

Developmental and Skill Effects on the Neural Correlates of Semantic Processing to Visually Presented Words

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Abstract: Functional magnetic resonance imaging (fMRI) was used to explore the neural correlates of semantic judgments to visual words in a group of 9- to 15-year-old children. Subjects were asked to indicate if word pairs were related in meaning. Consistent with previous findings in adults, children showed activation in bilateral inferior frontal gyri (Brodmann area [BA] 47, 45) and left middle temporal gyrus (BA 21). Words with strong semantic association elicited significantly greater activation in bilateral inferior parietal lobules (BA 40), suggesting stronger integration of highly related semantic features. By contrast, words with weak semantic association elicited greater activation in left inferior frontal gyrus (BA 45) and middle temporal gyrus (BA 21), suggesting more difficult feature search and more extensive access to semantic representations. We also examined whether age and skill explained unique variance in the patterns of activation. Increasing age was correlated with greater activation in left middle temporal gyrus (BA 21) and inferior parietal lobule (BA 40), suggesting that older children have more elaborated semantic representations and more complete semantic integration processes, respectively. Decreasing age was correlated with activation in right superior temporal gyrus (BA 22) and decreasing accuracy was correlated with activation in right middle temporal gyrus (BA 21), suggesting the engagement of ancillary systems in the right hemisphere for younger and lower-skill children. *Hum Brain Mapp* 27:915–924, 2006.

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INTRODUCTION

Previous studies on visual word comprehension in adults have shed light on the functional architecture of word rec-

ognition systems for printed words. These studies have identified brain regions for processing written language in bilateral inferior frontal gyri (Brodmann area [BA] 47, 45) and left middle temporal gyrus (BA 21) [Booth et al., 2002; Chee et al., 1999; Howard et al., 1992; Shaywitz et al., 2001; Simos et al., 1999]. These two regions are thought to be associated with higher-level language processing including the comprehension of meaning. Although these studies have explored the functional architecture of word recognition systems in adults, we do not know whether these findings can be generalized to children.

The roles of inferior frontal and middle temporal gyri in semantic processing have been explored in adults by comparing activation to semantic judgments involving closely related pairs (e.g., king–queen) versus distantly related pairs (e.g., net–ship). Distantly related pairs with weaker

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semantic association produced more activation in left inferior frontal gyrus as compared to closely related pairs. Greater activation in left inferior frontal gyrus was suggested to result from the difficulty of selecting appropriate semantic features, as distantly related pairs share few semantic features [Fletcher et al., 2000]. In support of this, many studies show greater inferior frontal gyrus activation in more difficult semantic tasks and in tasks with increased retrieval or selection demands. These studies include high versus low requirement for selection among alternatives [Thompson-Schill et al., 1997, 1999], weak versus strong association strength [Wagner et al., 2001], naming low versus high familiarity objects [Whatmough et al., 2002], generating novel versus repeated base nouns [Seger et al., 2000], naming low versus high agreement pictures [Kan and Thompson-Schill 2004], deep versus shallow processing of words [Fujii et al., 2002] and producing words for prespecified semantic categories versus over-learned letter sequences [Gurd et al., 2002]. In the current study, we manipulated the difficulty of the semantic task by varying the “free association strength” between the words in a pair [Nelson et al., 2004]. Based on the adult literature, we expected greater activation in the inferior frontal gyrus for low (compared to high) association pairs due to increased retrieval or selection demands.

Although we expected children to show brain activation patterns similar to those reported for adults during semantic processing tasks, we also expected to find skill and developmental differences on the tasks. A previous study that showed skill related differences in activation found an increase in accuracy associated with greater activation in the left occipitotemporal and temporoparietal region during category judgments of visually presented words [Shaywitz et al., 2002]. In contrast, a decrease in accuracy has been associated with greater activation in the right occipitotemporal region during category judgments, implying the recruitment of an ancillary system in the right hemisphere for poorer readers [Shaywitz et al., 2002]. Age-related differences in brain activation during semantic tasks have also been found in several studies. These studies found developmental increases in activation in the left inferior frontal gyrus during silent verb generation to auditorily presented concrete nouns [Holland et al., 2001], for verbal semantic fluency to auditorily presented categories [Gaillard et al., 2003], or for category judgments to visually presented words [Shaywitz et al., 2002]. Altogether, these studies suggest a developmental or skill increase in the left hemisphere network implicated in semantic processing (inferior frontal and middle temporal gyri) with a decrease in the recruitment of right hemisphere homologues.

The first goal of this study was to identify brain areas activated in 9- to 15-year-old children during a semantic judgment task to visually presented words. The second goal was to examine how the strength of semantic association between two words would influence brain activation, particularly in the inferior frontal gyrus. The third and final goal was to determine whether skill or age was uniquely corre-

lated with activation in temporoparietal and prefrontal regions.

MATERIALS AND METHODS

Participants

Thirty-five healthy children (mean age = 11.7 years, standard deviation [SD] = 2.1 years; ages 9–11, 14 children; ages 11–13, 12 children; ages 13–15, 9 children; 22 females, 13 males) participated in the functional magnetic resonance imaging (fMRI) study. Children were recruited from the Metropolitan Chicago area. Parents of children were given an informal interview to insure that they met the following inclusionary criteria: (1) native English speakers; (2) right-handedness; (3) normal hearing and normal or corrected-to-normal vision; (4) free of neurological disease or psychiatric disorders; (5) not taking medication affecting the central nervous system; (6) no history of intelligence, reading, or oral-language deficits; and (7) no learning disability or Attention Deficit Hyperactivity Disorder (ADHD). After the administration of the informal interview, informed consent was obtained. The informed consent procedures were approved by the Institutional Review Board at Northwestern University and Evanston Northwestern Healthcare Research Institute. Standardized intelligence testing was then administered, using the Wechsler Abbreviated Scale of Intelligence (WASI; The Psychological Corporation, 1999) with two verbal subtests (vocabulary, similarity) and two performance subtests (block design, matrix reasoning). Participants' standard scores (mean \pm SD) were 114 ± 14 on WASI verbal scale and 109 ± 15 on WASI performance scale.

