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Multimodal Alexia: Neuropsychological Mechanisms and Implications for Treatment

Esther S. Kim^{a,1}, Steven Z. Rapcsak^{b,c}, Sarah Andersen^{a,b}, and Pélagie M. Beeson^{a,b}

^aDepartment of Speech, Language, and Hearing Sciences, University of Arizona, P.O. Box 210071, Tucson, AZ, USA 85721

^bDepartment of Neurology, University of Arizona, P.O. Box 245023, Tucson, AZ, USA 85724

^cNeurology Section, Southern Arizona Veteran's Affairs Health Care System, 3601 S. 6th Ave., Tucson, AZ USA 85723

Abstract

Letter-by-letter (LBL) reading is the phenomenon whereby individuals with acquired alexia decode words by sequential identification of component letters. In cases where letter recognition or letter naming is impaired, however, a LBL reading approach is obviated, resulting in a nearly complete inability to read, or global alexia. In some such cases, a treatment strategy wherein letter tracing is used to provide tactile and/or kinesthetic input has resulted in improved letter identification. In this study, a kinesthetic treatment approach was implemented with an individual who presented with severe alexia in the context of relatively preserved recognition of orally spelled words, and mildly impaired oral/written spelling. Eight weeks of kinesthetic treatment resulted in improved letter identification accuracy and oral reading of trained words; however, the participant remained unable to successfully decode untrained words. Further testing revealed that, in addition to the visual-verbal disconnection that resulted in impaired word reading and letter naming, her limited ability to derive benefit from the kinesthetic strategy was attributable to a disconnection that prevented access to letter names from kinesthetic input. We propose that this kinesthetic-verbal disconnection resulted from damage to the left parietal lobe and underlying white matter, a neuroanatomical feature that is not typically observed in patients with global alexia or classic LBL reading. This unfortunate combination of visual-verbal and kinesthetic-verbal disconnections demonstrated in this individual resulted in a persistent multimodal alexia syndrome that was resistant to behavioral treatment. To our knowledge, this is the first case in which the nature of this form of multimodal alexia has been fully characterized, and our findings provide guidance regarding the requisite cognitive skills and lesion profiles that are likely to be associated with a positive response to tactile/kinesthetic treatment.

Keywords

acquired alexia; letter-by-letter reading; pure alexia; global alexia; alexia with agraphia; kinesthetic treatment

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¹Corresponding Author; Present Address: Department of Speech Pathology and Audiology, Faculty of Rehabilitation Medicine, University of Alberta, 2-70 Corbett Hall, Edmonton, Alberta, Canada T6G 2G4; Tel: (780) 248-1542; Fax: (780) 492-9333; esther.kim@ualberta.ca.

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1. Introduction

Damage to left temporo-occipital brain regions can give rise to a variety of alexia syndromes that differ in terms of severity, the nature of the underlying cognitive impairment, and neural substrates (Damasio & Damasio, 1983; Dejerine, 1892; Binder & Mohr, 1992; Cohen et al., 2003). The best documented of these syndromes is pure alexia, characterized by impaired reading in the context of relatively intact spelling. The hallmark of pure alexia is letter-by-letter (LBL) reading, wherein words are decoded by sequential identification of component letters. As a result, LBL readers demonstrate a “word length effect” in that reading latency increases and accuracy decreases as a function of the number of letters in the word. In cognitive neuropsychological terms, pure alexia is often described as a peripheral processing impairment involving letter identification, where visual information from written words fails to activate representations in the orthographic lexicon in a rapid, parallel manner (Behrman, Plaut & Nelson, 1998). Individuals with pure alexia typically compensate for their visual processing deficit by resorting to serial identification of letters. Insofar as letter naming is intact, this strategy provides a slow, but accurate, means of decoding words.

Despite the peripheral nature of the impairment, there is evidence that individuals with pure alexia can at least partially access lexical-semantic information for written words (see Behrman et al., 1998 for a review). For instance, frequency and imageability effects in reading (Arguin & Bub, 1993; Coslett & Saffran, 1989; Kay & Hanley, 1991), as well as greater than chance performance on lexical decision or semantic categorization tasks (Bub & Arguin, 1995; Coslett & Saffran, 1994; Shallice & Saffran, 1986) have been demonstrated in several patients with this syndrome. In fact, of the 57 reported cases of pure alexia reviewed by Behrman et al. (1998), only 13 did not show any lexical or semantic effects on any of the reading measures, suggesting that once central reading processes are engaged, they provide top-down support to facilitate letter identification.

In addition to peripheral impairments, however, central impairments in the form of degraded orthographic lexical representations have also been documented in a subset of LBL readers. Due to the loss of word-specific orthographic information, these patients present with additional features of surface alexia/agraphia characterized by impaired processing of irregular words and over-reliance on a sublexical phoneme-grapheme conversion strategy in reading and spelling (Bowers, Arguin & Bub, 1996; Friedman & Hadley, 1982; Hanley & Kay, 1992; Patterson & Kay, 1982; Rapcsak & Beeson, 2004). To be clear, such individuals are not “pure alexics.” Their parallel impairments of reading and spelling suggest that the same central orthographic representations mediate both tasks, consistent with a shared components model of written language processing (Tainturier & Rapp, 2001). Indeed, evidence from neuroimaging studies with normal readers corroborates that reading and spelling tasks produce overlapping activations in left inferior temporo-occipital cortex corresponding to the visual word-form area (VWFA; Cohen et al., 2000), suggesting that this region is a possible neural substrate of the orthographic lexicon (Beeson & Rapcsak, 2003; Cho, Rapcsak & Beeson, 2010; Rapp & Lipka, 2010). Consistent with this view, damage to the VWFA is a frequent finding in LBL readers, although the syndrome can also be caused by lesions that degrade or disrupt visual input to this region (Binder & Mohr, 1992; Cohen et al., 2003; Henry et al., 2005; Epelbaum et al., 2008).

