Age-related differences in the areas of Broca and Wernicke using functional magnetic resonance imaging

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Abstract

Background: previous studies have identified differences in the brain activation pattern between children and adults as well as between healthy subjects and patients using various imaging methods. Despite the increase of old people in the population, at present no study has applied a language task to investigate differences in adults.

Objective: we used a simple paradigm to elicit activation in young and old adults to investigate differences in the activation of the classical Broca and Wernicke areas.

Methods: using functional magnetic resonance imaging, we applied a simple language paradigm to 10 right-handed subjects in each age group. Words and letter strings were presented separately with the instruction to decide for each pair if it represents a synonym (in case of words) or identical strings (in case of letters). The corresponding changes in the brain activation for words and letters were contrasted for each individual subject and compared by statistical parametric methods.

Results: for all subjects, the paradigm resulted in the activation of Broca and Wernicke areas in the left hemisphere only. Group analysis demonstrated a higher level of activation in Broca as well as in Wernicke areas for the young adults in comparison with the old adults.

Conclusions: the applied, short paradigm provided consistent activation of the classical Broca and Wernicke areas in both age groups. These results demonstrate specific age-related differences in the processing of language stimuli during identical performance measures.

Keywords: Broca and Wernicke, age-related differences, blocked design, functional magnetic resonance imaging, language processing, language, elderly

Introduction

With the documented changes in neuroanatomical structures during ageing, in most cases a decline of specific cognitive functions occurs. However, there is a wide range in performance among healthy seniors, and it is possible to design cognitive tasks that yield identical behavioural results for young and a selected group of old adults. With the changes during the lifespan (like atrophy of the grey and white matter and neurochemical alterations), the comparable results in performance are suspected to be based on the functional plasticity of structures relevant to the processing of the stimuli and the generation of the response. The compensation could be a result of identical areas in young and old adults responsible for the cognitive demand, therefore a preserved function despite age-related differences or the ability of the brain to respond to structural changes by recruitment of additional regions to cope with the demand. Using functional magnetic resonance imaging (fMRI) methods, it is possible to visualise the localised activation pattern during the cognitive task and to analyse the resulting network in terms of differences due to the factor age. Despite the importance of these investigations in the light of a general shift towards an older population, at present studies have only been conducted to compare children and adults [1, 2] as well as healthy subjects and patients [3, 4] in terms of language-related differences using imaging methods.

Changes in memory processing with age are well known and represent a model for decline in performance during late adulthood. The difference in brain activity pattern due
to age is selective to depend on the specific nature of the task with implicit and short-term memory functions relatively preserved, while explicit and ‘prospective’ memory is affected to a substantial degree [5, 6]. Especially, the frontal lobe function was one focus of recent studies investigating the different brain activation pattern as a factor of age (by positron emission tomography (PET) and fMRI imaging methods) [7–9]. Basically, two approaches are possible to elicit differences: either to engage a paradigm that yields a comparable performance in both groups and therefore allows to visualise the changes with respect to age directly or to correlate the decline in performance to the activation pattern detected. In an elegant PET study [8], the older subjects were divided into a high- and low-performance group on the basis of a variety of psychological and memory tests and subsequently contrasted with the results of the young subject group. The observation of reduced hemispheric lateralisation in the high-performance older subjects compared to the low-performance group pointed towards a functional reorganisation, conceptualised by the authors in the term HAROLD (hemispheric asymmetry reduction in old subjects). These results have been extended to other areas beside the prefrontal cortex [10, 11].

During a simple motor task of thumb-to-index tapping, PET activations demonstrated an increased activation in the frontal cortex for old in comparison with young subjects [12]. A more detailed analysis revealed that the surprising result was based on the nature of the control condition, in this case resting state. The adjusted cerebral blood flow (CBF) within one of the activated regions for the control condition was at a higher level than during the actual movement period in the young subject group, resulting in the reported results. The authors discussed the possibility of cellular changes during ageing (tissue atrophy and synaptic loss) and the possibility of relative differences due to cognitive load (that the anticipation of the movement is higher in young subjects), but the findings were not conclusive.

