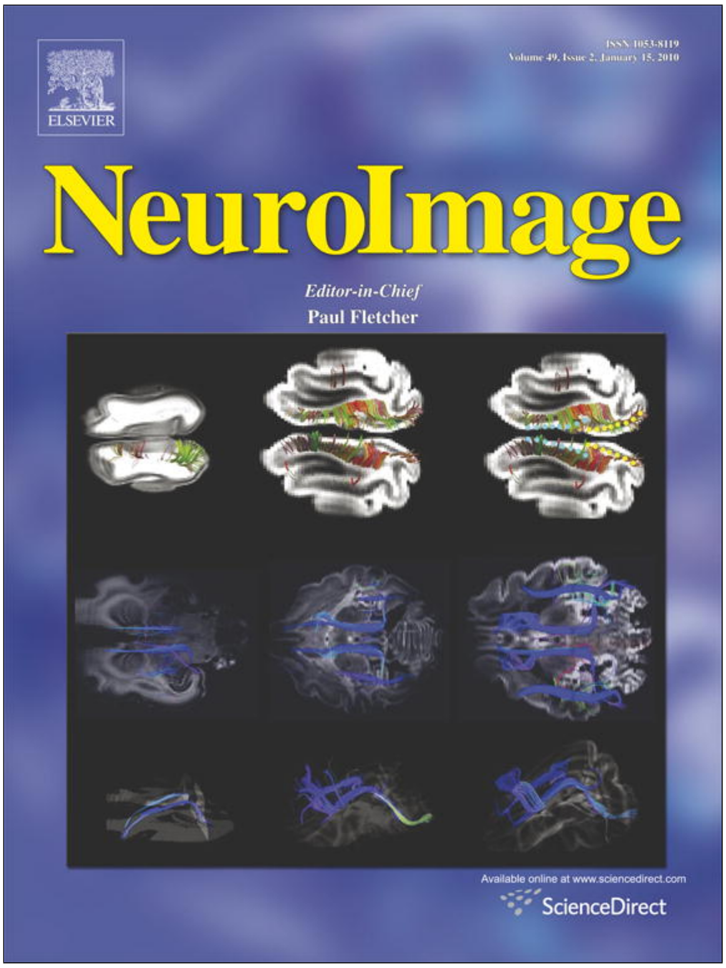
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Unconsciously deciphering handwriting: Subliminal invariance for handwritten words in the visual word form area

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ABSTRACT

Expert readers exhibit a remarkable ability to recognize handwriting, in spite of enormous variability in character shape—a competence whose cerebral underpinnings are unknown. Subliminal priming, combined with neuroimaging, can reveal which brain areas automatically compute an invariant representation of visual stimuli. Here, we used behavioral and fMRI priming to study the areas involved in invariant handwritten word recognition. Compared to printed words, easily readable handwritten words caused additional activity in ventral occipitotemporal cortex, particularly in the right hemisphere, while difficult handwriting also mobilized an attentional parietofrontal network. Remarkably, however, subliminal repetition effects were observed across printed and handwritten styles, whether easy or difficult to read, both behaviorally and in the activation of the left visual word form area (VWFA). These results indicate that the left inferotemporal VWFA possesses an unsuspected degree of fast and automatic visual invariance for handwritten words, although surprisingly this invariance can be reflected both as repetition suppression and as repetition enhancement.

Introduction

A key component of efficient reading is the ability to rapidly build up an abstract representation of letter strings invariant for irrelevant parameters such as font, case, size or location. There is evidence that the overall shape of written words is not important for word identification (Paap et al., 1984; Besner, 1989; Mayall et al. 1997), which is based, instead, upon the recovery of the identity of individual letters. A distinct issue concerns the format of the stored representations which are used in this process, with an ongoing debate on the relative importance of traces of specific perceptual episodes, as opposed to representations in which the surface details of previous episodes are not preserved (for contrasting reviews see Tenpenny, 1995; Bowers, 2000). At any rate, discarding case or font variations when reading printed words may not be the most demanding challenge that the visual system is commonly facing during reading. Handwriting (a term which we mostly use here to refer to cursive handwriting) raises an even greater challenge (Berwick and Winickoff, 1996). When deciphering handwritten words, readers successfully cope with the absence of physical delimitation between letters, with considerable intra-and inter-subject variability in the shape of letters, with the ambiguity of elementary strokes and loops, etc. While much effort has been devoted to the design of automated systems for deciphering handwriting, the mechanisms by which handwritten word recognition is achieved by the human brain are largely unknown. We propose to address this issue within a simple framework which we previously applied to the reading of normal or degraded printed words.

Previous research indicates that the fast and parallel identification of letters strings is performed by a neuronal hierarchy located in the left ventral visual stream, the visual word form system, whose fine properties are tuned through perceptual learning over years of intensive practice of reading (Cohen et al., 2000; Dehaene et al., 2005; Devlin et al., 2006; McCandliss et al., 2003; Shaywitz et al., 2004). Accordingly, performance is optimal with words displayed in familiar formats, as indexed by fast reading latencies independent of word length (Weekes, 1997). Whenever words are disrupted, e.g., by alternating cAsE (Lavidor, 2002; Mayall et al., 2001), by spacing letters, by rotating words or moving them outside of the fovea (Cohen et al., 2008), reading performance deteriorates: Latencies get slower,

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often with the emergence of a positive correlation of latencies with word length. There is imaging and neuropsychological evidence that such unfamiliar displays exceed the capacity of the ventral stream for perceptual invariance and require an additional intervention of dorsal parietal regions (Vinckier et al., 2006). One interpretation of the involvement of such attention-related structures is that, with suboptimal stimuli, a second pass serial processing may be required (Ans et al., 1998). Parietal cortex would modulate the activation of the ventral stream from top-down, for instance serially boosting the posterior segment of the visual word form system devoted to the representation of single letters (Cohen et al., 2008).

Handwritten and printed words differ in both their geometrical structure and their perceptual difficulty (Hellige and Adamson, 2007). The primary aim of this study is to determine the impact of those differences on the interplay of the ventral and dorsal streams during reading. The only available imaging study using handwritten stimuli did not address this issue, as it concentrated on the MEG oscillations induced in the motor cortex by the perception of printed vs. handwritten single letters (Longcamp et al., 2006). Relevant neuropsychological evidence is equally scant. In patients with pure alexia due to left occipitotemporal damage disrupting the visual word form system, the reading impairment affects handwritten words at least as severely as printed words (Dejerine, 1892). This suggests that, at least on a macroscopic scale, the same neural system subtends the perception of printed and handwritten words. Symmetrical right-hemispheric lesions do not yield perceptible reading impairments; however, they may impair the identification of the writer's identity on the basis of handwriting, while this ability is preserved in even severely alexic patients with left-sided lesions (Regard and Landis, 1988). Moreover, in normal subjects, the usual advantage of the right over the left visual field for reading is somewhat reduced for handwritten relative to printed stimuli (Hellige and Adamson, 2007). Such data point to a putative role of the right ventral cortex in the coding of handwritten words, although its causal involvement in word identification is unclear.

In the present imaging study, we will address the following questions and predictions. First, are identical ventral circuits involved in the processing of handwritten and printed words? We expected to observe left-predominant activations of the visual word form system, plus a possible right-hemispheric modulation for handwritten as compared to printed words. To address this point, we contrasted printed vs. handwritten stimuli. Second, do handwritten stimuli, by their very nature, always require an additional deployment of dorsal parietal attention mechanisms, as seen with degraded printed words (Cohen et al., 2008)? To answer this question, we contrasted easy vs. difficult handwritten styles, selected based on a preliminary behavioral experiment.

Third, at which level do printed and handwritten words converge on a common invariant representation? The ventral occipitotemporal visual word form system has been shown to host a case-invariant representation, which treats identically words printed in uppercase and in lowercase (Dehaene et al., 2001, 2004; Devlin et al., 2004). More abstract forms of invariance, however, are known to be achieved at a later stage; for instance, in Japanese readers, the convergence between logographic Kanji and syllabic Kana representations of the same words occurs only in the left posterior middle temporal gyrus (Nakamura et al., 2005), at a location where synonym priming (e.g., sofa-couch) is observed in English readers (Devlin et al., 2004). Is the distinction between printed and handwritten words similar to uppercase versus lowercase, or similar to Kanji versus Kana? To answer this question, we used subliminal repetition priming and the fMRI adaptation method (Grill-Spector and Malach, 2001; Naccache and Dehaene, 2001). We examined which brain areas showed repetition effects when the same word was presented twice (first subliminally, then consciously), compared to a similar non-repeated condition. In the crucial cross-script conditions, the prime word was printed (e.g., PIANO) while the target was handwritten (e.g., piano) or vice-versa. In this case, fMRI repetition effects should index areas where a common word code is computed along the reading pathway. If the visual word form area is able to achieve a fast, automatic and invariant representation, even across stimuli as different as a printed uppercase word and a hard-to-read handwritten word, then it should exhibit repetition priming across these notations.

Note that while subliminal priming has been extensively studied with printed primes, revealing an entire series of non-conscious processing stages (Dehaene, 2008), handwritten words have never, to the best of our knowledge, been used as subliminal stimuli even in behavioral experiments. Thus, it is interesting to ask, even at the behavioral level, whether or not priming occurs with such stimuli. If the processing of handwritten words requires attention, then they might not yield significant repetition effects when used as subliminal primes.

Our study comprised two stages. We first carried out a behavioral reading experiment which allowed us to sample a variety of writing styles and to determine indexes of difficulty. We then used these results to select three appropriate styles for the fMRI experiment: one printed font, one easy handwritten style, and one difficult handwritten style.

Methods

Experiment 1: Reading difficulty with various styles of handwriting

The aim of the first part of this study was to study reading performance with a variety of handwritten styles. We selected 6 sets of 40 French nouns, 4-, 6- or 8-letter in length, and of high or low lexical frequency (mean frequency: 53 and 2 per million, respectively) (http://www.lexique.org; New et al., 2004). Frequency did not differ across words of different length ($F(1,476)<1$, $P=0.97$) (Supplementary Table 1).

In order to generate stimuli, words were presented randomly in uppercase to 21 participants who were asked to copy each word in their usual handwriting. We selected 6 among the 21 handwritten styles, as diverse as possible (Fig. 1). All words were scanned and cropped. We also used one pseudo-manuscript computer font (Plume), and one common printed font (Arial). All stimuli were resized by applying a scaling factor to each style, so that the average width of words was constant across the 8 styles. The 480 words were randomly divided into 8 sets of 60 words (10 words for each combination of frequency × length). Each subject received one set of words in each of the 8 styles.

Words were displayed in black on a white background for an unlimited duration, within the central 10 degrees of the visual field. Sixteen participants (right-handed, native French speakers, 16–32 years old, 8 men) were asked to read aloud words. Responses triggered the presentation of the next word. Latencies were measured with a voice-key and responses were recorded for subsequent scoring.