Most LBL readers are reasonably accurate in decoding words by relying on a serial letter naming strategy. However, other patients with left temporo-occipital lesions have an additional letter identification/naming impairment that precludes the use of the compensatory LBL strategy, resulting in nearly total inability to read, or global alexia. It has been proposed that global alexia is attributable to a visual-verbal disconnection induced by damage to white matter pathways disrupting the transfer of visual information to left-

hemisphere perisylvian language areas (Dejerine, 1892; Binder & Mohr, 1992; Cohen et al., 2004). The responsible lesions generally involve the inferior temporo-occipital regions implicated in LBL reading, but there is also evidence of dorsal extension into occipital white matter pathways producing damage to callosal fibers traveling in the splenium and forceps major (Binder & Mohr, 1992). Patients with global alexia typically present with dense right hemianopia and thus can only process visual information from the left visual field projected to the right hemisphere. Therefore, the severe letter naming impairment of these patients suggests that successful use of a compensatory LBL reading strategy requires the structural integrity of interhemispheric connections between right hemisphere visual association cortex and left-hemisphere perisylvian language areas (Cohen et al., 2003; 2004).

Treatment for patients with severe alexia and impaired letter naming has involved the use of kinesthetic or tactile techniques to facilitate letter recognition. In such treatments, the patient either traces letters with his/her finger (kinesthetic approach; e.g., Maher, Clayton, Barrett, Schober-Peterson & Gonzalez Rothi, 1998), or has a helper trace letters into his/her palm to facilitate identification of component letters in a word (tactile approach; e.g., Sage, Hesketh & Lambon Ralph, 2005), or a combination of kinesthetic and tactile input is provided as the patient traces letters into the palm of his/her own hand (e.g., Lott, Friedman & Linebaugh, 1994). The rationale for these methods is that the combined stimulation from tactile/kinesthetic and visual input is expected to improve letter naming and thereby facilitate access to the orthographic lexicon. Once letter identification has reached an acceptable level, training is then geared toward improving speed and accuracy of reading. The benefit of tactile/kinesthetic input to assist in letter naming was acknowledged by Goldstein (1948) and documented in a number of subsequent case reports across a variety of language systems (Kashiwagi & Kashiwagi, 1989; Kreindler & Ioanescu, 1961; LaPointe & Kraemer, 1983; Luria, 1970; Stachowiack & Poeck, 1976). Of particular interest are studies that experimentally controlled for the specific effects of tactile or kinesthetic treatment in alexia with impaired letter naming. This includes the eight English-speaking cases summarized in Table 1. All of these individuals had acquired alexia with persistent letter naming impairments that limited their ability to effectively use a LBL compensatory strategy. As shown, letter naming accuracy ranged from 0% – 77% at the outset, and following various forms of tactile/kinesthetic treatment, letter naming skills were improved in all but one (Sage, et al., 2005). Additionally, all participants showed improved single-word reading accuracy and/or speed. Thus, the therapeutic value of tactile/kinesthetic treatments for global alexia appears to be relatively strong.

Response to tactile/kinesthetic reading treatment is dependent upon the ability to gain letter identity information via the tactile or kinesthetic modality. Relevant to this issue is the fact that there are some individuals for whom this skill is selectively impaired. A cohort of Japanese individuals with “kinesthetic alexia” who were unable to name letters or read words via the kinesthetic modality have been described by several investigative teams (Fukatsu, Fujii & Yamadori, 1998; Ihori, Kawamura, Fukuzawa & Kamaki, 2000; Ihori, Kawamura, Araki & Kawachi, 2002). Despite having intact visual reading and somatosensory function, some of these individuals demonstrated a kinesthetic-verbal disconnection attributed to damage to left parietal cortex and underlying white matter. Considered relative to the visual alexia literature, these observations suggest an apparent double dissociation between visual and kinesthetic impairments of reading. Specifically, damage to left occipito-temporal cortex results in defective visual identification of letters and words with preserved kinesthetic reading (e.g., Lott et al. 1994; Maher et al., 1998), whereas the opposite pattern is observed in patients with left parietal lesions (Fukatsu et al., 1998; Ihori et al., 2000; 2002).

In the present study, we explored the nature and treatment of an unusually severe case of acquired alexia accompanied by mild surface agraphia. Although the participant attempted to use a compensatory LBL reading strategy, success was limited due to her inability to correctly identify letters from visual input. At the outset, she was considered to be a good candidate for kinesthetic treatment; however, her modest response to treatment prompted further evaluation regarding the nature of her deficit. Detailed kinesthetic assessment and examination of her performance relative to a control group of participants with acquired alexia due to left temporo-occipital lesions further clarified the locus of the breakdown in cognitive functioning, and allowed us to hypothesize the regions of neural damage that contributed to her impairment. Ultimately, it became evident that the combination of deficits in this woman reflected a multimodal alexia profile not previously described in the literature.

2. Case History

2.1 Patient Description

ST was a 74-year old right-handed female with 12 years of formal education. Prior to retirement, she worked as an office manager and reported no developmental history of reading or spelling difficulties. At the time of study, ST was 15 months post onset of a hemorrhagic stroke affecting left temporo-parieto-occipital brain regions. She had previously suffered a right hemisphere stroke 4.5 years prior to study onset, which resulted in a small lesion in the superior frontal gyrus near the falx cerebri. This event resulted in a mild left hemiparesis that resolved a few months later, but no impairments of spoken or written language were associated with that event. The subsequent left hemisphere stroke resulted in persistent right homonymous hemianopia, anomia, and alexia with agraphia. Her spoken language profile was consistent with anomic aphasia, with an Aphasia Quotient of 77 on the *Western Aphasia Battery* (WAB; Kertesz, 1982) and a score of 14/60 (23% correct) on the *Boston Naming Test* (BNT; Goodglass, Kaplan, & Weintraub, 2001).

An MRI scan could not be obtained due to the presence of a pacemaker, so a CT scan was acquired at the time of this study. As shown in Figure 1, left hemisphere damage affected the inferior and middle temporal gyri (BA 20/21) and the inferior and lateral aspects of BA 37, encroaching upon the “visual word form area” (Cohen et al., 2000). The lesion also affected dorsal occipital cortex (BA 18, 19) and extended superiorly into the angular gyrus (BA 39) and underlying white matter. Extensive damage to interhemispheric callosal fibers traveling in the forceps major was also evident.