Functional Activation Tasks

In the word judgment task, two visual words were presented sequentially and the participant had to determine whether the word pair was related in meaning. The duration of each word was 800 msec followed by a 200-msec blank interval. A red fixation cross appeared on the screen after the second word, indicating the need to make a response during the subsequent 2,600-msec interval. Forty-eight word pairs were semantically related according to their free association values (mean = 0.45, SD = 0.19, ranging from 0.77 to 0.14) [Nelson et al., 2004]. These word pairs included both closely related pairs (e.g., web–spider) with higher association values and distantly related pairs (e.g., guide–tour) with lower association values. Twenty-four word pairs were semantically unrelated with zero association values (e.g., bone–mountain). The participants were instructed to press quickly and accurately with their right hand the yes button to the related pairs and the no button to the unrelated pairs.

There were three kinds of control tasks. The simple perceptual control had 24 pairs of single graphic symbols, among which parts of courier letters were re-arranged to make false fonts (24 letters, not Q or X). The complex perceptual control had 24 pairs of three-symbol stimuli, where none of the false fonts repeated in the same stimulus. Non-

TABLE I. Stimulus characteristics for first and second words in related and unrelated conditions

	Educator's Word Frequency Guide, 1996				Baayen et al., 1995			
	Written adults		Written children		Written adults		Spoken adults	
	Related	Unrelated	Related	Unrelated	Related	Unrelated	Related	Unrelated
First word frequency	17 (39)	22 (60)	26 (62)	11 (15)	86 (180)	53 (83)	83 (202)	51 (119)
Second word frequency	10 (21)	8 (19)	17 (32)	12 (27)	70 (109)	60 (117)	67 (133)	26 (65)
First word correlation ^a	-0.18		-0.17		-0.12		0.04	
Second word correlation ^a	-0.06		0.02		-0.01		0.09	

Values in parentheses indicate SD.

^a Correlations of word frequency with association strength in the related condition.

matches differed in one stimulus that occurred equally in the first, second, or third position. For both the simple and complex perceptual controls, a red fixation cross appeared on the screen after the second stimulus, indicating the need to make a response. Participants determined whether the pair of stimuli were identical or not by pressing a yes or no button. Both the words and graphic symbols were lower case, and were offset one half of a letter from each other in the pair (50% to the right and 50% to the left) so that judgment could not be based on visual persistence. For the complex perceptual control, the stimuli subtended a similar visual angle as the words. The third control task involved 30 baseline events. The participant was instructed to press a button when a black fixation cross at the center of the visual field turned red. We chose to compare the word pairs to this baseline event, because this event showed very high accuracy and the least variability (accuracy [mean ± SD] for the baseline, simple perceptual, and complex perceptual was 99% ± 1%, 98% ± 3%, and 92% ± 6%, respectively). The performance of this baseline event also showed little developmental difference (correlations between age and reaction time for the baseline, simple perceptual, and complex perceptual conditions were $r = -0.27, P = 0.12$; $r = -0.37, P < 0.05$; $r = -0.35, P < 0.05$, respectively). The contrast of the simple perceptual versus the baseline was used as an exclusive mask to exclude activation attributable to non-lexical visual processing.

Stimulus Characteristics

Several lexical variables were controlled across the related and unrelated conditions and for the high and low association pairs. First, no homophones were included in the experimental lists. Second, the number of nouns (55%–65%), verbs (25%–35%), and adjectives (10%–20%), based on their most frequent usage in the Oxford English Dictionary, was balanced across conditions. Third, all words were one or two syllables long. Fourth, words were matched for written word frequency for adults and children (The Educator's Word Frequency Guide, 1996) and for adult word frequency for written and spoken language [Baayen et al., 1995] (Table I). A 2-word (first, second) × 2-condition (related, unrelated) analysis of variance (ANOVA) showed no main effects or interactions with the different frequency measures. The cor-

relations of word frequency measures with association strength were not significant indicating that association effects should not be due to frequency differences.

Experimental Procedure

Before the fMRI session, participants were trained to keep their head still using an infrared tracking device and then they practiced one run of the semantic judgment task in a simulator to acclimate themselves to the scanner environment. Different stimuli were used in the practice and fMRI sessions. Within a week of the practice session, participants were administered the fMRI test session.

MRI Data Acquisition

Participants lay in the scanner with their head position secured with a specially designed vacuum pillow (Bionix, Toledo, OH). An optical response box (Current Designs, Philadelphia, PA) was placed in the participants' right hand. The head coil was positioned over the participants' head. Participants viewed visual stimuli that were projected onto a screen via a mirror attached to the inside of the head coil. Each participant performed two functional runs. The first run took 6.7 minutes and the second took 6.6 minutes.

All images were acquired using a 1.5-Tesla GE scanner. Gradient-echo localizer images were acquired to determine the placement of the functional slices. For the functional imaging studies, a susceptibility weighted single-shot blood oxygenation level-dependent (BOLD) echo planar imaging (EPI) method was used. Functional images were interleaved from bottom to top in a whole brain EPI acquisition. The following scan parameters were used: echo time (TE) = 35 msec, flip angle = 90 degrees, matrix size = 64 × 64, field of view = 24 cm, slice thickness = 5 mm, number of slices = 24; repetition time (TR) = 2,000 msec. The first functional run had 203 image volumes and the second had 198 image volumes. In addition, a high resolution, T1-weighted 3-D image was acquired (anatomical image SPGR, TR = 21 msec, TE = 8 msec, flip angle = 20 degrees, matrix size = 256 × 256, field of view = 22 cm, slice thickness = 1 mm, number of slices = 124). The orientation of the 3-D image was identical to the functional slices.

