Revista médica del
Hospital General de México

PERMANYER

Check for updates

ORIGINAL ARTICLE

Educational level and task performance influence on lexical access lateralization changes in healthy aging

Avril J. Nuche-Bricaire[1,2], David Trejo-Martinez[2], Nadia González-García[3], Oscar Contreras-Lizardo[2], José Marcos-Ortega[2], Ana I. Ansaldo[4], Luis González-Gómez[2], Elí Mendoza-Alavez[2] and Juan Silva-Pereyra[1]*

[1]Neuroscience Project, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla, Mexico; [2]Magnetic Resonance Imaging and Neurolinguistics Department, Hospital General de México "Dr. Eduardo Liceaga," Mexico City, Mexico; [3]Neuroscience Laboratory, Hospital Infantil "Dr. Federico Gómez," Mexico City, Mexico; [4]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montreal, Canada

Abstract

Hemispheric asymmetry reduction in older adults (HAROLD) model has claimed that older adults tend to display less lateralized brain activation patterns with respect to younger ones during memory, language, and naming tasks, but only a few times have these patterns been explored within older population. Furthermore, it is unclear if this phenomenon is a compensation response or an adaptive pattern that is not helping cognitive functions. Literature has assumed that education level (EL) could be critical, to explain such patterns. We aimed to control this as a variable by comparing neural correlates with an functional magnetic resonance imaging picture naming task in literate, healthy older adults with high and low EL. Our results showed that EL is not a determinant factor for activation of neural pattern reorganization prognosis. It was found that performance is a more reliable variable to observe neural pattern reorganization in the elderly. This study supports the de-differentiation hypothesis of HAROLD model because there is no reduction in lateralization of some highly-specialized structures in persons who maintained optimal lexical access, in contrast to those who had low scores in naming task.

Key words: *Functional magnetic resonance imaging. Hemispheric asymmetry reduction in older adults model. Educational level. Naming. Cognitive reserve.*

Introduction

High educational level (HEL) seems to have an impact for slowing down cognitive degeneration in dementia cases by generating some sort of cognitive reserve[1-5]. EL has been defined as a factor involved in word retrieval performance assessed by the Boston naming test[6-9]. In the aging process, differences in EL could be significant in terms of cognitive activity and brain compensation capacity[10-13]. In contrast, a lower EL (LEL) has been associated with faster decline of memory, mental state, and verbal ability[14,15].

The hemispheric asymmetry reduction in older adults (HAROLD) model[16] attempts to explain changes in neural activation patterns found in older adults. This model proposes that the reduction in hemispheric lateralization is "reflective of a general aging phenomenon more than a task-specific occurrence"[16]. This reduction is visible when we compare activation in young adults with that of older adults during different tasks of working and verbal memory.

Following the HAROLD model, Springer et al.[17] undertook a functional magnetic resonance imaging

Correspondence:
Avril J. Nuche-Bricaire
E-mail: avrilnuche@gmail.com

Date of reception: 10-04-2018
Date of acceptance: 16-07-2018
DOI: 10.24875/HGMX.M19000009

Available online: 21-03-2019
Rev Med Hosp Gen Mex. 2019;82(1):22-32
www.hospitalgeneral.mx

(fMRI) study comparing lateralization activity changes with age during a verbal episodic memory task. They came to the conclusion that older adults recruit more bilateral resources from prefrontal cortex as their EL rises. Similar to what has been observed in memory function, word retrieval efficiency also tends to decline with aging[18-22]. In a fMRI study, Wierenga et al.[23] compared activation during a naming task between younger and older adults, controlling 15 years of schooling for both groups. Their results support the HAROLD model as the group of older adults showed more bilateral activations. The older group displayed more activation of the homolog Broca's area, which is extended up to the right inferior frontal gyrus (IFG BA 47), right superior temporal gyrus (STG), and right insula and left lingual gyrus. Left IFG is considered strategical for the "semantic working memory system," in charge of manipulating and monitoring retrieval, and maintaining semantic representations stored in temporal semantic cortices[24]. The authors discuss that difficulty for lexical access in elders could be due to frontal atrophy that could generate a compensatory mechanism recruiting a larger frontal network and increasing activity in right hemisphere but not necessarily beneficial for efficacy and performance.

However, HAROLD phenomenon has been mostly studied by comparing activity between young and older adults, and until now just a few studies have compared activation between two groups of older adults with different biological and sociocultural characteristics[10, 25,26]. In addition, researchers still need to confirm the origin of this phenomenon. Cabeza[16] conceives it as an effect resulting from two possible causes: on the one hand, it could be a compensatory effect due to neural tissue loss in some areas of prefrontal cortex. In this case, activation increased in homolog structures could help to preserve the efficiency of cognitive functions[2]. On the other hand, this effect could result from a "dedifferentiation" effect in which the dominant hemisphere would lose its capacity to inhibit the other without actually contributing to function efficiency or even hampering its process.

Nevertheless, to the best of our knowledge, there are no studies that specifically analyze the effects of EL on the functional activation patterns in lexical access tasks among the older adult population. Using the HAROLD model, we have two aims for the present study: (1) measure lateralization neural patterns in healthy older adults with HEL and LEL during a picture-naming task and (2) test the compensation/de-differentiation hypothesis about functions of age-related asymmetry reductions by analyzing performance in a behavioral task in association with lateralization neural patterns.

Specifically, we predicted differences between EL groups, and these could rely on the semantic working memory system: IFG (BA 47) and temporal anterior cortices as a reflection of more and better strategies of people with HEL.

With respect to our second aim, high performers (Hi-P) and low performers (Low-P) would show different patterns of activation. Specifically, if hemispheric asymmetry reduction was present in Hi-P group, we would have an adaptive process of functional cognitive compensation; however, if these activation patterns appeared in low-performance group, then we would have a phenomenon that might imply functional disorganization or a disinhibition process creating interference in task performance efficiency.