2.2 Pre-Treatment Assessment

2.2.1 Reading—ST’s oral reading performance was assessed using the *Arizona Battery for Reading and Spelling* (ABRS, n.d.; Beeson, Rising, Kim, & Rapcsak, 2010), a list of 40 regular and 40 irregular words (balanced for frequency, length, and imageability), and 20 pronounceable non-words. Her oral reading was characterized by attempts to read letter-by-letter, but with numerous errors in letter identification. She frequently perseverated on the letters “A, R, S, T” and her LBL reading attempts often resulted in words formed by combinations of these letters, such as “arts,” “star,” and “start.” She correctly read 12/80 words (15%) and 0/20 nonwords. Reading errors consisted mostly of perseverative responses of the aforementioned words (52% of errors), non-responses (40% of errors), and visually similar words (8% of errors).

Visual word recognition skills were assessed using three lexical decision tasks from the *Psycholinguistic Assessment of Language Processing in Aphasia* (PALPA; Kay, Lesser & Coltheart, 1992), and an orthographic choice task in which she was asked to select the

correctly spelled word from 40 pairs consisting of a real word and a pseudohomophone (e.g., blame – blaim). On the easier tasks, such as *PALPA* 24 (recognizing words among illegal nonwords) and the orthographic choice task, she performed with relatively high accuracy (93% correct on both tasks). ST's accuracy decreased on more difficult lexical decision tasks requiring discrimination of words from legal nonwords (*PALPA* 25 and 27; 75% and 80% correct, respectively), but was still better than chance. No effects of frequency/imageability (*PALPA* 25) or spelling regularity (*PALPA* 27) were observed on these tasks.

Reading comprehension skills were examined using the written word-picture matching subtest from the *PALPA* (48), which requires choice of the correct picture for a written target from a field of five line drawings. She was highly accurate at this task (98%). Her performance indicated that when she was not required to produce an oral reading response, she was able to engage central lexical-semantic representations from written words, similar to other LBL readers (Saffran & Coslett, 1998).

2.2.2 Spelling—Written spelling, oral spelling, and recognition of oral spelling were assessed using the same items from the *Arizona Battery for Reading and Spelling* that were used to assess reading. As shown in Figure 2, written spelling, oral spelling, and recognition of oral spelling were better preserved than oral reading [$\chi^2(3) = 103.49, p < .0001$], but not completely intact. A regularity effect characterized her performance on these three tasks, but was most pronounced for oral and written spelling. Phonologically plausible errors predominated her written and oral spelling performance (e.g., choir → quire), consistent with a surface agraphia profile. The majority of errors on the recognition of oral spelling task were orthographically or phonologically related to the targets and some reflected letter omissions (e.g., t-w-e-n-t-y → went), a likely result of the increased demands on short-term memory.

2.2.3 Letter and visual processing—Because of her frequent letter naming errors, ST's letter processing skills were further evaluated using tasks to assess visual letter identification, letter naming, and letter production using different input and output modalities. Several subtests of the *PALPA* (Kay et al., 1992) were used to evaluate visual letter identification skills. As shown in Table 2, ST scored nearly perfectly on *PALPA* 18 (identification of mirror-reversed letters), *PALPA* 19 (matching upper-to-lowercase letters) and *PALPA* 20 (matching lower-to-uppercase letters), indicating that she had preserved knowledge of letter shapes in the visual modality. Despite this, her ability to name visually presented letters was severely impaired (6/26 letters, or 23% correct). She tended to spontaneously “trace” individual letters with her finger when attempting to name them, which resulted in an improvement in letter naming performance to 12/26 letters (46% correct). In contrast to her defective letter-naming from visual input, she could name letters more accurately (18/20 consonants; 90% correct) following auditory presentation of the corresponding phonemes (i.e. “What letter goes with the sound /b/?”).

ST's ability to produce letters also differed as a function of the input modality used. When asked to copy single letters, she was abnormally slow, but relatively accurate (25/26 letters correct). Her attempts to copy single words showed striking deficits, particularly for lowercase letters, as shown in Figure 3. She appeared to rely on a stroke-by-stroke reproduction of the visual pattern, more similar to picture drawing than copying words. This stood in stark contrast to her well-formed letters when writing letters and words to dictation (see Figure 3). The fact that she could write letters to dictation demonstrated intact “graphic motor programs” and motor control for writing, functions that are thought to depend on left-hemisphere neural systems (Rapcsak & Beeson, 2002). It seemed, then, that her difficulty in copying letters/words reflected a failure to access these programs from right hemisphere visual input. Taken together, the striking dissociation between ST's ability to name and

produce letters based on visual versus auditory input suggested a combination of visual-verbal and visual-motor disconnections, where visual information from the right hemisphere failed to access left hemisphere language and motor control areas.

ST's poor letter processing prompted further investigation of her visual perception and visual object recognition skills. First, to determine whether her poor copying performance was specific to letters, she was asked to copy a figure and reproduce it from memory (Figure 4). Although the overall integrity of the original figure was maintained in both productions, her copied performance was more labored and imprecise compared to her drawing from memory, providing further confirmation of a visual-motor disconnection. In addition, ST's visual object recognition was assessed with two tasks of spoken word – picture matching (*PALPA* 47 and a task involving choice of a specific living or non-living item from amongst 3 visually/semantically related foils). Her performance on these tasks was highly accurate (39/40 on *PALPA* 47 and 64/64 on the living/non-living task). As mentioned previously, she also performed well (98% correct) on *PALPA* 48 (written word-picture matching). Taken together, her performance on these tasks confirmed that her poor naming was not a result of a more pervasive visual-object agnosia.

2.2.4 Summary of pre-treatment assessment—ST presented with nonfunctional oral reading skills, with some preservation of lexical-semantic access from printed words presumably mediated by the intact right hemisphere. Her spelling skills were better preserved than oral reading skills, but central processing deficits were also evident given the regularity effects demonstrated in written spelling, oral spelling, and recognition of oral spelling. This profile of surface agraphia suggested that although the left-hemisphere orthographic lexicon could be accessed during spelling tasks that did not require interhemispheric transfer of information, word-specific orthographic knowledge was not completely intact.

