READING WITH HOMONYMOUS HEMIANOPIA:

EFFECTS AND REHABILITATION

by

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Abstract

Cerebral damage to the optic radiations or striate cortex causes ‘homonymous hemianopia’, blindness in the contralateral half of the visual field in each eye. In cultures that read left to right, a right hemianopia has a severe effect on reading efficiency, particularly when the central 5° are lost, because most of the information acquired during reading lies in the right parafoveal field. We explored the importance of right hemifield loss in diagnosing pure alexia (Experiments 1, 2). Later, we assessed the feasibility of an online training program for the rehabilitation of hemianopic dyslexia, and the eye-movement changes that might accompany learning (Experiment 3). In the first two experiments, human subjects performed several visual processing tasks, using a simulated hemianopia gaze-contingent display. We found that hemianopia alone can account for some previously reported impairments in pure alexia. Subsequently, we provide diagnostic criterion for using the word-length effect to discriminate between hemainopic dyslexia and pure alexia for various types of central involvement by right hemifield loss. In the final experiment, a pilot rehabilitation study, two patients with hemianopic dyslexia performed a 10-week on-line perceptual learning task to increase reading span, and improve reading efficiency. Following training, benefits were limited to an increase in the size of forward saccades in one patient (patient JW). We conclude that this training approach is feasible, though further studies are needed to establish efficacy.

Preface

All the experiments are based on work conducted in UBC's Human Vision and Eye Movement Laboratory (Eye Care Centre, Vancouver General Hospital), supervised by Dr. Jason JS Barton. I was responsible for creating the experiments, assisting with the design of the online training program, recruiting and recording subjects/patients, and writing a preliminary draft of the work. Dr. Jason Barton and I worked together on data analyses.

Part of the work in this thesis has been published in a peer-reviewed journal, and is found in Chapter 1.1 (introduction), Chapter 2 (methods, results), and Chapter 5.1 (discussion).

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*Indicates co-first authors. I was responsible for supervising an undergraduate student [Jing Ye Bao], and directly helping her with creating experiments, recruiting and recording subjects, data analyses, and writing a preliminary draft of the work. Dr. JG Taylor helped with experimental design and data analyses. Dr. Jason Barton performed the bulk of data analyses, and made final edits before submission for publication.

The UBC Clinical Research Ethics Board and Vancouver Coastal Health Authority approved this work. The certificate details are:

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To my mother

Chapter 1: Introduction

Cerebral damage to the optic radiations or striate cortex causes *homonymous hemianopia*, blindness in half the visual field of both eyes. Persistent hemianopia occurs in 20% of people with stroke (Isaeff et al 1974), and rarely improves beyond 6 months from onset (Zhang et al 2006), leaving patients with a fixed visual deficit. 40% of all hemianopic patients have *complete* right or left hemianopia, which severely affects their activities of daily living, including their ability to read (Zhang et al 2006). In fact, patients with *right hemianopia* report that reading difficulties are the primary challenge that prevents them from regaining full control over their own lives (Warren 2009). Right homonymous hemianopia affects reading more than left hemianopia for two main reasons. First, the reading span, the number of letters that can be processed during a fixation, is asymmetric. In cultures that read left to right, the span extends 15 letters or about 5° to the right but only 4 letters or about 1.3° to the left (Schuett et al., 2008; Rayner, Slattery, & Belanger, 2010). Second, during the sequential process of reading, each fixation also involves a preview of the upcoming text to the right, which helps the planning of where to place the next fixation (Schotter et al., 2012). The result is that patients with right hemianopia read slowly, moving along the text with more and longer fixations, and, more and smaller rightward saccades, as well as more regressive (leftward) saccades (Trauzettel-Klosinski & Brendler, 1998), a condition known as "hemianopic dyslexia" (Wilbrand, 1907; Zihl, 1995).

To date, little effort has been made to systematically improve the reading performance of these patients. The present study explores the impact of hemifield loss on reading in healthy subjects (Experiment 1,2), and examines the feasibility of a perceptual learning task for rehabilitation of *hemianopic dyslexia* in patients (Experiment 3).

1.1 The importance of differentiating hemianopia from pure alexia

The two most common types of acquired reading disorders are hemianopic dyslexia and pure alexia. Both types result often from damage to left occipital cortex, most frequently from infarcts in the territory of the posterior cerebral artery, yet have distinguishing features that make them unique. Although alexia can be part of a broader language disorder (aphasia) arising from left hemisphere damage, it can occur as an isolated deficit with intact auditory language and relatively preserved ability to write. This is called 'pure alexia', also known as 'alexia without agraphia', a condition in which normal reading fluency is impaired, and conceptualized as one of the relatively selective visual agnosias, as the ability to recognize other types of visual objects is relatively preserved. Impairment is a result of damage to the word and letter recognition system that allows readers to recognize words rapidly and accurately (Leff, 2006). Because of such damage, pure alexic subjects, if they are able to read at all, use a letter-by-letter reading strategy. [1]

The majority of subjects with pure alexia also have a right homonymous hemianopia (Leff, et al., 2001). Right homonymous hemianopia can also reduce reading efficiency when the defect affects the central 5 degrees of vision (Trauzettel-Klosinski & Brendler, 1998; Zihl, 1995). Hence an important point of diagnosis for clinical management and categorization for research study is the ability to distinguish between hemianopic dyslexia, in which slowed reading is due solely to the reduction in visual field, and alexia, in which there are higher level problems in processing letters and words.

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[1] While subjects with developmental dyslexia are also slowed in reading and can show a letter-by-letter approach, acquired and developmental problems in reading likely have different mechanistic problems.

To define criteria that distinguish pure alexia from hemianopic dyslexia, it would be valuable to study the visual and reading processes of patients who have only hemianopia, and no possibility of damage to higher level visual processes. However, proving that a patient has only right homonymous hemianopia and no other processing deficit potentially relevant to reading can be a challenge. With most occipital lesions, the damage is not confined to the striate cortex or the optic radiations but involves a variable degree of extra-striate damage, as mentioned above. One diagnostic feature of pure alexia is an elevated word-length effect, where the time taken to read a word is markedly increased by every additional letter it contains (Barton et al., 2014). As right homonymous hemianopia can also cause a moderately increased word-length effect (Leff, et al., 2006), it can be difficult to determine whether the slowed reading of a patient represents hemianopic dyslexia or a mild form of pure alexia. Recent work with gaze-contingent displays that simulate hemianopia in healthy subjects have shown that word-length effects of up to 160ms/letter can be due to the visual defect alone (Sheldon et al., 2012). This has raised concern because patients purported to have alexia in some studies have had a word-length effect less than this upper limit. In such patients it may be that reading problems are due to homonymous hemianopia alone. Indeed one review suggested that on the basis of modest word-length effects the diagnosis of pure alexia may need re-evaluation in 9 of 107 cases in the literature (Leff et al., 2001). For this reason, studies to isolate the effects of hemifield loss on tasks such as line bisection and visual search have been conducted with gaze-contingent displays that simulate homonymous hemianopia in healthy subjects (Mitra et al., 2010; Simpson et al., 2011). The findings in these types of studies can only be due to the field defect, as there is no question of cortical damage that might affect other cognitive processes.

In experiment one, we identified two studies of perceptual mechanisms in alexia that involved patients with only modest word-length effects (Rosazza et al., 2007; Sekular & Behrmann, 1996). Our goal was to re-evaluate the results of these studies by administering some of their key tests to healthy subjects under both normal viewing and simulated right homonymous hemianopia. If a similar pattern of impairment could be replicated under simulated hemianopic conditions, then the relevance of these previously reported findings to alexic mechanisms must be questioned.

Subsequently, we moved from a theoretical to a more practical question. Knowing that the word-length effect is a key diagnostic tool in differentiating hemianopic dyslexia from pure alexia, we wanted to determine to what extent macula-sparing had on the word-length effect. As mentioned previously, Sheldon et al. (2012) calculated an upper 95% prediction limit of 160ms/letter for word-length effects that could be attributed to *complete* right homonymous hemianopia. However, that study did not examine the impact of macula-sparing on the word-length effect, an important clinical issue given that some central field is commonly preserved in hemianopia (Leff, 2004).

In experiment two, we addressed this issue of macula-sparing using the same gaze-contingent technique in healthy subjects, as in a prior report (Sheldon et al., 2012). We asked whether the word-length effect varied as a function of the degree of central sparing in right homonymous hemianopia.

1.2 Rehabilitation of hemianopic dyslexia

As mentioned previously, right homonymous hemianopia affects reading more than left hemianopia because of the direction of the assymmetrical reading span in left-to-right readers. This reading perceptual span is the area within which effective processing occurs during reading. The perceptual span is plastic, and as a result English readers have a larger rightward perceptual span to accommodate their rightward reading eye movements. Studies have shown that left asymmetrical spans exist, instead, in right-to-left readers (Pollatsek et al., 1981), suggesting that there are no low-level factors preventing the ability of individuals to acquire a reading perceptual span in the opposite direction. The visual span, however, is the region within which fine detail such as letters is reliably identified, this is only possible within the foveal region and extends out 1° to either side of fixation (Schuett et al., 2008).

Surprisingly, studies have mainly focused on visual restoration therapy and compensatory training of eye and/or head movements, without much attention on improving reading performance. Visual restoration therapy is an attempt to induce neuroplasticity to reduce the area of visual loss by stimulating areas bordering the scotoma with light simulation (Schreiber et al., 2006); aiming to expand vision rather than compensate for visual field loss. It is controversial whether this approach works or instead induces compensatory gaze shifts in those subjects who appear to have obtained benefit. Saccadic and/or optokinetic compensatory training, however, are meant to improve visual search in the blind field (Pambakian et al., 2005). Yet, an absence of patient trials with compensatory saccadic training also leaves uncertainty regarding its efficacy (Pelak et al., 2007; Trauzettel-Klosinski, 2011).

One other research group has attempted to improve hemianopic dyslexia by training on scrolling text, which is meant to recruit optokinetic processes to encourage generation of larger

saccades while reading (Spitzyna et al., 2007); a program called ReadRight. While this does not precisely replace the large targeted rightward saccades made by healthy subjects who do have preview of the upcoming text, nevertheless, there may be benefit in making larger unguided rightward saccades. Although ReadRight (Ong et al., 2012) has many benefits including online accessibility and improved reading speeds following just 5 hours of training, optokinetic reading training does not address the limited leftward reading span of such patients. Even if one is able to make larger rightward saccades during reading, one is still left with the problem that, at the new fixation position, the normal reading span only allows one to read up to 4 letters in the intact left parafoveal field. This may then prove to be a processing bottleneck that limits further gains in reading efficiency. We seek to address this by proposing a perceptual learning approach to expand the leftward reading span. Our training parameters, such as varying word length and exposure duration, is designed to improve the efficiency of the recognition of words, of longer length and at shorter exposure durations. We hypothesized that the benefits of more efficient reading in the left hemifield of these subjects would be the following. First, we predict a decrease in the duration of fixations, as subjects become more efficient and rapid in acquiring information during fixations. Second, as they expand the area from which information is acquired, this should allow them to move forward along the line with saccades of larger amplitude, which should in turn reduced the number of saccades and fixations made per line. Finally, more accurate and efficient information acquisition should lead to a reduction in the number of regressive saccades, which are likely performed when there is uncertainty about or apparent incongruity with the information acquired in the previous fixation..

In experiment three, we explored the feasibility of using perceptual learning to increase the size of the leftward (intact) perceptual span in hemianopic dyslexics, to increase reading

efficiency. Perceptual learning is “the performance improvements in perceptual tasks as a result of practice or training” (Petrov et al., 2005). Previous studies have shown the effectiveness of perceptual learning for several low-level visual processes, such as contrast discrimination, orientation discrimination, and contour integration, possibly occurring in the primary visual cortex (see Sagi 2011 for Review). Such abilities are relevant to perception of complex two-dimensional objects like letters and words, which differ from each other in oriented lines and contours. Furthermore, there is evidence of effective perceptual learning in healthy subjects for high-level object representations (Baeck et al., 2012; Jiang et al., 2007), including faces (Hussain et al., 2009a, b), and that such training improves shape-sensitive object representations (Jiang et al., 2007).

We hypothesized that a perceptual learning approach for patients with *right* hemianopia will 1) increase their *left* parafoveal reading span, 2) increase paragraph reading speed (primary variable), 3) create more efficient scanning during reading, with larger saccades, briefer fixations, and fewer regressive (leftward) saccades (secondary variables), and 4) translate to benefits in daily life.

Chapter 2: Experiment 1 – The effects of homonymous hemianopia on experimental studies of alexia*

*The work in Chapter 2 was published in a peer-reviewed journal. See 'Preface' for details.

