

An fMRI Study of Word-Level Recognition and Processing in Patients with Age-Related Macular Degeneration

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PURPOSE. To compare the cortical networks that underlie word recognition and processing in patients with age-related macular degeneration (AMD) with those of normally sighted control subjects using functional magnetic resonance imaging (fMRI).

METHODS. Six patients with bilateral geographic atrophy who were using an eccentrically located preferred retinal location were recruited. Six younger and six older control subjects were also recruited. Patients and control subjects were asked to perform a three-letter (3Let) and a six-letter (6Let) word recognition task during fMRI on a 3.0-Tesla MRI scanner. The fMRI tasks were two-condition, blocked-design paradigms in which central fixation was alternated with a word recognition task requiring a forced, two-choice reaction time living/nonliving judgment.

RESULTS. When contrasted with controls, patients showed increased brain activation in a widespread cortical network that included regions identified as the frontal eye fields, both superior and inferior parietal lobules, and regions within the prefrontal cortex. Peak activation within these prefrontal regions was correlated with increased accuracy ($r = 0.875$, $P = 0.024$; $r = 0.848$, $P = 0.033$) and decreased reaction times ($r = -0.861$, $P = 0.028$; $r = -0.842$, $P = 0.036$) for the 3Let task within the group of patients. Correlations between peak activity and behavioral performance were also found in both the right (-0.818 , $P = 0.047$) and left ($r = -0.839$, $P = 0.037$) superior parietal lobules for the 3Let task. Similar relationships were found for the 6Let task.

CONCLUSIONS. Patients with AMD demonstrate increased prefrontal and parietal activation compared with controls. The authors posit that these increases reflect increased top-down involvement in basic word recognition to compensate for decreased sensory function. (*Invest Ophthalmol Vis Sci.* 2009;50:4487-4495) DOI:10.1167/iovs.08-2258

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Age-related macular degeneration (AMD) is one of the most common visual impairments in persons over 50 years of age.¹⁻³ The deficits in visual function as a result of AMD are debilitating because those affected lose their ability to carry out many of their daily activities that require resolving fine spatial detail such as reading.^{4,5} As central visual acuity becomes progressively poorer, a parafoveal locus for fixation, or preferred retinal locus (PRL), may be chosen because it provides better vision than the diseased fovea.^{6,7}

Functional magnetic resonance imaging (fMRI) studies providing evidence of plasticity of the human visual system after retinal degeneration are scarce. Two studies^{8,9} that have been conducted have focused on retinotopic mapping and whether those cortical areas that respond to central stimuli can adapt and be activated by more peripherally presented stimuli. The findings of these two studies are conflicting, and the contradiction may be based in the age of disease onset and, therefore, the adaptation periods for patients (plasticity was found in the Baker et al.⁸ study of patients with juvenile-onset macular degeneration), the differential nature of the task or test stimuli, or some remaining retinal sensitivity in diseased areas. In fact, one recent study by Masuda et al.¹⁰ found that brain activation in four subjects with AMD was dependent on the task and not the stimulus. Overall, responses were reduced in the foveal projection zone in response to passive viewing of a stimulus but activation in those same areas when a stimulus-related judgment was required of a subject.

Recent work from our laboratory demonstrated that patients with AMD show increases in frontal and parietal involvement even for basic oculomotor tasks.¹¹ These findings lead us to hypothesize that compensation for reduced vision does occur and takes the form of increased top-down involvement. However, it is likely that this increased cortical involvement requires greater attentional allocation than is needed in controls. This increased attentional involvement is observed as increased latencies and decreased accuracy. Because higher order cortical regions are recruited during even basic oculomotor functions, it would be reasonable to hypothesize that increased cognitive demands would lead to increased reliance on these attentional networks.

To test this hypothesis, we collected fMRI data while patients with AMD and normally sighted younger and older controls each performed a single-word reading and comprehension task. We hypothesized that the use of a PRL adds an additional level of complexity and task difficulty, even in this simple word recognition and comprehension task. In fact, previous behavioral research has demonstrated a cost (reduced accuracy or increased latency, or both) for single-word reading. The purpose of this study was to quantify that cost in terms of brain activation. In other words, is the use of a PRL, even in patients who use the PRL for daily activities, an activity that demands effort and attention when combined with even simple cognitive tasks? To assess this, we manipulated task difficulty by word length (three-letter words vs. six-letter words) and contrasted activation during the word recognition/judgment task with the maintenance of fixation alone. This contrast directly addresses whether there is an additive cost to the maintenance and use of a PRL during a cognitive task

TABLE 1. Age, Sex, Disease Duration, and Acuity for Both Eyes and PRL Size in the Better Eye for Each Patient with AMD

Patient	Age (Year)	Sex	Disease Duration (Years)	Acuity (OD)		Acuity (OS)		PRL Size (Degree/Better Eye)
				logMAR	Snellen	logMAR	Snellen	
1	76	Female	3	0.78	20/121	0.92	20/166	6/OD
2	83	Male	11	0.94	20/174	1.30	20/400	6/OD
3	55	Female	5	1.26	20/360	1.36	20/450	3/OD
4	64	Male	4	0.58	20/76	0.66	20/91	12/OD
5	82	Female	3	1.20	20/320	1.44	20/560	6/OD
6	70	Male	2	0.58	20/76	0.74	20/110	9/OS

compared with simply maintaining and using a PRL. The present study represents a first step toward understanding the cortical and neuronal changes that occur as a result of decreased vision in patients with AMD during the performance of complex cognitive tasks that rely on a degraded sensory system. The overall goal of the research program was to investigate the biological underpinnings of adaptation in patients who are using PRLs.

METHODS

Participants

The research was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki. Before participation all subjects provided informed written consent.

