The "Special Effect" of Case Mixing on Word Identification: Neuropsychological and Transcranial Magnetic Stimulation Studies Dissociating Case Mixing from Contrast Reduction

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Abstract

■ We present neuropsychological and transcranial magnetic stimulation (TMS) evidence with normal readers, that the effects of case mixing and contrast reduction on word identification are qualitatively different. Lesions and TMS applied to the right parietal lobe selectively disrupted the identification of mixed relative to single-case stimuli. Bilateral lesions and TMS applied to the occipital cortex selectively disrupted the identification of low-contrast words. These data suggest that different visual distortions (case mixing, contrast reduction) exert different effects on reading, modulated by contrasting brain regions. Case mixing is a "special" distortion and involves the recruitment of processes that are functionally distinct, and dependent on different regions in the brain, from those required to deal with contrast reduction. ■

INTRODUCTION

Studies of visual processes involved in skilled reading have frequently assessed the effects of visual format on word identification (e.g., Cornelissen, Tarkiainen, Helenius, & Salmelin, 2003; Mayall, Humphreys, & Olson, 1997; Ellis & Young, 1996; Coltheart, 1987; McClelland, 1977). Formats that distort the visual information used to recognize words should disrupt performance more than those that do not. One manipulation commonly used is that of case mixing. Words presented in mixed case take longer to read, and are more prone to errors, than words presented in familiar single case (Mayall & Humphreys, 2002; Mewhort & Johns, 1988). Effects of presenting letters in different cases are more severe than those of presenting letters in contrasting sizes (Mayall et al., 1997), suggesting that familiarity of co-occuring letter shapes contributes to word recognition (Whiteley & Walker, 1997; Treiman, Mullennix, Bijeljacbabic, & Richmondwelty, 1995; Greenberg & Vellutino, 1988; Treiman & Chafetz, 1987; Taft, 1979; Spoehr & Smith, 1973). For example, the visual description mediating skilled word recognition may comprise groups of familiar letter features, in addition to individual letter identities (Mayall, Humphreys, Mechelli, Olson, & Price, 2001; Mayall et al., 1997). However, at least part of the disruptive effect of case mixing may come about through visual degradation of the letter features, for example, because of lateral masking of large letters on small letters (Besner & Johnston, 1989).

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To argue that case mixing exerts a selective effect on the visual information used in reading, it is important to demonstrate that manipulations of case disrupt word identification in a manner that is qualitatively different from general effects of visual distortion. One way to do this is to show that different brain regions are recruited to deal with the processing of mixed-case words and with other forms of distortion (e.g., lowered contrast), when the two forms of distortion have been matched for difficulty. If the same processes are required to deal with all effects of distortion, then the same neural structures should be involved in all instances (at least provided that one form of distortion is not generally more difficult than the other, when additional brain regions may be recruited). We present evidence from neuropsychological patients and from the effects of transcranial magnetic stimulation (TMS) with normal readers, demonstrating that different neural regions modulate the effects of case mixing and effects of contrast reduction on word recognition. The data suggest that case mixing exerts a "special effect" on reading, consistent with a specific effect on the visual description used for word identification.

We report two experiments. In Experiment 1, we document the reading of three patients, two with damage to parietal cortex (G.K. and F.L.) and one with damage to the ventral occipital cortex (H.J.A.). The parietal patients were severely impaired at identifying words in mixed compared with lowercase, but showed no greater effects of contrast reduction than control participants. The occipital patient, however, showed a much less marked effect of case mixing while manifesting a strong effect of contrast reduction. In Experiment 2, we report converging evidence from the effects of TMS applied to the parietal and occipital cortex of normal readers.

EXPERIMENT 1: NEUROPSYCHOLOGICAL EVIDENCE

Prior neuropsychological evidence has demonstrated that patients with forms of peripheral dyslexia (Riddoch, 1990) can be selectively disrupted when words are presented in mixed compared with single case. This has been found in patients with attentional dyslexia following bilateral parietal damage (Hall, Humphreys, & Cooper, 2001; Humphreys & Mayall, 2001; Baylis, Driver, Baylis, & Rafal, 1994), and in patients with letter-by-letter reading after ventral occipito-temporal damage (Osswald, Humphreys, & Olson, 2002; Warrington & Shallice, 1980). The relative magnitude of the effects of case mixing on these different patients has never previously been examined, although in attentional dyslexia, the effects are typically expressed in accuracy, whereas in letter-by-letter readers, the effects are expressed in latencies. Hence, we might expect that effects are more substantial in attentional dyslexia (i.e., following bilateral parietal damage). The effects of contrast reduction in the two classes of patient have not been studied before. Here, we compare the effects of contrast reduction (Experiment 1a) and case mixing (Experiments 1b and 1c) on the two types of patient.