As stated, one of the challenges in studying acquired reading disorders is the distinction between pure alexia and hemianopic dyslexia. This is critical not only for diagnosis and management, but also in correct classification for research purposes. For example, inferences about the mechanisms of pure alexia made from results of experiments may not be valid if the patients studied actually have hemianopic dyslexia. Our review of the literature suggested that two papers that studied mechanisms of pure alexia may have suffered from this problem, in that several of the patients had word-length effects that were modest, and therefore could have been due to hemianopia alone. In this study, we replicated several tests (both orthographic and non-orthographic visual processing) from two prior studies on perceptual mechanisms in alexia (Rosazza et al., 2007; Sekular & Behrmann, 1996), using a simulated hemianopia gaze-contingent display in healthy subjects with no brain lesions. If we are able to obtain similar experimental results in such healthy subjects with a simulated hemianopia, this would call into question the inferences made in those studies about the mechanism of pure alexia. A key implication of such a result would be that the appropriate controls for future studies of pure alexia would include either hemianopic patients or healthy subjects with simulated hemianopia.

2.1 Methods

Subjects

Twelve healthy subjects (ten female) with a mean age of 24.8 years (s.d. 4.5) participated. All were right-handed except for one, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were recruited through Craigslist and paid $10 per hour. All had normal corrected vision, English as their first language and no report of reading problems. The institutional review boards of Vancouver General Hospital and the University of British Columbia approved the protocol, all subjects (and patients) in this and subsequent experiments gave written informed consent, and the experiments were conducted in accordance with the principles of the Declaration of Helsinki.

Apparatus

Subjects sat 40 cm away from the computer display. A headrest and a chinrest stabilized the head. Eye movements were recorded using an Eyelink 1000 eye tracker (www.sr-research.com). Left eye movements were recorded during binocular viewing. Experiment Builder 1.10.1241 was used to present and analyze the experiment.

Procedure

A gaze-contingent display paradigm simulated complete right homonymous hemianopia in half of the sessions (Mitra, et al., 2010). During hemianopic conditions, the entire screen to the right of the current point of fixation was set to the same luminance and colour of the background. To guard against inadvertent viewing of stimuli, if the subject's gaze was directed outside of the monitor or if the eye tracker lost track of the pupil, as could occur if the subject pulled their head

away from the head rest or closed their eyes, the entire screen assumed the colour of the background.

Subjects completed two sessions, at least one week apart, one with full-field viewing, and the second with simulated right hemianopia. We randomized half the subjects to perform full-field viewing first, and the other half to perform hemianopic viewing first. In each session, subjects performed five sets of experiments, in random order: Word-Length Effect, perceptual fluency, part-processing of shapes, orthographic integration, orthographic processing.

1. Word-Length Effect.

a. Reading Time. Subjects fixated on a central cross of 1.3° width. When ready, the examiner triggered the start of a trial with a key press. The cross was replaced by a central dot of 0.9° diameter at the same location. If fixation remained stable within 1° of this dot for 200ms, a single word appeared centered on the middle of a white screen, composed of black upper-case letters in Arial 35-point font, with height of 1.6° of visual angle. If this fixation criterion was not met within 4s, calibration was reassessed. The participant read the word aloud and then the examiner made a second key press to terminate the trial. A microphone recorded the subject's vocal response and the time between appearance of the word and the onset of their reply was the response time.

Recordings of each response were reviewed to ensure that the marker for latency had been triggered by reading of the word. We used an audio editor (Audacity 2.0.5, http://audacity.sourceforge.net) to verify the accuracy of the audio file response times reported by Experiment Builder. The trial was excluded if subjects did not read the entire word correctly.

There were 140 words, 20 for each of the 7 word lengths ranging from three to nine

letters. Words were randomly selected for each subject from a database of 420 words, chosen from the MRC psycholinguistics database (www.psy.uwa.edu.au/MRCDataBase/uwa mrc.htm), with a mean Kucera–Francis written frequency of 380 (s.d. 3553) per million words (Sheldon, et al., 2012).

b. Lexical Decision Task. To match the stimuli used by (Sekuler & Behrmann, 1996), we presented 3-, 5-, 7- and 9-letter words or non-words, of similar size and appearance as used for the reading time study above. Words were obtained from the English Lexicon Project and matched for written Kucera-Francis frequency. The mean frequency of the words was 159 (s.d. 73.87, range 91–450) occurrences per million words encountered. We created non-words by altering one letter in 3-letter words, altering two letters in 5- and 7- letter words, and altering three letters in 9-letter words.

Following a central fixation cross that spanned 1.4° of visual angle and had a random duration between 500 and 1500ms, a word or non-word appeared centrally and remained on the screen until the subject responded. Subjects indicated whether the stimulus was a word by pressing “W” for word or “O” for non-word.

For both reading aloud and lexical decision, we computed the word-length effect as the slope of the linear regression between reaction time and number of letters in the stimulus. We analyzed the word-length effect (ms/letter) with a repeated–measures ANOVA, with viewing session (full-field, hemianopia), and task (reading aloud, lexical decision) as factors, with subject as a random effect. We also calculated upper 95% prediction limits for the two hemianopic word-length effects, as $\text{mean}+2.59*(\text{s.d.})*\sqrt{((n+1/n))}$, where 2.59 is the t-statistic for $p = .025$ and 11 degrees of freedom, and n is the number of subjects.

2. Perceptual fluency.

a. Finding A's. Stimuli lists were obtained from the *Kit of Factor-Referenced Cognitive Tests* (Ekstrom, French, & Harman, 1976) and composed of lower-case black letters on a white screen, in Courier 14-point font, with a width of 0.4° of visual angle. Subjects were to scan the page and call out any words containing the letter "a" (Figure 1A). They were presented with 4 pages at a pace of 45 seconds per page, each of which contained 5 vertical columns with 21 words ranging from 4 to 8 letters in length in each column. Subjects were informed that each column contained 5 words with the letter "a" for a total of 25 target words per page, and that the number of words correctly identified determined their scores.

b. Number Comparison. Paired number strings obtained from the *Kit of Factor-Referenced Cognitive Tests* (Ekstrom, et al., 1976) were presented in two columns on a single page (Figure 1A). There were 48 pairs ranging from 2 to 13 numbers in length, presented in Courier 14-point font with height of 0.4° of visual angle. Each number pair had an associated letter (a-x and a-xx) that separated the pairs. Subjects were given 1.5 minutes to call out the associated letter of any pairs of digit strings that were different. They were informed that their total score would be the number of correct minus the number of incorrect call-outs.

To analyze the results for Finding A's and Number Comparison, we used paired t-tests to assess whether the results for hemianopic and full-field sessions differed.

3. Part-processing of shapes.

This followed the procedure of (Sekuler & Behrmann, 1996), which used stimuli based on a prior study of shape processing (Donnelly, Humphreys, & Riddoch, 1991). Shapes were black line drawings on a white screen, spanning on average approximately 14° of visual angle in

width and 11° in height, composed of parts that were separated line segments each containing one angle (Figure 1B). Shapes were defined first by the number of parts, which could be four, five, six, or seven, and second by whether the global arrangement had good or poor configuration. Shapes with good configuration had their parts aligned so that they possessed the gestalt property of good continuation. Shapes with poor configuration were created by rotating each part of a shape with good continuation by 15° counter-clockwise. For both poor and good configuration shapes, a target shape was created by flipping one line segment around its longitudinal axis, so that its vertex pointed towards the center of the object. On a trial, the subject's task was to determine if the shape was one of these target shapes or not. Each trial began when a central fixation cross spanning a width of 1.4 ° of visual angle appeared and persisted with a random duration of between 500 and 1500ms, after which time the cross disappeared and the shape appeared. The shape remained until the subjects had responded by pressing "T" for a target and "O" for a non-target, with reaction time for correct responses as the dependent variable. The block had 64 trials, half with good and half with poor configuration, with equal numbers of target and non-target trials, and equal numbers of trials for each number of parts.

We analyzed reaction time with a repeated-measures ANOVA, with viewing session (full field, hemianopia), configuration (poor, good), and part number (4, 5, 6, 7) as factors, and subject as a random effect.

4. Orthographic integration: Cumulative and successive presentation of words.

We created two lists of 80 six-letter high-frequency words matched for written Kucera-Francis frequency (mean 124 (s.d. 109, range 43–847) occurrences per million words), one to be

used in the full-field session and one in the hemianopic session. Stimuli were composed of black upper-case letters on a white screen, in 30-point Arial font, spanning 1.4° degrees of visual angle. The procedure followed those of the previous reports (Rosazza, et al., 2007; Warrington & Langdon, 2002). There were two types of presentations in each session, both presenting words by displaying their letters sequentially, starting from the left-most letter (Figure 1C). In the cumulative presentation, once a letter had appeared, it remained visible on the screen. In the successive presentation, each letter disappeared when the next appeared to its right: thus only one letter was visible at any time.

A trial began with a blank screen that was shown for 200ms, after which the stimulus appeared. Subjects read the word aloud, after which the stimulus was replaced by a blank screen until the subject made a key press to begin the next trial. Words were presented first in an ABBA sequence of blocks, where A was a block of 20 words in the cumulative presentation, and B a block of 20 words in the successive presentation. After a rest break, a second sequence of four blocks in a BAAB sequence were presented, but with the word assignment reversed, so that the words seen in the cumulative presentation were now seen in the successive presentation, and vice versa. Within each individual block of 20 words, stimuli were randomly assigned to 4 different exposure durations of 100-, 200-, 300-, and 500-ms per letter, with 5 words per exposure duration. Half of the subjects were randomly assigned to have blocks in which exposure duration increased in an orderly fashion from 100 to 500ms as the block progressed, while the other half had blocks in which exposure duration decreased.

We analyzed reading accuracy with a repeated-measures ANOVA, with viewing session (full-field, hemianopia), presentation (cumulative, successive), and duration (100, 200, 300,

500ms) as factors, with subjects as a random effect. We used Tukey's honestly significant difference (HSD) test to explore the basis of any interactions.

5. Orthographic processing: Syllable task.

The procedure followed that of (Rosazza, et al., 2007). Stimuli were composed of black lower-case letters on a white screen, in Arial 35-point font and spanning 1.6° visual angle. Subjects fixated a central cross for a random duration between 500 and 1500ms. This was followed by 150ms of a blank white screen, following which a centrally presented letter string appeared. We created two sets of 160 triplets (strings of three letters), 80 each for condition A and condition B.

Of the 80 triplets in condition A, 40 were orthographic syllables (e.g. 'ata') and 40 non-orthographic letter strings that could not be pronounced (e.g. 'tpv'), randomly mixed in one block. In condition A, subjects were asked to report the three letters in each string: an orthographic effect would be better performance with orthographic than non-orthographic letter strings. A subject's response was considered correct if all three letters were reported correctly: hence the score was out of 40 for both orthographic and non-orthographic stimuli. For comparison with (Rosazza, et al., 2007), we also tabulated the number of letters reported correctly over all trials.

In condition B the 80 triplets were all orthographic syllables, and subjects were asked to pronounce the syllable. An effect of explicit integration of letters into syllables would be better performance in condition B, when syllables are read aloud, than with naming the letters of the orthographic syllables in condition A. All subjects did condition A first, then condition B.

The results for accuracy were first analyzed with a repeated-measures ANOVA, with viewing session (full-view, hemianopia) and syllabic condition (condition A non-orthographic, condition A orthographic, condition B) as main factors, with subject as a random effect. To compare the syllabic effects on performance with those reported by (Rosazza, et al., 2007), we created an orthographic effect metric for condition A, by subtracting the percent accuracy score for non-orthographic stimuli from that for orthographic stimuli, and computed the mean and standard deviation to define 95% prediction intervals for this orthographic effect. Similarly, we created a syllabic integration metric by subtracting the percent accuracy score for orthographic stimuli in condition A from that for condition B, and computed the 95% prediction interval for the effect of syllabic integration.

2.2 Results

1. Word-length effect.

Word length effects were significant for both lexical decision time and reading aloud, in both full-field and hemianopic sessions (all $p<.001$). There was a main effect of task (Figure 2), due to smaller word-length effects for reading aloud ($F_{(1,33)} = 13.39$, $p<.0009$). There was a main effect of viewing session, due to larger word-length effects for hemianopia ($F_{(1,33)} = 20.56$, $p<.0001$). However, there was no interaction between task and viewing session, indicating that hemianopia had a similar effect on the word-length effect for either reading aloud or lexical decision time (Figure 2). For reading aloud, hemianopia increased the word-length effect from 15ms (s.d. 9ms) to 61ms (s.d. 46ms), with a 95% upper prediction limit of 155ms for the hemianopic word-length effect. This is comparable to the upper limit of 161ms previously reported for computer-simulated hemianopia (Sheldon, et al., 2012). For lexical decision time, it

increased the word-length effect from 53ms (s.d. 33ms) to 95ms (s.d. 64ms), with a 95% upper prediction limit of 269ms for the hemianopic word-length effect.

