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Research report

Age-related language lateralization assessed by fMRI: The effects of sex and handedness

Rodolphe Nenert [a,*], Jane B. Allendorfer [a], Amber M. Martin [a], Christi Banks [c], Jennifer Vannest [c], Scott K. Holland [c], Jerzy P. Szaflarski [a,b]

[a] Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA
[c] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

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ABSTRACT

Previous studies focusing on the relationship between lateralization of language function and age suffer from lack of a balanced distribution of age and handedness among participants, especially in the extremes of age. This limits our understanding of the influence of these factors on lateralization of language circuitry. The hemispheric asymmetry reduction in older adults (HAROLD) model suggests that under similar circumstances, involvement in cognitive processes of prefrontal (and potentially other) cortical areas tends to be less lateralized with age. In this study, we aimed to investigate the link between age, gender, and language lateralization in a large group of healthy participants with a relatively even distribution of age and handedness in order to further test the HAROLD model. 99 healthy men (33 left-handed; age range 18–74 years) and 125 women (44 left-handed; age range 19–76) were recruited. All participants underwent fMRI at 3T with a semantic decision and a verb generation tasks and received a battery of linguistic tests. Lateralization indexes (LI) were calculated for each participant based on fMRI results for each task separately. LIs were found to be significantly decreasing with age only in right-handed men and only in temporo-parietal cortical area. LIs did not change with age in other brain regions or in left-handed subjects. Our results do not support the HAROLD model and suggest a potentially different relationship between aging and lateralization of language functions.

1. Introduction

Language is one of the most highly integrative functions of the human brain (Friederici, 2011). In 1876, Broca associated the occurrence of aphasia with a lesion within the left hemisphere in right-handed humans building the foundation for research on hemispheric localization and lateralization of language (Broca, 1876). The first years of non-invasive brain imaging research confirmed that language function has a strong bias toward left hemisphere, increasing from birth through emerging adulthood in both, left and right handed individuals (Pujol et al., 1999; Springer et al., 1999; Szaflarski et al., 2002). Mechanisms behind the functional lateralization of language have not yet been fully explained (Allendorfer et al., 2016; Mazoyer et al., 2014; Piervincenzi et al., 2016) though some theories propose that both hemispheres have equal potential to support language from birth and that emerging left hemisphere specialization suppresses right hemisphere participation in language function during early childhood (Finger et al., 2003). This theory is supported by studies of language function and lateralization in children with perinatal left hemisphere brain infarcts where the right hemisphere takes over the left-hemispheric language functions (Dick et al., 2013; Raja Beharelle et al., 2010; Tillema et al., 2008) crowding out the typically right-hemispheric functions (Gleissner et al., 2003; Yuan et al., 2006). Division of labor between hemispheres typically correlates with better performance (Donnelly et al., 2011; Jacobs, 1999; Kosslyn, 1987; Plaut and Behrmann, 2011), and cerebral lateralization has been shown to be affected by multiple developmental and pathological factors including personal and familial handedness, age, prematurity, perinatal stroke, epilepsy, TBI and other neurologic insults occurring during development indicating, at least partial, susceptibility of early developmental factors driving language lateralization (Corballis, 2009; Scheinost et al., 2015).

Before the advent of fMRI, language lateralization was thought to be deeply linked to handedness and gender (Annett, 1976). In a review of studies focused on linguistic tasks, Vigneau and

* Corresponding author at: Department of Neurology, 312 Civitan International Research Center, 1719 6th Avenue South, Birmingham, AL 35294-0021, USA.
E-mail address: rnenert@uabmc.edu (R. Nenert).