Experiment 2: Brain imaging study

Stimuli

The aim of the second part of this study was to study brain activations associated with the processing of handwritten and printed words. From the first part of the study, we selected three styles for experimental stimuli: the printed Arial font (uppercase and lowercase) and an easy and a difficult lowercase handwritten style (Fig. 1).

We selected a subset of the material of the first part of the study: 4 sets of 12 nouns, 4- or 8-letter in length, and of high or low frequency. Frequency was matched between short and long words ($F(1.44)=2.41$, $P=0.13$) (Supplementary Table 1). Moreover half of the words in each set referred to natural objects (e.g., a lion), and the other half referred to artifacts (e.g., a skirt).

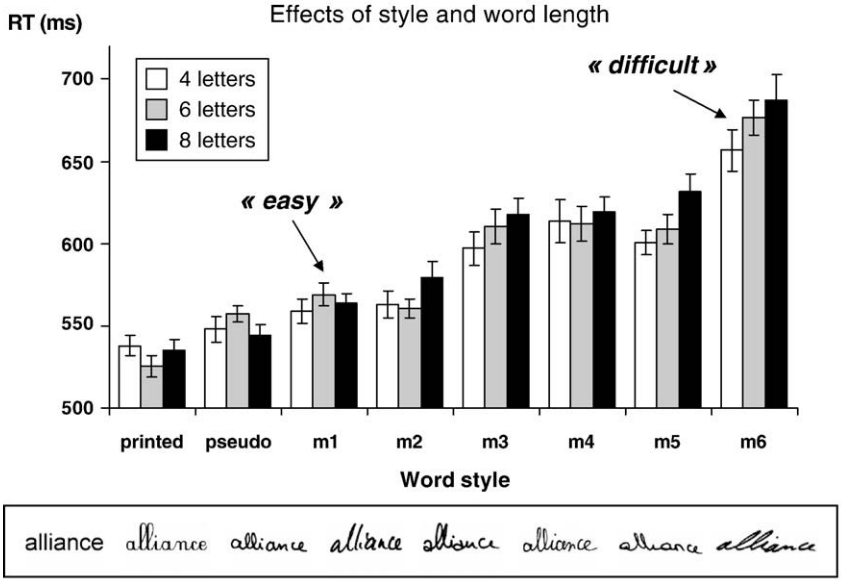

Fig. 1. Mean of median reading latencies for words of 4, 6, or 8 letters (white, grey, and black bars, respectively), displayed in a variety of styles (the printed Arial font, the pseudo-manuscript Plume font, and a sample of 6 handwritten styles). Handwritten styles varied in difficulty, as indexed by overall reading latency and by the influence of word length. The easiest and the most difficult handwritten styles were selected for the fMRI experiment. Error bars represent ± 1 SEM across subjects after subtraction of each subject's overall mean. Below the histogram is a sample of stimuli.

Experimental design

Structure of experimental trials. Each trial consisted of the following sequence: a 400 ms fixation cross, a 50 ms mask, a 50 ms prime word, a 200 ms target word, a 1100 ms fixation cross, and a 16 ms blank screen. The masks were quasi-random combinations of circles and squares. The optimal duration of primes was determined in pilot experiments using primes of 29 ms or 57 ms duration. We determined that 50 ms primes should be long enough to induce a significant priming effect, while being short enough not to be consciously perceived.

Subjects were not informed about the presence of prime words. They were asked to decide as quickly and accurately as possible whether the target word referred to a natural or to a man-made object, and to respond by pressing a right-hand or a left-hand button. Response hands were counterbalanced across subjects.

Overall design. There were six categories of trials, depending on the style used for primes, and the style used for targets (Fig. 1). For three categories of trials, we varied the styles of the target (lowercase printed, easy handwritten, or difficult handwritten, abbreviated as “p,” “e,” and “d”), while the prime word was printed in uppercase (abbreviated as “P”). For the three other categories of trials, we varied the style of the prime (lowercase printed, easy handwritten, or difficult handwritten) while the target word was printed in uppercase. Note that primes and targets never shared the same case, so that priming effects could not be due to the repetition of low-level visual features, but should emerge at least from an invariant representation of abstract letter identities. Moreover for each of the six categories of trials, the target and the prime were the same word on half of the trials and different words on the other half. In «different» trials, the prime and target always belonged to different semantic categories (natural or artificial), to the same frequency category (high or low), and had the same length. The list of 48 words was divided in two equivalent sets of 24 words. Each set was used for conditions Pp, Pe, and Pd in one half of the subjects, and for conditions pP, eP, and dP in the other half of subjects. Thereby for a given subject, prime words were never seen as conscious targets in the same style as the primes, in order to avoid spurious priming effects due to direct specification of response codes (Abrams and Greenwald, 2000). Each word was presented six times as a target to every subject (three types of trials X same vs. different prime and target), making up a total of $48 \times 6 = 288$ experimental trials. In addition, a 13th category of trial, with prime and target words replaced by blank screens, was used as a baseline. Participants performed 3 experimental sessions, each comprising 5 initial training trials followed by 360 trials presented in random order (288 experimental trials plus 72 baseline trials).

Assessment of the perception of masked primes. Immediately after the imaging session, participants performed two forced-choice tests inside the scanner to evaluate the visibility of the primes. At this stage they were explicitly informed about the presence of hidden primes. Stimuli had the same structure as in the activation task. In the first test, participants were required to perform the same semantic decision task on the primes that they had previously performed on the targets (288 trials). In the second test, prime words were replaced by a blank screen in half of the trials, and participants had to decide whether the prime was absent or present (192 trials).

fMRI acquisition and analysis

Acquisition parameters. We used a 3-Tesla MRI (Siemens Trio TIM) with a 12 channel head coil, and a gradient-echo planar imaging sequence sensitive to brain oxygen-level dependant (BOLD) contrast (44 contiguous axial slices, 3 mm thickness; TR = 2400 ms; angle = 90°, TE = 30 ms, in-plane resolution = 3×3 mm, matrix = 64×64; iPAT = 2). In each run, 312 functional volumes were acquired. The first 4 volumes were discarded to reach equilibrium. T1-weighted images were also acquired for anatomical localization.

Statistical analysis. Individual data processing, performed with SPM5 software, included corrections for EPI distortion, slice acquisition time, and motion; normalization to the MNI anatomical template; Gaussian smoothing (5 mm FWHM); and fitting with a linear combination of functions derived by convolving the time series of the stimulus categories with the standard haemodynamic response function implemented in the SPM5 software (a combination of 2 gamma functions, with a rise peaking around 6 s followed by a longer undershoot), without including in the model the temporal derivatives of those functions. Individual contrast images were computed for each stimulus type minus baseline, then smoothed (4 mm FWHM), and eventually entered in an ANOVA for random effect group analysis. Note that the histograms in Figs. 5 and 6 represent values of the very same smoothed contrast images at selected voxels, averaged across subjects. Unless stated otherwise we used a voxelwise threshold of $P < 0.001$, with a threshold for cluster extent of $P < 0.05$ corrected for multiple comparisons across the whole brain (minimum cluster size: 112 voxels). Considering that primes were presented subliminally and had little impact on RTs, we expected relatively small effects on BOLD signal. Therefore, for repetition effects, we used a voxelwise threshold of $P < 0.01$, still with a threshold for cluster extent of $P < 0.05$ corrected (minimum cluster size: 388 voxels). Correction for multiple comparisons was performed within the overall reading network (i.e., activation by all pooled stimuli minus baseline, at the usual threshold), using the small volume correction implemented by the SPM software.

For the analysis of activation asymmetry, individual normalized anatomical images were flipped, and then normalized back to the original normalized anatomy; the corresponding normalization matrices were applied to the flipped contrast images, allowing for an accurate match of the left and right hemispheres; flipped contrast images were then subtracted from the original contrast images. The resulting difference images were smoothed (4 mm FWHM), and were entered in the same ANOVA as before, allowing us to test the interaction of any given contrast with the left/right hemisphere factor. We used a voxelwise threshold of $P < 0.01$, with a threshold for cluster extent of $P < 0.05$ corrected for multiple comparisons within the volume activated by the contrast whose asymmetry was tested. All effects which are reported as asymmetrical in the Results section comply with those statistical criteria.

Subjects

Fourteen right-handed, native French speakers, 18 to 32 years old (9 men), gave written informed consent to participate in the present fMRI study. None of the subjects had participated in Experiment 1. They had no history of neurological or psychiatric disease. Their vision was normal or corrected to normal. The project was approved by the regional ethical committee.

Results

Reading difficulty with various styles of handwriting

In Experiment 1, subjects were asked to read aloud a variety of printed and handwritten words (Fig. 1 and Supplementary Table 2). Overall, subjects made 7.6% errors and had a mean correct RT of 591 ms. The median RT was computed for each subject and each condition (style × length × frequency) and entered in an ANOVA with subjects as a random factor.

First, latencies differed between script styles ($F(7,105) = 55.7$, $P < 0.001$). RTs were the shortest for printed words (533 ms), slightly longer for the pseudo-manuscript font (550 ms, $F(1,15) = 18.9$, $P < 0.001$), and again longer for handwritten styles than for the pseudo-manuscript font ($F(1,15) = 106.8$, $P < 0.001$). Across handwritten styles, latencies ranged from 564 to 674 ms. Second, responses were slower for longer words ($F(2,30) = 3.3$, $P = 0.05$). Despite the absence of a significant length effect for individual styles and of a significant interaction of style × length, Fig. 1 suggests that this length effect was due only to some of the manuscript styles, mostly among the slowest ones. Indeed, the slope of the length effect was significantly correlated with overall RT across styles ($r = 0.80$; $t(6) = 3.3$; $P = 0.017$). Third, RTs were shorter for high-frequency (568 ms) than for low-frequency words (614 ms) ($F(1,15) = 46.7$, $P < 0.001$). This frequency effect was larger for the styles yielding the slowest responses (interaction frequency × style: $F(7,105) = 3.30$, $P < 0.01$).

Error rates showed a similar pattern with respect to style and frequency: Slowest styles and low-frequency words yielded higher error rates. However the length factor showed a speed–accuracy trade-off: Whenever longer words yielded longer latencies, they also yielded fewer errors.

