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MR Imaging Study**

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ORIGINAL
RESEARCH

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Nonlinear Changes in Brain Activity During Continuous Word Repetition: An Event-Related Multiparametric Functional MR Imaging Study

BACKGROUND AND PURPOSE: Changes in brain activation as a function of continuous multiparametric word recognition have not been studied before by using functional MR imaging (fMRI), to our knowledge. Our aim was to identify linear changes in brain activation and, what is more interesting, nonlinear changes in brain activation as a function of extended word repetition.

MATERIALS AND METHODS: Fifteen healthy young right-handed individuals participated in this study. An event-related extended continuous word-recognition task with 30 target words was used to study the parametric effect of word recognition on brain activation. Word-recognition-related brain activation was studied as a function of 9 word repetitions. fMRI data were analyzed with a general linear model with regressors for linearly changing signal intensity and nonlinearly changing signal intensity, according to group average reaction time (RT) and individual RTs.

RESULTS: A network generally associated with episodic memory recognition showed either constant or linearly decreasing brain activation as a function of word repetition. Furthermore, both anterior and posterior cingulate cortices and the left middle frontal gyrus followed the nonlinear curve of the group RT, whereas the anterior cingulate cortex was also associated with individual RT.

CONCLUSION: Linear alteration in brain activation as a function of word repetition explained most changes in blood oxygen level-dependent signal intensity. Using a hierarchically orthogonalized model, we found evidence for nonlinear activation associated with both group and individual RTs.

Parametric functional MR imaging (fMRI) studies using block designs have proved to be a powerful methodology to characterize the relationship between 1 experimental parameter and the blood oxygen level-dependent (BOLD) signal intensity. When applied to studies of memory function, parametric designs have revealed regions with linearly increasing activation as a function of increased working or episodic memory load¹⁻⁴ and regions correlating with the amount of successfully encoded items.⁵ Often 2 or 3 parametric steps were used to detect a linear correlation between the experimental parameter of interest and the BOLD response in various brain regions. However, in some studies, the BOLD response appeared to be more properly characterized by a nonlinear function, an inverted U relationship for example.⁶⁻⁸ A larger number of parametric steps is required to accurately characterize such a function. We previously showed that stimulation of the primary visual cortex by using 17 different stimulation frequencies allowed reliable determination of individual inverted U-shaped response curves.⁸ With a cognitive paradigm however, the number of parametric steps might be more difficult to expand, for instance as a consequence of limited cognitive processing capacity.

The current study, primarily methodologic in nature, had 2 main objectives. The first objective was confirmatory: to determine whether our parametric version of this memory task, by using a large number of parametric steps (repetitions, ie, word recognition), revealed activation in regions previously

reported in studies on verbal episodic memory recognition (ie, frontal or prefrontal,⁹⁻¹⁵ parietal,¹² medial temporal,^{16,17} anterior cingulate cortex, occipital, and cerebellar regions¹⁸).

Studies on repeated stimulus presentation (priming and habituation studies, for example) generally show a linear decrease in brain activations.¹⁸ Even though our continuous, item-specific word-repetition task cannot simply be classified as a priming or habituation task, we mainly expected to find linear decreases in brain activation. In addition, we hypothesized that there would be nonlinear decreases in brain activation as a function of word repetition. Because, to our knowledge, changes in brain activation as a function of continuous multiparametric word recognition have not been studied before by using fMRI, speculations on which brain regions might show different types of activity patterns are considered premature. Thus, our second (main) aim was to identify regions with linear changes in brain activation and, what is more interesting, regions with nonlinear changes in brain activation.

Methods

Participants

Fifteen participants, free from neurologic disorders or visual abnormalities, participated in the experiment (9 men and 6 women; mean age, 22.8 years; range, 19–27 years). Informed consent was obtained from all participants. Strength of handedness was measured by means of a hand-preference questionnaire with 16 items. The scores could range from -16 (extremely left handed) to +16 (extremely right handed). All participants had a score of +13 or more.

MR Imaging Data Acquisition

Imaging was performed on a 1.5T Vision MR imaging scanner (Siemens, Erlangen, Germany) by using the standard circularly polarized head coil. Foam pads were used to minimize head motion, and par-

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ticipants wore earplugs to reduce scanner noise. For functional imaging, we used T2-weighted echo-planar imaging (TR = 2.275 seconds, TE = 64 ms, flip angle = 90°). Twenty axial 5-mm-thick sections with an in-plane resolution of 3 mm and an intersection gap of 1 mm covered the entire brain and were acquired from top to bottom.