ST also demonstrated marked difficulty in naming letters presented in the visual modality. This impairment could not be attributed to a general anomia for letters, nor a more pervasive visual processing deficit affecting letter shape recognition. Rather, her inability to access letter names from visual input appeared to indicate a visual-verbal disconnection. Further, a visual-motor disconnection was evident based on her labored, imprecise copying performance.

3. Kinesthetic Treatment

ST was highly motivated to improve her reading, therefore, a behavioral treatment protocol for single-word reading was a logical first step in remediating her written language impairments. The goal of treatment was to improve her ability to read words using a kinesthetic approach to facilitate the recognition of component letters. Although labor intensive, the hope was that once letters could be accurately identified based on combined visual and kinesthetic input, ST could then use a compensatory LBL reading strategy. Several factors led us to believe this treatment approach would be appropriate: a) she attempted to use a LBL strategy when reading; b) she could accurately (albeit slowly) copy single letters; c) she spontaneously traced letters when attempting to name them and this strategy seemed to improve her performance; and d) her profile appeared similar to several cases described in the literature for whom a kinesthetic strategy had facilitated single word reading (see Table 1).

An adaptation of a lexical spelling treatment (i.e., Copy and Recall Treatment, CART, Beeson, Rising & Volk, 2003) was used to strengthen letter recognition and naming via the kinesthetic modality. CART has previously been used to retrain spelling for targeted words,

without a focus on letter naming (Beeson, Hirsch & Rewega, 2002; Beeson et al., 2003); however, for ST, the procedure included repeated copying of targeted words along with the naming of each letter. The approach was intended to facilitate LBL reading by providing kinesthetic input to assist in letter identification along with support from lexical-semantic information derived from a picture of the target word. The stimuli consisted of high-frequency, imageable nouns ranging from 3–5 letters in length that ST could both name and spell correctly. The items were trained in sets of six using a multiple baseline design. The words contained all letters of the alphabet, except for the letter “x,” which she always named correctly. For each word, a picture and the printed word were provided. ST was instructed to look at the picture, then copy the word while naming each letter aloud, and finally to say the word. As intended, her performance on the letter-naming task was supported by her residual abilities to name and spell each of the pictured items. Daily homework following the same procedure was provided for each set of words. Probes of letter naming with and without use of the kinesthetic strategy, as well as reading of trained words were taken at each treatment session. Training progressed from one set to the next when a criterion of 5/6 words read correctly over two treatment sessions was met. The treatment approach differed from previous studies reviewed in Table 1, in that it was designed to give ST repeated practice copying and naming letters within a lexical-semantic context, with the intention of strengthening the connection between each letter name and its associated visual representation and kinesthetic movement.

3.1 Response to Treatment

Hour-long treatment sessions were conducted twice weekly for a total of 8 weeks (16 hours total). In addition, ST completed structured daily homework exercises for 30 min/day, resulting in an additional 28 hours of practice. During that time, ST learned to read the trained words, meeting criterion for each set within two to three treatment sessions. She also improved her ability to recognize letters individually, but this improvement was dependent on the combined visual and kinesthetic input derived from use of the kinesthetic strategy. Letter naming accuracy (when using the kinesthetic strategy) improved from an average of 54% (14/26) before treatment to 85% (22/26) over the last three sessions. The kinesthetic approach was quite laborious, however, often requiring several “copies” of a letter before it was correctly named. Letter naming attempts without using the kinesthetic strategy remained markedly impaired, although ST improved slightly from 6/26 letters (23% correct) pre-treatment to 9/26 (35% correct) over the last three treatment sessions. This was significantly worse than her post-treatment letter naming when using the kinesthetic strategy [$\chi^2(1) = 50.02, p < .0001$].

At the end of eight weeks, treatment was discontinued as ST was leaving town for an extended period of time. The reading battery (ABRS) was re-administered prior to her departure in order to assess whether there was any generalization to untrained items. ST’s oral reading performance improved slightly (12% to 17% correct overall, a difference that was not statistically significant [$\chi^2(1) = .65, p = .42$]). At that time, ST attempted to read letter-by-letter, supported by the kinesthetic strategy; however, her reading attempts were extremely laborious and prone to error. Multiple attempts at copying letters added considerable demands on working memory as she tried to decode the written words. In addition, some of her reading errors reflected intrusions of trained words that were visually similar to or began with the same letter as the target.

When ST returned five-months later, her letter naming was again probed. When naming the letters was based on vision alone, her performance was relatively unchanged at 9 of 26 letters correct (35%). Letter naming was better when she was allowed to use the kinesthetic strategy to aid in identification in that she named 62% (16/26) of letters correctly. This was a significant decline from 85% (22/26) accuracy at the end of treatment [$\chi^2(1) = 12.42, p < .$

001]) however, suggesting that without constant practice, treatment gains were fragile. She remained unable to effectively use the kinesthetic strategy to decode words for reading.

3.2 Treatment Summary

The goal of the treatment program was to support letter identification by associating visual and kinesthetic information with top-down lexical-semantic facilitation through repeated copying of letters in words. Although ST improved her letter naming performance following kinesthetic treatment, these gains were tenuous and performance returned to pre-treatment levels following a break where constant practice was not maintained. Moreover, improved naming of letters in isolation did not result in a corresponding increase in single-word reading accuracy, and word reading remained laborious. This limited response to treatment stood in contrast to several other cases reported in the literature (Table 1), where improvements in letter naming and single word reading were observed following treatment using a kinesthetic strategy. The failure of kinesthetic treatment to result in a lasting improvement of letter identification and single word reading prompted further assessment of the nature of ST's deficit.

