

The neural substrates of writing: A functional magnetic resonance imaging study

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Background: Hypotheses regarding the neural substrates of writing have been derived from the study of individuals with acquired agraphia. Functional neuroimaging offers another methodology to test these hypotheses in neurologically intact individuals.

Aims: This study was designed to identify possible neural substrates for the linguistic and motor components of writing in normal English-speaking individuals.

Methods & Procedures: Functional magnetic resonance imaging was used with 12 adults to examine activation associated with generative writing of words from semantic categories contrasted with writing letters of the alphabet and drawing circles. In addition, the generative writing condition was contrasted with a subvocal generative naming condition.

Outcomes & Results: Semantically guided retrieval of orthographic word forms for the generative writing condition revealed activation in the left inferior and dorsolateral prefrontal cortex, as well as the left posterior inferior temporal lobe (BA 37). However, no activation was detected in the left angular gyrus (BA 39). The motor components of writing were associated with activation in left fronto-parietal cortex including the region of the intraparietal sulcus, superior parietal lobule, dorsolateral and medial premotor cortex, and sensorimotor areas for the hand.

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Conclusions: These observations suggest an important role of the left posterior inferior temporal cortex in lexical-orthographic processing and fail to support the long-held notion that the dominant angular gyrus is the storage site for orthographic representations of familiar words. Our findings also demonstrate the involvement of left superior parietal and frontal premotor regions in translating orthographic information into appropriate hand movements.

Writing requires the coordination of several cognitive, linguistic, and perceptual-motor operations. In the context of cognitive models of language, the writing process can be divided into central and peripheral components (Ellis, 1988; Rapcsak & Beeson, 2000; 2002; Shallice, 1988). The central components are linguistic in nature and are responsible for the retrieval of appropriate words and for the provision of information about correct spelling. As depicted in a simplified manner in Figure 1, orthographic knowledge is normally activated by combined input from semantics and phonology. Although neuropsychological evidence suggests that writing is possible even when phonological codes are unavailable (Basso, Taborelli, & Vignolo, 1978; Levine, Calvanio, & Popovics, 1982; Rapp, Benzing, & Caramazza, 1997), subvocal speech typically accompanies writing under normal circumstances (Ellis & Young, 1995). The peripheral components of the writing process serve to translate orthographic representations into handwriting by a series of procedures that guide the motor control of the hand.

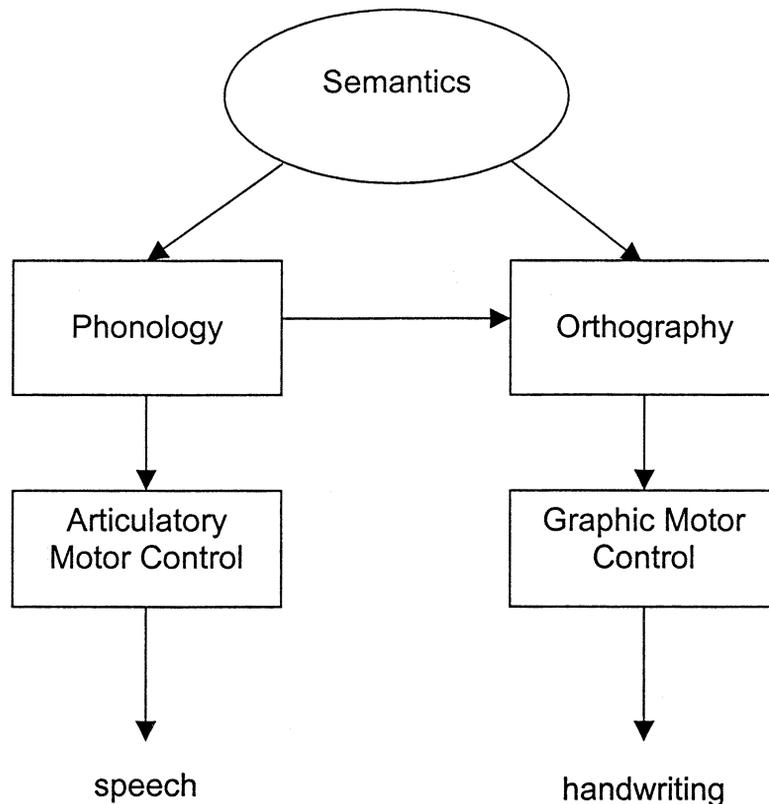


Figure 1. A simplified model of semantically guided retrieval and writing of single words.

The neuroanatomical regions likely to support the central and peripheral components of writing have been postulated primarily on the basis of neuropsychological studies of individuals with various forms of acquired agraphia (Roeltgen, 1994; Rapcsak & Beeson, 2000, 2002). Two historical contributions mark the early efforts to identify the neural substrates of writing. In 1891, Dejerine suggested that orthographic representations for familiar words were stored in the dominant angular gyrus in the form of visual images. With regard to the peripheral components of writing, Exner (1881) proposed a cortical centre for controlling the skilled movements for handwriting located at the foot of the second frontal convolution. These early neuroanatomical hypotheses held up rather well during the ensuing century, and there has been considerable elaboration regarding the cognitive components and neural mechanisms of writing (Rapcsak & Beeson, 2002; Roeltgen, 1994).

Neuropsychological evidence regarding the possible localisation of orthographic knowledge comes from individuals with lexical agraphia, a syndrome characterised by reliance on phonological spelling strategies due to damage to orthographic representations (Beauvois & Dérouesné, 1981). Individuals with lexical agraphia have difficulty spelling irregular words (e.g., choir), but can spell words with regular spelling (e.g., mint) and nonwords (e.g., dilt) by relying on phoneme–grapheme correspondence rules. Reliance on phonological rather than orthographic knowledge for spelling is evident by the prevalence of phonologically plausible spelling errors (e.g., comb—kome). Most cases of lexical agraphia are associated with damage to left extrasylvian temporo-parietal cortex with relative preservation of left perisylvian regions thought to support the phonological spelling procedures (Beauvois & Dérouesné, 1981; Roeltgen, 1993; Roeltgen & Heilman, 1984). Consistent with Dejerine's proposal, damage has been noted in and around the left angular gyrus (BA 39) in a number of patients. However, lexical agraphia also has been associated with lesions that involve more ventral regions including the posterior middle and inferior temporal gyri and the fusiform gyrus (BA 37) (Croisile, Trillet, Laurent, Latombe, & Schott, 1989; Patterson & Kay, 1982; Rapcsak, Rubens, & Laguna, 1990). Similarly, the Japanese equivalent of lexical agraphia, in which writing of kanji ideograms is impaired with relative preservation of kana phonograms, has been documented in cases of posterior inferior temporal damage (Kawahata, Nagata, & Shishido, 1988; Sakurai, Sakai, Sakuta, & Iwata, 1994; Soma, Sugishita, Kitamura, Maruyama, & Imanaga, 1989).