Task Procedures

From within the bore of the scanner, participants looked through a mirror mounted on the head coil to a back-projection screen positioned at the end of the scanner table. Stimuli generated on a laptop computer were projected through a window on the screen with a data projector. The experiment involved the sequential visual presentation of 365 stimuli (330 words and 35 control stimuli). In 1 hand, participants held an MR imaging-compatible response box with 4 buttons (LUMItouch; Lightwave Medical Industries, Vancouver, British Columbia, Canada). For each stimulus, a response with the right hand was requested by pressing a key with either the index or the middle finger. Reaction time (RT, ie, the time between onset of stimulus and response registration) was recorded for all responses, and responses were classified as correct/incorrect to allow assignment of event types for event-related (ER) fMRI analysis (see the following paragraph).

In the continuous word-recognition task, every 2.5 seconds, 1 of 30 Dutch mono- or bisyllabic nouns was presented to the participants (the interval between nouns was 0.5 seconds). By using a stimulus time interval of 2.5 seconds and, therefore, not allowing the hemodynamic response curve to reach its baseline, we used fast ER fMRI. This enabled us to study such an extensive word-recognition task, which otherwise would take too long. The 30 target words were presented 10 times each, in random order (each presentation, therefore, was either a new word or a first, second, . . . , or ninth repetition); additionally 30 distracter words (new words that were not repeated) were intermingled with the target words during the second half of the experiment. All stimuli were concrete imaginable nouns, such as the Dutch words for “chair” and “shoe,” for example. Participants were told that words would be repeatedly presented, and for each presentation, they had to indicate whether the word was new or familiar by pressing a button with the right index or middle finger, respectively. Additionally, at the beginning and the end of the experiment, participants followed the instruction to press the left and right button while no memory component was involved (displayed as “left” or “right” on the screen). This was done randomly 20 times at the beginning and 15 times at the end. In total, the experiment lasted 15.28 minutes, and 403 scans were acquired per participant. The number of functional images for baseline (left-right responses), new words, and repeated words were 39, 66, and 298, respectively.

Data Analysis

fMRI analysis was carried out by using FEAT (FMRI Expert Analysis Tool) Version 5.4, part of FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl). Prestatistical processing consisted of motion correction,¹⁹ nonbrain removal,²⁰ spatial smoothing by using a Gaussian kernel of full width at half maximum, 8-mm; mean-based intensity normalization of all volumes by the same factor; and high-pass temporal filtering (Gaussian-weighted load sharing facility straight line fitting, with $\sigma = 64.0$ seconds). Time-series statistical analysis was done with local autocorrelation correction.²¹

Six regressors were included in the model, representing the following:

1) Left-right responses on presentations of the left-right press instructions at the beginning and the end of the experiment (baseline).

2) Correct responses to the 60 presentations of new words (of which 30 were repeated later and 30 were distracters presented only once).

3) Correct responses to repeated words, with the assumption that each occurs with constant equal amplitude.

4) Same as regressor 3 but with linearly altering amplitude as a function of presentation number (1–9).

5) Same as regressor 3 but with varying amplitude according to group average RT (group averages of all first-repetition trials, all second-repetition trials, etc).

6) Same as regressor 3 but with varying amplitude according to individual RT (individual averages of all first-repetition trials, all second-repetition trials etc).

Evoked hemodynamic responses to each event type were modeled as delta functions in the regressors, convolved with a double-gamma hemodynamic response function.

Regressor 4 was orthogonalized with respect to 3; 5, with respect to 3 and 4; and 6, with respect to 3, 4, and 5. Hence, the model was hierarchically built with any overlap between regressor 3, 4, 5, and 6 removed. The model also included the temporal derivatives of each regressor. This analysis gave 6 images of parameter estimates, representing the signal intensity explained by each of the regressors, as well as the 6 corresponding variance images.

Specific effects of interest were tested by applying appropriate linear contrasts to the parameter estimates of interest: i) new words versus baseline (contrast: $-1,1,0,0,0,0$); ii) constant activation during word repetition (contrast: $0,0,1,0,0,0$); iii) changing activation during word repetition, linearly associated with number of repetitions (contrast: $0,0,0,1,0,0$); iv) changing activation of repeated words associated with the group average RT (contrast: $0,0,0,0,1,0$); and v) alterations associated with individual RT (contrast: $0,0,0,0,0,1$).

fMRI images were registered to standard space images.^{19,22} These transformations were applied to contrast images and corresponding images of variances to bring them to standard space.

