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Relative laterality of the N170 to single letter stimuli is predicted by a concurrent neural index of implicit processing of letter names

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While previous research reports a consistently left-lateralized N170 to whole words relative to control stimuli, much less is known about the nature of single letter processing. Yet single letter processing is of both theoretical and practical interest, as letters form an initial unit of literacy learning for alphabetic scripts and may be particularly useful in the study of literacy development. In the present study, adult fluent readers completed an implicit processing one-back task while event-related brain potentials (ERPs) were recorded. Separate blocks included single letter or matched false-font stimuli. Results indicated that single letters elicited a bilateral (rather than left-lateralized) enhancement of the N170 relative to the false font stimuli. Although participants did not make overt rhyming judgments, letters preceded by a rhyming as compared to non-rhyming letter (e.g., e–b versus e–h) also tended to elicit an N450 rhyme effect, as previously reported in explicit letter rhyme tasks. Moreover, individuals with a larger N450 rhyme effect showed greater relative left-lateralization of the response to single letters. Taken together, these findings suggest that early neural specialization for orthographic stimuli extends to the case of single letters and, further, that automatic mappings between visual symbols and phonological codes can account for at least some portion of the relative left-lateralization of early neurophysiological responses to printed text. These findings help resolve discrepancies in the existing literature concerning relative laterality of early neural responses to single letters and provide critical baseline data for future developmental neuroimaging studies.

1. Introduction

For readers of an alphabetic script, letter knowledge represents an early building block for successful literacy acquisition (Adams, 1990; Foulin, 2005; Kaminski & Good, 1996; Whitehurst & Lonigan, 1998). Across several studies, letter name knowledge and letter naming fluency are consistently strong predictors of future reading success (Badian, 1995; Foulin, 2005; Kaminski & Good, 1996; Wagner & Torgesen, 1987). Although the nature of this relationship remains an issue of debate (for a review, see Foulin, 2005), it has been proposed that letter naming provides early scaffolding for later literacy skills. For example, letter naming provides early experiences linking orthography to phonology and may assist with later formation of letter-sound correspondences important to decoding skills (Foulin, 2005). Indeed, one hallmark of reading disorder is a difficulty mastering decoding skills and attending to smaller units within printed words (National Institute of Child Health and Human Development, 2000; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Thus, understanding the neural bases of single letter processing holds relevance for investigations of both typical and atypical reading development, particularly during the early years of literacy acquisition.

1.1. Word-level processing

The precise temporal resolution of event-related brain potentials (ERPs) and magnetoencephalography/magnetic source imaging (MEG/MSI) render these neuroimaging techniques particularly useful for studying the *temporal dynamics* of neural specialization for print. Previous ERP and MEG/MSI studies of literacy have generally focused on word-level processing. For example, ERP studies indicate that printed text in a known script is differentiated from various low level control stimuli within 200 ms of processing (e.g., faces, shape strings, or false font scripts; for a review, see Maurer & McCandliss, 2007). These studies have examined the N170, a negative-going component over occipito-temporal regions that peaks ~140–200 ms after stimulus presentation. For readers of an alphabetic script, the N170 amplitude is consistently larger over left-hemisphere regions for words and word-like stimuli (e.g., pseudowords) relative to low-level control stimuli (Applebaum, Liotti, Perez,

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Fox, & Woldoff, 2009; Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999; Kim, Yoon, & Park, 2004; Maurer, Brandeis, & McCandliss, 2005; Maurer & McCandliss, 2007). While most studies have used relative lateralization indices, some studies also report that the N170 to single words is left-lateralized in an absolute sense, with early neural responses to words larger over left- than right-hemisphere electrode sites (Bentin et al., 1999; Maurer, Zevin, & McCandliss, 2008). Similar results have been reported using MEG/MSI, with stronger responses to words relative to control stimuli over left-hemisphere occipito-temporal regions during the first few hundred milliseconds of processing (Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999).

A handful of ERP and MEG/MSI studies have examined the emergence of print specialization during literacy acquisition, though these studies have also emphasized whole word processing (e.g., Maurer, Brem, Bucher, & Brandeis, 2005; Maurer, Brem, Kranz, et al., 2007; Simos et al., 2001). The use of implicit processing tasks, such as one-back tasks, are typically used in these studies as they can be completed whether or not a participant can read (e.g., based on the visual shape of the stimuli) while still eliciting consistently relative left-lateralized N170 enhancements in adult fluent readers. Interestingly, during the initial stages of reading acquisition, children show a bilateral or even right-lateralized N170 enhancement to words relative to control stimuli (Maurer, Brem, et al., 2005; Maurer, Brem, Kranz, et al., 2007). In contrast, for children with low letter knowledge, there is no evidence for differences in the N170 amplitude to words versus control stimuli (Maurer, Brem, et al., 2005). Developmental studies using MEG/MSI reveal similar differences in the laterality of processing in adults and children, with children less likely to display the strong relative left-lateralized responses during the first few hundred milliseconds of word processing (Simos et al., 2001). Initial relative right-lateralization of the N170 during literacy acquisition is hypothesized by some (e.g., Maurer & McCandliss, 2007) to reflect a visual expertise effect, similar to that observed for face stimuli or novel trained objects in adults (Rossion, Gauthier, Goffaux, Tarr, & Crommelinck, 2002), that does not show relative left-lateralization until words are automatically mapped to left-lateralized phonological systems. Under this phonological mapping hypothesis, relative left-lateralized N170 responses to single words emerge as a result of automatic links between orthography and phonology (Maurer & McCandliss, 2007).