Patients

We included six patients (three women, three men) with AMD, ranging in age from 55 to 83 years. Visual acuities in the patients' better eyes ranged from 20/76 (0.58 logMAR) to 20/360 (1.26 logMAR). All patients had bilateral geographic atrophy. All patients were using an eccentric PRL as determined from fundus fixation photographs, a procedure used in a previous publication,¹² and a microperimeter (Nidek; Padova, Italy). PRL sizes were assessed using our functional fundus imaging system (FFIS), which measures visual acuity at 27 locations within the macular region. This procedure has been described in earlier publications.¹²⁻¹⁵ The patients' PRLs ranged from 3° to 12° horizontally. The PRL measurement was based on the lateral extent of measures that fell within 2 lines of the patients' best acuity within the fixation region.

Detailed information on age, sex, disease duration, acuity, and PRL size for the patients with AMD are presented in Table 1.

Control Subjects

We recruited six younger normally sighted controls and six normally sighted subjects who were demographically equivalent in both age and sex to the patients with AMD (older controls). The younger control group consisted of three women and three men, ranging in age from 22 to 31 years (median age, 25 years). The older control group consisted of four women and two men, ranging in age from 54 to 78 years (median age, 73 years). All the normally sighted control subjects had corrected vision of at least 20/20 in both eyes. Comparisons between patients with AMD and demographically equivalent older controls provided information on the effects of disease, whereas comparisons between younger controls and patients with AMD provided information on the likely interaction between disease and age. The limitation of this choice of normally sighted controls performing the task using central vision is that the effects of attention are not controlled. Specifically, the patients use PRLs that require the use and maintenance of peripheral vision requiring significant effort and covert shifts of attention, whereas the controls do not have this resource-dependent requirement. Because of this, the choice of control group could be either normally sighted controls completing the task with central vision (as

we have chosen here) or normally sighted controls completing the task with PRLs to match those of the patients. The challenge of the latter choice is that the patients with AMD have had time to adapt to the use of the PRL, while the disease progresses. Any control group would not have this period of adaptation or the sensory demand to use it. As such, these controls would address the issue of attentional demands in the use of a new PRL but would not match patients because of adaptation time.

Experimental Methods

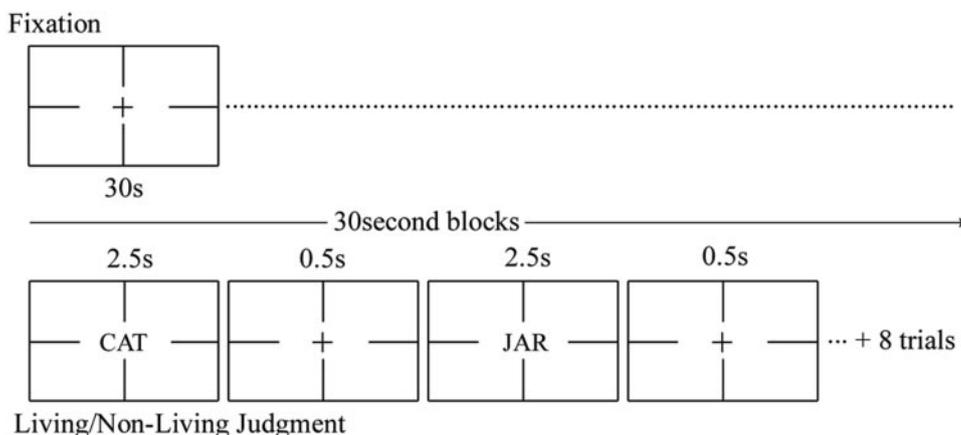
Sequence of Experiments. The study consisted of a single training and eye movement monitoring session to ensure task performance that was then followed immediately by fMRI data acquisition. In the training session, the patients and control subjects were given instructions and practice on both the three-letter (3Let) and six-letter (6Let) word recognition tasks. Although quantitative measurements of eye movements were not collected in the scanner, they were monitored and digitally recorded during fMRI data acquisition (MRIx Technologies, Bannockburn, IL). These videos were reviewed for all patients and controls to ensure task performance.

Imaging Tasks. All visual targets were designed at an appropriate size based on the patients' PRL sizes and visual acuity levels (e.g., the letter targets were the equivalent of a Snellen 20/600 optotype size). All paradigms were designed to require subject feedback to provide performance parameters including accuracy and response time. Patients were placed inside the MRI with their heads stabilized not only by the use of pads but also by the use of fixed headphones. Additionally, a visual feedback system was used to further reduce head motion.¹⁶

3Let or 6Let Word Recognition Tasks. The 3Let word recognition paradigm and the 6Let word recognition paradigm were presented using a blocked-design consisting of six 30-second cycles of steady fixation alternated with six 30-second cycles of the word recognition task. For ease of instruction, the 3Let task and the 6Let task were presented in separate paradigms. All paradigms began with 12 seconds of discarded data acquisition to ensure equilibrium of the longitudinal magnetization. The paradigm began with a 30-second rest condition to allow adaptation to the scanner environment by the subjects. Orthogonal lines running vertically and horizontally with a width of 0.4° were provided to help patients locate the targets in each paradigm. Each letter within the word subtended 2° of visual angle and was equivalent to a 20/600 optotype and was, therefore, large enough to be resolved by all patients. Although not drawn to scale, a schematic of these methods is presented in Figure 1.

For the word recognition tasks, either a single three-letter or a single six-letter word was presented in the center of the screen. Subjects were required to complete a forced, speeded, two-choice discrimination task that required a living/nonliving distinction. For example, if the target word was *cat*, subjects should have indicated that the word represented a living thing. If the word instead was *jar*, the required response was nonliving. During the stimulus period, the word was presented for 2500 ms. An intertrial interval of 500 ms was presented after each word. Because the objective of the study was to

FIGURE 1. Schematic of the experimental methods. Participants were presented with six cycles of central fixation (*top*) alternating with a living/nonliving word judgment task (*bottom*). Fixation blocks were presented for 30 seconds each. Within the living/nonliving task, a single word was presented centrally for 2.5 seconds and was followed by a 0.5-second fixation screen. Each 30-second block included the presentation of ten word-judgment trials. To assist the patients with AMD, gridlines were presented vertically and horizontally, leading into the location where either the word or fixation would appear.



examine the entire network involved in all aspects of word recognition and not the component processes, a rest condition was used that required the maintenance of fixation on a 2° cross located in the center of a screen.

