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Repetition of letter strings leads to activation of and connectivity with word-related regions

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Abstract

Individuals learn to read by gradually recognizing repeated letter combinations. However, it is unclear how or when neural mechanisms associated with repetition of basic stimuli (i.e., strings of letters) shift to involvement of higher-order language networks. The present study investigated this question by repeatedly presenting unfamiliar letter strings in a one-back matching task during an hour-long period. Activation patterns indicated that only brain areas associated with visual processing were activated during the early period, but additional regions that are usually associated with semantic and phonological processing in inferior frontal gyrus were recruited after stimuli became more familiar. Changes in activation were also observed in bilateral superior temporal cortex, also suggestive of a shift toward a more language-based processing strategy. Connectivity analyses reveal two distinct networks that correspond to phonological and visual processing, which may reflect the indirect and direct routes of reading. The phonological route maintained a similar degree of connectivity throughout the experiment, whereas visual areas increased connectivity with language areas as stimuli became more familiar, suggesting early recruitment of the direct route. This study provides insight about plasticity of the brain as individuals become familiar with unfamiliar combinations of letters (i.e., words in a new language, new acronyms) and has implications for engaging these linguistic networks during development of language remediation therapies.

Keywords

letter strings; fMRI; connectivity; reading; learning; plasticity

Individuals learn to read by recognizing letter combinations (or graphemes) as familiar and associating phonological and semantic codes with them. There are several theoretical models of how individuals learn to read, but it is unknown what neural changes are involved. It is especially unclear what changes occur during the early stages of the learning process during which individuals gain familiarity with unfamiliar letter combinations (e.g., learning a foreign language, unfamiliar acronyms). Identification of the neural mechanisms involved in these changes may contribute to designing better remediation strategies for individuals who have difficulty reading. The present study used activation, region-of-interest (ROI), and connectivity analyses of functional magnetic resonance imaging (fMRI) data to

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investigate the neural structures involved in the process of gaining familiarity with unfamiliar combinations of letters.

The dual-route model is the best known model of how individuals read (Coltheart, 1993; 2005; Warrington & Shallice, 1980). This model posits that there are two routes associated with reading: the graphophonological route (also referred to as lexical, indirect or dorsal route) and the lexicosemantic route (also referred to as nonlexical, direct, or ventral route). According to this model, the graphophonological pathway involves the conversion of graphemes to phonemes, which then leads to accessing of word meaning, whereas the lexicosemantic route directly accesses both the visual form and meaning of the word. Readers initially use the graphophonological route, but as words become familiar, readers rely more on the lexicosemantic route for increased efficiency.

There are distinct neural systems involved in each of the two routes (Jobard, Crivello, & Tzourio-Mazoyer, 2003). The graphophonological route is associated with the dorsal (temporo-parietal) system and the lexicosemantic route with the ventral (occipito-temporal) system. The dorsal system activates a parietal attention network (Cohen et al., 2008), including the angular gyrus and supramarginal gyrus in the inferior parietal lobule and the posterior part of the superior temporal gyrus, i.e., Wernicke's Area (Pugh, 2001) The ventral system leads to fast visual decoding of words and includes activation of occipitotemporal areas and areas involved in semantic function, such as lateral extrastriate areas, left inferior occipitotemporal region, superior temporal areas, supramarginal gyrus and the triangular/opercular part of the inferior frontal gyrus. An additional system near the inferior frontal gyrus (IFG; BA 44/45, Broca's Area) is associated with phonological coding (Pugh, 2001).

The dual-route model depends on orthographic regularity (or the frequency of letter combinations in the language) and predicts that familiar acronyms would be processed differently than unfamiliar pseudowords. However, a recent study showed that familiar acronyms generated electrophysiological repetition effects that were similar to words and pseudowords (Laszlo & Federmeier, 2007), suggesting that brain responses to letter strings are sensitive to familiarity of the whole strings rather than orthographic components. This idea is supported by a neuroimaging study that examined the neural correlates of familiarity (Tagamets et al., 2000). Words, pseudowords, letter strings and false font strings (letter-like shapes based on similarity to real letters in shape, size and visual complexity) were examined in a one-back matching task. Pseudowords, letter strings and false fonts vary on a dimension of similarity to familiar words and in their associations with phonological and semantic representations. The left ventral pathway was the most strongly activated network in response to words, pseudowords and letter strings; however, the amount of activation in the left posterior middle temporal cortex decreased as stimuli were less familiar. In general, as stimuli became less familiar, activated regions were less left-lateralized and there was increased recruitment of parietal regions, suggesting more reliance on visuospatial processing for the less familiar strings.

A connectivity study of these same data helped to further clarify mechanisms involved in processing these different types of stimuli (Bokde et. al, 2001). Ventral IFG (BA 47), generally thought to subserve semantic function, had strong functional connectivity with temporal cortex only for words. Dorsal IFG, more associated with phonological processing, showed connectivity with temporal cortex in the words, pseudowords, and letter strings conditions, but not in false fonts, suggesting integration of visual and phonological processes for all stimuli with real letters regardless of familiarity.

Distinct repetition effects have also been observed when comparing familiar vs. unfamiliar visual stimuli. For instance, fusiform was less activated to repetitions of familiar stimuli, but

more activated to repeated unfamiliar stimuli in the part of the fusiform that would later encode these stimuli (Henson, 2001; Henson, et al., 2000). Moreover, the magnitude of these changes in posterior right fusiform depended on the lag between stimuli, with increased repetition response with lag to familiar stimuli and decreased response with lag to unfamiliar stimuli. Other studies have also shown reduced activation to both repeated familiar and repeated unfamiliar stimuli over short time periods.(e.g., fusiform gyrus (Saggar et al., 2010; Xue & Poldrack, 2007), superior parietal lobule, temporal–occipital cortex, lateral occipital cortex (Saggar et al., 2010), and prefrontal cortex (Dale et al., 2000)).

It is likely that different mechanisms are recruited over different time periods during the course of learning. Paradigms that use repetition to study changes over longer periods have shown increases in activity post-intervention. For example, a year-long phonologically mediated reading intervention with individuals with dyslexia led to improved reading fluency and increased activation in left inferior frontal gyrus (BA 45) and left middle temporal gyrus (BA 21) (Shaywitz, 2004) after the intervention. Another study indicated that repeated practice for both moderate (80 trials) and extended (880 trials) training on a visuospatial working memory task activated frontal (inferior, middle and precentral gyri and superior frontal sulcus), parietal, and anterior and posterior cingulate regions. These activations (except the posterior cingulate) decreased with practice, possibly reflecting increased neural efficiency rather than functional reorganization (Garavan et al., 2000). In contrast, individuals who practiced working memory tasks for five weeks (30 trials per day) showed increased activity in prefrontal and parietal regions (Olesen et al., 2004). These findings could be explained by an inverted U-shaped function. For instance, after four weeks of training (two times a day) on a visuospatial n-back task, increases in activation in right inferior frontal gyrus and right intraparietal sulcus were associated with better performance after 2 weeks, but decreased activation (and stable behavioral performance) after four weeks (Hempel et al., 2004).

Changes in strategy may also explain changes in neural activity over time (Jonides, 2004). Reorganization or activation of new regions may be observed with change in strategy. Examining the connectivity between regions could demonstrate how these regions may reorganize or redistribute activity over time (Kelly & Garavan, 2005) and whether changes in activation are due to familiarity or strategy changes.