Discussion

The main goal of Experiment 1 was to explore the reading difficulty of various styles and to select relevant stimuli for fMRI. Reading times demonstrated that the various styles that we tested varied strongly in difficulty, as indexed both by the overall performance level and by the existence of an effect of word length. For the subsequent fMRI experiment, we selected two handwritten styles: An “easy” style which had both the shortest mean RT (567 ms) and the least influence of word length (1 ms/letter), and a “difficult” style which had both the longest mean RT (673 ms) and the largest influence of word length (8 ms/letter). Note, however, that although those two parameters (mean latency and length effect) were correlated across styles, they also dissociated to some extent. For instance, handwritten styles m1 and m4, although yielding slower responses than printed words, showed no hint of a length effect (Fig. 1). In the future, it might therefore be interesting to dissociate the underlying brain mechanisms. We suggested in the introduction that handwritten words may differ from printed words (1) in the duration and precise topography of parallel processing in the ventral pathway, and (2) in the intervention of parietal structures for the serial processing of word fragments. One may speculate that those two mechanisms are reflected behaviorally as overall slowing and length effects, respectively, an interesting possibility for further research.

Another interesting aspect is the non-additivity of the style and frequency effects. If the visual recognition of handwritten words was resolved at an early stage, prior to lexical access, then one would have expected purely additive effects of style and frequency (Sternberg, 1998). However we found a strong interaction of those two factors, suggesting that, at least for difficult styles, lexical information plays a role in resolving the ambiguity of the visual stimulus, perhaps through top-down mechanisms. Indeed, this is the explanation classically given for the word superiority effect (Reicher, 1969), which is likely to be exacerbated for handwritten stimuli.

Behavioral results during fMRI: subliminal priming

During the fMRI experiment, subjects were asked to classify target words according to their semantic category, as either natural or

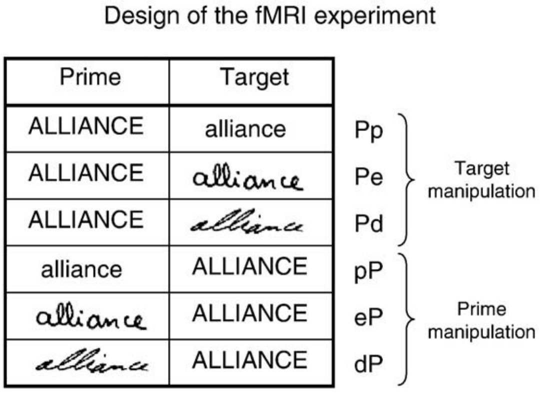

Fig. 2. Illustration of the six types of experimental fMRI trials, based upon six combinations of uppercase and lowercase printed (P and p), easy handwritten (e), and difficult handwritten (d) primes and targets. In the top three types of trials, the style of visible targets was manipulated. In the bottom three types of trials the style of masked primes was manipulated. In half the trials the prime and the target were the same word, as illustrated, while they were different in the other half of trials.

artificial, and to respond by pressing a button. Targets could be displayed in a printed or an easy handwritten or a difficult handwritten style. Each target was preceded by a subliminal prime whose style was also manipulated and which could be the same word as the target or not (see Fig. 2 for an illustration of the full design). In this section, we first analyze the subjects' response patterns, particularly the presence of subliminal repetition priming, and then verify the invisibility of the masked primes.

Overall subjects made 7.5% errors and had a mean correct RT of 620 ms. For each subject, we computed the median correct RT for each cell of an ANOVA with subjects as random factor, and prime/target styles and word repetition as within-subject factors (Fig. 3 and Supplementary Table 3).

First, RTs were different across the six categories of trials ($F(5,65)=85.0$, $P< 0.001$). This overall effect was entirely due to the style of the targets: Responses were slower to difficult handwritten targets (694 ms) than to easy handwritten targets (636 ms, $F(1,13)=75.0$, $P< 0.001$), which were slower than printed targets (628 ms, $F(1,13)=36.4$, $P< 0.001$). There was no effect of the style of prime words when the target style was held constant ($F(2,26)<1$). Second, there was overall a significant priming effect: Responses were faster for same (621 ms) than for different trials (639 ms) ($F(1,13)=28.9$, $P< 0.001$). Third, the effects of style and priming were interacting (interaction $F(5,65)=13.6$, $P< 0.001$): Only printed primes induced a behavioral priming effect (29 ms; $F(1,13)=63.6$, $P< 0.001$), while there was no effect for handwritten primes ($F(1,13)=1.1$, $P= 0.31$). Fourth, among trials with printed primes, trials with a difficult handwritten target benefited more from repetition priming than did the three other categories of trials (interaction $F(1,13)=7.69$; $P= 0.016$), which did not differ among them ($P= 0.29$). Finally, an additional ANOVA showed that RTs were longer to 8-letter words (638 ms) than to 4-letter words (622 ms; $F(1,13)=33.049$, $P< 0.001$), while there was no effect of frequency ($F(1,13)<1$, $P= 0.96$) and no interaction of the two factors.

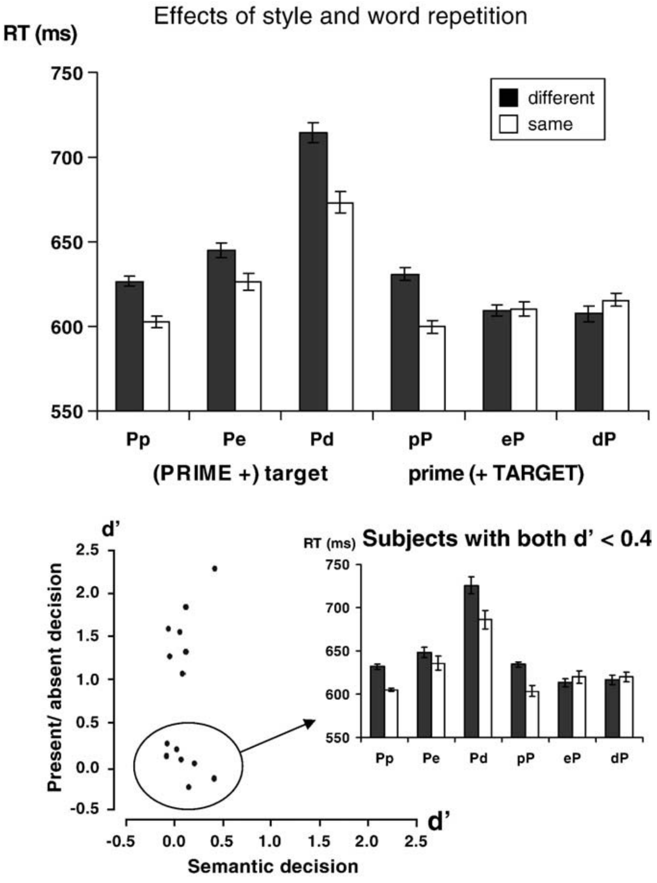

Fig. 3. Behavioral measures obtained during fMRI. Top panel, mean of median response latencies during the semantic classification task (natural or man-made) as a function of the style of the prime and the target (P: uppercase printed; p: lowercase printed; e: easy manuscript; d: difficult manuscript), and of the sameness of the prime and target words (black bars: different; white bars: same). Latencies mostly depended on the style of visible targets ($P= p< e<d$). Moreover there was a repetition priming effect whenever prime words were printed, while there was no priming with manuscript primes. Error bars represent ± 1 SEM across subjects after subtraction of each subject's overall mean. Bottom panel, plot of d' values for the semantic and the present/absent decision tasks (left). All subjects had a semantic d' close to 0. Analyzes restricted to subjects with both $d'<0.4$ (right) were virtually identical to the overall analyzes, showing that priming effects were independent of whether participants were aware of the prime or not.

Assessment of the perception of masked primes

In order to study the perception of masked primes, we asked participants to perform two forced-choice tests: a semantic decision and a present/absent decision on the masked primes. We computed a measure of prime perceptibility (d') for each subject and each task (Fig. 3). For the semantic decision task, the d' ranged from −0.1 to 0.41 across subjects, and was on average slightly but significantly larger than zero ($t(13)=2.2$, $P= 0.048$). For the present/absent discrimination task, the d' ranged from −0.24 to 2.30, and was on average larger than zero ($t(13)=3.60$, $P= 0.0033$). To make sure that the pattern of visibility of the primes did not vary across the types of trials, we also computed d' values separately for each type of trial. For both tasks, d' values did not differ significantly across types of trials (both $F(5,13)<1$). Interestingly, seven subjects had present/absent d' values close to 0 ($d'<0.4$), and the seven other subjects had d' values above 1. We took advantage of this bimodal distribution and verified that the priming effect observed in the main task persisted after restricting the analysis to the seven subjects whose d' values were both close to 0 (Fig. 3) (overall priming: $F(1,6)=56.0$, $P< 0.001$; priming restricted to trials with printed primes: $F(1,6)=95.1$, $P< 0.001$). Accordingly, in an ANOVA including a between-subject group factor (present/absent d' below vs. above 1), there was no significant interaction of the priming effect with group ($F(5,60)<1$). Thus, the observed behavioral priming effects did not depend on conscious perception of the primes.

To further study a putative link between prime visibility and the priming effect, we computed for each subject a priming index defined as the ratio (RT different trials − RT repeated trials)/(RT different trials), and studied the regressions of this index on semantic and present/absent d' values across subjects (Greenwald et al., 1996). Correlations were not significant ($P= 0.26$ and $P= 0.91$, respectively), confirming that priming effects were not dependent on prime visibility. Moreover, the intercepts of those regressions were significantly larger than zero ($P= 0.0004$ and $P= 0.008$, respectively), providing an interpolated estimation of the priming index for a null d' (Greenwald et al., 1996). In summary, although the presence of primes may have been occasionally detectable, the priming effect was not a consequence of this partial visibility.

Discussion

Behavioral data gathered during scanning replicated the gradation of overall difficulty between printed, easy, and difficult handwritten words observed in the preliminary experiment. Moreover, subliminal word repetition facilitated responses to the targets in several conditions, including the crucial cross-notation condition in which the prime was printed and the target was handwritten, suggesting that an abstract level of invariant representation, common to these two notations, can be attained for subliminal stimuli. The priming effect induced by printed primes was largest when targets were most difficult, presumably because this less automatized condition left greater room for a reduction in response times, while priming effects were smaller whenever targets were easy enough for subjects to encode them with optimal speed even without the help of repetition.

Interestingly, however, behavioral priming was asymmetrical, as it was only seen when the primes were printed, but not when they were handwritten. It is perhaps unsurprising that the difficult handwritten words elicited no priming, because their slow identification presumably indicates a lack of automaticity and the engagement of attention-driven serial deciphering. However, easy handwritten primes also had no measurable impact on behavior, suggesting that they were not processed as efficiently by the visual system as did printed primes. Caution is required, however, as response time is a compound measure of numerous underlying stages that, as we shall now see, can be more efficiently distinguished using fMRI (Dehaene et al., 2004; Sternberg, 1998).

Imaging results

After delineating the overall reading network, the fMRI analysis will proceed in three stages. We will study in turn (1) the influence of the style of conscious target words on brain activations, (2) the influence of the style of masked primes, and (3) the depth of processing of masked words as indexed by the effect of word repetition.