Instructions to Participants

Normally sighted controls were instructed to maintain central fixation during periods in which the fixation cross was present. Patients with AMD were asked to use their PRLs to maintain fixation and carry out the task. All participants were instructed to respond to the word judgment task as quickly and accurately as possible.

Imaging Parameters. A 3.0-Tesla whole body scanner (EXCITE 2.0; GE Medical Systems, Waukesha, WI) using serial gradient echo, echo-planar imaging (plane = axial; TR = 2999 ms; TE = 30.7 ms; flip angle = 90°; NEX = 1; bandwidth = 62 kHz; voxel size = 3.125 mm × 3.125 mm × 3 mm; acquisition matrix = 64 × 64; FOV = 20 × 20 cm²; slice thickness/gap = 3/1 mm/mm; slices = 34) was used for the 3Let and 6Let paradigms. The paradigms were presented in the scanner on a visor and were coordinated with behavioral and physiological measurements (MRI χ Technologies).

After the completion of each functional imaging session, a single three-dimensional (3D) high-resolution anatomic scan was acquired (3D inversion recovery fast spoiled gradient recalled; plane = axial; TR = 9 ms; TE = 2.0 ms; flip angle = 25°; NEX = 1; bandwidth = 15.6 kHz; acquisition matrix = 256 × 256; FOV = 22 × 16.5 cm²; slice thickness/gap = 1.5/0 mm/mm; slices = 124).

Imaging Analysis. A series of analyses was carried out on the image data for the younger controls ($n = 6$), the older controls ($n = 6$), and the group of patients with AMD. This group level analysis was followed with a case-series analysis of each patient with AMD. The latter analysis allows for better characterization of individual differences that may better characterize the heterogeneity common in this patient group. We describe the preprocessing that was initially carried out on the individual data and our methods for identifying relevant regions of interest (ROIs). After this, we describe a series of analyses that were conducted to identify the regions involved in completing the tasks for younger control subjects, older control subjects, and AMD patients and to quantify the responses within each of the identified regions. A random effects analysis (with individual subjects treated as random effects) was then carried out on the younger controls and, separately, on older controls and patients with AMD to detect significant groupwise ROIs. Direct comparisons between controls and patients groups were also carried out (two-sample voxelwise comparisons). These group analyses were followed with extraction of our primary dependent measure, which included the volume of activation (mm³) and peak signal change from the ROIs applied to the data.

Data Screening, Image Preprocessing, and Statistical Analysis. Before any statistical processing, the data were screened for excessive head motion, as calculated within AFNI software (National

Institute of Mental Health, Bethesda, MD; <http://afni.nimh.nih.gov/afni>).¹⁵ Any data set exceeding 3 mm of in-plane head motion was excluded from further analysis. The application of this criterion excluded data from two additional patients, two younger controls, and one older control. Data from these five subjects are not reported in any other portion of this article. The final sample included six patients with AMD, six younger controls, and six older controls. Additionally, to reduce novelty effects, the first complete cycle of the tasks was excluded from further analyses to ensure acclimation to the scanning environment.

The fMRI data were preprocessed on a voxelwise basis in FIASCO (Online Analysis of Functional MRI Datasets on Parallel Platforms; <http://portal.acm.org/citation.cfm?id=279911>)¹⁷ before the calculation of any statistics. This type of calculation then means any group differences are effects that are above and beyond the use of the PRL because the baseline condition is fixation for patients and controls. After the drift was corrected, outliers were identified and excluded. An outlier was defined as any image in the time series data that fell 2 SD from the mean of the series. To be included in further analysis, we required that at least 50 volumes of fixation and 50 volumes of the eye movement task would remain after our outlier censorship. A 3D head motion correction¹⁷ was then applied to the remaining data.

To determine the extent of activation, voxelwise t -statistics for blood oxygenation level-dependent (BOLD) contrast between the eye movement and stationary fixation conditions for each paradigm were calculated in FIASCO.¹⁷ To accommodate for the shape of the hemodynamic response, data from the first 6 seconds of each 30-second block were discarded.¹⁸ To control for multiple comparisons, we applied a false discovery rate (FDR) of 0.05 to the data from each subject. The FDR controls for the proportion of false positives among only those voxels that exceed the statistical threshold and, therefore, reduces the likelihood of type I errors.¹⁹ The data were then imported into AFNI²⁰ and transformed into Talairach-Tourmoux coordinates. This step involves interpolation of the data. A cluster threshold requiring 12 contiguous (in any direction) active voxels (equivalent to four voxels in original image space) was then applied.²¹ The interpolated functional data were smoothed using an isotropic Gaussian kernel (full-width half-maximum, 3 mm³). Random effects analysis was carried out separately on the group of younger controls, the group of older controls, and the group of patients with AMD. Group data for younger and older controls was thresholded at $P = 0.05$.