If relative left-lateralization of early neural responses is indicative of reading expertise, atypical relative lateralization to print might be expected in the case of reading of disorder. Indeed, electrophysiological responses to printed words have been useful in the study of reading disorder, revealing atypical processing of words at early stages of perceptual processing. For example, among children with reading difficulty, N170 specialization for words follows a different developmental trajectory (Kast, Elmer, Jancke, & Meyer, 2010; Maurer, Brem, Bucher, et al., 2007). For example, Maurer, Brem, Bucher, et al. (2007) and Maurer, Brem, Kranz, et al., 2007 examined N170 responses to words versus control symbol strings in a longitudinal study. Children were assessed in both kindergarten and second grade, with groups of on-track and reading-impaired children identified retrospectively based on second grade reading scores. On-track readers showed an emerging enhancement of the N170 to words relative to symbol strings during this time period, primarily arising from an increased amplitude response over left hemisphere occipito-temporal electrode sites to word stimuli. In contrast, children who were impaired readers in second grade showed less differentiation in N170 amplitude between words and symbol strings across both time points, and little evidence for left-hemisphere specific increases in N170 amplitude to words from kindergarten to second grade. A separate study reported continued aberrant patterns of N170 lateralization in adults with phonological dyslexia, who showed less consistently left-lateralized N170 responses to words, with a bilateral N170 observed to pseudowords and/or words (Dujardin et al., 2011).

Taken together, these studies indicate that in adult fluent readers, the visual system distinguishes whole words from other classes of visual stimuli within 200 msec, and also that aspects of this specialization exhibit developmental shifts during literacy acquisition. However, as the studies reviewed above emphasize whole word processing, they do not elucidate the neural mechanisms underlying specialization for more elementary units of script processing such as single letters. Yet single letter processing is of both theoretical and practical interest, as letters form an initial unit of literacy learning for alphabetic scripts. Moreover, as it may be difficult for pre-readers or individuals with reading disorder to perform experimental tasks involving whole words, the use of paradigms based on single letter processing have potential utility for studying very early stages of literacy development.

1.2. Single letter processing

In contrast to the large literature on word-level processing, only a handful of ERP and MEG/MSI studies have examined the time course of single letter processing. Moreover, results across this small set of studies are inconsistent as regards early processing differences, even when restricted only to studies of monolingual speakers reading a first-learned script. For example, relative to control stimuli, early occipito-temporal neural responses to letters have been reported to be larger in amplitude both bilaterally (Wong, Gauthier, Woroch, DeBuse, & Curran, 2005) and primarily in left-hemisphere regions (Tarkiainen et al., 1999), with one study finding little evidence for any difference between N170 responses to letters and various control stimuli over either hemisphere (Pernet et al., 2003).

One challenge across previous studies is the use of different control stimuli and primary tasks. Previous studies have used a range of contrasting control stimuli (Chinese characters/false fonts, simple geometric shapes, and a diverse set of object categories) as well as primary task demands (one-back, low-probability requests for recall of the previous item, and specific stimulus detection). In addition, most studies have not been specifically designed to address single letter processing, so the experimental designs are not optimized for this contrast. Moreover, given the hypothesis that at least some portion of relative left-lateralization of the N170 for whole words represents automatic links between orthography and phonology (Maurer & McCandliss, 2007), one might expect discrepancies across studies to be related to the degree to which participants engage in phonological coding when processing single letters, as well as the degree of phonological coding possible for the control stimuli.

Interestingly, an emerging ERP literature reports that letter names are processed phonologically and can elicit traditional rhyme effects similar to those observed with whole word stimuli (Coch, George, & Berger, 2008; Coch, Hart, & Mitra, 2008; Coch, Mitra, George, & Berger, 2011). In this explicit rhyming paradigm, Coch and colleagues present pairs of letters whose names either rhyme (e.g., E and T) or do not rhyme (e.g., E and L). ERPs to the second (target) letter are compared as a function of whether the letter rhymes or does not rhyme with the prime letter. Over centro-parietal electrode sites, an N450 letter rhyme effect is observed in this paradigm, with a larger negativity to nonrhyming as compared to rhyming targets, typically from ~300 to 550 ms post-stimulus onset (Coch, George, et al., 2008; Coch, Hart, et al., 2008). Moreover, this rhyme effect is remarkably similar to that reported previously for printed word rhyming (e.g., Grossi, Coch, Coffey-Corina, Holcomb, & Neville, 2001; Rugg, 1984), suggesting that the letter rhyme effect indexes similar phonological processes as those engaged during whole word processing. As well, recent evidence suggests that this effect is observed in children as young as six- to eight-years of age (Coch et al., 2011).