In contrast to the neuropsychological evidence favouring a critical role of the temporo-parietal cortex in lexical spelling, Hillis and colleagues (2002) recently suggested that Broca's area plays a role in accessing orthographic representations. In a study of hyperacute stroke patients (within 24 hours of stroke) using magnetic resonance diffusion and perfusion imaging, they found a significant correlation between hypoperfusion and/or infarct of the left inferior frontal cortex (BA 44) and impaired performance on written naming and spelling of irregular real words. At least some of those participants showed reliance on phoneme–grapheme correspondence rules as evidenced by phonologically plausible errors typical of lexical agraphia. Recovery of spelling was documented following reperfusion of Broca's area, leading Hillis et al. (2002) to assert that this region appears to be essential for accessing orthographic representations of at least some types of words. This relationship was not evident in all participants whose spelling performance implicated impairment of orthographic representations in that only 8 of 17 showed perfusion/diffusion abnormalities in Broca's area, so the specific contribution of this region to lexical spelling remains unclear.

Information regarding the neural substrates of peripheral writing procedures comes from neuropsychological studies of individuals with defective motor control of handwriting. Of particular interest are cases of apraxic agraphia in which poor letter formation cannot be accounted for by more elementary sensorimotor impairment affecting the writing hand (Rapcsak, 1997; Rapcsak & Beeson, 2000; Roeltgen, 1993; Roeltgen, Sevush, & Heilman, 1983). The underlying problem in apraxic agraphia appears to be an impairment of graphic motor programs that contain information about the spatio-temporal characteristics of the hand movements necessary to form letters. The most common neuroanatomical site of damage associated with apraxic agraphia is the region surrounding the left intraparietal sulcus, including the superior parietal lobule and superior portions of the supramarginal and angular gyri (Alexander, Fischer, & Friedman, 1992; Otsuki, Soma, Arai, Otsuka, & Tsuji, 1999; Rapcsak & Beeson, 2000; Roeltgen et al., 1983). Consistent with Exner's (1881) proposal, apraxic agraphia can also result from damage to the dorsolateral premotor area located at the foot of the second frontal convolution (i.e., Exner's area) (Anderson, Damasio, & Damasio, 1990; Hodges, 1991). Finally, features of apraxic agraphia have also been documented following damage to the supplementary motor area (SMA) (Rubens, 1975; Watson, Fleet, Rothi, & Heilman, 1986). Taken together, the lesion data suggest that the motor programming for writing is mediated by a distributed neural network that includes superior parietal regions as well as dorsolateral and medial premotor cortex (Rapcsak & Beeson, 2002).

Functional neuroimaging in neurologically intact individuals offers another methodology to test hypotheses regarding the neural substrates of writing based on observations in patients with agraphia. For instance, a study by Petrides, Alivisatos, and Evans (1995) using positron emission tomography (PET) employed writing to dictation as a comparison condition in a study designed to examine activation during verbal memory tasks and verbal repetition. When writing was contrasted with verbal production conditions, activation was detected in the left posterior temporal area (BA 37) that was attributed to the retrieval of orthography. In another study, Nakamura and colleagues (2000) specifically examined the role of the posterior inferior temporal area in the context of writing in Japanese subjects. Using functional magnetic resonance imaging (fMRI), they found activation in the posterior inferior temporal cortex (BA 37) for kanji writing as well as during mental recall of kanji characters without actual writing. This region was not active during oral reading or when making semantic judgements for the same stimuli, suggesting its specific role in generating orthographic output. Because the temporal lobe activation in the Nakamura et al. (2000) study was ventral to that reported by Petrides et al. (1995) by about 20 mm, the former authors suggested there may be regional differences in the temporoparietal cortex specific to alphabetical languages versus non-alphabetical writing systems such as kanji. Additional neuroimaging data regarding orthographic processes in alphabetical languages have not been available to address this question.

Other neuroimaging studies have provided information potentially relevant to the motor control of handwriting. PET and fMRI studies of English orthography (Menon & Desmond, 2001; Petrides et al., 1995; Seitz et al., 1997) and Japanese kana and kanji orthography (Katanoda, Yoshikawa, & Sugishita, 2001; Kato, Isoda, Takehara, Matsuo, Moriya, & Nakai, 1999; Sugishita, Takayama, Shiono, Yoshikawa, & Takahashi, 1996) have shown predominantly left-hemisphere activation in the region of the intraparietal sulcus, dorsolateral premotor cortex, and bilateral SMA in a variety of writing tasks.

The few neuroimaging studies with neurologically intact individuals have provided insights regarding the neural mechanisms of writing. However, these studies did not use

experimental conditions specifically designed to isolate the linguistic versus motor components of the writing process. As a result, the specific functional role of cortical regions activated by different writing tasks remains to be determined. The purpose of the present study was to use functional magnetic resonance imaging (fMRI) to examine the neural substrates of central and peripheral components of writing. To do so, generative writing of single words was contrasted with writing the alphabet, drawing circles, and generative naming. Based on neuropsychological findings in patients with lexical agraphia, we hypothesised that the left angular gyrus (BA 39) and the left posterior inferior temporal lobe (BA 37) would show activation during tasks that require the retrieval of orthographic knowledge. In addition, we expected the generative writing task would elicit activation patterns common to generative naming, given the shared semantic and phonological components. With regard to graphomotor components, we hypothesised that motor control for writing would involve the region in and around the left intraparietal sulcus, the left dorsolateral premotor area known as Exner's area, the medial frontal cortex (SMA), and sensorimotor regions involved in the implementation of hand movements.

METHOD

Participants

A total of 12 healthy right-handed adults (6 male: 6 female) ranging in age from 20 to 53 years (mean = 38.4 years) participated in this study. English was the first and primary language of all participants, and the mean years of education was 17.5 (\pm 5 years). They had no history of developmental language or learning disabilities, memory impairment, neurological disease or injury, or psychiatric problems. The Edinburgh handedness inventory (Oldfield, 1971) was administered, which confirmed right-handedness in all participants (mean laterality quotient = 90). Informed written consent was obtained from all individuals prior to participation in this study.

Conditions

The participants were administered two protocols, each consisting of three conditions (tasks). For one protocol, the three conditions were generative writing of single words, writing letters of the alphabet, and drawing circles (words/alphabet/circles). The second protocol included generative writing of single words, subvocal generative naming of single words, and a rest condition (writing/naming/rest).

Generative writing of single words was elicited by asking participants to write names of exemplars from provided semantic categories (i.e., written word fluency). The instruction was, "Write names of _____", using one of the following semantic categories: animals, fruits, musical instruments, vegetables, sports, tools, transportation, occupations, insects, drinks, or weapons.¹ The brief verbal instruction was presented within a 3-second time frame, followed by a 30-second response interval (or epoch) that ended with the instruction, "stop". Prior to scanning, participants were told that they should try to generate words throughout the 30 seconds. They were also instructed to write one word on top of the other so that hand movement was minimised. For the letter-

¹ We acknowledge that control was not exerted over the potential influence of various semantic categories used to elicit responses (Martin, Wiggs, Ungerleider, & Haxby, 1996); however, we assume that the use of a variety of categories served to minimise (i.e., randomise) such influences, which were not the focus of this study.

writing condition, participants were asked to “Write the alphabet”. They were instructed to write letters throughout the 30-second epoch, so that once they reached “z”, they were to start at “a” again. Participants were instructed to write letters on top of one another, rather than writing in a line across the page, again to minimise arm and hand movement. The third condition consisted of drawing circles throughout the duration of the 30-second epoch. Participants were encouraged to draw continuous circles and to minimise arm movement, so that the resulting pattern typically looked like spirals. The three conditions were implemented five times during a single functional imaging run, with the order varied across participants. The protocol was repeated using different semantic categories for the generative writing condition during a second functional imaging run.