Methods

Participants

Volunteers were accepted if they do not present hypertension or cardiovascular and thyroid diseases so hypertension would not be a factor of alteration in BOLD effect[25,27]. To confirm normal cognitive state, a neuropsychological profile was elaborated for each volunteer (PIEN "Test-Barcelona")[28]. 28 older adults, Spanish native-speakers, and right-handed were accepted for the study. HEL group n = 13 (7 females, mean age = 63.6 years, and mean schooling = 18.4 years). LEL group n = 15 (10 females, mean age = 65.5, and mean schooling = 6 years). All participants were informed about their rights and signed an informed consent letter elaborated following the standards of the Hospital General de México's Ethics Committee. Patients received only their neuropsychological and MRI structural results. This study has been supported by Research General Management at México´s General Hospital with register No. DI/11/403/04/126 and UNAM register No. PAPIIT IN200817.

Procedure

fMRI naming task

Every participant was presented 120 images (45 described actions, 45 objects, and 45 were control condition). Each image was shown for 2500 ms randomly ordered in each presentation, inter-stimuli intervals were programmed randomly from 4400 to 8800 ms.

Task was programmed using E-prime 2 Software, length about 13 min.

Experimental condition

Participants were asked to state aloud the name of the object or action that they were watching. All images were black and white drawings taken from the International Picture-Naming Project (http://crl.ucsd.edu/experiments/ipnp/) and selected for Spanish language. In the same way, use frequency and capacity of stimuli were considered, for HEL group 15% of stimuli were changed for other less frequent.

Control condition

To subtract the visual and articulatory activations corresponding to lexical retrieval, the same images used for the experimental condition were distorted for the control condition. Participants were asked not to try to figure out its shape but utter the pseudoword "LOLE."

Recording of answers in fMRI task

Loud answers were monitored *in situ* and recorded using the Sound Forge Pro10 Software (Sony Creative Software Inc.) for its analysis out of line. For recording inside MRI, a non-metallic extension cord for the microphone was designed.

Training sessions

They took place during the neuropsychological interview. Each subject was presented with 200 images different from the ones shown in the experimental session to avoid learning effect. Participants were asked to answer aloud to confirm that they understood the task and that they were capable of perceiving and understanding the images.

Answer onset time analysis

Overt answers during the fMRI session were analyzed taking the beginning of the first audio wave form of every overt answer (speech) and subtracting 200 ms, considered as the time for articulatory codification process, to analyze the moment for lexical access only, following the Jescheniak et al.[29] model of speech production. We considered this time as an onset for SPM analysis.

Assessment of the compensation-dedifferentiation hypothesis of the HAROLD model

Regarding our second objective, we reorganized data in terms of Hi-P and Low-P. The median of correct answers for the whole sample was defined (86.1% = 78 images correctly named out of 90). We obtained two groups: below median (from 68 to 78 correct answers) and surpass the median score (from 79 to 88 correct answers). Low-performance group (n = 10) was composed of 4 HEL and 6 LEL individuals. Hi-P group (n = 18) was integrated by 9 subjects with HEL and 9 with LELs.

Mistake classification

We considered as errors the lack of answer (omission), the occasions when the uttered word had no relation with the object, or when the answers were not verbs in the case of action-related images.

fMRI acquisition

T1-weighted gradient echo pulse sequence anatomical images (TR = 4000 ms, TE = 106 ms, FOV 230 mm, flip angle = 90°, and voxel size $0.7 \times 0.7 \times 5$ mm^3) and functional images (EPI sequence: data matrix: 64×64; FOV 192 mm^2; TE 50 ms; TR 3800 ms) were obtained from a 1.5 T Siemens Avanto system equipped with a standard head coil. Functional T1-weighted images were collected covering the entire brain continuously, acquiring 36 interleaved slices (3 mm thick), and parallel to the anterior-posterior commissural plane (voxel size 3 mm^3).

fMRI preprocessing

Functional data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; see http://www.fil.ion.ucl.ac.uk/spm) following the standard procedure. Briefly, functional images for each subject were corrected for differences in slice acquisition times referring to the slices mean; realigned to correct head movement; spatially normalized to the stereotaxic space of Talairach and Tournoux using the Montreal Neurological Institute space[30]; and smoothed using an isotropic 8 mm FWHM Gaussian kernel.

fMRI analysis

Bold events for each word type (verbs, nouns, and control response) were modeled as pseudodelta functions coinciding with the stimulus onset and convolved with the synthetic hemodynamic response function. Brain responses associated with each experimental condition were estimated according to the general linear model for an event-related design at each voxel. Only correct trials were modeled to identify brain regions involved in successful naming (see mistake classification above). In the first level analysis, T-statistical parametric maps for every voxel were obtained for each subject (intra-subject effects) by applying linear contrasts to the parameter estimations for the events of interest (fixed effects). Subsequently, in a second level analysis, between-subjects activations were calculated for each condition (intragroup and between groups) by employing a two-sample *t*-test (random effects). Signals from cluster maxima ($p = 0.001$ K threshold superior to 10 voxels) were extracted, activation maxima refer to the Talairach space[32]. To correct multiple comparisons and to control for false positives and false negatives too, we applied the non-parametric morphology-based hypothesis testing (MBHT)[31], this procedure makes possible to detect moderate activation level regions, whose cannot be detected by conventional approaches, such as Family Wise Error (FWE) or High Dynamic Range (HDR), but which are spatially extensive, by explicitly relating the magnitude of the signal in each voxel to that of its neighbors[31].

Results

Behavioral results

Participants' performance was analyzed with a two-way ANOVA, which included the two groups (HEL and LEL) as the "inter-subject" factor and the image type (objects or actions) as the "intra-subject" factor. This analysis did not show any significant differences by group ($F < 1$), neither by the effect of interacting with the type of image (object, action or control type) ($F < 1$).

Statistical parametric mapping results

To compare word type activation patterns, correct answers to object images were called "nouns" and correct answers to action images were called "verbs." A third category called "words" included "nouns + verbs." This was created for contrast analysis to analyze whole lexical access function.