Although it is clear that there are differences in brain activity between unfamiliar and familiar stimuli, it is unclear how familiarity leads to encoding stimuli as meaningful units. The present study investigated changes that occur with repeated exposure to unfamiliar letter strings over a short period of time presented in the context of a one-back task. Repeated letter strings during a one-back task would not have associated responses to the specific stimulus, so changes in activation would be due to familiarity, not a learned response. The overarching hypothesis of the present study was that repeated exposure of unfamiliar stimuli will reflect not only familiarity effects, but also activation and/or connectivity changes related to integration of letter strings into a language framework involving orthographic, phonological, and possibly semantic function in later repetitions. More specifically, it was hypothesized that repetition of letter strings would lead to increased activation in BA 44/45 of the inferior frontal gyrus, an area that is frequently activated in studies using language tasks. This area was expected to show increased activation if the letter strings were treated more like words over time. In addition, it was expected that posterior middle temporal cortex would be more activated in the late condition compared to the early condition if letter strings were processed more like words, since this region has been found to be activated more in response to familiar than unfamiliar lexical stimuli (Tagamets et. al, 2000). It was expected that visual association areas (e.g., fusiform gyrus) and frontal language-related

regions would be more strongly correlated with each other within late runs than early runs and that connectivity between these regions would increase over time.

Material and methods

1. Participants

Twelve healthy right-handed native English speakers between the ages of 21 and 44 (6 females, mean age = 32, mean education = 15 years (range = 12–19) participated in the study.. After an initial phone screening, all participants were assessed with the SCID and the Structured Interview for DSM-IV Personality Disorders (SID-P, Pfohl, Blum, & Zimmerman, 1997). Participants received the Wide Range Achievement Test 4 (WRAT 4) and the Wechsler Test of Adult Reading (WTAR) in order to rule out language and reading disorders. Participants were free of major medical conditions, had no psychiatric illness and no first-degree relatives with psychiatric disorders, had no current substance/alcohol abuse or dependence, no diagnosable neurological condition, and passed the MR safety screening. The Institutional Review Boards of the University of Maryland School of Medicine and the Johns Hopkins School of Medicine approved the study protocol. All participants were fully informed regarding the nature of the protocol and each gave informed consent.

2. Behavioral task

Participants performed a block-design one-back visual matching task during both the control and the task condition. The task condition consisted of four-character consonant letter strings (Letter Strings condition; e.g., QTVP) presented one at a time. Control blocks had single geometric shapes, the same as were used in our previous study (Tagamets et. al., 2000), i.e. a filled circle: ● and outlined square: □. Although the visual complexity was not matched to the letter strings, the shapes were already familiar, thus, providing a baseline that was not expected to show significant changes due to familiarity. Therefore, comparisons between early and late time periods should yield changes that are mainly due to changes in processing the letter strings. For both conditions, participants were instructed to press a button if the current stimulus matched the one immediately previous. Except for those instances, stimuli were not repeated within a single run. Stimuli were centrally presented for 200 ms at an ISI (Inter-Stimulus Interval) of one per 1000 milliseconds. There were 30 trials in a block, and the series began and ended with a control block, resulting in 120 control trials and 90 letter sting trials in each run. The total time for each run was about 3½ minutes. The runs were repeated 7 times with the same stimuli but a different order of stimuli in each run, and a seven-minute interval between the beginnings of successive runs. At the end of these letter string repetition runs, a final run was performed using common four-character words as stimuli (Words condition; e.g., TONE), using the same task and the same control condition as in the letter string runs. The purpose of this run was to identify locations and exact coordinates for word-specific regions in this group of subjects for the ROI analyses and for comparisons to the letter strings. All but two participants completed the words run and a post-scan interview about strategies that they used to complete the tasks, their comfort in the magnet, and the visual quality of the displays.

3. fMRI

3.1 fMRI acquisition—Volumes were acquired with a Siemens Vision 1.5 T scanner with a fast gradient system. Interleaved Echo-Planer Images (EPI) of 20 axial 5 mm thick slices (4 mm slice plus 1 mm gap) were obtained. Matrix size was 64 × 64 and in-plane resolution was 3.75 × 3.75 mm, with TR = 2000 ms (repetition time), TE = 40 ms (echo time), flip angle = 90°, and a 240 × 240 mm FOV. Scanning for each series started 12 seconds before data collection and task performance began in order to allow spin saturation to reach steady state, and 105 volumes were collected for each fMRI time series.

3.2 Preprocessing—Preprocessing using SPM8 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8) was done as follows: (a) differences in slice acquisition times were corrected, (b) motion effects were corrected by coregistration to the mean of the images (c) volumes were spatially normalized to a standard template (MNI, Friston et al., 1995) and (d) volumes were smoothed by convolution with a Gaussian kernel function (Full Width Half Maximum = 10 mm).

3.3 Contrast analyses

3.31 Whole-brain analysis: A whole-brain random effects analysis was implemented to examine regions activated in each condition. Task minus control contrast images for each subject's first level analysis were entered into second-level two-sample t tests comparing the first two of the seven runs ('early') to the last two of the seven runs ('late'). An uncorrected threshold of $p<0.005$ and a cluster size of 10 or greater were used to examine the contrasts between early and late runs. Whole-brain contrast analyses were also performed for task versus control for each of the three conditions, i.e. for the conditions early letter strings, late letter strings, and words, as well as between words and each of the early and late letter strings conditions. Clusters with a FWE-corrected value of $p <0.05$ are reported, and local peaks of voxels that reached uncorrected $p < 0.001$ within each cluster are also reported in the tables.

3.32 ROI analysis: A region-of-interest (ROI) analysis in four ROIs was conducted to increase the power to detect differences. These regions were selected according to a priori hypotheses (outlined in the Introduction) about which regions would show familiarity-related changes in BOLD activation over time: left inferior frontal gyrus (IFG; BA 45 and BA 47), left fusiform gyrus and left posterior middle temporal gyrus (posterior MTG) (BA 37/BA 21). Within these regions, four sets of coordinates that were more active for words than the other conditions were chosen from Tagamets et al. (2000), which used the same task and control conditions as used here. The nearest local maxima to each of these coordinates in the words condition that was completed by the subjects of the present study were used as the ROI coordinates for this study. Coordinates for left fusiform were also near fusiform areas in prior studies in which words and pseudowords were compared to consonant letter strings (Devlin et al., 2006) and pseudoletters were viewed before and after writing practice (James & Atwood, 2009). The coordinates were: left IFG (BA 47: −44 34 −18), left inferior/middle frontal gyrus (BA 45/46: −42 28 18), left fusiform (BA 37: −46 −54 −24), and left posterior MTG (BA 21: −60 −52 −4).

Spherical ROIs (4mm radius, i.e., about one FWHM in diameter) were created and corrected using the small volume correction (SVC) in SPM8. Peak-level statistics that are significant at an uncorrected *p*-value <0.05 in these ROIs are reported here.