4. Kinesthetic Assessment

The intended purpose of the kinesthetic treatment strategy was for ST to supplement degraded visual input with letter shape information acquired through a kinesthetic modality. Despite our prediction that repeated practice copying letters would strengthen the links between letter-form information acquired kinesthetically and the letter name, ST was unable to use this kinesthetic strategy to decode and read single words letter-by-letter. Thus, in addition to the visual-verbal disconnection that was responsible for her global alexia, she seemed to also display elements of kinesthetic alexia in that she could not gain letter identity information via the kinesthetic modality. Assessment of her ability to process kinesthetic stimuli was conducted to delineate the cognitive mechanisms underlying ST's persistent, severe reading impairment. Her performance was examined relative to a control group of individuals with acquired alexia due to left temporo-occipital damage.

4.1 Patient Control Group

Seven individuals (6 males, 1 female) with acquired alexia following stroke in the distribution of the left posterior cerebral artery (PCA) were examined. They were all right handed, had a mean age of 71.2 years, and were an average of 7.3 years post onset of stroke. Their spoken language profiles were consistent with anomic aphasia, and their average WAB Aphasia Quotient was 95.6 (sd = 4.2, range = 89.2 – 99.6). Relative to ST, their single-word reading (assessed using the *Arizona Battery for Reading and Spelling*; Beeson et al., 2010) was better preserved (77% correct), and all participants were 100% accurate in copying and naming single letters. A significant word-length effect had been previously documented in five of these individuals, and at the time of testing for this study, their single-word reading remained abnormally slow, as evidenced by an average of 1675 msec (range = 885 – 3807 msec) to read four to seven letter words compared to 612 msec by age-matched controls. The PCA stroke group's spelling performance (76% correct) was similar to ST's (70% correct). Like ST, they also demonstrated regularity effects in their spelling performance consistent with a surface agraphia profile suggesting damage to the left-hemisphere orthographic lexicon (Figure 5).

4.2 Procedure

During individual test sessions, the examiner presented kinesthetic information for individual letters by passive movement of the participant's hand to trace uppercase letter shapes with the index finger. Participants were seated with eyes closed with the examiner

standing beside them in order to move the right index finger on the table in front of them. After a letter was presented, the participant was asked to reproduce the letter shape unassisted (*kinesthetic letter production*), and then to immediately attempt to name the letter aloud (*kinesthetic letter naming*). Although the eyes were to remain closed during stimulus presentation, they were allowed to open them as they reproduced the letter shape. All responses were videotaped to double check for accuracy, and were scored as correct if the same letter was written, even if the exact letter shape or order of the strokes differed from those presented by the examiner. The same procedure was also completed using the left hand. Accurate completion of these tasks required letter-shape recognition from kinesthetic input, activation of corresponding graphic motor programs, and access to letter name codes (cf. Ihori et al., 2002).

4.3 Results

The PCA stroke group performed near ceiling on both the kinesthetic letter production and kinesthetic letter naming tasks, regardless of which hand was used. When stimuli were presented to the right hand, control participants correctly reproduced and named an average of 25/26 letters and 24/26 letters, respectively. Left hand results were similar, but were on average one letter less accurate. ST was similarly able to accurately reproduce letters perceived kinesthetically with her right and left hands (25/26 and 24/26 letters correct, respectively). On occasion, ST formed the letter shapes in a different (but acceptable) manner compared to the model presented by the examiner (e.g. writing an upper case “E” with curves rather than with right angles). This behavior was also observed in some instances in the control participants, and suggested preserved kinesthetic letter shape recognition and access to abstract graphic motor programs. Despite relatively preserved letter recognition, ST could only name 9/26 (35%) letters. She often reverted to guessing “A, R, S, T” when she could not immediately name the letter. Taken together, these results suggested that ST’s kinesthetic alexia was caused by a kinesthetic-verbal disconnection similar to some of the cases described in the Japanese literature (Fukatsu et al., 1998; Ihori et al., 2000; 2002). The kinesthetic-verbal disconnection was not evident in the patient control group, however, prompting a closer examination of the lesion profile in ST relative to the PCA stroke group and the cases of kinesthetic alexia reported in the literature.

4.4 Lesion Analysis

ST’s lesion was mapped onto axial slices of a template brain aligned with her CT brain scan using MRIcro (Rorden & Brett, 2000), with areas of lesion interpolated for intervening slices. The resultant reconstruction is displayed on a sagittal slice in Figure 6a. As seen in this figure and on the clinical scan shown in Figure 1, areas of damage included inferior temporo-occipital cortex with superior extension into medial occipito-parietal region, angular gyrus (BA 39) and the underlying white matter, including the forceps major. In contrast, composite lesion maps of the seven control participants with alexia due to PCA strokes displayed on the same sagittal slice indicate damage confined to left inferior temporo-occipital cortex, without the superior extension into parietal cortex and without compromising the callosal fibers traveling in the forceps major (Figure 6b). In summary, ST had a lesion that was well-situated to disconnect callosal fibers carrying visual information to the left hemisphere language areas (i.e., a visual-verbal disconnection resulting in global alexia) and she also had damage to left parietal cortex and underlying white matter to produce bilateral kinesthetic alexia (i.e., a kinesthetic-verbal disconnection). These neuroanatomical features are absent in the PCA alexic group who had less severe visual reading impairment and no evidence of kinesthetic alexia.

5. Discussion

In this study, an individual with severe alexia and mild surface agraphia underwent kinesthetic treatment intended to re-train and improve letter identification skills, with the hope that a compensatory letter-by-letter reading strategy could then be used. The combined visual and kinesthetic stimulation resulted in improved letter identification, but the procedure was too slow and error-prone to provide a successful strategy to decode untrained words. Moreover, gains in letter identification skills were tenuous without consistent practice. Further investigation into the nature of this woman's persistent reading deficits revealed she had a combination of visual-verbal and kinesthetic-verbal disconnections, thus resulting in a multimodal alexia syndrome.