The writing/naming/rest protocol consisted of the generative writing condition, along with a subvocal generative naming condition for the same semantic categories, and a rest condition. The generative writing task was the same as that described above, wherein participants were asked to “Write names of _____”. Generative naming was cued with the instruction, “Think names of _____”. The semantic categories included five of the following: animals, musical instruments, tools, fruits, sports, and occupations. For the rest condition, participants were instructed to keep their eyes closed and to simply imagine looking at the night sky in response to the command, “Look at the night sky”. This was intended to prompt participants to discontinue the word-generation task. In a manner analogous to the words/alphabet/circles protocol, 3-second command and 30-second response intervals were used for each condition, and the conditions were repeated for a total of five times for each of two functional imaging runs.

Prior to scanning, participants were oriented to the conditions and brief practice was provided in a reclining chair to approximate the experience of writing in the scanner. During scanning, the head was stabilised using foam padding placed under the neck and around the head as needed to pack the space between the head and inner surface of the coil. A velcro strap was secured just above the elbows to minimise arm movement during writing. A pad of paper was placed on the participant’s lap prior to scanning, which was held in place with the left hand, and a pencil was grasped in the right hand. Participants were instructed to close their eyes during functional scanning in order to minimise eye movement, and to write in their typical script (either cursive or print, upper or lowercase). Instructions were presented by live voice through MR-compatible headphones (Resonance Technologies).

Following the imaging, participants were tested outside the scanner on the generative writing and naming tasks, so that an estimate of performance could be made.

Scanning procedure

Scanning was carried out on a 1.5 Tesla Signa whole-body MRI system (General Electric, Milwaukee, WI) equipped with a standard quadrature head coil. Contiguous multislice T2*-weighted functional images were obtained using a spiral echoplanar imaging sequence with the following parameters: 3000 ms TR; 40 ms TE; $22 \times 22 \text{ cm}^2$ field of view; 64×64 matrix; and 6 mm slice thickness. A total of 19 oblique slices aligned parallel to the base of corpus callosum were imaged. High resolution, T1-weighted anatomical reference images were obtained as a set of 124 contiguous sagittal slices using a three-dimensional spoiled-gradient-echo sequence (SPGR; TR = 24 ms; TE = 5 ms; flip angle = 45; slice thickness = 1.5 mm).

Each scanning run was preceded by the acquisition of two baseline images (6 seconds) to allow the magnetic resonance signal to reach equilibrium. The total scanning

time for each run was 8 minutes, 15 seconds with 165 images acquired (50 images per condition).

Statistical analyses

The data were analysed with Statistical Parametric Mapping software (SPM99; Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm>). The time series for each participant were motion corrected and spatially normalised to the Montreal Neurological Institute (MNI) standardised Talairach atlas space using a 12-parameter affine approach and a T2*-weighted template image (Friston, Holmes, Worsley, Poline, Frith, & Frackowiak, 1995). Following the normalisation procedure that resampled all scans to 2-mm³ isotropic voxels, the data were spatially smoothed with an isotropic Gaussian filter at 8 mm full width at half maximum (FWHM). Because we hypothesised that writing is supported by a distributed neural network, whole-brain analyses were planned to examine the functional contribution of different cortical areas. In addition, region of interest analyses were planned in order to more closely examine the contribution of posterior temporo-parietal regions including Brodmann areas 39 and 37.

Whole-brain analyses. Functional MRI analyses were performed on a voxel-by-voxel basis, employing a general linear model approach as implemented by SPM99 (Friston et al., 1995; Worsley & Friston, 1995; Worsley, Marrett, Neelin, Vandal, & Friston, 1996). This regression model reveals areas of activation unique to the specified contrasts, and thus allows isolation of cognitive processes of interest. Three comparisons were made for the first protocol: generative writing versus drawing circles (generative writing – circles); generative writing versus writing the alphabet (generative writing – alphabet); and writing the alphabet versus drawing circles (alphabet – circles). The generative writing – circles contrast was expected to provide information about activity related to semantically guided retrieval of orthographic information and also the motor planning and execution of hand movements necessary to write letters. The generative writing – alphabet contrast also should reveal activation related to the retrieval of orthographic word forms, but should remove the common activation associated with writing letters. Finally, the alphabet – circles contrast should isolate processes necessary for motor programming and execution of handwriting movements, without producing activation in regions dedicated to lexical-semantic processing. The contrast with circle drawing was also intended to remove some of the cognitive and sensorimotor processes that were engaged in all the conditions that relate to attention and motor control associated with holding and moving the pencil.

For the second protocol, the contrast of generative writing of words versus the sub-vocal generative naming of words (generative writing – generative naming) was of interest. This contrast provided an attempt to isolate orthographic and motor components for writing while controlling for semantic and phonological components common to both spoken and written production of words.

The contrasts were analysed for each participant as individual time series followed by a multisubject analysis using the random effects procedure described by Holmes and Friston (1998). For the group analyses, the threshold for significance was set at $T = 4.02$, corresponding to an uncorrected probability of $p < .001$, and an extent threshold of ≥ 50 voxels. The whole-brain analyses were designed to confirm participation of a number of left hemisphere cortical regions relevant to writing that were identified *a priori* on the

basis of neuropsychological studies. Due to the confirmatory nature of these analyses, the uncorrected (rather than corrected) probability levels were used.²

Region of interest analyses. In addition to the analysis of whole brain activation, predefined areas of interest in the left angular gyrus (BA 39) and left posterior inferior temporal lobe (BA 37) were examined. The region of the angular gyrus was defined as a $20 \times 20 \times 20$ mm volume with the stereotactic coordinates for the centrepoint of $x = -44$, $y = -54$, $z = 24$. These coordinates were those used by Horwitz, Rumsey, and Donohue (1998) and reflected consensus of the imaging literature relative to the location of the angular gyrus (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995; Démonet, Chollet, Ramsay, Cardebat, Nespoulous, Wise, et al., 1992; Howard et al., 1992; Price, Wise, Watson, Patterson, Howard, & Frackowiak, 1994). The posterior inferior temporal lobe was defined as a $20 \times 30 \times 20$ mm volume with a centrepoint located at $x = -50$, $y = -56$, $z = -12$. This region encompassed both lateral and ventral portions of BA 37, with the anterior–posterior dimension extending from BA 20 to BA 19, respectively. The nonoverlapping search volumes for BA 37 and BA 39 were examined for each individual participant, and for the aggregated group data for the following contrasts: words–circles, words–alphabet, alphabet–circles, and writing–naming. A small volume correction procedure was used (corrected $p \leq .01$) with extent threshold of ≥ 20 voxels. This procedure adjusts the p -value for multiple comparisons based on the volume of the region of interest rather than the entire brain.