ROI Identification and Analysis. Random effects analyses were conducted on the normalized maps for the group of six younger controls and (separately) for the group of six older controls. To determine the ROIs that were implicated in each paradigm, a mixed-effects analysis was conducted on the normalized activation maps for these groups of subjects so that those clusters that were significantly implicated during the experimental protocol were identified. The clusters of activated voxels were localized to brain regions commonly recognized

TABLE 2. ROIs, Corresponding Brodmann Regions, ROI Size, (mm³) and Coordinates of Each ROI Center

	BA	ROI Size	Center of ROI		
			x	y	z
Prefrontal cortex	45				
Left		58358	-33	-33	36
Right		55796	34	-35	35
Frontal eye fields	8				
Left		23542	42	-6	44
Right		24496	-43	-5	43
Visual cortex	17/18				
Left		21848	10	-88	-8
Right		21856	-11	-88	-8
Supplementary eye fields	6				
Left		6613	5	8	53
Right		7306	-5	8	52
Visual cortex	19				
Left		14663	24	-88	16
Right		14662	-23	-89	17
Inferior parietal	7/40				
Left		26409	48	-41	39
Right		26690	-49	-41	39

as part of the visuospatial network, including the left and right frontal eye fields, supplementary eye fields and supplementary motor areas, left and right parietal lobules along the intraparietal sulci, and visual cortical regions (V1, V2, V3, V5/MT). Because the paradigms were not designed to map subregions within visual cortex and because the anatomic landmarks were unclear, we combined our ROIs representing V2 and V3. Based on these analyses and the neuroimaging literature on word recognition, we defined the anatomic boundaries of these regions of interest to characterize the extent of task-related activation. These regions were first identified on the averaged anatomic image and included the left and right frontal eye fields that were defined to include the precentral sulci and immediately adjacent gyri²²; the supplementary motor areas, including the supplementary eye fields that were identified as the tissue anterior to the precentral sulcus along the medial frontal lobes and posterior to the caudate nucleus²³; the superior parietal lobule, which was drawn superior to the intraparietal sulcus and posterior to the postcentral sulcus^{23,24}; left and right inferior parietal lobule (inferior and posterior to the intraparietal sulcus including the supramarginal gyrus)²⁵; primary visual cortices (along the calcarine fissure to the cuneus and lingual gyrus)²⁶; secondary and tertiary visual cortex (from the borders of V2 to the middle occipital gyrus)²⁵; and fusiform gyrus (from the mammillary body to the anterior tip of the parieto-occipital sulcus).²⁶ We broadly define the prefrontal cortex (PFC) using Brodmann definitions to include the area between the superior rostral sulcus and inferior rostral sulcus and dorsally by

the anterior cingulate. Peak clusters of activation and volume of activation were extracted from each ROI for each subject individually for each comparison. The voxel with the maximum *z*-score within each ROI for the younger and older control group data and the corresponding size of the ROI are presented in Table 2.

RESULTS

Behavioral Data

Accuracy and response latencies on both the 3Let and 6Let tasks are presented in Figure 2. Although the trend was for the patients with AMD to have reduced accuracy, overall this observation was not significant ($F_{(2,17)} = 1.726, P = 0.211$). The patients with AMD did have increased latencies for responding on correct ($F_{(2,17)} = 8.999, P = 0.003$) and incorrect ($F_{(2,17)} = 12.259, P = 0.001$) trials compared with controls.

Baseline Networks in Controls: 3Let Task

Representative slices depicting regions in the group of younger controls (Fig. 2A) and the group of older controls (Fig. 2B) for contrasts between the 3Let task and central fixation are presented in Figure 3 (left). Both groups of controls showed activation in a network that includes the frontal eye fields, supplementary eye fields, and supplementary motor areas, regions in the left and right middle frontal gyrus, regions localized to the left and right dorsolateral prefrontal cortex, left and right inferior and superior parietal lobules (with a differential involvement in the left, in contrast to the right, for inferior and superior parietal lobules), fusiform gyrus (bilaterally), and primary, secondary, and tertiary visual cortex. The group of older controls showed activation in all these regions but also showed activation in the middle temporal gyrus and bilaterally in the ventrolateral prefrontal cortex.

Baseline Networks in Controls: 6Let Task

Representative slices depicting regions implicated during the 6Let task relative to central fixation for the group of younger controls (Fig. 3F) and the group of older controls (Fig. 3G) are presented in Figure 3 (right). Similar to the network observed during the 3Let task, controls showed activation in the frontal eye fields, supplementary eye fields and supplementary motor areas, postcentral sulcus, regions in left and right middle frontal gyrus, regions localized to the left and right dorsolateral prefrontal cortex, left and right inferior and superior parietal lobules (with a differential involvement in the left compared with the right for inferior and superior parietal lobules), fusiform gyrus (bilaterally), and primary, secondary, and tertiary visual cortex. Unlike in the 3Let task, the older controls did not show activation in the ventrolateral prefrontal cortex.

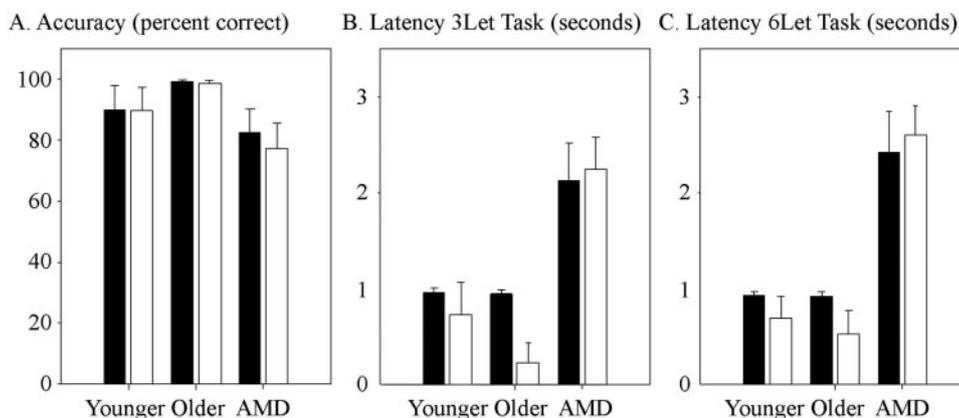


FIGURE 2. (A) Accuracy (percentage correct) for younger controls, older controls, and patients with AMD for the 3Let (black bars) and 6Let (white bars) tasks. Response latencies, in seconds, for correct (black bars) and incorrect (white bars) for the 3Let tasks (B) and the 6Let (C) tasks.