3.4 Connectivity analyses

3.41 Seed-voxel analysis: To investigate functional connectivity of each of these ROIs with the whole brain, the eigenvariates (weighted means of the region for each run) corresponding to either the early or late condition were extracted from 4 mm radius spheres in a main effects analysis for each condition (early or late). The eigenvariates were then entered as covariates in whole-brain regression analyses for the early and late condition, respectively. This procedure was repeated for each ROI.

3.42 ROI-based connectivity analysis: To investigate whether the a priori ROIs were correlated with each other, correlations between eigenvariates from each ROI were computed in early and late runs.

3.5 Regression predicting changes in connectivity—An exploratory regression was computed to investigate whether regions that were activated during the first run predicted changes in connectivity between early and late runs between left IFG (BA 47: −44 34 −18) and left posterior MTG (BA 21: −60 −52 −4). Eigenvariates were extracted (4 mm sphere) from the entire time series' for the first and last runs (1st and 7th) for each subject in the first-level analysis for left IFG and left posterior middle temporal cortex. Correlations between left IFG and left posterior MTG over the entire run were computed for each subject, once for the early condition (run 1) and once for late (run 7), yielding an early r-value and a late r-value for each subject. The early r-value was subtracted from the late r-value to compute the change score for the subject, i.e. the change in connectivity. These change scores were entered as covariates in a second-level regression analysis against run 1.

Results

1. Behavioral data

Paired sample t-tests indicated that the mean reaction time of the first two runs of the control task (498 ms, S.D. = 41 ms) and the last two runs of the control task (514 ms, S.D. = 35 ms) did not differ ($t = -1.56$, $p = 0.15$). Mean accuracy of the two runs (early runs: 89%, S.D. = 8%; late runs: 90%, S.D. = 7%) also did not differ ($t = -.72$, $p = 0.49$) on the control task. The mean reaction time on the letter strings task did not differ between early (524 ms, S.D. = 43 ms) and late (498 ms, S.D. = 34 ms) runs ($t = 1.85$, $p = .10$). Mean accuracy for the letter strings (early: 91%, S.D. = 8%; late: 89%, S.D. = 8%) also did not differ ($t = .66$, $p = .53$).

Reaction time did not differ between the letter string and control tasks during either the early runs ($t = -1.4$, $p = .19$) or late runs ($t = 1.6$, $p = .14$). Accuracy did not differ between the letter strings and control tasks during either the early runs ($t = -1.1$, $p = .30$) or the late runs ($t = 1.2$, $p = .25$).

2. Contrast analyses

2.1 Whole-brain analysis—Whole-brain cluster-level FWE-corrected fMRI results are listed in Table 1 and shown in Figure 1A. The early versus late contrast did not yield any clusters that were significantly different. However, the late versus early contrast yielded two clusters (one left-hemisphere and one right hemisphere), which included bilateral superior temporal gyrus (BA 22) and left inferior frontal gyrus (BA 45/47). Enhanced activation was observed in these regions during the later runs compared to the earlier runs (Table 1 and Figure 1A).

Whole-brain analyses of each condition (early letter strings, late letter strings, and words) versus the control task are shown in Figure 1B and in Supplementary Table 1, 2 and 3. There is considerable overlap among all three conditions in the posterior visual areas, with focal activations in multiple early visual and visual association areas. The words condition also shows significant activations in left inferior frontal cortex and bilateral posterior middle temporal cortex. An additional cluster in posterior middle temporal cortex (BA 21: −60 −52 −4) did not survive the cluster threshold, but it is located 12 mm from the location that was previously found to be unique to real words using the same task (Tagamets et. al., 2000). This location was chosen for the ROI analyses (i.e., BA 21) in the present study. In the late letter strings condition, bilateral frontal regions that were activated overlapped with activations in the words condition, but these were absent in the early condition

Comparisons of the early letter strings condition with words yielded no significant differences in either direction. There was a single cluster in the anterior cingulate cortex (BA

24, −2 24 26), FWE-corrected cluster-level p = 0.001, which was greater in the late letter strings condition than in the words condition (Table 4). There were no regions that were more activated for words than the late letter strings condition.

2.2 ROI analyses—The early letter strings > late letter strings contrast did not yield any voxels within any of the ROIs that met a threshold of $p < 0.05$. In the late letter strings > early letter strings contrast, only the left inferior/middle frontal gyrus (BA 45/46: −42 28 18) differed between conditions ($t = 2.2$, $p = 0.016$).

2.3 Time course trends—Changes in signal over the course of the experiment were examined for regions that demonstrated a change between early letter strings and late letter strings runs in either the whole-brain or ROI analysis (Figure 2). These three regions were: left inferior/middle frontal gyrus (BA 45/46), left inferior frontal gyrus (BA 45/47) and left superior temporal gyrus (BA 22). All three regions demonstrated a general increase in activity throughout the experiment. Figure 2 shows signal strength for all seven runs of the letter strings condition for each ROI. The words condition had no significant activation in the two regions that were chosen from the whole-brain analysis of late versus early conditions (left BA 22 and BA 45/47). These regions showed suppressed activation in the early letter strings condition compared to the control condition. This suppression decreased with successive repetitions. The BA 45/46 location was a local maximum within a cluster that was activated in the words condition, with a voxel-level uncorrected p = 0.001. This region had no activation in the early letter strings condition, and demonstrated a steady rise that approached the activation level in the words condition by the late condition.

3. Connectivity analyses

3.1 Seed-voxel analysis—Regions that were correlated with each seed-voxel at a voxel-level FWE-corrected value of $p < 0.05$ are shown in Table 2 and Figure 3.

Connectivity between the left IFG (BA 47) and other regions was not significant during the early condition. However, during the late condition, BA 47 was correlated with left inferior temporal gyrus (BA 37), left anterior inferior temporal gyrus (BA 20), left posterior middle temporal gyrus (BA 21), and visual areas.

During the early condition, left fusiform (BA 37) was significantly correlated only with left lingual gyrus (BA 18). During the late condition, left fusiform was significantly correlated with bilateral middle occipital gyrus (BA 18/BA 19), left inferior temporal gyrus (BA 20), cuneus (BA 18), bilateral declive, left inferior frontal gyrus (BA 44/45) and left middle frontal gyrus (BA 11).

The left posterior middle temporal cortex (BA 21) was not correlated with any other regions in the early condition, but was correlated with the left cuneus in the late condition.

In order to examine all potentially relevant connections, two additional regions from the whole-brain analysis were chosen as seed voxels: left BA 22 and BA 45/47. During the early condition, BA 45/47 was correlated with bilateral insula, bilateral inferior frontal gyrus (BA 47), bilateral superior temporal gyrus (BA 22), and right middle frontal gyrus (BA 11). During the late condition, BA 45/47 was correlated with the left cingulate gyrus, right inferior frontal gyrus (BA 45), right insula (BA 13) and left parietal cortex (BA 7).

During the early condition, BA 22 was correlated with left precentral gyrus and right superior temporal gyrus (BA 42), but was not correlated with any regions during the late condition.

3.2 ROI-based connectivity analysis—Table 3 and Figure 4 show the second-level correlations between all pairs of the 6 ROIs across subjects during early and late conditions.

The left inferior/middle frontal gyrus (BA 45/46) ROI was not significantly correlated with any of the other ROIs in either the early or late runs. The two additional ROIs, IFG (BA 45/47) and STG (BA 22), which were found to increase activation with repetition in the whole-brain subtraction analyses, were correlated with each other to a similar degree in both early and late runs.