The identification of language-related regions within the brain using fMRI is important for diagnosis before surgical intervention and therapy as well as for the understanding of changes in the cognitive system during ageing. At present, publications have investigated the use of paradigms activating language areas mainly for the identification of eloquent areas before the surgery of tumours [13], in cases of stroke-related changes to brain function [3] or changes related to focal epilepsy [14, 15], and in the challenging field of understanding the complex integration of perception, lexical and grammatical reference systems in language comprehension [16–18].

The results show that visual word presentation mainly engages the posterior superior temporal gyrus (Wernicke) and the posterior inferior frontal gyrus (Broca) together with other areas related to the nature of the task applied [19].

The reason for only few studies applying language tasks to different adult age groups might be based on the difficulty to design a paradigm which is simple enough to result in comparable behaviour irrespective of age, which allows for control of cognitive demands in subjects and keeps the time spent in the scanner as short as possible. The design presented by Fernandez and colleagues [20] elicits a significant increase in the blood oxygen level-dependent (BOLD) response in language-relevant regions with a minimum time spent in the scanner bore. Additionally, the design is based on the subtraction of two controlled (active) conditions, and the response behaviour is recorded for each condition, with the advantage to monitor the cognitive demands and to prevent the mentioned problems with a simple fixation control or resting state baseline. The aim of this study was to evaluate the design in two adult age groups and to compare the resulting activation pattern in terms of hemispheric lateralisation and significance level.

**Material and methods**

**Paradigm and subjects**

Ten healthy young subjects (four females, mean age 23.5, range 21–36) and 10 healthy old subjects (five females, mean age 59.4, range 54–76) participated in the study. All subjects were right-handed and screened for neurological impairments, psychiatric illness and history of concussion or seizure. Informed consent was obtained in a manner approved by the ethics committee of the Medical High School Magdeburg.

The instructions were given outside the scanner during the general information about the study and again immediately before the functional scanning part. The paradigm consisted of two conditions in a blocked design presentation. Subjects were visually presented with either two words or two consonant strings above and below a fixation point (each presentation lasting 4 s, stimulus duration 3 s). One run consisted of eight consecutive blocks (24 s duration), with each block constructed of different words/consonant pairs (six stimuli), resulting in a presentation time of 192 s. To allow the T1 signal to stabilise, 8 s of fixation before each run was added and later erased before data analysis. Subjects were instructed to press a button with the right index finger for identical consonant strings (e.g. dqfgh–dqfgh) or if the word pair represented a synonym (e.g. ear–auto) or not (e.g. apple–house). It was emphasised that the correct answer was more important than a fast response. The stimuli were equally balanced for identical/synonym cases, controlled for length and only occurred once during the session.

**Imaging**

Data acquisition was performed on a neurooptimised GE 1.5 T Signa Horizon LX system equipped with a standard birdcage head coil. For each subject, the session consisted of structural and functional imaging (with identical orientation of 16 slices aligned to the anterior and posterior commissure, 7 mm thickness with 1 mm gap, covering the whole brain volume), resulting in a total session time of about 10 min. During structural scans, high-resolution T1-weighted images (512^2 matrix, 2D spin echo sequence) and T1-weighted inversion recovery spin echo EPI (echo planar imaging) images (64^2 matrix) were acquired. During the functional part, two runs were acquired using a T2*-weighted gradient echo EPI (TR = 2 s, TE = 40 ms, 64^2 matrix) consisting of 100 volumes each.
Data were analysed using the Statistical Parametric Package from London (SPM99, http://www.fil.ion.ac.uk/spm). For individual subjects, functional images of the two runs were realigned to the first scan of the first run (after deletion of the first four volumes representing the fixation period). The resulting images were resliced into the Montreal Neurological Institute (MNI) coordinate space using the provided template (resulting in isometric 3-mm voxels). Finally, smoothing with a 10-mm full-width half-maximum Gaussian filter was applied. Images of the two runs were then combined by fixed level analysis using a boxcar function corrected for temporal delay of the BOLD response, resulting in images for the contrast of words versus consonant string presentation (significance threshold for corrected values of P<0.05). Contrast images of individual subjects were then subject to random level analysis using one-sample t-test (grand average of all subjects) and two-sample t-test to elicit the differences between age groups (young versus old adults and vice versa). Finally, region of interest (ROI) analysis for the areas of Broca and Wernicke was performed. The regions were constructed on the basis of the peak activation of the grand average data in these areas (at a corrected threshold of P = 0.05) with anatomical restraints using the MarsBar software tool implemented in SPM99 [21].