RESULTS

When tested outside the scanner, participants generated an average of 9.3 words per 30-second epoch for the generative writing condition in the words/alphabet/circles protocol, and 9.6 words for the generative writing condition in the writing/naming/rest protocol. As expected, more words were generated during generative naming, which did not require a written response, with an average of 14 words spoken per 30-second epoch. When writing the alphabet, participants averaged 55 letters during the 30-second epoch.

All 12 participants yielded imaging data that were adequate for analysis. Tables 1–4 summarize the group data indicating the activation foci that exceeded a threshold of $T = 4.02$ (uncorrected $p < .001$; extent threshold ≥ 50 voxels) for the following contrasts: generative writing – circles, generative writing – alphabet, alphabet – circles, and generative writing – generative naming. Contrasts between the rest condition and the generative writing and generative naming conditions were also examined. Because these contrasts reflected activation across the entire network of brain areas that support these complex tasks, they were of limited value for our purposes, and are not presented here. The group results for the contrasts of interest are displayed as surface-rendered projections on a standardised atlas brain in Plate 1 (situated between pages 656 and 657), providing an overview of the regional activation associated with each contrast. The strong predominance of left hemisphere activation is apparent for all contrasts. The results from the contrasts of interest are described below.

²Because the random effects model reduces the statistical power needed to detect subtle effects, we judged that the uncorrected probability level of .001 optimised the trade-off between adequate statistical power and Type 1 error, given our sample size.

TABLE 1
Significant regions of activation for the contrast of generative writing of words versus drawing circles

<i>Brain area</i> <i>Cluster region</i>	<i>Cluster extent</i> <i>(in voxels)</i>	<i>Max voxel level T value</i>	<i>x, y, z MNI coordinates</i>
Contrast: generative writing – drawing circles			
Temporal			
L posterior inferior temporal cortex (BA 37/20)	103	5.63 5.14	-42, -54, -12 -54, -54, -16
Parietal			
L superior parietal region (BA 7)	1773	11.28 10.83 9.64	-32, -66, 42 -22, -68, 62 -24, -52, 52
Frontal			
L inferior/middle frontal gyrus (BA 46)	1829	11.89 10.36 9.88	-42, 26, 16 -40, 20, 24 -48, 20, 30
L inferior frontal gyrus (BA 47) and putamen	1589	14.74 6.93 6.52	-36, 24, -12 -24, -4, -2 -20, 10, -6
L middle frontal gyrus (BA 6; Exner's area)	885	9.67 7.92 7.00	-26, 4, 58 -14, -10, 64 -32, -2, 56
Bilateral medial frontal cortex (BA 32/6; cingulate gyri and SMA)	1673	10.94 8.75 8.74	-8, 20, 48 10, 14, 48 -4, 12, 52
R inferior frontal gyus (BA 47)	68	7.11	38, 26, -8
R middle frontal gyrus (BA 6)	156	6.70 6.03 5.43	28, 0, 56 36, 2, 58 30, -8, 50
Cerebellum			
L anterior cerebellum	124	6.17 5.13	-34, -50, -36 -32, -48, -26
L anterior cerebellum	50	5.62	-26, -36, -30
L posterior cerebellum	421	8.69 6.85 6.02	-2, -60, -16 8, -62, -20 10, -66, -28
R anterior cerebellum	91	6.45 5.29	22, -42, -32 28, -44, -38

All regions listed were significant for $p < .001$ (uncorrected) with an extent threshold ≥ 50 voxels.

Generative writing versus drawing circles

When generative writing was contrasted with circle drawing, the intention was to remove activation related to general motor control of the pen, retaining activation related to semantically guided retrieval of orthographic word forms and the motor procedures necessary to write letters. The generative writing – circles contrast resulted in a significant region of activation in the left posterior inferior temporal region in BA 37 extending into BA 20. This region is evident in the lateral view of the left hemisphere in Plate 1a (situated between pages 656 and 657), and is shown in coronal and axial planes

TABLE 2
Significant regions of activation for the contrast of generative writing of words versus writing the alphabet

<i>Brain area Cluster region</i>	<i>Cluster extent (in voxels)</i>	<i>Max voxel level T value</i>	<i>x, y, z MNI coordinates</i>
Contrast: generative writing – writing alphabet			
Temporal			
L posterior inferior temporal cortex (BA 20/37)	94	5.84 5.70	–54, –54, –16 –44, –52, –12
Parietal			
L superior parietal region (BA 7)	173	7.57 5.81 4.25	–30, –66, 42 –28, –56, 38 –30, –62, 52
Frontal			
L precentral sulcus (BA 4/6)	106	7.26	–28, –20, 46
L insula and middle frontal gyrus (BA 46)	4821	15.02 11.00 10.72	–32, 18, 16 –44, 14, 14 –40, 20, 26
L middle frontal gyrus (BA 10)	291	9.02 5.73	–28, 54, 12 –28, 46, 14
L SMA (BA 6)	76	5.41 5.06 4.97	–16, –8, 56 –8, –8, 62 –14, 0, 54
Bilateral cingulate gyri (BA 32)	1582	13.60 11.98 11.40	–6, 22, 48 10, 34, 22 –8, 32, 24
R SMA (BA 6)	61	5.85	16, –18, 50
R inferior frontal gyrus (BA 46)	54	5.43	40, 30, 16
R inferior frontal gyrus (BA 47)	73	9.42	40, 22, –6
Cerebellum			
medial cerebellum	227	7.09 5.09 4.95	0, –62, –18 –2, –50, –28 –2, –54, –18
Other			
R caudate	91	6.36 4.64	20, –14, 24 22, –26, 20
R caudate	74	6.57	30, 8, 22
L posterior cingulate	170	8.48 6.80 5.40	–16, –52, 4 –2, –54, –2 –8, –60, 6

All regions listed were significant for $p < .001$ (uncorrected) with an extent threshold ≥ 50 voxels.

in Plate 2a (white arrows). Moving dorsally, a large region of activation is evident in the left superior parietal region in Plate 1a. As shown in the axial section in Plate 2a (pink arrow), the activation follows the course of the intraparietal sulcus, extending to the postcentral gyrus and into the superior parietal lobule (see coronal section Plate 2a, pink arrow).