2. Perceptual fluency: Finding A's and number comparison.

Hemianopia significantly reduced the score for finding As (Figure 3), from 40.6 (s.d. 7.8) for full-field viewing to 20.0 (s.d. 7.9) for hemianopic viewing ($t_{(11)} = 4.65$, $p<.0001$). A similar effect was seen for number comparison, with the score being 10.4 (s.d. 2.2) for full-field viewing and 3.2 (s.d. 2.1) for hemianopic viewing ($t_{(11)} = 5.31$, $p<.0001$). This closely replicates the findings reported in Figure 4 of (Sekuler & Behrmann, 1996).

3. Part-processing of shapes.

The ANOVA showed a main effect of viewing session ($F_{(1,165)} = 364.8$, $p<.0001$), due to faster responses with full-fields than with hemianopia (Figure 4). There was no effect of part number ($F_{(3,165)} = 1.55$, $p=.20$), nor any interaction involving part number. There was a main effect of configuration, with faster responses to good than poor configurations ($F_{(1,165)} = 45.1$, $p<.0001$). There was no interaction between viewing session and configuration ($F_{(1,165)} = 1.65$, $p = 0.20$). Reaction times were 131ms (s.d. 68ms) faster for shapes with good configuration under hemianopic viewing, while their advantage was 88ms (s.d. 69ms) under full-field viewing, a difference of 43ms that was not significant. In Sekuler and Behrmann (Sekuler & Behrmann, 1996) the good-configuration advantage for patients was on average 276ms, compared to a mean of 131ms for control subjects with full fields, a difference of 145ms that was significant at a $p<.05$ level. However, we note that the difference between hemianopic and full-field sessions for the good-configuration advantage ranged up to 293ms in individuals.

4. Orthographic integration: Cumulative and successive presentation of words.

There was a main effect of viewing session, due to worse accuracy in the hemianopic session ($F_{(1,165)} = 267$, $p<.0001$). There was a main effect of presentation, with better accuracy for the cumulative presentation ($F_{(1,165)} = 139$, $p<.0001$). There was an interaction between viewing session and presentation ($F_{(1,165)} = 104$, $p<.0001$), with Tukey's HSD test showing a significant advantage for cumulative presentation with hemianopic viewing, but no advantage over successive presentation during full-field viewing (Figure 5A).

There was a main effect of stimulus duration ($F_{(3,165)} = 3.97$, $p<.010$), with Tukey's HSD test showing better accuracy for the 500ms than the 100ms duration. There was an interaction between stimulus duration and viewing session ($F_{(3,165)} = 2.96$, $p <.034$), with Tukey's HSD test showing no effect of duration under full-field viewing but the results at all durations differing from each other under hemianopic viewing.

Ultimately, the interactions in this analysis are driven by the fact that performance under full-field viewing is at ceiling for both successive and cumulative presentations, while accuracy is much reduced by hemianopic viewing, more so for successive presentations, and at briefer durations.

The prior report had described two patterns of results in their subjects (Rosazza, et al., 2007). LDS did poorly with successive presentation but much better with cumulative presentation, whereas the improvement with cumulative presentation was more modest in FC. This was cited as evidence that letter integration was intact in LDS but impaired in FC. Inspecting the performance of our individual subjects showed variations in performance that resembled those in LDS and FC. For example, subject HM under hemianopic viewing had difficulty with the successive presentation, but had a large mean 60% gain accuracy when letters

were presented cumulatively (Figure 5B). In fact, his performance with cumulative presentation was nearly perfect and no different from full-field viewing. On the other hand, subject IC under hemianopic viewing showed a smaller 40% gain in hemianopic accuracy with cumulative presentation, and accuracy was still substantially reduced compared to full-field viewing (Figure 5C). This suggests that orthographic integration under hemianopic viewing is excellent in HM, but impaired in IC.

5. Orthographic processing: Syllable task.

Again, with full-field viewing subjects were nearly perfect in accuracy (Table 1). Hemianopic viewing substantially reduced performance on all metrics. This was reflected in a main effect of viewing session ($F_{(1,55)} = 478$, $p<.0001$). There was no main effect of or interaction with syllabic condition.

The key comparisons targeted in (Rosazza, et al., 2007) were two: first, between the syllable and non-syllable performance in condition A, when subjects had to name each letter, and second, between the syllable conditions in condition A and condition B, when the subject had to pronounce the syllable. To evaluate the syllabic effects reported individually for LDS and KC (Rosazza, et al., 2007), we calculated the absolute difference in percent accuracy between two conditions, and determined the upper 95% prediction limit for performance.

For the contrast between syllables and non-syllables in condition A, during full-field viewing the mean difference was 0% (s.d. 4.9) with an upper 95% prediction limit of 13.2%. During hemianopic viewing, the mean difference was 2.9% (s.d. 12.8), with an upper 95% prediction limit of 37.5%.

For the contrast between condition A and B for syllables, during full-field viewing the mean difference was 1.6% (s.d. 3.6), with an upper 95% prediction limit of 11%. During hemianopic viewing, the mean difference was 0.0% (s.d. 27.4), with an upper 95% prediction limit of 73%.

Thus, while there is no significant effect of syllable in either contrast, performance becomes more variable across subjects under hemianopic viewing (Figure 6). We note that the reported advantage of syllables over non-syllables in condition A were 12% for FC and 19% for LDS, and the advantage for condition B over condition A were 5% for FC and 19% for LDS (Rosazza, et al., 2007). Their conclusion that an effect of syllabic structure is seen in LDS but not FC would be supported if their performance were compared to our data for full-field viewing; however, this is not the case when the comparison is made to the data for hemianopic viewing, because of the increased variance during the latter (Figure 6).

2.3 Comment

Our hemianopic simulation first replicated an increased word-length effect for reading aloud, and showed that a similar increased word-length effect occurred for a lexical decision task. We then studied the effects of simulated right homonymous hemianopia on two object processing tasks and two orthographic tasks used in prior studies of patients with reading problems (Rosazza et al., 2007; Sekuler & Behrmann, 1996). We found that the ability to search for A's in an array or to compare two number strings was impaired by simulated hemianopia. While the processing of shape parts was also slower under hemianopic viewing, we could not confirm a significant difference in the effect of configuration between full-field and hemianopic viewing. Investigations of reading words whose letters were sequentially presented showed that

this was more difficult under hemianopic viewing, particularly when the letters did not remain on the screen (i.e. the successive presentation). When the letters did remain (i.e. the cumulative presentation) some subjects achieved nearly perfect scores, while others improved but still had difficulty. Finally, the study of the ability to report short letter strings showed that syllabic structure did not shift performance under either full-field or hemianopic viewing, but hemianopic viewing did increase the variability of the results and reduced accuracy in general. See Section 5.1 for an in-depth discussion.

In summary, some impairment that has been attributed to the processing defects underlying alexia may actually be due to right homonymous hemianopia. Our results underline the importance of considering the contribution of accompanying low-level visual impairments when studying high-level processes.

Chapter 3: Experiment 2 – The impact of macula-sparing on single-word reading in right hemianopia

In this study, we used the Word-Length Effect task previously reported (Sheldon et al., 2012), to investigate the impact of right hemianopia on single-word reading. We asked whether the word-length effect varied as a function of the degree of central sparing in right homonymous hemianopia, important in the diagnosis of pure alexia, as not all subjects with the latter have a complete hemianopia.

3.1 Methods

Subjects

Ten healthy subjects (two male) with a mean age of 28 years (s.d. 3.9) participated. All were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Subjects were recruited through the University of British Columbia and paid $10 per hour. All had normal corrected vision, English as their first language and no report of reading problems or history of neurological disorders.

Apparatus

See Experiment 1.

Stimuli

We used 6 word lists that had been generated for a previous experiment (Eklinder Björnström, Hills, Hanif, and Barton, 2014). Words of these lists had been chosen from MRC Psycholinguistic database (Wilson, 1988). There were 6 word lists, each containing 70 words, 10 each for 7 different word lengths ranging from 3 to 9 letters. The Kucera-Francis written frequency of the words was matched between the different word-lengths, with an overall average frequency of 64.2 (range 16 to 258) occurrences per million words. The latter matching was done by arranging the words of each word length in descending order of frequency and assigning them singly in that order to each list (e.g. words 1, 7, 13, etc in the frequency order go to list 1, words 2, 8, 14 etc. go to list 2, words 3, 9, 15, etc. go to list 3, and so on). ANOVA of Kucera-Francis written frequency with word-length and list as main factors confirmed that there was no effect of length or list: hence our lists and word-lengths are well matched for written frequency.

A simulated right homonymous hemianopia gaze-contingent method, as in Experiment 1, was used. To simulate different degrees of central sparing, the view of the display was preserved in a semi-circle around fixation on the otherwise blind side. The radius of this circle varied between 0° (no macula-sparing, or complete hemianopia), 2°, 5°, 8°, and 10°. In addition we had a control condition of full-field viewing.

Procedure

Prior to each testing session, subjects performed 10 practice trials; these words were not used in testing. The same procedure as in Experiment 1's, "Word-length effect", was used. However, subjects completed 420 randomized trials: 6 lists of 10 different words of 7 word-lengths (3 to 9 letters), with each list assigned to a viewing condition (full field, or 0°, 2°, 5°, 8°,

or 10° of macular sparing hemianopia). The order of viewing condition was randomized, as was the assignment of word list to viewing condition. Testing took about 60 minutes, with a 5-10min break at the half-way point to minimize fatigue.

Analysis

We used repeated measures ANOVA with the main factor of macula-sparing (0°, 2°, 5°, 8°, 10° or full field), with subjects as a random effect. This was done first for mean reading time and second for the word-length effect as the dependent variable. We used pair-wise linear contrasts to explore the origins of significant main effects. For the word-length effect at each macula-sparing condition, we calculated upper 95% prediction limits, as $mean+2.68*(s.d.)*\sqrt{((n+1/n))}$, where 2.68 is the t-statistic for $p = .025$ and 9 degrees of freedom, and n is the number of subjects.

3.2 Results

Mean reading time

There was a main effect of macula-sparing on mean reading time ($F(5,45) = 106.8$, $p<.0001$, Figure 7A). Linear contrasts showed that all conditions differed from each other, with the exception of the contrast between 10° macula-sparing and either 8° macula-sparing or full-field viewing. The mean data followed an exponential function, not reaching an asymptote until about 10° of macula-sparing.

Word-length effect

There was a main effect of macula-sparing on the word-length effect ($F(5,45) = 4.93$, $p<.0011$, Figures 7B, 8). Linear contrasts showed that full-field viewing had a smaller word-length effect than all other conditions except for 10° macula-sparing, while in turn 10° sparing had a smaller word-length effect than either 0° or 5° macula-sparing. Of note, there was no difference between 0°, 2° and 5° macula-sparing. As a consequence, the best fitting curve would be a sigmoid function, in contrast to the results for mean reading time.

We also calculated upper 95% prediction intervals for the effects of hemifield loss (Table 2). Limits were somewhat less for 2° and 5° of macula-sparing than for 0°, because of the lower variance for the former two viewing conditions.

3.3 Comment

These results provide diagnostic criterion for discriminating between hemianopic dyslexia and pure alexia for various types of central involvement by right hemifield loss. Incorporating the prior reports on word-length effect (Sheldon et al., 2012; Bao et al, 2015), we would suggest an upper limit of 170ms/letter for complete hemianopia, 130ms/letter for any degree of macula-sparing up to 5°, 100ms/letter for a field defect with central sparing of between 5 and 10°, and 45ms/letter for patients with full visual fields (Table 2). See Section 5.2, for an in-depth discussion.

Chapter 4: Experiment 3 – Reading training for hemianopic dyslexia through perceptual learning

Knowledgeable about reading impairment in hemianopia, we devised an online reading training program using perceptual learning strategies to improve reading efficiency, important for daily living. We predicted that word-recognition training would alter ocular motor parameters, and improve reading eye movements. This is merely a pilot study, additional recruitment is necessary.

4.1 Methods

Patients

5 hemianopic patients were recruited. 3 of the 5 patients were classified on the basis of their large word-length effects as having pure alexia in addition to right homonymous hemianopia and therefore were ineligible for training. Patients were assessed for degree of visual field loss using standardized perimetry (Figure 9); all had complete right homonymous hemianopia. The analyzed patient group (Table 3) consisted of 2 hemianopic dyslexic patients (2 males, mean age 66.5 years, s.d 3.5), however pre-training assessments were conducted in all 5 patients.

Patients were tested prior to and following training on standard assessments of reading span (Chung et al., 2004; Legge et al., 2001), and reading speed. For entry criteria, we measured the Word-Length Effect (Sheldon et al., 2012) to exclude subjects with alexia, and the Montreal Cognitive Assessment (MoCA) to exclude general cognitive impairment (all training patients

scored >24/30). Patients had no prior history of neurological impairment. All patients reported difficulty with reading, compared to prior to onset of vision loss. Standard neuropsychological assessments ensured patients were not impaired in other cognitive aspects: these include the Boston Naming Test, the Visual Object and Space Perception battery, and Wechsler Abbreviated Scale of Intelligence (Table 4). Both hemianopic dyslexic patients had no other physical or neurological impairments; both were walking independently, but reported frustration with bumping into things due to vision loss. All patients were right-handed except for one, as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). All were recruited through the Eye Care Centre, Vancouver General Hospital (Neuro-Ophthalmologic clinic of Dr. Jason Barton).