Methods

Three subexperiments are reported, evaluating the effects of manipulating contrast (Experiment 1a) or case mixing (Experiments 1b and 1c) on reading. We examined two patients with bilateral parietal lesions and one patient with occipital lesions, as well as a group of age-matched controls. Participants were required to name words as fast and as accurately as they could. In the contrast experiment, words were presented in single case, in either low or high contrast. In the case experiment, the words were presented in high- (Experiment 1b) or low contrast (Experiment 1c), either in single or mixed case.

Participants

G.K. G.K. was born in 1936 and left school at the age of 14 years. He was a businessman who started a successful import–export company and often traveled overseas. In 1986, he suffered two strokes, which occurred 3 months apart. This resulted in lesions of (1) the right temporo-parietal region, (2) the right occipito-parietal region, and (3) the left temporo-parietal region (see the study of Gilchrist, Humphreys, & Riddoch, 1996, for a magnetic resonance imaging [MRI] scan). Following the second stroke, G.K. was temporarily cortically blind and aphasic, but these difficulties recovered over time. G.K. presented a number of neuropsychological problems including: Balint's syndrome (simultanagnosia and optic ataxia, see the studies of Edwards & Humphreys, 2002; Cooper & Humphreys, 2000; Balint, 1909), left neglect and extinction (Gilchrist et al., 1996), and attentional dyslexia (Hall et al., 2001). G.K. was able to read many single words (making occasional left neglect errors), but he could not read aloud the constituent letters of the words. Nonword reading was impossible.

F.L. F.L. was born in 1936 and was a carpenter. He suffered carbon monoxide poisoning in 1994, which resulted in lesions of the left intraparietal sulcus and bilateral damage to the lateral occipital gyrus and lenticular nuclei (see the work of Humphreys & Forde, 1998, for an MRI scan). This led initially to severe memory problems, a low-level agnosia, and difficulties in word recognition. By the time of testing for this article, the agnosia had largely resolved, although memory problems and difficulties in word recognition remained. Like G.K., F.L. presents as an attentional dyslexic, with better reading of words than their constituent letters (Mayall & Humphreys, 2002).

H.J.A. H.J.A. was born in 1920 and suffered a stroke in 1981, which resulted in bilateral ventral occipital lesions, including the lingual, fusiform, and occipito-temporal gyri (see the study of Riddoch, Humphreys, Gannon, Blott, & Jones, 1999, for an MRI scan). After the stroke, H.J.A. had severe problems in the visual recognition of faces and common objects, as well as photographs and line drawings. Drawing and writing were relatively intact. H.J.A. had achromotopsia, normal visual acuity, and a superior altitudinal field deficit of both the left and right visual fields, whereas the lower visual field was spared. H.J.A. reads in a letter by letter fashion, showing abnormally pronounced effects of word length on reading (Humphreys & Riddoch, 1987).

Controls

The performance of the patients was compared with two groups of five controls. For Experiment 1a (contrast), the mean age of the controls was 69 years old (SD = 10). The controls for Experiment 1b (case, high contrast) had a mean age of 66 years old (SD = 13). The controls for Experiment 1c (case, low contrast) had a mean age of 71 years old (SD = 6).

Apparatus and Stimuli

For both subexperiments, the stimuli were presented on a 17-in. Samsung 753s-monitor at an approximate viewing distance of 70 cm using E-Prime software (Psychology Software Tools, Pittsburgh, PA) ran on a Pentium 4

(1.8 GHz). The stimuli for both experiments were generated using the same software used by Mayall et al. (2001) and were light gray on a dark gray background (low-contrast condition in Experiment 1a) or white on a dark gray background (high contrast in Experiment 1a, and both conditions in Experiment 1b).

Subexperiments 1a and 1b both used two lists of 100 six-letter words, with the mean frequency of occurrence of respectively 156 and 145 occurrences per million (Kucera & Francis, 1967). These lists were assigned to the different conditions within an experiment, so that each participant would see each word twice, once in Experiment 1a and once in Experiment 1b. Data collection for Experiment 1a occurred at least 6 months after Experiment 1b, making any effects of learning unlikely. All the patients had stable long-term deficits, and showed equivalent performance in the conditions that matched across the subexperiments, with high-contrast, same case words. Experiment 1c used two lists of 50 six-letter words, with a mean frequency of 47 and 52 occurrences per million.

Procedure

Both Experiments 1a and 1b consisted of 200 trials;[1] Experiment 1c had 100 trials. For Experiment 1a, half of the trials were presented in low contrast and half in high contrast. For Experiments 1b and 1c, half of the trials were presented in single case, with the other half presented in mixed case. Only high-contrast stimuli were used in Experiment 1b, and only low-contrast stimuli were used in Experiment 1c. Every trial started with a 1-sec fixation cross in the center of the screen. The cross was then replaced with the stimulus word. Participants were asked to name the word as quickly and as accurately as possible. A verbal response (naming the word) was then registered by the experimenter using the mouse to record reaction time (RT). The experimenter was blind to the stimuli being presented. This procedure was used, rather than using a voice key to trigger the responses, because the patients generated very long RTs (particularly G.K.), and there were problems with the voice key sometimes being triggered inadvertently. Also, given the long RTs, any inaccuracy due to responding to the patient's verbal output was minimal, relative to the variance across trials. Responses were scored as correct or incorrect.