Higher level (group level) analysis was carried out by using mixed effects analysis.²³ Group averages were calculated for each of the contrasts by using a 1-sample *t* test by using fixed-effects analysis ($P < .001$, uncorrected). Second, we also applied a random-effects analysis to study which effects remained significant ($P < .001$, uncorrected).

Results

Behavioral Data

Percentages of correct responses and RTs to the first presentation of words (new word presented, responded to with the “new word” response button) and the 9 word repeats (R1-R9, responded to with the “familiar word” response button) are shown in Fig 1.

Accuracy. The average percentage of correct responses for the first presentation of words was 94.8% (SD = 3.81). The average percentage of correct responses for word recognition increased exponentially from 83.1% (SD = 12.02) for the first repetition to 99.6% (SD = 1.08) for the ninth repetition.

Latency. The average RT for correct responses to new words was 859 ms (SD = 97.40). For word repetition, the RT showed an exponential decrease from the first repetition (M = 903 ms, SD = 83.36) to the ninth repetition (M = 701 ms, SD = 194.32, Fig 1). Note that the group average RT diminished in an asymptotic fashion. Given the comparable RT variances for each repetition, it is very likely that the individual RT

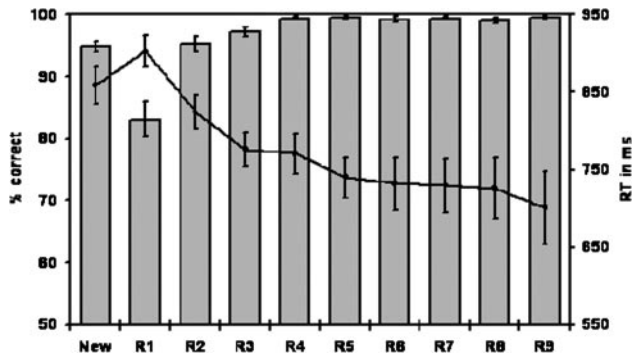


Fig 1. Mean percentages of correct responses (bar charts) and mean RTs in milliseconds (line chart) of 15 participants to new words (identified as a new word) and repeated words (R1-R9). Error bars depict the standard error of the means.

also diminishes in an asymptotic fashion. Group and individual averages were used to study word recognition as a function of continuous word repetition in regressors 5 and 6, respectively.

Brain Activation

In the fixed-effects analyses, “new words versus baseline” revealed positive activation in the left inferior frontal gyrus, bilateral middle frontal gyrus, anterior cingulate cortex, bilateral nucleus lentiformis, and left motor cortex (Fig 2). New words versus baseline did not reveal decreased brain activation. Analysis of correct responses to repeated words, assuming the mean amplitude to be constant with time, revealed activation in the right inferior, middle, and superior frontal gyrus; anterior cingulate cortex; right posterior central sulcus; and left precentral sulcus (Fig 3).

On repeated-word presentations, we mainly found linearly decreasing activation in the bilateral inferior frontal gyrus, bilateral middle frontal gyrus, bilateral thalamus, superior parietal gyrus, superior frontal gyrus, and anterior cingulate cortex regions (Fig 4).

No regions of linear increase were found as a function of continuous word repetition. The activation in the anterior cingulate cortex was negatively associated with group average (with diminishing RTs, activation in the anterior cingulate cortex increased) (Fig 5A). The posterior cingulate cortex (PCC) and left middle frontal gyrus activity were positively associated with group RT (diminishing RTs were associated with a decrease in PCC and middle frontal gyrus activation) (Fig 5B). The anterior cingulate cortex was also negatively associated with individual RT (diminishing RTs were associated with an increase in anterior cingulate cortex activation) (Fig 5C). Figure 6 illustrates the plotted Z-scores for each regressor in the most significant brain area for both constant activation (right inferior frontal gyrus) and activation following group RT (PCC), respectively. Figure 6 shows that the model brain activation with constant equal amplitude as a function of word repetition fits significantly well to the actual data in the right inferior frontal gyrus, whereas the other regressors (linear, nonlinear) do not (significantly) fit the experimental data. The data in the PCC fit significantly well to the model positive brain activation following group average RT. We found no significant fit in the PCC for brain activation, assuming the amplitude to remain constant or change linearly, or brain ac-

tivation following individual RT as a function of word repetition.

