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Analyzing Reading Specialization Using fMRI, rs-fcMRI, and Development

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Analyzing Reading Specialization Using fMRI, rs-fcMRI, and Development

by

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ABSTRACT OF THE DISSERTATION

Analyzing Reading Specialization Using fMRI, rs-fcMRI, and Development

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Professor Steven E. Petersen, Chairperson

Reading is an important, phylogenetically new skill. While neuroimaging studies have identified brain regions used in reading, it is unclear to what extent these regions become specialized for use predominantly in reading versus other tasks. The goal of this dissertation is to investigate the extent to which reading specialization exists at the region and network level, with a focus on orthography, the visual processing of words and letters.

I used task-based and resting state functional connectivity (rs-fcMRI) studies to investigate the specialization of orthographic processing, purportedly localized to a left occipito-temporal fusiform cortex region. In Chapter 2, we find no visual region specialized for words or letter strings as compared to line drawn pictures and Amharic character strings (which compose the Ethiopian writing system). Rather, the region appears to be generally involved in visual processing with properties useful for reading, including the ability to process complex stimuli in groups.

In Chapter 3, we use rs-fcMRI to demonstrate functional relationships between the left occipito-temporal fusiform cortex and spatial attention regions rather than regions consistently activated in reading tasks.

In Chapter 4, we extend these findings by looking at the pattern of functional connectivity in a large network of reading-related regions found in a meta-analysis of reading studies. Using

graph theoretic measures on resting state data, we did not find preferential functional connections between regions predominantly used in reading. Rather, we showed the network was basically composed of previously described, more general communities. Comparing the network structure of children and adults also shows few reading specific changes, but rather a change from local to distributed network structure, also seen previously.

In Chapter 5, we describe a comparison of activity during matching and naming tasks, and show task-dependent processing differences in reading-related regions. Such differences also indicate a lack of specificity for reading, and suggest the need for careful task design.

Together these results indicate a lack of neural specialization for reading at either the regional or network level, suggesting that fluent reading is instead performed by co-opting existing neural systems.

CHAPTER 1: INTRODUCTION

Reading is one of the most important academic skills acquired in the western world, yet it is also a non-universal, phylogenetically new skill. This combination offers the unique opportunity to study an important skill that is unlikely to have an evolutionarily predetermined neural basis. The study of reading allows insight into both how a skill acquired through years of training and experience uses and shapes neural processing, as well as the possibility of a better understanding of the underlying causes of illiteracy, a major societal problem.

The importance of reading

Clearly, many professions require fluent reading, as does making informed decisions about finances, health care, and elections, as well as more mundane daily skills such as navigating from place to place, grocery shopping, and paying bills. Reading, as measured by print exposure, accounts for variations in vocabulary and world knowledge independent of IQ and schooling (see Stanovich KE, 1993 for a review). Nonetheless, 5-17% of Americans fail to develop fluent reading despite adequate instruction (Stanovich KE, 1986).

However, the statistic that 5-17% of the population fails to develop fluent reading hides a larger societal issue. There are significantly higher rates of illiteracy in poor populations -- 44% of adults living below the poverty line have less than basic literacy (i.e are unable to read and comprehend even short sentences) relative to the 17% of the general population living below the poverty line (Baer J et al., 2009). Additionally, people with low literacy skills are at an educational disadvantage. Fifty-five percent of adults lacking basic literacy completed only some high school (and did not graduate) relative to 15% of the general population, and only 9% of those lacking basic literacy completed a vocational, associates or bachelors degree relative to 30% of the general population (Baer J *et al.*, 2009). Fourth grade children qualifying for free or reduced price lunch have average reading levels of 196 (on a 600 point scale that measure literacy through adulthood), compared to 227 for fourth graders who do not qualify for free or reduced lunch (Donahue PL et al., 2001). Children of parents with lower levels of education (less than high school or high school graduates as compared to college graduates) have lower average reading skill at all ages, from kindergarten (West J et al., 2001) to fourth grade (Donahue PL et al., 2001) to high school (Campbell JR et al., 2000). Together, these trends set up a potential cycle of illiteracy and poverty, whereby each influences the other and reduces the possibility of upward mobility.

An understanding of how fluent reading is instantiated in the brain and how that fluency develops can help clarify how to identify and treat those with reading delays or difficulties. Better identification and remediation can only help to reduce the number of people without basic literacy and close the literacy gap related to socioeconomic status that helps perpetuate poverty.