Image Analysis

Data analysis was carried out using *SPM2* (statistical parametric mapping). The functional images were corrected for differences in slice-acquisition time to the middle volume and were realigned to the first volume in the scanning session using affine transformations. No participant had more than 3.5 mm of movement in any plane and the mean amount of movement in the maximum plane (z translation) was 1.0 mm. Co-registered images were normalized to the Montreal Neurological Institute (MNI) average template (12 linear affine parameters for brain size and position, 8 non-linear iterations, and $2 \times 2 \times 2$ nonlinear basis functions). Statistical analyses were calculated on the smoothed data (10-mm isotropic Gaussian kernel), with a high-pass filter (128-second cutoff period) to remove signal drift, cardiac and respiratory effects, and other low-frequency artifacts. We used global normalization to scale the mean of each scan to a common value to correct for whole brain differences over time.

Data from each participant was entered into a general linear model using an event-related analysis procedure [Josephs and Henson, 1999]. Word pairs were treated as individual events for analysis and modeled using a canonical hemodynamic response function (HRF). Parameter estimates from contrasts of the canonical HRF in single-subject models were entered into random-effects analysis using one-sample *t*-tests across all participants to determine whether activation during a contrast was significant (i.e., parameter estimates were reliably greater than 0). Four general types of analyses were done with the use of the exclusive mask of the simple perceptual versus the baseline. First, we compared the related and unrelated pairs separately to the baseline condition. Second, we examined the correlation of the continuous variable of association strength for the related pairs [Nelson et al., 2004] with signal intensity. Positive correlations indicated progressively greater activation for word pairs with higher association strength, whereas negative correlations indicated progressively greater activation for word pairs with lower association strength. Third, we used multiple regression to correlate the continuous variable of age in months with signal intensity in the related and unrelated pairs, including performance accuracy in the scanner as a covariate. This allowed us to examine age-related increases or decreases in activation that were independent of accuracy differences. Fourth, we used multiple regression to correlate the continuous variable of accuracy on the semantic judgment task with signal intensity in the related and unrelated pairs, including age in months as a covariate. This allowed us to examine accuracy-related increases or decreases in activation that were independent of age. Reading skill thus referred to performance accuracy in the present study as individual's accuracy was an appropriate measure of reading skill during semantic association in children [Blumenfeld et al., in press]. All reported areas of activation were significant using $P < 0.001$ uncorrected at the voxel level with a cluster size greater than or equal to 14 voxels.

RESULTS

Behavioral Performance

Statistical analyses revealed no main effects or interactions involving accuracy or reaction times on the practice versus fMRI sessions, indicating that the environment of the scanner did not adversely affect the behavioral performance of the children. Furthermore, the children could effectively perform the task in the fMRI scanner, as all mean accuracy levels were above 95% and no individual participant scored below 80% in any condition. The accuracy (mean \pm SD) for the related, unrelated, and baseline events was $95\% \pm 5\%$, $96\% \pm 4\%$, and $99\% \pm 2\%$, respectively. A one-way ANOVA on accuracy was significant, $F(2,68) = 9.94$, $P < 0.01$, because the baseline event was more accurate than either the related event, $t(34) = 4.55$, $P < 0.01$, or the unrelated event, $t(34) = 3.90$, $P < 0.01$. The related and the unrelated pairs were not significantly different. The reaction times (mean \pm SD) for the related, unrelated, and baseline events were $1,250 \pm 298$ msec, $1,351 \pm 319$ msec, and $1,305 \pm 318$ msec, respectively. One-way ANOVA on reaction times was significant, $F(2,68) = 6.49$, $P < 0.01$, because the related events were faster than were the unrelated events, $t(34) = 4.62$, $P < 0.01$. The reaction times for the related and baseline events as well as for the unrelated and baseline events were not significantly different. The correlation between accuracy and association strength was not significant, $r(48) = 0.06$, $P = 0.66$; nor was the correlation between reaction times and association strength, $r(48) = -0.18$, $P = 0.22$.

Brain Activation Patterns

Table II and Figure 1 show greater activation for the related and unrelated pairs compared to the baseline condition. Both related and unrelated pairs produced greater activation in bilateral inferior frontal gyri (BA 45, 47) and left middle temporal gyrus (BA 21). The unrelated pairs produced additional activation in left anterior cingulate (BA 32). The direct comparison of the related and unrelated pairs produced greater activation in left inferior parietal lobule (BA 40).

The correlation between signal intensity and the strength of semantic association for related word pairs is shown in Table III and Figure 2A. Greater activation was correlated with higher association values in right inferior parietal lobule (BA 40) extending to the intraparietal sulcus. Greater activation was correlated with lower association values in left middle temporal gyrus (BA 21).

In an earlier study of spoken words using the same semantic association task [Chou et al., 2006], we showed that higher association was correlated with greater activation in left inferior parietal lobule and that lower association was correlated with greater activation in left inferior frontal gyrus. Because the correlation analysis observed in these two regions did not exceed our standard threshold and because we saw correlations for the

TABLE II. Greater activation for the related or unrelated conditions compared to the baseline condition