Results

The data for the controls were analyzed as a repeated measures analysis of variance (ANOVA), with difficulty as a within-subjects factor (high vs. low contrast in Experiment 1a and single vs. mixed case in Experiments 1b and 1c) and degradation type as a between-subjects factor with three levels (contrast, case [high contrast], or case [low contrast] in Experiments 1a, 1b, and 1c, respectively).

The accuracy data for each patient were analyzed separately using χ^2 to test whether performance differed for effects of contrast (Experiment 1a) or for case mixing (Experiments 1b and 1c). The patients' RTs were analyzed separately for the three subexperiments in between-subjects ANOVAs with each RT treated as a separate subject and with contrast or case (Experiment 1a or 1b and 1c respectively) as within-subjects and patient as the between-subjects variable.

Controls

Reaction time. There were significant main effects of degradation type, $F(2,12) = 9.7$, $p = .003$, and difficulty, $F(1,12) = 33$, $p < .001$. The interaction of type and difficulty was not significant, $F(1,8) = 1.4$, $p = .29$. RTs were overall slower in Experiment 1a (with a contrast manipulation) compared with Experiment 1b (case manipulation), and were slower still in Experiment 1c (low-contrast case manipulation). In each instance participants were slower to respond to the more difficult condition: low contrast (cf. high contrast) in Experiment 1a, and mixed case (cf. lowercase) in Experiments 1b and 1c.

Accuracy. There were no significant effects (all effects $F < 1$). Errors were very low (less than 1% in all conditions).

Patients: Effects of Contrast

Reaction time. There was a significant effect of contrast on RTs in Experiment 1a, $F(1,188) = 65.34$, $p < .001$, as well as a significant effect of patient, $F(2,188) = 64.03$, $p < .001$. The interaction between contrast and patient was also significant, $F(2,188) = 36.23$, $p < .001$. When comparing the individual patients, this Contrast × Patient interaction was significant for G.K. versus H.J.A., $F(1,107) = 66.75$, $p < .001$, as well as for F.L. versus H.J.A., $F(1,124) = 65.63$, $p < .001$. However, this interaction was not significant for a comparison between the two parietal patients ($F < 1$). H.J.A. showed larger effects of contrast than the two parietal patients.

Accuracy. There was a significant difference in accuracy for words presented in low and high contrast for H.J.A., $\chi^2(1) = 47.43$, $p < .001$; there was no effect of contrast for either of the parietal patients, both $\chi^2(1) < 1$. H.J.A. made more errors for words presented in low contrast, compared with high contrast (Table 1).

Patients: Effects of Case Under High-contrast Conditions

Reaction time. For naming latencies, there were significant main effects of case in Experiment 1b, $F(1,188) =$

Table 1. Accuracy (%, in boldface) and RT (sec, in italics) Data for Experiments 1a (Low vs. High Contrast), 1b (Single vs. Mixed Case, All in High Contrast), and 1c (Single vs. Mixed Case, All in Low Contrast)

Patient	*Lesion*	*Low Contrast*	*High Contrast*	*Single Case (High Contrast)*	*Mixed Case (High Contrast)*	*Single Case (Low Contrast)*	*Mixed Case (Low Contrast)*
G.K.	Parietal	**65**	**67**	**67**	**34**	**56**	**24**
		7.9	*7.5*	*11.4*	*19.2*	*16.7*	*25.0*
F.L.	Parietal	**82**	**84**	**84**	**60**	**78**	**52**
		4.0	*3.7*	*2.7*	*4.0*	*5.0*	*6.1*
H.J.A.	Occipital	**44.4**	**97.2**	**97**	**99**	**68**	**64**
		15.2	*5.4*	*3.9*	*5.0*	*12.1*	*12.9*
Controls	None	**99.6**	**99.8**	**100**	**99.2**	**100**	**98.5**
		1.5	*1.4*	*1.1*	*1.2*	*1.7*	*1.8*

27.08, $p < .001$, as well as patient, $F(2,188) = 97.34$, $p < .001$. The interaction between case and patient was also significant, $F(2,188) = 9.93$, $p < .001$. When comparing the individual patients, the Case × Patient interaction was significant for G.K. compared with the two other patients [vs. F.L.: $F(1,92) = 7.22$, $p = .009$; vs. H.J.A.: $F(1,129) = 13.79$, $p < .001$]. G.K. showed particularly large effects of case mixing on reading latency. Both parietal patients showed a reliable effect of case mixing on reading speed [G.K.: $t(33) = 2.8$, $p = .008$; F.L.: $t(59) = 3.74$, $p < .001$]. Although H.J.A. was also slower with mixed than single-case words, this difference was not reliable, $t(96) = 1.09$, $p = .279$.