In the random-effects analyses, constant activity throughout continuous word repetition revealed significant activation in the right middle frontal gyrus, superior frontal gyrus, anterior cingulate cortex, right posterior central sulcus, and left precentral sulcus. The bilateral middle frontal gyrus and the thalamus and bilateral parietal gyrus remained significant for the linear decrease, whereas the right PCC remained significantly positively associated with group RT. Other signal intensity alterations as functions of word repetition were no longer significant using random-effects analysis.

Discussion

In the present study, we investigated linear as well as nonlinear changes in BOLD–signal intensity associated with multiple stimulus repetitions in a cognitive paradigm. To this end, we designed a verbal recognition task, in which 30 words were presented 10 times, enabling us to study BOLD–signal intensity changes as function of 9 recognition steps. On repeated presentations, accuracy improved and response latency diminished in an asymptotic fashion. In the fixed-effects analyses, brain activity for both constant brain activation and linear decrease during continuous word repetitions (Figs 3 and 4) revealed regions in general agreement with studies on recognition success.¹⁸ By adding asymptotic regressors to the model (group average RT and individual RT), we could determine nonlinear changes in brain activation during continuous word repetition (Fig 5A–C). The anterior cingulate cortex was negatively associated with group average RT, and the posterior cingulate cortex and left middle frontal gyrus activity were positively associated with group RT. Moreover, the anterior cingulate cortex was also negatively associated with individual RT. Note that random-effects analyses did not reproduce some of the activations seen with our fixed-effects approach. The inverse relationship between the anterior cingulate cortex and individual or group RT was not significant when using random-effects analyses. The right PCC, however, did remain positively associated with group RT, when using random-effects analyses.

We chose to use RT as a regressor in this model because we believe this reflects facilitated processing of repeated words. However, there might be other regressors that better explain the data, the average correct responses (accuracy data), for example. Furthermore, it should be noted that the reported *P* values, for both fixed and random effects analyses, were not corrected for multiple comparisons.

We acknowledge the unbalanced design of 60 novel stimuli versus 270 repeated stimuli, introducing a bias toward an “old” response, which increases with the duration of this word-repetition task and is confounded with the parametric effect of word repetition. Investigators in future parametric studies may want to balance their design toward more equally distributed stimulus-response probabilities.

Episodic memory encoding is consistently associated with mainly prefrontal cortex activity, but temporal and cingulate cortex activity are reported also. In the case of verbal items, these prefrontal activations are invariably left-lateralized.¹⁸ Activation for new words versus baseline in the current study, showing predominantly left prefrontal and anterior cingulate

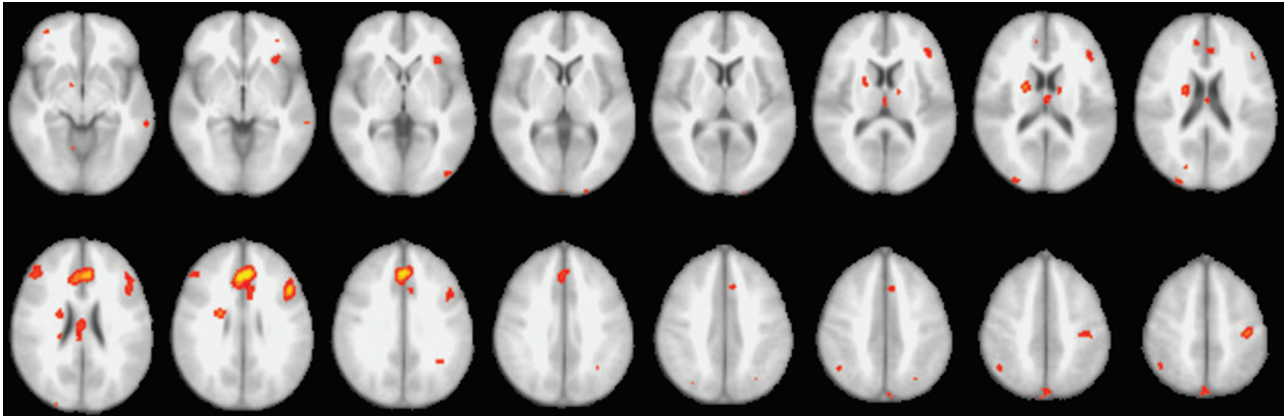


Fig 2. Brain areas showing positive activity for encoding (new words) versus baseline, by using fixed-effects analyses. Positive activity is found in the left inferior frontal gyrus, bilateral middle frontal gyrus, nucleus lentiformis, left motor cortex, and anterior cingulate cortex. Z-values of 3.0–4.7 correspond with changing brain activation colors from red to yellow, respectively. The right side of the brain on the image corresponds with the left hemisphere, and vice versa.

