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Letter processing automatically recruits a sensory–motor brain network

Karin H. James^{a,*}, Isabel Gauthier^b

^a Department of Psychological and Brain Sciences, Indiana University, 1101 E. 10th Street, Bloomington, IN 47405, USA

^b Vanderbilt University, Nashville, TN, USA

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Abstract

Behavioral, neuropsychological and neuroimaging research suggest a distributed network that is recruited when we interact with letters. For the first time, we combine several letter processing tasks in a single experiment to study why letters seem to engage such disparate processing areas. Using fMRI, we investigate how the brain responds to letters using tasks that should recruit systems for letter perception, letter writing, letter copying and letter imagery. We describe a network of five cortical regions including the left fusiform gyrus, two left pre-central areas, left cuneus and the left inferior frontal gyrus that are all selectively engaged during a 1-back matching paradigm with letters. Our results suggest involvement of these regions to different extents in different tasks. However, the regions also form an integrated network such that letter perception also engages motor regions while writing recruits letter-specific visual regions as well. We suggest that this distributed network is a direct result of our sensory–motor interactions with letters.

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1. Introduction

Organisms attend to and process sensory information that generate and guide actions within their environment. These actions, in turn, allow more sensory information to be gathered and processed. In this sense, action cannot be disentangled from perception. Theories of object recognition, however, rarely consider how the motor system, through action, may influence how we process and ultimately recognize objects. Theories of embodied cognition (Barsalou, 1999; Johnson, 1987; Wilson, 2002) in contrast, stress that concepts are constructed via our interactions with the world, that is, how we interact with objects affects how we think about them. Thus, the motor information that results from our interaction with objects may be stored and linked to other types of information about objects, including visual appearance (e.g. Chao & Martin, 2000; Schwartz & Holton, 2000; Wexler, Kosslyn, & Berthoz, 1998). In this study, we investigate the neural substrates that support the overlearned perceptual and motor interactions that we have with one specific category, that of letters.

According to embodied cognition models, interactions in sensory–motor systems during experience lead to a distributed representation of an object concept. Perception of an object via a single sensory modality (e.g. vision) can therefore engage this distributed representation (see Allport, 1985, for one version of this theory and Barsalou, Simmons, Barbey, & Wilson, 2003). For example, looking at a ball would activate motor programs associated with kicking and throwing; for a flutist, seeing a flute may recruit motor programs for playing, as well as auditory representations. These ideas are easily applied to objects that have clear functions. Pencils and hammers, for example, are objects that we frequently interact with using our motor and visual systems together—indeed, integration of the two systems is crucial for successful use of such objects. Motor systems in the brain are activated when we simply look at objects that we are accustomed to manipulating (Grezes & Decety, 2002), even without our having to act upon the objects at that time. Motor system activation is more pronounced when we need to make judgments about manipulability of objects rather than about the function of objects (Boronat et al., 2004; Buxbaum & Saffran, 2002; Simmons & Barsalou, 2003). However, some objects have multiple functions, only some of which involving action. It is thus interesting to ask whether motor systems associated with an object class are engaged regardless of the task, or whether this

* Corresponding author. Tel.: +1 812 856 0659.

E-mail address: khjames@indiana.edu (K.H. James).

recruitment is task specific (Bub, Masson, & Bukach, 2003). In the case of letters, for example, are motor programs associated with writing the letter, or saying the letter's name aloud, also activated?

Letters represent an interesting category with which to study questions of interactions among sensory–motor brain systems. Letters are read but rarely manipulated, although they are also written, and perhaps nowadays even more often, typed. Letter shapes do not ‘afford’ (Gibson, 1979) an action the way a push or hammer does. That is, the form of the letter does not, itself, suggest how we should interact with it. There is little work directly addressing whether objects without obvious affordances, but with motor associations, can activate the motor systems during visual perception. Here, we investigate the distributed nature of letter representations by asking whether motor representations are engaged when letters are seen (but not written) and whether visual representations are engaged when letters are written (but not seen). For this purpose, in addition to visual perception and letter copy conditions, we included conditions that dissociate perception and action with letters. In one condition, subjects wrote letters based on the visual presentation of a geometrical shape (“write the first letter of the shape’s name”), compared to a control condition where they drew the shape themselves. In addition, because writing from memory may require mental imagery, another control condition involved imagining the first letter of the name of a shape. Our results suggest that motor systems associated with writing letters recruit cortical areas previously associated only with visual perception of letters. In addition, visual perception of letters was found to recruit motor regions associated with writing. Such results demonstrate that sensory–motor experience with an object class results in an integrated system that can be activated upon the evocation of an object regardless of immediate task requirements.

1. Neural activation during letter perception

Much research has investigated the neural circuitry involved in word reading. A large network of cortical areas is involved in word reading, including a dorsal posterior system (angular gyrus, supramarginal gyrus and superior temporal sulcus) (Black & Behrmann, 1994), left inferior frontal lobe and posterior superior temporal sulcus (Bookheimer, 2002; Gabrieli, Poldrack, & Desmond, 1998); and even right hemisphere structures (Kircher, Rammer, Tous, Williams, & McGuire, 2001), as well as a posterior ventral network including the occipito-temporal region (Crackowiak, Friston, Frith, Dolan, & Mazziotta, 1997; Pugh et al., 2001). Within this last system, the region that has received the most attention as a candidate for early visual processing of printed text is the left fusiform gyrus (Cohen et al., 2000; McCandliss, Cohen, & Dehaene, 2003; Polk et al., 2002).

In contrast to this large body of research on word recognition, relatively little is known about single letter visual recognition. We may initially learn letters in isolated form, although they are seen most frequently in the context of a word. Recent evidence suggests that we retain some neural specialization for the parts (letters) of the stimuli with which we are continually exposed (words). For example, a lateral occipital region adapts