These findings indicate that both adults and children access and process letter names at a phonological level, at least when an explicit letter rhyme task is used. However, it is unclear whether similar effects can be observed during an implicit processing paradigm that does not require rhyme judgments or letter naming. Yet, if such evidence for letter rhyming is observed in an implicit processing task, it may help explain inter-participant and inter-study variability in the N170 response to single letter stimuli relative to control stimuli. For example, to the extent that left-lateralized N170 enhancements for printed text relative to control stimuli reflect, in part, automatic links between orthography and phonology, it might be predicted that individuals exhibiting an N450 letter rhyme effect during an implicit processing task will be more likely to show left-lateralized N170 enhancements to single letter stimuli relative to control stimuli during the same task. Identifying the time course of neural specialization for single letters in adult fluent readers, including N170 and letter rhyme effects, will also provide a useful baseline for future developmental neuroimaging studies of single letter processing in children.

1.3. Overview of the present study

In the present study, ERPs were recorded while adult fluent readers completed a one-back implicit processing task using lowercase single letters and matched false font symbols. False font symbols were created by digitally rearranging portions of the letter stimuli but did not bear any superficial resemblance to letters, numbers, or other easily labeled shapes. All letter stimuli were potentially rhyming with at least one other letter in the stimulus set, with half of the letter stimuli rhyming with the letter name ‘e’ (e, b, c, g, t, v, and z). The analysis included assessment of N170 specialization for single letters relative false-font control stimuli, N450 letter rhyme effects, and associations between these two indices of single letter processing.

2. Methods

2.1. Participants

Sixteen adult college students (10 male, 6 female) participated in the current study. All participants were right-handed, literate, and native monolingual English speakers with normal or corrected-to-normal vision. No participants reported a history reading or language disorder. Participants received $10/h for their participation.

2.2. Stimuli

Stimuli consisted of a set of 14 lowercase letters (e, b, c, g, t, v, z, i, y, a, j, k, q, and u) and 14 matched false font symbols. False font symbols were created by digitally rearranging portions of the letter stimuli to form a separate false font symbol corresponding to each lowercase letter. False font symbols matched the overall size and luminance of the lowercase letters but did not bear any superficial resemblance to letters, numbers, or other easily labeled shapes. Example stimuli are presented in Fig. 1.

Following previous studies of letter rhyming (Coch, George, et al., 2008; Coch, Hart, et al., 2008), all letter stimuli potentially rhymed with at least one other letter in the stimulus set. Half of the letters rhymed with the letter “e” and formed the “e-rhyme” set: (e, b, c, g, t, v, and z). The remaining letters formed other rhyme sets: (i, y), (a, j, k), and (q, u). Letter frequency in a large scale corpus drawn from the New York Times (Jones & Mewhort, 2004) did not differ between the set of “e-rhyme” letters and “other-rhyme” letters, measured either as frequency rank, $t\ (12)=0.104$, $p=0.919$ ($M_{\text{e-rhyme}}=11.4$, $M_{\text{other-rhyme}}=14.6$) or absolute frequency of occurrence within the corpus, $t\ (12)=-0.583$, $p=0.571$ ($M_{\text{e-rhyme}}=2{,}571{,}806$, $M_{\text{other-rhyme}}=2{,}420{,}244$).

2.3. Procedures

Stimuli were presented in Futura white font on a black background on a screen about 36 in. from the subject. Stimuli subtended 0.8–1.6° of visual angle. Stimuli appeared on the screen for 1500 ms, separated by a 500-millisecond interstimulus interval during which an asterisk appeared at fixation, as shown in Fig. 1.

Participants completed a one-back repetition detection task and pressed a button following the immediate repetition of a stimulus. Repetitions occurred on 20% of trials. No explicit rhyme judgments were made during the task. However, on average 25% of letter stimuli rhymed with the immediately preceding letter (e.g., the letter “a” preceded by “k”), with letters in the “e-rhyme” set having a roughly 50% probability of rhyming with the immediately preceding letter.

Letter and false font stimuli were presented in separate blocks. The false font blocks perfectly mirrored the letter block, with the false font version of letter stimuli replacing its corresponding letter. In total, participants completed four blocks of trials (two with letters, two with false fonts), with letter and false font blocks interleaved. Each block lasted roughly 2.5 min, with a total of 112 standard stimuli of each type presented across the four blocks. Approximately 56 of the standard stimuli were in the e-rhyme set, with 25 rhyming and 31 nonrhyming. (Slight variations in the actual number of e-rhyme stimuli presented were possible given the randomization sequence for selecting stimuli from the full set of possible letters.) Starting stimulus type (letter or false font) and starting response hand (left/right) was counterbalanced across participants. For all participants, response hand (left/right) remained constant for the first two blocks and switched for the final two blocks. Reaction and time and accuracy data were collected, but were unavailable from one participant due to equipment error.