The instantiation of a phylogenetically new skill in the brain

An evolutionarily newly acquired skill, such as reading, may be instantiated in two, non-mutually exclusive, ways. First, reading could utilize general brain regions and neural processes that are also used for other purposes. Second, reading development could fundamentally reshape the neural processing in a way that “co-opts” reading-related brain regions and results in networks used relatively specifically in reading (as theorized in Dehaene and Cohen, 2007). Again, these possibilities are not mutually exclusive and a combination of the two could exist. For example, reading could use general visual processors for evaluating the written letter and word components, but develop a relatively specialized region or regions for orthographic to phonologic conversions. Likewise, reading could use several general processing regions linked together into a specific reading network.

In this dissertation, I attempt to evaluate these possibilities -- both at the individual region and at the network level. To begin to study the specificity of functional regions we have focused on a left occipito-temporal fusiform region thought to be important in orthographic (visual word form) processing. Orthographic processing is the first step in reading and is the process that differentiates reading most clearly from spoken language, making it an interesting choice for such study. We have also investigated the specificity of functional relationships of this left occipito-temporal fusiform region. Additionally, the network structure of a large set of reading-related regions was evaluated. Finally, we have addressed the question of specificity of regions and processing for reading in a somewhat orthogonal way, by studying task-related differences in reading-related processing.

In this chapter, I will briefly review what is known about the neural instantiation of orthographic processing and its specificity for reading. Then, there will be a discussion about resting state functional connectivity MRI (rs-fcMRI), the method we will use to define and examine functional relationships between brain regions. This will include a short overview of networks and algorithms used to detect network structure. Finally, I will attempt to describe the utility of carefully characterizing the tasks used in functional imaging studies, and how an understanding of task-related differences may inform the specificity of reading-related processing.

Specialization for orthographic processing

Reading requires transforming visual inputs (orthography) into phonologic, semantic, and/or spoken outputs, and behavioral and neural evidence of processing specialization has been put forth for each of these components. However, for the purpose of this dissertation, we will focus on orthographic processing.

Behavioral evidence suggests the brain contains at least two types of visual letter representations- small chunks that can be converted to phonemes, such as those used for reading pseudowords, and large chunks of multiple phonemes or whole words. On a gross level, adult readers are better at responding to words than meaningless letter strings. Adults are faster to make matching judgments on words than strings of random letters (LaBerge D and J Samuels, 1974), non-letter stimuli (Burgund ED et al., 2006) or Amharic characters (Vogel AC et al., 2007). Additionally, adults exhibit a word superiority effect, whereby they are faster to identify whether a target letter is present inside a real word than if the target is presented in a random string of letters (Reicher GM, 1969). This word-superiority effect has been taken as evidence of top-down feedback from a word level representation onto individual letter representations. Moreover, adults have relatively little increase in response time to name high frequency real words of different lengths, while length has a significant effect on response time to name pseudowords (Weekes BS, 1997). This length by lexicality interaction is presumably due to representations of high frequency real words existing at the level of whole words (or at least large chunks), while pseudowords must be processed at the level of single graphemes.

In addition to the behavioral study of orthographic specialization, there is a long history presupposing a specific neural location for orthographic processing. In the late 19th century, Dejerine first reported a lesion to left occipito-temporal cortex resulting in alexia, or a loss of fluent reading (Dejerine J, 1892). The finding that lesions to occipito-temporal cortex cause relatively specific reading deficits has been replicated repeatedly in the last 120 years (i.e., Cohen L et al., 2003; Gaillard R et al., 2006; Kinsbourne M and EK Warrington, 1962; Warrington ET and T Shallice, 1980). Relatedly, psychological models of reading began including a “logogen” or whole-word analyzer, in the 1970s (as reviewed in Carr TH and A Pollatsek, 1985). With the advent of neuroimaging research, the concept of a region devoted to the analysis of word forms was translated to studies of brain activation (for the first report see (Petersen SE et al., 1988).

Since the late 1990s, neuroimaging studies have converged on a region in the left fusiform cortex near the occipito-temporal junction as important for the higher level visual processing of words during reading (Cohen L and S Dehaene, 2004; Cohen L et al., 2002; McCandliss BD et al., 2003). Meta-analyses of functional neuroimaging studies show this region to be one of the most consistently reported regions of activation (Jobard G et al., 2003; Mechelli A et al., 2003; Turkeltaub PE et al., 2002; Vigneau M et al., 2006). There seems to be activity in this region when viewing words regardless of case, size, and location (Cohen L et al., 2002), and some report increased activity for words relative to consonant strings, digits and objects in this area (McCandliss BD et al., 2003; Polk TA et al., 2002; Vinckier F et al., 2007). As mentioned previously, lesions including this occipito-temporal fusiform region often result in acquired alexia. Together, these findings have led Cohen and colleagues to term this piece of occipito-temporal fusiform cortex the visual word form area (VWFA, Cohen L and S Dehaene, 2004; Cohen L et al., 2002; McCandliss BD et al., 2003), and argue that in the course of acquiring fluent reading it becomes specialized for visual word forms and predominantly used in reading (Dehaene S and L Cohen, 2007).