The contributing cognitive deficits and the underlying neural substrates responsible for ST's multimodal alexia are depicted in Figure 7. She was unable to read aloud visually presented words due to a combination of right hemianopia (resulting from left occipital damage) and the additional disconnection of visual input from the right hemisphere. ST attempted to read using a LBL strategy to decode single words, but she was unsuccessful in doing so. A LBL strategy relies on the following requisite skills: recognition of visual letter shapes and activation of abstract letter identities, letter naming, holding letter names in short-term memory, and finally combining serially identified letters to access the orthographic lexicon. ST performed accurately on letter processing subtests of the *PALPA* (18, 19, 20) confirming she had intact letter shape knowledge and abstract letter activation in the visual modality. She could also recognize orally spelled words, a skill that confirmed that short-term memory and the ability to combine serially identified letters were relatively intact (Greenwald & Gonzalez Rothi, 1998; Cohen et al., 2003). The main factor preventing ST from successfully reading LBL was that she could not access letter name codes from visual input despite preserved processing of visual letter shape information. We are confident that this was indeed a modality-specific *access* issue rather than a manifestation of general anomia, because she could accurately generate letter names when performing oral spelling, and she could name letters associated with auditorily presented phonemes. Moreover, she could recognize letter names presented in the auditory modality when asked to name orally spelled words. These observations are consistent with the hypothesis that ST's inability to read words in a LBL fashion was the result of a visual-verbal disconnection between preserved visual letter shape knowledge and the corresponding letter name codes.

As described in Dejerine's seminal case (1892) and more recently by Binder and Mohr (1992) and Cohen et al. (2003), the global alexia that results from such a visual-verbal disconnection is attributed to a near complete isolation of left hemisphere language areas from all visual input. The typical lesion profile in these cases entails damage to left inferior temporo-occipital cortex combined with a disruption of interhemispheric callosal fibers. Individuals with damage restricted to left inferior temporo-occipital cortex are usually able to read using a LBL strategy despite the presence of a right hemianopia (Binder & Mohr, 1992; Cohen et al., 2003). In these cases, letter identity information processed initially by right hemisphere visual areas is able to access left hemisphere language areas in a slow, serial manner. Therefore, it is the additional callosal disconnection preventing interhemispheric transfer of all visual information that shifts an individual from pure alexia (with the ability to read LBL) to global alexia as depicted in Figure 7. Indeed, ST demonstrated such a lesion encompassing left temporo-occipital regions, along with damage to callosal fibers traveling in the forceps major, accounting for her global alexia profile. Her preserved ability to access letter name codes during oral spelling, recognition of oral spelling, and when naming letters associated with phonemes provided evidence that left perisylvian cortical regions critical for the retrieval of phonological representations for letters (Cohen et al., 2003, 2004; Huang, Carr & Cao, 2002; Joseph, Gathers & Piper, 2003)

were spared. Although the proposed visual-verbal callosal disconnection resulted in ST's poor performance on all oral reading tasks, she nonetheless demonstrated preserved reading abilities on lexical decision and written word comprehension tasks. There is evidence to suggest that the right hemisphere can mediate access to lexical-semantic information from written words in tasks that do not require explicit stimulus identification (Coslett & Saffran, 1998; 1989; 1994; Saffran & Coslett, 1998). It appears then, that ST's accurate performance on lexical decision and written word comprehension tasks that did not require a spoken response, and therefore the callosal transfer of information to left-hemisphere language areas, was mediated by right-hemisphere cognitive systems.

Our rationale for implementing the kinesthetic treatment with ST was to enable her to read words by supplementing impaired visual letter identification through kinesthetic facilitation, as documented in other cases described in the literature. However, two functional impairments prevented our treatment approach from having its intended effect. The first was a kinesthetic-verbal disconnection, in that she also could not access letter name codes based on kinesthetic input, as depicted in Figure 7. The second was a visual-motor disconnection that prevented ST from accurately copying letters and words.

The successful use of a kinesthetic facilitation strategy relies on the ability to gain letter identity information using this modality. Kinesthetic reading requires intact somatosensory perception, retrieval of "kinesthetic images" (Ihori et al., 2002) for letters stored in graphic motor programs (Rapcsak & Beeson, 2002), and the activation of the corresponding letter name codes. ST's kinesthetic alexia could not be attributed to impaired somatosensory perception of letter shape information or defective activation of graphic motor programs, as we have shown that she was able to write letters accurately with both hands based on kinesthetic input. In fact, she sometimes reproduced letters using different strokes than those presented, but with acceptable allographic variation for that letter, indicating that she could access the letter's abstract graphic motor program. However, just as she could not name visually presented letters, she could not access letter name codes based on kinesthetic information resulting in bilateral kinesthetic alexia. Lesion-deficit correlation studies in neurological patients and neuroimaging studies in normal subjects have provided converging evidence that the left superior parietal lobule (SPL)/intraparietal sulcus (IPS) is an important neuroanatomical substrate for the retrieval of graphic motor programs that guide the written production of letters with both hands (for a review see Beeson et al., 2003; Rapcsak & Beeson, 2002). Critically, it has been shown that left SPL/IPS is activated during kinesthetic reading in normal subjects (Takeda et al., 1999) and damage to this region produces kinesthetic alexia (Fukatsu et al., 1998; Ihori et al., 2000; 2002). ST's lesion spared the left SPL, but did partially compromise the inferior portion of left IPS and underlying white matter. Her preserved ability to write letters during spontaneous writing, writing to dictation, and when writing from kinesthetic input is consistent with the relative sparing of graphic motor programs stored in the left SPL/IPS. Therefore, we propose that her kinesthetic alexia was the result of a kinesthetic-verbal disconnection caused by damage to white matter pathways traveling between left SPL/IPS and perisylvian language areas. Because she could accurately reproduce kinesthetically perceived letters with both her right and left hands, we assume that callosal connections transferring somatosensory information from the left hand (initially processed in the right hemisphere) to the left hemisphere were intact. Specifically, it has been proposed that during kinesthetic reading and letter reproduction, somatosensory information from the left hand is transferred to left SPL/IPS via the anterior or dorsal part of the posterior body of the corpus callosum (Ihori et al., 2000). Although in ST's case the left SPL/IPS could receive kinesthetic letter shape information from either hand and activate the appropriate graphic motor programs, damage to underlying white matter tracts prevented downstream access to corresponding letter name codes. Such a kinesthetic-verbal disconnection has been documented in a number of Japanese cases (Fukatsu et al., 1998,

Ihori et al., 2000; 2002), but the presence of this condition has not been examined in English-speaking cases. In addition, the impact of this constellation of the deficits has not been considered relative to the rehabilitation of acquired alexia.