Condition and region	Hemisphere	BA	z-test	Voxels	<i>x, y, z</i>
Related-null					
Middle frontal/inferior frontal gyrus	L	6/47/45	7.35	1414	-51, 5, 41
Inferior frontal gyrus	R	47	5.43	121	33, 23, -1
Medial frontal gyrus	L	8	6.47	465	-6, 23, 43
Fusiform/middle temporal gyrus	L	37/21	5.94	411	-39, -36, -16
Posterior cingulate gyrus/cuneus	R	30/17	5.56	688	3, -69, 12
Thalamus	L	—	4.51	81	-21, -29, -1
Unrelated-null					
Inferior frontal/middle frontal gyrus	L	47/45/6	7.37	1790	-33, 29, -6
Inferior frontal gyrus	R	47	5.86	240	33, 26, -4
Medial frontal/anterior cingulate gyrus	L	8/32	7.09	739	-6, 17, 43
Middle temporal/fusiform gyrus	L	21/37	6.66	538	-51, -41, 6
Cuneus/posterior cingulate gyrus	R	17/30	6.27	1305	15, -69, 12
Precuneus	L	7	4.75	47	-23, -44, 55
Precentral gyrus	R	6	4.53	32	42, -6, 58
Postcentral gyrus	L	2	3.81	17	-54, -19, 22
Thalamus	R	3	3.75	17	53, -9, 50
Thalamus	L	—	4.45	157	-24, -26, 1
Midbrain	R	—	3.70	14	9, -18, -9
Related-unrelated					
Inferior parietal lobule	L	40	6.23	1111	-30, -65, 42
Superior frontal gyrus	L	8	4.67	214	-30, 17, 54
Precuneus/posterior cingulate gyrus	L	7/30	4.60	119	-6, -35, 29

Coordinates of activation peaks are given in the Talairach stereotactic space. L, left; R, right; BA, Brodmann's area of activation; Voxels, number of voxels in cluster. Only clusters >14 are presented.

auditory modality [Chou et al., 2006], we used the inclusive mask from that study to examine the left inferior frontal gyrus and left inferior parietal lobule activation in correlation analyses at a more liberal threshold. We used the correlation map from the auditory modality as an

inclusive mask ($P < 0.05$ uncorrected) to test the correlation of association value and activation, using a threshold of $P < 0.005$ uncorrected. The analysis showed that for visually presented words, higher association was correlated with activation in left inferior parietal lobule (BA 40)

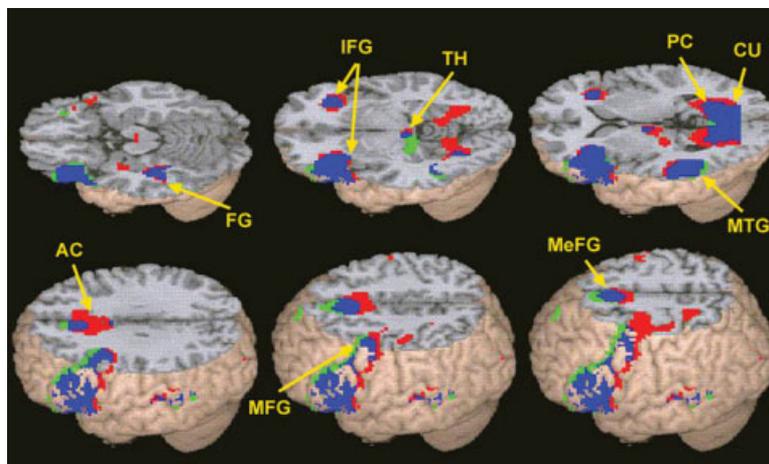


Figure 1.

Brain activations for the related versus baseline (green) and for the unrelated versus baseline (red). The overlap between the two contrasts is represented in blue. Both the related and unrelated pairs produced greater activation in bilateral inferior frontal gyri (IFG), left middle frontal gyrus (MFG), left medial frontal gyrus

(MeFG), left middle temporal gyrus (MTG), left fusiform gyrus (FG), right posterior cingulate gyrus (PC), right cuneus (CU), and left thalamus (TH). The unrelated pairs produced additional activation in left anterior cingulate (AC).

TABLE III. Correlation of activation with semantic association for related word pairs

Modulation and region	Hemisphere	BA	z-test	Voxels	<i>x, y, z</i>
Higher association					
Precuneus	L	7	4.67	285	-18, -68, 45
Superior temporal gyrus	R	22	4.11	53	48, -52, 11
Inferior parietal lobule	R	40	3.75	34	45, -59, 39
Middle frontal gyrus	L	10	3.56	14	-33, 56, 6
	R	9	3.67	32	33, 31, 32
Inferior parietal lobule ^a	L	40	2.77	50	-40, -50, 44
Lower association					
Middle temporal gyrus	L	21	3.56	14	-53, -44, 5
Inferior frontal gyrus ^a	L	45	2.68	11	-53, 16, 5

Coordinates of activation peaks are given in the Talairach stereotactic space. L, left; R, right; BA, Brodmann's area of activation; Voxels, number of voxels in cluster. Both increasing activation for higher association pairs and increasing activation for lower association pairs are shown.

^a Voxels reach $P < 0.005$ uncorrected with the use of an inclusive mask [Chou et al., 2006].

and that lower association was correlated with greater activation in left inferior frontal gyrus (BA 45).

The correlation between age in months and signal intensity in the semantic task, partialling out the effect of accuracy, is shown in Table IV and Figure 2B (Fig. 2B only shows the results for the related pairs). Increasing age was correlated with greater activation for the related pairs in left inferior parietal lobule (BA 40) and using the same inclusive mask as described

above, in left middle temporal gyrus (BA 21). Decreasing age was correlated with greater activation for the related pairs in right medial frontal (BA 10) and right superior temporal gyri (BA 22). There were no age effects for the unrelated pairs.

After partialling for age, increasing accuracy for related pairs was correlated with greater activation in left paracentral lobule ($Z = 4.13$, voxels = 102, Talairach coordinates [-9, -18, 42], $P < 0.001$ uncorrected) and using the same

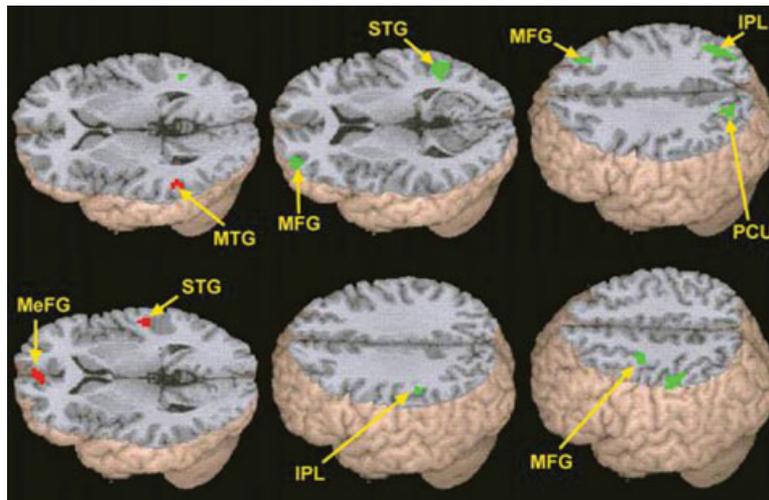


Figure 2.