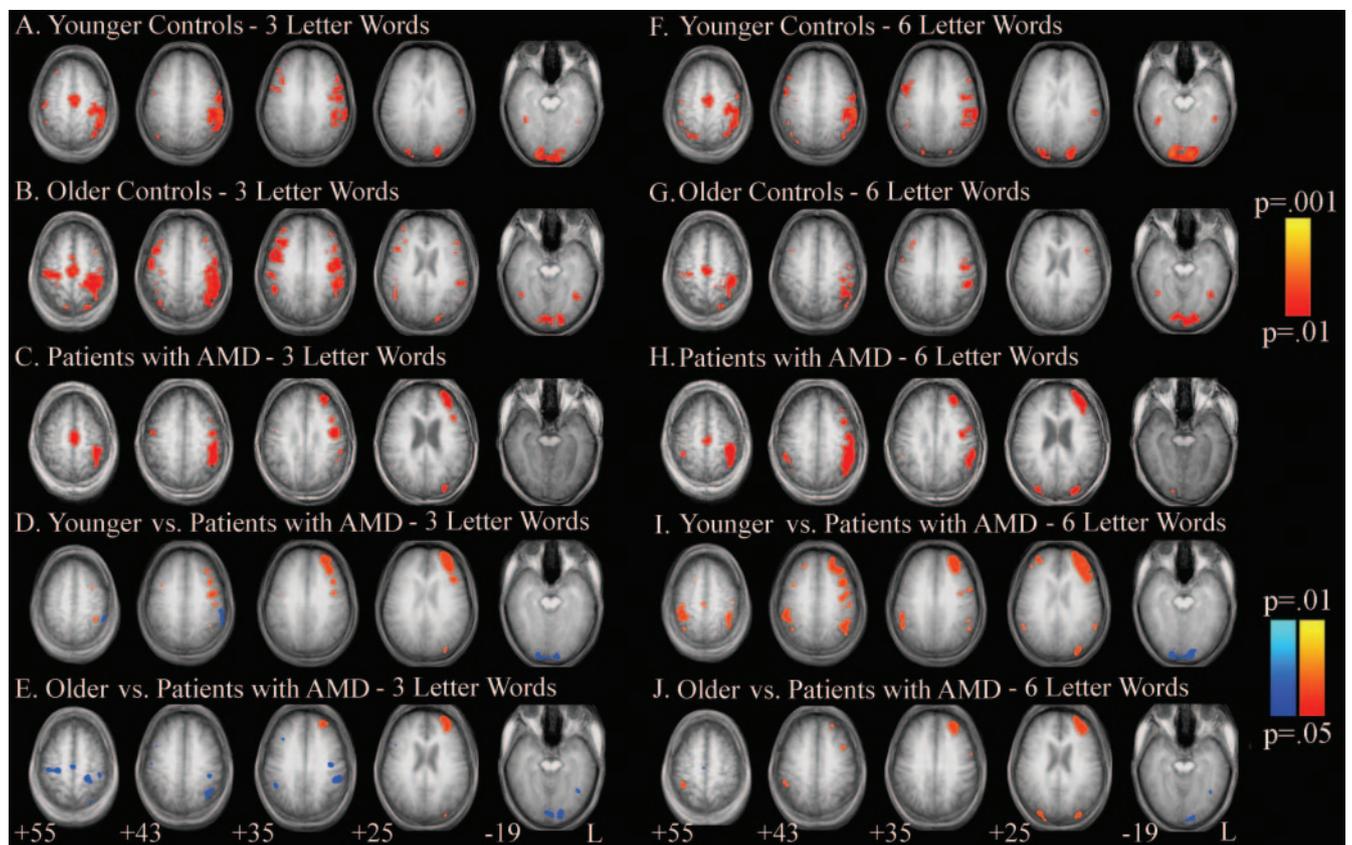


FIGURE 3. Significant regions of activation that showed increased activity during the 3Let (*left*) and the 6Let (*right*) tasks compared with fixation. Activation maps are presented for the group of younger controls (A, 3Let task; F, 6Let task), older controls (B, 3Let task; G, 6Let task), and patients with AMD (C, 3Let task; H, 6Let task) and for comparisons between younger controls and patients with AMD (D, 3Let task; I, 6Let task) and between older controls and patients with AMD (E, 3Let task; J, 6Let task). In (D) and (E), regions with greater activation for controls are indicated in *blue*, and regions with greater activation in patients are indicated in *red*. All comparisons exceeded a minimum threshold of $P = 0.05$ corrected for multiple comparisons.

Baseline Networks in Patients with AMD: 3Let Task

During the 3Let task, patients with AMD (Fig. 3C) showed activation in the supplementary motor/eye regions, bilaterally in the frontal eye fields, along the inferior and superior portions of the left parietal lobule, and in a region in the left dorsolateral prefrontal cortex.

Baseline Networks in Patients with AMD: 6Let Task

A similar pattern of activation that was observed for the 3Let task in the group of patients with AMD was seen with the 6Let task. In other words, activation was observed in the supplementary motor regions including the supplementary eye fields, the left inferior and superior parietal lobules, bilaterally in the frontal eye fields, and in the left dorsolateral prefrontal cortex. Additional activation was observed in inferior and superior parietal lobules.

Comparisons between Patients with AMD and Controls: 3Let Task

Because the calculation of individual subject maps was created before random effects analysis using fixation as a control, these group effects included a baseline condition for effort required to maintain and use the PRL. As such, any significant regions of interest can be interpreted as the combination of effects of the cognitive task (reading) in addition to the networks required

for movement of the PRL. Voxelwise, two-sample *t*-tests were conducted on the data from the patients with AMD compared with younger (Fig. 3D) and older (Fig. 3E) control subjects. Consistent with the visual inspection of differences between groups, younger and older controls showed increased activation in regions in left superior and inferior parietal lobules and in primary and secondary visual cortices relative to the group of AMD patients. Comparisons between the patients with AMD and the group of older controls (Fig. 3E) identified additional significant clusters of activation bilaterally in the frontal eye fields, bilaterally in superior parietal regions, in the supplementary motor regions and eye fields, and in a region in left fusiform gyrus with significantly greater activation for the older control group.