EL

Activation within each group

Comparison inside HEL group did not show significant differences ($p < 0.001$) in any of the three contrasts (words, verbs, or nouns > control). Comparison within LEL group presented significant activation for words > control condition in right postcentral gyrus (BA 1), as well as in left posterior tail of caudate nucleus and left cingulate gyrus (BA 31) (Fig. 1). Only the latter showed significant results for the correction test of multiple comparisons ($p < 0.054$). Results for all significant activations are exposed on table 1. Verbs > control and nouns > control contrast did not show any significant differences within the LEL group either.

Comparison between groups

Significant activations for words > control condition (HEL > LEL) occurred in the right anterior cingulate gyrus (BA 24). Then, for the opposite contrast LEL > HEL (words > control condition) significant activations appeared in paracentral gyrus (BA 3,4). However, none of these activations reached the threshold of relevance for the multiple contrast correction testing (MBHT).

The verbs condition did not show significant activations in any of the tested contrasts, not even if the significance threshold was lowered to $p < 0.005$. Likewise, when comparing nouns > control condition (HEL > LEL), no significant activations were found. The opposite contrast, LEL > HEL, did show significant activations in the superior parietal (BA 7) and the bilateral precuneus (Table 1), even though none of them successfully passed the MBHT correction testing.

Task performance

Regarding our second objective, participants' data were reorganized according to their performance in the naming task: Hi-P and Low-P groups, regardless of their EL. We took into account the same first level analysis for each subject.

Activation within each group (Table 2)

For words > control contrast, Hi-P group showed significant activations in the thalamus, as well as in the right temporal transversal gyrus (BA 41), and the left cerebellum culmen (Fig. 2). Temporal gyrus and left cerebellum maintain significativeness on MBHT correction. Low-P group did not show any significant differences in this contrast. For the verbs > control condition (Table 2), Hi-P group showed significant activations in regions of the left claustrum, but this could not surpass the MBHT correction. Low-P group showed activation

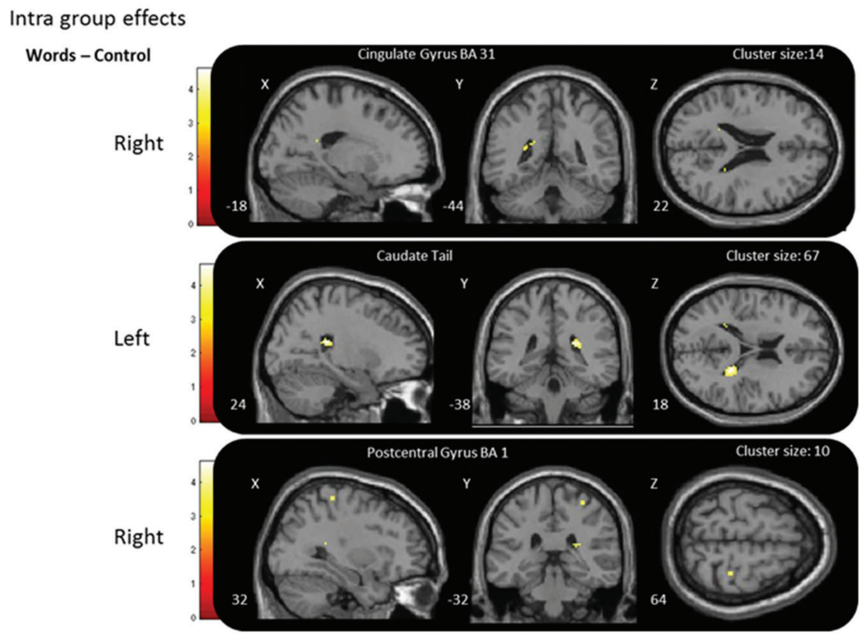

Figure 1. Parametrical statistical maps of regions significant activation during a picture naming task, when comparing the word condition within the low educational level group. Note the only significant activation that surpassed non parametrical correction for multiple comparisons (MBHT) was left cingulate Gyrus (BA 31). (The color scale shows the values of the t test). Maps were analyzed below the threshold of $p < 0.001$ and were corrected to avoid the multiple comparison mistakes, according the morphology based hypothesis test (MBHT) with a significance of $p < 0.05$.

Table 1. EL significant statistical parametric activations for the EL groups

Group	Contrast	Hemisphere	Brain region	Talairach coordinates (X/Y/Z)	Cluster size	Z score (peak voxel)	MBHT (independent *t*-test)
LEL	Words-CTRL	Left	Cingulate gyrus (BA31)	-18/-44/-22	14	3.15	0.054*
LEL	Words-CTRL	Right	Caudate tail	24/-38/-18	67	3.99	0.127
LEL	Words-CTRL	Right	Post central gyrus (BA1)	32/-32/-64	10	3.27	0.211
HEL-LEL	Words-CTRL	Right	Cingulate Gyrus (BA24)	12/-2/-30	11	3.48	0.141
LEL-HEL	Words-CTRL	Right	Postcentral Gyrus (BA3)	30/-32/-62	29	3.52	0.133
LEL-HEL	Words-CTRL	Right	Precentral Gyrus (BA4)	36/-24/-58	29	3.24	0.276
LEL-HEL	Nouns-CTRL	Left	Precuneus	-28/-70/-50	51	3.56	0.11
LEL-HEL	Nouns-CTRL	Right	Precuneus	2/-54/-52	74	3.91	0.139
LEL-HEL	Nouns-CTRL	left	Superior Parietal (BA7)	-18/-56/-60	21	3.32	0.204
LEL-HEL	Nouns-CTRL	Right	Superior Parietal (BA7)	40/-62/-48	25	3.33	0.094

All regions presented are significant at $p < 0.001$ uncorrected from SPM8. Even when we can observe a bilateral distribution for neural activity between groups, non-parametric correction for multiple comparisons (MBHT) keep left cingulate gyrus (AB 31) as the only significant activation within LEL group. LEL: Low educational level, HEL: High educational level.

of the caudate nucleus, and this one did reach statistical significance after being corrected (Fig. 2).