The generative writing – circles contrast also revealed significant frontal lobe activation that was much more extensive in the left than the right hemisphere. Activation was evident in the inferior frontal cortex in BA 47 extending into BA 45/44 and deep to

TABLE 3
Significant regions of activation for the contrast of writing the alphabet versus drawing circles

<i>Brain area</i> <i>Cluster region</i>	<i>Cluster extent</i> <i>(in voxels)</i>	<i>Max voxel level T value</i>	<i>x, y, z MNI coordinates</i>
Contrast: writing alphabet – drawing circles			
Parietal			
L superior parietal region (BA 7/5)	547	9.80	–22, –68, 62
		6.46	–32, –46, 64
		6.16	–22, –64, 50
R inferior parietal lobule (BA 40) and postcentral gyrus (BA 2)	132	5.45	38, –44, 52
		5.03	40, –36, 60
		4.25	48, –32, 44
Frontal			
L inferior frontal gyrus (BA 44, 9)	129	8.31	–50, 6, 20
		5.76	–50, 12, 28
L precentral gyrus (BA 4) and middle frontal gyrus (BA 6)	125	5.03	–52, –6, 46
		4.75	–54, 2, 42
		4.48	–48, –12, 52
L middle frontal gyrus (BA 6 Exner's area)	165	5.35	–36, –4, 54
		4.68	–22, –4, 56
		4.28	–32, –14, 60

All regions listed were significant for $p < .001$ (uncorrected) with an extent threshold ≥ 50 voxels.

the putamen. As shown in Plate 1a, there was extensive activation in dorsolateral prefrontal cortex (BA 46/9) and the posterior middle frontal gyrus (BA 6) corresponding to Exner's area, which is also shown in the axial plane in Plate 2a (green arrow). Activation in the medial frontal cortex included portions of the anterior cingulate gyri (BA 32) extending to medial SMA (BA 6). Bilateral cerebellar activation was also noted (Table 1). Cortical activation in the right hemisphere was localised to the inferior and middle frontal gyri (BA 47 and BA 6, respectively).

Generative writing versus writing the alphabet

When generative writing is contrasted with writing letters of the alphabet, the resulting activation should reflect semantically guided retrieval of orthographic word forms. Consistent with this hypothesis, this contrast resulted in left posterior inferior temporal lobe activation in roughly the same region as observed for the generative writing – circles contrast (Plate 1b). Activation in the left superior parietal region was notably reduced in comparison to that observed in the generative writing – circles contrast (compare Plates 2a and 2b, pink arrows), as might be expected due to the common element of motor programming for writing letters in words and writing the alphabet. As shown in the axial slice in Plate 2b (pink arrow), the focus of activation in the parietal region was in the intraparietal sulcus near the occipito-parietal junction, with little extension into the superior parietal lobule.

Similar to the generative writing – circles contrast, the generative writing – alphabet contrast resulted in significant activation in the left inferior and dorsolateral prefrontal cortex (including BA 47, 46, 45, and 10) extending deep into the left insula. There was

TABLE 4
Significant regions of activation for the contrast of generative writing of words versus generative naming

<i>Brain area</i> <i>Cluster region</i>	<i>Cluster extent</i> <i>(in voxels)</i>	<i>Max voxel level T value</i>	<i>x, y, z MNI coordinates</i>
Contrast: generative writing – generative naming			
Parietal			
L precentral/postcentral gyri (BA 4/3), superior and inferior parietal lobule (BA 5 and BA 40)	2974	10.69 10.42 10.02	–34, –46, 62 –42, –40, 56 –38, –22, 52
L superior parietal region (BA 5/7)	68	6.53 4.33	–4, –50, 68 –8, –58, 68
L inferior parietal lobule (BA 40) and superior temporal gyrus (BA 42)	69	6.05 5.31	–64, –24, 20 –60, –18, 8
R supramarginal gyrus (BA 40)	63	5.12 4.63	48, –40, 62 44, –44, 56
Frontal			
Bilateral medial frontal cortex (BA 6/24)	756	11.73 7.59	–2, 2, 56 –2, –10, 48
Subcortical			
L Thalamus	168	11.49	–18, –24, 2
Cerebellum			
R anterior cerebellum	916	9.98 8.35 8.08	8, –56, –18 22, –44, –32 14, –48, –24

All regions listed were significant for $p < .001$ (uncorrected) with an extent threshold ≥ 50 voxels.

also activation in the posterior portion of the middle frontal gyrus (BA 6 Exner's area) (Plate 2b, green arrow). Bilateral activation of medial frontal cortex was similar to that obtained in the generative writing – circles contrast including anterior cingulate (BA 32) and SMA (BA 6). Activation in the cerebellum was limited to the medial regions (Table 2). In the right hemisphere, activation was evident in the inferior frontal cortex in BA 47 and BA 46 (Plate 1b).

Writing the alphabet versus drawing circles

The contrast of writing the alphabet versus circle drawing was intended to isolate the cortical regions responsible for graphic motor programming and the execution of hand-writing movements. As expected, the contrast yielded no significant activation in the left temporal lobe, confirming that the primary role of this region in writing involves lexical-semantic processing. Activation detected in the parietal lobe was less extensive than that observed in the generative writing – circles contrast, but greater than that detected in the generative writing – alphabet contrast in which letter writing was a common component (Plate 1). As shown in Plate 2c (pink arrow), activation was predominantly localised to the superior parietal region, and did not appear to extend into the intraparietal sulcus as observed in the two contrasts that involved generative writing of words. Left frontal lobe activation was restricted to the premotor regions including the inferior and middle frontal gyri (BA 44/9 and BA 6), and the primary motor area for the hand (BA 4). Activation in

the right hemisphere was restricted to the postcentral gyrus extending into the dorsal portion of the inferior parietal lobule (BA 40). There was no suprathreshold activation in the medial frontal cortex or the cerebellum for this contrast.

Generative writing versus generative naming

By contrasting the generative writing condition with the subvocal generative naming condition, our intention was to detect activation specific to the retrieval of orthography, graphomotor programming, and implementation of writing movements. The generative writing – generative naming contrast resulted in prominent activation in the left superior parietal lobule, Exner's area, the left primary sensorimotor area for the hand, bilateral SMA, and the right cerebellum (Plate 1d). There was a region of activation in the left posterior perisylvian region including BA 40 and BA 42. Notably absent was the extensive left prefrontal activation observed in the generative writing – circles and generative writing – alphabet contrasts, as well as the left inferior temporal lobe activation.

Region of interest analyses

The region of interest analyses for the group data revealed significant activation in BA 37 when generative writing was contrasted with drawing circles (Plate 3a, situated between pages 656 and 657) and writing the alphabet (Plate 3b). When the data from individual participants were examined, significant foci of activation were detected in this region for all 12 on the generative writing – circles contrast and 11 of 12 participants for the generative writing – alphabet contrast (Table 5). In comparison, the small volume search in the region of the left angular gyrus (BA 39) did not yield significant activation for the group on either of these contrasts. The data from individual participants revealed that only 6 out of 12 participants had significant clusters of activation in the angular gyrus region (Table 5).

For the alphabet – circles contrast, the group analysis revealed significant activation in the BA 37 search region, however, the cluster maxima was located posterior to that detected for the generative writing – circles and generative writing – alphabet contrasts. Peak activation was near the inferior temporo-occipital junction (BA 37/BA 19), and was significant in 10 of 12 individual participants. There was no significant activation in the angular gyrus region for the group analysis of the alphabet – circles contrast, and only 5 of 12 individual participants showed activation in that region (Table 5).

Similar to the alphabet – circles contrast, the generative writing – generative naming contrast showed significant activation located in the posterior portion of the BA 37 region. Peak activation for the group was located in the inferior temporo-occipital region extending into BA 19 (Plate 3d), and activation in this region was significant for 9 of the 12 participants. There was no significant activation for the group in the angular gyrus, with only 5 of 12 participants yielding significant activation for this contrast.