Comparisons between Patients with AMD and Controls: 6Let Task

Two-sample *t*-tests conducted on the group data for the 6Let task from the patients with AMD relative to the younger controls (Fig. 3I) demonstrated that patients showed increased activation in the supplementary motor regions, frontal eye fields, areas in inferior and superior aspects of the parietal lobule, bilaterally in dorsolateral and ventrolateral prefrontal cortex, and the left middle temporal gyrus. In contrast, younger control subjects showed increased activation only in primary and secondary visual cortices in contrast to the group of patients with AMD. Patients with AMD also showed overall increased activation compared with older controls on the 6Let task

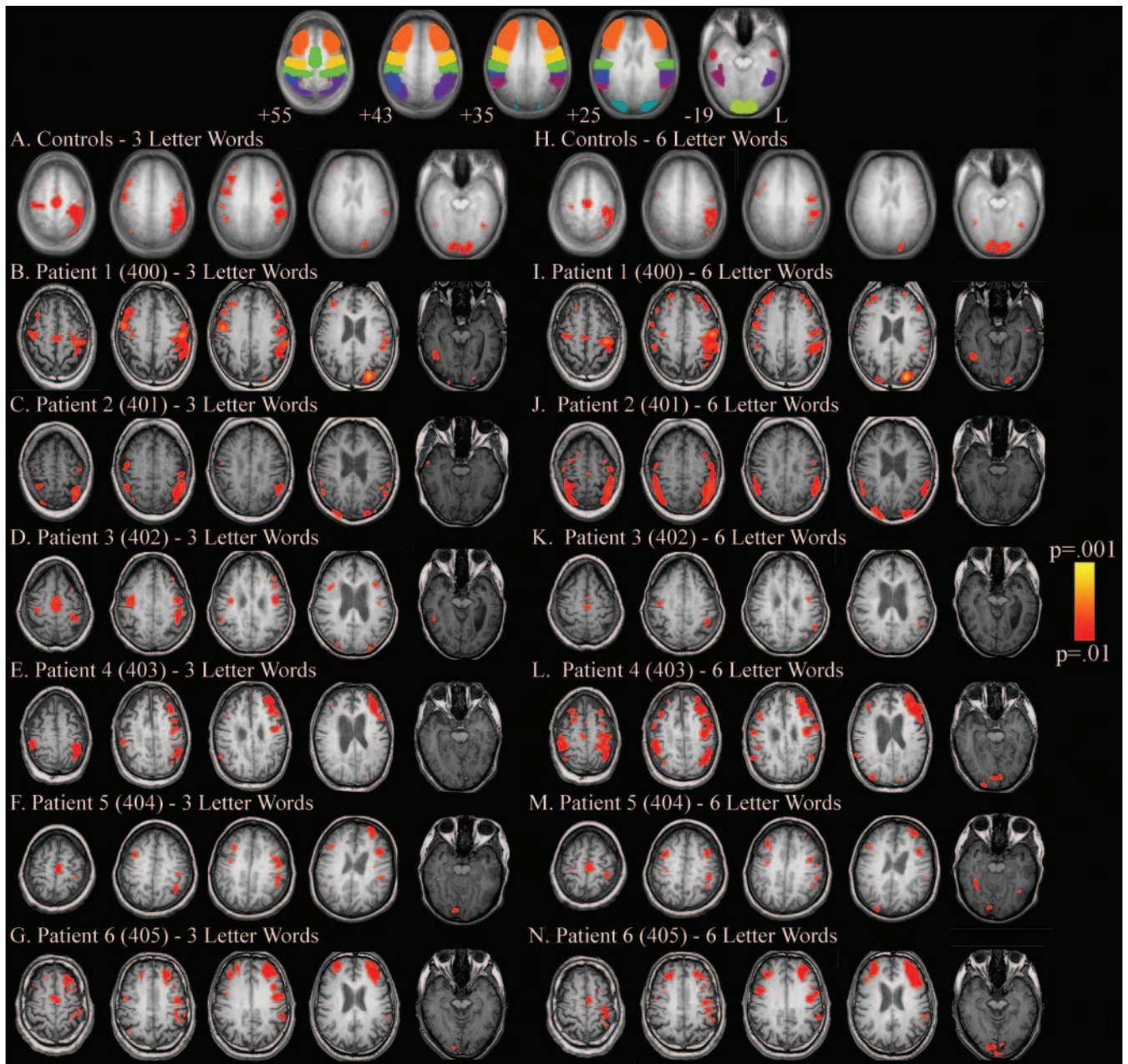


FIGURE 4. ROIs are presented at the top of Figure 3 and include the inferior parietal lobule (*dark blue*), superior parietal lobule (*purple*), supplementary motor area/supplementary eye fields (*light pink*), dorsolateral prefrontal cortex (*orange*), frontal eye fields (*dark yellow*), primary motor area (*green*), V3 (*light blue*), medial temporal lobe (*red*), fusiform gyrus (*dark pink*), and primary visual cortex (V1/V2; *green*). Data from the entire group of controls are presented for the 3Let (Fig. 3A) and 6Let tasks (Fig. 3H). Activation maps are presented for each patient for the 3Let (*left*) and 6Let (*right*) tasks. All data exceed a threshold of $P = 0.01$ corrected for multiple comparisons.

(Fig. 3J). Consistent with the visual inspection of differences between groups, patients with AMD showed increased activation in the left dorsolateral prefrontal cortex, left frontal eye fields, right superior parietal lobule, and bilaterally in the inferior parietal lobule. In contrast, older controls showed greater activation than patients with AMD only in primary and secondary visual cortices and in a region identified in the left fusiform gyrus.

Variability in Activation Data

Because of increased variability in the activation data for patients with AMD, each subject was examined individually and as a part of the group. Representative slices, consistent

with those chosen for the group data, are presented in Figure 4.

