 mm, corrected p-value <0.05. Higher intensity of activations in the right-handed children when compared to left-handed children are related to higher number of subjects included in the right-handed group.

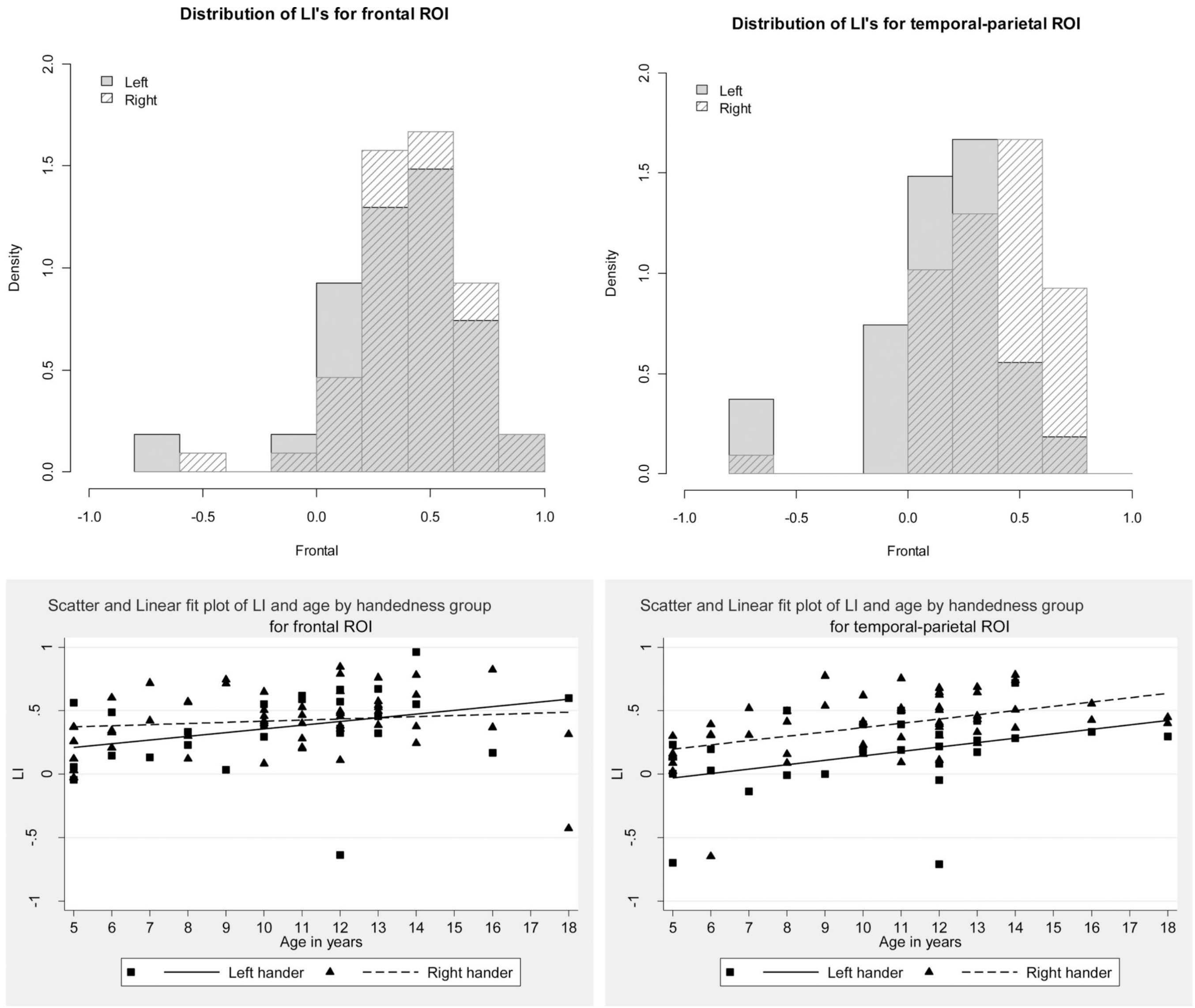

**Figure 2.**

Top: Distribution of LIs in the frontal and temporal-parietal ROI’s for right- and left-handed children. Bottom: Lateralization growth curves for the left- and right-handed children for the two ROI’s. Linear regression fits are shown along with individual lateralization index values of each subject by age.