upon repeated presentation of letters, but not with repeated presentation of faces (Gauthier, 2000). Similarly, Gros, Boulanouar, Viillard, Cassol, and Celsis (2001) found neural adaptation effects for the repetition of letter stimuli that were stronger in the left than the right ventral temporal lobe, whereas repetition effects for repeated symbols were bilateral. Three additional fMRI studies compared single letters to objects or symbols. One study found common letter and object activity as well as a trend toward a letter-specific area, both in the left fusiform gyrus (Joseph, Gathers, & Piper, 2003). Another study found activation in the left middle occipital gyrus when participants attended to letters compared to when they attended to symbols or to the color of these stimuli (Flowers et al., 2004). The third study found letter-sensitive regions in the precentral gyrus, left fusiform and medial occipital regions (Longcamp, Anton, Roth, & Velay, 2003). A more recent study in left-handed subjects found no fusiform activation, but more dorsal, right middle temporal gyral activation when comparing letters to pseudoletters (Longcamp, Anton, Roth, & Velay, 2003). Most recently, in addition to a posterior fusiform region selective for letter-strings, we found an anterior fusiform region that responded more to isolated letters presented visually than to Chinese characters or digits, but which did not respond selectively to letter-strings (James, James, Jobard, Wong, & Gauthier, 2005). The more posterior fusiform area that overlapped with the ‘Visual Word Form Area’ (e.g. Cohen et al., 2000) was more selective to letter strings than single letters (James et al., 2005). These findings suggest that specific neural substrates are recruited for visual processing of single letters. However, there is also evidence that left fusiform activation to letters may be somewhat task specific. In one study by Flowers et al. (2004), letter specific activation was only demonstrated if subjects attended to the letters, not to other aspects of the same visual display, implying that letter processing is not completely automatic and is influenced by task requirements (Flowers et al., 2004). Passive viewing of letters has been found to activate ventral temporal regions (Gros et al., 2001; Polk et al., 2002), but perhaps not as reliably as more active tasks (Polk et al., 2002). Working memory tasks with letters (such as the n-back task) engages the left fusiform gyrus (James et al., 2005; Polk et al., 2002). One group found that the left fusiform is not selectively engaged in letter processing when the task involves discrimination of visual stimuli (letters versus symbols or shapes), but is selectively engaged when letter categorization is required (Pernet, Celsis, & Demonet, 2005). These results imply that the left fusiform is involved in explicit, top-down, letter processing (Pernet et al., 2005) given that selective activation is only seen when letter processing is intentional (n-back tasks, passive viewing) (Flowers et al., 2004; James et al., 2005; Polk et al., 2002) and not when letter processing is incidental to the task (Flowers et al., 2004).

1.2. Neural systems involved in writing

The study of patients with pure agraphia (inability to write letters and words as a result of brain damage) has revealed that writing errors can reveal something about the neural systems involved in writing. Some patients with dysgraphia write well,

except for some errors with certain letters. For example, some patients commit letter substitution errors, “TABLE” is written as “FABLE” (Rapp & Caramazza, 1997). The substitute letters usually resemble the target letter in stroke direction and length, and thus have a motoric similarity (e.g. R versus D) (Del Grosso Destrieri, Farina, Alberoni, Nicchelli, & Marianai, 2002; Lambert, Viader, Eustache, & Morin, 1994; Rapp & Caramazza, 1997), as opposed to a visuospatial similarity (e.g. A versus R). This suggests that apart from a level of letter representation based on the visual letter form (outlined in theories by Ellis (1982) and Margolin (1984), and demonstrated empirically by Miozzo and De Bastiani (2002)), there is also a representational level that contains the motor programs necessary to produce the strokes required to write a given letter (Rapp & Caramazza, 1997). In addition, the difficulties are letter (and sometimes digit) specific, that is, shape drawing that involves similar stroke sequences is not affected by this damage. One particularly interesting patient could not write or perceive letters but could write and perceive numerals (Anderson, Damasio, & Damasio, 1990). A similar patient could write the number zero, but not the letter “O” (Delazer, Lochy, Jenner, Domahs, & Benke, 2002). Although the first patient had suffered damage to Exner’s area in the left middle frontal gyrus, the second had damage in the left parietal lobe. These cases suggest a parieto-frontal network involved in storing letter-specific visual and motor programs.

It is interesting that the limited neuroimaging work on writing also points to the parietal and inferior frontal lobes. Menon and Desmond (2001) compared a writing-to-dictation task to a fixation baseline and found activity in the left superior and inferior parietal lobe, as well as in frontal areas including left premotor cortex and supplementary motor areas. When comparing silent naming of objects to finger writing, Katanoda, Yoshikawa, and Sugishita (2001) found significant activation to writing in the superior parietal lobule and in the superior and middle precentral gyrus. A similar result was obtained when finger writing was compared to finger tapping. When comparing writing-to-dictation to copying, frontal areas were only active during the writing-to-dictation condition, whereas copying tasks engaged posterior parietal regions (Matsuo et al., 2000). Therefore, to a certain extent, writing-to-dictation and copying letters may be neurally dissociable.

In sum, a superior parietal—frontal network that subserves writing is apparent but the functional roles of specific areas are still unclear. For example, the superior parietal lobe is activated during a mental writing task (Sugishita, Takayama, Shiono, Yoshikawa, & Takahashi, 1996) suggesting that this region supports imagery for words, but perhaps not the processing of motor information necessary for actual writing. In addition, this region might be involved in many aspects of drawing non-letter shapes (Makuuchi, Kaminaga, & Sugishita, 2003). Parietal regions have also been engaged in grapheme to phoneme conversion (e.g., Pugh et al., 2001), although it is not clear whether or not this process would occur during the visual recognition of single letters. The role of the frontal regions involved in writing has been explained by their proximity to motor association areas, or to language production areas that may be recruited by subvocalization. One area that has received significant attention has

been Exner’s area (inferior frontal just dorsal to Broca’s area) (Exner, 1881; Lesser, Lueders, & Dinner, 1984; Lubrano, Roux, & Demonet, 2004; Matsuo et al., 2003). However, the function of this area in writing is still a topic of debate (Lesser et al., 1984; Lubrano et al., 2004). Exner’s area may be involved in writing per se, or perhaps any fine motor movement of the hand, or it could possibly represent a general motor production region. In fact, some researchers contend that it is not dissociable from Broca’s area (Lesser et al., 1984).

1.3. Sensory–motor interactions and letters

Behavioral evidence supports the idea that motor experience with letters is stored, and may be used during visual letter recognition. Freyd and her colleagues have found that the way we write letters affects the way we perceive them. Writing a letter in the standard manner produces small writing errors (spaces, overshooting lines, etc.) that are easily ignored when we subsequently view the letter. In contrast, writing errors that are caused by having to write a letter using an unusual sequence of movements (in a reversed stroke order, for example) are easily detectable and can adversely affect recognition (Babcock & Freyd, 1988; Freyd, 1983). In addition, Tse and Cavanagh (2000) demonstrated that perception of apparent motion relies on previous experience about motor interactions with written forms. Orliaguet, Kandel, & Bois (1997, Kandel, Orliaguet, & Viviani, 2000) and his colleagues have found that the ability to predict which letter is forthcoming in a sequence of letters depends upon knowledge of motor anticipation rules (spatio-temporal factors that constrain the writing of letter sequences).

There is also some evidence that stored motor information can help visual recognition of letters in alexic patients. Individuals with pure alexia have profound difficulty reading words and many also have difficulty perceiving individual letters (e.g., Arguin & Bub, 1993). However, if a patient is shown a letter and is allowed hand movements, they will sometimes trace out the form of the letter, which then facilitates letter recognition (Bartolomeo, Bachoud-Levi, Chokron, & Degos, 2002). In addition, there is some evidence that training alexic patients to trace and draw letters can be an effective treatment for their letter recognition difficulties (Seki, Yajima, & Sugishita, 1995). Thus, motor information about interactions with letters affects and facilitates visual recognition. These findings also suggest that visual perception may covertly access letter-specific motor programs. However, the neural substrates mediating these sensory–motor interactions are virtually unknown (but see Longcamp et al., 2003, 2005, for one example).