Apparatus

See Experiment 1.

Pre- and post-training assessments

a. Paragraph reading

Stimuli and testing procedure were obtained from a previous experiment (Ahlen et al., 2013). Stimuli were six standardized paragraphs (3 used for pre-assessments and 3 for post-assessments) from the International Reading Speed Test or 'IReST' (Trauzettel- Klosinski and Dietz, 2012), which had been entered and saved as graphic files with Adobe Photoshop CS 8.0. The texts were displayed centrally in 12-point Verdana font, which at the viewing distance of 37cm presented about 3 letters per degree of visual angle.

The paragraphs were paired according to their difficulty level so that the same subject read 3 different paragraphs with a similar level of difficulty for pre- and post-assessments.

Paragraphs were randomized for each session, and were counterbalanced so that one subject in pre-assessments and the other subject in post-assessments read the same three paragraphs.

Prior to testing, 9-point calibration was performed, which was then validated to an accuracy of less than 1.0° of error. Patients fixated on a central cross spanning 1.3° of visual angle. For a trial to begin, fixation had to occur with a position error of less than 1.0° for 200ms. If not, a black dot appeared at the center and calibration was repeated. Patients were instructed to read as quickly and accurately as possible, and to press a button on a keyboard when they were finished. Eye movement recordings were obtained. Following each paragraph, Patients responded to a comprehension question based on the paragraph just read.

b. Word-length effect

See Experiment 1, "Word-length Effect". Patients BM and BB sat 50 cm and 31 cm away from the screen, respectively (instead of the standard 40cm).

c. Visual span

To match the protocol used by (Legge et al., 2001; Legge et al., 2007), random lists of 160 trigrams (3-letter syllabic and non-syllabic stimuli) were created in Excel. Preliminary data was collected from 5 healthy subjects on several lists of trigrams to ensure that the stimuli used for pre-assessments were matched in difficulty to those used for post-assessments. Stimuli were lower-case trigrams in Courier New 9-point font, so that 3 letters spanned 1° of visual angle, at 36cm away from the screen. A fixed width font was used because of the constant center-to-center spacing between letters, which simplifies the measurement of visual-span profiles (Legge et al., 2007). Trigrams were presented to the left of fixation only, and were tested with center letters at

positions 0 to -7 (8 positions). For trigrams with centers at position -1 or 0, only 2 letters and 1 letter appeared, respectively. There were 20 trials for each trigram position. The ordering of trigrams was randomized, no repeats were allowed, and the trigram exposure time was 100ms; too brief to permit an eye movement to the trigram target.

Patients were instructed to maintain fixation on the central cross throughout testing, and to report the trigrams from the left-most letter to the right-most letter. They were encouraged to guess. Trigrams were correct only if all three letters were accurately reported, and in the correct order.

d. Activities of Daily Living Questionnaire

We assessed impairments in daily living due to visual field defect with the National Eye Institute Visual Function Questionnaire 39 (NEI VFQ-25+optional items), which contains 39 questions evaluating general health and vision, difficulty with activities, and response to visual problems (Mangione et al., 2001). This addresses whether training improves reading-specific or general visual behaviour in our patients' daily lives.

Training

All participants were introduced to the online training program (https://hvemlab.org/words/wordtraining/) during their pre-training assessment. At home, patients completed 3 training sessions per week on their own computer, with a minimum 13" monitor, each session approximately 30 minutes, an intensity and duration similar to previous studies showing effective perceptual learning (see Schuett, 2009 for Review). Training was limited to one session per day, with all three sessions to be completed by the Sunday evening of

each week. Depending upon the rate of progression through the blocks, training was anticipated to last between a minimum of 7 weeks and a maximum of 21 weeks. If patients did not reach their peak performance after one week of training, they were asked to perform one more week of the same word-length (repeat words were possible in this case), thus training was personalized to each individual's performance.

Training Stimuli

We obtained words of 3-9 letters in length from the English Lexicon Project database (http://elexicon.wustl.edu). The mean HAL frequency (Lund & Burgess, 1996) of the words was 102,326 (s.d. 565,244; range 961-23,099,033) occurrences per million words encountered. An equal number of non-words were generated from the same database, and consisted of random words with the first-, middle-, or last-2 letters scrambled to produce a non-word. 375 words were chosen for each word-length. Stimuli were printed in 20-point Courier New font, and patients sat at a typical viewing distance of 40cm away from the screen. This corresponded to a width of 0.14° of visual angle, so that 3 letters spanned 1° of visual angle. Stimuli were presented to the left of fixation, so that their right end aligned with the fixation point, in patients' undamaged hemifield. As training is done on-line at home, there is no possible monitoring of where the subject is fixating on the screen. However, it is stressed to patients that fixating anywhere other than at screen center is counter-productive: fixating to the left will cause some letters to fall into their blind region, while fixating to the right will place the letters further in the periphery, reducing their visibility. Similarly, fixating higher or lower will increase the eccentricity of the stimuli. Hence we expected patients to rapidly develop a stable fixation at screen center to optimize their performance, and maintain fixation at center throughout training. Words and non-

words were tested in random order for each word-length.

Training Protocol

Following each trial, patients indicated with a keypress whether the stimulus was a word or a non-word. The difficulty level of a trial was determined by the duration of presentation. In each session, a staircase procedure decreased the duration of presentation of the text stimulus after correct responses and increased duration after incorrect responses, so that patients were always training near their current limits. Viewing duration ranged from 306ms (easiest level) to 17ms (most difficult level), decreasing in increments of 17ms. The minimum viewing duration was chosen for because an intact left hemifield can identify up to 3 letters at 20ms (Habekost, 2006), making 17ms difficult enough to limit the chance of reaching ceiling. Feedback was given following each correct (green checkmark) and incorrect (red cross) response. As well, following each session patients could also view their performance for that session. Training followed a staircase procedure whereby the number of correct responses required to move up or down the staircase remained constant but step sizes varied (Kaernback, 1991). A 1-up-6-down staircase was implemented, in which a correct response resulted in patients moving up the staircase (increased difficulty) by one level, whereas an incorrect response resulted in patients moving down the staircase (decreased difficulty) by six levels, so that patients performed at an 85.7% correct level. A staircase stops when a subject makes 100 reversals (50 up, 50 down) around a given level. At this point they are considered to have reached threshold, and a further 200 trials were presented at that level to reinforce training. With these settings, each session lasted approximately 30 minutes.

The first block of sessions involved 3-letter words. Sessions were repeated 3 times a

week until patients reached a performance-duration criterion, after which they graduated to the next block, which has 4-letter words. This continued until patients reached the final block, with 9-letter words.

Analysis

Progression through training was assessed for each patient on a per-session basis. A minimum of three sessions was required. Each session was compared to the prior session. At the end of each training block (three sessions), promotion to the next block occurred when performance reached a certain plateau (ie. no change was made between two subsequent sessions). This was done to ensure that patients performed optimally before moving onto a more difficult training block. Improvement was characterized as a >5% increase in performance threshold between the current and prior session. One additional session was given only when a significant decrease from the prior session resulted.

All analyses were within patient, no cross-patient analyses were conducted. From paragraph reading, we obtained reading speed, and a number of ocular-motor measures. We examined the total number of fixations, mean fixation duration, number of forward saccades, amplitude of forward saccades, and number of regressive saccades made during silent paragraph reading. We used a paired t-test to determine the change in eye-movement measures following training. For single-word reading, we computed the word-length effect (ms/letter) as the slope of the linear regression between reaction time and number of letters in the stimulus. We later compared two linear regressions (pre- and post-training) to determine the change in slopes.

For the visual span, we constructed visual-span profiles of letter-recognition accuracy (percent correct) versus horizontal letter position. Percent correct is accumulated for each letter

slot (20 trials total at each letter slot). A letter was scored as correct if it was reported in the proper position in the trigram. See (Legge et al., 2001) for more details. Results were obtained from the left hemifield only.

4.2 Results

Within training results

Patients completed all training blocks, from 3-letters (training block 1) to 9-letters (training block 7). JN repeated block 7, for a total of eight weeks of training. JW repeated blocks 6 and 7, for a total of nine weeks of training. Overall performance (Figure 10, top) showed that JW was significantly worse ($t(4) = 4.22$, $p < .0134$) in training block 1 (3-letters) compared to training block 2 (4-letters). Conversely, JN performed training without statistically significant difference in performance between training blocks, except for a significant decrease in performance from block 6 (8-letter words) to block 7 (9-letter words) ($t(7) = 2.95$, $p < .0211$).

Effects of training on reading speed: paragraph and single-word

For paragraph reading (Figure 11), JN performed comparably prior to (150wpm) and following (147wpm) training ($t(1) = 3.41$, $p > .0761$). Similarly, JW showed no change prior to (117wpm) and following (115wpm) training ($t(1) = 0.088$, $p > .9375$). Accuracy for comprehension of paragraphs was high, with patients scoring 100% on all questions. For single-word reading (Figure 11), word-length effect did not change for JN ($t(10) = 1.44$, $p > 0.1777$), nor for JW ($t(10) = 0.2062$, $p > 0.8408$). Accuracies for single words were high, with patients reading 96% of words correctly. Incorrect words were not used in analysis.

Effects of training on ocular-motor measures

Ocular-motor parameters (Figure 12) showed that JN fixated longer ($t(1) = 12.3$, $p < .0.006$), yet had no change in the number of fixations used ($t(1) = 1.80$, $p > .2131$). No changes in the number of forward saccades ($t(1) = 0.229$, $p > .8402$) or regressive saccades ($t(1) = 0.162$, $p > .885$) were seen, and no improvement in the size of forward saccades ($t(1) = 2.07$, $p > .174$) was made. Similarly, JW used the same number of forward ($t(1) = 0.081$, $p > .9422$) and regressive ($t(1) = 0.677$, $p > .5679$) saccades prior to and following training, but made significantly larger forward saccades ($t(1) = 4.79$, $p < .004$). No change in fixation duration ($t(1) = 0.002$, $p > .998$) and number of fixations ($t(1) = 0.152$, $p > .8929$) was seen.

Effects of training on visual span size

Visual span profiles (Figure 13) revealed no change in visual span size following training (JN: $t(7) = 1.46$, $p > .1687$; JW: $t(7) = 0.204$, $p > .8417$). JN was quite accurate (~80% correct; range: 50-90%) at recognizing letters of up to 3 positions left of fixation, and JW was most accurate (~88% correct; range: 82-95%) at recognizing letters closest to fixation (letter position 0), but had difficulty recognizing any letters beyond letter position -1.

Activities of daily living

The questionnaire is scored out of 100. JN and JW reported no change based on their questionnaire responses. JN scored 75 prior to training and 74 following training. JW scored 90 prior to training and 91 following training. Scoring was calculated using: The National Eye Institute 25-Item Visual Function Questionnaire v.2000 scoring manual.

4.3 Comment

Reading speed, ocular-motor parameters, visual-span, and a personal report on performance in activities of daily living, were assessed in two hemianopic dyslexic patients. Because of time constraints, and the difficulty in recruiting patients, we were limited to a sample size of 2. Albeit little-to-no improvement following training, we provide explanations in support of our training program. See Section 5.3, for an in-depth discussion.

Chapter 5: Discussion

5.1 Experiment 1

This study emphasizes the importance of taking homonymous hemianopia into consideration when assessing the reading abilities of patients diagnosed with pure alexia. As many alexic patients have right homonymous hemianopia as well (Leff, et al., 2001), inferences from studies about underlying visual recognition mechanisms are only valid if it can be shown that the results are not attributable to the associated homonymous hemianopia. Unfortunately, the impact of hemianopia has only exceptionally been considered (Basagni, Patane, Ferrari, & Bruno, 2014; Pflugshaupt, et al., 2009).

Effects of homonymous hemianopia need to be accounted for particularly when the patients involved have modest word-length effects, which raises doubts as to whether they truly have pure alexia or simply have right hemianopic dyslexia. Such patients may account for as many as 10% of studied cases in the literature (Barton, et al., 2014; Leff, et al., 2001). While the results of a number of mechanistic studies could bear re-examination, we identified as examples two studies in which experiments had been conducted on patients with right homonymous hemianopia and modest word-length effects. In (Rosazza, et al., 2007), the word-length effect for reading aloud was 90ms/letter for FC and 160ms/letter for LDS. In (Sekuler & Behrmann, 1996) it was 101ms/letter for DS and 93ms/letter for MW, and in the lexical decision task, 119ms for DS and 304ms/letter for MW.