Accuracy. Both of the parietal patients were less accurate at reading mixed than single-case words, $\chi^2(1) = 14.29$, $p < .001$ for F.L., and $\chi^2(1) = 21.78$, $p < .001$ for G.K. There was no effect of case on H.J.A.'s reading accuracy ($p = .621$, Fisher's Exact test).

Patients: Effects of Case Under Low-contrast Conditions

Reaction time. There were significant main effects of case on naming times in Experiment 1c, $F(1,60) = 11.09$, $p = .001$, as well as a main effect of patient, $F(2,60) = 42.77$, $p < .001$. There was a trend for an interaction between case and patient, $F(2,60) = 2.93$, $p = .061$. Comparisons were made between the individual patients. The Case × Patient interaction was borderline significant for G.K. compared with the two other patients [vs. F.L.: $F(1,36) = 4.3$, $p = .045$; vs. H.J.A.: $F(1,35) = 3.94$, $p = .055$]. As in Experiment 1b, G.K. showed particularly large effects of case mixing on reading latency. The case mixing effect was reliable for G.K., $t(11) = 2.22$, $p = .024$, on a one-tailed paired t test, and marginally reliable for F.L., $t(25) = 1.45$, $p = .081$. The case effect did not approach significance for H.J.A. ($t < 1$).

Accuracy. Both of the parietal patients were also less accurate at reading mixed than single-case words, $\chi^2(1) = 14.86$, $p < .001$ for F.L., and $\chi^2(1) = 21.33$, $p < .001$ for G.K. There was no effect of case on H.J.A.'s reading accuracy, $\chi^2(1) = 2.65$, $p = .104$.

Case Effect Under High and Low Contrast

We compared the patient data for Experiments 1b and 1c to test if the effects of case mixing and contrast reduction are additive or interactive. Naming latencies were analyzed for each patient as a between-subjects repeated measures ANOVA, with each RT treated as a separate subject, case (single or mixed) as within-subjects variable, and experiment (1b: high contrast; 1c: low contrast) as the between-subjects variable. The interaction between case and experiment was not significant for any of the three patients (all $F < 1$).

Accuracy data for each patient separately were analyzed in a log linear analysis, with case and experiment as factors. For the two parietal patients, G.K. and F.L., the final model contained a significant interaction between accuracy and case, $\chi^2(1) = 43.46$, $p < .001$, and $\chi^2(1) = 29.57$, $p < .001$, respectively, but this interaction was not significant for the occipital patient H.J.A. In addition, G.K. and H.J.A. showed a significant interaction between accuracy and experiment [for G.K.: $\chi^2(1) = 4.46$, $p = .035$; H.J.A.: $\chi^2(1) = 81.49$, $p < .001$], indicating that they made more errors overall under low-contrast conditions. Crucially though, none of the patients showed a significant interaction between case and experiment, showing that the effects of both manipulations were additive for the conditions used in this study.

Discussion

The results show a clear double dissociation between lesion site and the type of visual manipulation (case or contrast). The two patients with parietal lesions (G.K. and F.L.) showed a marked impairment when reading mixed-case words relative to single-case words in both accuracy and naming latency. This replicates previous results with both patients (Hall et al., 2001; Humphreys & Mayall, 2001). The parietal patients were slower to read low-contrast words compared with high-contrast words (in Experiment 1a and in Experiment 1c cf. Experiment 1b), but crucially, there was no interaction between case and contrast. In addition, neither of the parietal patients showed any detrimental effect on accuracy when the stimuli were presented in low contrast, compared with high contrast.

Importantly, the effects of case mixing were much larger on the parietal patients than on the controls, even when the effects were scaled by the RTs to read single-case words (to equate for differences in baseline RTs between the patients and the controls). For G.K., the effect size was 168% and 150% of his baseline RTs in Experiments 1b and 1c, respectively. For F.L., there was an effect size of 146% and 123%, respectively. For controls, the effect size was 106% of their baseline RTs in both Experiments 1b and 1c. The effects of contrast, on the other hand, were roughly the same on the parietal patients and the controls, when performance was scaled by the baseline RTs (effect sizes in Experiment 1a: 106% for G.K., 109% for F.L., and 107%, SD = 3.9, for the controls).