1.4. Neural activation during letter imagery

Imagining letter structure is a process that is presumed to occur prior to writing from memory. Even when writing from dictation, accessing the motor program that is necessary for writing a letter may follow accessing information about a letter’s structure. An image of a letter that is used for writing purposes may simply be a description of the movements that are involved in producing the letter, an ‘abstract motor program’

app & Caramazza, 1997). There is evidence that brain activity during mental imagery of objects overlaps with activity during visual perception of the same objects (D'Esposito et al., 1997; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 2000), the amount of overlap between imagery and perception has been estimated to be approximately two thirds of total activation (Kosslyn, Thompson, & Alpert, 1997). Other groups have found some overlapping neural activation for imagining movements and actually executing them (Decety, 1996; Gerardin et al., 2000; Parsons et al., 1995). Therefore, one would expect that some mental imagery of letters might occur in or near areas that are active during visual perception of letters (e.g., left fusiform gyrus), while imagery for the purpose of writing may occur in near motor areas that are engaged during writing.

Behavioral, neuropsychological and neuroimaging research suggest a distributed network that is activated when we interact with letters. This distributed network of activity may be a reflection of our varied experience with letters. The purpose of this study is to further investigate the function of the many cortical regions involved in the different ways we interact with letters: in particular, we were interested in motor areas that may be automatically recruited during letter perception and in the visual areas that may be automatically recruited when writing letters. For this purpose, we included in a single study conditions that could recruit systems for letter perception, letter writing, letter copying and letter imagery.

Materials and methods

1. Participants

Participants were graduate students or research assistants in the Psychology Department at Vanderbilt University. All gave informed consent according to the guidelines of the institutional review board of the Vanderbilt University Medical Center and were paid for their participation. All participants reported normal or corrected to normal visual acuity and no history of neurological disorders, and were right handed. There were five females and three males, with ages ranging from 20 to 42 years with a median age of 25 years.

2.2. Stimuli and procedure

All testing was conducted using Macintosh computers and RSVP software (<http://www.cog.brown.edu/~tarr/RSVP>). The stimuli were presented on two small LCD screens mounted within a Visuastim XGA goggle system (MRI Devices Inc. (<http://www.mrvideo.com>)) that was worn by the participant inside the scanner. The virtual sizes of the screens were 76.2 cm × 57.2 cm and were viewed from a virtual distance of 120 cm. All stimuli subtended approximately (2.3–3.0) × (2.3–3.0) degrees of visual angle, except the words, that were 2.3 × (4.0–4.4) degrees of visual angle. In addition, stimuli were presented with their location varying from trial to trial by about one half of a degree of visual angle around the center of the screen ("jitter"). The jitter was small enough that the central stimulus did not extend outside of central vision.

Stimuli varied depending on run type (Fig. 1) and are discussed further below. The right hand of each subject was placed in a wrist strap that was attached to a stylus pad. This apparatus ensured that the arm and wrist were connected securely to the plastic pad at all times. They held a plastic pen (without ink) and kept it on the stylus pad during testing. The pad was secured to their torso wherever felt most comfortable. The subjects were instructed and trained to only move their hand while writing and were informed of the importance of keeping their upper arm and shoulder still. The upper arm and shoulder were heavily padded to keep them from moving during the scans. The subjects were allowed to practice writing until they felt comfortable with the apparatus. They also held a four-button response pad in their left hand for use in the localizer runs. Prior to entering the magnet, subjects were given instructions for the entire experiment, and were trained on interpreting the instruction screens that appeared before each experimental block (Fig. 2).

2.3. Perception runs

The first two runs used black and white images of common objects, faces and letters. We included 26 different examples of each stimulus type. The objects were chosen from the Tarr object database (<http://www.cog.brown.edu/~tarr/projects/databank.html>) for simplicity and ease of naming. The faces were "Mooney"-type faces used in previous work (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999) and the letters were uppercase and presented in three different font types that were randomized: "Times", "Comic" and "Arial" (see Fig. 1a). Although we tried to reduce differences between these stimuli in spatial frequency spectra (faces were "silhouettes, objects were black and white and simplified), there remain differences in low-level properties. Nonetheless, faces are an interesting contrast with letters because they form another object category with which we are very familiar and efficient, while objects are

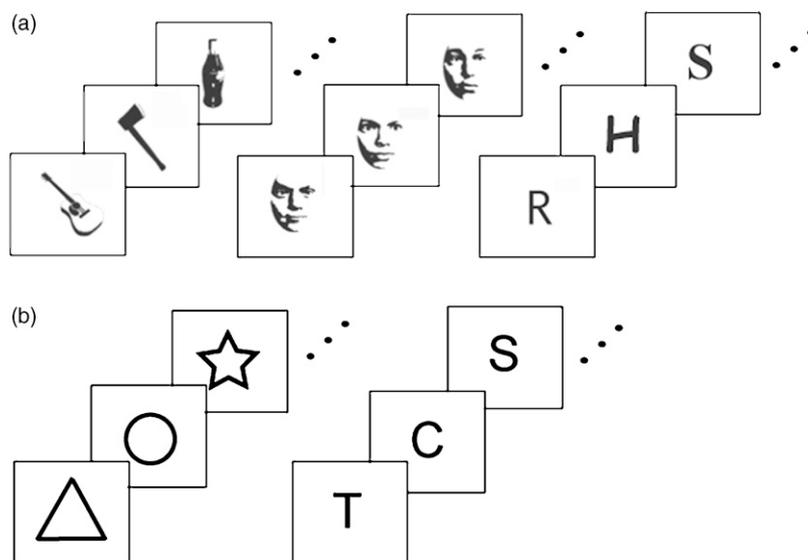


Fig. 1. The stimuli used in (a) the letter perception runs and (b) the draw/imagine runs. See text for details.

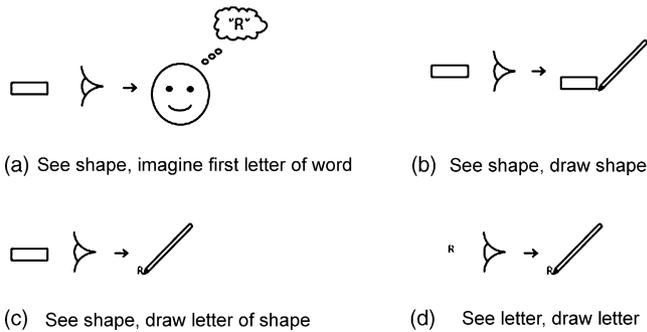


Fig. 2. The visual instructions used in the draw/imagine runs: (a) instructions for the letter imagery task, (b) instructions for the copy shape task, (c) instructions for the writing from memory task, and (d) instructions for the copy letter task. Subjects had practice interpreting the instruction screens prior to entering the scanning environment.

interesting because they can be easily named, like letters. The comparison of letters and shapes in the draw/imagine runs can provide additional evidence as to visual selectivity that does not depend on low level differences. Together, these contrasts can provide evidence for selectivity for letters that cannot be easily explained by naming, familiarity or low-level features.