2.4. Electrophysiological recording and analysis

EEG data were collected using an Active-Two BioSemi System (Biosemi, Amsterdam, Netherlands). The electrode montage included 32 Ag–AgCl-tipped electrodes attached to an electrode cap according to the 10/20 system. Recording sites included FP1/2, F7/8, FT7/8, F3/4, FC5/6, C3/4, C5/6, P3/4, O1/2, CP1/2, PO3/4,

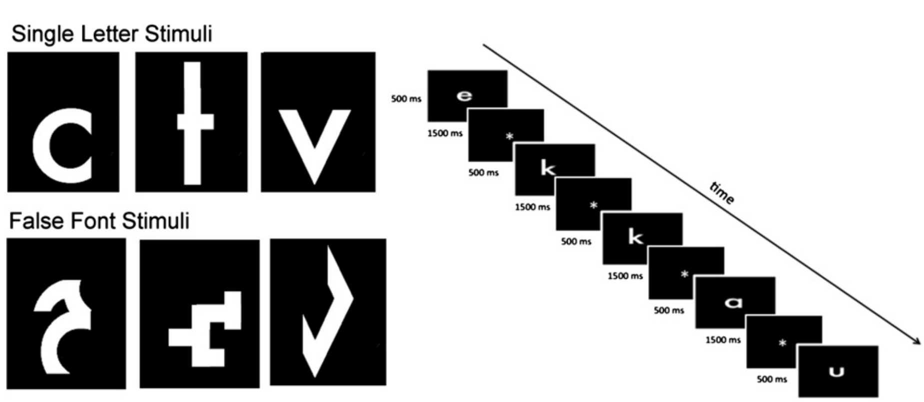

Fig. 1. Participants completed a one-back repetition task, with separate blocks of single letters or matched false font stimuli. Stimuli appeared for 1500 ms, with a 500 ms interstimulus interval. While no explicit rhyme judgments were made, letter names could rhyme with the immediately preceding letter (e.g., the letter “a” preceded by “k”).

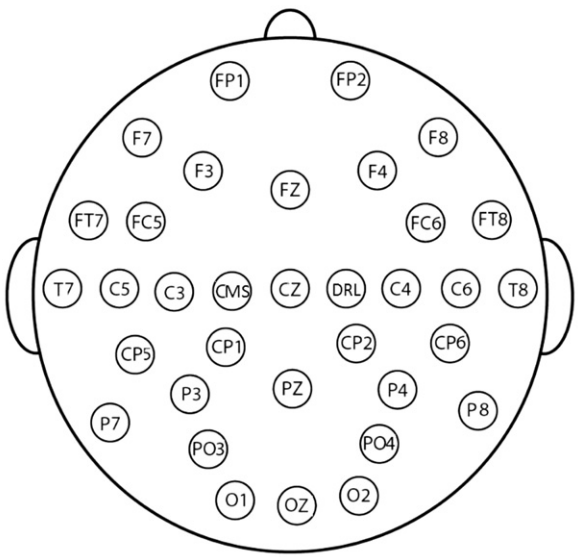

Fig. 2. Electrode configuration for ERP recording. Electrodes used in analysis of N170 and rhyme effects are specified in the main text.

T7/8, CP5/6, P7/8, Fz, Cz, Pz and Oz, as shown in Fig. 2. Additional electrodes were placed at the outer canthi of each eye and beneath the right eye to monitor blinks and eye movements, and on the left and right mastoids. Online, signals were recorded relative to the Common Mode Sense (CMS) active electrode at a 1024 Hz sampling rate. Left and right horizontal eye channels were re-referenced to one another, and the vertical eye channel was re-referenced to FP1.

Offline, ERP analyses were carried out using the EEGLAB toolbox in Matlab (Delorme & Makeig, 2004). Data were down-sampled to 256 Hz, band-pass filtered from 0.1 to 40 Hz, and digitally re-referenced to the average of the left and right mastoid electrodes. Although many studies of N170 modulation use an average-head reference, the linked mastoids were used to allow a common reference across measures of the N170 and rhyme effect, which has used a linked mastoid reference in previous papers. (Previous studies indicate that a left-lateralized N170 to words is still apparent when linked mastoids are used as a reference, though these effects might be slightly attenuated; Applebaum et al., 2009; Joyce & Rossion, 2005). Epochs time-locked to the presentation of standard (non-repeating) letter and false font stimuli were extracted from −100 to 1000 ms. Trained research assistants identified any epochs in the data contaminated by eye movements, blinks, or muscle artifact by visual inspection. Trials contaminated by artifacts were removed prior to averaging.

First, separate ERPs to letter and false font standards were created for each subject at each electrode site over a 500 ms epoch from stimulus onset, using a 100 ms prestimulus-onset baseline. The average number of useable trials per condition was 90 (SD=15) for letter standards and 90 (SD=16) for false font standards, with ~20% of trials removed due to artifact. Based on visual inspection of the individual subject data and with reference to previous studies, the N170 was measured from 150 to 180 ms over left and right electrodes in the temporo-parietal region, corresponding to electrodes P7 and P8. These mean amplitude measurements were then submitted to a 2×2 within-subjects ANOVA. Factors included stimulus type (letter/false font) and hemisphere (left/right).