Regarding nouns > control contrast, Hi-P group showed significant activations in the right transversal temporal gyrus (BA 41), as well as in the left fusiform gyrus (BA 37) and cerebellum culmen, none of these three activations surpassed MBHT correction. Within the Low-P group, no differences for nouns > control condition were found.

Table 2. Task performance (intragroup effects)

Group	Contrast	Hemisphere	Brain region	Talairach coordinates (X/Y/Z)	Cluster size	Z score (peak voxel)	MBHT (independent t-test)
Hi-P	Words - CTRL	Right	Thalamus	4/-4/-6	15	3.66	0.724
Hi-P	Words - CTRL	Right	Transverse temporal gyrus (BA41)	34/-34/-12	22	3.47	0.051*
Hi-P	Words-CTRL	left	Cerebellum culmen	0/-40/-0	21	3.42	0.038*
Hi-P	Verbs - CTRL	Left	Claustrum	-22/-18/-18	30	4.03	0.229
Low-P	Verbs - CTRL	Left	Caudate nucleus	-20/-18/-22	16	3.67	0.000
Hi-P	Nouns - CTRL	Right	Transverse temporal gyrus (BA41)	34/-34/-12	22	3.47	0.801
Hi-P	Nouns - CTRL	Left	Fusiform gyrus (BA37)	-42/-52/-10	29	3.79	0.294
Hi-P	Nouns - CTRL	Left	Cerebelum culmen	0/-40/-0	21	3.42	0.845

Statistical parametric activations for task performance groups (within group effects) uncorrected. We show with an asterisk the activations that remain significative after MBHT correction for multiple comparisons, which is transverse temporal gyrus and left cerebellum culmen for words contrast within Hi-P group; and Caudate nucleus for verbs contrast within Low-P group. All regions presented are significant at $p < 0.001$ uncorrected; MBHT (independent t-test) = MBHT for multiple comparisons correction (methods section). MBHT: morphologic-based hypothesis test, Hi-P: high performers, Low-P: low performers.

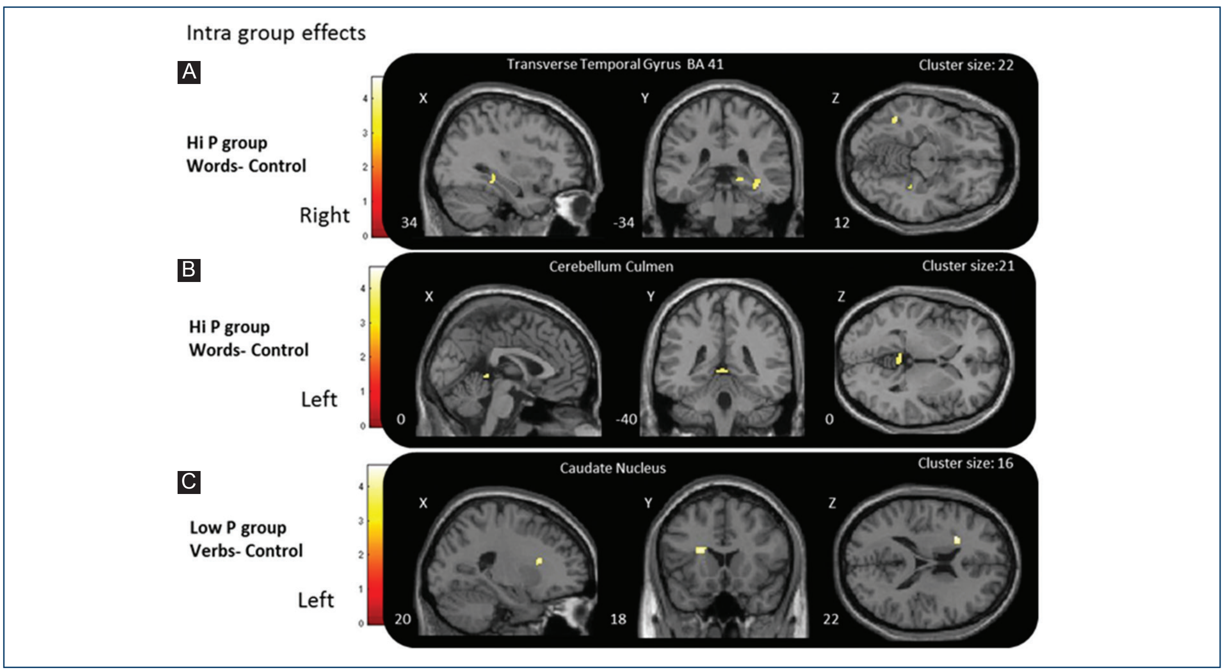

Figure 2. Parametric statistical maps of regions showing significant activations during a naming task. Activations within each group- high and low performance-are compared: **(A and B)** Activations within the high performance group (HI-P) for the Words contrast. **(C)** Significant activations within the low performance group (Low-P) for the Verbs condition. Significance threshold at $p < 0.001$ and they are corrected according to the Morphology Based Hypothesis testing (MBHT) $p < 0.05$.

Comparison between groups (Table 3)

For the words > control contrast, Hi-P > Low-P activity was shown in the right STG (BA 22), left IFG (BA 47), and left medial temporal gyrus (BA 21). Right BA 47, as well as AB 22, kept their significance after the MBHT correction (Fig. 3). Low-P > Hi-P contrast did not present any significant activation for words > control condition. For the verbs > control condition (Table 3), Low-P > Hi-P contrast showed significant clusters in the right precentral gyrus (BA 6) and frontal medial gyrus (BA 8), this last zone kept its significance after MBHT correction (Fig. 3).