We administered two block-designed runs of these stimuli. Each run contained nine blocks (three of each condition). Each block contained 16 stimuli and each stimulus was presented for 825 ms followed by a 175 ms blank screen. Each block was followed by a 10 s fixation cross. In addition, each run began and ended with a 20-s fixation cross. Subjects were required to perform a one-back matching task for the stimuli within each block, responding by pressing a button with their left index finger only when two stimuli presented consecutively were identical.

2.4. Draw/imagine runs

The stimuli in the subsequent six-write/draw runs consisted of shapes and letters. Sixteen shapes were used: square, circle, rectangle, pear, star, trapezoid, heart, oval, apple, arrow, cross, moon, octagon, diamond, hexagon, and half circle. Sixteen letters were presented in capital form in Arial font. Ten of the letters (A, C, D, H, M, O, P, R, S, T) were the first letter of the names of the 16 shapes, and the remaining six letters were B, E, G, J, K, and N (see Fig. 1b).

These five runs also used a block design. Each run had 18 18 s blocks. There were six stimuli per block that were presented for 3 s each. Preceding each block, an instruction screen was displayed for 2 s followed by a 2-s pause. Instruction screens were pictorial representations of the task requirements that subjects practiced interpreting prior to the experiment (e.g., a picture of a pen and a shape for the “draw shape” runs; see Fig. 2). Following each block a 10 s fixation cross was presented. There was also a 20-s baseline cross before the beginning of each run and a 16-s cross at the end of each run.

Subjects were required to make a drawing response or to imagine the letter. In three conditions they were presented with a simple shape and asked to copy the shape (draw shape given shape), write the first letter of the name of the shape (write letter given shape), or imagine the first letter of the name of the shape (imagine letter given shape). In another condition they were given a letter and were required to copy the letter (write letter given letter). We therefore had conditions that allowed us to compare different responses to the same stimuli.

2.5. Imaging parameters and analysis

Imaging was performed using a 3-T, whole body GE MRI system and a birdcage head coil located at the Vanderbilt Medical Center (Nashville, USA). The field of view was 24 cm × 24 cm × 14.0 cm, with an in-plane resolution of 64 × 64 pixels and 20 contiguous oblique coronal scan planes per volume (whole brain), resulting in a voxel size of 3.75 mm × 3.75 mm × 7.0 mm. Images were collected using a T2*-weighted EPI acquisition (TE = 25 ms, TR = 2000 ms,

flip angle = 70°) for blood oxygen-level dependent (BOLD) based imaging (Ogawa et al., 1993). High-resolution T1-weighted anatomical volumes were also acquired using a 3D fast spoiled grass (FSPGR) acquisition (TI = 400 ms, TE = 4.18 ms, TR = 10 ms, FA = 20°). The functional data underwent slice time correction, 3D motion correction, linear trend removal, and Gaussian spatial blurring (FWHM 4 mm) using the 2D analysis tools in Brain Voyager™. Individual functional volumes were co-registered to anatomical volumes with an intensity-matching, rigid-body transformation algorithm. Individual anatomical volumes were normalized to the stereotaxic space of Talairach and Tournoux (1988) using an eight-parameter affine transformation, with parameters selected by visual inspection of anatomical landmarks. Applying the same affine transformation to the co-registered functional volumes placed the functional data in a common brain space, allowing comparisons across subjects. Voxel size of the normalized functional volumes was standardized at 1 mm × 1 mm × 1 mm using trilinear interpolation.

The functional data were analyzed using the Brain Voyager™ multi-study GLM (general linear model) procedure and in-house programs written in Matlab™ (<http://www.themathworks.com>). A GLM analysis allows for the correlation of predictor variables or functions with the recorded activation data (criterion variables) across scanning sessions. The predictor functions are based on the blocked stimulus presentation paradigm of the particular run being analyzed and represent an estimate of the predicted hemodynamic response during that run. To properly model the hemodynamic response, the predictors are represented as the stimulus protocol boxcar functions convolved with the appropriate gamma function ($\Delta = 2.5$, $\tau = 1.25$) estimate of a typical hemodynamic response (Boynton, Engel, Glover, & Heeger, 1996). Regions-of-interest were determined based on group statistical parametric maps (SPMs) that were considered above threshold if they met the following criteria in our random effects analysis: (1) significant at $p < .001$, uncorrected, with a cluster threshold of 10 contiguous 3 mm isometric voxels. (2) Peak activity within a cluster at least $p < .0001$, uncorrected. Note that the maps presented in the figures are thresholded at $p < .001$. For individual analyses, activation was considered significant if it was $q < .05$, corrected, using the false discovery rate (FDR) method, which controls for the expected proportion of false positive voxels among those that are suprathreshold (Genovese, Lazar, & Nichols, 2002). A cluster threshold of 10 contiguous isometric 3 mm voxels was also applied. All individual peak Talairach co-ordinates, ranges, t -values, and q statistics are reported in Table 1.

3. Results and discussion

Our analyses proceeded in three steps: first, using group analyses, we identified brain areas involved in perception, drawing, writing and visual imagery of letters based on *a priori* contrasts. Second, based on these areas identified at the group level, we localized regions-of-interest (ROIs) within each individual subject (when possible) based on the same contrasts (see Table 1 for peak Talairach co-ordinates). Finally, to investigate the overlap of representations across different tasks, we compared the activity within each of these ROIs for all other conditions that were not used to define the region. An additional ROI was considered, corresponding to the motor area (left premotor cortex, BA6) engaged during the passive viewing of letters and during writing in Longcamp et al. (2003). This premotor activity ranged from TC $X(-51)$ to (53) ; $Y(-2)$ to (-6) ; $Z(41-43)$. We used Talairach coordinates $-53, -6, 41$ for the center of our ROI because this focus falls within that range and anatomically looks like the peak resulting from their contrast of letters minus pseudoletters. We defined a region spanning ± 5 Talairach coordinates and centered on this focus in each individual. We compared the conditions with each ROI using a repeated measures ANOVA on the conditions after averaging %BOLD signal change across active voxels.

Table 1

Talairach coordinates and range of activations for each individual subject in each ROI