The data for the parietal patients differed from those for the ventral occipital patient, H.J.A. H.J.A. showed relatively small effects of case mixing. There was no effect on his reading accuracy. Case mixing did slow his RTs, and the effect size was somewhat larger than in the controls, even with RTs scaled by baseline latencies. Nevertheless, the effect size for H.J.A. was substantially less than that of the parietal patients (an effect size of 128% for H.J.A.). However, although the case effects for H.J.A. were modest, the effects of contrast reduction were striking. In Experiment 1a, there was a 53% drop in accuracy, and RTs to read low-contrast words were more than double those to identify high-contrast words (effect size = 253%). The difference between H.J.A.'s performance with low- and high-contrast words in Experiments 1b and 1c was slightly less marked (a 33% drop in accuracy for low-contrast words, in Experiment 1c, although RTs were over two times slower), but it was still pronounced. The data indicate that H.J.A. is highly sensitive to contrast reduction and relatively less sensitive to case mixing; on the other hand, the parietal patients are highly sensitive to case mixing and relatively less sensitive to contrast reduction.

The reduced effects of contrast reduction, when comparing across Experiments 1b and 1c, relative to the effects of Experiment 1a, are likely because contrast was blocked in Experiments 1b and 1c. This may have allowed contrast effects to become accommodated to some degree, relative to when contrast varied across trials (Experiment 1a).

In addition to these selective effects of case and contrast, there was also an overall difference on reading accuracy across the patients, with G.K. being overall worse than F.L. and H.J.A. This is likely because G.K.'s reading is affected by spatial neglect, as well as by his attentional dyslexia, leading him to make errors even with high-contrast, same-case words (Hall et al., 2001). This overall difference though is not critical to the assessments of the way that contrast and case impact on G.K.'s reading.

EXPERIMENT 2: EFFECTS OF TRANSCRANIAL MAGNETIC STIMULATION

Although the neuropsychological data are interesting, the individual patients do not present the clearest evidence for the localization of the effects. G.K. has lesions that involve occipito-parietal as well as temporo-parietal regions. F.L. suffered carbon monoxide poisoning, which typically produces multiple disseminated lesions, and although the clearest damage is to the left parietal cortex, there are lesions elsewhere. In addition, it cannot be ruled out that the different sensitivities we observed for changes in contrast or case mixing may be because of different strategies for reading adopted by the patients after some degree of cortical reorganization to compensate for the lesions. For example, H.J.A. may have adopted letter-by-letter reading in compensation for an impairment in identifying whole word forms (Humphreys & Riddoch, 1987), and this could reduce effects of case mixing on performance. To provide converging evidence on the roles of the occipital and parietal cortex in modulating effects of contrast and case mixing, Experiment 2 was carried out. Here, we applied TMS to the occipital and parietal regions in control participants, comparing the effects on reading with that produced by sham stimulation. TMS disrupts cortical activity only briefly, making it unlikely that any effects observed here may be because of cortical reorganization or long-term changes in reading strategy. Previous TMS studies have demonstrated that there can be raised visual contrast thresholds following stimulation of the occipital pole (Paulus, Korinth, Wischler, & Tergau, 1999; Kammer & Nussek, 1998). Effects of occipital stimulation on reading have also been reported by Lavidor and Walsh (2004) and Lavidor, Ellison, and Walsh (2003). We may expect then that occipital stimulation would increase effects of contrast reduction on reading. On the other hand, Braet and Humphreys (2006) have found that the effects of case mixing are increased when TMS is applied to the right parietal lobe. However, the influence of parietal stimulation on the effects of contrast or of occipital stimulation on case mixing has not been examined. Mayall et al. (2001; see also Mechelli et al., 2000) have assessed the effects of case mixing and contrast using positron emission tomography (PET). They found that mixed-case stimuli generated increased activation in the right superior parietal lobe, whereas contrast reduction generated increased activation in the lingual gyrus (along with decreased activity in the fusiform gyrus). These data suggest that effects of case and contrast are modulated by different brain regions in normal readers, but they do not show the necessary involvement of the different regions in the two effects. This was tested here.

Methods

Participants were required to name words as fast and accurately as they could. In the contrast experiment (Experiment 2a), words were presented in single case, in either low or high contrast. In the case experiment (Experiment 2b), the words were presented in low contrast, either in single or mixed case. Both experiments contrasted the effects of stimulation of the occipital pole (V1), the right posterior parietal lobe, or sham TMS over the vertex.

The TMS experiments differ from the conditions used for the patients in the following ways: The stimuli were presented briefly and were replaced by a blank background until the participant made a response, and low-contrast stimuli were used when the effects of case mixing were examined. This was done because we have previously failed to obtain TMS effects on mixed-case stimuli, when the stimuli were presented in high contrast for an unlimited duration (see Braet & Humphreys, 2006, Experiment 1). This may be because, unless the stimuli were presented under challenging visual conditions, performance on the naming task was too easy to be disrupted with the stimulation used.

Participants

Experiment 2a (contrast) involved eight participants (five men, three women), aged between 18 and 37 years old. Experiment 2b (case) had 10 participants, aged 18–22 years old, of whom two were men. Participants who had not taken part in TMS studies before were given an information leaflet explaining the procedures before deciding whether to participate. All participants gave written consent to participate, were native speakers of English, had normal or corrected-to-normal vision, and reported an absence of epilepsy or other neurological disorders in themselves or immediate members of their family (first-degree relatives). The study had approval of the local ethics committee and conformed to the Declaration of Helsinki (1964) and safety procedures for repetitive TMS as outlined by Wasserman (1998).