DISCUSSION

The aim of the present investigation was to examine the neural substrates of the central and peripheral components of the writing process. Self-generated writing of single words engaged left-hemisphere regions including the posterior inferior temporal cortex, superior parietal lobule and intraparietal sulcus, inferior and dorsolateral prefrontal cortex, lateral and medial premotor cortex, and sensorimotor areas for the hand. Additional insights into the functional role of these various cortical regions were obtained by contrasting

TABLE 5
Small volume search

<i>Contrast</i>	<i>Area 37</i> (-50, -56, -12)				<i>Area 39</i> (-44, -54, 24)			
	<i>Cluster extent (voxels)</i>	<i>Max voxel (t)</i>	<i>maxima x, y, z</i>	<i># Ss</i>	<i>Cluster extent (voxels)</i>	<i>Max voxel (t)</i>	<i>maxima x, y, z</i>	<i># Ss</i>
Generative writing – circles	417	5.63	-42, -54, -12	12/12	–	–	–	6/12
Generative writing – alphabet	300	5.84	-54, -54, -16	11/12	–	–	–	6/12
Alphabet – circles	80	4.95	-48, -68, -18	10/12	–	–	–	5/12
Generative writing – generative naming	27	3.96	-52, -70, -4	9/12	–	–	–	5/12

Results of small volume search for significant activation in the left inferior temporo-occipital region (BA 37) and left angular gyrus (BA 39) using $20 \times 30 \times 20$ mm and $20 \times 20 \times 20$ mm volumes, respectively. Threshold set at $p < .01$ with extent of ≥ 20 voxels. Note: # Ss = number of subjects with significant activation in region of interest.

generative writing with writing the alphabet, and circle drawing, and by comparing patterns of activation associated with generative writing versus generative naming. Our findings are discussed below relative to the central procedures involved in the retrieval of orthographic knowledge, and the peripheral procedures required for the graphomotor control of handwriting.

Retrieval of orthography

Contrary to the long-held notion that the left angular gyrus (BA 39) plays a critical role in spelling (Dejerine, 1891), there was not significant activation in this cortical region for the contrasts intended to isolate procedures for single-word writing. This finding was surprising given that the left angular gyrus is considered a common lesion site in patients with lexical agraphia (Rapcsak & Beeson, 2000; Roeltgen, 1993; Roeltgen & Heilman, 1984). Instead, the generative writing condition in our study resulted in activation in the left posterior inferior temporal cortex, including the fusiform gyrus (BA 37) and inferior temporal gyrus (BA 37/20). As noted earlier, damage to this region has also been associated with lexical agraphia (Croisile et al., 1989; Patterson & Kay, 1982; Rapcsak et al., 1990) and with kanji agraphia in Japanese subjects (Kawahata et al., 1988; Sakurai et al., 1994; Soma et al., 1989). The group findings were consistent with regional activation in individual participants in that all 12 subjects showed significant activation in BA 37 during generative writing, whereas only half of those subjects showed concomitant activation in BA 39. These findings consistently demonstrate the participation of the posterior inferior temporal cortex in spelling; however, it appears that the angular gyrus may also make a contribution to spelling in at least some individuals.

Our findings are consistent with other neuroimaging studies of writing that examined the left temporo-parietal region (Nakamura et al., 2000; Petrides et al., 1995). Specifically, the regions of peak activation that we observed in the inferior temporal lobe on the generative writing – circles contrast ($x = -42$, $y = -54$, $z = -12$) and the generative

writing – alphabet contrast ($x = -54, y = -54, z = -16$) were in close proximity to the area of overlap identified by Nakamura et al. (2000) during the written production and mental recall of kanji characters ($x = -50, y = -64, z = -14$). The loci of activation in the present study and that of Nakamura et al. (2000) were ventral to that reported by Petrides et al. (1995) which centred around coordinates in the middle temporal gyrus ($x = -50, y = -66, z = 5$). These differences are not attributable to the use of different writing systems (alphabetic versus pictographic) as our results with English closely matched those obtained with Kanji script (Nakamura et al., 2000). Rather, the differences may relate to methodological variations in the task demands or contrasts.

The convergence of our findings with other neuroimaging studies and neuropsychological case reports of lexical and Kanji agraphia favours localisation of orthographic representations to the left posterior inferior temporal cortex. However, it was noteworthy that activation in this region was common to both the generative writing and generative naming conditions, suggesting that it may reflect lexical-semantic or phonological operations shared by speech and writing, rather than orthographic processing *per se*. The apparent overlap in the inferior temporal lobe for writing and naming is not entirely surprising given that this general region is considered a multimodal language processing area (Cabeza & Nyberg, 2000; Démonet et al., 1992; Price, 1998). Consistent with this notion, activation in BA 37 has been documented for a variety of tasks involving comprehension or production of spoken words (Démonet et al., 1992; Howard et al., 1992; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Warburton et al., 1996). Functional imaging studies of single-word reading have also shown activation in this region (Beauregard, Chertkow, Bub, Murtha, Dixon, & Evans, 1997; Cohen et al., 2000; Price, et al., 1994; Tagamets, Novick, Chalmers, & Friedman, 2000). Although the posterior temporal lobe activation in these studies has been typically attributed to orthographic processing, it is important to keep in mind that oral reading also involves the activation of semantic and phonological codes (cf. Price, Moore, & Friston, 1997).

Consistent with the overlap of anatomical regions involved in semantic, phonological, and orthographic processing in left posterior temporal cortex suggested by functional imaging studies, patients with lexical agraphia following damage to this region frequently show evidence of associated anomia and/or alexia (Croisile et al., 1989; Patterson & Kay, 1982; Rapsak et al., 1990; Roeltgen, 1993; Sakurai et al., 1994; Soma et al., 1989). However, evidence that this general anatomical region may be functionally subdivided was provided by Sakurai and colleagues (1994) who studied the co-occurrence of anomia in cases of alexia with agraphia for kanji after left posterior inferior temporal lesions. They found that those with severe anomia had lesions that extended more anteriorly than those with unimpaired naming or mild anomia, suggesting that the greatest overlap for naming and writing may be situated in the anterior portion of BA 37.

In the present study, the region of interest analysis in the inferior temporal region yielded some anterior–posterior differentiation by condition. The generative writing – generative naming contrast showed a focus of activation associated with writing but not subvocal naming located at the inferior temporo-occipital junction involving posterior BA 37 extending into BA 19. Although this activation could be specific to lexical orthographic processing, it should be pointed out that this region was also activated in alphabet – circles contrast. These observations suggest that activation in this cortical area is more likely to play a role in the retrieval of information about letter shapes. Consistent with this hypothesis, activation in the inferior occipital lobe was similarly documented in the context of visual imagery of letter shapes in a SPECT study by Goldenberg, Podrek,

Steiner, Willmers, Suss, and Deecke (1989). In addition, other studies that examined the processing of visually presented letters showed activation located in the left fusiform gyrus and extrastriate regions (BA 18/19) that was distinct from activation associated with visually presented words localised to BA 37 (Price, Wise, & Frackowiak, 1996; Tagamets et al., 2000). Taken together, these findings suggest that orthographic knowledge about familiar words may be represented in cortical regions anterior to those involved in the retrieval of information about the visual features of individual letters. Furthermore, cortical regions located more anteriorly in BA 37/20 may be involved in semantic processing.