However, the degree of specialization and appropriateness of referring to this brain region as the "visual word form area" has been debated since the inception of the term (see "The myth of the visual word form area" Price CJ and JT Devlin, 2003 for a review). While some groups have reported more activity for letter strings than consonant strings and false fonts (Cohen L and S Dehaene, 2004; Cohen L et al., 2002; Polk TA et al., 2002; Vinckier F et al., 2007), others have reported the opposite (Cohen L et al., 2003; Tagamets MA et al., 2000; Xue G et al., 2006). There are numerous reports of activity in this region when viewing picture stimuli (Bar M et al., 2001; Ben-Shachar M et al., 2007; Ploran EJ et al., 2007; Price CJ and JT Devlin, 2003; Starrfelt R and C Gerlach, 2007), including equivalent activity for pictures and words (Van Doren L et al., 2010). Moreover, there has been some doubt as to the specific location of lesions producing alexia (Hillis AE et al., 2005; Price CJ and JT Devlin, 2003), as well as the specificity of letter processing disruption from lesions to this area. A number of groups have found evidence that patients with pure alexia also show impairments in naming objects, particularly under visually demanding circumstances such as very fast presentation rates (Friedman RB and MP Alexander, 1984 as reported in Price CJ and JT Devlin, 2003) or high visual complexity (Behrmann M et al., 1998). Starrfelt and colleagues demonstrated that alexic patients are deficient in processing both digits and letters (Starrfelt R et al., 2009). Due to this controversy, we will refer to this region as the putative VWFA throughout the document to emphasize that this label is the subject of continued debate but still allow for easy anatomical description.

In Chapter 2, I will present data regarding the specificity of the putative VWFA for reading and further explore the processing properties of this region-- namely, whether orthographic processing performed in occipito-temporal fusiform cortex involves the processing of complex visual stimuli in groups larger than single letters.

rs-fcMRI as a measure of functional relationships

Functional MRI is not the only imaging method that can be used to study the specificity of reading-related processing. As described above, it is conceivable that reading-related specialization occurs via the formation of strong functional relationships between regions, rather than specialization within any given region. Resting state functional connectivity MRI (rs-fcMRI) provides a method for studying these functional relationships.

Task related responses are only part of the BOLD signal; these task responses ride on top of large, very slow BOLD signal fluctuations occurring in the range of 0.01 to 0.1 Hz. These slow, spontaneous fluctuations occur regardless of whether the subject performs a task and are the basis of rs-fcMRI signal.

In 1995, Biswal and colleagues first reported that, at rest, low frequency BOLD signal fluctuations appear to define relationships between functionally related regions (Biswal B et al., 1995). Specifically, this group found the low-frequency timecourse of a region in somatomotor cortex correlates well with timecourses in the contralateral somatomotor cortex, as well as with timecourses in bilateral ventral thalamus and bilateral supplementary motor areas. These correlations in timecourses are referred to as “functional connectivity”.

These correlations appear to be strongest between functionally related regions (Biswal B et al., 1995; Dosenbach NUF et al., 2007; Fox MD et al., 2005; Greicius M et al., 2003; Lowe MJ et al., 1998), even when those regions do not possess direct anatomical connections (Vincent JL et al., 2007). This observation has led to suggestions that the rs-fcMRI signal reflects the statistical history of co-activity between brain regions, and that this signal can therefore inform researchers about *functional* relationships within the brain (Dosenbach NUF et al., 2007; Fair DA, NUF Dosenbach et al., 2007; Kelly AMC et al., 2009). Consistent with this idea, recent work has demonstrated that visual perceptual learning (Lewis CM et al., 2009), repetition priming (Stevens WD et al., 2010) and memory training (Tambini A et al., 2010) can modify rs-fcMRI signal correlations between brain regions.