Results

Results of the behavioural data revealed no differences in the reaction time for the two age groups (ANCOVA, F<1), and incorrect judgements occurred in <3% of the trials supporting the feasibility of the task for different age groups. Reaction time differences for word versus string presentations missed the statistical threshold but had a tendency to be longer during the string decision (old adults F = 3.35, P = 0.07; young adults F = 2.9, P = 0.09).

The critical contrast of word presentation versus letter presentation demonstrated activation in the areas of Broca and Wernicke in each individual subject. Combining all subjects in a grand average analysis by feeding these contrasts into a random effects analysis, three major areas, all located in the dominant left hemisphere only, were activated above the corrected statistical threshold of P<0.05 (Figure 1a). These areas were identified in terms of anatomical location, peak coordinates and statistical significance (all values based on the corrected voxel level with a threshold of P<0.05) as (i) Broca’s area (inferior prefrontal gyrus), coordinates in SPM MNI template space: x = -52, y = 24, z = 12, t = 8.39 and z = 5.5; (ii) the superior frontal gyrus, x = -8, y = 44, z = 48, t = 7.86 and z = 5.35; and (iii) Wernicke’s area (superior temporal gyrus), x = -64, y = -52, z = 8, t = 7.35 and z = 5.12 (Table 1). In order to evaluate age-specific differences, a second level two-sample t-test was performed on the basis of the critical contrast. No activation was detected above the corrected statistical threshold of P<0.05 for young versus old and the reversed comparison, but the uncorrected contrast showed activation clusters in the inferior prefrontal and superior temporal gyrus corresponding to Broca and Wernicke, respectively. In order to increase the statistical power, we calculated the mean-corrected parameter estimates for these two regions of Broca and Wernicke (ROI analysis, Figure 1b). In both areas in the left hemisphere, a significant higher activation (Broca t = 5.9, Wernicke t = 4.09) for young subjects in comparison with old subjects was detected above the corrected threshold of P<0.05.

Discussion

We investigated age-related differences in the areas of Broca and Wernicke using a simple and well-controlled language paradigm. The results—in contrast to our hypothesis that comparable performance would be archived by recruitment of additional areas or enlargement of the primary regions responsible for the processing of language stimuli—revealed activation of Broca’s and Wernicke’s region at a lower significance level in the old subject group in comparison with the young subject group. With the control of identical task demands provided by no significant differences in response behaviour or reaction time, the observed differences can be attributed to the factor age exclusively.

The investigation of language has been limited by the needs to apply complex designs and to assure sufficient statistical power in imaging methods (usually more than an hour of scan-time). A wealth of prior studies in functional imaging have investigated study designs for the identification of the main language-relevant regions—such as Broca’s and Wernicke’s—using silent word generation, antonym generation and picture naming (for comparison of these paradigms [22]). The disadvantages of these designs include either long scanning procedures, fixation periods as control conditions or no record of the subject’s response to the given task. Together, these factors might have contributed to the variability of activation patterns, especially as the level of the BOLD signal is dependent on the subtraction of conditions and the overall cognitive demand. Our study design has been shown to overcome these limitations and provides robust results within 10 min of scanning time. Even more important, subject’s response behaviour is recorded for each presented item, and it is therefore possible to monitor the performance and feasibility of the paradigm in different age groups.