Correlation of activation with semantic association for the related word pairs on the top row. Higher association (green) was correlated with greater activation in left precuneus (PCU), right inferior parietal lobule (IPL) extending to the intraparietal sulcus, right superior temporal gyrus (STG), and bilateral middle frontal gyri (MFG). Lower association (red) was correlated with greater activation in left middle temporal gyrus (MTG). Correlation of

activation with age for the related word pairs on the bottom row. Increasing age (green) was correlated with greater activation in left inferior parietal lobule (IPL) and left middle frontal gyrus (MFG). Decreasing age (red) was correlated with greater activation in right medial frontal gyrus (MeFG) and right superior temporal gyrus (STG).

TABLE IV. Correlation of activation with age for the related and unrelated word pairs

	Regions	Hemisphere	BA	z-test	Voxels	<i>x, y, z</i>	
Increase with age	Related	Inferior parietal lobule	L	40	3.84	55	-45, -33, 40
		Middle frontal gyrus	L	6	3.77	28	-30, -10, 42
		Middle temporal gyrus ^a	L	21	2.73	24	-53, -50, 0
Unrelated	Postcentral gyrus	L	3	4.07	259	-39, -21, 48	
	Middle frontal gyrus	R	6	3.77	20	24, 6, 60	
Decrease with age	Related	Medial frontal gyrus	R	10	3.71	19	1, 52, 0
		Superior temporal gyrus	R	22	3.70	25	56, -20, 1
		Posterior cingulate gyrus	R	29	3.34	17	6, -46, 13
Unrelated	Superior temporal gyrus	R	22	4.45	135	53, -23, 4	
		L	22	3.74	24	-56, -12, -2	
		L	42	3.67	21	-62, -26, 13	
		R	24	3.63	14	12, -9, 45	

Coordinates of activation peaks are given in the Talairach stereotactic space. L, left; R, right; BA, Brodmann's area of activation; Voxels, number of voxels in cluster. Both increasing activation with age and decreasing activation with age are presented.

^a Voxels reach $P < .005$ uncorrected with the use of an inclusive mask [Chou et al., 2006].

inclusive mask as described above, in left inferior parietal lobule (BA 40, $Z = 2.79$, voxels = 14, Talairach coordinates [-60, -45, 41], $P < 0.005$ uncorrected). Decreasing accuracy for related pairs was correlated with greater activation in right middle temporal gyrus (BA 21, $Z = 4.55$, voxels = 29, Talairach coordinates [65, -24, -5], $P < 0.001$ uncorrected). No significant correlation was found between signal intensity and accuracy for unrelated pairs.

DISCUSSION

Networks Involved in Semantic Processing

The neural correlates of semantic processing to visually presented words were examined with a task requiring association judgments as to whether word pairs were related in meaning. Previous studies in adults implicate the inferior frontal and middle temporal gyri in semantic processes [Booth et al., 2002; Chee et al., 1999; Howard et al., 1992; Shaywitz et al., 2001; Simos et al., 1999]. Our finding that both the related and unrelated word pairs activated left middle temporal gyrus and bilateral inferior frontal gyri is consistent with these findings. Some argue that the middle temporal gyrus is involved in the representation of verbal semantic information [Blumenfeld et al., in press; Booth et al., 2002; Martin, 2001], whereas the inferior frontal gyrus is involved in on-line semantic monitoring such as searching posterior representations for overlapping semantic features [Fletcher et al., 2000; Kapur et al., 1996].

Although the related and unrelated pairs mainly showed overlap in patterns of activation, the unrelated word pairs additionally activated anterior cingulate cortex. This region has been associated with attention, response selection, executive control, and on-line monitoring [Botvinick et al., 1999; Carter, et al., 1998, 1999]. In addition, this region has been implicated in attentional modulation of semantic processing [Chan et al., 2004; Mummery et al., 1999; Peelle et al., 2004].

The unrelated pairs may have produced activation in the anterior cingulate because the search for overlapping semantic features was extensive but unsuccessful within the assigned time. This suggestion is supported by the finding that unrelated pairs had significantly longer reaction times than related pairs did and that longer reaction times were correlated with greater activation in the anterior cingulate ($Z = 2.95$, voxels = 17, Talairach coordinates [10, 36, 19], $P < 0.005$) for the unrelated condition. The increased processing load for unrelated pairs may place greater demands on available resources during semantic judgments.

Association Strength Modulates Activation in the Semantic Network

Stronger semantic association was correlated with greater activation in left inferior parietal lobule (BA 40). Activation in this region has been identified previously in semantic tasks, including associative judgments [Binder et al., 1997], similarity judgments [Price et al., 1999], category judgments [Pugh et al., 1996], and concrete versus abstract word judgments [Chee et al., 1999]. Some studies have interpreted the left inferior parietal lobule activation as related to feature integration and semantic categorization to form a coherent concept so that semantic relationships between words can be determined [Grossman et al., 2003; Smith, 1995]. Neuroanatomical connectivity patterns also suggest that semantic-lexical integrative processes involve heteromodal association cortices in the inferior parietal lobule [Mesulam, 1998]. High association pairs may involve greater integration because there are more overlapping features between the words or because the shared features are more characteristic of each of the words [Fletcher et al., 2000]. Greater integration for high association word pairs may account for the increase in left inferior parietal lobule activation with increasing association strength.