We did find that the results suggesting impaired orthographic integration and processing reported for LDS and FC (Rosazza, et al., 2007) could be reproduced by simulated right homonymous hemianopia in otherwise healthy and literate subjects. Furthermore, the different patterns of performance that were said to support a failure of orthographic integration in FC but

not in LDS could be found in different healthy subjects under this simulation. That is, some of subjects showed better, nearly normal performance under the cumulative presentation, while others remained impaired. Also, the impact of syllabic structure on the reporting of trigrams by LDS and FC fell within the range of results we found for simulated right homonymous hemianopia. The contrasting performances of LDS and FC on these orthographic tasks were key factors in the conclusion that they had different types of pure alexia, with the proposal that FC had a deficit in integrating letters into higher level units like syllables and words, and LDS a defect in letter processing with better integration, suggesting that her visual word form area was not totally damaged (Rosazza, et al., 2007). Our study suggests that the results from these orthographic experiments cannot be used to support such conclusions about alexia, as homonymous hemianopia alone could account for the pattern of the findings of both LDS and FC.

Interpreting the results of (Sekuler & Behrmann, 1996) regarding non-orthographic visual processing is more problematic because many results are reported at a group level, and the alexic group included not just the two subjects DS and MW with modest word-length effects, but two other subjects, TU and MA, who had larger word-length effects of around 500 to 1000ms/letter. Thus, though all four had right homonymous hemianopia (Behrmann, Plaut, & Nelson, 1998; Sekuler & Behrmann, 1996), on the basis of their word-length effects the evidence for an additional diagnosis of pure alexia is strong in TU and MA and questionable in DS and MW. While we cannot separate the reported results of these subjects, we found nevertheless that the impairments in the scanning of letter and number strings reported in their experiment 3 can be replicated in our healthy subjects with simulated hemianopia. They concluded from their results (and also from the results of picture scanning, which we did not examine) that alexia was not

specific to reading-related items. However, if these difficulties with number strings are due to homonymous hemianopia, then the lack of specificity for words follows naturally.

In their experiment 4, an investigation of processing of object parts (Sekuler & Behrmann, 1996) they found first, that the patient group was slower overall, and second, that this deficit was more pronounced in the absence of strong perceptual cues like good configuration, though only at a marginally significant level. We found that simulated right homonymous hemianopia also slowed part processing, but we did not find a greater impairment from homonymous hemianopia when object configuration was poor. However, the variability in effects was such that some of our individual subjects showed a disproportionate effect of configuration under hemianopic conditions that was greater than the mean effect shown for their patient group compared to controls. Hence caution is required regarding their conclusion that the processing of non-orthographic stimuli in alexia is fragile and may be disrupted by "the absence of perceptual cues like good continuation" (p.961), as we cannot entirely exclude the possibility that this effect is also driven by homonymous hemianopia.

5.2 Experiment 2

It was (Sheldon et al., 2012) who used a simulated approach to help define the boundaries between hemifield loss alone and pure alexia. However, partial hemianopia is not uncommon, and a diagnostic criterion for diagnosing pure alexia with partial right homonymou hemianopia is currently unknown.

First, our results replicated the magnitude of word-length effects reported in prior studies (Sheldon et al, 2012; Bao et al, 2015) for both full-field viewing and for complete right hemianopia (Table 2). Our full-field viewing results are also comparable to those in many other

studies of reading time in healthy subjects (Barton et al, 2014) and our simulated right hemianopic data are similar to those reported in patients with right hemianopic dyslexia (Leff et al, 2001; Leff et al, 2006; Sheldon et al, 2012). Second, we found that, while mean reading time followed an approximately exponential decline with increasing degrees of macula-sparing, the word-length effect was relatively constant until sparing of central vision exceeded about 5 degrees.

The reason for the divergence between mean reading time and word-length effect is not clear, however. Previous studies of healthy subjects with simulated complete hemianopia and of patients with pure alexia show that these two variables are strongly correlated across subjects (Sheldon et al, 2012; Barton et al, 2014). At present, it seems that for less than 5°, all words benefited from increasing sparing considering the size of individual letters spanned approximately 1° of visual angle. Beyond 5°, however, the smaller words no longer benefit from increased sparing because words spanning 3-4° in length become entirely visible beyond this point. However, words of longer length, that span more degrees of visual angle, continue to be partially obscured, and further increases in macula-sparing would result in decreased reading times and smaller word-length effects.

To conclude, we further defined the boundary between hemainopic dyslexia and pure alexia, specifically for varying degrees of central hemifield loss. Distinguishing between hemianopic dyslexia and pure alexia is important because the very different mechanisms behind the reading problems of these two conditions means that the rehabilitative approaches suitable for each will differ.

5.3 Experiment 3

Through our knowledge on reading impairment in hemianopia from previously reported studies, we devised the current reading training program for rehabilitation of hemianopic dyslexia. The importance of reading in daily living is immense, yet few programs target reading alone. This pilot study was the first at exploring whether expansion of the leftward perceptual span following perceptual training in right hemianopia was feasible. As the availability of therapists can be a limiting factor, this project explored a less costly and more widely available 21st century solution to rehabilitation, online programs that can be done at home with long-range supervision.

Patients successfully completed all training sessions, and following each session verbal feedback was obtained. All had positive feedback, reporting that they felt increasingly comfortable recognizing words of longer length following each session. When hemifield loss involves the central 5 degrees, 92% of patients with right hemianopia complain of reading difficulties despite otherwise intact language skills (Schuett et al., 2008). Therefore, to assess reading performance, we obtained a number of ocular-motor parameters, and reading speed, prior to and following training. Reading speed and, number of fixations, fixation duration, number of forward and regressive saccades, and amplitude of forward saccades were assessed in two hemianopic dyslexic patients. Consistent with prior reports in right hemianopia (McDonald et al., 2006; Schuett et al., 2008), JN and JW had abnormal ocular-motor parameters, including a large number of fixations, longer durations of fixations, and saccades of smaller amplitude (Figure 3;4). JN and JW showed no improvement from training, except for a significant increase in the size of forward saccades for JW (Figure 3;4). Surprisingly, JN's fixation duration increased (Figure 4), contrary to our predictions. We had predicted that perceptual training in the

left parafoveal field would 1) increase the size of forward saccades, 2) minimize the number of regressive saccades, and 3) produce fewer fixations and of shorter duration.

What we found to be particularly interesting was, although both patients reported difficulty in reading, both had relatively high reading speeds to begin with (JN: 150wpm, JW: 117wpm). Reading speed impairment is dependent on a number of factors, including side of visual field damage, and severity of parafoveal visual field loss. Specifically, reading time (words per minute) has an inverse relationship with visual field sparing, which is apparent in both right- and left-sided field loss, but is more pronounced in right hemianopia (Zhil, 2000). Studies have reported mean reading speeds of 68wpm (Leff et al., 2001), 98wpm (Leff et al., 2006), and 89wpm (Spitzyna et al., 2007) in right hemianopia. This might explain the lack of improvement in reading speed following perceptual training, in the current study. JN and JW had relatively high reading speeds prior to training, leaving little room for improvement.

Reading efficiency is manifest in the eye movements used during reading. Fixation duration, for instance, is prolonged if word processing is difficult, evident by a larger word-length effect (63ms/letter for JN, 234ms/letter for JW). In right hemianopia, the lack of a right visual hemifield produces a delay in programming the next saccade, leading to longer fixations. If patients had a larger perceptual span, however, fixation duration would be shortened, because a larger window for information processing would allow more efficient lexical processing.

Another explanation for the lack of improvement in reading following training could be perceptual span size, the visual region within which text information is used to guide reading eye movements (McConkie & Rayner, 1975). If patients had a perceptual span more than 4 character spaces leftward of fixation, they'd show little-to-no benefit from training. If true, a larger than normal leftward perceptual span would explain why JN finished training block 6 (8-letter words)

with minor difficulty (Figure 2). This is merely a speculation. Without a measure of perceptual span, we cannot conclude that perceptual span size had any involvement in the lack of reading improvement following training, a limitation in the current study.

Albeit lack of a perceptual span measure, we obtained visual-span profiles showing letter accuracy of up to 8 letter positions left of fixation. Visual-span plots (Figure 13) also showed no effect from training on visual-span, the number of letters that are accurately identifiable in a single fixation.

Furthermore, we considered whether the lack of reading improvement from training was a consequence of training *implementation*. Was our training program created optimally for increasing the size of the perceptual span? The next few paragraphs will discuss this in more detail.

Implementation of the training program is reflected in: training duration, protocol, and environment. First, training duration was chosen from previous reports on perceptual learning (See Schuett, 2009 for Review). Additionally, Schuett et al. (2008) used a similar approach where patients engaged in training for 30-45mins per session over a 2-week period. ReadRight (Ong et al., 2012) recommends as little as one 20-min session per day of training of up to 15 hours total. This suggests a higher intensity of training but over a shorter period of time. For instance, increasing training sessions from every second day in the current study, to every single day, but maintaining 30-45 minute sessions, and over a 2-3 week period instead of the current 7-week minimum.

Second, the training protocol was adopted from prior reports on reading training through perceptual learning in healthy individuals and in patients with macular degeneration (Chung et al., 2004; Chung, 2011). Letter recognition training can expand the visual span and increase

reading speed in healthy subjects, with improvements lasting more than three months (Chung et al., 2004). A similar training approach has been used to improve parafoveal reading in patients with macular degeneration (Chung, 2011). Training of hemianopic dyslexia should be if anything more helpful than training in macular degeneration, because of the simple fact that the hemianopic field defect is usually stable, while macular degeneration continues to progress. The fact that damage is limited to one hemisphere should mean that training is directed at a region of vision (the left parafoveal field) that is quite normal. While there are some reports of ipsilateral contrast sensitivity deficits with contralateral hemianopia (Hess and Pointer, 1989), and possibly reduced useful field of view (Rizzo and Robin, 1996), the former are generally modest and not likely to affect high-contrast stimuli like letters, and the latter is more of an issue for peripheral than for parafoveal vision.

Third, although Schuett et al. (2009) recommends a supervised error-less learning environment for optimum rehabilitation of hemianopic dyslexia, online training with long-range supervision has been proven to be effective, as seen by ReadRight (Ong et al., 2012). As discussed earlier, it would be ideal for patients to maintain fixation in the center of the screen to avoid missing the briefly flashed stimulus. This would encourage them to maintain central fixation and limit head- and/or eye-movements to other parts of the screen, which would otherwise interfere with the acquisition of information processing and delay treatment progress (Zihl, 2000).

The perceptual learning method seems to concur with prior reports on the benefits of perceptual training. A few minor changes might result in improvement following training. For one, recruiting patients whose reading speeds are less than 100wpm. Secondly, increasing training intensity from 3 sessions per week to 5 sessions per week. Lastly, conducting the

training in a controlled setting until it can be confirmed that patients are in fact training properly, before training is done online and at home.

5.4 Conclusions

Our experiments showed that first, hemianopia alone could account for the results previously reported in alexic patients with right hemianopia. We conclude that distinguishing the effects of hemianopia from those of pure alexia is critical for investigations of the mechanisms underlying pure alexia, and that inferences about high-level perception from results must await demonstration that the results are not attributable to low-level effects such as visual field loss. Second, when simulated hemianopia is varied as a function of the degrees of central sparing, single-word reading is most difficult for 5 degrees of sparing or less. Subsequently, we've devised word-length effect criteria for word-length effects with various degrees of central sparing, which can be used in the diagnosis of pure alexia. Last, we showed that on-line perceptual training in two hemianopic dyslexic patients over an extended period is feasible, though we found only modest results. A larger study of hemianopic subjects with more severe reading impairment is required to establish efficacy.

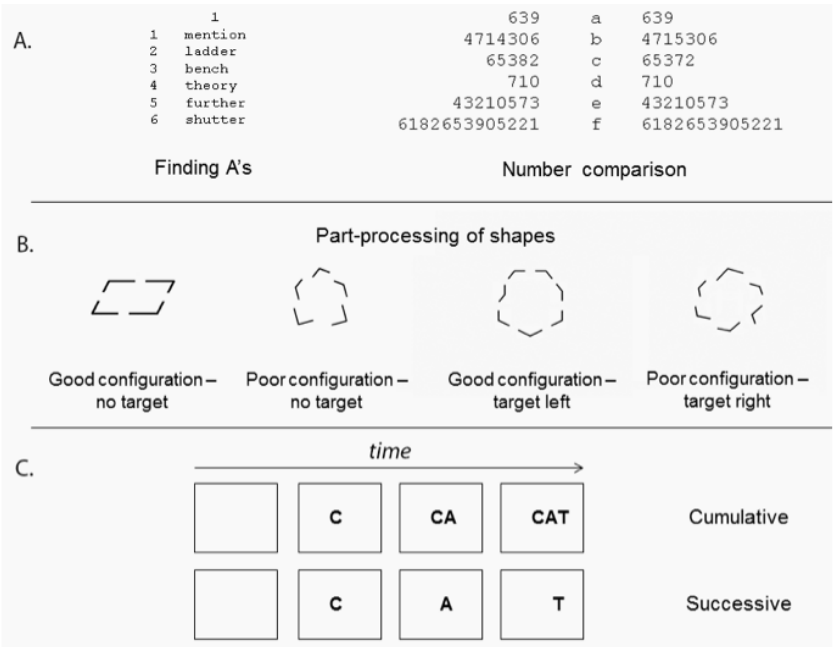

Figure 1. Examples of stimuli for Experiment 1. A. In the Finding A task (left), subjects name the numbers of corresponding to the words that contain the letter A. In the Number Comparison task (right) they indicate by letter whether the two numbers in that row are identical or not. B. Part-processing of shapes. Subjects indicate whether there is a line element whose vertex points into the center of the shape, as seen on the left side of the third stimulus and the right side of the fourth stimulus. Shapes can have four to seven line segments, as shown. Line segments are collinear in shapes with good configuration. C. Orthographic integration: Cumulative and successive presentation of words. Letters of a word appear one at a time on the screen at a rate of 100 to 500ms for each letter. In the cumulative condition the letters remain visible as the next appears. In the successive condition they disappear with the appearance of the next letter.