The other impairment which prevented our treatment from having its intended effect was a disruption in visual-motor connections necessary for accessing left-hemisphere graphic motor programs from visual input, interfering with ST's ability to copy letters and words efficiently. Due to a right homonymous hemianopia resulting from her stroke, the only visual information that ST had available to copy letters/words was from her left visual field processed in the right hemisphere. Copying letters required information from right-hemisphere visual areas to reach left SPL/IPS. As noted earlier, ST's graphic motor programs themselves were intact, based on her well-formed letters in spontaneous writing, writing to dictation, and when writing letters from kinesthetic input. However, it was evident from her defective performance in copying letters and words that access to these motor representations from visual input was impaired. Her word copying resembled slavish stroke-by-stroke reproductions of the visual pattern rather than the fluid copying performance of normal subjects that takes advantage of stored motor patterns for writing (see Figure 3). It was not surprising that her copying of lowercase words was worse than uppercase, likely due to the greater visual similarity and graphomotor complexity of lowercase letters (Graham, Patterson & Hodges, 1997). We postulate that a disruption to splenial callosal fibers carrying visual information from right occipital cortex to left SPL/IPS was the probable neuroanatomical explanation for ST's visual-motor disconnection. ST's inability to quickly and accurately copy letters made this functional disconnection particularly problematic when attempting to use the kinesthetic facilitation strategy for reading.

Ultimately, it was evident that ST demonstrated a unique combination of deficits that have been described independently in patients with global alexia and kinesthetic alexia. The damage resulting from her hemorrhagic stroke affected the neuroanatomical regions that have been previously implicated in each of these syndromes. The unusual combination of behavioral deficits produced by the atypical lesion configuration resulted in severe, multimodal alexia depicted in Figure 7, which proved resistant to treatment. Although ST's severe visual-verbal disconnection, and to an extent her visual-motor disconnection were evident during pre-treatment assessment, the severity of her kinesthetic-verbal disconnection was not.

At the outset, we pursued a kinesthetic treatment approach because ST appeared to be similar to the individuals in Table 1 who improved their reading skills following tactile and/or kinesthetic treatment approaches. However, closer examination of the behavioral and lesion profiles revealed interesting similarities between ST and the Sage et al. (2005) case, who also did not improve letter naming in response to treatment. The authors reported that their participant (FD) was not able to accurately copy (i.e., trace) single letters from visual representation, and that he did not always follow typical motor sequences when attempting to trace a letter. This deficit prompted them to trace the letters into the participant's hand in an attempt to provide tactile input regarding letter identities. FD failed to improve letter naming in response to this treatment, rather, he responded positively to a treatment that facilitated a whole-word reading approach which was administered immediately prior to the tactile treatment. The authors provide evidence to support FD's shift away from a LBL reading strategy to a whole-word approach following the initial treatment, and he appeared to maintain the whole-word reading approach throughout the tactile treatment, despite its focus on serial decoding of letters. Of particular interest is the fact that FD was also the only other case whose lesion extended dorsally from occipito-temporal regions into the parietal lobe and underlying white matter tracts as did ST's lesion. Both FD and ST experienced hemorrhagic strokes, thus explaining why their lesions extended outside of the left posterior

cerebral artery distribution that was the focus of damage in the patient controls in our study, as well as the other cases included in Table 1. Thus, there appears to be both behavioral and lesion evidence to suggest that FD may have experienced a multimodal alexia similar to ST.

As noted at the outset, a letter-by-letter reading profile with impaired letter naming may prompt the use of a kinesthetic strategy to improve single word reading in individuals with acquired alexia. However, our findings in ST suggest that in order to derive benefit from this approach, the individual must be able to name kinesthetically presented letters and have sufficient verbal span capacity to hold component letters in memory to identify single words. Moreover, if attempting to train letter identification through the kinesthetic modality, the individual must be able to accurately copy single letters. It may be useful to consider lesion information when evaluating candidacy for kinesthetic reading treatment. Preliminary evidence from our case and Sage et al.'s (2005) case suggest that lesions extending into left parietal lobe may be associated with kinesthetic alexia.

An in-depth investigation of ST's severe reading impairment allowed us to clarify the cognitive mechanisms and neural substrates underlying her multimodal alexia syndrome. However, this study had a number of limitations that must be considered. First, as with any single case study, care must be taken when attempting to generalize the behavioral and neuroanatomical results. Second, time constraints limited the duration of kinesthetic treatment to eight weeks for this individual, which is less than most of the treatment studies reviewed in Table 1. Although we posit her unique combination of visual-verbal, visual-motor and kinesthetic-verbal disconnections accounted for her limited response to treatment, it is possible that with longer treatment durations these deficits may have shown some degree of remediation. Finally, it should be noted that in cases where the kinesthetic facilitation of LBL reading fails, there may still exist a potential for improvement by using a whole-word approach to facilitate right-hemisphere reading (Sage et al. 2005) that was not attempted in our patient.

RESEARCH HIGHLIGHTS

1. Examined mechanisms of visual and kinesthetic reading in a case of severe alexia.
2. Multimodal alexia due to visual-verbal and kinesthetic-verbal disconnections.
3. Visual-verbal disconnection attributed to callosal damage.
4. Kinesthetic-verbal disconnection attributed to left parietal lobe damage.

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Figure 1.
CT scans showing ST's left temporo-parietal-occipital lesion. Images were acquired in the axial plane with 10 mm slices parallel to the canthomeatal line.

Figure 2.