The overall reading network

We contrasted the average activation when pooling across the six active conditions minus baseline. There were extensive activations in a bilateral network (Supplementary Fig. 1), including strong bilateral ventral occipitotemporal clusters. The statistically strongest peak across the whole brain fell at coordinates MNI-46-62-14 ($Z=20.0$), closely matching previous measures of the position of the VWF area (e.g., Cohen et al., 2002; Jobard et al., 2003). Although its extension was bilateral, most components of the network showed higher activations in the left hemisphere, including the occipitotemporal pathway (Supplementary Fig. 1). Note that the opposite contrast showed extensive deactivations relative to baseline in the so-called resting-state network (Raichle et al., 2001).

Activations related to the style of visible target words

We first studied the influence of the style of conscious targets on brain activations. To this end, we analyzed the three conditions with lowercase targets which could be printed, easy handwritten, or difficult handwritten, always preceded by uppercase printed primes (abbreviated as Pp, Pe, and Pd in figures; three leftmost pairs of bars in

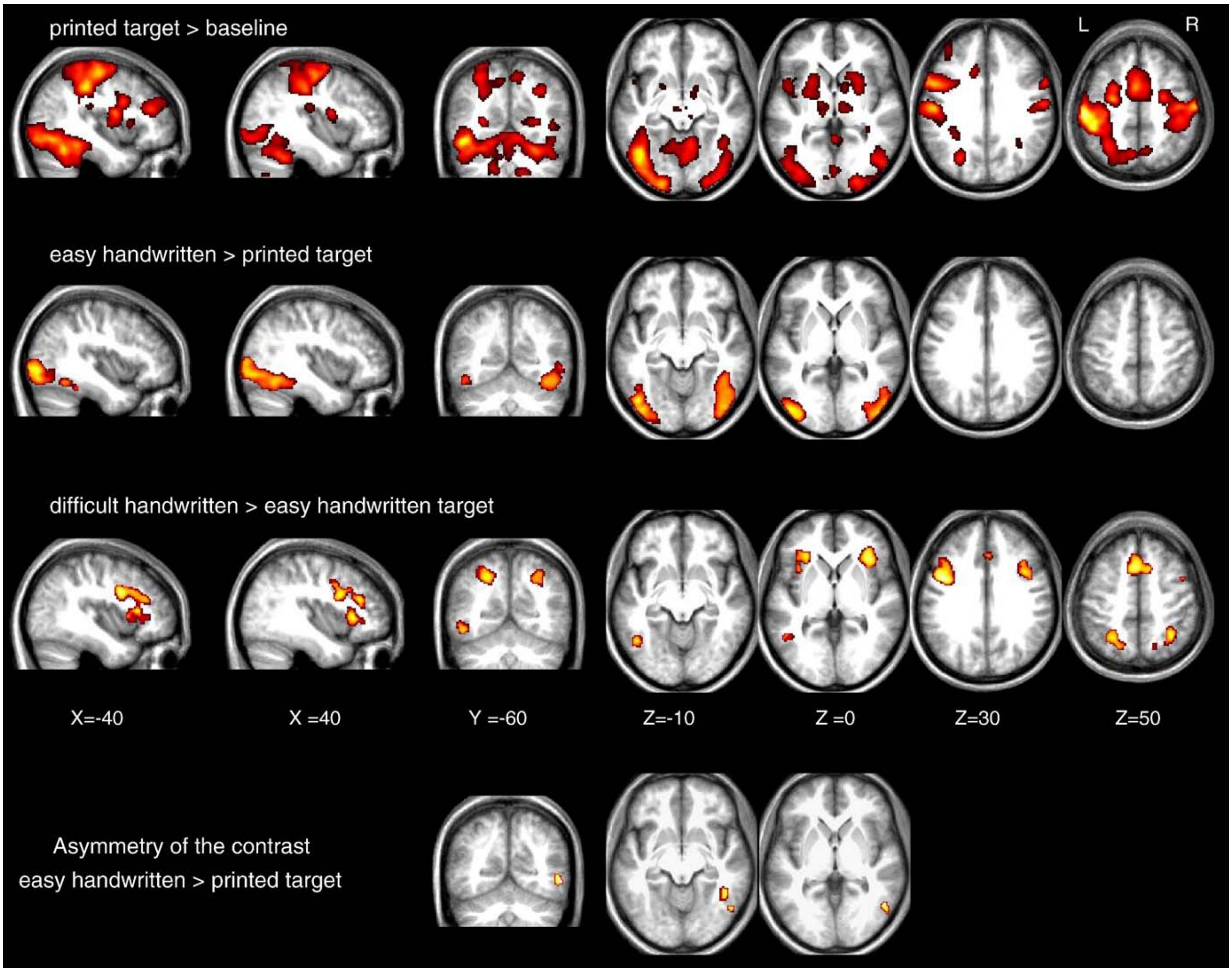

Fig. 4. Activation related to the style of visible target words. The contrast of printed targets relative to baseline illustrates the overall reading network (top row). Relative to printed words, easy handwritten words yielded ventral occipitotemporal activation (second row). Relative to easy handwritten words, difficult handwritten words induced additional activation in the visual word form area and in a bilateral frontoparietal network (third row). The bottom row shows the significant right-hemispheric predominance of the contrast of easy handwritten minus printed words in the inferior temporal and fusiform gyri. All contrasts are thresholded at $P < 0.05$ for cluster extent, corrected for multiple comparisons, with a voxelwise threshold of $P < 0.001$ (top three rows) or $P < 0.01$ (bottom row).

histograms). Those conditions were the primary source of information about the networks activated during the conscious reading of handwritten words. Activations should reflect mostly the processing of visible targets, with only marginal influence of the masked primes. Moreover, comparisons between conditions are free of any influence of the style of primes, which were always uppercase printed. Trials with same or different primes and targets were pooled.

Activations relative to baseline

Inspection of activations for each of the three target styles relative to baseline (Supplementary Fig. 2) showed highly similar left-predominant networks. Particularly, in all three conditions, occipito-temporal activations were strongly left-predominant, the peak of the VWF area being the spot of maximal asymmetry for the three considered conditions ($P < 10^{-13}$ at the VWFA peak for each of the three tests of asymmetry). Still, although highly similar the networks did not appear identical: (1) in the ventral occipitotemporal cortex printed words yielded mostly left-hemispheric activations, while handwritten words elicited larger and more bilateral activations, and (2) there was a more extensive bilateral frontoparietal network activated by difficult words. We next assessed formally those differences.

Comparisons between styles of target words

In order to restrict analyses to actual activations relative to baseline, each subtraction between two target styles was masked by the contrast of the first term of the subtraction minus rest (voxelwise $P < 0.01$) (Fig. 4).

The contrast of easy handwritten minus printed targets showed bilateral ventral occipitotemporal clusters, extending from the occipital pole to about $y = -40$, and peaking about 2 cm posterior to the main peak of the VWF area as identified in the overall reading network (left: MNI-44-84-6; $Z = 7.59$; right: MNI 52-76-6; $Z = 6.33$). Within this activated volume, there was significant right-hemispheric predominance in the inferior temporal gyrus (MNI 54-62-4; $Z = 3.30$; 100 voxels) prolonged by a more anterior fusiform cluster just below significance for cluster extent (MNI 44-44-14; $Z = 3.27$; 77 voxels) (Fig. 4).

The contrast of difficult handwritten minus easy handwritten targets showed a left fusiform cluster peaking within millimeters of the main peak of the VWF area as identified in the overall reading network (MNI-46-60-10; $Z = 4.33$), and a large bilateral network including the inferior frontal sulcus, SMA, anterior insula/Broca's area, and intraparietal cortex (Table 1). Lowering the voxelwise threshold to $P < 0.01$ (clusterwise $P < 0.05$ corrected) showed the VWF area cluster extending forward to about $y = -30$, with a strong peak in the anterior VWF area (MNI-40-44-14; $Z = 4.93$). Within this network, there was significant left-hemispheric predominance in the left inferior frontal sulcus (MNI-40 2 26; $Z = 4.55$).

As expected, the contrast of difficult handwritten minus printed targets showed the union of the two preceding contrasts, i.e., bilateral ventral activations plus the bilateral frontoparietal network. The three opposite contrasts (easy handwritten minus difficult handwritten, and printed minus each handwritten) showed no significant activations.

Table 1
Peaks of the network activated by difficult handwritten targets more than by easy handwritten targets (voxelwise threshold $P < 0.001$; threshold for cluster extent $P < 0.05$ corrected).

Structure	Hemisphere	MNI coordinates	*Z*-score
Occipitotemporal (VWFA)	Left	−46 −60 −10	4.33
		−40 −44 −14	4.93*
Anterior insula/Broca's area	Left	−30 26 4	5.25
	Right	34 26 2	5.80
Inferior frontal sulcus	Left	−42 4 28	5.70
	Right	40 10 26	4.81
SMA	Left	−2 16 48	5.30
	Right	10 16 44	5.09
Intraparietal	Left	−22 −62 44	4.79
	Right	34 −54 46	5.06

* Voxelwise threshold $P < 0.01$; threshold for cluster extent $P < 0.05$.

Summary and complementary analyses

Target-related activations may be summarized as follows. First, printed targets activated the usual left-predominant network relative to baseline, including the ventral visual cortex. Second, moving from printed to easy manuscript targets induced additional activation in the posterior ventral cortex, peaking around $y = -80$, with significant right-hemispheric predominance. In order to illustrate the impact of the style of target words on activation patterns in the ventral visual cortex, we selected voxels of interest by using the overall contrasts of the three pooled conditions in which target style was manipulated minus baseline. We selected the three statistically highest peaks within the left ventral cluster allowing for a spatial sampling of this region, plus two symmetrical right-hemispheric local maxima. This selection criterion was thus orthogonal to all contrasts between target styles. As visible on activation histograms (Fig. 5), this posterior region around $y = -80$ showed no activation difference between easy and difficult manuscript targets ($P > 0.1$ at the left and right peak voxels). Third, moving from easy to difficult manuscript targets induced activation increase in a bilateral frontoparietal network. Fourth, the mid-segment of the VWF system and the symmetrical right-hemispheric region, around $y = -60$, showed both effects, with an increase from printed to easy manuscript ($P < 0.01$ at both the left and the right peaks), and from easy manuscript to difficult manuscript targets ($P < 0.01$ at both the left and the right peaks) (Fig. 5). Interestingly, the most anterior peak of the VWF area ($y = -44$) identified by contrasting difficult minus easy handwritten targets showed only an effect of difficulty ($P = 0.012$ between easy and difficult targets) with no difference between printed and easy handwritten targets ($P > 0.1$) (Fig. 5). Thus, moving from back to front in the VWF system, we observed a progressive replacement of the effect of script type (opposing printed versus both handwritten styles) with the effect of difficulty (opposing easy versus difficulty handwritten words). Note that although suggestive, this spatial pattern was statistically marginal. Activations in the three left occipitotemporal peak voxels were entered in an ANOVA, with voxel and target type as within-subject factors. The interaction of voxel × target type was marginally significant ($F(4,52) = 2.3$; $P = 0.07$). Actually, the difference between easy and difficult handwritten targets changed significantly across regions ($F(2,26) = 5.5$; $P < 0.01$), while the difference between printed and easy handwritten targets did not ($F(2,26) = 1.7$; $P = 0.2$).