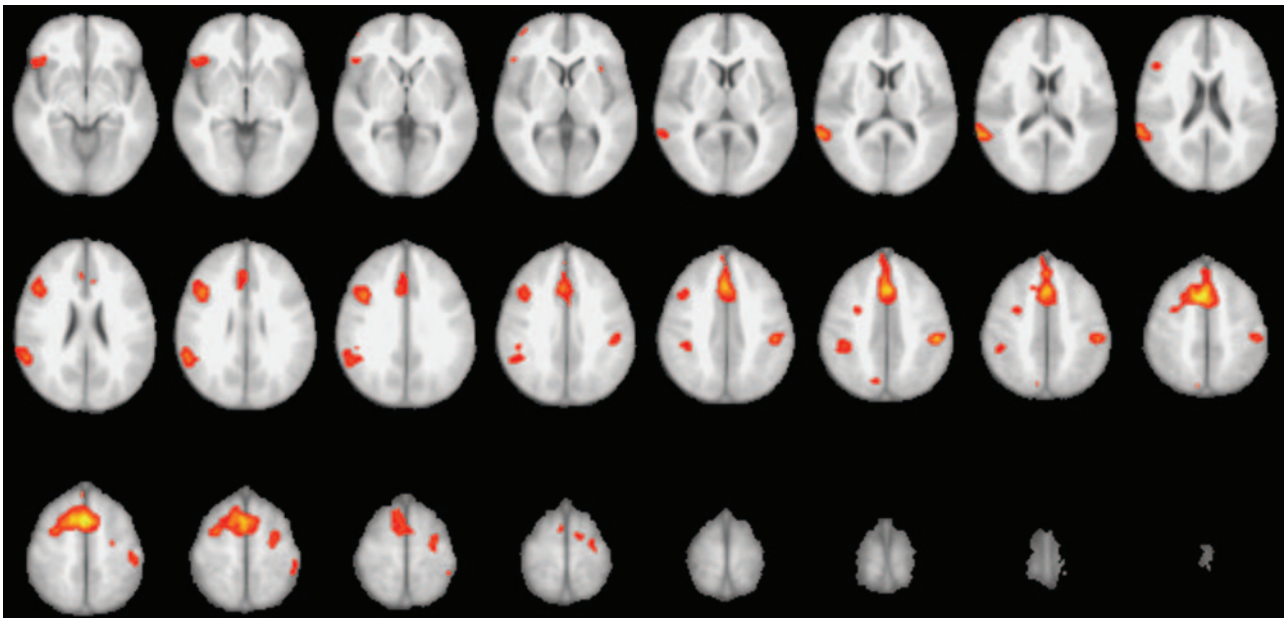


Fig 3. Correct responses to repeated words, each occurring with the same amplitude, reveal, in a fixed-effects analysis, activation in the right inferior, middle, and superior frontal gyrus; anterior cingulate cortex; right posterior central sulcus; and left precentral sulcus. Z-values of 3.0–5.8 correspond with changing brain activation colors from red to yellow, respectively. The right side of the brain on the image corresponds with the left hemisphere, and vice versa.

cortex activation, is consistent with these previously reported findings.

Analyses of correct responses to repeated words, assuming the mean amplitude to be constant with time, revealed both frontal and cingulate cortex activation and a clear tendency for right-sided lateralization. These findings are in agreement with studies on episodic memory recognition.¹⁸

Recently, neurofunctional research has focused on separating distinct neuronal networks for recollection and familiarity processes.^{13,24,25} Recollection has been shown to reveal significant BOLD changes compared with familiarity in the superior frontal, posterior cingulate cortex, and the inferior and superior parietal cortex. Familiarity, on the other hand, reveals significant changes in BOLD response compared with recollection in the middle and medial frontal gyrus, anterior cingulate cortex, superior temporal gyrus, and precuneus.¹³ Our companion electroencephalography (EEG) study,²⁶ using an identical continuous word-recognition task, showed that con-

tinuous word-repetition affects recollection rather than familiarity. Even though this continuous word-repetition task was not designed to study these specific aspects in isolation, the present fMRI findings suggest that familiarity and recollection processes are both involved in our continuous word-recognition task.