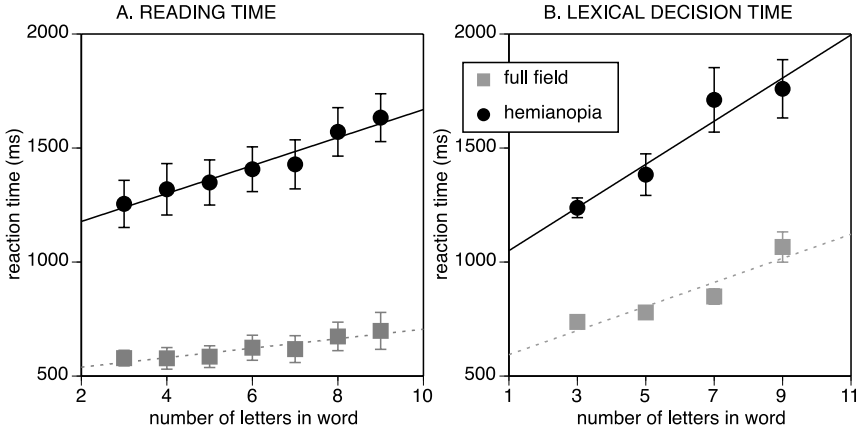

Figure 2. Word-length effects, Experiment 1. Reaction time A) to begin reading a word aloud, and B) to indicate whether the stimulus was a word (lexical decision) is plotted as a function of the number of letters in the word. Mean and +/- one standard error are shown, with lines fitted by linear regression.

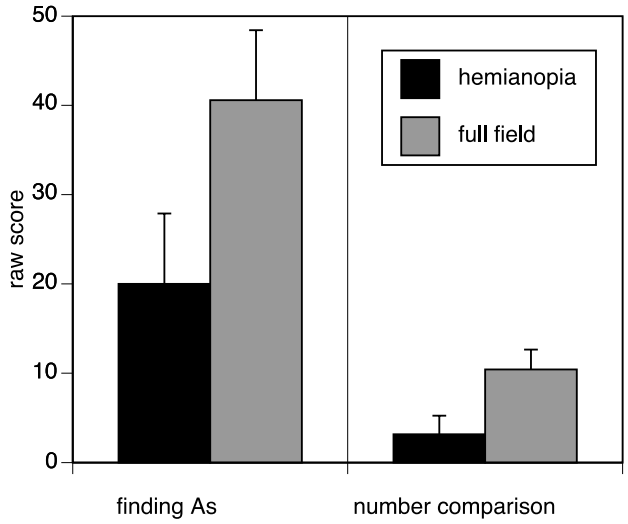

Figure 3. Accuracy for the finding A's task (left), and number comparison task (right), Experiment 1. Mean with error bars indicating +/- one standard deviation are shown.

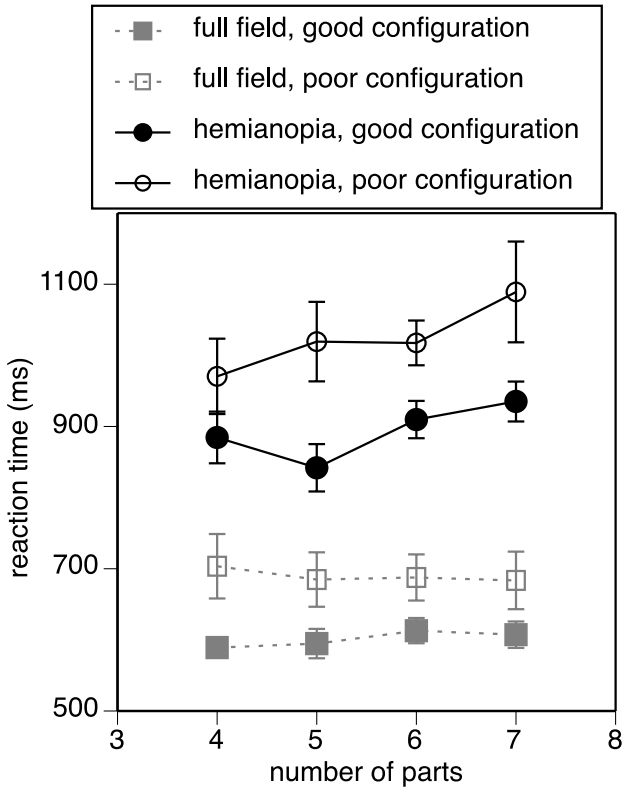

Figure 4. Part-processing of shapes, Experiment 1. Reaction times are shown with error bars indicating +/- one standard error. The difference between responses to stimuli with good versus poor configuration can be seen for full-field and hemianopic viewing sessions.

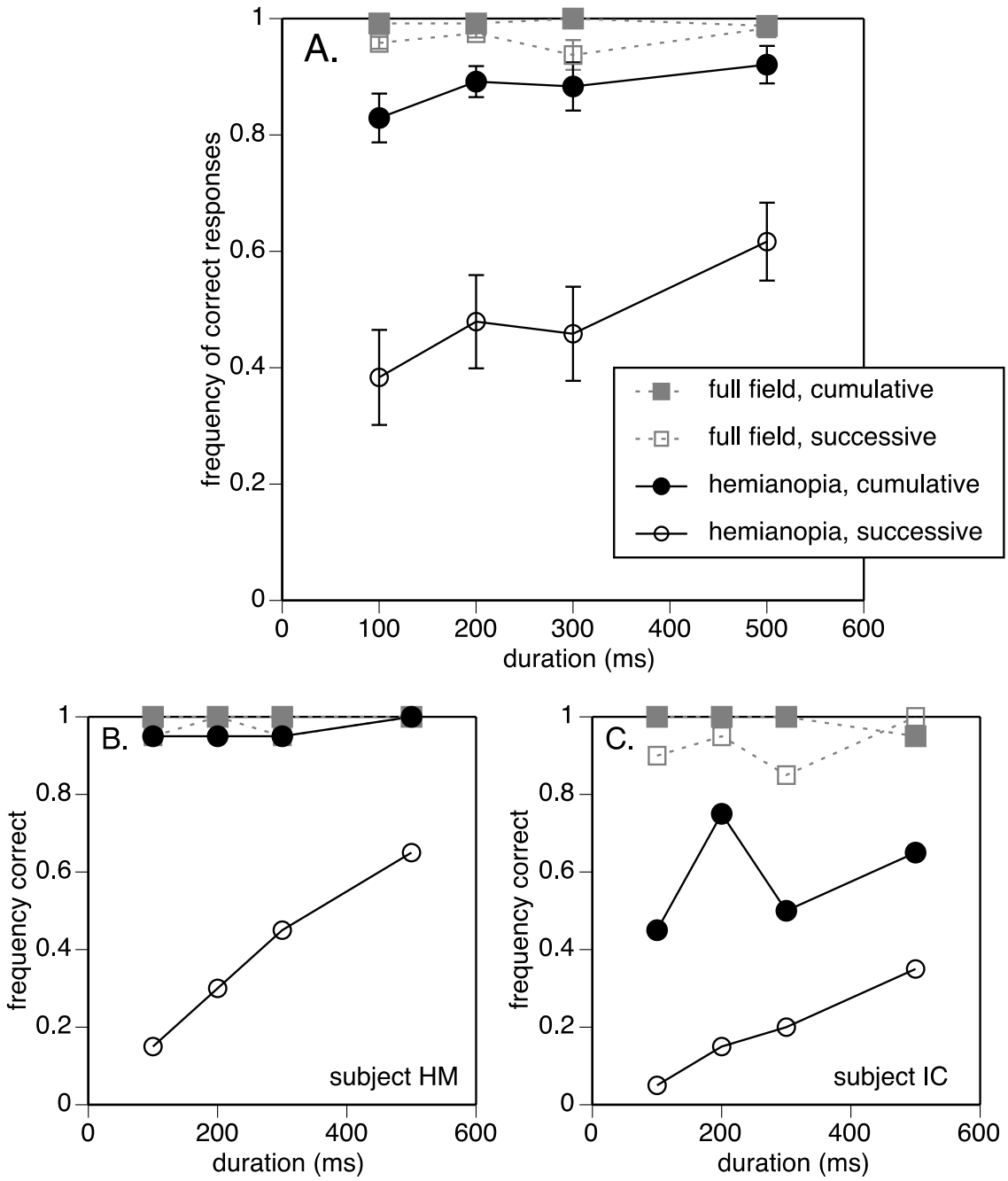

Figure 5. Orthographic integration: cumulative versus successive presentation, Experiment 1. A. Group mean data, with errors bars showing +/- one standard error. With full-field viewing subjects perform at ceiling for both types of presentation. With hemianopic viewing, they have more difficulty with the successive presentation, particularly at shorter stimulus durations. B. Data for subject HM. C. Data for subject IC.

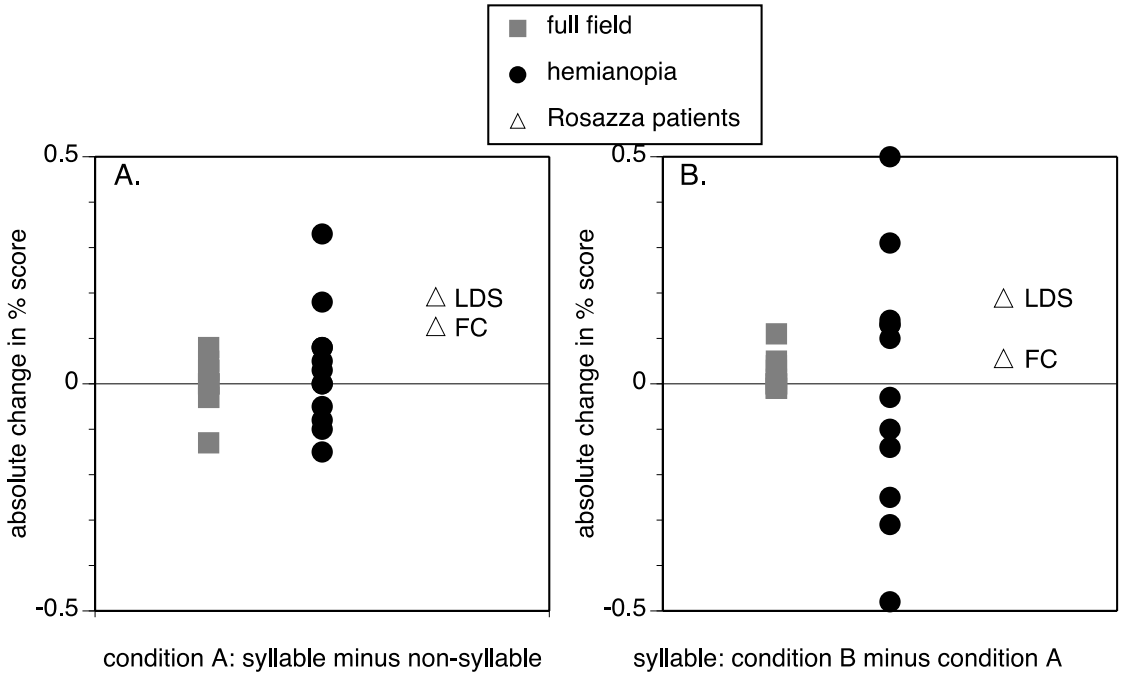

Figure 6. Orthographic processing: syllable task, condition contrasts, Experiment 1. A. difference in score between syllable and non-syllable tasks. B. Difference in score between condition A (name letters) and condition B (read aloud the syllable).

Table 1. Results for orthographic processing: syllable task, Experiment 1.