Activations related to the style of masked prime words

We then studied activations related to the style of masked primes. To this end, we analyzed the three conditions with lowercase primes (printed, easy handwritten, or difficult handwritten), which were always followed by uppercase printed targets (abbreviated as pP, eP, and dP in figures; three rightmost pairs of bars in histograms). As all trials shared the same style of target, comparisons between conditions were free of any influence of the style of targets. Trials with same or different primes and targets were pooled.

Activations relative to baseline

Inspection of activations relative to baseline only suggested that activations were slightly stronger for printed primes than for handwritten primes in the bilateral ventral cortex (Supplementary Fig. 2).

Comparisons between styles of prime words

In order to restrict analyses to actual activations relative to baseline, each subtraction between two prime styles was masked by the contrast of the first term of the subtraction minus rest (voxelwise

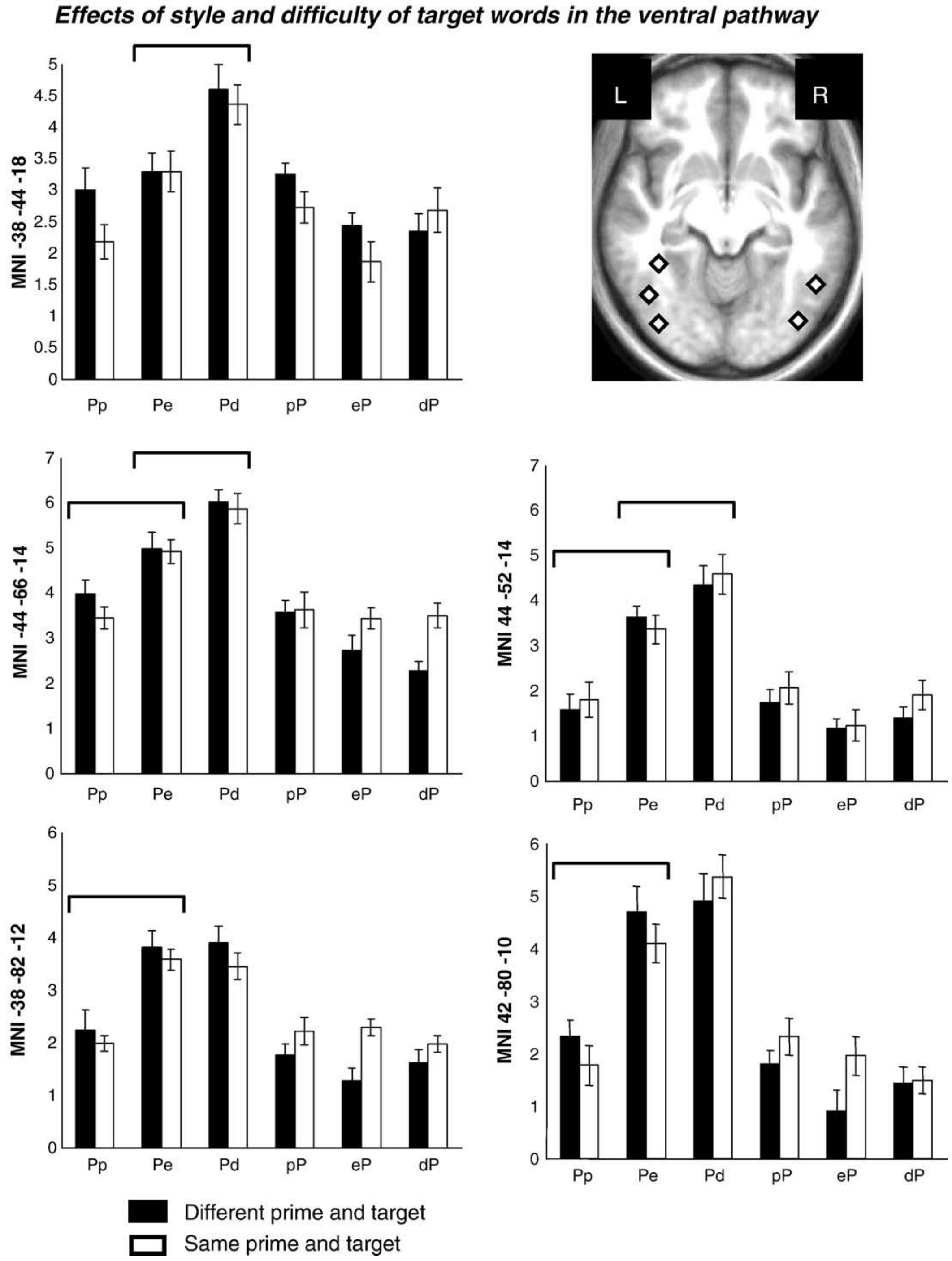

Fig. 5. Activation profiles at peaks of the ventral visual stream. This figure aims at illustrating the role of the style of conscious targets, as illustrated by the three leftmost pairs of bars in each graph (corresponding respectively to printed, easy handwritten, and difficult handwritten styles). For completeness we show the entire profile of fMRI activation as a function of prime style, target style, and word repetition. The two most posterior peaks show higher activations for manuscript than for printed words, and no effect of difficulty. The most anterior left-hemispheric peak shows only an effect of difficulty. Intermediate mid-fusiform peaks show effect of both printed vs. manuscript style, and of difficulty. Brackets indicate significant differences ($P < 0.01$). Note that the selection criterion for those voxels (peaks of the pooled contrast of Pp, Pe, and Pd minus baseline) was orthogonal to the contrasts between types of targets.

$P < 0.01$). The contrast of printed minus easy primes showed activations in the VWF area (MNI-48-66-22; $Z = 4.56$) and in the left inferior frontal sulcus (IFS) (MNI-52 14 30; $Z = 3.94$) (Fig. 6). This difference was left-predominant in the left IFS region (MNI-56 14 28; $Z = 3.49$). When lowering the voxelwise threshold to $P < 0.01$ (clusterwise $P < 0.05$ corrected) there was an additional left intraparietal cluster (MNI-22-66 36; $Z = 4.21$).

The contrasts of printed minus difficult primes showed the same IFS cluster, while the VWF area cluster was significant at the lower voxelwise threshold ($P < 0.01$, clusterwise $P < 0.05$ corrected). The two opposite contrasts (easy and difficult handwritten primes minus printed primes), and the comparisons between easy and difficult primes showed no significant differences.

Summary

The style in which primes and targets were presented had a strikingly opposite impact on activations, but this may be due to the same reason, namely, a lesser automaticity of word recognition with

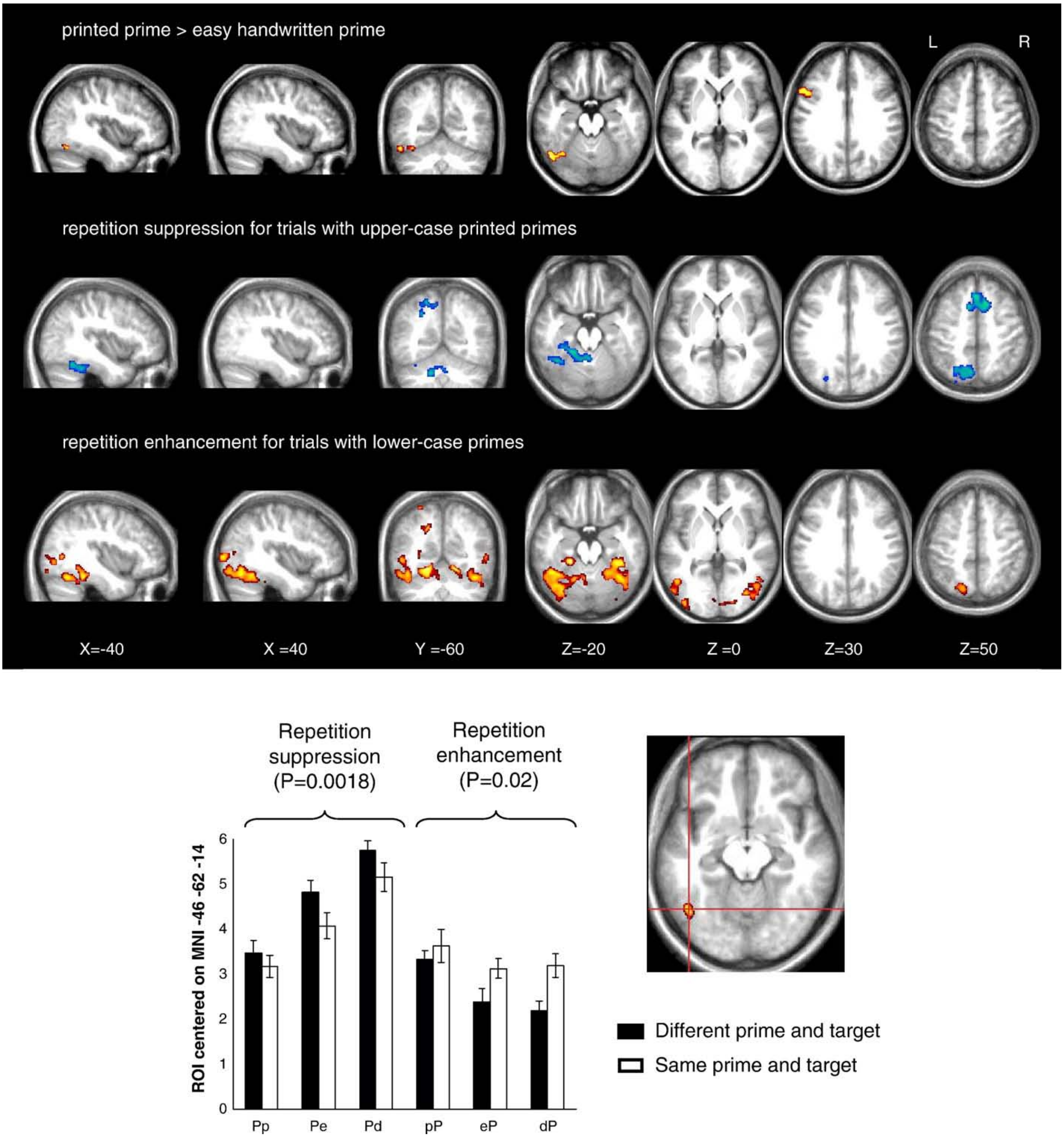

Fig. 6. Activations related to masked prime words. Relative to handwritten words, printed words activated the left ventral temporal cortex and inferior frontal sulcus (top row). The predominant influence of word repetition was repetition suppression for trials with uppercase printed primes (middle row), and repetition enhancement for trials with lowercase (handwritten or printed) primes (bottom row). All contrasts are thresholded at $P< 0.05$ for cluster extent, corrected for multiple comparisons, with a voxelwise threshold of $P< 0.001$ (top row) or $P< 0.01$ (bottom 2 rows). The bottom panel illustrates the pattern of repetition suppression and enhancement in the VWFA, in a region of interest centered on the main peak of the overall reading network.

handwritten stimuli. Handwritten targets yielded stronger activations than printed targets, presumably because of the greater time and effort needed to read them, as previously discussed. Conversely, masked handwritten primes elicited weaker activations than printed primes in the VWF area and other left-hemispheric regions, presumably because their fast automatic bottom-up processing was less efficient.