Differentiating between several possible “functional connection” profiles of the putative VWFA will help us clarify its role in reading. We hypothesize that if the putative VWFA is used predominately for orthographic processing in reading, it should have functional connections to not only other visual regions but to phonological processors such as the left supramarginal gyrus (SMG) and left inferior frontal gyrus (IFG), semantic processors such as the left angular gyrus (AG) and middle temporal gyrus (MTG), and possibly even supplementary motor area (Alario FX et al., 2006), mouth motor cortex and auditory cortex. If, in contrast, the putative VWFA is a general visual processor that is not only used in reading but in other visual tasks that utilize similar processes, we expect to see functional connections to other visual regions but not with reading-related regions such as the left IFG, SMG, or AG. We test these hypotheses and describe the actual functional connectivity profile of the putative VWFA as well as the developmental changes in that connectivity profile in Chapter 3.

Large scale functional network definition

Resting state functional connectivity MRI research has shown that groups of regions that often activate (or deactivate) at the same time have correlated rs-fcMRI timecourses. For example, visual processing regions in occipital cortex correlate strongly (Lowe MJ et al., 1998) as do regions within the default mode network (Greicius M et al., 2003), the task control networks (Dosenbach NUF et al., 2007; Seeley WW et al., 2007), and the attention networks (Fox MD et al., 2006). A growing number of studies have utilized rs-fcMRI signal to explore changes in brain networks over development in typical (e.g., Fair DA et al., 2009; Fair DA, NUF Dosenbach et al., 2007; Fransson P et al., 2010; Kelly AMC et al., 2009; Stevens MD et al., 2009; Supekar K et al., 2009) and atypical (e.g., Gozzo Y et al., 2009; Myers EH et al., 2010; Smyser CD et al., 2010) development and disease states (e.g., Church JA et al., 2009; Cullen KR et al., 2009; Hampson M et al., 2009; He BJ et al., 2007; Jones TB et al., 2010). Thus, using rs-fcMRI correlations to group brain regions into networks and to describe network structure has become an important step in understanding relationships between regions. However, before we characterize brain "networks", we must describe what we mean by a "network".

Networks are studied in a wide variety of fields. An entire branch of mathematics, called graph theory, is devoted to the study of networks. Networks, from both an intuitive and a more formal graph theoretical perspective, are collections of items (or nodes) that possess pair-wise relationships (called edges). The brain, of course, is a network at many levels. With perfect knowledge, one could define a brain network composed of billions of interconnected neurons, with a (general) hierarchical arrangement of, for example, cortical neurons into columns, functional areas (e.g. V1, V2), and functional systems (e.g. visual or somatosensory systems) (Churchland PS and TJ Sejnowski, 1991). However, the spatial and temporal resolution of rs-fcMRI only allows for the study of networks at the level of areas and functional systems. An rs-fcMRI based network analysis defines individual brain regions (here defined in by a conjunction of fMRI studies) as nodes and the rs-fcMRI correlations between these regions as edges.

However, many networks can be viewed as being composed of sub-networks. For example, a person's social network might consist of a group of friends, a group of coworkers, and a group of teammates, each with rather dense internal relationships, but few relationships between groups. Likewise, the many neural regions defined from our functional analyses may also be composed of different "groups" that predominantly work together, such as visual or auditory processing regions. These groupings of nodes, or sub-network structures, are called communities or modules. Communities have been found in a wide variety of complex networks, and tend to group nodes with shared characteristics (Newman ME, 2010). Viewing networks in terms of communities can simplify and clarify both the form and significance of the overall network structure.

In functional brain networks, communities should identify brain regions with similar features or functions that are potentially functional systems. Community detection tools such as modularity optimization algorithms (Newman ME, 2006; Newman ME and M Girvan, 2004) or Infomap (Rosvall M and CT Bergstrom, 2008) can be applied to matrices of rs-fcMRI correlation values to detect communities of brain regions. These algorithm-based community assignments are attractive because they are quantitative, objective, and work in situations where the eye cannot easily discern community structure (for example, when the relationships between large numbers of regions are in question).

If regions consistently activated in reading are predominantly used in reading, they should comprise a distinct network or community, as described by the aforementioned community detection algorithms. Additionally, this structure should become progressively distinct with increasing age (as age generally correlates with reading skill). However, if these regions perform more general functions, the presence or absence of specific relationships to one another may depend on their general processing properties. In Chapter 4 we use rs-fcMRI to determine the network and sub-network structure of reading-related regions in adults and across development, in an attempt to discern evidence for brain-wide reading specialization.