Table 3. Task performance (between groups effects) statistical parametric activations for task performance groups (between-group effects) uncorrected

Group	Contrast	Hemisphere	Brain region	Talairach coordinates (X/Y/Z)	Cluster size	Z score (peak voxel)	MBHT (independent t-test)
Hi-P - Low-P	Words-CTRL	Right	STG (BA22)	60/-4/-6	15	3.61	0.132
Hi-P - Low-P	Words-CTRL	Left	Medial temporal gyrus (BA21)	-56/-14/-10	61	3.9	0.138
Hi-P - Low-P	Words-CTRL	Left	IFG (BA47)	-40/-26/-2	19	3.82	0.03**
Low-P - Hi-P	Verbs-CTRL	Right	Precentral gyrus (BA6)	44/-16/-26	28	4.23	0.244
Low-P - Hi-P	Verbs-CTRL	Right	Medial frontal gyrus (BA8)	14/-30/-38	14	3.66	0.005***
Hi-P - Low-P	Verbs-CTRL	Left	IFG (BA47)	-40/-26/-2	70	4.37	0.928
Hi-P - Low-P	Verbs-CTRL	Left	Middle temporal gyrus (BA21)	-54/-16/-10	57	4.94	0.738
Hi-P - Low-P	Verbs-CTRL	Right	Middle temporal gyrus (BA22)	60/-4/-8	25	4.3	0.006***

We show with an asterisk the activations that remain significative after MBHT correction for multiple comparisons. That is, left IFG for the Hi-P<Low-P contrast (words); right medial frontal gyrus for the Low-P>Hi-P contrast (verbs); and right middle temporal lobe for Hi-P<Low-P contrast (verbs). All regions presented are significant at $p < 0.001$ uncorrected; MBHT (independent t-test) = MBHT for multiple comparisons correction, MBHT: morphologic-based hypothesis test, IFG: inferior frontal gyrus, Hi-P: high performers, Low-P: low performers.

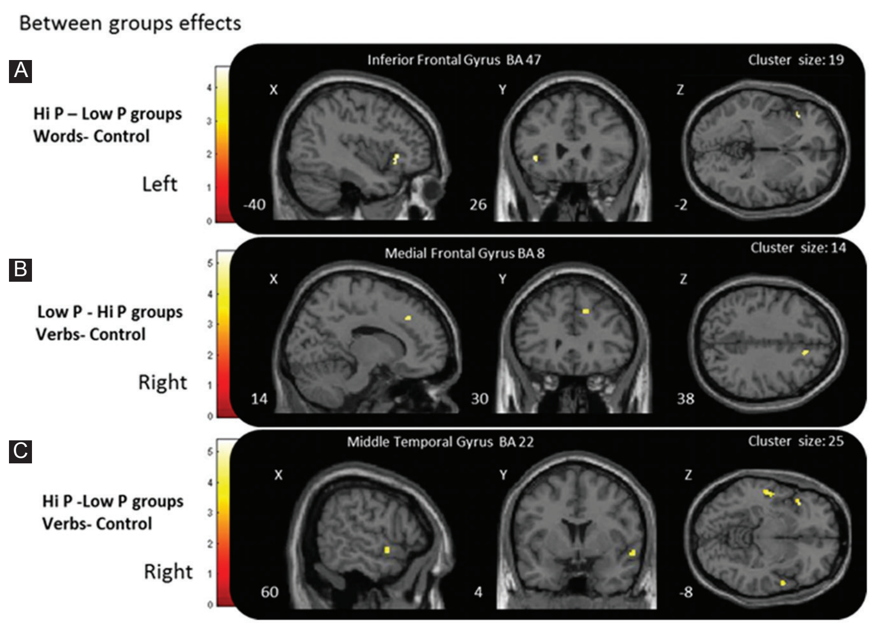

Figure 3. Statistical maps for regions showing significant activations during overt naming task, for comparing fMRI task performance between Low and High performance groups (color scale represent t values). (A) High performance group (Hi-P) < Low Performance group activations for Verbs < control condition Hi-P activations for Verbs < Ctrl condition. **(B)** Low performance group (Low P) < High Performance group activations for Verbs < control condition. **(C)** High Performance group (Hi P) < Low Performance group for Verbs < control condition. Maps are thresholded at p < 0.001 and corrected by the Morphology Based Hypothesis Test (MBHT) at p < 0.005.

On the opposite contrast (Hi-P **>** Low-P**)**, activations were present in right STG (BA 22), as well as in left medial temporal lobe (BA 21) and left IFG (AB 47). MBHT correction only allowed significance for the right STG (BA 22) (Fig. 3). For the nouns > control condition, SPM did not show significant activations in any contrast.

Discussion

The first objective of this study was to analyze the effect of EL on brain activation patterns during lexical access in healthy elderly, that is to say, whether EL had direct repercussions on brain lateralization reorganizing trough aging. Brain metabolic activation was measured in older adults with HEL and LEL during a picture-naming task. Following the HAROLD model, our hypothesis assumed that there would be less lateralization in people with HELs compared to the LEL group. We also expected to find differences between both groups in areas such as the IFG (BA 47) and the anterior temporal cortex as a result of better and more numerous working memory strategies employed by people with HELs.

Our results showed that both groups of healthy older adults - without cardiovascular diseases or hypertension - different only for their number of regular schooling years show no differences in their brain lateralization patterns when compared to one another. We observed only one structure where differences are significant within the LEL group, corresponding to the left posterior cingulate gyrus (BA 31). These activations are interesting because they are consistent with those found in studies carried out in illiterate people and individuals with LEL.[33-37] Castro-Caldas et al.[38] as well as Petersson et al.[15] showed differences in areas of the posterior cingulate cortex, as well as in areas of the splenium of the corpus callosum and the inferior parietal cortex[15]. In the same way, when Springer et al.[17], analyzed different ELs, they found differences in the activation of the right posterior cingulate cortex and the temporoparietal region. The posterior cingulate gyrus (BA 31) is one of the structures more consistently active during tasks involving the semantic system[39]. The posterior cingulate cortex, as well as the cortex adjacent to splenium of the corpus callosum, has strong connections with the hippocampus through the cingulate bundle[40]. The posterior cingulate cortex could be acting as an interface between semantic retrieval and the episodic codification systems. In this sense, our results support the hypothesis that people with a LEL could be showing how they have preferred a lexical access route based on semantic representations and episodic memory to assure its efficiency[14]. These results could describe that people who have had only a few years of training in a schooling system could be developing many other strategies to link semantic representations and their lexical tags; however, we cannot certainly say that those results would be related to any alteration of the hemispheric dominance of language functions. That is to say that having few schooling years during childhood is not, in any way, a factor which would condemn cognitive functions in aging; neither has it seemed to determine changes on functional lateralization of language.