Second, separate ERPs to letters immediately preceded by a rhyming as compared to nonrhyming letter were created for each subject at each electrode site over a 1000 ms epoch from stimulus onset, using a 100 ms prestimulus onset baseline. This analysis was restricted to the seven letters in the "e-rhyme" set (e, b, c, g, t, v, and z) such that stimuli had an approximately equal probability of being preceded by a rhyming as compared to nonrhyming letter. The average number of useable trials per condition was 20 (SD=4) for rhyming letters and 24 (SD=6) for nonrhyming letters, with ~20% of trials removed due to artifacts. All participants had at least 10 trials per rhyme or nonrhyme letter condition, with ranges from 11 to 30. Based on visual inspection of the data and with reference to previous studies, mean amplitude was measured from 300 to 500 ms post-stimulus onset over a set of three centro-parietal electrodes: PZ, CP1, and CP2. To assess whether a rhyme effect was evident over this centro-parietal region of interest, a paired t-test compared the mean amplitude as a function of rhyme condition (rhyming/non-rhyming).

Finally, to examine the relationship between relative N170 laterality and the rhyme effect, separate indices of each effect were calculated. To compute an index of relative N170 laterality for letter stimuli, the difference in mean amplitude from 150 to 180 ms in the left and right hemisphere electrodes (P7 and P8) was calculated separately for the letter and false font stimuli, with the score for false fonts subtracted from the score for letters, i.e., Relative Laterality= $(LT_{left}-LT_{right})-(FF_{left}-FF_{right})$. Positive values of relative laterality indicated relatively more *right-lateralized* responses to letters over false-font symbols, while negative values indicated the opposite. To compute an index of the rhyme effect, the mean amplitude from 300 to 500 ms of the difference wave (rhyme–nonrhyme) was calculated over PZ, CP1, and CP2, such that positive values indicated a larger rhyme effect, or a more negative N450 response for letters immediately preceded by a nonrhyming as compared to rhyming letter. To assess whether relative laterality of the N170 was related to magnitude of the rhyme effect, a pairwise correlation was conducted between these two measures, following checks that data met the assumptions for correlation analysis.

3. Results

3.1. Behavioral data

Accuracy was high in both the letter and false font blocks, though responses were faster and more accurate overall in the letter condition: Repetition detection accuracy, M=98% letter blocks (SD=4), M=92% false font blocks (SD=7), t (14)=2.59, $P<0.03$; Reaction time M=604 ms letter blocks (SD=152), M=654 ms false font blocks (SD=154), t (14)=−2.74, $P<0.02$.

3.2. N170 letter effects

Fig. 3 shows the grand average to letters and false font stimuli at electrodes P7 and P8. Visual inspection confirmed the presence of a clear N170 peak at these two electrodes, which appeared to be right-lateralized and modulated by stimulus type. Statistical analysis confirmed these observations. Collapsed across stimulus types, the N170 was larger over the right than left hemisphere, main effect of hemisphere: F (1, 15)=5.126, $P<0.05$, partial η^2=0.255: right hemisphere=−3.92 μV (SE=0.79), left hemisphere=−2.53 μV (SE=0.70). Moreover, letter stimuli elicited a larger N170 than false font stimuli, and this effect was equivalent across both hemispheres, main effect stimulus type: F (1, 15)=10.715, P=0.005, partial η^2=0.417; Hemisphere × Stimulus Type interaction: F (1, 15)=0.139, P=0.715, partial η^2=0.009: letter magnitude=−3.68 μV (SE=0.67), false font magnitude=−2.78 μV (SE=0.72), see Fig. 3. Thus, while both single letters and false font stimuli elicited a right-lateralized N170, the overall amplitude of the N170 was larger bilaterally for single letters relative to false font stimuli.

3.3. N450 letter rhyming effects

Fig. 4 shows the grand average to letters preceded by a rhyming as compared to non-rhyming letter over the centro-parietal region

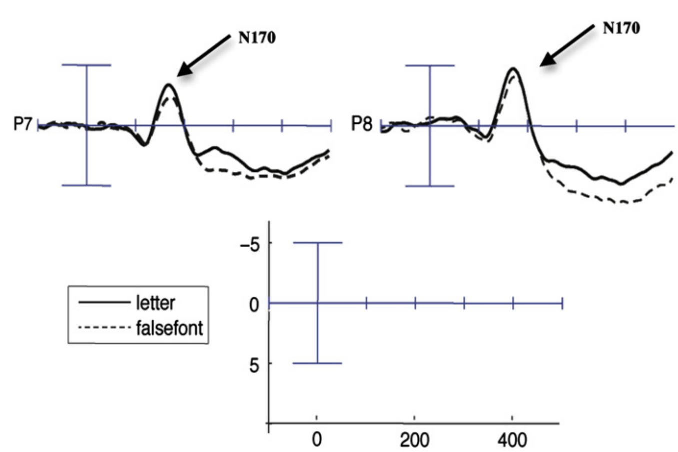

Fig. 3. Grand average ERP waveforms to single letter (solid line) as compared to false font (dotted line) standards. Mean amplitude from 150 to 180 ms indicated a larger amplitude response bilaterally in response to letters as compared to false font stimuli.