	Condition A						Condition B	
	Letters		Syllables		Non-syllables		Syllables	
	Score/240	%	Score/40	%	Score/40	%	Score/80	%
Full-field	237 (2.8)	99	38.8 (1.4)	97	38.8 (1.5)	97	79.0 (0.7)	99
Hemianopia	167 (24)	69	12.2 (8.9)	30	11.0 (6.2)	28	24.3 (15.5)	30

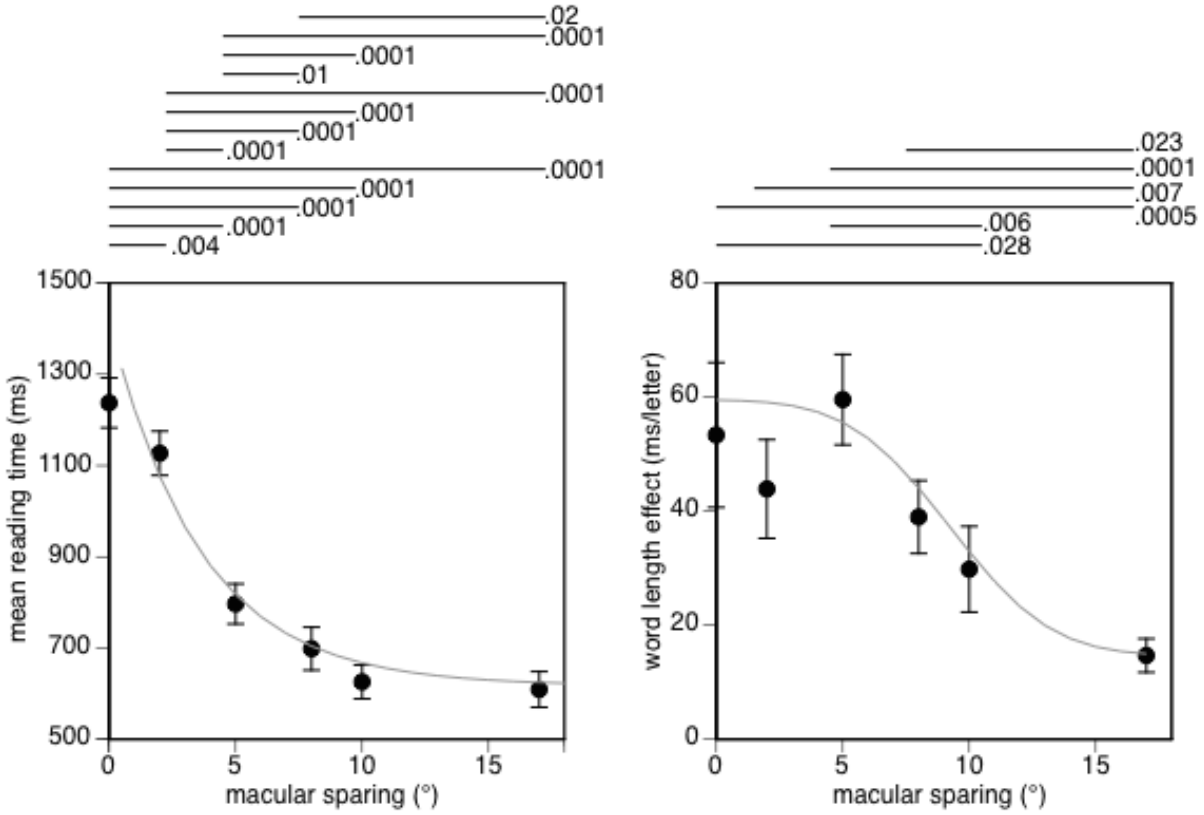

Figure 7. A. Mean reading time (averaged across all word lengths) as a function of the degree of macula-sparing, Experiment 2. Grey line is an exponential function fit to the data for illustrative purposes. B. Word-length effect as a function of the degree of macula-sparing. Grey line is a sigmoid function fit to the data for illustrative purposes. Full-field viewing is given a default value of 17°. Above each graph are depicted the significant results of linear contrasts between pairs of viewing conditions, with p-values given. Error bars indicate +/- one standard error.

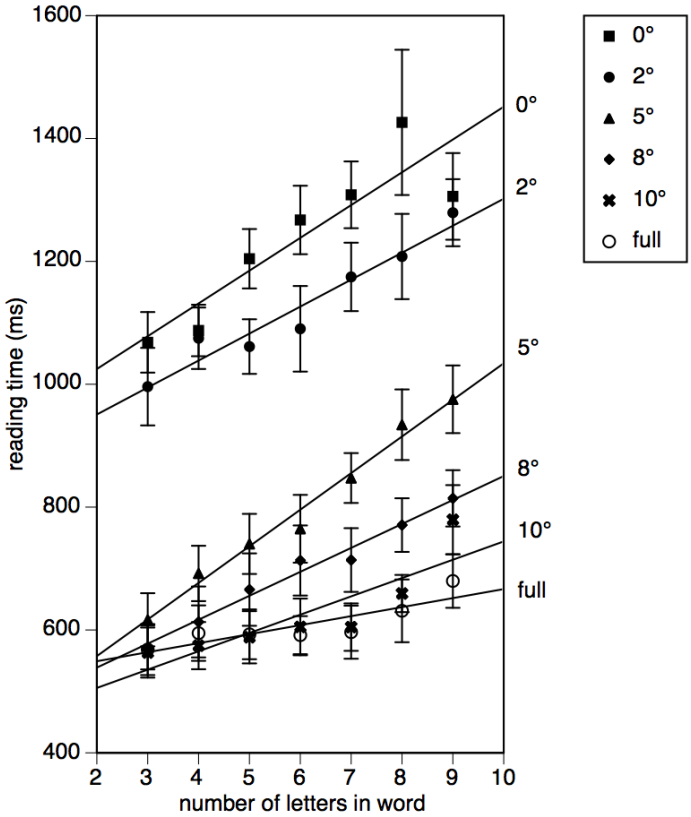

Figure 8. Mean reading time as a function of number of letters in a word for the six different viewing conditions, Experiment 2. Error bars show +/- one standard error. Slopes of the linear regression of the mean values are shown.

Table 2. Prediction intervals for the effects of hemifield loss, Experiment 2.

	Macular sparing (°)	Mean (ms)	s.d.	95% upper limit
Current study	0	53.4	40.2	166
	2	43.9	27.4	121
	5	59.6	25.1	130
	8	39	20.2	96
	10	29.8	23.8	97
	full	14.7	9.3	41
Sheldon et al, 2012	0	37.7	46.9	161
	full	14.2	13.7	51
Bao et al, 2015	0	61.3	46.1	186
	full	14.5	8.7	38

Table 3. Patient data, Experiment 3.

	JN	JW	KA	BM	BB
Gender	M	M	M	M	M
Age at testing	69	64	54	48	81
Handedness	left	right	right	right	right
Time since lesion (years)	12	6	16	2	1
Cause of hemianopia	haemorrhage	infarct	haemorrhage	tumour	haemorrhage
Word length effect (ms/letter)	63	234	486	1683*	7972*
Diagnosis	hemianopic dyslexic	hemianopic dyslexic	pure alexic	pure alexic	pure alexic
MoCA	26/30	22/30	20/30	25/30	18/30
Corrected visual acuity (near right, near left)	20/30, 20/20	20/25, 20/25	20/40, 20/50	20/40, 20/40	20/30, 20/30

*short version of single-word reading: 20 trials instead of 160; note: BB's WLE is a rough estimation, he had difficulty pronouncing single letters and only after a few wrong guesses would result in the correct response.

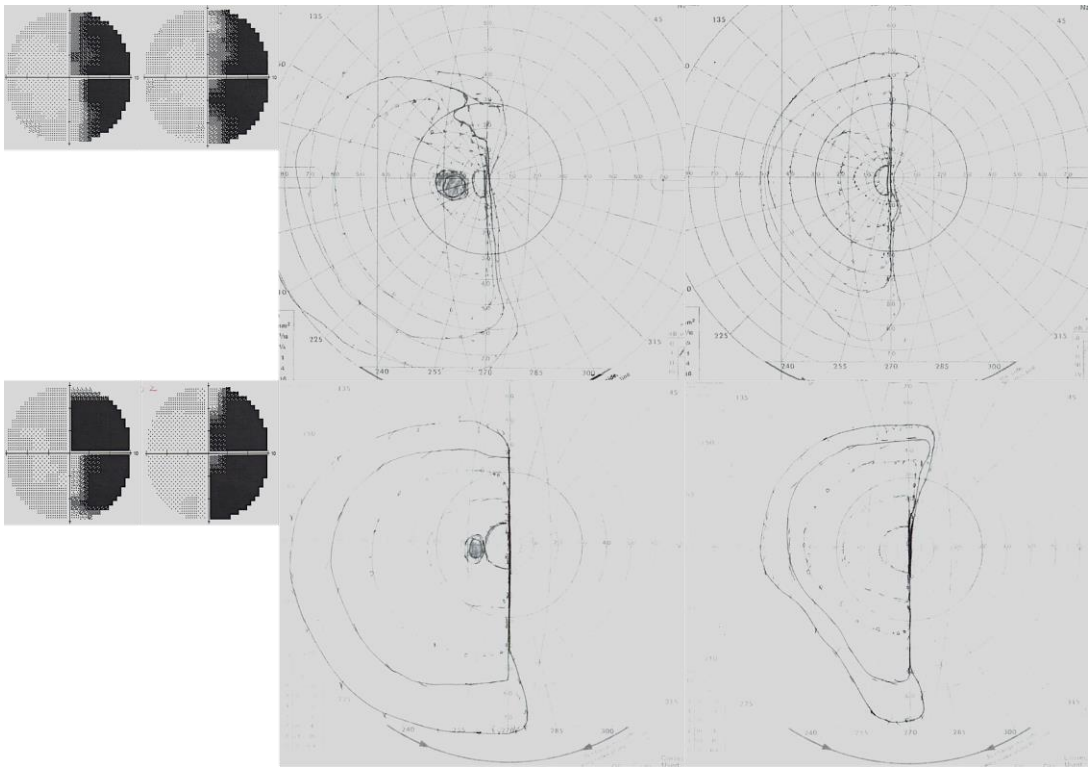

Figure 9. Perimetry results, Experiment 3. Humphrey 10-2 (left) showing right homonymous hemianopia affecting the central 10 degrees (shaded regions), and Goldmann (right). JN (top) and JW (bottom).

Table 4. Neuropsychological assessments, Experiment 3.

		Max	JN	JW	KA	BM	BB
Attention							
Temporal		**100**	100	99	100	98	14*
Spatial		**6**	6	6	5	6	5
Benton Left-Right		**20**	20	20	18	17	17
General Intelligence							
Wechsler Abbreviated Scale of Intelligence: Full-2 Scale IQ		**157**	119	79*	59*	70*	109
Memory							
Story A, immediate recall		**25**	13	7	4	7	4
Attention							
Visual Search		**60**	51	52	51	20*	21*
Visual Object and Space Perception							
Object Perception:	Screening test	**20**	18	19	20	19	16
	Incomplete letters	**20**	19	17	20	18	10*
	Silhouettes	**30**	22	11*	23	14*	7*
	Object decision	**20**	18	16	18	16	13*
	Progressive silhouettes**	**20**	12	13	5	17*	20*
Spatial Perception:	Dot counting	**10**	10	10	10	9	6*
	Position discrimination	**20**	18	13*	19	12*	14*
	Number location	**10**	8	5*	9	9	7#
Boston Naming Test							
		60	58	51*	21*	18*	22*

**higher score indicates more impaired performance; *indicates impaired performance; #indicates borderline performance. Note: scores for immediate recall were not compared against normal averages because normative data for this memory subtest was not available.