Nevertheless, the sample size was a limitation for our study. Possibly, if it would have been larger, we could have obtained statistical significance in activation areas that did not pass the multiple comparison correction. Nonetheless, it is important to insist on our variable control: stimuli were balanced in terms of frequency for EL, and participants were selected according to their cardiovascular health, to control for physiological as well as cognitive variables for isolating, as much as possible, the experimental variable. These results allow us to discuss and reconsidering the EL as a trustworthy variable. Nevertheless, years of schooling are an extremely wide concept and could fail to define cognitive development, academic progress, quantity, and quality of information storage. Besides, there is the blood supply variable; this could be much more significant to preserve brain tissue avoiding the reduction of asymmetry; however, more studies in this field could clarify this question. Finally, when considering task performance regardless EL, our results show a larger number of significantly active regions. This finding, alone, suggests that EL as a variable, defined just as a number of schooling years at developmental age does not allow us to observe differential effects in naming tasks for elders. Thus, we show that task performance is a more reliable and valid measure to build hypotheses that may provide helpful data for finding the factors that contribute to a successful aging process.

Our second goal was to evaluate the compensation/de-differentiation hypothesis associated with the asymmetry reduction in elderly. We assumed that if this lack of lateralization had a beneficial function, it would then appear in the group showing better performance, or on the contrary, if such reduction was a response without an adaptive benefit to face the aging process, then it should appear in the group presenting a larger number of mistakes. For this reason, participants' results were regrouped following their number of mistakes on the naming task, regardless of their EL. Our results show that the Hi-P group has significant activity in right temporal gyrus (BA 41), as well as in cerebellum culmen with a left side tendency. It is interesting to notice that the right cerebellum has been reported as being a structure with significant activity in different language tasks[41]. Functional connectivity fMRI studies have shown that cerebellum presents opposite lateralization for language than the one observed in the cortex[42-46]. Even if Hi-P group's activations appear in the culmen, coordinates locate the activation peak already within the left hemisphere, as well as in right superior and posterior temporal lobes; this could imply some reorganization of lateralization in cortical and subcortical structures, probably to preserve the efficiency of the lexical retrieval function.

In addition, when we subtract the Low-P group activation to the Hi-P group activation for the words > control contrast (verbs and nouns), the IFG (BA 47) was more significantly activated, this could mean that the group with better performance could be recruiting a significantly larger number of resources from the left IFG than the Low-P group. This region is strongly related with semantic processing working memory[24], although not necessarily with lexical storage. Taking together, this data could be understood as the IFG was in charge of monitoring and keeping of verbal working memory span of semantic representations stored in the temporoparietal structures[47]. Wierenga et al.[23] results commented above, compared activation between young and older adults during a picture-naming task. They reported that both groups performed well, and their findings showed that older adults present more activation in the right Broca's area (BA 44,45) and in the right IFG (BA 47) than young adults. Together, their findings and our results could suggest that the inverse lateralization pattern is not only an effect observed between younger and older people, but also between two groups with similar ages. As our results showed the left hemisphere keeps its dominance in some key structures for task execution and control, such less specialized, as the IFG, but not necessarily in others as the temporal plane of Wernicke's area that carry out sensory integration and lexico-semantic storage[29,39,48].

In contrast, the Low-P group shows their most significant activity on the left caudate nucleus. This structure has been said to have important implications on the ability to inhibit unselected words during lexical retrieval[49]. Gil Robles et al.[50] carried out an intrasurgical electric stimulation study on six patients. According to their findings, caudate functions may be specific to language because there were no facial or limb motor effects during stimulation. Consistently with these results, studies on diseases affecting basal ganglia, such as Parkinson, Huntington, and HIV, have shown that verbal fluency tasks can predict the integrity of the basal ganglia[51,52]. According to the semantic memory hybrid neuronal model proposed by Hart et al.[53], the caudate nucleus interacts with the area localized anterior to the supplementary motor area (preSMA) and with the thalamus for semantic retrieval process. PreSMA region seems to be involved in beginning and ending the specific semantic category search, while thalamus sends information to the cortex and modulates the concepts activation, and the caudate seems to be responsible for taking the right decisions, helping for thalamocortical transmission and correct word selection depending on the search's intention; i.e., the caudate suppresses the competitor items by decreasing or inhibiting thalamocortical interaction. Caudate involvement in this process seems to depend on task difficulty[53], what could be related to our study as there is higher activation within the group with more mistakes.

In the same sense, when we subtract the Hi-P group activation to the Low-P group activation, the Low-P group also showed significant cortical activity. Significant activations were found for verbs > control contrast in the right frontal medial gyrus (BA 8) corresponding to homologous PreSMA, which has been linked to the thalamus and the caudate head as an essential part to carry out word generation and category research processes[53]. Therefore, these structures form a searching, attention, and selection circuit for which the left medial frontal cortex is a key part to initiate, control, monitor, and terminate the search once the selection process is over. Our results showed that likewise the Hi-P group, participants with higher mistake rates (Low-P) show a HAROLD phenomenon but in the right frontal medial area (BA 8). Hence, as with the Hi-P group, we can see reorganization of the lateralization patterns, but it seems that when this happens in structures that are essential for the task, function efficiency starts to fail. This could mean that lateralization reduction does not have a compensatory effect.