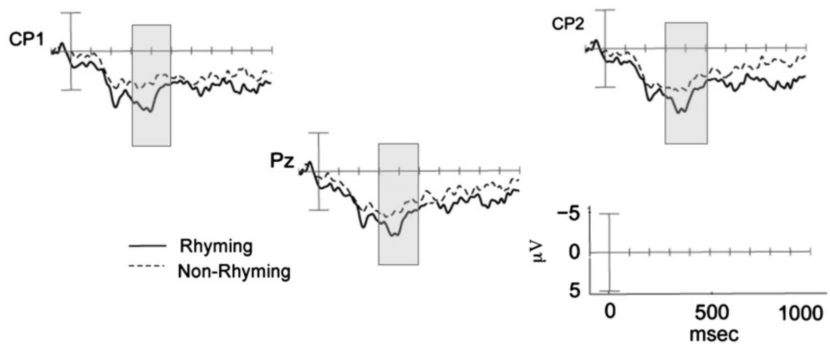

Fig. 4. Grand average ERP waveforms showing the N450 rhyme effect over centroparietal electrodes. Single letters were immediately preceded by a rhyming letter (solid line) or non-rhyming letter (dashed line). Mean amplitude from 300 to 500 ms was more negative in response to letters immediately preceded by a non-rhyming as compared to rhyming letter in this implicit processing one-back repetition detection task.

of interest. Visual inspection suggested that, similar to previous studies using explicit rhyme judgments, the amplitude of the N450 was modulated by rhyme status, i.e., whether the immediately preceding letter had a rhyming or non-rhyming letter name. Statistical analyses indicated a trend for the amplitude of the N450 to be more negative to letters immediately preceded by a non-rhyming as compared to rhyming letter, paired samples $t(15)=2.081$, $P=0.055$: non-rhyme mean amplitude $=4.47\ \mu V$ ($SD=3.63$), rhyming mean amplitude $=6.43\ \mu V$ ($SD=3.47$). This suggests that, similar to previous studies in which explicit rhyme judgments are made, a more negative N450 is observed when a letter in a one-back task is preceded by non-rhyming, as compared to rhyming, letter. To ensure that this reflected a true rhyme effect and not an artifact of transitional probabilities, a parallel analysis was conducted using the false font stimuli. If this were a true rhyme effect, there should be no evidence of an N450 difference between false font stimuli corresponding to the e-rhyme and e-nonrhyme conditions. This was indeed the case: paired samples $t(15)<1$, $P=0.43$.

3.4. N170-rhyme effect correlations

Correlation analysis was used to examine whether the magnitude of the N450 rhyming effect was linearly related to relative laterality of the N170 to single letters. A pairwise correlation indicated a significant correlation between relative laterality of the N170 for letters and magnitude of the rhyme effect ($r=-0.52$, $P<0.05$). As shown in Fig. 5, participants with relatively more left-lateralized N170 responses to letters as compared to false font stimuli (i.e., more negative laterality indices) showed larger implicit rhyme effects.

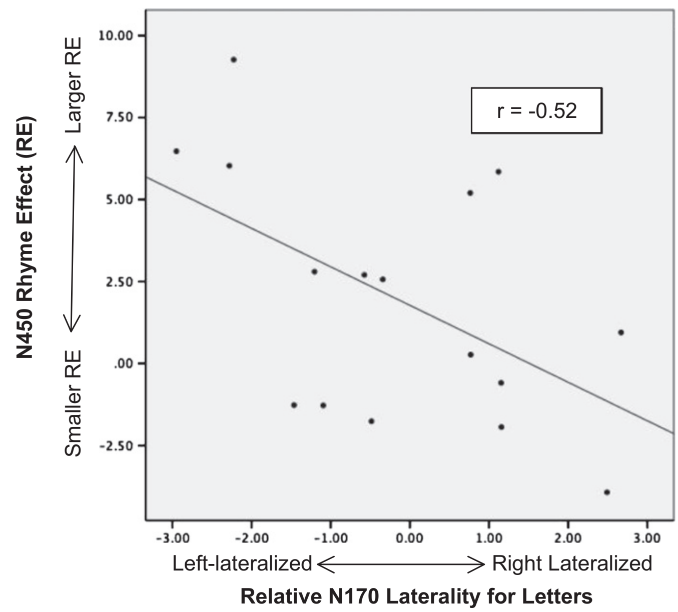

Fig. 5. Correlation between Relative N170 laterality (negative values indicate greater relative left-lateralization for letters) and magnitude of the N450 rhyme effect.

4. Discussion

The present study provides evidence that adult fluent readers display early neural specialization for processing single letters. However, the nature of this specialization differs from that previously reported for whole words, and is evident as a bilateral (rather than left-lateralized) relative enhancement of the N170. Moreover, relative left-lateralization of the N170 to single letters is strongly predicted by a neural measure of implicit access to letter names and letter rhyme detection during the task. This suggests that early neural specialization for orthographic stimuli extends to the case of single letters and, further, that automatic mappings between visual symbols and phonological codes can account for at least some portion of the relative left-lateralization of early neurophysiological responses to printed text.