ST's performance on oral reading, recognition of oral spelling, written and oral spelling of regular words, irregular words and nonwords (same stimuli used for all four tasks)

Direct Copy lowercase	Direct Copy uppercase	Writing to Dictation
provide <u>p p v t d</u>	HAPPY <u>HA CEY</u>	"gang" <u>GANG</u>
greet <u>g r e c t</u>	STRICT <u>S T R I C T</u>	"mile" <u>M I L E</u>
though <u>t o u g h</u>	THOUGH <u>T H O U G H</u>	"doubt" <u>DOUBT</u>
		"lose" <u>LOOSE</u>
		"grumble" " <u>GRUMPLE</u>
		"drive" <u>DRIVE</u>
		"honest" <u>HONEST</u>

Figure 3.
Sample of ST's performance on direct copy of words (lower and upper case) versus writing words to dictation

Figure 4.
Sample of ST's performance on direct copy of a figure versus drawing figure from memory

Figure 5.
ST's versus patient control group's performance on spelling regular words, irregular words and nonwords

6a

6b

Figure 6. Comparison of lesion location in ST (6a) and the lesion overlay of seven individuals with damage in the distribution of the left posterior cerebral artery (6b)

Figure 7.

A depiction of the cognitive deficits and neural substrates associated with four peripheral alexia syndromes. Letter-by-letter reading results when parallel transmission of letter identity information to the orthographic lexicon is disrupted, but serial transmission of visual information from right occipital cortex to left-hemisphere language areas is still possible. Global alexia occurs with the additional disruption of transcallosal visual information from the right hemisphere. Kinesthetic alexia is a disconnection of tactile/kinesthetic information from left parietal regions to left perisylvian cortex, where letter naming is accomplished (This is one subtype of kinesthetic alexia and is the underlying mechanism in our patient. See Ihori et al. (2002) for a description of additional forms of kinesthetic alexia). Finally, multimodal alexia reflects a combination of global and kinesthetic alexia. Note that for clarity of presentation, not all cognitive processes and relations are depicted in this figure; in particular, not shown is the engagement of graphic motor programs for written spelling.

Table 1

Summary of lesion and behavioral characteristics of published cases of acquired alexia receiving kinesthetic treatment to improve reading

Author Year	Lott et al. 1994	Lott & Friedman 1999 (Exp 1)	Greenwald & Gonzalez Rothi 1998	Maher et al. 1998	Sage et al. 2005 (Treatment 2)	Lott et al. 2010 (Phase 1 and Phase 2)
Participant	TL	DL	MR	VT	FD	DBR
Age/Gender	67/M	67/M	72/F	43/F	73/M	84/F
Time post onset	14 months	5 months	13 months	30 months	< 6 months	> 24 months
Aphasia profile	Transcortical sensory	Moderate anomic	Anomic	Not aphasic	Anomic	Fluent
R visual field deficit	Yes	Not reported	Yes	Yes	Yes	Not reported
Damage:						
L Temporo-occipital	Yes	Yes	Yes	Yes	Unknown	Yes
L Parietal	No	No	No*	No	Unknown	No*
Oral reading accuracy (words)	25% (8/32) ¹	7% (2/30) ²	0% ³	0% ³	77% (44/60)	3% (1/30) ²
Recognition of oral spelling	91% (29/32) ¹	100% (8/8) ²	96% ³	100% ³	Not reported	88% (28/32)
Written spelling	97% (31/32) ¹	80% (8/10) ²	67% ³	100% ³	54% (13/24) ⁴	78% (25/32)
Pre-tx letter naming	49% baseline mean	62% (16/26)	12% (3/26) UC	0%	69% (18/26) LC	73% (19/26) LC
Treatment Approach	Tactile/Kinesthetic	Tactile/Kinesthetic	Kinesthetic	Kinesthetic	Tactile	Tactile/Kinesthetic
Stimuli & Task	Letters/words copied in palm w/ capped pen	Tx 1. Letters copied in palm w/ capped pen Tx 2. Speeded LBL reading	Letters traced w/ finger	Sentences traced w/ finger	Letters, letter sequences, words traced into palm by helper	Tx 1. 5 stage approach including letters traced w/ finger into palm Tx 2. Speeded LBL reading
Treatment amount (approx)	60 hours	Tx 1 18 hrs Tx 2 14 hrs	25 hours	18 hours	7 wks with daily homework	Tx 1 5 hrs Tx 2 38 hrs
Tx outcome: letter naming	Improved [†]	Improved with strategy	Improved [†]	Improved using strategy Unchanged	Unchanged	Improved Without strategy Improved Without strategy

Author Year	Lott et al. 1994	Lott & Friedman 1999 (Exp 1)	Greenwald & Gonzalez Rothi 1998	Maher et al. 1998	Sage et al. 2005 (Treatment 2)	Lott et al. 2010 (Phase 1 and Phase 2)
	w/o strategy					
Tx outcome: word reading (trained)	Improved accuracy using strategy	Improved accuracy	Improved accuracy using strategy	Improved speed using strategy	Improved speed/accuracy [†]	Tx 1. Reading did not improve Tx 2. Improved speed & accuracy
word reading (untrained)	Improved accuracy using strategy	Improved accuracy using strategy		Improved speed using strategy [†]	Improved speed/accuracy [†]	Tx 2. Improved speed & accuracywsw

¹ Friedman Part 1 Speech list (Lott et al., 1994);

² Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983);

³ Battery of Adult Reading Function (Rothi et al., 1986);

⁴ Psycholinguistic Assessments of Language Processing in Aphasia (Kay et al., 1992);

LC = lower case

* damage extending to parieto-occipital junction

[†] Not indicated whether the strategy was used during post-testing.

Table 2**ST's Performance on Letter Processing Tasks**

	Score	% Correct
Visual Letter Identification		
<i>PALPA</i> 18: Mirror reversal letter identification	36/36	100%
<i>PALPA</i> 19: Upper-lower case match	26/26	100%
<i>PALPA</i> 20: Lower-upper case match	25/26	96%
Letter Naming		
Visual Input	6/26	23%
Auditory Input (e.g., "What letter goes with /b/?")	18/20	90%
Kinesthetic Input (right hand)	9/26	35%
Kinesthetic Input (left hand)	10/26	38%
Letter Production		
Visual Input (direct copy of single letters)	25/26	96% ¹
Auditory Input (writing letters to dictation)	26/26	100%
Kinesthetic Input (right hand)	25/26	96%
Kinesthetic Input (left hand)	24/26	92%

¹ Abnormally long time to complete task relative to control individuals