Regarding grammatical categories, it is remarkable that participants made most mistakes with verbs. In fact, the most common error was having a verb image named with a noun, despite the training that participants received before the task. Verb generation and action image naming have been strongly linked with left medial frontal gyrus activations[54-56]. Besides, aphasia studies describe that verb naming is the main difficulty for patients with frontal injuries, as opposed to patients with posterior injuries[54,57-59]. Even more, Mesulam[56] affirms that naming deficit can give us clear signs of cognitive impairment and dementia in early stages. Hence, we can hypothesize that the differentiation by grammatical categories could offer clues about the location of those deficits and the systems affected. For this reasons, more research concerning naming and mild cognitive impairment could help find better ways to make early diagnosis and design better rehabilitation programs.

In summary, our results showed a reduction of lexical access functional lateralization among older adults when compared according to their task performance. However, such reduction shows different patterns for each performance level. Older adults that achieve better performance for lexical access function keep a left lateralization pattern for key structures in semantic processing working memory like the IFG (BA 47), even if they show more interaction with homologous temporal and subcortical structures implicated with semantic processing. In contrast, older adults who made more mistakes during the task showed a pattern of greater activation in right frontal areas, homologous to those described as being central for initiation and persistence of lexical retrieval while keeping typical lateralization of subcortical structures. These results were in accordance to the HAROLD model, because we found a reduction in lateralization within elderly groups and allow us to provide data supporting the dedifferentiation hypothesis because the group presenting the inverse lateralization pattern in key structures for lexical access is the one integrated by people who made more mistakes during the task. This finding allows us to think of new questions about the functioning of different paths for lexical retrieval and the way these paths may get modified during the aging process.

Conclusions

EL, taken as the number of schooling years, according to our data, is not a determining factor for the reorganization of hemispheric asymmetry patterns. On the other hand, our study supports the de-differentiation hypothesis of the HAROLD model. That is, people who showed optimal performance for naming task, keep their left dominance of highly specialized structures for this function, as the IFG (BA 47). In contrast, people with lower scores in the same task show greater activation of homolog cortical structures involved in the initiation, searching, and ending lexical retrieval processes (right medial frontal gyrus, BA 8).

Acknowledgments

We thank to Functional Neurosurgery, Stereotactic and Radiosurgery Unit at México´s General Hospital for the support and openness to this project and Dr. Daruny Vázquez for language improvement.

References

1. Degen C, Schröder J. Training-induced cerebral changes in the elderly. Restor Neurol Neurosci. 2014;32:213-21.
2. Farias ST, Mungas D, Hinton L, Haan M. Demographic, neuropsychological, and functional predictors of rate of longitudinal cognitive decline in hispanic older adults. Am J Geriatr Psychiatry. 2011;19:440-50.
3. Soto-Añari M, Flores-Valdivia G, Fernández-Guinea S. Level of reading skills as a measure of cognitive reserve in elderly adults. Rev Neurol. 2013;56:79-85.
4. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11:1006-12.
5. Vadikolias K, Tsiakiri-Vatamidis A, Tripsianis G, et al. Mild cognitive impairment: effect of education on the verbal and nonverbal tasks performance decline. Brain Behav. 2012;2:620-7.
6. Neils J, Baris JM, Carter C, et al. Effects of age, education, and living environment on Boston naming test performance. J Speech Hear Res. 1995;38:1143-9.
7. Welch LW, Doineau D, Johnson S, King D. Educational and gender normative data for the boston naming test in a group of older adults. Brain Lang. 1996;53:260-6.
8. Zec RF, Burkett NR, Markwell SJ, Larsen DL. Normative data stratified for age, education, and gender on the boston naming test. Clin Neuropsychol. 2007;21:617-37.
9. Zec RF, Burkett NR, Markwell SJ, Larsen DL. A cross-sectional study of the effects of age, education, and gender on the boston naming test. Clin Neuropsychol. 2007;21:587-616.
10. Hatta T, Iwahara A, Hatta T, et al. Developmental trajectories of verbal and visuospatial abilities in healthy older adults: comparison of the hemisphere asymmetry reduction in older adults model and the right hemi-ageing model. Laterality. 2015;20:69-81.
11. Berlingeri M, Danelli L, Bottini G, Sberna M, Paulesu E. Reassessing the HAROLD model: is the hemispheric asymmetry reduction in older adults a special case of compensatory-related utilisation of neural circuits? Exp Brain Res. 2013;224:393-410.
12. Cui GH, Yao YH, Xu RF, et al. Cognitive impairment using education-based cutoff points for CMMSE scores in elderly Chinese people of agricultural and rural Shanghai China. Acta Neurol Scand. 2011;124:361-7.
13. Soares EC, Ortiz KZ. Influence of schooling on language abilities of adults without linguistic disorders. Sao Paulo Med J. 2009;127:134-9.
14. Murayama N, Iseki E, Tagaya H, et al. Intelligence or years of education: which is better correlated with memory function in normal elderly japanese subjects? Psychogeriatrics. 2013;13:9-16.
15. Silva C, Faísca L, Ingvar M, Petersson KM, Reis A. Literacy: exploring working memory systems. J Clin Exp Neuropsychol. 2012;34:369-77.
16. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 2002;17:85-100.
17. Springer MV, McIntosh AR, Winocur G, Grady CL. The relation between brain activity during memory tasks and years of education in young and older adults. Neuropsychology. 2005;19:181-92.
18. Allen PA, Bucur B, Grabbe J, Work T, Madden DJ. Influence of encoding difficulty, word frequency, and phonological regularity on age differences in word naming. Exp Aging Res. 2011;37:261-92.
19. Hanna-Pladdy B, Choi H. Age-related deficits in auditory confrontation naming. Psychol Aging. 2010;25:691-6.
20. Kavé G, Mashal N. Age-related differences in word-retrieval but not in meaning generation. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2012;19:515-29.
21. Mackay AI, Connor LT, Albert ML, Obler LK. Noun and verb retrieval in healthy aging. J Int Neuropsychol Soc. 2002;8:764-70.
22. Whiting E, Chenery HJ, Copland DA. Effect of aging on learning new names and descriptions for objects. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2011;18:594-619.
23. Wierenga CE, Benjamin M, Gopinath K, et al. Age-related changes in word retrieval: role of bilateral frontal and subcortical networks. Neurobiol Aging. 2008;29:436-51.
24. Martin A, Chao LL. Semantic memory and the brain: structure and processes. Curr Opin Neurobiol. 2001;11:194-201.
25. Chokron S, Helft G, Perez C. Effects of age and cardiovascular disease on selective attention. Cardiovasc Psychiatry Neurol. 2013;2013:185385.
26. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 2002;17:1394-402.
27. Albert ML, Spiro A 3rd, Sayers KJ, et al. Effects of health status on word finding in aging. J Am Geriatr Soc. 2009;57:2300-5.
28. Rodríguez MÁ. Versión mexicana del Test Barcelona Abreviado: perfiles Normales. 1999.
29. Jescheniak JD, Schriefers H, Garrett MF, Friederici AD. Exploring the activation of semantic and phonological codes during speech planning with event-related brain potentials. J Cogn Neurosci. 2002;14:951-64.
30. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized talairach space. J Comput Assist Tomogr. 1994;18:192-205.
31. Marroquin JL, Biscay RJ, Ruiz-Correa S, et al. Morphology-based hypothesis testing in discrete random fields: a non-parametric method to address the multiple-comparison problem in neuroimaging. Neuroimage. 2011;56:1954-67.
32. Talairach J, Tournoux P. Co-Planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: an Approach to Cerebral Imaging. New York: G. Thieme: 1988.
33. Carreiras M, Seghier ML, Baquero S, et al. An anatomical signature for literacy. Nature. 2009;461:983-6.
34. Frith U. Literally changing the brain. Brain. 1998;121 (Pt 6):1011-2.
35. Petersson KM, Reis A, Askelöf S, Castro-Caldas A, Ingvar M. Language processing modulated by literacy: a network analysis of verbal repetition in literate and illiterate subjects. J Cogn Neurosci. 2000;12:364-82.