However, changes were found in the network involving left fusiform (BA 37), posterior middle temporal cortex (BA 21), and left IFG (BA 47). Left fusiform (BA 37) and posterior middle temporal cortex (BA 21) were significantly correlated with each other in both early and late runs, with similar r-values in both conditions (see Table 3 and Figure 4). While BA 47 was not significantly correlated with any of the other ROIs in the early run, it became significantly correlated with both posterior MTG (BA 21) and fusiform (BA 37) in the late run, thus forming a cluster of three ROIs that were all highly correlated with each other in the late condition. The connectivity patterns show two separate networks that are suggestive of the indirect route (BA 22 and BA 45/47) and the direct route (BA 21, 37, and 47; see Figure 4). The former is connected in both early and late conditions, suggesting phonological encoding in both conditions. Areas 37 and 21 are connected to the frontal region BA 47 only in the late condition, suggesting the possibility of reorganization toward a more direct route of reading.

4. Additional analyses

Two additional analyses were undertaken in order to examine potential mechanisms associated with these changes. First, a mediation analysis was performed to examine whether one of the posterior ROIs (BA 37 and BA 21) mediates changes in connectivity between the other ROI and BA 47. In addition, an exploratory analysis was done to determine whether activations during early letter strings predicted changes in connectivity between early and late runs between posterior MTG (BA 21) and IFG (BA 47).

4.1 Mediation analysis—The relationship between three ROIs (left IFG / BA 47, left fusiform / BA 37 and left posterior MTG / BA 21)) was tested with a mediation analysis (Baron & Kenny, 1986) using three linear regression models (Figure 5). The procedure requires first, that the independent variable (IV; posterior MTG/BA 21) correlate with the dependent variable (DV, BA 47), $p = 0.011$. Second, the potential mediator (fusiform/ BA 37) must correlate with the IV (BA 21), $p = 0.001$. Third, the mediator (BA 37) should predict the DV (BA 47) even when the variance associated with the IV (BA 21) is removed, $p < 0.001$. Finally, for complete mediation, the correlation of IV and DV, with mediator variance removed, should not differ from zero. The relationship of posterior MTG/BA 21 to BA 47 was not significant when the variance associated with BA 37 was removed, $p = .89$. Thus, BA 37 completely mediated the relationship between posterior MTG BA 21 and BA 47. A similar analysis showed that posterior MTG/BA 21 does not mediate the relationship between fusiform BA 37 and BA 47.

4.2 Identifying regions that predict increases in connectivity between early and late sessions—An exploratory regression was computed to investigate whether activation in any regions during the first run would predict changes in connectivity between early and late runs between left IFG (BA 47: −44 34 −18) and left posterior MTG (BA 21: −60 −52 −4). Results are reported at a voxel-level uncorrected p-value < 0.001 with cluster size >10 voxels. Activation during the first experimental session in left middle/superior temporal gyrus (BA 21/22; −50 −28 0), right inferior frontal gyrus (BA 9; 52 12 38) and

anterior cingulate (BA 32; −10 40 0) were positively correlated with increases in connectivity between left IFG (BA 47) and left posterior MTG (BA 21) between early and late runs.

Discussion

The aim of this study was to determine whether repetition of unfamiliar letter strings over a short period of time leads to increased involvement of visual word-form, phonological and/or semantic regions that are usually activated in response to words. In combination, the whole-brain, ROI analyses, and connectivity analyses indicate that reorganization of activation patterns from visual to more word-like processing began to take place during the first hour of repeated exposure. These results suggest that participants may have started to treat the letter strings as words (or complete units) in later runs by attending to phonological characteristics and searching for similar legal words that have semantic meaning.

1. Whole-brain analyses

The whole-brain analysis showed increased activation in bilateral superior temporal gyrus (STG) and left inferior frontal gyrus in the late runs compared to the early runs. These results are consistent with the hypothesis that regions associated with phonology and semantics are more activated during later runs than during early runs. The right-hemisphere regions, though not a focus of the original hypotheses, have been associated with language processing in prior studies. Bilateral dorsal STG (BA 22) has been implicated in phonetic and prelexical phonological processing during phonological priming and sublexical speech perception (Turkeltaub, 2010; Wilson, 2010). In the left-hemisphere, BA 22 has been activated while speaking written words and may be related to accessing meaning (Philipose et al., 2007). Rapid changes (within 20 minutes) in STG have also been found in a study of time-compressed speech comprehension (Adank & Devlin, 2010), suggesting an adaptability relevant to everyday language function. Given that both left and right STG were suppressed in the early period and became more active in late runs suggests that over time, participants may have attended to the phonological characteristics of the letter strings and were reminded of words that have those characteristics.

The regions that increased activation with repetitions showed a steady increase with successive letter string repetitions. Two of these regions, BA 45/47 and STG (BA 22), did not show activation in the words minus control contrast. These regions have been implicated in an inner speech network (Allen et. al., 2008), and since the control task is also likely to involve inner speech, contrasts between the control and words conditions may not show activation differences in these regions. Suppression of these regions in the early letter strings condition may reflect the need for more attention to visual properties of the letters.

Although it is possible that there were changes in the control task with repetitions, the words condition results suggest that any such changes were not substantial. The words task was presented last, after all of the letter string repetitions, using the same control condition. The locations of activations in words versus the control task are very similar to those that we have previously found using the same task and control conditions (Tagamets et. al., 2000).

2. ROI analyses

ROI-analyses also supported the idea that regions associated with phonological processing are activated more during later runs. For example, greater activation of left inferior/middle frontal gyrus (BA 45/46; −42 28 18) in the late conditions compared to the early conditions is consistent with the idea that participants treated letter strings more like words during later runs. This location was significantly active only in the real words and pseudowords

conditions in our previous study (Tagamets et al., 2000). The coordinates used in the present study are also close to the region in Purcell et al. (2011) in which BA 45 (−44 26 10) was associated with covert reading compared to a checkerboard viewing task. Because this region is thought to be involved in creating and maintaining short term memory representations of phonological information for reading and spelling (Philipose et al., 2007; Purcell et al., 2011) and sentence generation (Haller, 2005), it is possible that participants in the present study changed strategies for the one-back task during the course of the experiment. It is likely that they started the task by trying to remember the letter strings as separate letters, but switched to processing them as units with associated pronunciations by the end of the session1.

3. Connectivity analyses

Investigation of connectivity changes can shed light on reorganization of neural circuits. For example, posterior middle temporal gyrus (MTG) is involved in associating visual representations with phonology or semantics (Graves et al., 2010; Tagamets et al., 2000). In our previous study using the same general design, posterior MTG was most active in the words condition and decreased in a graded manner in the pseudowords, letter strings and false fonts conditions (Tagamets et al., 2000), which suggests this region was more active in response to visual representations that were associated with pronunciations or meaning. If participants used a phonological encoding approach during the task, one would expect posterior MTG to show increased connectivity/correlation with phonological regions. However, this was not observed in either the early or late conditions, perhaps due to reasons outlined in footnote 1.