Apparatus and Stimuli

For both subexperiments, the stimuli were presented on a 17-in. Gateway VX720 monitor at an approximate viewing distance of 100 cm, using E-Prime software (Psychology Software Tools) run on a Pentium 4 (1.8 GHz). The stimuli were generated using the same software as in the study of Mayall et al. (2001) and were light gray (low contrast in Experiment 2a and 2b) or white (high contrast in Experiment 2a only) on a dark gray background (3.1° visual angle). All stimuli were presented in the center of the screen for 200 msec.

Each subexperiment used six lists of 50 six-letter words, with a mean frequency of respectively 55, 49, 47, 52, 48, and 53 occurrences per million (Kucera & Francis, 1967). These lists were assigned to the different conditions within an experiment, which were counterbalanced over participants, so that for any participant, each individual word would be presented once.

Stimulation

The stimulator used was a Magstim Rapid with two external boosters, in conjunction with a double circular 70-mm coil, which produces a maximum output of 2.2 T. With this coil configuration, the magnetic fields generated by both halves of the coil will add up, ensuring that the induced current is strongest in the region directly beneath the center of the coil (Jalinous, 1998).

Before the first experimental block, each participant's individual motor threshold (MT) was established by finding the lowest stimulation intensity at which finger movements could be elicited reliably to visual observation with single-pulse stimulation of the motor cortex. The stimulation during both experiments involved a train of three TMS pulses with an interpulse interval of 50 msec with the first pulse occurring 50 msec before stimulus onset. The total number of TMS pulses in an experiment was 900 (including 300 pulses of sham TMS), with an intertrial interval of 1 sec + the RT of the participant.[2] Stimulation intensity was 10% below individual MT. For Experiment 2a (contrast), the average stimulation intensity was 47% (SD = 6) of stimulator output; for Experiment 2b (case), it was 46% (SD = 12). The coil was replaced after every block of 300 pulses to prevent overheating.

In both experiments, three stimulation sites were used: occipital, parietal, and sham vertex. For occipital stimulation, the center of the coil was placed 3 cm above the inion, with the handle of the coil pointing upward so that induced current would flow anterior posterior. For parietal stimulation, the center of the coil was placed over the same scalp coordinates where we have previously found case-specific effects (Braet & Humphreys, 2006) close to P4 in the 10-20 electrode system. Induced current flow for this site was posterior–anterior and lateral–medial toward the vertex. In the sham condition, the coil was held over the vertex, but angled tangentially to the skull so that any cortical effects are unlikely to occur and was included to control for nonspecific effects of TMS, such as caused by the sound (see Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001, for an evaluation of sham TMS). Both the parietal site and the vertex (Cz in the 10-20 electrode system) were marked on an electrode cap before the experiment taking place. The occipital site (3 cm anterior to the inion) was determined at the start of the experiment for each participant.

Procedure

Both subexperiments consisted of three blocks (parietal stimulation, occipital stimulation, and sham) for each of 100 trials, the order of which was counterbalanced across participants. The three blocks were always completed within a single session of testing.

In Experiment 2a, half of the trials contained words in low contrast and half in high contrast, all in the same case. In Experiment 2b, half the items were single case and half were mixed case, all in the same contrast. There were 50 trials in each condition in each subexperiment. TMS was administered on each trial. Trials were presented in a semirandom order (randomized before the experiment) for each experiment.

Every trial started with a 1-sec fixation cross in the center of the screen that was then replaced with the stimulus word that participants were asked to name as quickly and accurately as possible. Response latencies were measured with a voice key,[3] and accuracy was scored manually.

The stimulus words remained on the screen for only 200 msec and were then replaced by a blank screen, which stayed on until the participant gave a response.

Results

The data for each subexperiment were analyzed in a repeated measures ANOVA, with site of stimulation (V1, parietal, or sham) and difficulty (low vs. high contrast or mixed vs. single case for Experiments 2a and 2b, respectively) as within-subjects factors. Task (contrast manipulation or case manipulation) was included as a between-subjects variable. RTs and errors were analyzed separately.

Reaction Time

There was a significant main effect of difficulty, $F(1,16) = 26.97$, $p < .001$, with overall slower RTs in the more difficult condition (low contrast for Experiment 2a: 601 vs. 580 msec for high-contrast stimuli; mixed case for Experiment 2b: 613 vs. 589 msec for lowercase stimuli). No other main effects or interactions were significant (all $F < 1$).