Influence of word repetition

We then studied the depth of the processing of masked words by analyzing fMRI repetition effects on activation profiles. Note that it is necessary to carefully distinguish repetition suppression (RS), a reduction in fMRI signal on repeated trials when the same word is presented as prime and as target, from repetition enhancement (RE),

Table 2
Peaks of repetition effects (voxelwise threshold $P < 0.01$; threshold for cluster extent $P < 0.05$ corrected within the reading network).

Structure	Hemisphere	MNI coordinates	*Z*-score
Suppression in trials with uppercase printed primes			
SMA	Left	−8 12 52	3.79
	Right	12 16 52	4.34
Intraparietal	Left	−16 −62 54	3.52
Anterior fusiform/parahippocampal	Left	−36 −36 −26	4.14
Enhancement in trials with lowercase primes			
Intraparietal	Left	−18 −62 36	3.35
Occipital	Left	−26 −68 4	4.42
	Right	36 −76 −2	3.39
Fusiform/parahippocampal	Left	−44 −52 −18	4.05
	Right	38 −40 −22	3.95

an increase in fMRI signal on repeated trials. As we shall see, surprisingly, both effects are present in our experiment.

Overall repetition effects

Our experimental design included two distinct blocks of conditions: one in which prime style was fixed (uppercase printed primes) and target style varied, and another in which target style was fixed (uppercase printed targets) while prime varied (see Fig. 2). We therefore analyzed these blocks separately.

In the first block of trials, when the primes were in uppercase printed style, there was RS in the bilateral SMA, the left anterior fusiform and hippocampus, and the left occipitoparietal cortex. No significant RE was observed (Table 2 and Fig. 6). In the other block, with lowercase printed and handwritten primes, there was RE in bilateral occipital, ventral, and mesial temporal cortex, and in the left intraparietal cortex. No significant RS was observed (Table 2 and Fig. 6). Thus, remarkably, the repetition priming effect switched from a reduction to an enhancement as a function of whether the primes were printed and the targets were handwritten, or vice-versa. Furthermore, there was a substantial overlap of these RS and RE networks, mostly in the left occipital, temporal, and parietal cortex. In other words, the very same voxels switched from RS to RE as a function of prime and target style. We assessed this formally through an SPM contrast which tested the reversal of the repetition priming effect between the two blocks (formally, this is a contrast pooling RS in conditions Pp/Pe/Pd, and RE in the conditions pP/eP/dP, masked by both the RS and the RE contrasts at voxelwise $P < 0.05$). This contrast isolated the left occipitotemporal cortex, the left intraparietal cortex, the left IFS, and the right inferotemporal cortex. Note that, as shown in Fig. 6, there was some extension of repetition effects to the cerebellum, particularly of RS to deep structures, and of RE to more lateral cortical regions (for a review see Stoodley and Schmahmann, 2009).

Actually, beyond areas where repetition effects were significant, the same pattern of RS/RE inversion applied qualitatively to most of the reading network. Within the entire reading network, we examined the sign of repetition effects irrespective of their significance. Almost the whole network showed both suppression for uppercase printed primes (80% of voxels) and enhancement for lowercase printed or handwritten primes (92% of voxels). Note that the same pattern prevailed in the resting-state network (77% and 91% of voxels showed the same pattern of suppression and enhancement as in the reading network), i.e., in regions whose baseline activation decreased during the active task, although they might still be involved in reading.

Cross-case and cross-type priming

We then looked at the same data, but drawing finer distinctions, in order to address the following two questions: Did we replicate previously reported cross-case repetition effects between uppercase and lowercase printed words (Dehaene et al., 2001, 2004; Devlin et al., 2004)? And in which areas did we obtain cross-type repetition effects, i.e., between printed and handwritten words? The latter question is essential in order to understand where in the brain an invariant coding of handwritten and printed words first occurs.

Cross-case repetition effects. When lowercase printed targets were preceded by uppercase printed primes, there were no repetition effects at the usual threshold. When lowering the threshold for cluster extent, there was RS in the left fusiform cortex (MNI-38-46-14; $Z = 3.00$; 76 voxels) and in the left inferior frontal sulcus (MNI-40 28 12; $Z = 3.52$; 165 voxels). There was no RE with this category of trials. Conversely, when uppercase printed targets were preceded by lowercase printed primes, there was significant RE in the left lingual (MNI-16-72-14; $Z = 3.86$), fusiform (MNI-34-58-20; $Z = 2.98$), and inferior temporal (MNI-46-64 4; $Z = 3.63$) gyri and in the right superior parietal lobe (MNI 30-42 72; $Z = 3.42$). There were symmetrical right-hemispheric activations slightly below the threshold for cluster extent. There was no RS with this category of trials. In summary, as visible on most activation histograms (Figs. 5 and 6), uppercase printed primes yielded the expected RS effect, while lowercase printed primes induced RE.

Cross-type repetition effects. When handwritten targets were preceded by printed primes, there was RS in the left anterior fusiform (MNI-36-36-26; $Z = 3.92$) and precuneus (MNI-8-72 42; $Z = 3.33$), and the bilateral SMA (MNI 12 16 52; $Z = 4.09$), while there was no RE. Conversely, when printed targets were preceded by handwritten primes, there was RE in a large strip of left ventral fusiform cortex (MNI-42-54-18; $Z = 3.90$) extending from about $y = -75$ to $y = -40$, a smaller and more anterior cluster in the right ventral occipitotemporal cortex (MNI 40-40-22; $Z = 3.85$), the left IFS (MNI-52 22 32; $Z = 3.58$), plus a right thalamic/caudate cluster (MNI 8-4 6; $Z = 3.52$), while there was no RS. Like in the previous section, we assessed formally the reversal of the repetition priming effect when the handwritten and printed words switched roles as primes and targets (formally, this is a contrast pooling RS in conditions Pe/Pd and RE in conditions eP/dP, masked by both the RS and the RE contrasts at voxelwise $P < 0.05$). This contrast showed a long stretch of activation in the left ventral cortex, including the classical location of the visual word form system and ranging from the occipital lobe (MNI-38-84-18; $Z = 2.94$) to the mid and anterior fusiform region (MNI-38-54-24; $Z = 4.18$; MNI-26-34-24; $Z = 3.37$), in the left inferior temporal sulcus (MNI-46-60-12; $Z = 3.83$), in the left intraparietal cortex (MNI-16-72 46; $Z = 3.87$), in the left thalamus (MNI-16-20 6; $Z = 4.08$), and in the right inferotemporal cortex (MNI 40-40-22; $Z = 3.81$).

Classifying voxels according to the sign of the repetition effect, this pattern prevailed in most of the overall reading network, in which most voxels showed RS for handwritten targets (80% of voxels) and RE for handwritten primes (91% of voxels).

Correlates of behavioral priming

The correspondence between neural and behavioral repetition priming is ill-understood, as there are clear cases of dissociation between them in both human fMRI and monkey neurophysiology (Dehaene et al., 2004; McMahon and Olson, 2007). To probe the putative fMRI correlates of behavioral priming in response times in our experiment, we pooled all conditions for which significant behavioral priming (reduction in RT) was observed, i.e., the four categories of trials with a printed prime. There was fMRI repetition suppression only in the bilateral SMA (MNI-10 12 52; $Z = 4.21$), and no significant repetition enhancement.

Discussion

Handwriting and the ventral stream

The first aim of this study was to determine whether identical ventral circuits are activated during the perception of handwritten and printed words. The main source of evidence was the comparison between trials with printed, easy handwritten, or difficult handwritten targets (all following a printed prime word).

Clearly, the same areas were activated irrespective of style, with a strongly left-predominant maximum in the VWF area. Moreover, the perception of the most demanding targets, i.e., difficult handwritten words, boosted ventral activations precisely at the main peak of the VWF area. This pattern suggests that the perception of handwritten words relies primarily on the same left-lateralized regions as printed words. Indeed, the fact that pure alexic patients with left-sided lesions show most severe deficits with handwritten words supports the involvement of the VWF area in reading handwritten words.

Handwritten targets activated the ventral stream more than printed targets. This contrasted with the opposite pattern of weaker activations by subliminal handwritten primes than by printed primes. Assuming that the processing of subliminal primes reflects only bottom-up processing within the ventral stream in the absence of attention-driven amplification, this suggests that handwritten words, whose shape are unfamiliar and atypical, are not as good stimuli as printed words for the bottom-up activation of detectors for letters and other word fragments. However, when handwritten words remain visible for a sufficient duration, enough perceptual evidence can be gathered over time in the ventral cortex to reach an identification threshold (Heekeren et al., 2008). This increased processing time would result behaviorally in overall longer response latencies for handwritten than for printed words, and in a higher BOLD activation level.

Despite its overall left-predominance, the ventral network activated by handwritten targets was significantly less asymmetrical than the network for printed targets, mostly at a relatively anterior location (MNI $y = -44$) (irrespective of reading difficulty). Thus, handwriting appears to rely more extensively on the right-hemispheric visual system than printed script. A putative contribution of the right visual cortex to handwritten words is confirmed by subtle visual field asymmetries in behavioral studies. Hellige and Adamson (2007) showed that the additional perceptual difficulty of handwritten vs. printed words is smaller in the left than in the right visual hemifield. This asymmetry may relate to the general postulated role of the right hemisphere in holistic as opposed to analytic processing. Scant neuropsychological observations also indicate that patients with right ventral lesions may be impaired at identifying writers on the basis of their style, while word reading per se is spared (Regard and Landis, 1988). This suggests that the right ventral cortex contralateral to the anterior segment of the VWF area is sensitive to shape properties which are necessary to writer identification, but not to the invariant letter recognition. Indeed, priming tasks with split-field stimuli suggest that alphabetic strings are encoded in a more invariant format, less dependent on physical shape and case, when they are viewed in the RVF than in the LVF (Burgund and Marsolek, 1997; Marsolek et al., 1992, 1996). Accordingly, using a masked priming paradigm, Dehaene et al. (2001) have evidenced case-specific physical repetition priming in the right extrastriate cortex (for similar effects with object perception see Koutstaal et al., 2001). In the present study, as further discussed below, we found repetition priming across handwritten and printed styles only in the left, but not the right, ventral occipitotemporal cortex, further confirming that the left VWF area shows greater invariance properties than the right, and also suggesting that the right fusiform activations to handwritten words may relate to functions other than word identification per se.