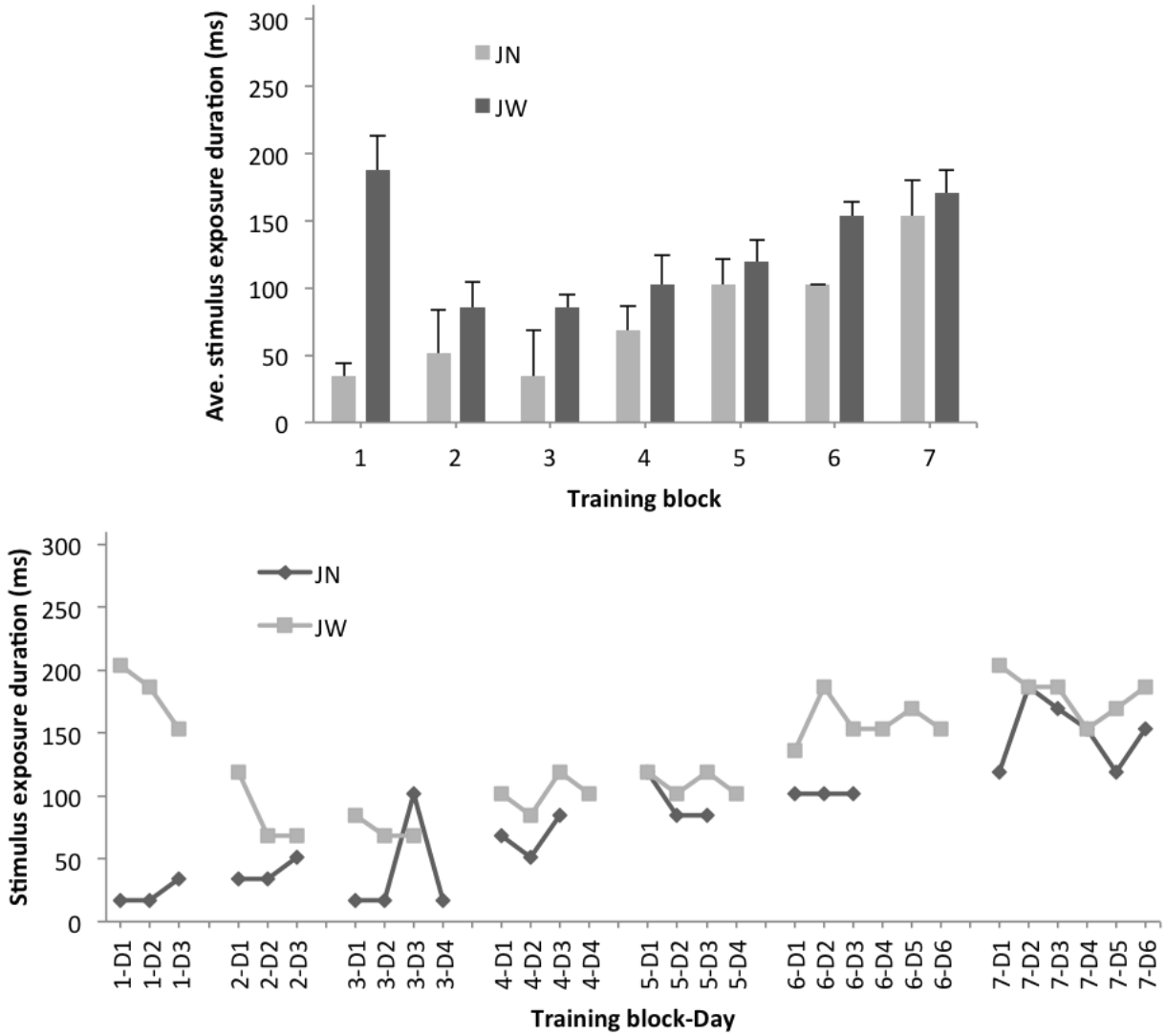

Figure 10. Within training results, Experiment 3. Data for individual patients is reported. Top graph: average of all training days within a training block, taking into account all peaks and troughs for each session (day). Error bars correspond to +/- one standard deviation. Bottom graph: average of the top 50 peaks for each session (day) and training block.

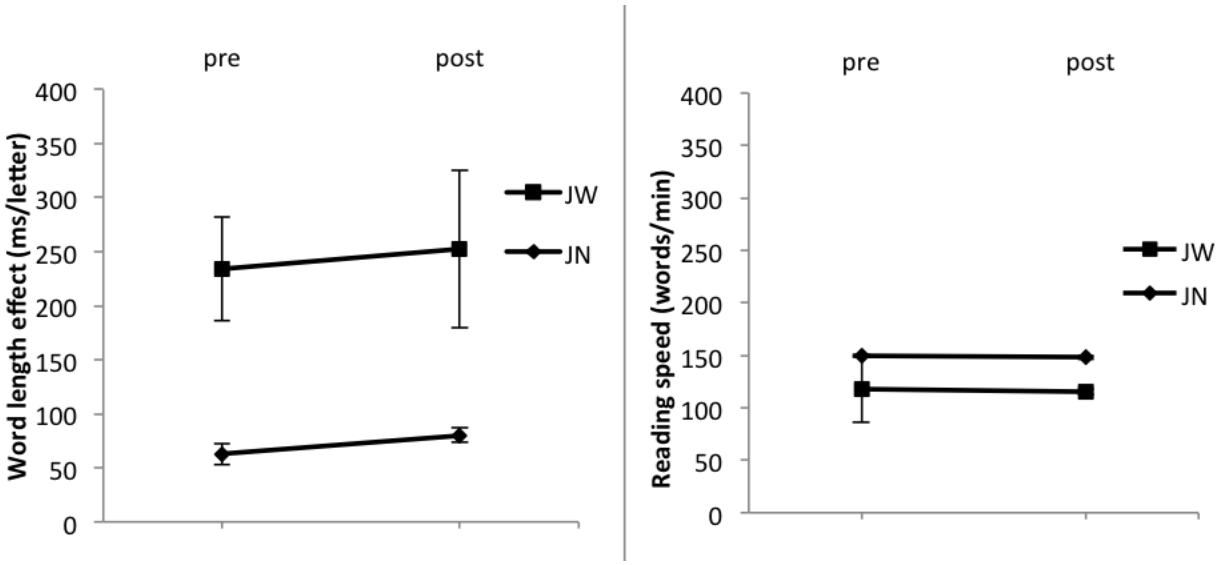

Figure 11. Paragraph and single-word reading, Experiment 3. Data for individual patients is reported. Right graph: reading speed is plotted before and after training; obtained from paragraph reading. Error bars correspond to one standard deviation. Left graph: the word-length effect is plotted before and after training; obtained from single-word reading. Error bars correspond to +/- one standard error of the mean.

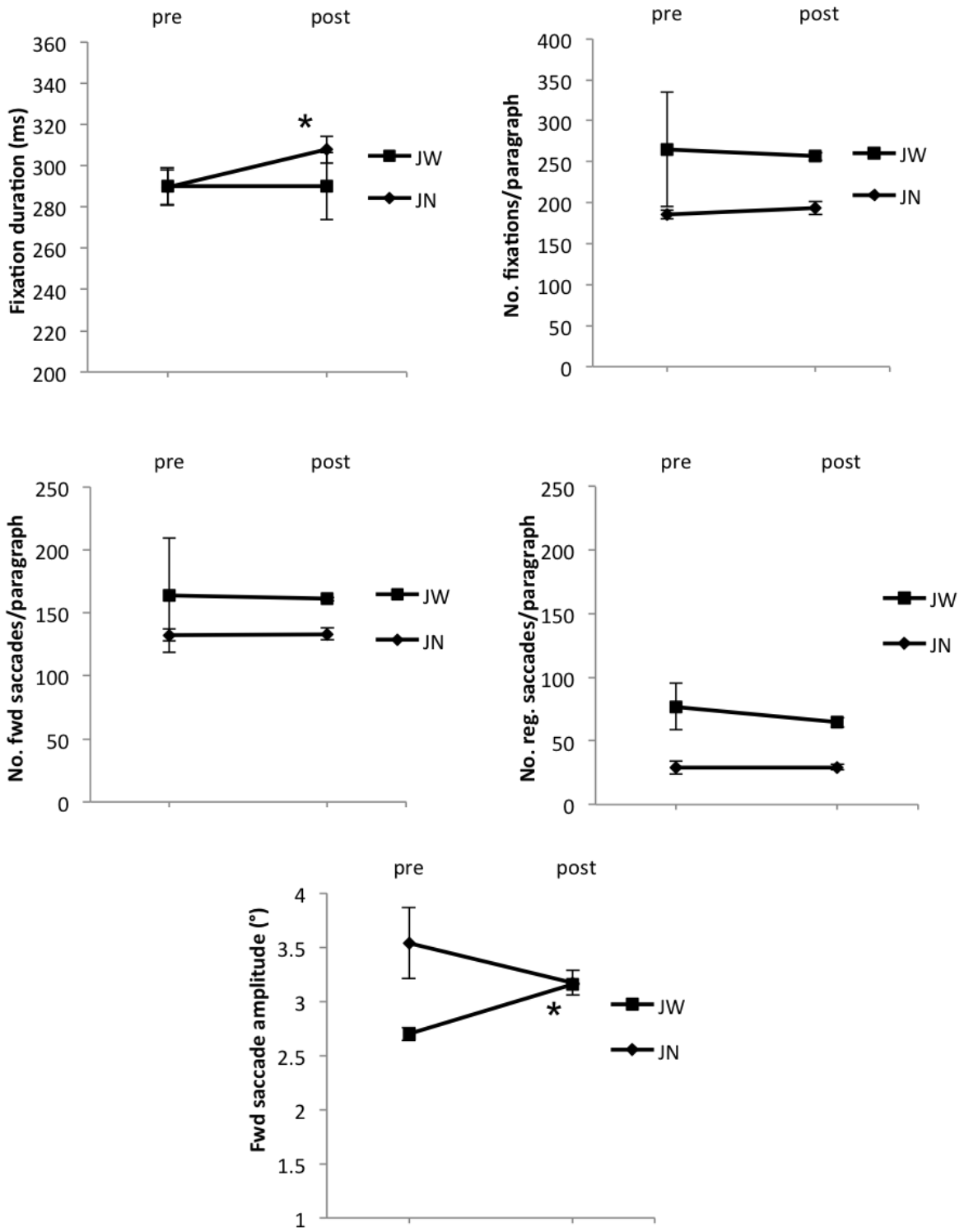

Figure 12. Ocularmotor results, Experiment 3. Top graphs show fixation duration and number of fixations. Middle graphs show number of forward and regressive saccades. Bottom graph shows amplitude of forward saccades. Error bars correspond to +/- one standard deviation. *indicates statistical significance.

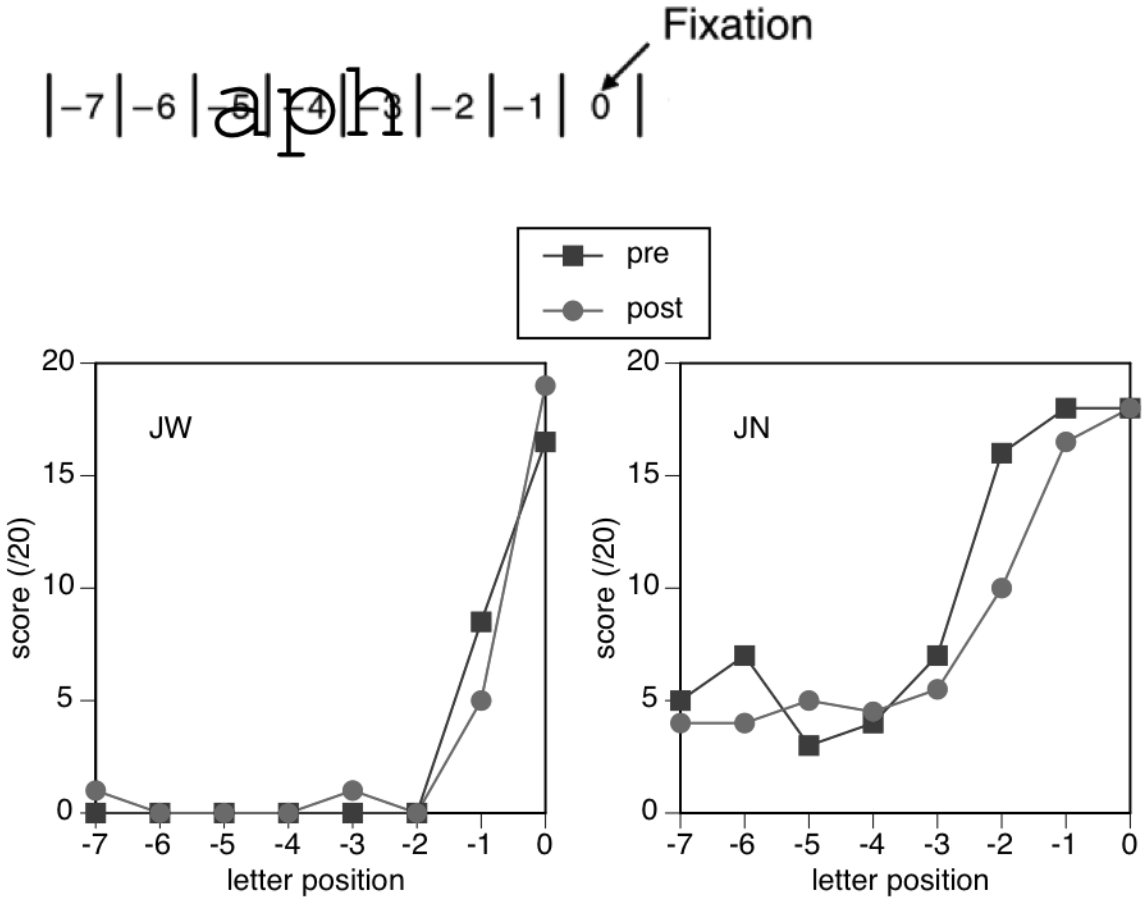

Figure 13. Visual-span profiles, Experiment 3. Left plot: pre and post results for JW. Right plot: pre and post results for JN. Letter positions were scored out of 20. Percent correct (number correct/20) was obtained for each letter slot. A schematic cartoon above illustrates the letter-recognition task used to measure visual-span profiles. A sample trigram is shown in letter position -4.

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