Results of whole-brain seed-voxel analyses indicated that the left posterior MTG region was not correlated with any regions during the early conditions, but was correlated with the cuneus during the late condition. As the cuneus has been activated in tasks requiring grapheme-phoneme translation (Chen et al., 2002) and in nonlexical decoding (Osipowicz et al., 2011), it is possible that participants were using phonological information from the letter strings to perceive them as whole units during the later runs compared to the early runs. However, connectivity patterns of the other seed voxels and the ROI-based analyses, discussed later, suggest an alternative explanation involving the direct reading pathway.

Activation of left IFG (BA 47) was not correlated with any regions during the early conditions, but was correlated with activation in left-sided language areas: posterior MTG (BA 21), anterior inferior temporal (BA 20) and visual regions (inferior temporal gyrus, middle occipital gyrus, lingual gyrus) in the late condition. Because BA 47, usually associated with meaningful stimuli or effortful semantic retrieval (Nelson et al., 2009), was correlated with these regions only during late conditions, it is possible that participants were treating the letter strings more as words or were attempting to retrieve similar legal words in the late condition. These results suggest the beginnings of reorganization in the direct pathway.

The left fusiform ROI was correlated only with left lingual gyrus during the early condition. During the late condition the fusiform was correlated with a number of mostly left-sided visual and frontal areas: bilateral middle occipital gyrus (BA 18/19), left inferior temporal gyrus (BA 20), cuneus, left inferior frontal gyrus (BA 44/45), cerebellum, and left middle

[1]According to post-experiment interviews, two (out of ten) subjects reported switching from a visual strategy to a phonological strategy. Five subjects reported using a phonological strategy the entire time, one reported using both types of strategies the whole time, one reported using a visual strategy the whole time and one reported using a phonological strategy first and then switching to a visual strategy. However, it is unclear how and for how long these strategies were implemented. Thus, reliability of these self-reports is uncertain, and the sample size is too small to examine these self-reported strategies systematically.

frontal gyrus (BA 11). Thus, participants were likely engaging in simple visual processing during the early runs and later invoked a wider network of regions involved in the integration of orthographic, phonological, and possibly semantic features over the course of the experiment.

The role of fusiform was further clarified by connectivity analyses between a priori ROIs within conditions and by a mediation analysis. During both the early and late conditions, the posterior MTG and fusiform ROIs were significantly correlated with each other. During the late condition, inferior frontal gyrus (BA 47) was also recruited into this network. The mediation analysis suggested that posterior MTG and BA 47 interactions were mediated by fusiform gyrus. Thus, the interaction of phonological information (associated with posterior/ middle temporal cortex) and semantic function (BA 47), was mediated by visual information (fusiform). This pattern suggests increased integration of phonological, orthographic, and semantic information with increased visual familiarity and, as noted earlier, a possible reorganization to include the direct pathway.

The relationship between BA 47 and posterior MTG was further examined in an exploratory analysis that tested which regions during the early letter strings run would predict repetition-related changes in connectivity between left IFG (BA 47) and left posterior MTG (BA 21). This analysis indicated that higher activation in left middle/ superior temporal gyrus (BA 21/22), right inferior frontal gyrus (BA 9) and anterior cingulate (BA 32) during the early run predicted later increases in connectivity between left IFG (BA 47) and left posterior MTG. Although these results warrant caution due to their exploratory nature and the small sample size, they suggest that prelexical processing of phonological information (associated with STG), spatial working memory processes (right IFG) and response conflict/decision-making processes (anterior cingulate) predict how left IFG and left posterior/middle temporal cortex increase connectivity with practice.

Conclusions

The goal of this study was to examine changes in linguistic processes that occur with repetition of items during a short time period (about one hour), which corresponds to a typical training session. We examined changes in brain activations and connectivity that occur with repeated exposure to unfamiliar letter strings in a context in which they must be processed quickly (one-back matching task). We hypothesized that regions that process linguistic features would be recruited over time to facilitate task-performance; thus letter strings would be processed similarly to words with repeated exposure. We expected that this reorganization would be reflected by integration of visual, phonological, and possibly semantic functions that together support interpretation of the letter strings as whole entities, similar to words. Results support this hypothesis, indicating that repeated exposure to unfamiliar letter strings leads to changes in language-related brain regions even in a relatively short time period. During initial exposure, auditory cortex (STG, BA 22) had significant communication with a frontal region that has been associated with language processing (BA 45/47), while the fusiform and posterior MTG had high connectivity with each other. After repeated exposures, these two networks remained segregated. The BA22 - BA 45/47 pathway remained the same, while the fusiform-MTG pathway extended into inferior frontal cortex (BA 47) with substantial increases in connectivity between BA 47 and both the fusiform and posterior MTG. This suggests reorganization that involves the direct pathway, which integrates orthographic, lexical, and semantic information. The mediation analysis suggests that the fusiform plays a pivotal role in this process, meditating connectivity between BA 47 and posterior MTG. The exploratory analysis that determined which regions during early runs predicted changes in connectivity between posterior MTG and BA 47 revealed a network that involves control processes and visuospatial and auditory

regions. This network suggests that executive functions play an important role in mediating the integration of visual, phonological, and semantic attributes of new words. Overall, these results provide information about the initial neural changes that occur as individuals become familiar with unfamiliar combinations of letters (i.e., words in a new language, new acronyms). Although recruitment of semantic regions was not expected for repeated letter strings in a task that did not require semantic operations, these findings suggest that remediation programs that concurrently involve orthographic, phonological, and semantic strategies may be effective for developing successful interventions for reading disabilities.

Highlights

- Repeating new letter combinations initiates activation and connectivity changes
- Early focus on perceptual features
- Later focus on linguistic features (possible search for similar words/ meanings)
- Connectivity analyses suggest reorganization to include lexico-semantic network
- May be informative for development of language remediation strategies

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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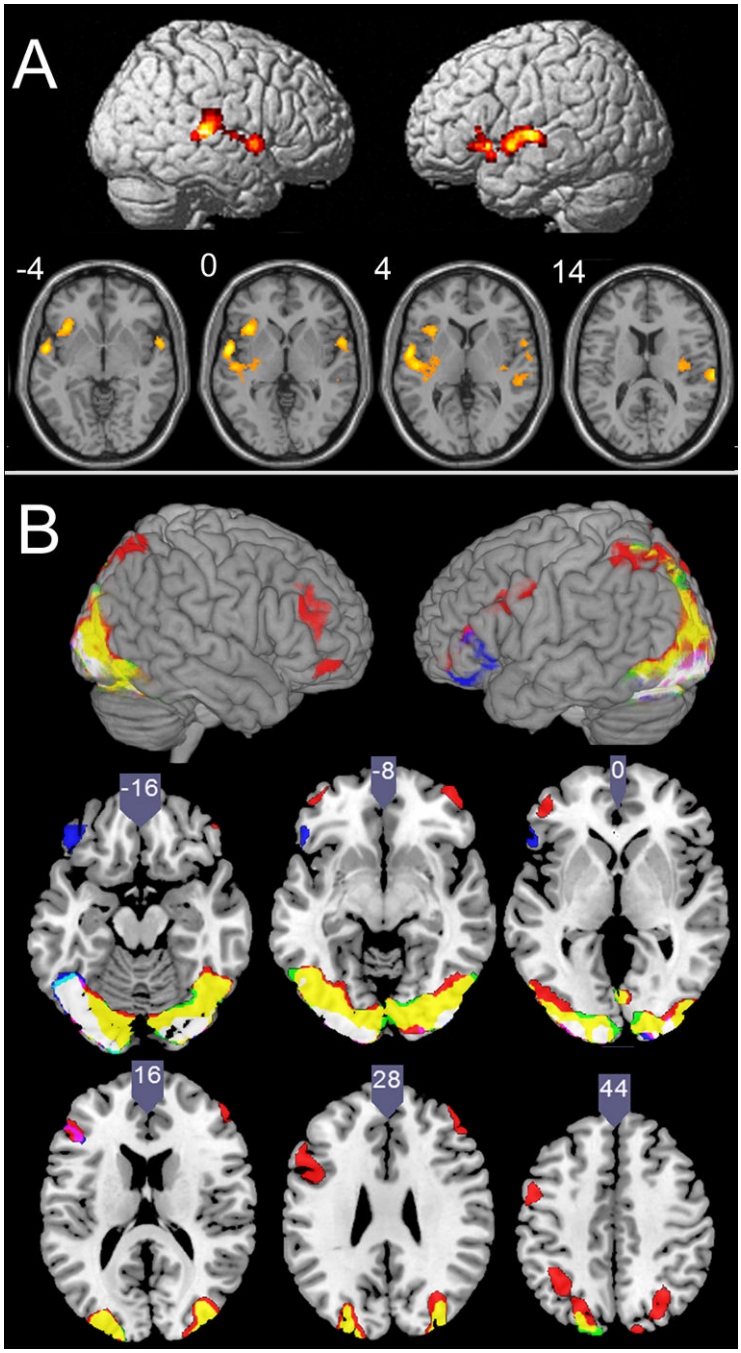