Speculatively, one might also relate the greater bilaterality of visual activations to handwritten script to the more bilateral fusiform activations observed with Chinese and Japanese ideographic characters than for alphabetic stimuli (Bolger et al., 2005), as well perhaps as the greater right fusiform activation for Kanji than for Kana Japanese scripts (Nakamura et al., 2005). Although Chinese and Japanese characters now exist in print, in many common fonts their shape directly derives from the way in which they are handwritten.

Handwriting and attention networks

Our second goal was to examine the impact of the greater difficulty associated with reading handwriting upon the activation of ventral visual and dorsal attention networks. To this aim, we contrasted a difficult vs. an easy handwritten style, distinguished behaviorally by a drastically difference in mean reading times as well as the presence or absence of an effect of word length. At the brain activation level, schematically, going from easy to difficult handwritten targets had a comparable impact on activations as degrading words by means of rotation, spacing of letters, or displacement away from the optimal viewing position (Cohen et al., 2008). We observed a frontoparietal network, including bilateral intraparietal, anterior insula/Broca's area, inferior premotor cortex and SMA, plus an increase of ventral activations in the VWF area. Speculatively, these observations may reflect the need to deploy additional parietofrontal attentional networks to resolve the ambiguities associated with the difficult handwriting characters, as well as the subsequent attentional amplification of reading pathways under the control of dorsal cortex (Chawla et al., 1999; Kastner et al., 1998; Somers et al., 1999).

In Cohen et al. (2008), the peak of the VWF area amplification was relatively posterior (MNI $y = -70$), a location which is thought to encode the identity of single letters, according to the local combination detector model of the VWF system (Dehaene et al., 2005). We interpreted this effect as a need to return to serial letter-by-letter reading when printed words were degraded. In the present study, however, the effect of difficulty peaked in somewhat more anterior sectors of the VWF area (MNI $y = -60$ to -40). This may indicate that in order to decipher difficult handwritten words, readers emphasize the coding of larger groups of letters such as bigrams. Indeed, the ambiguity of individual handwritten letters is such that it presumably would not be helpful or even possible to perform letter-by-letter reading with such stimuli. For this very reason, pure alexic patients who resort to the letter-by-letter reading strategy are typically utterly unable to read handwritten materials.

While the difficulty of handwriting had a strong impact on activation elicited by target words, which were clearly visible, it is interesting to note that there was no corresponding increase in activation when this difficulty variable was manipulated across the subliminal primes, which were not consciously seen. In other words, primes written with the difficult script caused the same activation as primes written with the easy script. This observation suggests that only conscious targets could trigger the effortful serial attentional processes required for the identification of difficult handwriting.

Convergence of handwritten and printed words in the VWF area

The third issue which we addressed was the level of convergence and invariant representation of printed and handwritten words along the reading pathway. We expected that regions subtending a representation common to both formats should show cross-type repetition priming (i.e., between printed and handwritten versions of the same word). Indeed, the behavioral results showed significant priming, at least in trials with uppercase printed primes and handwritten targets. We therefore focused primarily on this contrast when analyzing the fMRI cross-type repetition effects. The main finding was that subliminal printed primes exert significant repetition suppression on handwritten targets around the main peak of the VWF area. This suggests that printed and handwritten words converge on an early prelexical representation in the ventral stream. The situation is thus similar to the convergence of lowercase and uppercase printed words (Dehaene et al., 2001, 2004; Devlin et al., 2004). The VWF area is likely to contain orthographic detectors sufficiently robust to be activated across large changes in script style, from familiar printed to difficult handwritten styles.

In contrast, in a masked priming experiment similar to the present one but with Japanese readers, Nakamura et al. (2005) found that the earliest convergence of Kanji and Kana words occurred downstream along the word processing pathway, in the posterior lateral temporal cortex, a region where Devlin et al. (2004) also found suppression between synonym words such as sofa-couch. Thus, not all word repetition effects originate from the VWF area. The present results, together with the past literature, suggest that this region specifically contributes to orthographic invariance, but not to phonological, lexical, or semantic resemblance.

Unconscious processing of handwritten words: repetition suppression and enhancement

When searching for cross-type priming, we focused primarily on the conditions where the subliminal prime was printed and the visible target was handwritten. This is because, in the converse direction, we expected little priming. Our reasoning was that if the identification of handwritten words, particularly in a difficult style, required attentional effort, then they should not reach high-level representation levels when presented subliminally. Behavioral results were congruent with this expectation, as handwritten primes did not facilitate responses to subsequent repeated target words. Accordingly, brain activations showed no repetition suppression. However, subliminal handwritten primes yielded significant repetition enhancement, mostly localized to the left ventral cortex. This leads to the conclusion that subliminal handwritten primes were actually processed at least up to an abstract orthographic level, although there was no trace of such processing in response time priming.

The classical interpretation of repetition suppression is that a subliminal prime is able to traverse part of the processing pathway prepared for the conscious task, and thus to provide partial, subthreshold evidence that acts as a bias at each of several successive processing stages (Dehaene, 2008). When the target in turn traverses the same series of stages, if it corresponds to the same word, less evidence needs to be accumulated before a decisive response threshold is reached, and hence both response time and activation level are reduced. This account nicely captures the present results, including the fact that greater savings were seen when the target was in a difficult handwritten script (which putatively provided less evidence per unit of time). The supplementary motor area, which is the only region that showed repetition suppression in all conditions where behavioral repetition priming occurred, may be one of the end stages where the accumulation of evidence towards an explicit motor decision eventually occurs. In that respect, the present repetition suppression data confirm previous reports that the activation induced by a subliminal prime can spread non-consciously through an entire series of processing stages, all the way to the motor level (Dehaene, 2008; Dehaene et al., 1998).

Repetition enhancement, conversely, seems to occur mostly under conditions where a degraded stimulus is initially hard to recognize, but is facilitated by repeated presentation (Henson, 2003; van Turennout et al., 2000; Wheatley et al., 2005). Turk-Browne et al. (2007) compared the presentation of repeated vs. novel scenes, while manipulating visual quality. With high-visibility scenes, they observed behavioral priming and RS in the parahippocampal place area (PPA). With low-visibility scenes, there was no behavioral repetition effect, while there was RE in the PPA cortex. Assuming an analogy between low-visibility pictures and handwritten words, and between high-visibility pictures and printed words, this pattern of results is remarkably parallel to the present study. Still, it is rather surprising to find RE under subliminal conditions as we did (for related data see Schnyer et al., 2002), because masking is thought to prevent long-duration reflective processes (for evidence of RE only under supraliminal conditions see Kouider et al., 2007). However, a tentative account of the present results may be proposed in terms of automatic backward priming. It may be suggested that handwritten primes challenge the word recognition system and thus initially induce only weak visual activations, just sufficient for some subjects to detect their presence better than chance, but not allowing for accurate word-specific encoding. Thus, this initial activation would not climb sufficiently high in the processing hierarchy to cause behavioral priming. The subsequent presentation of an identical and clearly visible printed word, however, would allow for a post-hoc top-down reinterpretation of the previous prime-induced activation. At this point, presumably posterior to the critical events leading to the response time, a backward reinterpretation of the initial prime-induced activation would occur, allowing it to progress in the visual recognition hierarchy, thus causing significantly more activation and therefore a repetition enhancement effect. Note that this interpretation capitalizes on the lack of temporal resolution of fMRI. It predicts that, if the present experiment was replicated with a time-resolved method such as electro- or magneto-encephalography, repetition suppression and enhancement effects would be seen at very different moments relative to prime presentation.

Another noteworthy aspect of the priming profile is that the RS/RE inversion also occurred for printed primes (although to a lesser extent). With printed words, we observed clear RS only in trials with uppercase primes and lowercase targets. There was no repetition suppression effect, and even a trend towards repetition enhancement, in trials with the opposite case succession (lowercase prime, uppercase target). This unexpected asymmetry in the results differs from the clear cross-case repetition suppression observed in previous studies of the same condition (Dehaene et al., 2004; Devlin et al., 2004; Kouider et al., 2007). What was different in the present experiment? By design, our experiment necessarily included an asymmetry in the frequency with which the different styles were consciously seen by the subjects (see Fig. 2). Half of the visible targets consisted of uppercase printed words, while only one sixth consisted of lowercase printed words (and another third of handwritten words). These differing amounts of conscious exposure to uppercase and lowercase words might have induced top-down changes in subjects' expectancies. There is now ample evidence that the cognitive set induced by conscious strategies affects the processing of subliminal stimuli and their impact on behavioral priming (Kiefer, 2007; Kunde et al., 2003; Naccache et al., 2002). Here, the high expected probability of uppercase targets may have facilitated the processing of masked uppercase primes and enhanced their priming effect. Tentatively, we may wonder whether this factor also played a causal role in the switch from fMRI repetition suppression to repetition enhancement for handwritten targets and primes. Clearly, however, we are lacking a detailed theory of neural and behavioral priming effects that could predict the occurrence and even the sign of these effects (for an emerging Bayesian framework for repetition effects see Friston, 2005).

We close this discussion by noting, however, that the sign of repetition effects is irrelevant when it comes to using fMRI repetition as a marker of access to an invariant neural code. In that respect, the occurrence of both repetition suppression and repetition enhancement within the left visual word form system, when the same word is successively presented in handwritten and in printed form, provides incontrovertible evidence that this area achieves invariant word recognition across remarkably different formats of word presentation.

Conclusion

The present study is the first to examine, at both behavioral and cerebral levels, the mechanisms underlying our remarkable ability to recognize handwritten words. Our results reveal, perhaps unsurprisingly, that handwritten words are less optimal stimuli than printed words and require more processing time. Interestingly, additional activation is seen in the ventral visual pathway, notably in the right hemisphere, whose exact contribution remains to be determined. Our most important conclusion, however, is that the left-hemispheric visual word form area (VWFA) appears capable of abstracting away from the extreme variations induced by handwriting. Subliminal fMRI repetition effects were observed across printed and handwritten styles, whether easy or difficult to read. Thus, the left inferotemporal VWFA possesses an unsuspected degree of fast and automatic visual invariance for handwritten words, although surprisingly this invariance can be reflected both as repetition suppression and as repetition enhancement.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.09.034.