Accuracy

There was a significant main effect of difficulty, $F(1,16) = 21.59$, $p < .001$, but not stimulation site ($F < 1$). There was a trend for a main effect of type of degradation, $F(1,16) = 3.34$, $p = .086$. There were trends for an interaction between site and difficulty, $F(2,32) = 3.25$, $p = .052$, and for the interaction between difficulty and type of degradation, $F(1,16) = 3.42$, $p = .083$. The three-way interaction among degradation type, site, and difficulty was found to be significant, $F(2,32) = 19.33$, $p < .001$. This interaction was broken down by examining the effects of each type of degradation separately.

Contrast

There was a significant main effect of contrast, $F(1,7) = 11.39$, $p = .012$, but not site, $F(2,14) = 3.07$, $p = .078$. The interaction between site and contrast was also significant, $F(2,14) = 6.54$, $p = .01$. This Site × Contrast interaction was significant for the comparison between occipital (V1) and sham stimulation, $F(1,7) = 4.24$, $p = .041$, and for the comparison between occipital (V1) and parietal stimulation, $F(1,7) = 18.67$, $p = .003$. It was not reliable for the comparison between sham and parietal stimulation ($F < 1$). TMS had a selective, disruptive effect on low-contrast words relative to high-contrast words when the occipital (V1) region was stimulated. This pattern was not found when stimulating either the parietal site or when using sham TMS (see Figure 1).

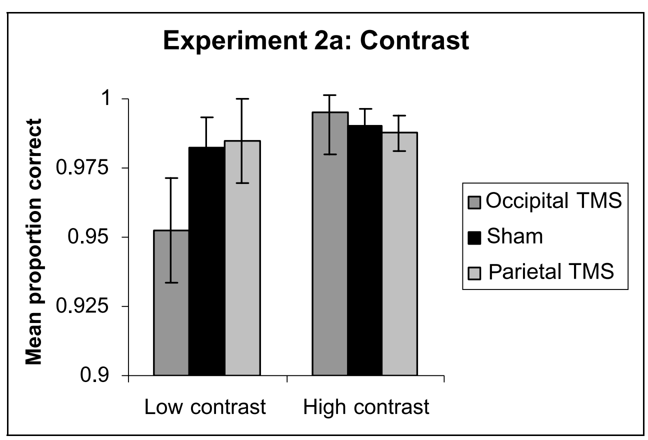

Figure 1. Experiment 2a (contrast) accuracy. Error bars represent 1 *SE*.

Case Mixing

There was a significant main effect of case, $F(1,9) = 15.44$, $p = .003$, but not stimulation site ($F < 1$). The interaction between case and site was also significant, $F(2,18) = 18.42$, $p < .001$. This interaction was significant when comparing parietal with sham stimulation, $F(1,9) = 14.76$, $p = .004$, and parietal with occipital (V1) stimulation, $F(1,9) = 29.82$, $p < .001$. There was no differential effect of occipital (V1) versus sham stimulation, $F(1,9) = 2.65$, $p = .138$. Stimulation of the parietal site led to an increase in errors for mixed-case words relative to single-case words. This pattern was not found when using sham stimulation or when stimulation was applied to the occipital (V1) site (see Figure 2).

Discussion

The results using TMS replicate and extend prior studies. As in our prior work, stimulation of the right parietal lobe was found to increase the case mixing effect, disrupting mixed-case words more than single-case words (cf. Braet & Humphreys, 2006). This was not just a general effect of difficulty, however. Right parietal stimulation did not have a differential effect on the reading of low compared with high-contrast words. The opposite effects occurred with occipital (V1) stimulation. Here, there were no differential effects on reading mixed- versus single-case words compared with sham stimulation, but there were differential TMS effects on low-versus high-contrast words. In addition, we see that in Experiment 2b (case), where all stimuli were presented in low contrast, participants tend to make the most errors for lowercase words with occipital stimulation compared with parietal or even sham stimulation, although this effect did not reach significance. The stimulation effects are predicted by prior PET studies of case and contrast effects on reading (involving the right parietal cortex and lingual gyrus, respectively, see the works of Mayall et al., 2001; Mechelli et al., 2000), but here we show that the different brain regions are necessary to deal with the different distortion effects. The results highlight that the effects of contrast reduction and case mixing are not dealt with in a common manner by the brain; different neural regions, and we suggest different functional mechanisms, are involved.

For both stimulation sites, the TMS effect was expressed as a reduction of accuracy, although there were no clear effects on naming latencies. This is surprising, because it is typically easier to affect response latencies with TMS compared with accuracy (e.g., Walsh & Rushworth, 1998). In a previous study (Braet & Humphreys, 2006), the effects of our stimulation protocol affected either RTs or accuracy, and we used a combined measure (efficiency score, see Townsend & Ashby, 1983) to best express the overall effect.