Stronger semantic association was also correlated with greater activation in right inferior parietal lobule (BA 40). Activation in this region has also been identified in some semantic tasks, including semantically anomalous judgments of word pairs [Kang et al., 1999], covert word generation for semantically ambiguous words versus semantically precise words [Chan et al., 2004], and high-imagery versus low-imagery sentence comprehension [Just et al., 2004]. These authors interpreted the right inferior parietal lobule activation as related to spatial processing or spatial working memory. Indeed, some studies have found bilateral inferior parietal lobule activation in semantic tasks [Thierry et al., 1998], with the left inferior parietal lobule associated with semantic processing and the right inferior parietal lobule associated with spatial processing of visually presented letters [Mottaghy et al., 2002, 2003]. High association pairs (e.g., web-spider) in our study may have generated visual imagery or visual features of words that activated right inferior parietal lobule.

Weaker semantic association was correlated with greater activation in left inferior frontal gyrus (BA 45). Previous studies in adults suggest that the left inferior frontal gyrus is involved in effortful semantic processing, particularly when there is increased demands on the process of selecting relevant semantic knowledge or when comparing words along all semantic features [Blumenfeld et al., in press; Fletcher et al., 1998; Thompson-Schill et al., 1997, 1999; Whatmough et al., 2002]. The inferior frontal gyrus has also been implicated in conditions with increased retrieval demands [Kikyo et al., 2002; Kirchoff et al., 2000; Seger et al., 2000; Wagner et al., 2001]. Of particular relevance to the current study, semantic judgments in adults to lower association pairs produced more activation in left inferior frontal gyrus as compared to higher association pairs [Fletcher et al., 2000]. Greater activation for lower association pairs could result from increased demands on the retrieval or selection of appropriate semantic features. Weaker semantic association in our study was also correlated with greater activation in the left middle temporal gyrus (BA 21). Activation in this region has been implicated in the representation of verbal semantic information [Blumenfeld et al., in press; Booth et al., 2002; Martin, 2001]. Greater activation in this region for low association pairs may result from a more extensive access to semantic representations in order to identify overlapping features.

Developmental and Skill Differences in Activation

Increasing age and accuracy in our study were correlated with greater activation in the left inferior parietal lobule (BA 40). Our age effect is consistent with a study that reported developmental increases in left inferior parietal lobule during word generation tasks to visually and auditorily presented words [Brown et al., 2005] and our accuracy effect is consistent with a previous study that reported more activation for higher accuracy children when performing category judgments to visually presented words [Shaywitz et al., 2002]. Higher accuracy children are presumably better at integrating the meanings of the two related words, so greater activation in the

inferior parietal lobule with better performance may be related to this more complete and effective semantic integration. This suggestion is supported by our finding reported above that higher association pairs, which can be more effectively integrated, also showed more activation than lower association pairs in the inferior parietal lobule.

Increasing age was also correlated with greater activation in the left middle temporal gyrus (BA 21). Studies have shown that increasing skill and learning on semantic tasks are associated with greater activation in the temporal region [Blumenfeld et al., in press; Sandak et al., 2004; Shaywitz et al., 2002]. Greater activation may be associated with increasing elaboration of semantic representations, i.e., a greater number of semantic representations with more interconnections between these representations. Behavioral research shows that as vocabulary knowledge increases, the child's semantic system is gradually elaborated due to the greater number of conceptual links [McGregor and Appel, 2002; McGregor et al., 2002]. As reported above, we also found that weaker association strength is correlated with greater activation in the left middle temporal gyrus, suggesting that this region may be critical in the representation of verbal semantic information. Older children in our study may have shown greater activation in the left middle temporal gyrus because their semantic representations are more elaborated, resulting in the access of many overlapping semantic features between the words.

Our results support the idea that younger and less skilled readers rely more on the right hemisphere for reading. We found that decreasing age was correlated with greater activation in right superior temporal gyrus (BA 22). Greater activation in right superior temporal gyrus has also been associated with the effect of word presentation rate, suggesting an emphasis on the stimulus-dependent perceptual properties of words (e.g., phonological features) but not on semantic processing [Mechelli et al., 2000; Noesselt et al., 2003]. It may be that the younger children have more difficulty mapping the visual to the auditory word form and therefore show greater activation in auditory association areas. Greater involvement of the right hemisphere as a function of skill was also shown in our study in the correlation of lower accuracy with greater activation in right middle temporal gyrus (BA 21). This finding is consistent with a report that poorer readers engage an ancillary system in the right temporoparietal region during category judgments to visually presented words [Shaywitz et al., 2002]. It may be that the less skilled readers are involved to a greater degree in coarser coding that allows distant and unusual semantic features to be analyzed. Some studies have proposed that the right lateral temporal cortex involves computations that enable the association between distantly related concepts, whereas the left lateral temporal cortex performs fine-tuned semantic computations that involve closely related concepts [Beeman et al., 2000; Bowen and Beeman, 1998]. Lower performers may adopt relatively coarser semantic computations in the right middle temporal gyrus in response to word pairs and hence perform less accurately at identifying semantic associations.

Decreasing age in our study was also correlated with greater activation in medial frontal gyrus (BA 10), consistent with our previous finding for semantic association judgments in the auditory modality [Chou et al., 2006]. Studies with go no-go tasks that tap into response inhibition show that children produce greater activation than adults in this region [Booth et al., 2003; Casey et al., 2001]. These findings suggest that the greater activation in this region for children reflects their greater effort in protecting relevant representations from interference due to competing information. Greater activation in this region has also been reported in adults for a Stroop interference task that required subjects to name a target picture while ignoring a distractor word [de Zubicaray et al., 2001]. Interference in Stroop tasks can be resolved by either suppression of distractor information or selective enhancement of target information [MacLeod, 1991]. Adults also activate this region during verbal response suppression requiring the suppression of instructed categories and the production of alternative categories [de Zubicaray et al., 2000]. The decreasing activation with age in the medial frontal gyrus in our study therefore implies that younger children are less able to inhibit inappropriate features during semantic search.