Studies on explicit memory have consistently revealed an increase in brain activation for recognition, for example Nyberg et al.¹⁷ We, however, expected to find decreased brain activation on repeated-word presentations as a consequence of less effortful processing. Our behavioral results indeed suggested better encoding and retrieval and hence facilitated processing. Previous imaging studies on priming have consistently revealed linear reductions in brain activation, supposedly associated with faster, more efficient processing.^{11,12,18,27-31} Even though our explicit memory instructions are in contrast with implicit (nonintentional) memory studies, we believe that our continuous word-recognition task has

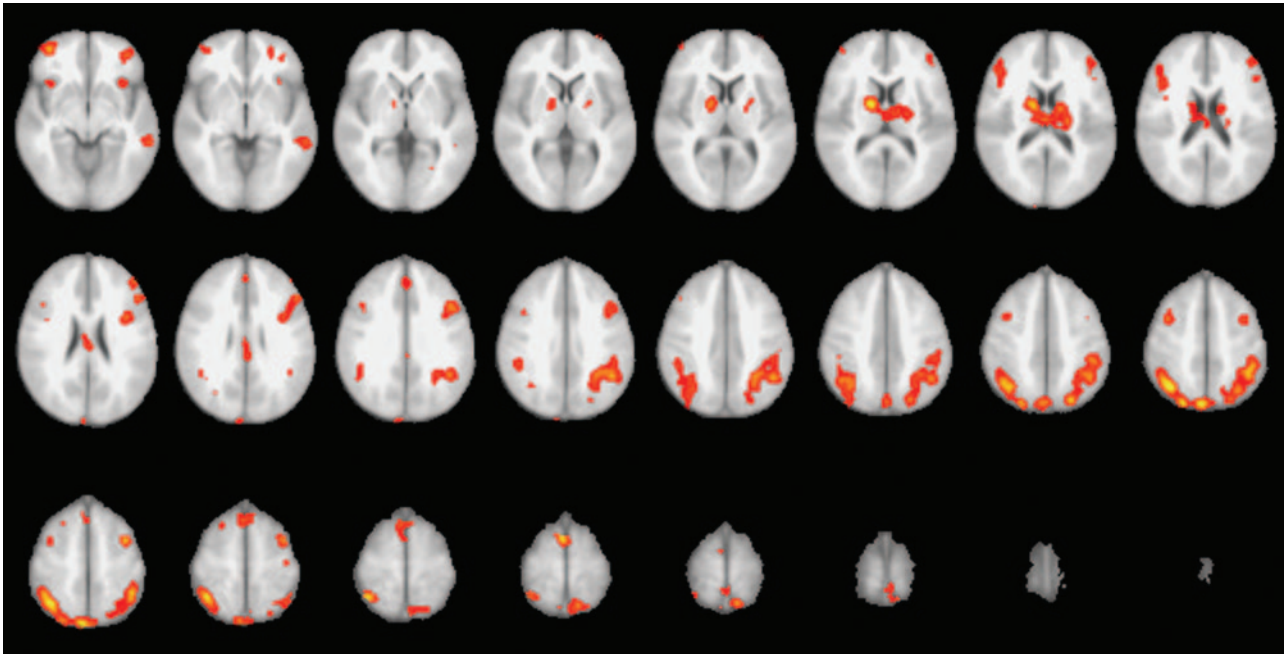


Fig 4. Brain areas showing a linear decrease in activity as a function of word recognition, by using fixed-effects analyses. Linear changes in brain activation are found in prefrontal, thalamus, anterior cingulate cortex, and parietal regions. Z-values of 3.0–5.1 correspond with changing brain activation colors from red to yellow, respectively. The right side of the brain on the image corresponds with the left hemisphere, and vice versa.