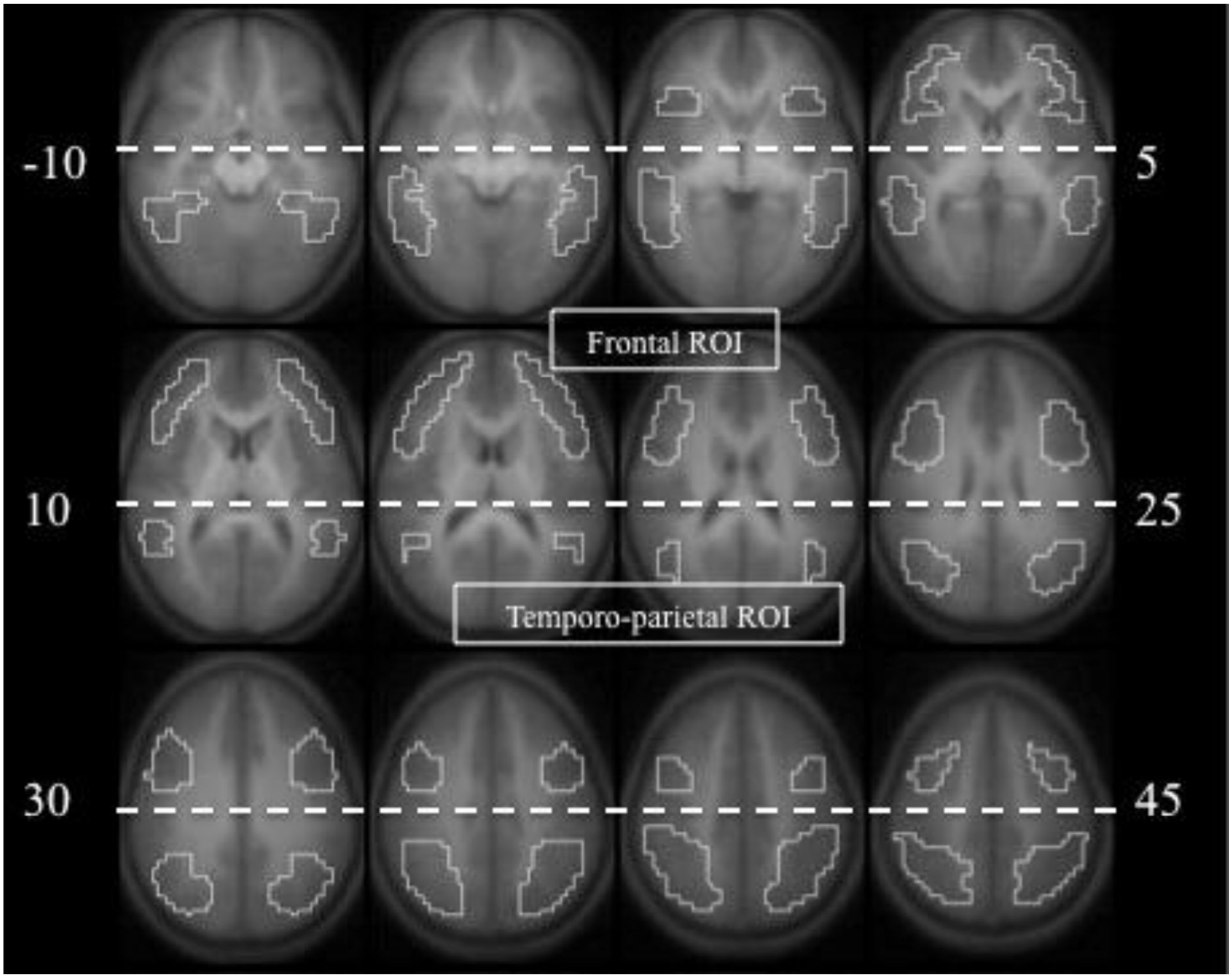

**Figure 3.**

Composite grey-scale T1 image showing regions of interest (ROI) used for computation of lateralization index (LI) for all subjects based on the results of ICA of all included subjects (N = 81). This region of interest is similar to the ICA "component D" described in our previous publication (Karunanayaka, Schmithorst et al. 2010). Spatial coordinates of the left frontal centroid are −36, 13, 24 and of the left temporal centroid −38, −50, 23; images are in radiologic convention with left in the brain corresponding to the right in the figure. Frontal lobe ROIs are shown anterior to the dashed white line and the temporo-parietal ROIs are shown posterior to the dashed line.