Few studies have investigated related changes of young versus old adults in the activation pattern during cognitive [23, 24] or motor tasks [25], despite their relevance for the clinical and neuroscience communities. One reason might be related to the problem of the indirect detection of neuronal activity by the BOLD signal in functional MRI, which is dependent on the local vascular integrity. However, results provided by the study of Buckner and colleagues [24] demonstrated no limitations for this method. Furthermore, in our study, the activation pattern of the old adults included only areas specific for the processing of language with respect to perceptual and cognitive load comparable to the pattern in young adults. One reason for the reported age differences was suspected in ill-defined nature of the ‘baseline’ condition used in various studies (fixation), which we replaced in our paradigm by an active control condition and behavioural response...
monitoring. Therefore, the current approach and resulting data support the use of functional imaging methods in the field of ageing research.

For each subject in our sample, activated regions were restricted to the left hemisphere (contralateral to the dominant hand). Although other studies have reported areas in both hemispheres in response to language tasks in right-handed subjects, the degree seems to be related to the level of difficulty and complexity of the applied paradigm as well as the threshold used in the statistical evaluation [22]. Our study was designed specifically to shorten the overall investigation time and to elicit robust activation within the regions of Broca and Wernicke, with the result of a limited cognitive demand in comparison with other, more complex language studies [26].

The results were unexpected as previous studies pointed towards a dynamic change in the neuronal system during age-related changes. Mapping the grey matter density over an age range from 7 to 87 years, Sowell et al. [27] demonstrated differences in the effects of age to be prominent in the shape of function between the lateral prefrontal (almost linear) and left posterior temporal cortex (inverted U-shaped), suggesting differences in the brain activity pattern for a cognitive task during lifespan. Memory studies have reported a reduced laterality for older subjects when task performance was identical to young subjects [7, 28]. These results were specific to implicit and short-term memory functions, while explicit

Table 1. Results of the critical contrasts with respect to cerebral regions shown based on the corrected voxel level ($P<0.05$)

<table>
<thead>
<tr>
<th>MNI coordinates</th>
<th>Threshold value</th>
</tr>
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<tbody>
<tr>
<td>$x$</td>
<td>$y$</td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>$-52$</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>$-8$</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>$-60$</td>
</tr>
</tbody>
</table>

MNI-based stereotactic coordinates, significance of peak voxel-based $t$ and $z$ values.

Figure 1. (a) Statistical activation is shown for the contrast of word versus string presentation including all sessions (grand average): increased activation (voxel $z$ score $>3.25$, $P<0.001$ uncorrected) was rendered on the surface of the MNI reference brain provided by SPM software package. Common regions include inferior (Broca) and superior frontal gyrus as well as superior temporal gyrus (Wernicke). (b) Region of interest (ROI)-based group comparison within the areas of Broca (left panel, red) and Wernicke (right panel, blue). In both panels, on the left side, the reconstructed ROI projected on the coronal and axial anatomic background (MNI reference brain) and on the right side the effects of interest were based on the mean for young and old adults.
memory did not show a different neural response pattern for old subjects. Our data extend these observations into the language domain, where age-related structural changes seemed not to be compensated by additional neuronal recruitment to achieve comparable task performance—at least not during the language task employed here.

Key points
- Despite documented changes in neuroanatomical structures which occur as we age, only a few studies have investigated the expected changes in the brain activation pattern using fMRI methods.
- We optimised a language design to investigate the areas of Broca and Wernicke and applied it to two different adult age groups (mean 23 and 59 years), with the result of reliable activation of key language areas within 10 min of total scanning time.
- All subjects activated the areas of Broca and Wernicke in the dominant hemisphere only, with the young adult group showing a more significant level of activation despite equal performance results in both groups.
- While studies investigating cognitive function have demonstrated hemispheric lateralisation, in our study, old adults did not recruit additional brain areas during the language task to cope with the age-related changes in brain structure.

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References

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