Figure 1.

A. Whole-brain contrast of late runs versus early runs. Maxima within these clusters exceeding a voxelwise $p < 0.001$, as shown in Table 1, are located in left superior temporal gyrus (−54 0 2) and (−48 −16 4), left inferior frontal gyrus (−34 22 0), right superior temporal gyrus (BA 42: 68 −24 14 and BA 22: 58 6 0). No significant activations were found in the early versus late contrast.

B. Task versus control contrasts of early, late, and words conditions. Green: early; Red: late; Blue: words. Areas activated by more than one task are blended colors: Yellow: both early and late; Cyan: both early and words; Violet: both late and words; White: All three conditions.

Data are shown at voxel-level $p < 0.005$ (uncorrected) and cluster size $p < 0.05$, FWE-corrected.

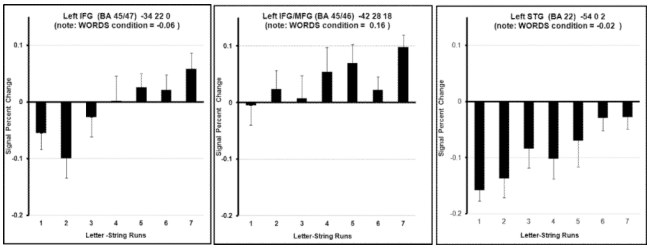

Figure 2.

Signal change within selected ROIs across the seven runs of the experiment. Preselected ROI-based contrasts yielded changes only in left inferior/middle frontal gyrus (BA 45/46: −42 28 18). Also shown are two of the regions that showed increases in late versus early in the whole-brain analysis: left superior temporal gyrus (−54 0 2) and left inferior frontal gyrus (−34 22 0). Error bars depict standard error.

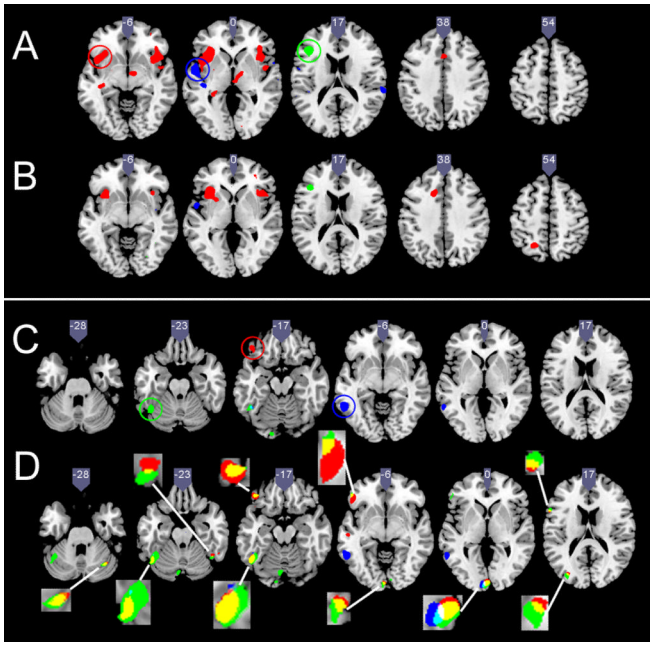

Figure 3.

Seed voxel analyses of selected regions of interest (ROIs). Seed voxel analyses were performed with the four pre-selected ROIs, and also two of the locations that showed increases in the whole-brain analyses of late versus early conditions: left STG (BA 22: −54 0 2) and left IFG (BA 45/47: −34 22 0).

A and B: ROIs that either decreased connectivity or did not change in late versus early conditions. Colors denote areas of significant connectivity with each of the seed voxels. Green: left inferior/middle frontal gyrus (BA 45/46: −42 28 18); Red: left inferior frontal cortex (BA 45/47: −34 22 0); Blue: left superior temporal gyrus (BA 22: −54 0 2). Circles in A indicate the locations of the seed voxels, and are shown only in the early condition. The same voxels were used in the late condition (B).

A. Early condition. The BA 45/47 had significant connectivity with multiple brain regions in the early condition, including contralateral BA 45/47, left IFG, left STG, thalamus, and right frontal and temporal cortex.

B. Late condition. Only the BA 45/47 ROI has significant connectivity with other regions: left cingulate gyrus, right inferior frontal gyrus, right insula and left parietal cortex.

C and D: ROIs that increased connectivity in the late condition compared to early. Colors denote areas of significant connectivity with each of the seed voxels. Green: Fusiform cortex (left BA 37: −46 −54 –24); Red: Inferior frontal cortex (BA 47: −44 34 −18); Blue: Posterior middle temporal cortex (BA 21: −60 −52 −4); Yellow: Overlap of connectivity with BA 37 and BA 47; Cyan: Overlap of connectivity with BA 37 and BA 21; White: overlap of connectivity with all three ROIs.

C. Early condition. Circles indicate the locations of the seed voxels, and are shown only in the early condition. The same ROIs were used in the late condition. During the early condition, only the fusiform ROI has significant connectivity with another region, the primary visual cortex. This is also present during the late condition, with the addition of connectivity with the other two ROIs (slices –6 and 0).

D. Late condition. During the late condition, the fusiform (green, BA37) and BA 47 (red) are correlated with each other. Both are also correlated with areas in the cerebellum, right fusiform, bilateral middle occipital cortex, primary visual cortex, and inferior frontal cortex. The posterior middle temporal ROI (BA 21, blue) overlaps with fusiform and BA47 connectivity with left fusiform and primary visual areas. Note that there is no overlap of

connectivity between only BA 47 and BA 21 (which would be violet), supporting the results of the mediation analysis, which suggests that the fusiform (BA 37) mediates connectivity between BA 21 and BA 47.