Subject	X	Y	Z	Range X	Range Y	Range Z	t-Value	q-Value
Fusiform letter area (ROI 1)								
S1	-33	-35	-10	-26:-45	-32:-37	-3:-10	5.96	<.00001
S2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S3	-39	-51	-3	-35:-47	-46:-59	1:-4	2.98	<.001
S4	-30	-43	-3	-20:-41	-39:-48	2:-8	2.00	<.03
S5	-36	-47	-6	-29:-39	-32:-55	0:-10	4.64	<.0001
S6	-36	-54	-4	-25:-44	-44:-57	0:-10	5.97	<.00001
S7	-32	-52	-7	-24:-42	-48:-58	0:-11	3.97	<.0001
S8	-33	-44	-12	-32:-36	-40:-45	-6:-13	2.80	<.001
Inferior frontal gyrus (ROI 2)								
S1	-40	15	20	-39:-42	14:17	19:22	2.97	<.001
S2	-43	12	22	-41:-44	10:13	21:23	2.15	<.05
S3	-42	15	25	-39:-43	11:16	24:27	2.98	<.001
S4	-40	13	23	-38:-42	12:14	22:24	2.99	<.001
S5	-43	15	23	-42:-44	13:16	22:25	4.64	<.0001
S6	-38	13	20	-37:-39	12:15	19:22	3.10	<.001
S7	-39	12	20	-38:-40	11:13	18:21	2.21	<.01
S8	-46	15	25	-42:-47	12:17	22:28	5.67	<.0001
Dorsal precentral (ROI 3)								
S1	-35	-20	51	-33:-36	-19:-23	50:54	3.11	<.001
S2	-32	-25	53	-30:-33	-22:-27	51:56	4.98	<.0001
S3	-33	-21	55	-30:-34	-19:-23	54:56	5.97	<.0001
S4	-31	-23	53	-28:-30	-20:-24	52:55	1.96	<.05
S5	-36	-20	48	-34:-37	-19:-23	47:49	3.21	<.001
S6	-34	-19	52	-31:-36	-18:-21	50:53	2.22	<.01
S7	-30	-23	53	-28:-32	-22:-24	51:54	3.21	<.001
S8	-38	-21	54	-36:-41	-19:-22	53:57	5.78	<.0001
Ventral precentral gyrus (Longcamp) (ROI 4)								
Not applicable, we used the same ROI in each subject, taken from the Longcamp et al. (2003) study (see text)								
Cuneus (ROI 5)								
S1	-14	-80	23	-12:-15	-78:-81	22:24	3.67	<.001
S2	-16	-79	28	-14:-18	-78:-80	27:30	4.97	<.0001
S3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S4	-17	-82	25	-16:-19	-80:-83	24:27	1.69	<.05
S5	-14	-75	27	-13:-15	-73:-76	26:28	3.45	<.001
S6	-16	-79	30	-14:-17	-78:-81	28:32	3.63	<.001
S7	-15	-75	26	-13:-16	-74:-76	25:27	1.89	<.05
S8	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

1. ROI 1, letter perception (left fusiform gyrus)

Using conditions in the perception runs, we identified an area selective for visual perception of letters relative to perception of objects and faces in the left anterior fusiform gyrus (see Fig. 3a); Talairach coordinates (TC) [x, y, z] -37, -49, -5; peak $t = 5.40$, $p < .0001$. The location of this area is consistent with those in prior studies (Flowers et al., 2004; James et al., 2005; Joseph et al., 2003; Longcamp et al., 2003).

An individual focus of activity corresponding to this area was identifiable in seven out of eight subjects. Within this individually defined area, we compared activity in the other four conditions from the draw/imagine runs (draw letter given letter, draw letter given shape, draw shape given shape and imagine letter given shape). An ANOVA revealed a significant effect of condition ($F_{5,30} = 3.52$, $p < .01$), warranting post hoc tests. The two conditions that led to the most activity in this region (and statistically comparable, $t_6 = 1.76$, n.s.) involved letter percep-

tion (draw letter given letter) and letter imagery (imagine letter given shape). Interestingly, there was more activity in this region when subjects wrote letters than when they drew shapes, given identical shape stimuli ($t_6 = 3.75$, $p < .01$). Similarly, there was more activity when subjects imagined a letter than when they drew a shape, given the same shape input ($t_6 = 3.1$, $p < .01$).

The activity in this area cannot be explained by task difficulty (such as the difficulty of transforming a visual input into a different output: e.g., shape to letter): we found greater activation when subjects copied a letter (given a letter) than when they copied a shape (given a shape) ($t_6 = 4.20$, $p < .01$), although neither condition required a transformation. Rather, this fusiform region appears to be specialized for processing letters, regardless of the task (visual matching, copying, writing, or imagining). Given its location in the occipito-temporal visual pathway known to be important for the visual recognition of objects, it is reasonable to assume this region is involved in the visual processing of letters, be it bottom-up or top-down (via imagery).