These data provide support for a general and consistent increase in prefrontal activation for patients compared with controls. However, the variability in the data does require several qualifications to be placed on the interpretation of the data. One is that patients are more variable than controls. As such, increases in activation compared with those in controls in the group maps are reflective of consistently increased activation in regions such as the prefrontal cortex. However, comparisons that are significant in the opposite direction could be interpreted to indicate that the controls as a whole show increased activation or to suggest that increased variability in

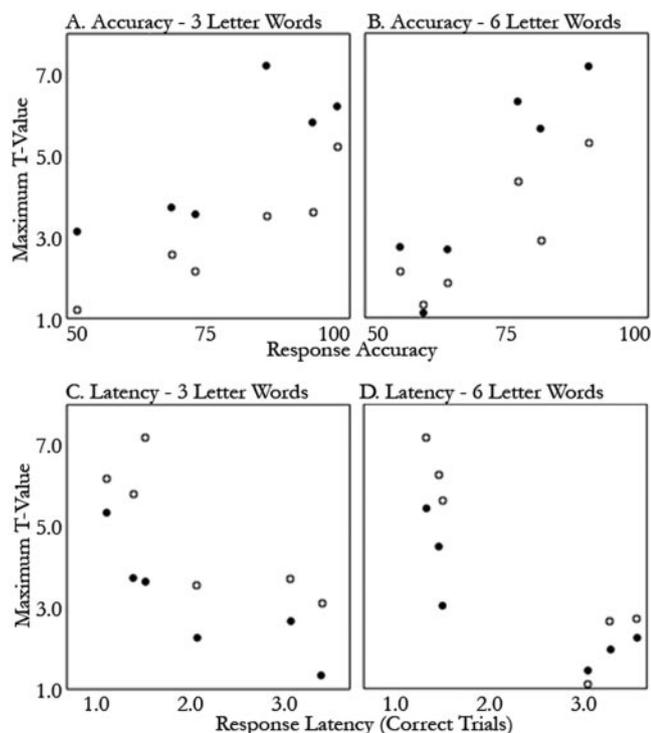


FIGURE 5. Peak activation in the left (filled circles) and right (open circles) dorsolateral prefrontal cortex (DLPFC) is plotted against accuracy (percentage correct) on the living/nonliving judgment task (top row) and against latency (seconds) for correct responses (bottom row) for both the 3Let and 6Let tasks.

the patients resulted in those specific regions not showing consistent activation.

Relationship between Peak Activation and Performance

Because the primary difference between patients and controls extracted from the group image analysis had to do with decreased activation in the primary visual areas and increased activation in parietal and prefrontal for patients compared with controls, the voxel with the peak signal change was extracted within the left and right inferior parietal lobules, prefrontal cortex, and primary visual cortex for each subject. Bivariate 2-tailed Pearson correlations were used to examine the relationship between peak activation and performance on the 3Let and 6Let tasks for each group of subjects (younger controls, older controls, patients with AMD).

There were no significant correlations ($P < 0.05$) for younger or older controls with regard to their behavioral performance on the 3Let task. In contrast, for the patients with AMD, there was a significant positive correlation between activation in the right dorsolateral prefrontal cortex in the 3Let task with accuracy of response ($r = 0.875$, $P = 0.024$) and significant negative correlations with latencies for correct ($r = -0.861$, $P = 0.028$) and incorrect ($r = -0.886$, $P = 0.019$) responses. Similar relationships were found for the left dorsolateral prefrontal cortex with accuracy ($r = 0.848$, $P = 0.033$) and correct ($r = -0.842$, $P = 0.036$) and incorrect ($r = -0.845$, $P = 0.034$) reaction times. Data underlying the correlations between dorsolateral prefrontal cortex (DLPFC) activity and behavioral data in patients with AMD are presented in Figure 5. Although there was a trend for a similar relationship between accuracy and activation in the inferior parietal lobules in patients with

AMD, it did not reach significance for the left or right inferior parietal lobule (left: $r = -0.725$, $P = 0.103$; right: $r = -0.793$, $P = 0.060$). There was, however, a significant negative correlation between response latency to correct and incorrect trials with peak activation in left and right inferior parietal lobules (left inferior parietal lobule, correct: $r = -0.839$, $P = 0.037$; left inferior parietal lobule, incorrect: $r = -0.908$, $P = 0.012$; right inferior parietal lobule, correct: $r = -0.818$, $P = 0.047$; right inferior parietal lobule, incorrect: $r = -0.898$, $P = 0.015$). In the patients with AMD, no relationship was observed between peak activation in visual cortices and performance.

As in the 3Let task, there were no significant correlations ($P < 0.05$) for the younger controls between peak activation and behavioral performance on the 6Let task. For patients with AMD, there were significant negative correlations between reaction times on incorrect trials with peak activation in the right dorsolateral prefrontal cortex ($r = -0.950$, $P = 0.004$), left dorsolateral prefrontal cortex ($r = -0.903$, $P = 0.014$), and right inferior parietal lobule ($r = -0.878$, $P = 0.021$) for the group of older controls. Similarly, patients with AMD showed significant positive correlations between accuracy of response and peak activation in the left and the right dorsolateral prefrontal cortex (left: $r = 0.933$, $P = 0.007$; right: $r = 0.828$, $P = 0.042$). Patients with AMD also demonstrated significant negative correlations between peak activation in the left and right dorsolateral prefrontal cortex with speed of response for correct and incorrect trials (left DLPFC, correct: $r = -0.915$, $P = 0.011$; left DLPFC, incorrect: $r = -0.959$, $P = 0.002$; right DLPFC, correct: $r = -0.837$, $P = 0.038$; right DLPFC, incorrect: $r = -0.840$, $P = 0.036$). There was also a significant relationship for patients with AMD relative to peak activation in the left inferior parietal lobule for correct responses ($r = 0.841$, $P = 0.036$) and a trend with incorrect reaction time ($r = -0.782$, $P = 0.066$). As with the 3Let task, there were no significant correlations between peak activation in visual cortices and behavioral performance.