36. Reis A, Petersson KM, Castro-Caldas A, Ingvar M. Formal schooling influences two-but not three-dimensional naming skills. Brain Cogn. 2001;47:397-411.
37. Petersson KM, Silva C, Castro-Caldas A, Ingvar M, Reis A. Literacy: a cultural influence on functional left-right differences in the inferior parietal cortex. Eur J Neurosci. 2007;26:791-9.
38. Castro-Caldas A, Petersson KM, Reis A, Stone-Elander S, Ingvar M. The illiterate brain. Learning to read and write during childhood influences the functional organization of the adult brain. Brain. 1998;121 (Pt 6):1053-63.
39. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex. 2009;19:2767-96.
40. Vogt BA, Vogt LJ, Perl DP, Hof PR. Cytology of human caudomedial cingulate, retrosplenial, and caudal parahippocampal cortices. J Comp Neurol. 2001;438:353-76.
41. Highnam CL, Bleile KM. Language in the cerebellum. Am J Speech Lang Pathol. 2011;20:337-47.
42. Krienen FM, Buckner RL. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex. 2009;19:2485-97.
43. Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage. 2009;44:489-501.
44. Marien P, Engelborghs S, Fabbro F, De Deyn PP. The lateralized linguistic cerebellum: a review and a new hypothesis. Brain Lang. 2001;79:580-600.
45. De Smet HJ, Baillieux H, De Deyn PP, Mariën P, Paquier P. The cerebellum and language: the story so far. Folia Phoniatr Logop. 2007;59:165-70.
46. Jansen A, Flöel A, Van Randenborgh J, et al. Crossed cerebro-cerebellar language dominance. Hum Brain Mapp. 2005;24:165-72.
47. Fuster JM. Cortex and Mind: unifying Cognition. Oxford, UK: Oxford University Press; 2003.
48. van Heuven WJ, Schriefers H, Dijkstra T, Hagoort P. Language conflict in the bilingual brain. Cereb Cortex. 2008;18:2706-16.
49. Ali N, Green DW, Kherif F, Devlin JT, Price CJ. The role of the left head of caudate in suppressing irrelevant words. J Cogn Neurosci. 2010;22:2369-86.
50. Gil Robles S, Gatignol P, Capelle L, Mitchell MC, Duffau H. The role of dominant striatum in language: a study using intraoperative electrical stimulations. J Neurol Neurosurg Psychiatry. 2005;76:940-6.
51. Ye Z, Milenkova M, Mohammadi B, et al. Impaired comprehension of temporal connectives in Parkinson's disease a neuroimaging study. Neuropsychologia. 2012;50:1794-800.
52. Thames AD, Foley JM, Wright MJ, et al. Basal ganglia structures differentially contribute to verbal fluency: evidence from human immunodeficiency virus (HIV)-infected adults. Neuropsychologia. 2012;50:390-5.
53. Hart J Jr., Maguire MJ, Motes M, et al. Semantic memory retrieval circuit: role of pre-SMA, caudate, and thalamus. Brain Lang. 2013;126:89-98.
54. Luzzatti C, Raggi R, Zonca G, et al. Verb-noun double dissociation in aphasic lexical impairments: the role of word frequency and imageability. Brain Lang. 2002;81:432-44.
55. Luzzatti C, Aggujaro S, Crepaldi D. Verb-noun double dissociation in aphasia: theoretical and neuroanatomical foundations. Cortex. 2006;42:875-83.
56. Mesulam MM. Primary progressive aphasia a language-based dementia. N Engl J Med. 2003;349:1535-42.
57. Damasio AR, Tranel D. Nouns and verbs are retrieved with differently distributed neural systems. Proc Natl Acad Sci U S A. 1993;90:4957-60.
58. Federmeier KD, Segal JB, Lombrozo T, Kutas M. Brain responses to nouns, verbs and class-ambiguous words in context. Brain. 2000;123 Pt 12:2552-66.
59. Shapiro K, Shelton J, Caramazza A. Grammatical class in lexical production and morhpological processing: evidence from a case of fluent aphasia. Cogn Neuropsychol. 2000;17:665-82.