Studying task related effects informs reading specificity

Concomitant with the assumption that brain regions used in reading are specific to this cognitive skill, there has been the assumption that reading-related processes, and thus reading-related brain regions, are automatically activated whenever a word is viewed. The concept of automatic activation of reading-related processes has a long history, dating back to at least William James (James W, 1890). Behavioral studies of reading have provided some evidence for the automatic activation of reading pathways when viewing (or matching or scanning) words. For example, in the classic word-color Stroop effect, subjects are slower to report the ink color of words that name a different color than the ink color, an indication that the word itself has been processed despite its lack of relevance to the task at hand (see MacLeod CM, 1991). Additionally, early functional neuroimaging studies generally supported the concept of “automatic activation”. Many studies that do not require reading aloud (i.e. Cohen L et al., 2003; Dehaene S et al., 2001; Polk TA et al., 2002; Price CJ et al., 1996; Tagamets MA et al., 2000; Turkeltaub PE et al., 2003) elicit activity in presumptive reading-related regions, including left putative VWFA, SMG, AG, and IFG regions.

However, there is some evidence that task manipulation may alter reading-related neural processing in at least some brain regions. For example, activity differences, measured when contrasting the processing of letters and digits, are reduced in an orthographic processing region when subjects are asked to name the stimuli aloud relative to silent reading (Polk TA et al., 2002). Starrfeldt and Gerlach (Starrfelt R and C Gerlach, 2007) have also shown differential stimulus effects for color versus category naming in the putative VWFA. More regions with differential activation in dyslexic and typical readers are found when subjects read words aloud than when subjects perform an implicit reading task (Brunswick N et al., 1999). Tasks that emphasize specific processing components of reading, such as rhyme matching versus spelling, also show clear distinctions in BOLD activity in regions such as the SMG, IFG and VWFA (Bitan T et al., 2007; Booth JR et al., 2004).

In Chapter 5, we directly test whether changing task demands causes changes in the neural processing of words and pseudowords, by comparing the pattern of BOLD activity for matching and naming three classes of stimuli: words, pseudowords with all legal letter combinations, and nonwords with illegal letter combinations. If the pattern of BOLD activity for processing these different string types differs with task, there is unlikely to be automatic activation of reading related processing. One explanation for such a finding is that the type of processing performed in these regions is not specific to reading per se but is more general, and thus can be brought online as needed by the task at hand. Perhaps more importantly, though, finding a lack of similar processing for all string types in the implicit (matching) and explicit (reading) tasks should have major implications for study design, arguing against the use of implicit tasks in studying reading related processing.

Summary

In this dissertation, I will describe our efforts to study reading specialization at both the individual region and the network levels. In Chapter 2, I detail a study of the neural specialization of orthographic processing. This study examines both the extent to which words and letters are the predominant visual stimuli processed in the left occipito-temporal fusiform cortex and the processing properties making this region particularly useful for reading. The rs-fcMRI defined functional relationships of the putative VWFA and changes in these relationships with age and reading skill are recounted in Chapter 3. Together, these chapters indicate a lack of specificity for words and letters in the left occipito-temporal fusiform cortex. These chapters also describe a set of processing properties and relationships that make the left occipito-temporal fusiform cortex region particularly useful for, though not specific to, reading. These findings are extended in Chapter 4, where a study of the reading network as a whole is described in adults and through development. We also find no evidence of a specific reading network in this analysis. Finally, I report a study of task related differences in Chapter 5, which not only brings into doubt the specificity of reading-related processing but also shows the importance of careful task design.

Together the studies presented here strive to demonstrate that reading does not fundamentally transform the neural architecture but rather utilizes existing neural processes and networks that at least in part continue to be used more generally as well. The results also hint at potential new methods for investigating delayed or disordered reading.

CHAPTER 2. THE VISUAL WORD FORM AREA IS NOT SPECIALIZED FOR WORDS

General Introduction

Reading is used throughout our daily lives - from reading scientific papers to reading directions and recipes. Fluent reading is a major predictor of success in school and life (Stanovich KE, 1986). Yet, reading is also a phylogenetically recent development and is still only recently widespread in the developed world. Students that develop into fluent readers take many years of training to acquire proficiency, and though much progress has been made in the effort to describe the behavioral and neural underpinnings of this acquisition (Schlaggar BL and BD McCandliss, 2007), many open questions remain. Thus, an understanding of how the brain instantiates fluent reading and the types of neural processing that have come to be used for this evolutionarily recent task is of considerable interest, from both a basic science and a public health perspective.