In conclusion, the children in our study showed activation in similar brain regions to those reported in previous studies of adults, including bilateral inferior frontal gyri and left middle temporal gyrus. We also showed that greater activation in left inferior frontal and middle temporal gyri were associated with decreasing association strength between words, suggesting that distantly related pairs required more semantic feature selection and access to the semantic representations to correctly identify semantic associations. In contrast, greater activation in the left inferior parietal lobule was correlated with increasing association strength between words, suggesting that closely related pairs allow for a more complete semantic integration. Although children showed generally similar patterns of activation to previous reports on adults, there were some interesting individual differences. Increasing age was associated with greater activation in the left middle temporal gyrus and inferior parietal lobule, suggesting that older children have a more elaborated semantic representational system and more effective semantic integration. Decreasing age and skill were associated with greater activation in the right superior temporal and right middle temporal gyrus, suggesting that younger children and poorer readers use an ancillary system in the right hemisphere to aid performance.

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REFERENCES

- Baayen RH, Piepenbrock R, Gulikers L. 1995. The CELEX Lexical Database (Version Release 2) [CD-ROM]. Philadelphia, PA: Linguistic Data Consortium, University of Pennsylvania.
- Beeman MJ, Bowden EM, Gernsbacher MA (2000): Right and left hemisphere cooperation for drawing predictive and coherence inferences during normal story comprehension. *Brain Lang* 71:310–336.
- Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T (1997): Human brain language areas identified by functional magnetic resonance imaging. *J Neurosci* 17:353–362.
- Blumenfeld HK, Booth JR, Burman DD (in press): Differential prefrontal-temporal neural correlates of semantic processing in children. *Brain Lang*.
- Booth JR, Burman DD, Meyer JR, Gitelman DR, Parrish TB, Mesulam MM (2002): Modality independence of word comprehension. *Hum Brain Mapp* 16:251–261.
- Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, Li W, Parrish TB, Gitelman DR, Mesulam MM (2003): Neural development of selective attention and response inhibition. *Neuroimage* 20:737–751.
- Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999): Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402:179–181.
- Bowen EM, Beeman MJ (1998): Getting the right idea: semantic activation in the right hemisphere may help solve insight problems. *Psychol Sci* 9:435–440.
- Brown TT, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL (2005): Developmental changes in human cerebral functional organization for word generation. *Cereb Cortex* 15:275–290.
- Carter CS, Botvinick MM, Cohen JD (1999): The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci* 10:49–57.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
- Casey BJ, Durston S, Fossella JA (2001): Evidence for a mechanistic model of cognitive control. *Clin Neurosci Res* 1:267–282.
- Chan AH, Liu HL, Yip V, Fox PT, Gao JH, Tan LH (2004): Neural systems for word meaning modulated by semantic ambiguity. *Neuroimage* 22:1128–1133.
- Chee MW, O'Craven KM, Bergida R, Rosen BR, Savoy RL (1999): Auditory and visual word processing studied with fMRI. *Hum Brain Mapp* 7:15–28.
- Chou TL, Booth JR, Burman DD, Bitan T, Bigio JD, Lu D, Cone NE (2006): Developmental changes in the neural correlates of semantic processing. *Neuroimage* 29:1141–1149.
- de Zubicaray GI, Wilson SJ, McMahon KL, Muthiah S (2001): The semantic interference effect in the picture-word paradigm: an event-related fMRI study employing overt responses. *Hum Brain Mapp* 14:218–227.
- de Zubicaray GI, Zelaya FO, Andrew C, Williams SC, Bullmore ET (2000): Cerebral regions associated with verbal response initiation, suppression and strategy use. *Neuropsychologia* 38:1292–1304.
- Educator's Word Frequency Guide (1996): Brewster, NY: Touchstone Appliance Science Associates, Inc.
- Fletcher PC, Shallice T, Dolan RJ (1998): The functional roles of prefrontal cortex in episodic memory. I. Encoding. *Brain* 121:1239–1248.
- Fletcher PC, Shallice T, Dolan RJ (2000): "Sculpting the response space"—an account of left prefrontal activation at encoding. *Neuroimage* 12:404–417.
- Fujii T, Okuda J, Tsukiura T, Ohtake H, Suzuki M, Kawashima R, Itoh M, Fukuda H, Yamadori A (2002): Encoding-related brain