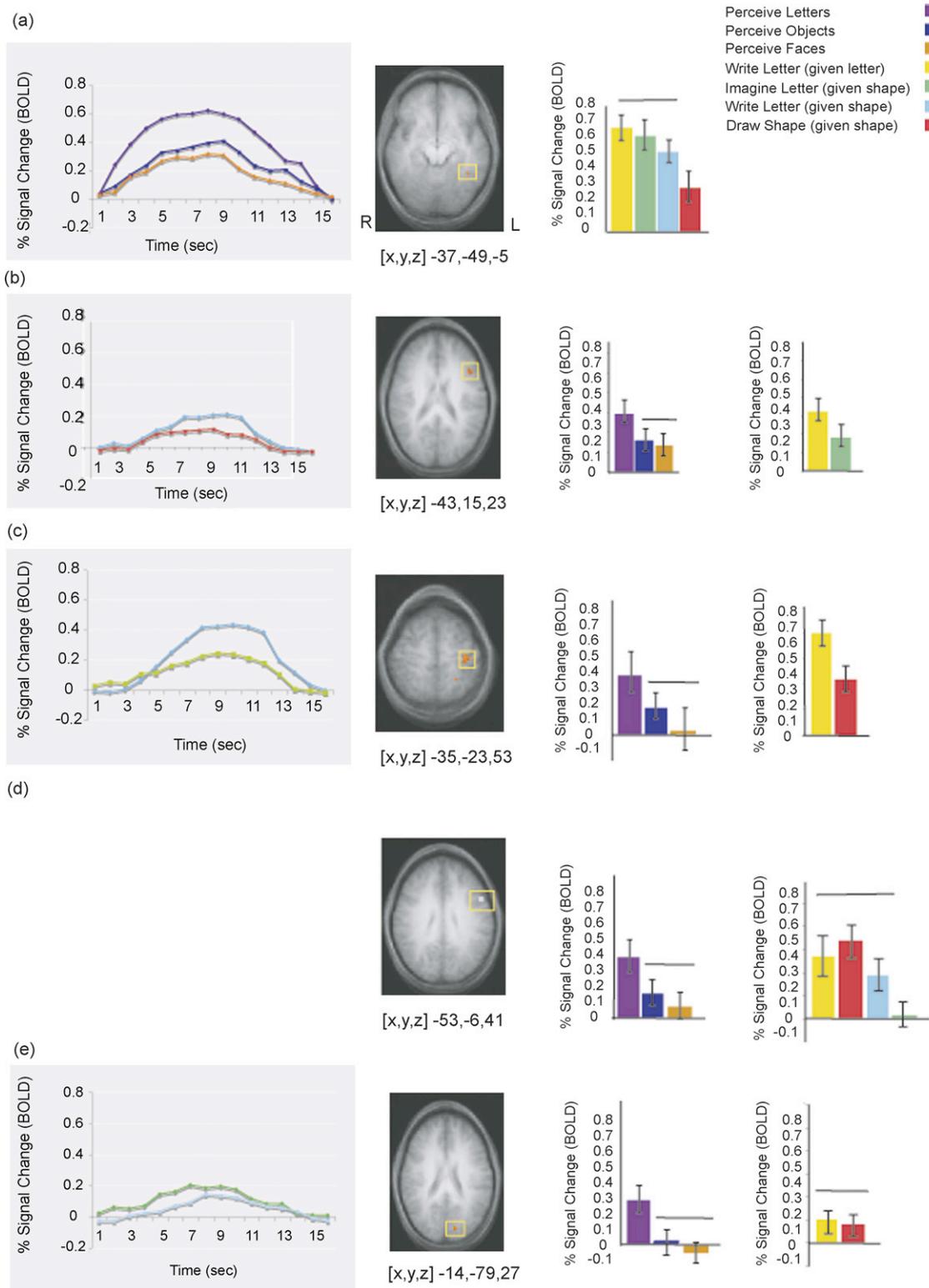


Fig. 3. Left: average time course activations ($n=8$) in four or our five ROIs, reflecting neural activation associated with each condition that was used to localize the ROIs (d was not localized in this fashion). Center: group SPMs for our five regions-of-interest (ROIs). Right: percent BOLD signal change (relative to a fixation baseline) in each ROI for the conditions that were not used to localize the ROI. Black horizontal lines indicate conditions that were not significantly different ($\alpha=.05$). All maps (except (d)) are random effects thresholded at $p<.001$, uncorrected. (a) Area of activation that is significantly greater for the letter perception condition compared to the object perception and face perception conditions (left fusiform gyrus). (b) Activation that is greater for drawing letters from memory than drawing shapes (left inferior frontal gyrus). (c) Areas that respond more to drawing letters from memory than imagining letters (left dorsal precentral gyrus). (d) A depiction of the ROI taken from the Longcamp et al. (2003) study that represents part of the motor region that responded when letters were perceived (left ventral precentral gyrus). (e) Activation map that resulted when writing letters was subtracted from imagining letters (left cuneus).

2. ROI 2, letter writing from memory (left inferior frontal gyrus)

To investigate brain regions important for writing letters, we compared the condition where subjects were writing a letter (given a shape) to a baseline of drawing a shape (given a shape). This contrast resulted in two foci of activity, one in the left inferior frontal gyrus (left IFG—TC [x, y, z] -43, 15, 23; peak $t = 4.92$, $p < .0001$) (see Fig. 3b) and the second in the left precuneus (TC [x, y, z] -20, -71, 19; peak $t = 4.942$, $p < .001$). We selected the inferior frontal gyrus as an ROI, because this area is associated with motor programming and eight/eight subjects showed overlapping activation in this area with the group map contrast, only four subjects had individual precuneus ROIs.

Activation in the left IFG ROI differed significantly during the perception conditions ($F_{2,14} = 4.3$, $p < .03$). In particular, letters led to more activity than both objects and faces ($t_7 = 2.6$, $p < .05$ for objects and $t_7 = 3.8$, $p < .01$ for faces). When the remaining conditions were analyzed, we found that the imagine letter condition resulted in greater activation than the draw letter (given letter) condition ($t_7 = 2.6$, $p < .05$). Thus, this area appears to be important for retrieving letter shape from memory: it responds more to writing letters than to drawing shapes, and also more to imagining letters (presumably an intermediate step in drawing letters) than to copying them.

Although activation is especially high in conditions that require transforming the visual input (from shape to letter), we think it is unlikely that the left IFG merely responds to the greater difficulty involved in these tasks, because of the results from our perception runs. Letter perception engaged this area more than shape or face perception, although letter perception is not a more difficult task (see James et al., 2005). This area overlaps with precentral regions associated with language production in the forms of speech (Broca's area) and writing (Exner's area) (Lubrano et al., 2004). Pure agraphia has been shown in patients with lesions of Exner's area (Anderson et al., 1990) and neuroimaging has confirmed that this area is crucial for writing in Japanese (Matsuo et al., 2003; Tokunaga et al., 1999) and in English when compared with naming (Katanoda et al., 2001). Exner's area is also dissociable from the more dorsal frontal eye fields (Matsuo et al., 2003), also involved in reading and presumably, copying. The present results expand on our knowledge of the function of the left IFG in letter processing, suggesting that it is involved in the letter-specific transformations necessary for writing but not for copying letters. The specificity for letters compared to even familiar shapes distinguishes the left IFG from posterior parietal regions often documented as involved in writing (Matsuo et al., 2000; Menon & Desmond, 2001; Otsuko, Soma, Arai, Otsuka, Tsuji, 1999) but not specific to writing letters (Makuuchi et al., 2003).

The letter-specific response in the left IFG during the perception runs suggests that matching letters automatically engages some of these motor transformations: interestingly, seeing a letter might automatically engage writing programs, which may be relatively inhibited during a copying task. This could be because the motor program for a letter may not match the specific shape of the letter to copy.

3.3. ROI 3, letter writing (left precentral gyrus)

Another way of investigating brain regions involved when writing letters is to contrast writing with imagining letters. The contrast of write letter (given shape) minus imagine letter (given shape) resulted in three foci of activation: one in the left superior temporal gyrus (STG)(TC: [x, y, z] -37, -49, 17, $t_7 = 8.42$, $p < .00001$), a second in the left dorsal precentral gyrus (TC: [x, y, z] -35, -23, 53, $t_7 = 8.83$, $p < .00001$) and a third in the left postcentral gyrus (TC: [x, y, z] -38, -27, 49, $t_7 = 11.3$, $p < .00001$). We focused here on the large precentral activation as our ROI because all subjects showed activation in this area (see Fig. 3c). Although the STG area was also of interest (because of possible phonetic processing), we found no significant differences in any of our other conditions in this region ($F_{2,12} = 1.3$, n.s. and $F_{5,30} = 1.7$, n.s.). The postcentral gyrus activation was assumed to be due to somatosensory feedback during the write/draw conditions and therefore did not warrant further investigation for the purposes of the present work.

Within the precentral ROI, a significant difference among the stimuli in the perception runs was obtained ($F_{2,14} = 6.96$, $p < .005$). Letters evoked greater activity than did objects ($t_7 = 3.14$, $p < .01$) or faces ($t_7 = 3.79$, $p < .01$). In addition, there were also significant differences among the conditions from the draw/imagine runs ($F_{3,21} = 15.96$, $p < .0001$). Copying letters resulted in a greater response than did copying shapes ($t_7 = 2.52$, $p < .05$). This, coupled with the significant subtraction of the draw letters condition minus the imagine letters condition suggests that this is a letter-specific motor area. Dorsal precentral gyrus has been thought to be a homologue of the dorsal premotor area (PMd) of the macaque brain (Grezes & Decety, 2001), and lies roughly at the hand area of motor cortex (Grafton, Fagg, Woods, & Arbib, 1996). This area has also been shown to be active during language processing, suggesting a close link between reading and gesturing or writing during language processing (Meister et al., 2003). Interestingly, it responded here regardless of whether letters were perceived, written from memory or copied. One possibility is that it is involved in generating visual-to-motor transformations: In the case of copying, from visual images to motor output, or in the case of transforming stored visual images to writing in the case of writing from memory.