DISCUSSION

Overall, control subjects with normal sight and patients used a similar brain network to perform the living/nonliving judgment that word recognition requires. Consistent with what would be expected given a degraded visual signal because of poorer visual acuities, the patients showed significantly reduced activation in the early visual areas. However, in contrast to controls, patients with AMD showed increased frontal and parietal contributions. It is this latter finding that addresses the main study objective. We hypothesized that the use of a PRL to carry out a simple cognitive task requires an attentional contribution greater than observed in controls. Controls and patients were required to maintain fixation, and this maintenance of fixation was the baseline. Patients did this using their PRLs. Based on previous work in our laboratory, we hypothesized that the use of a PRL is in itself an attentionally demanding and effortful task. Given this, we predicted an additive cost in conditions that required patients to maintain the PRL and use this PRL to read. We found support for this hypothesis in increased activation for the patients relative to the control group in the frontal eye fields, parietal lobules, and prefrontal cortex, areas known to be associated with increased eye movement, attention, and memory.¹¹

Significant correlations were found between the level of peak brain activation in these regions of interest and the behavioral performance for the patients with AMD on the 3Let and 6Let word recognition tasks. For the 3Let task, patients showed significant relationships between increased accuracy,

decreased reaction times, and increased levels of activation in the left prefrontal cortex and between decreased reaction times and increased levels of activation in the left and right inferior parietal lobules. In contrast to the patient data, no significant correlations were found between levels of brain activation and behavioral performance for the younger or older control subjects. For the 6Let task, the patients showed significant relationships between increased accuracy and decreased reaction times with higher activation in the left and right prefrontal cortex. In addition, there was a significant correlation between correct responses and increased activation in the left inferior parietal lobule. For the 3Let and 6Let tasks, no relationship was found between activation in the visual cortices with behavioral performance for patients with AMD. On the 6Let task, the only relationship found for the normally sighted control subjects was within the older control group such that decreased reaction times were associated with increased activation in the left and right prefrontal cortex and the right inferior parietal lobule.

We believe that the imaging data demonstrating increased activation within the prefrontal and parietal lobules taken together with the strong relationship between performance and activation provide evidence of compensation in the patients with AMD. This would suggest that what is deemed a difficult task by participants with normal vision will be exponentially more difficult for patients with AMD. Although most rehabilitation programs keep difficulty in mind,¹² these data provide evidence not only to justify that attention to difficulty, they also provide suggestions regarding what controls should be included. For example, the use of tasks that rely on the frontal lobes, such as those involving a component of task switching or working memory, may provide a conflict for resources for the patient with AMD and should be avoided. The simple idea is that with decreased sensory input, as occurs with macular degeneration, patients can compensate by using higher order skills such as attention and visual search. For example, with reduced "pop-out" effects resulting from reduced vision, patients may have to use alternative strategies for the routine search of a visual target. Similarly, during reading patients have to increase their reliance on overt shifts of attention, which are cognitively demanding, whereas normally sighted controls can make simple covert shifts of attention, which require fewer cognitive resources.

These data also support the argument that changes in cortical activation resulting from AMD are not driven purely by changes in the visual input from a stimulus but instead depend on an interaction between the forced use of a PRL (because of central vision loss) with task demands. Previous work in our laboratory found that predictable visual tracking is less dependent on the frontal lobes, whereas visually guided saccades to stimuli in unpredictable locations do require additional processing resources.¹¹ These findings do not contradict recent reports that activation specifically in early visual areas is dependent on the task required and less dependent on the stimulus signal itself.¹⁰ In fact, the present data extend the conclusion of this work to suggest that cortical signals are reflective of a stimulus only so far as to say that the loss of signal requires the development and use of a PRL, which requires additional cognitive resources.

One limitation of the present study is the reliance on healthy controls using central vision to complete the task as a baseline. Ideally, the patient group would only differ from controls on the presence of disease. For example, if the chosen control group routinely used peripheral vision to accomplish visual tasks and they also matched patients in age, then the interpretation of the data would be related solely to loss of central vision and not to loss of central vision plus the use of a PRL. Because controls chosen in this study do not use a PRL,

the observed findings likely are attributed not just to the disease itself but also in part to the attentional demands in maintaining a PRL and the degree of adaptation in using that PRL. Other studies have chosen to use younger controls and have instructed them to view stimuli with a peripheral locus. This is an interesting choice and does address the motor component and the location of stimuli on the retina. However, this selection does not come without complications. Control subjects who use PRLs to complete a task do not have the benefit of practice, nor do they have the advantage of adaptation over time during disease progression. As such, we chose for this baseline study to use healthy controls with their natural eye movements and retinal locus and to compare task condition activation to fixation activation for both groups. The fixation condition provides further information about the attentional demands required to maintain a PRL.

The use of fMRI to monitor the progress of patients in rehabilitation and to uncover the biological basis of reading strategies may provide insight into why some patients with compromised vision are able to perform well while others are not despite similar levels of vision and the same disease process.²⁷ The interest of our laboratory is not in retinotopic mapping of the visual cortex but on investigating alterations in the networks associated with macular degeneration during performance of cognitively demanding tasks. The present data suggest that these alterations may reflect increased attention and effort relative to normally sighted controls. In other words, what is difficult for controls will become differentially difficult for patients with AMD because for them the baseline state for processing visual information already requires increased cortical involvement. These data are consistent with the fMRI findings of Masuda et al.¹⁰ With regard to the neurophysiology, we agree with their conclusion that sensory degradation may result in activation as a result of new cortical pathways being formed that carry task-dependent signal or disinhibition of preexisting task-dependent cortical signals that are inhibited in an undisturbed visual system. Overall, the present data provide additional support for differential cortical involvement as a function of task difficulty for patients with AMD. This study also highlights the need for research into the effects of AMD on each of the component processes in word recognition from perception to orthographic decoding to the extraction of meaning.

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