Data are shown at $p < 0.1$ (FWE-corrected) to facilitate visualization of the areas reported in the table at $p < 0.05$ (FWE-corrected).

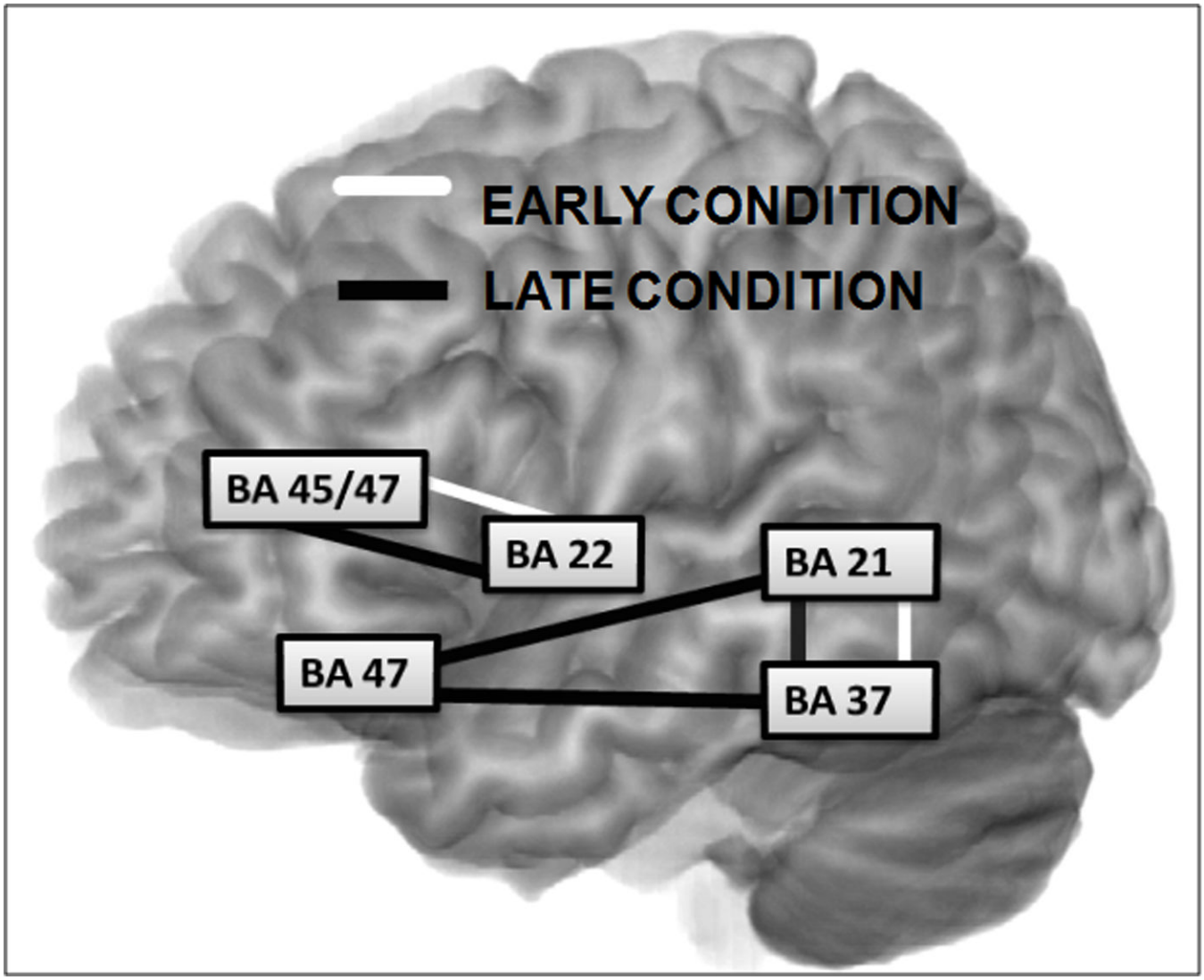

Figure 4.

ROI-based connectivity analyses. Only significant connections are shown ($p < 0.05$, as shown in Table 3). White lines denote significant connections in the early condition. Black lines indicate significance in the late condition. BA 45/46 (−42 28 18) did not have any significant connectivity in either the early or late conditions, so it is not depicted. Connectivity patterns suggest two separate networks that roughly correspond to the indirect route (BA 22 ←→ BA 45/47) and the direct route (BA 21, 37 and 47). While the indirect route is connected in both early and late conditions, the direct route appears only in the late condition.

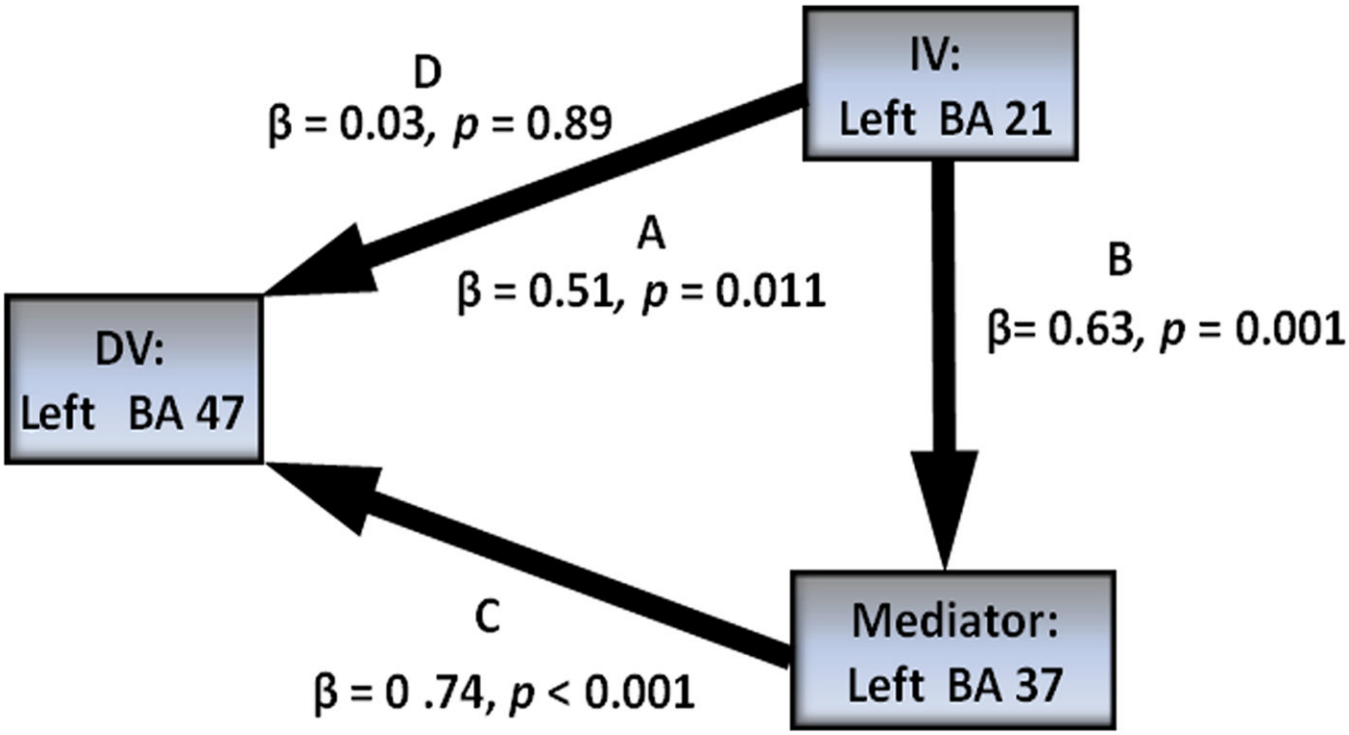

Figure 5.
Mediation analysis showing the relationship between three ROIs (IV: left posterior middle temporal cortex/BA 21; mediator: left fusiform gyrus/BA 37; DV: left inferior frontal gyrus/BA 47) during the late runs. Coordinates are the same as for the ROIs in Figures 3 and 4.