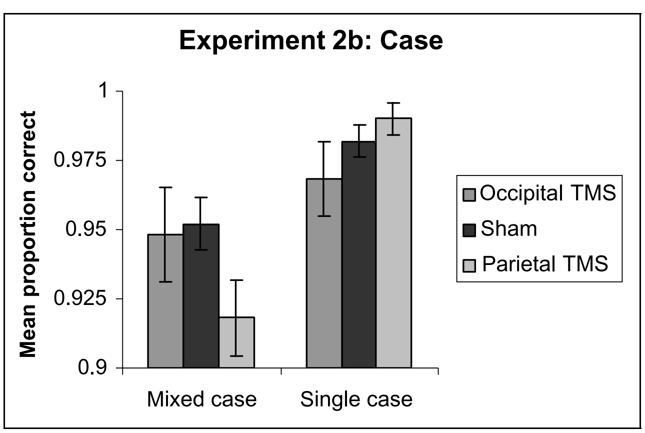

Figure 2. Experiment 2b (case) accuracy. Error bars represent 1 *SE*.

GENERAL DISCUSSION

We have presented neuropsychological evidence along with evidence from TMS effects in normal readers, distinguishing between the effects of contrast reduction and case mixing on reading. The data indicate that parietal cortex is necessarily involved in the reading of mixed-case stimuli, but it is less critical for same-case stimuli. The parietal cortex is also not necessarily involved in the dealing with low- versus high-contrast words, because lesions/TMS applied to parietal cortex did not increase the effect of contrast reduction. The opposite results arose with ventral occipital lesions/TMS. Here, there were enhanced effects of contrast reduction after occipital damage/TMS, but no enhanced case mixing effect.

These results suggest that effects of contrast reduction are overcome within the occipital cortex without requiring further recruitment of the parietal cortex (at least for the levels of contrast reduction used in this study). This is consistent with accounts that effects of contrast reduction are "normalized" at early stages of visual processing and that the visual description used in later stages of processing is relatively less dependent on contrast. For example, Goodyear and Menon (1998), using blood oxygen level-dependent functional MRI, report an increase in activity in V1, but not in the extrastriate areas, when contrast luminance was increased. Likewise, Avidan et al. (2002) found a monotonic increase in contrast invariability, from "early" to "late" visual areas (i.e., V1, V2, Vp, V4/V8 through to the lateral occipital complex). Although object perception is generally found to be quite robust to changes in contrast, this is not true for early visual areas, with activity in V1 being highly dependent on changes in contrast. Henrie and Shapley (2005) looked at single unit activity and local field potentials (LFPs) in the macaque primary visual cortex (V1). They found a monotonic relationship between single cell activity in V1 and luminance contrast. They also report that as contrast increases, LFP increases in amplitude and becomes more structured, suggesting a more synchronized firing of neurons in V1 (a higher signal-to-noise ratio). Our present TMS results can likely be explained along the same lines: the occipital TMS introduces sufficient neural noise to disrupt the representation of low-contrast words, but not of high-contrast words.

On the other hand, case mixing disrupts some of the critical information used to read words over and above general effects of noise to visual features (manipulated through contrast reduction). This critical information is likely to include clusters of familiar letter features, which co-occur in lowercase words and that change when case mixing is introduced (Hall et al., 2001; Mayall et al., 2001). Because of the loss of this supraletter information, additional processes need to be recruited to enable mixed-case words to be identified. These processes may include mental transformation of the shapes of the letters to a common format (as the parietal lobe has been implicated in tasks involving spatial transformations; e.g., Bestmann, Thilo, Sauner, Siebner, & Rothwell, 2002; Kassubek, Schmidtke, Kimmig, Lücking, & Greenlee, 2001; Ungerleider, Courtney, & Haxby, 1998; see also Braet & Humphreys, 2006) and/or the serial processing of the letters present (dependent on spatial attention, modulated through the parietal cortex; cf. Corbetta & Shulman, 1998). In either instance, the results show that these additional processes are implemented in the parietal cortex. Patients with parietal damage are less able to call on these compensatory processes and seem overdependent on recognition via familiar visual codes derived via ventral visual pathways (Cohen & Dehaene, 2004; Deheane, Le Clec'H, Poline, Le Bihan, & Cohen, 2002). Because the familiar visual code is disrupted by case mixing, such patients find mixed-case words particularly problematic. Crucially though, the present data demonstrate that case mixing differs both neurally and functionally from other forms of visual degradation, such as contrast reduction. We suggest that this is because case mixing is special, because it disrupts supraletter information used in word identification.

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Notes

1. For H.J.A., only 144 words were presented in Experiment 1a because of time constraints. Half were high contrast, and half were low contrast.
2. Chen et al. (1997), using 20-Hz trains with a duration of 1.6 sec, report that these are unsafe when stimulating higher than MT, when the intertrial interval was 1 sec or less. Jahanshahi et al. (1997) investigated safety of 20-Hz trains of 4 pulses, also at an intensity close to MT, and did not find these to be unsafe.
3. To prevent the voice key from being triggered by the TMS onset, the voice key was delayed to start recording RTs only after the last TMS pulse in a trial.

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