- activity during deep processing of verbal materials: a PET study. *Neurosci Res* 44:429–438.
- Gaillard WD, Sachs BC, Whitnah JR, Ahmad Z, Balsamo LM, Petrella JR, Braniecki SH, McKinney CM, Hunter K, Xu B, Grandin CB (2003): Developmental aspects of language processing: fMRI of verbal fluency in children and adults. *Hum Brain Mapp* 18:176–185.
- Grossman M, Koenig P, Glosser G, DeVita C, Moore P, Rhee J, Detre J, Alsop D, Gee J, fMRI study (2003): Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. *Brain* 126:292–311.
- Gurd JM, Amunts K, Weiss PH, Zafiris O, Zilles K, Marshall JC, Fink GR (2002): Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: an fMRI study with clinical implications. *Brain* 125:1024–1038.
- Holland SK, Plante E, Weber Byars A, Strawsburg RH, Schmithorst VJ, Ball WS Jr (2001): Normal fMRI brain activation patterns in children performing a verb generation task. *Neuroimage* 14:837–843.
- Howard D, Patterson K, Wise R, Brown WD, Friston K, Weiller C, Frackowiak R (1992): The cortical localization of the lexicons. Positron emission tomography evidence. *Brain* 115:1769–1782.
- Josephs O, Henson RN (1999): Event-related functional magnetic resonance imaging: modelling, inference and optimization. *Philos Trans R Soc Lond B Biol Sci* 354:1215–1228.
- Just MA, Newman SD, Keller TA, McEleney A, Carpenter PA (2004): Imagery in sentence comprehension: an fMRI study. *Neuroimage* 21:112–124.
- Kan IP, Thompson-Schill SL (2004): Effect of name agreement on prefrontal activity during overt and covert picture naming. *Cogn Affect Behav Neurosci* 4:43–57.
- Kang AM, Constable RT, Gore JC, Avrutin S (1999): An event-related fMRI study of implicit phrase-level syntactic and semantic processing. *Neuroimage* 10:555–561.
- Kapur S, Tulving E, Cabeza R, McIntosh AR, Houle S, Craik FI (1996): The neural correlates of intentional learning of verbal materials: a PET study in humans. *Brain Res Cogn Brain Res* 4:243–249.
- Kikyo H, Ohki K, Miyashita Y (2002): Neural correlates for feeling-of-knowing: an fMRI parametric analysis. *Neuron* 36:177–186.
- Kirchhoff BA, Wagner AD, Maril A, Stern CE (2000): Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J Neurosci* 20:6173–6180.
- MacLeod CM (1991): Half a century of research on the Stroop effect: an integrative review. *Psychol Bull* 109:163–203.
- Martin M. 2001. Functional neuroimaging of semantic memory. In: Cabeza RK, editor. *Handbook of functional neuroimaging of cognition*. Cambridge: MIT Press. p 153–186.
- McGregor KK, Appel A (2002): On the relation between mental representation and naming in a child with specific language impairment. *Clin Linguist Phon* 16:1–20.
- McGregor KK, Friedman RM, Reilly RM, Newman RM (2002): Semantic representation and naming in young children. *J Speech Lang Hear Res* 45:332–346.
- Mechelli A, Friston KJ, Price CJ (2000): The effects of presentation rate during word and pseudoword reading: a comparison of PET and fMRI. *J Cogn Neurosci* 12:145–156.
- Mesulam MM (1998): From sensation to cognition. *Brain* 121:1013–1052.
- Mottaghy FM, Doring T, Muller-Gartner HW, Topper R, Krause BJ (2002): Bilateral parieto-frontal network for verbal working memory: an interference approach using repetitive transcranial magnetic stimulation (rTMS). *Eur J Neurosci* 16:1627–1632.
- Mottaghy FM, Gangitano M, Krause BJ, Pascual-Leone A (2003): Chronometry of parietal and prefrontal activations in verbal working memory revealed by transcranial magnetic stimulation. *Neuroimage* 18:565–575.
- Mummery CJ, Shallice T, Price CJ (1999): Dual-process model in semantic priming: a functional imaging perspective. *Neuroimage* 9:516–525.
- Nelson DL, McEvoy CL, Schreiber TA (2004): The University of South Florida word association, rhyme, and word fragment norms.
- Noesselt T, Shah NJ, Jancke L (2003): Top-down and bottom-up modulation of language related areas—an fMRI study. *BMC Neurosci* 4:13.
- Peelle JE, McMillan C, Moore P, Grossman M, Wingfield A (2004): Dissociable patterns of brain activity during comprehension of rapid and syntactically complex speech: evidence from fMRI. *Brain Lang* 91:315–325.
- Price CJ, Mummery CJ, Moore CJ, Frakowiak RS, Friston KJ (1999): Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. *J Cogn Neurosci* 11:371–382.
- Pugh KR, Shaywitz BA, Shaywitz SE, Constable RT, Skudlarski P, Fulbright RK, Bronen RA, Shankweiler DP, Katz L, Fletcher JM, Gore JC (1996): Cerebral organization of component processes in reading. *Brain* 119:1221–1238.
- Sandak R, Mencl WE, Frost SJ, Rueckl JG, Katz L, Moore DL, Mason SA, Fulbright RK, Constable RT, Pugh KR (2004): The neurobiology of adaptive learning in reading: a contrast of different training conditions. *Cogn Affect Behav Neurosci* 4:67–88.
- Seger CA, Desmond JE, Glover GH, Gabrieli J (2000): Functional magnetic resonance imaging evidence for right-hemisphere involvement in processing unusual semantic relationships. *Neuropsychology* 14:361–369.
- Shaywitz BA, Shaywitz SE, Pugh KR, Fulbright RK, Skudlarski P, Mencl WE, Constable RT, Marchione KE, Fletcher JM, Klorman R, Lacadie C, Gore JC (2001): The functional neural architecture of components of attention in language-processing tasks. *Neuroimage* 13:601–612.
- Shaywitz BA, Shaywitz SE, Pugh KR, Mencl WE, Fulbright RK, Skudlarski P, Constable RT, Marchione KE, Fletcher JM, Lyon GR, Gore JC (2002): Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biol Psychiatry* 52:101–110.
- Simos PG, Papanicolaou AC, Breier JI, Wheless JW, Constantinou JE, Gormley WB, Maggio WW (1999): Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. *J Neurosurg* 91:787–796.
- Smith EE. 1995. Concepts and categorization. In: Kosslyn SMO, editor. *An invitation to cognitive science*. 2nd ed. Cambridge (MA): MIT Press. p 1–25.
- Thierry G, Doyon B, Demonet JF (1998): ERP mapping in phonological and lexical semantic monitoring tasks: A study complementing previous PET results. *Neuroimage* 8:391–408.
- Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ (1997): Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc Natl Acad Sci U S A* 94:14792–14797.
- Thompson-Schill SL, D'Esposito M, Kan IP (1999): Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron* 23:513–522.
- Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA (2001): Recovering meaning: left prefrontal cortex guides controlled semantic retrieval. *Neuron* 31:329–338.
- Whatmough C, Chertkow H, Murtha S, Hanratty K (2002): Dissociable brain regions process object meaning and object structure during picture naming. *Neuropsychologia* 40:174–186.