3.4. ROI 4, motor response (left premotor cortex)

When we investigated the activation from the present study in the ROI selected from Longcamp et al. (2003), a significant difference was observed between conditions in the perception runs ($F_{2,14} = 4.9$, $p < .02$), and post hoc *t*-test revealed greater activation to viewing letters than objects ($t_7 = 2.83$, $p < .05$) and faces ($t_7 = 2.79$, $p < .05$). This result provides complementary evidence for Longcamp et al. (2003) assertion that the motor cortex is activated during letter viewing—indeed, it generalizes the result from passive viewing to a 1-back identity matching task (see Fig. 3d).

Interestingly, following up on the main effect of condition in the draw/imagine runs ($F_{5,30} = 4.9$, $p < .002$), we found that this

premotor region was more active when subjects drew shapes than when they wrote letters (given a shape) ($t_7 = 3.76, p < .01$). Activity was also high for draw letters (given letter), which, together with the previous result, suggest that this area is particularly recruited when copying a visual input is required. In addition, the greater activation when subjects draw a letter (given a shape) compared to imagining a letter (given a shape) ($t_7 = 2.78, p < .05$) suggests that this region is more generally involved in motor tasks. Because this region falls within pre-motor areas of the cortex, this is not surprising. It is important to note that Longcamp et al. (2005) were able to rule out the possibility that this activity is due to subvocalization by showing that it switches from the left to the right hemisphere in left handed subjects.

The selectivity in the perception run is consistent with the idea that letters, but not faces or objects, trigger covert motor activity due to our experience writing letters (Longcamp et al., 2003). Our results suggest that this premotor region is not letter-specific and is probably recruited whenever we write, copy or draw. This is somewhat inconsistent with Longcamp et al. (2003) finding that this precentral region was activated upon writing letters but not when subjects drew pseudoletters (no writing condition was included in Longcamp et al. (2005)). One interesting possibility is that the familiarity of the shape to be drawn modulates the activity in this region: largest for letters, followed by the familiar shapes we used and finally least for the novel pseudoletters used by Longcamp and colleagues.

3.5. ROI 5, letter imagery (left cuneus)

Another contrast was intended to reveal areas recruited by visual imagery of letters: imagine letters (given shape) minus write letter (given shape). Although both of these conditions may be conceived as requiring some form of imagery, only the imagine letters (given shape) condition requires visual imagery. It is interesting to ask whether visual areas are recruited by visual imagery for letters beyond the left fusiform area identified as ROI 1. Indeed, this contrast resulted in activation in the left cuneus (TC: $[x, y, z] = -14, -79, 27; t_7 = 5.24, p < .0001$) (see Fig. 3e) and was found in six/eight subjects.

During the perception runs, the left cuneus responded more to perceiving letters than objects ($t = 2.85, p < .05$) and faces ($t = 2.90, p < .05$), but no difference between objects and faces ($t = 1.05, n.s.$). This, and the activity for the imagine condition in ROI 1, is consistent with the common finding of overlap between regions involved in visual perception and visual imagery (Ganis et al., 2004; O'Craven & Kanwisher, 2000). This area may be related to that involved in the parietal damage leading to agraphia (Menon & Desmond, 2001; Miozzo & De Bastiani, 2002). Although the results from the perception runs is suggestive, however, we did not have a condition requiring imagery for shapes and it is therefore difficult to determine the letter-selectivity of this region. One likely possibility is that while the left fusiform area holds letter representations or performs letter-specific computations, this area of the left cuneus and precuneus is more generally involved in visual imagery (e.g. Ganis et al., 2004). The selectivity for letters over faces and objects in the perception run could be caused by stimulus differences

(still present, despite the fact that these stimuli were matched for size). Supporting this inference, the selectivity for letters over the more similar shapes used in the draw/imagine conditions did not reach significance ($t = 1.05, n.s.$).

4. General discussion

We have found a network of five cortical regions in the left hemisphere (fusiform gyrus, dorsal and ventral precentral gyrus, inferior frontal gyrus and cuneus) that are all selectively engaged during a 1-back matching task with letters. However, our results suggest various degrees of specialization for letters in this network, and varied involvement in various tasks that are frequently performed with them.

A left fusiform region (ROI 1) responds to perceiving, writing and imagining letters. It appears to be the most letter-selective area in this network, responding more to the processing of letters than to that of faces, objects as well as simple shapes, consistent with prior work (James et al., 2005; Longcamp et al., 2003) and its location near other category-selective areas such as the FFA and the PPA (Downing, Chan, Peelen, Dodds, & Kanwisher, 2005; Gauthier et al., 1999; Kanwisher, McDermott, & Chun, 1997). Although this area is near the visual word form area described by Cohen and colleagues (Cohen & Dehaene, 2004; McCandliss et al., 2003), at least one study dissociates selectivity for single letters from that for words and pseudowords, both within the left fusiform gyrus (James et al., 2005). This selectivity for letters in skilled readers generalizes to expertise with other writing systems such as Chinese (Wong et al., in preparation). Similar to other category-selective areas (Ganis et al., 2004; Kosslyn et al., 1997; O'Craven & Kanwisher, 2000), this region responds not only during bottom-up perception of letters but also during top-down letter processing, either during a visual imagery task as well as for writing from memory (potentially because of covert visual imagery). This activation could be due to visual representations of letters being accessed, explaining its engagement during all tasks involving letters.

Exner's area is the premotor region thought to contain motor programs necessary for writing letters (Exner, 1881). One of our ROIs falls roughly within this region (ROI 2) and was involved whenever letter shapes were retrieved from memory. It is unclear whether the need to retrieve other familiar shapes from memory would also recruit this region, but its letter-selective activation in the perception runs suggests some degree of specificity to letters. This finding supports previous work suggesting that this region is crucial for writing (e.g. Anderson et al., 1990), but further specifies the potential role of this region: it seems to be important when writing from memory, perhaps in accessing a visual representation of letters for the purpose of writing.

We also investigated a left dorsal precentral region (ROI 3), one that was localized by subtracting letter imagery from letter drawing (both when a shape was seen). This area was engaged during all letter writing and perception tasks and less so during shape drawing, suggesting a specialization for letter writing as well as the automatic engagement of motor programs during letter perception. The pattern of activity in this area is similar to that of the more ventral ROI 4, corresponding to Longcamp

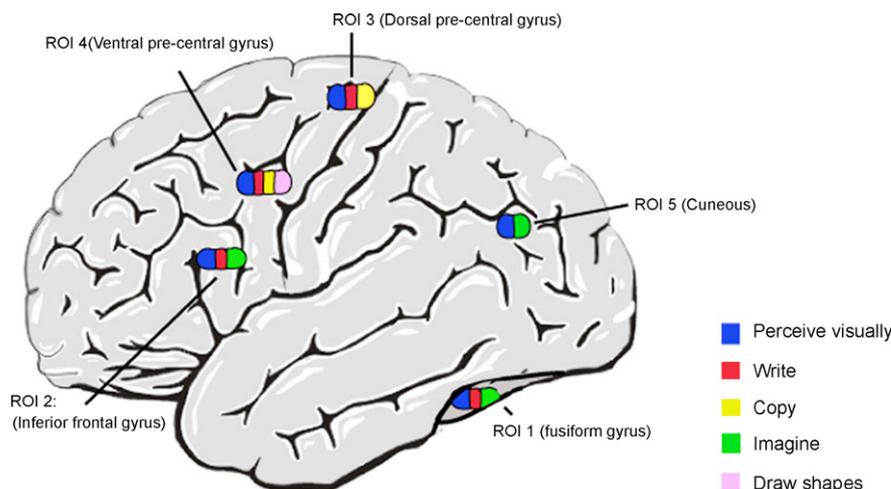


Fig. 4. A schematic of the results from the present study demonstrating a multimodal network of activation for letter processing.