References

Abrams, R.L., Greenwald, A.G., 2000. Parts outweigh the whole (word) in unconscious analysis of meaning. Psychol. Sci. 11, 118–124.

Ans, B., Carbonnel, S., Valdois, S., 1998. A connectionist multiple-trace memory model for polysyllabic word reading. Psychol. Rev. 105, 678–723.

Berwick, D.M., Winickoff, D.E., 1996. The truth about doctors' handwriting: a prospective study. Bmj 313, 1657–1658.

Besner, D., 1989. On the role of outline shape and word-specific visual pattern in the identification of function words:NONE Q. J. Exp. Psychol. 41A, 91–105.

Bolger, D.J., Perfetti, C.A., Schneider, W., 2005. Cross-cultural effect on the brain revisited: universal structures plus writing system variation. Hum. Brain Mapp. 25, 92–104.

Bowers, J.S., 2000. In defense of abstractionist theories of repetition priming and word identification. Psychon. Bull. Rev. 7, 83–99.

Burgund, E.D., Marsolek, C.J., 1997. Letter-case-specific priming in the right cerebral hemisphere with a form-specific perceptual identification task. Brain Cogn. 35, 239–258.

Chawla, D., Rees, G., Friston, K.J., 1999. The physiological basis of attentional modulation in extrastriate visual areas. Nat. Neurosci. 2, 671–676.

Cohen, L., Dehaene, S., Naccache, L., Lehéricy, S., Dehaene-Lambertz, G., Hénaff, M.A., Michel, F., 2000. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain 123, 291–307.

Cohen, L., Lehericy, S., Chochon, F., Lemer, C., Rivaud, S., Dehaene, S., 2002. Language-specific tuning of visual cortex? Functional properties of the visual word form area. Brain 125, 1054–1069.

Cohen, L., Dehaene, S., Vinckier, F., Jobert, A., Montavont, A., 2008. Reading normal and degraded words: contribution of the dorsal and ventral visual pathways. Neuroimage 40, 353–366.

Dehaene, S., 2008. Conscious and nonconscious processes: distinct forms of evidence accumulation? In: Engel, C., Singer, W. (Eds.), Decision making, the human mind, and implications for institutions. MIT Press, Cambridge, MA.

Dehaene, S., Naccache, L., Le Clec, H.G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., van de Moortele, P.F., Le Bihan, D., 1998. Imaging unconscious semantic priming. Nature 395, 597–600.

Dehaene, S., Naccache, L., Cohen, L., Bihan, D.L., Mangin, J.F., Poline, J.B., Riviere, D., 2001. Cerebral mechanisms of word masking and unconscious repetition priming. Nat. Neurosci. 4, 752–758.

Dehaene, S., Jobert, A., Naccache, L., Ciuciu, P., Poline, J.B., Le Bihan, D., Cohen, L., 2004. Letter binding and invariant recognition of masked words. Psychol. Sci. 15, 307–313.

Dehaene, S., Cohen, L., Sigman, M., Vinckier, F., 2005. The neural code for written words: a proposal. Trends Cogn. Sci. 9, 335–341.

Dejerine, J., 1892. Contribution à l'étude anatomo-pathologique et clinique des différentes variétés de cécité verbale. Mémoires de la Société de Biologie 4, 61–90.

Devlin, J.T., Jamison, H.L., Matthews, P.M., Gonnerman, L.M., 2004. Morphology and the internal structure of words. Proc. Natl. Acad. Sci. U. S. A. 101, 14984–14988.

Devlin, J.T., Jamison, H.L., Gonnerman, L.M., Matthews, P.M., 2006. The role of the posterior fusiform gyrus in reading. J. Cogn. Neurosci. 18, 911–922.

Friston, K., 2005. A theory of cortical responses. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360, 815–836.

Greenwald, A.G., Draine, S.C., Abrams, R.L., 1996. Three cognitive markers of unconscious semantic activation. Science 273, 1699–1702.

Grill-Spector, K., Malach, R., 2001. fMR-adaptation: a tool for studying the functional properties of human cortical neurons. Acta. Psychol. (Amst) 107, 293–321.

Heekeren, H.R., Marrett, S., Ungerleider, L.G., 2008. The neural systems that mediate human perceptual decision making. Nat. Rev. Neurosci. 9, 467–479.

Hellige, J.B., Adamson, M.M., 2007. Hemispheric differences in processing handwritten cursive. Brain Lang. 102, 215–227.

Henson, R.N., 2003. Neuroimaging studies of priming. Prog. Neurobiol. 70, 53–81.

Jobard, G., Crivello, F., Tzourio-Mazoyer, N., 2003. Evaluation of the dual route theory of reading: a metanalysis of 35 neuroimaging studies. Neuroimage 20, 693–712.

Kastner, S., De Weerd, P., Desimone, R., Ungerleider, L.G., 1998. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. Science 282, 108–111.

Kiefer, M., 2007. Top-down modulation of unconscious 'automatic' processes: a gating framework. Adv. Cogn. Psychol. 3, 289–306.

Kouider, S., Dehaene, S., Jobert, A., Le Bihan, D., 2007. Cerebral bases of subliminal and supraliminal priming during reading. Cereb. Cortex 17, 2019–2029.

Koutstaal, W., Wagner, A.D., Rotte, M., Maril, A., Buckner, R.L., Schacter, D.L., 2001. Perceptual specificity in visual object priming: functional magnetic resonance imaging evidence for a laterality difference in fusiform Cortex. Neuropsychologia 39, 184–199.

Kunde, W., Kiesel, A., Hoffmann, J., 2003. Conscious control over the content of unconscious cognition. Cognition 88, 223–242.

Lavidor, M., 2002. An examination of the lateralized abstractive/form specific model using MiXeD-CaSe primes. Brain Cogn. 48, 413–417.

Longcamp, M., Tanskanen, T., Hari, R., 2006. The imprint of action: motor cortex involvement in visual perception of handwritten letters. Neuroimage 33, 681–688.

Marsolek, C.J., Kosslyn, S.M., Squire, L.R., 1992. Form-specific visual priming in the right cerebral hemisphere. J. Exp. Psychol. Learn. Mem. Cogn. 18, 492–508.

Marsolek, C.J., Schacter, D.L., Nicholas, C.D., 1996. Form-specific visual priming for new associations in the right cerebral hemisphere. Mem. Cognit. 24, 539–556.

Mayall, K., Humphreys, G.W., Olson, A., 1997. Disruption to word or letter processing? The origins of case-mixing effects. J. Exp. Psychol. Learn. Mem. Cogn. 23, 1275–1286.

Mayall, K., Humphreys, G.W., Mechelli, A., Olson, A., Price, C.J., 2001. The effects of case mixing on word recognition: evidence from a PET study. J. Cogn. Neurosci. 13, 844–853.

McCandliss, B.D., Cohen, L., Dehaene, S., 2003. The visual word form area: expertise for reading in the fusiform gyrus. Trends Cogn. Sci. 7, 293–299.

McMahon, D.B., Olson, C.R., 2007. Repetition suppression in monkey inferotemporal cortex: relation to behavioral priming. J. Neurophysiol. 97, 3532–3543.

Naccache, L., Dehaene, S., 2001. The priming method: imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. Cereb. Cortex 11, 966–974.

Naccache, L., Blandin, E., Dehaene, S., 2002. Unconscious masked priming depends on temporal attention. Psychol. Sci. 13, 416–424.

Nakamura, K., Dehaene, S., Jobert, A., Le Bihan, D., Kouider, S., 2005. Subliminal convergence of Kanji and Kana words: further evidence for functional parcellation of the posterior temporal cortex in visual word perception. J. Cogn. Neurosci. 17, 954–968.

New, B., Pallier, C., Brysbaert, M., Ferrand, L., 2004. Lexique 2: a new French lexical database. Behav. Res. Methods Instrum. Comput. 36, 516–524.

Paap, K.R., Newsome, S.L., Noel, R.W., 1984. Word shape's in poor shape for the race to the lexicon. J. Exp. Psychol. Hum. Percept. Perform. 10, 413–428.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98, 676–682.

Regard, M., Landis, T., 1988. Two cases of prosopagnosia and alexia. I. Neuropsychological Findings in Advances in the Biosciences. Pergamon, New York.

Reicher, G.M., 1969. Perceptual recognition as a function of meaningfulness of stimulus material. J. Exp. Psychol. 81, 274–280.

Schnyer, D.M., Ryan, L., Trouard, T., Forster, K., 2002. Masked word repetition results in increased fMRI signal: a framework for understanding signal changes in priming. Neuroreport 13, 281–284.

Shaywitz, B.A., Shaywitz, S.E., Blachman, B.A., Pugh, K.R., Fulbright, R.K., Skudlarski, P., Mencl, W.E., Constable, R.T., Holahan, J.M., Marchione, K.E., et al., 2004. Development of left occipitotemporal systems for skilled reading in children after a phonologically-based intervention. Biol. Psychiatry 55, 926–933.

Somers, D.C., Dale, A.M., Seiffert, A.E., Tootell, R.B.H., 1999. Functional MRI reveals spatially specific attentional modulation in human primary visual Cortex. Proc. Natl. Acad. Sci. U. S. A. 96, 1663–1668.

Sternberg, S., 1998. Discovering mental processing stages: the method of additive factors. In: Scarborough, D., Sternberg, S. (Eds.), An invitation to cognitive science: methods, models, and conceptual issues. MA, MIT Press, Cambridge, pp. 703–863.

Stoodley, C.J., Schmahmann, J.D., 2009. Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. Neuroimage 44, 489–501.

Tenpenny, P.L., 1995. Abstractionist versus episodic theories of repetition priming and word identification. Psychon. Bull. Rev. 2, 339–363.

Turk-Browne, N.B., Yi, D.J., Leber, A.B., Chun, M.M., 2007. Visual quality determines the direction of neural repetition effects. Cereb. Cortex 17, 425–433.

van Turennout, M., Ellmore, T., Martin, A., 2000. Long-lasting cortical plasticity in the object naming system. Nat. Neurosci. 3, 1329–1334.

Vinckier, F., Naccache, L., Papeix, C., Forget, J., Hahn-Barma, V., Dehaene, S., Cohen, L., 2006. “What” and “Where” in word reading: ventral coding of written words revealed by parietal atrophy. J. Cogn. Neurosci. 18, 1998–2012.

Weekes, B.S., 1997. Differential effects of number of letters on word and nonword naming latency. Q. J. Exp. Psychol. 50A, 439–456.

Wheatley, T., Weisberg, J., Beauchamp, M.S., Martin, A., 2005. Automatic priming of semantically related words reduces activity in the fusiform gyrus. J. Cogn. Neurosci. 17, 1871–1885.