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colleagues showed that among right-handed humans a majority of studies report peaks of activity in the left hemisphere with lower participation from the right hemisphere (Vigneau et al., 2011). These authors have shown that activity in the right hemisphere during linguistic task was likely to be under the influence of the left hemisphere whereas the left hemisphere seemed to process information in an intra-hemispheric manner (Vigneau et al., 2011). In left-handed and ambidextrous humans, incidence of atypical language lateralization was found to be higher than in right-handed individuals (Knecht et al., 2000; Pujol et al., 1999; Szaflarski et al., 2012, 2002). Recent studies found that atypical language lateralization (i.e., symmetrical or right-lateralized) was present in about 10–12% of right-handers and 22–25% of non-right-handed individuals (Mazoyer et al., 2014; Allendorfer et al., 2016) which is somewhat lower than the data from previous lesional and epilepsy studies (Dewarrat et al., 2009; Pedersen et al., 1995; Rasmussen and Milner, 1977). Moreover, it has been shown that in adults language lateralization continues to evolve with age (Springer et al., 1999; Szaflarski et al., 2006). The relationship between sex and language lateralization, if present, also seems to be driven by age (Allendorfer et al., 2012b; Hirnstein et al., 2013; Szaflarski et al., 2012). The results of the previous studies are in agreement with the HAROLD (hemispheric asymmetry reduction in older adults) model with respect to language functions becoming less lateralized with increasing age (Cabeza, 2002). This model states that under similar circumstances, prefrontal activity during cognitive performance tends to be less lateralized in older adults when compared to younger adults, either reflecting a compensatory function or a dedifferentiation process (Cabeza, 2002). It was also suggested that HAROLD model could be generalized to other brain areas such as temporal and parietal areas based on early PET, fMRI and EEG results (Bellis et al., 2000; Elmo, 1987; Grady et al., 2002, 2000; Nelson et al., 1990). Many studies have shown that the aging brain maintains a certain level of neuro-functional plasticity (see Greenwood (2007) for a review), revealed by the recruitment of supplementary brain regions to maintain a satisfactory level of behavioral performance (Berlingeri et al., 2010; Cabeza, 2002). Among all the theoretical models that have been proposed in order to summarize these effects (Grady, 2008) the HAROLD model remains one of the most popular. However, the accuracy of this model has been challenged by some studies (Berlingeri et al., 2013). Using the functional disruption capability of rTMS, Rossi and colleagues were able to demonstrate a "HAROLD effect" (a decrease in behavioral performance regardless which side of the frontal lobe was inhibited) but only during the recall phase of the memory task they used (Rossi et al., 2004). The presence of a "HAROLD effect" during the encoding phase of a memory task was later confirmed but only in well-performing elderly participants (Manenti et al., 2011). Interestingly a contradictory result was found in a fMRI study (Duverne et al., 2009) that observed a "HAROLD effect" also during the encoding phase of a memory task but only in elderly participants who performed poorly, suggesting that the observed reduction in brain functional asymmetry may not necessarily be reflecting a compensatory mechanism and other possible effects driving the lateralization changes with age need to be considered. The observed discrepancies between the studies could be related to differences not only in methodology but also be due to variability in the included participants such as lack of large sample sizes with a homogeneous distribution of age and handedness among participants. In this study, we aimed to investigate the link between age, sex, and language lateralization in a large group of left- and right-handed participants and with wide range of age distribution in order to further test the HAROLD model of cerebral lateralization. The hypothesis guiding this research, based on the literature discussed above, was that consistent with the HAROLD model we would observe decreasing language lateralization with age on both fMRI tasks with decreasing activation in the dominant and increasing activation in the non-dominant language regions.

2. Results

2.1. Behavioral results

Pre-scanning, within scanner and post-scanning behavioral performance is reported in Table 2. Overall, participants performed within the range of standard scores expected for healthy participants confirming representative nature of the enrolled participants.

2.2. FMRI results

FMRI results for both tasks are depicted in Fig. 2. Results are very similar to those obtained with the same tasks in previous studies using different cohorts (Allendorfer et al., 2012a,b, Szaflarski et al., 2012, 2006, 2002). Main areas of activation include frontal inferior (Broca's area) and, superior temporal gyri, cerebellum, angular gyrus and cingulate gyrus.

2.3. Task-related lateralization index (LI) results

LIs were computed for each participant, each fMRI task, and each region of interest. Percentage of atypical (positive value for cerebellum and negative value for every other region of interest) LIs for each region of interest and each fMRI task in men, women, right-handed, and left-handed participants is provided in Table 3. For both fMRI tasks, the proportion of atypical LIs is similar in men compared to women in all ROIs: ~20% for cerebellum and between 10 and 15% for all other region of interests (Chi-square tests were computed to compare proportions of atypical LI between men and women with all p values >0.5). In contrast to this finding, a clear difference in the proportion of atypical LIs can be observed between right-handed and left-handed participants except for cerebellum; that proportion is consistently higher for the left-handed group. As expected, the proportion of atypical LIs is between 5 and 7% for the right-handed participants (16–20% for cerebellum) and between 20 and 25% for participants with atypical handedness. For cerebellum, for both groups the atypical lateralization occurred in ~20% of participants. Chi-square tests were performed to compare proportion of atypical LI between left handed and right handed participants with all p values <0.001 except for cerebellum where p = 0.19. Results of direct comparison (two-sample t-tests) of LI values for the same groups are provided in Table 4. No significant differences were found between men and women, for both fMRI tasks and all region of interest. LI values were significantly different between right-handed participants and participants with atypical handedness except for temporo-parietal and cerebellar regions of interest examined with the verb generation task. However, even in these 2 regions, the direction of the difference was in the expected direction indicating that the results of LI examination were typical (similar hemisphere dominance) of the results observed in previous studies addressing this question (Griffis et al., 2015; Mazoyer et al., 2014; Pujol et al., 1999; Springer et al., 1999; Szaflarski et al., 2012, 2006, 2002).

Next, we investigated the relationship between LI and age among participants. To accomplish this, curve fit estimations were computed using SPSS 24 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY) between LI values obtained for each participant, each fMRI task, and each region of interest. Participants were divided into subgroups corresponding to their handedness and gender. Previous study found that relation between LI and age