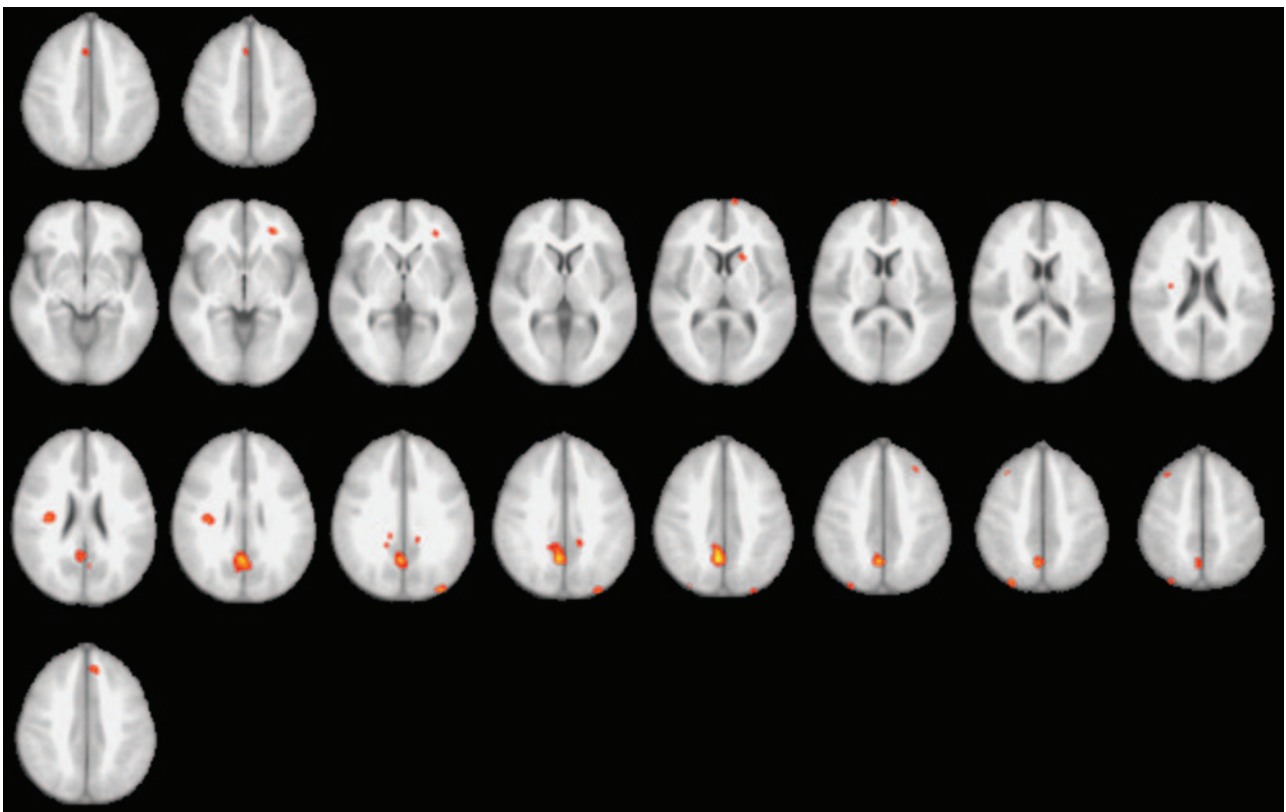


Fig 5. *A*, Brain areas negatively associated with group average RT, shown in the top row, found to be the anterior cingulate cortex. Changing brain activation colors from red to yellow correspond with Z-values of 3.0–4.3, respectively. *B*, Both center rows reveal brain areas positively associated with group average RT. Regions involved were found to be the posterior cingulate cortex and left middle frontal gyrus. Changing brain activation colors from red to yellow correspond with Z-values of 3.0–4.3, respectively. *C*, The bottom row shows that the anterior cingulate cortex was also negatively associated with individual RT. Brain regions involved were calculated by using fixed-effects analysis ($P < .001$, uncorrected). Changing brain activation colors from red to yellow correspond with Z-values of 3.0–3.8 for the bottom row. The right side of the brain on the image corresponds with the left hemisphere, and vice versa.