Although we have primarily focused on parieto-temporal cortex, the generative writing – circles and generative writing – alphabet contrasts also produced robust activation in the left prefrontal cortical region. Because these regions were not active in the generative writing – generative naming contrast, it suggests that they were related to semantically guided retrieval of lexical representations. These findings differ from those of Hillis et al. (2002) who suggested that Broca's area played a specific role in accessing orthographic representations. Acknowledging the lack of convergence with our findings, Hillis et al. (2002) offered the explanation that their stimuli included verbs, whereas our subjects retrieved only nouns. Whether Broca's area makes a special contribution to spelling verbs awaits empirical confirmation.

Motor control for writing

Regarding the neural substrates of the motor control of writing, our findings support the role of superior parietal and frontal premotor regions for translating orthographic information into the appropriate hand movements. Extensive activation was detected in the left intraparietal sulcus and the superior parietal lobule for generative writing (generative writing – circles contrast), whereas writing letters of the alphabet (alphabet – circles) yielded activation primarily in the superior parietal lobule that did not extend into the sulcus. The generative writing – alphabet contrast indicated that activation in the superior parietal lobe was common to writing words and writing letters of the alphabet. Thus it appeared that whereas both tasks require activation of letter-specific graphic motor programs, the automaticity of writing the alphabet imposed fewer demands for motor planning than writing words. This finding is similar to that of Seitz et al., (1997) who used PET to examine writing letters and novel ideograms. They found bilateral rCBF increases in the intraparietal sulcus when subjects were asked to write letters with exact precision and when learning to write novel ideograms, but this activation was not evident when subjects wrote rapid repetitions of a single letter or once the ideograms were well learned. The latter conditions engaged only the superior parietal lobule, as did the alphabet writing in the present study. Therefore, it appears that within the parietal lobe, the region of the intraparietal sulcus plays a more critical role in motor planning for highly complex or novel hand movements.

Parietal lobe activation was accompanied by activation in the dorsolateral premotor region corresponding to Exner's area when writing words and writing the alphabet. The generative writing – alphabet contrast did not completely cancel out the activation in this region, despite the fact that a greater number of letters were likely to have been generated when writing the alphabet versus generative writing for a semantic category. The activation obtained in the words – alphabet contrast was anterior to that obtained in the alphabet – circles contrast. In other words, the activation from the alphabet – circles contrast was in closer proximity to the primary motor area for the hand. This difference

could reflect a continuum of complexity for motor programming that decreases as the primary motor strip is approximated; however, it remains to be determined whether such regional differences are truly meaningful.

The neural support for the implementation of the motor commands for handwriting was best observed in the writing – naming contrast. As expected, the contrast resulted in extensive activation in the left sensorimotor cortex for the hand. In addition, there was activation in the superior parietal lobule, Exner's area, bilateral SMA, and the right cerebellum. These findings are consistent with other neuroimaging studies and suggest that these regions play an important role in the motor planning and execution of handwriting movements (Sugishita et al., 1996; cf. Kato et al., 1999; Katanoda et al., 2001; Menon & Desmond, 2001).

Conclusion

The results of this study are promising with regard to the use of functional magnetic resonance imaging to investigate the neural substrates of writing. The central or linguistic components of writing were localised to left posterior inferior temporal cortex, rather than the left angular gyrus. The temporal lobe areas involved in writing appear to overlap with cortical areas engaged in lexical-semantic processing for a variety of language tasks. Additional neuropsychological and neuroimaging studies are needed to determine whether it is possible to identify distinct subregions within posterior temporal cortex dedicated to semantic, phonological, and orthographic processing. Regarding the peripheral or motor components of the writing process, our findings confirmed the critical role of a left-hemisphere fronto-parietal network involving the intraparietal sulcus, superior parietal lobule, dorsolateral and medial premotor cortex, and sensorimotor cortex for the hand. Given that the application of functional neuroimaging techniques to the study of writing lags behind other language modalities, considerable work remains to be accomplished. We anticipate fruitful application of other methodologies including cognitive conjunction, factorial, and parametric designs to complement the cognitive subtraction method reported here (Price et al., 1997).

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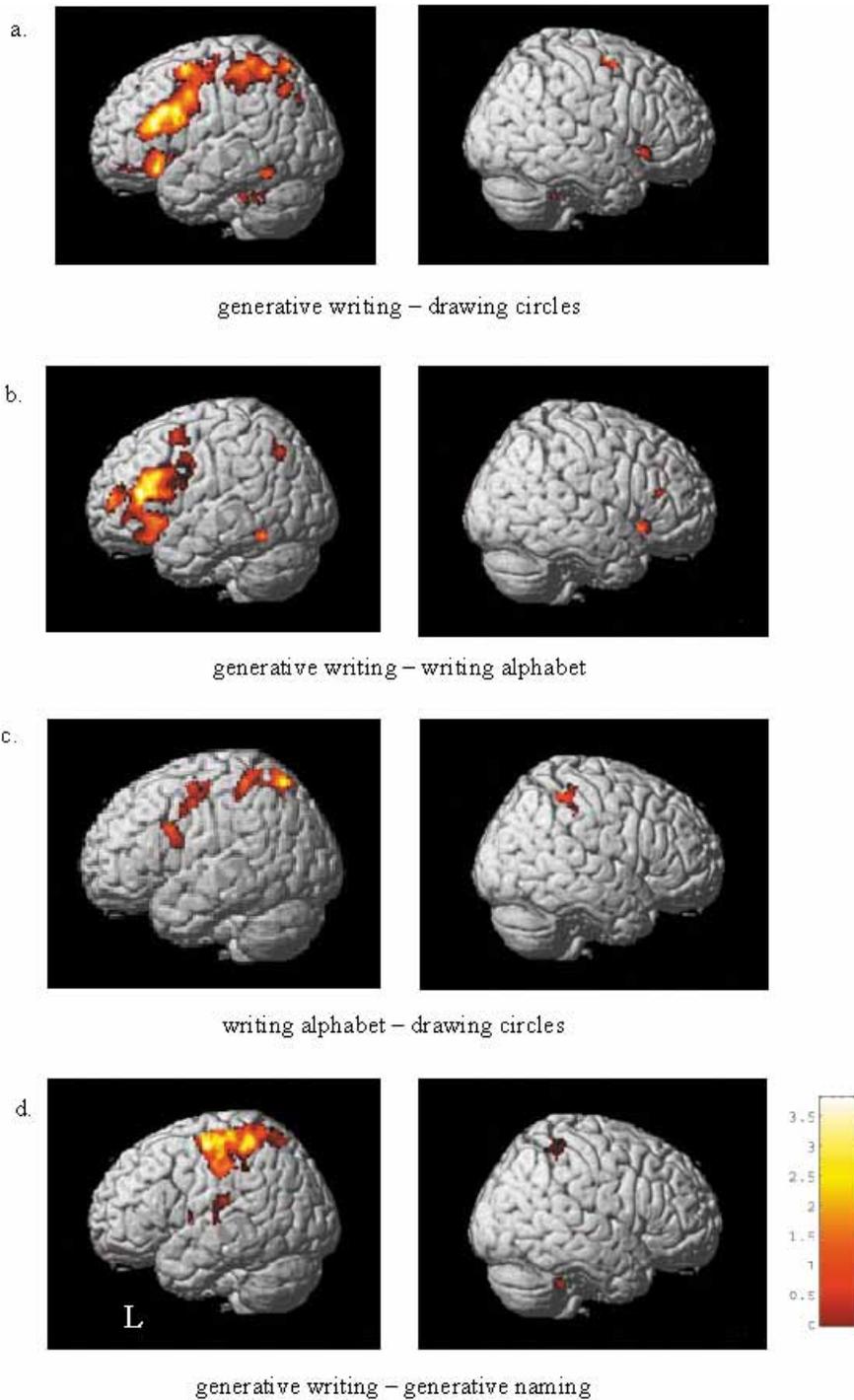