Table 1

Clusters From the Whole-brain Analysis of the Late versus Early Runs.

Cluster size	*p*	T	x	y	z	Region
1049	0.002	4.87	−54	0	2	Left Superior Temporal Gyrus (BA 22)
		3.95	−34	22	0	Left Inferior Frontal Gyrus (BA 45/47)
		3.91	−48	−16	4	Left Superior Temporal Gyrus (BA 22)
		3.59	−32	26	−4	Left Inferior Frontal Gyrus (BA 47)
690	0.020	3.96	68	−24	14	Right Superior Temporal Gyrus (BA 42)
		3.68	58	6	0	Right Superior Temporal Gyrus (BA 22)

Note. p-values are FWE-corrected cluster-level statistics. Coordinates given are local maxima of voxels within the clusters that reach an uncorrected $p < 0.001$.

Table 2

Voxels Correlated with Each Seed-voxel During Early and Late Runs.

Seed-voxel	Early runs	*p*	Late runs	*p*
Left Inferior Frontal Gyrus (BA 47: −44 34 −18)		n.s.	Left Fusiform Gyrus (BA 37: −52 −58 −18)	0.006
			Left Anterior Inferior Temporal Gyrus (BA 20: −36 −12 −38)	0.012
			Left Middle Temporal Gyrus (BA 21: −54 −22 −10)	0.018
			Lingual Gyrus (−2 −92 −2)	0.034
			Left Middle Occipital Gyrus (BA 18/19: −30 −78 14)	0.040
Left Inferior/Middle Frontal Gyrus BA 45/46 (−42 28 18)		n.s.		n.s.
Left Fusiform Gyrus (BA 37: −46 −54 −24)	Left Lingual Gyrus (BA 18: −14 −92 −18)	0.032	Bilateral Middle Occipital Gyrus (BA 18/BA 19: −32 −82 14 and 38 −92 14)	0.004 0.045
			Left Inferior Temporal Gyrus (BA 20: −32 −4 −44)	0.006
			Left Cuneus (BA 18: −4 −96 −2)	0.015
			Bilateral Declive (−6 −76 −18 and 32 −66 −28)	0.017 0.038
			Left Inferior Frontal Gyrus (BA 44/45: −58 16 22)	0.022
			Left Middle Frontal Gyrus (BA 11: −42 38 −18)	0.044
Left Posterior Middle Temporal Gyrus (BA 21: −60 −52 −4)		n.s	Left Cuneus (−8 −96 2)	0.039
Left Inferior Frontal Gyrus (BA 45/47: −34 22 0)	Bilateral Insula (−34 14 2; 40 14 2)	< 0.001	Left Cingulate Gyrus (−16 18 38)	0.005
	Bilateral Inferior Frontal Gyrus (BA 47 −42 14 −8 and 44 16 −4)	< 0.001 0.005	Right Inferior Frontal Gyrus (BA 45: 42 20 4)	0.030
			Right Insula (BA 13: 34 22 6)	0.042 0.042
	Left Superior Temporal Gyrus (BA 22) (−54 −46 8)	0.002	Left Parietal Cortex (BA 7: −22 −58 56)	
	Right Inferior Frontal Gyrus (38 30 0 and 36 16 −6)	0.003 0.026		
	Right Superior Temporal Gyrus	0.045		

Seed-voxel	Early runs		Late runs	
		p		*p*
	(BA 22: 46 2 −4)			
	Right Thalamus (8 −8 −4)	0.007		
	Right Middle Frontal Gyrus (BA 11: 34 50 −10)	0.041		
Left Superior Temporal Gyrus (BA 22: −54 0 2)	Left Precentral Gyrus (−62 −8 10)	0.025		n.s.
	Right Superior Temporal Gyrus (BA 42: 64 −32 18)	0.017		

Table 3

Second-level Correlations Between ROIs During Early and Late Runs.

	Left Inferior Frontal Gyrus (BA 47: −44 34 −18)	**Left Inferior/Middle Frontal Gyrus (BA 45/46: −42 28 18)**	**Left Fusiform Gyrus (BA 37: −46 −54 −24)**	**Left Posterior Middle Temporal Gyrus (BA 21: −60 −52 −4)**	**Left Superior Temporal Gyrus (BA 22: −54 0 2)**
Early					
Left Inferior/Middle Frontal Gyrus (BA 45/46: −42 28 18)	0.26 (0.21)				
Left Fusiform Gyrus (BA 37: −46 −54 −24)	−0.33 (0.11)	0.19 (0.38)			
Left Posterior Middle Temporal Gyrus (BA 21: −60 −52 −4)	0.05 (0.83)	0.40 (0.06)	0.58* (0.003)		
Left Superior Temporal Gyrus (BA 22: −54 0 2)	0.07 (0.73)	0.34 (0.10)	−0.04 (0.84)	−0.22 (0.31)	
Left Inferior Frontal Gyrus (BA 45/47: −34 22 0)	−0.18 (0.40)	0.13 (0.53)	0.01 (0.95)	0.09 (0.67)	0.50* (0.01)
Late					
Left Inferior/Middle Frontal Gyrus (BA 45/46; −42 28 18)	−0.20 (0.35)				
Left Fusiform Gyrus (BA 37: −46 −54 −24)	0.77* (0.00)	0.13 (0.53)			
Left Posterior Middle Temporal Gyrus (BA 21: −60 −52 −4)	0.51* (0.01)	0.16 (0.47)	0.63* (0.001)		
Left Superior Temporal Gyrus (BA 22: −54 0 2)	−0.08 (0.72)	0.02 (0.92)	−0.24 (0.27)	−0.07 (0.75)	
Left Inferior Frontal Gyrus (BA 45/47: −34 22 0)	−0.15 (0.48)	0.01 (0.96)	−0.16 (0.47)	−0.08 (0.70)	0.48* (0.02)

Note.

* $p < 0.05$

Table 4

Clusters From the Whole-brain Analysis of the Late Runs versus Words.

Cluster size	*p*	T	x	y	z	Region
1019	0.001	5.87	−2	24	26	Left Anterior Cingulate Cortex (BA 24)
		5.33	−10	12	44	Left Anterior Cingulate Cortex (BA 32 / SMA)
		4.90	−6	20	38	Left Anterior Cingulate Cortex (BA 24)

Note. p-values are FWE-corrected cluster-level statistics. Coordinates given are local maxima of voxels within the clusters that reach an uncorrected $p < 0.001$.