4.1. N170 laterality to single letters

In the present study, the absolute laterality of the N170 to both letter and false font stimuli was right-lateralized, with single letters showing an enhanced response bilaterally relative to the matched false font stimuli. Thus, the nature of single letter processing was different in important ways from the previously reported left-lateralized relative and absolute responses to whole words in alphabetic scripts (Applebaum et al., 2009; Bentin et al., 1999; Kim et al., 2004; Maurer, Brandeis, et al., 2005; Maurer & McCandliss, 2007). These differences may be related to the processing demands of whole words as compared to single letters. For example, it has been proposed that relative left-lateralization of the N170 to words is driven in part by automatic links that form between orthography and left-lateralized phonological systems (Maurer & McCandliss, 2007; McCandliss & Noble, 2003). Thus, it is possible that links to phonology may be less pronounced or less automatized in the case of single letters, which might contribute to the absence of left-lateralized absolute responses in the present study, as well as the inconsistent previous reports of the relative laterality of early neural responses to single letters in comparison to various control stimuli (e.g., see Pernet et al., 2003; Tarkiainen et al., 1999; Wong et al., 2005).

The design of the present study permitted a direct assessment of the degree to which phonological access might account for some portion of the relative left-lateralization of responses to printed stimuli. Previous studies report an N450 letter rhyme effect during explicit rhyme judgments, such that letters preceded by a non-rhyming as compared to rhyming letter (e.g., E–L versus E–T) elicit a larger negativity over centro-parietal electrode sites (Coch, George, et al., 2008; Coch, Hart, et al., 2008). Here, we were able to ask whether this N450 letter rhyme effect was apparent in adult fluent readers during an implicit processing task. Interestingly, the data indicated a trend for a letter rhyme effect, even in the absence of explicit rhyme judgments. That is, when seeing letters, participants were accessing the letter name and processing whether that letter name rhymed with the previously presented letter, even if not required to do so. However, this effect appeared to emerge earlier than that reported in explicit letter rhyme tasks, was less robust than that reported in previous explicit rhyme paradigms, and may vary across individuals. Indeed, individuals with larger N450 implicit letter rhyme effects also exhibited the greatest degree of relative left-lateralization to single letters. Importantly, this correlation was not a simple artifact of the overall amplitude of ERP responses because it was observed for the *relative* left-lateralization index, which was scaled for overall ERP magnitude through the subtraction process. This suggests that when the links between orthography and phonology are processed automatically, greater relative left-lateralization of early neural responses is observed.

The present findings may help clarify the extant literature on single letter processing, which is largely inconsistent as regards the relative laterality of early neural responses. The two previous studies reporting differences between single letter and low-level control stimuli have indicated both bilateral (Wong et al., 2005) and left-lateralized (Tarkiainen et al., 1999) enhancements relative to control stimuli. However, as these studies were not designed exclusively to assess single letter processing, when interpreting the results it is important to consider the larger set of stimuli included in the study design as well as the primary task demands. Tarkiainen et al. (1999) used MEG/MSI and reported primarily left-hemisphere sites showing preference for single letters over matched control stimuli. However, in that study, single letters were tested alongside other pronounceable orthographic stimuli including two-letter bigram syllables and four-letter words, with geometric shape strings matched in length serving as contrasting control stimuli (one-, two-, or four-item shape strings). Participants were probed on ~2% of trials to report the previously presented item. The nature of the additional orthographic stimuli — syllables and words — as well as the task demands may have prompted a more linguistically mediated strategy in this study, in which verbal labels for stimuli were assigned or extracted automatically as part of early processing. In contrast, similar to the present study, Wong et al. (2005) reported bilateral N170 enhancements for letters compared to control stimuli. In the study by Wong et al., in addition to single letters, five-character consonant strings were presented, with contrasting control stimuli including both Chinese characters and pseudofonts matched in length. Participants completed a one-back task based on the central stimulus (i.e., repetition detection for single-item displays or, for five-character displays, repetition of the central stimulus). In the context of this task, it is possible that automatic links to phonology were less likely to be engaged, as no stimuli were pronounceable as words, and in all cases participants needed only attend to a single central stimulus to perform the task. Thus, the present findings, while being consistent with Wong et al. (2005), also offer a compelling explanation for the differences observed in past studies.

Cast in a broader framework, the present findings suggest that the relative laterality of early neural responses to text stimuli may not be reflective of a truly automatic process. Instead, N170 laterality for orthographic stimuli may be influenced by links to phonology that are engaged to a greater or lesser degree not only as a function of experience with orthographic stimuli, but also as a function of the contextual aspects and task demands in a given study. In the case of whole words, phonological processing may be more automatic, at least in adult fluent readers, and thus engaged more consistently across different studies, leading to consistent relative left-lateralization even in implicit one-back tasks. In contrast, while single letters may be distinguished from low-level control stimuli at early stages of neural processing, the relative laterality of this early N170 effect may be more labile as a function of the larger experimental context and task demands. However, given that absolute laterality for letters in the present study was still right-lateralized, the factors driving absolute and relative left-lateralization of the N170 are clearly more complex than just the formation of relatively automatic phonological mappings. It is likely that many factors contribute both to absolute and to relative left-lateralization, as suggested in past literature, including the spatial frequency of stimuli, stimulus repetition, and task demands (e.g., see Mercure, Dick, Halit, Kaufman, & Johnson, 2008; Proverbio & Adorni, 2009; Simon, Petit, Bernard, & Rebaï, 2007).