Plate 1. Surface-rendered projections of statistical maps reflecting activation during (1a) generative writing of words versus repetitive drawing of circles; (1b) generative writing of words versus writing letters of the alphabet; (1c) writing letters of the alphabet versus repetitive drawing of circles; (1d) generative writing of words versus generative subvocal naming of words. Display threshold set at $T = 4.02$ (uncorrected $p < .001$; extent threshold ≥ 50 voxels).

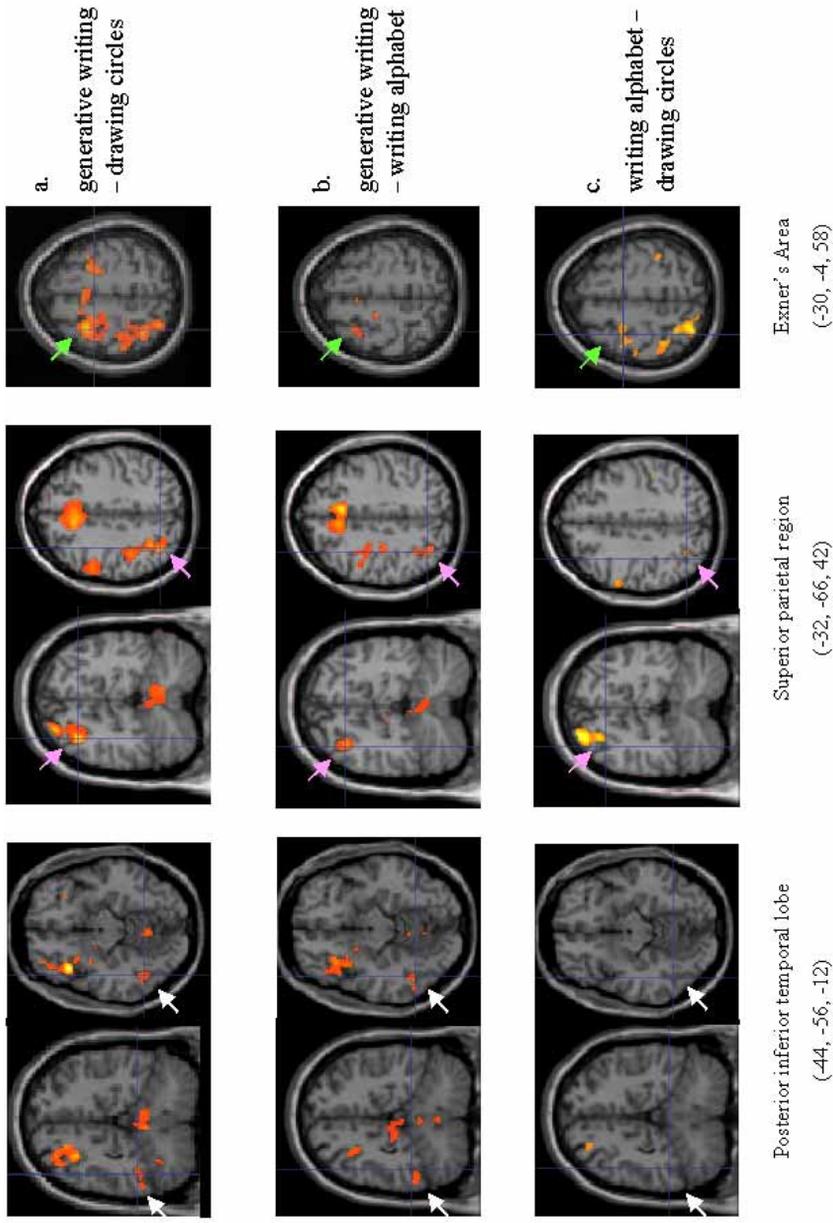
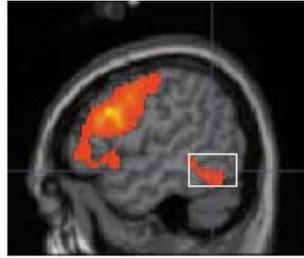
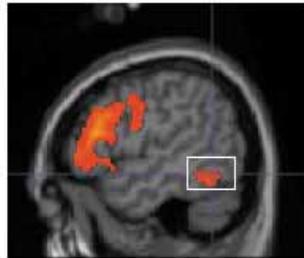


Plate 2. Coronal and axial sections showing activation in the posterior inferior temporal lobe (white arrows), superior parietal region (pink arrows), and Exner's area (green arrows) for the contrasts: (2a) generative writing of words versus repetitive drawing of circles; (2b) generative writing of words versus writing letters of the alphabet; (2c) writing letters of the alphabet versus repetitive drawing of circles. Display threshold set at $T = 4.02$ (uncorrected $p < .001$; extent threshold ≥ 50 voxels).

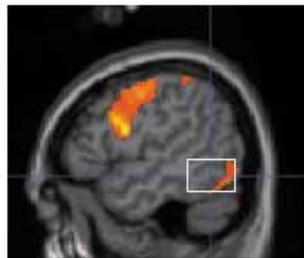
a.
generative writing –
drawing circles



b.
generative writing –
writing alphabet



c.
writing alphabet –
drawing circles



d.
generative writing –
generative naming

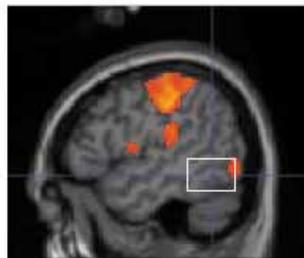


Plate 3. Sagittal sections showing results of region of interest analysis in the left inferior temporo-occipital region for the contrasts: (3a) generative writing of words versus repetitive drawing of circles; (3b) generative writing of words versus writing letters of the alphabet; (3c) writing letters of the alphabet versus repetitive drawing of circles; (3d) written naming versus generative subvocal naming. White rectangle indicates the region of interest for the small volume correction. Display threshold set at $p < .01$ (small volume correction), extent threshold ≥ 20 voxels.