al.'s letters versus pseudoletters contrast. Both regions do not seem to respond to letter imagery and both are letter-selective during the perception task, although the more ventral region responds as much to copying shapes as to copying letters while the dorsal region was more selective for letter writing. Therefore, the dorsal region may be more specific to writing letters, whereas the ventral region may constitute a more general motor output, being engaged during both shape drawing and letter writing. Interestingly, the more ventral precentral region (ROI 4) is near the area that has been identified as the frontal eye fields (Matsuo et al., 2003), a region involved in programming eye movements that are likely to occur during both reading and writing tasks as well as during drawing and perceiving shapes.

Finally, a region of the left cuneus (ROI 5) that was recruited during visual imagery of letters was also engaged during the perception of letters and shapes, more than the perception of faces and objects, a result that could be driven by low-level image differences, or by the fact that letters and shapes more easily evoke drawing than the faces and objects.

An interesting question concerns the role of parietal regions in letter processing. Although others have demonstrated a parietal-occipital network involved with writing (Katanaoda et al., 2001; Matsuo et al., 2000; Menon & Desmond, 2001; Iwata, 1984), and agraphia has been associated with parietal damage (Roeltgen, 1993), we find various areas in the frontal lobe that are activated during writing, but no parietal region. The absence of parietal activation in this study seems curious on the surface, but not less so when we consider possible roles for the parietal lobe in prior writing studies. Although the posterior parietal lobe (and more specifically the angular gyrus) has often been suggested to be involved in writing (e.g. Menon & Desmond, 2001), it has also been shown to be active during shape drawing (Makuuchi et al., 2003), and mental writing (without any motor component) (Sugishita et al., 1996). One possible explanation for these findings is that this region of the parietal lobe is involved with imagery for motor output in general (also hypothesized in Roeltgen, 1993). Thus, its recruitment for drawing shapes (Makuuchi et al., 2003) can account for the absence of parietal activation during our letter minus shape subtractions.

Our method does not reveal the connectivity or the timecourse of activity in these different regions, but we can speculate (see Fig. 4). When we see a letter, an 'image' of the letter may be constructed in the letter-selective parts of the left fusiform gyrus and in related areas that may not be letter-selective, such as the left cuneus. Following this initial bottom-up representation, the frontal cortex may be next engaged for further processing, for instance the precentral cortex areas important for handwriting. During visual imagery, activity may flow in the opposite direction from frontal areas, including Exner's area storing letter-specific motor programs, to the fusiform and cuneus. Likewise, to draw a letter from memory, letter-specific motor programs in Exner's area would be engaged before this activity is transferred to ventral precentral regions for the final motor programming. Whether the left fusiform is engaged early in combination with Exner's area to generate the image of the letter, or is engaged later as the result of the planned handwriting, is unknown. When subjects copy, activity in Exner's area may be inhibited and information may flow directly from the fusiform to dorsal precentral regions, then again to ventral precentral for motor programming.

Considering the distributed nature of the network supporting letter perception and writing, the reasons why agraphia and alexia result from brain damage of such disparate regions of the brain is perhaps now more clear. The putative visual processing areas are also involved with letter writing, and the so-called motor regions are also engaged during visual perception. Therefore, there may be some functional redundancy in the system. This explanation can account for the finding that damage to a fusiform region may not only result in alexia, but also in some forms of agraphia—the engagement of the fusiform during writing suggests that in some cases, damage may lead to agraphia (e.g. as described in Roeltgen, 1993; Rapp & Caramazza, 1997). Similarly, motor production may be able to help when visual areas are damaged, as is the case with some alexic patients, because motor programs may access visual images that may be spared (Bartolomeo et al., 2002). These images may in turn be enough for recognition to occur, in a sense bypassing input and accessing a representation through the motor system (see Fig. 4 for a schematic of functional areas).

Clearly, our sensory–motor experience with letters, in the course of learning to read and learning to write, has led to the development of a complex neural network which appears to be tightly integrated. Although these different areas, in various combinations, can support the different actions we can perform with letters, the extent to which the system often functions as a whole is perhaps most interesting. Here, we find that letter perception automatically activates motor regions, and writing (even without *seeing* a letter) automatically activates letter-specific ‘perceptual’ regions. The influence that past experience in one modality has on subsequent performance in another modality has been shown behaviorally (e.g. Freyd, 1983; Orliaguet et al., 1997; Tse & Cavanagh, 2000). Such integration within sensory–motor systems likely results from our extensive and multi-modal (seeing, writing, hearing) interactions with letters, which to a larger extent do not occur in the case of other shapes. This is not to say that the entire system is letter-specific: one also sees similar perceptual motor interactions at the neural level when we process stimuli such as tools (Grezes & Decety, 2002). Arguably, any stimulus that is learned with sensory and motor associations may recruit this (or a similar) integrated neural system. An excellent example of this is the finding of motor activation in the brain when hearing action sentences or viewing verbs (Tettamanti et al., 2002). Similarly, James and Gauthier (2003) found that teaching associations between novel objects and auditory features (e.g., buzzes) or action features (e.g., “hops”) was sufficient to later produce automatic activation in brain areas supporting the perception of sound or biological motion during a simple visual task with these objects.

Letters are a fascinating example of a category for which perceptual expertise can lead to specialized visual areas (Flowers et al., 2004; James et al., 2005; Joseph et al., 2003; Longcamp et al., 2003) as well as to the recruitment of an extensive network of regions supporting overlearned sensory–motor interactions. The cognitive neuroscience of reading has mainly focused on the mechanisms and neural substrates important to process words, or letter sequences. Recent work on the visual perception of single letters suggested the value of also studying specialization for the smallest units of visual word processing (Flowers et al., 2004; Gauthier, Wong, Hayward, & Cheung, 2006; James et al., 2005; James & Gauthier, 2003; Longcamp et al., 2003; Wong, Gauthier, Woroch, DeBuse, & Curran, 2005; Wong & Gauthier, 2006). Not only can using single letters help simplify experimental designs that target early visual processing, but there is also evidence that neural specialization for letters and non-word strings can be dissociated (James et al., 2005). The current work demonstrates that we can base the study of the neural components of writing in the processing of single letters. Future research will need to specify how this distributed multimodal network for the processing of single letters operates within the broader networks involved in writing meaningful sequences of letters.

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