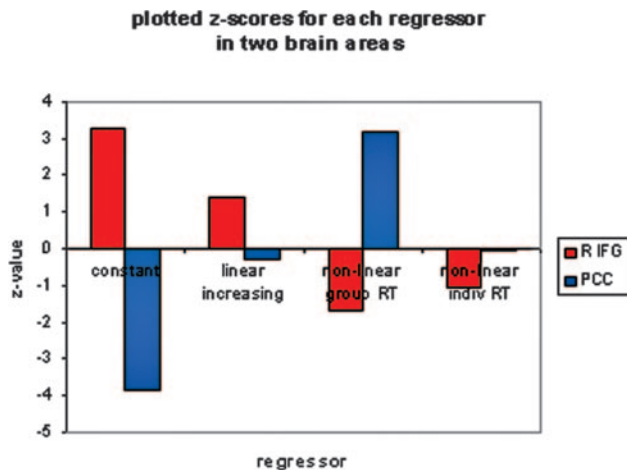


Fig 6. Plotted Z-scores for each regressor in the most significant brain areas for constant activation and activation following group RT. For the RIFG there is a significant fit to the experimental data for the model “brain activation with constant amplitude as function of word repetition.” No significant fit was found for linear or nonlinear regressors. For the PCC, we found a significant fit for the model “positive nonlinear brain activation following group RT,” whereas no significant fit was found for constant, linear, or nonlinear brain activation following individual RT. RIFG indicates right inferior frontal gyrus; indiv, individual.

features comparable with priming tasks. The decreasing activation (Fig 4) found in the frontal lobe is in accordance with studies on verbal-recognition success. The location of this response is in accordance with both word-recognition and attention studies.¹⁸ The activation found in the thalamus region presumably reflects the role of this particular region in memory and attention processes.³² The decreasing activation of the parietal cortex is found in word-recognition studies requiring receptive lingual processing.¹⁸ Cabeza et al³³ have suggested that attention-related activity during episodic memory tasks is reflected in a frontoparietal-cingulate cortex-thalamus network. These activation areas are in accordance with regions found in the current episodic memory study.

More detailed analysis of the asymptotic behavioral data (group RT and individual RT) shows a (tendency toward a) ceiling effect after 4 word repetitions. There is hardly any improvement in accuracy and response latency as a function during further repetitions (5–9). Even though a behavioral ceiling effect is reached after 4 repetitions, this does not imply that a parallel ceiling effect in brain activation should have been reached. In the companion EEG study, Van Strien et al²⁶ found a linear effect of repetition for electric activity in a 500- to 800-ms time window across all 9 word repetitions, without any evidence of a ceiling effect. Therefore, we believe asymptotic brain activation as a function of parametric word repetition deserves further investigation.

Other studies have shown that the relation between a parameter of interest and brain activation is often not adequately described by a linear function, for visual stimulation,^{8,34,35} auditory stimulation,⁶ and working memory.⁷ Nonlinear behavioral responses are usually explained in terms of processing effort; an increase in cognitive load would eventually show a decrease in task performance and a corresponding decrease in brain activation.^{2,7,13} What is most interesting, in the present study, the activation in the anterior cingulate cortex was negatively associated with group average RT (with diminishing

RTs, activation in the anterior cingulate cortex increased), by using fixed-effects analyses (Fig 5A). The posterior cingulate and left middle frontal gyrus activity were positively associated with group average RT (diminishing RTs were associated with a decrease in posterior cingulate cortex and middle frontal gyrus activation), by using fixed-effects analyses (Fig 5B). Note the remaining significant positive association of the right posterior cingulate cortex with group-average RT, when using random-effects analyses. The anterior cingulate cortex was also negatively associated with individual RT (diminishing RTs were associated with an increase in anterior cingulate cortex activation), by using fixed-effects analyses (Fig 5C). Due to the hierarchically orthogonalized design, the group RT regressor had no overlap with linear or constant regressors. Furthermore, individual RT regressors had no overlap with group RT, linear, or constant regressors. The anterior cingulate cortex is known to be involved in recollection,^{24,25} attention processes,³⁶ and error monitoring,³⁷ whereas the PCC is involved in familiarity processes.^{24,25}

Conclusion

In conclusion, our study illustrates the applicability of an ER parametric design in an extended continuous word-recognition paradigm. Continuous word recognition reveals brain regions known to be involved in both attention processing, recollection, and familiarity processes. Linear alteration in activity as a function of word repetition explained most changes in BOLD signal intensity. What is most interesting, due to the hierarchically orthogonalized model, we found brain activation both negatively and positively associated with group RT and negative activation associated with individual RT. Therefore, in paradigms in which behavior measures are best described in an asymptotic/nonlinear fashion, the addition of nonlinear regressors to the model needs to be considered. The applicability of nonlinear regressors in other cognitive paradigms deserves further investigation.

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