Clarifying our understanding of the factors that influence the relative lateralization of early neural responses may be particularly important to understanding development and deviance of early neural responses to both words and letters during literacy acquisition. One intriguing possibility is that relative, and perhaps also absolute, left-lateralization depends not only on forming phonological mappings to visual stimuli, but also on attending to smaller units of analysis when making this mapping. This suggestion would be consistent with the results of a recent training study that used an artificial orthography with a hidden embedded alphabet (Yoncheva, Blau, Maurer, & McCandliss, 2010). In this study, a group of adults received a brief, 20 min training session with a novel symbol script in which portions of holistic word symbols consistently corresponded to particular phonemes. Attentional focus during training was manipulated by instructing half of participants to focus on the symbol as a holistic unit and the other half to focus on mapping portions of the symbol to individual phonemes (i.e., explicit attention to the alphabetic principle). Despite differences in training, participants in both conditions learned the symbol-label mappings well. Following the training, ERPs were recorded while participants completed an explicit phonology-based task in which they indicated whether a visually presented symbol matched an auditorily presented word. Results indicated that absolute laterality of the N170 varied as a function of attentional focus during training (no control stimuli were included): adults instructed to focus on the symbols holistically showed a *bilateral* N170 response to the symbols whereas adults trained to map the symbols to phonemes showed a *left-lateralized* N170 response. In contrast, a separate companion study reported that neither group showed a left-lateralized N170 response during an implicit processing one-back task, though there was an overall increase following training in amplitude of the N170 to words in the novel script, particularly over right hemisphere sites (Maurer, Blau, Yoncheva, & McCandliss, 2010). These findings suggest that the ability to identify and process smaller orthographic-to-phonological units of words may facilitate the development of rapid, left-lateralized neural responses important to fluent reading, and further underscores the role of task demands in patterns of lateralization observed, at least for newly acquired scripts.

These studies using an artificial orthography also suggest an important caveat to the phonological mapping hypothesis. Given that participants in both training groups became quite good at mapping words to symbols, it appears to be the focus on smaller sublexical units that drives left-lateralization of the N170. This may be particularly important given the literature suggesting that individuals with reading disorder are less likely to show relative left-lateralization of early neural responses to whole words (Dujardin et al., 2011; Kast et al., 2010; Maurer, Brem, Bucher, et al., 2007). Indeed, individuals with reading disorder can become quite good at memorizing individual words holistically, with specific difficulties identifying smaller subunits and attending to letters in non-initial positions (e.g., McCandliss, Beck, Sandak, & Perfetti, 2003; National Institute of Child Health and Human Development, 2000). Thus, relative left-lateralization of the N170 to words relative to control stimuli might be less about making the simple mapping between speech and print, and more about the unit of analysis used in this mapping and the scaffolding such mappings puts into place. Interestingly, this also suggests a possible recast of the developmental literature of N170 specialization to printed words. The early relative right-lateralization of the response to words in comparison to control stimuli that later becomes relatively left-lateralized has been interpreted as reflecting the formation of automatic links between orthography and phonology (Maurer, Brem, Bucher, et al., 2007; Maurer & McCandliss, 2007). However, if children are able to read all of the words included in the stimulus set, then relative left-lateralization may instead index the strategy being deployed, and whether children are making use of smaller units of analysis and decomposing the words into parts.

From a development neuroimaging perspective, sublexical units of analysis may be particularly important in the study of literacy acquisition. As suggested above, successful reading might be less about the ability to read whole words and form print-sound associations than the ability to decompose a word into constituent parts. As such, paradigms that tap into the neural bases of sublexical units may be particularly useful in the study of reading development. Moreover, given that single letters offer a less complex stimulus than whole words, studies using single letters may be easier to translate to younger or even pre-reading populations, as well as groups with reading disability, where task performance can be more easily equated between readers of different ages or ability levels. Thus, the present paradigm has potential utility for developmental studies. Functional MRI studies have used single letters for this reason (e.g., Turkeltaub, Flowers, Lyon, & Eden, 2008; Yamada, Stevens, Harn, Chard, & Neville, 2011). Parallel studies of the temporal dynamics of single letter and sublexical processing during development will provide a complementary perspective on literacy development. It is possible, for example, that in the case of reading disorder, single letters are not differentiated from low-level control stimuli until later stages of processing not indexed by the N170. This could suggest differences in class-level specialization, or the role for smaller units of analysis in providing the critical scaffolding for both successful reading development and the establishing of efficient neural circuits to support fluent reading. Such developmental studies will represent an important direction of future research.

5. Conclusion

Findings from the present study provide strong support for the role of phonological processing in the relative left-lateralization of early neural responses to single letter stimuli. These findings help resolve discrepancies in the existing literature concerning the relative laterality of early neural responses to single letters, and also offer a new perspective on previous reports of relative left-lateralized N170 responses to whole words. Future work can examine the developmental time course of specialization for the single letter processing, and the potential predictive utility of neural responses to single letter and other sublexical units for future reading development.

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