Reading aloud requires transforming visual inputs into spoken outputs using orthographic, phonologic, semantic, and articulatory processes. While the neural localization of these transformations is still under study, a region in the left fusiform cortex, near the occipito-temporal junction, has been described as important for the higher level visual processing of words during reading (Cohen L and S Dehaene, 2004; Cohen L et al., 2002; McCandliss BD et al., 2003). As far back as 1892, lesions to this region have been known to result in a relatively specific impairment of fluent reading (Cohen L et al., 2003; Dejerine J, 1892; Gaillard R et al., 2006; Warrington ET and T Shallice, 1980). Meta-analyses of functional neuroimaging studies show this occipito-temporal fusiform region to be one of the most consistently reported locations of activation during single word reading (Jobard G et al., 2002; Mechelli A et al., 2003; Turkeltaub PE et al., 2003; Vigneau M et al., 2006). There seems to be activity in this region when viewing words regardless of case, size and location (Cohen L et al., 2002), and some reports indicate increased activity for words relative to consonant strings, digits and objects (McCandliss BD et al., 2003; Polk TA et al., 2002; Vinckier F et al., 2007). These findings have led Cohen and colleagues to term this piece of occipito-temporal fusiform cortex the visual word form area (Cohen L and S Dehaene, 2004; Cohen L et al., 2002; McCandliss BD et al., 2003).

However, the appropriateness of referring to this brain region as the "visual word form area" has been debated essentially since the term was coined (see "The myth of the visual word form area" Price CJ and JT Devlin, 2003 for a complete review). Though some groups have reported more activity for letter strings than consonant strings and false fonts (Cohen L et al., 2002; McCandliss BD et al., 2003; Polk TA et al., 2002; Vinckier F et al., 2007), others have reported the opposite (Cohen L et al., 2003; Tagamets MA et al., 2000; Xue G et al., 2006). There are numerous reports of activity in this region when viewing picture stimuli (Bar M et al., 2001; Ben-Shachar M et al., 2007; Ploran EJ et al., 2007; Price CJ and JT Devlin, 2003; Starrfelt R and C Gerlach, 2007), including reports of equivalent activity for pictures and words (Van Doren L et al., 2010). Moreover, the specificity of lesion locations producing alexia has been questioned (Hillis AE et al., 2005; Price CJ and JT Devlin, 2003), as well as the specificity of letter processing disruption from lesions to the left occipito-temporal fusiform cortex (Behrmann M et al., 1990; Behrmann M et al., 1998; Starrfelt R et al., 2009). A number of groups have found evidence that patients with pure alexia also show impairments in naming objects, particularly under visually demanding circumstances including rapid presentation rates (Friedman RB and MP Alexander, 1984) and increased complexity (Behrmann M et al., 1998). It has also been shown that at least some alexic patients are deficient in processing both digits and letters (Starrfelt R et al., 2009). Due to this controversy, we will refer to this region as the "putative VWFA" both to emphasize that this label is contentious, and to allow for convenient anatomical description.

Despite (or perhaps because of) the uncertainty over the specificity of the processing performed in the putative VWFA, the nature of that processing has been the subject of much study. Studies manipulating lexicality have consistently demonstrated that the putative VWFA shows less activity for words than for pseudowords (Bruno JL et al., 2008; Kronbichler M et al., 2007; Mechelli A et al., 2003), regardless of whether the pseudoword has a real word homophone or not (Bruno JL et al., 2008; Kronbichler M et al., 2007). Consistent with decreased putative VWFA activity for familiar words relative to pseudowords, several groups have reported a negative relationship between putative VWFA activity and word frequency (less activity for higher frequency words) (Graves WW et al., 2010; Kronbichler M et al., 2004). Visual training of non-native language logographic characters leads to decreased activity in the putative VWFA in response to those characters (Xue G et al., 2006; Xue G and RA Poldrack, 2007). Generally, these results suggest that activity in the putative VWFA decreases with increased exposure to specific visual forms.

Additionally, the putative VWFA seems capable of performing visual processing at multiple levels of visual analysis. A recent study by Schurz and colleagues demonstrated a length by lexicality effect in the putative VWFA, such that there is increased activity for long pseudowords relative to short pseudowords with no corresponding effect of length for real words (Schurz M et al., 2010). This length by lexicality interaction indicates sensitivity to both whole word forms and chunks of words in the occipito-temporal region. Cohen and colleagues have also found sensitivity in the putative VWFA to letter strings of variable lengths, ranging from bigrams to whole words, though they argue this sensitivity exists in a posterior to anterior gradient moving from letters to whole words (Cohen L and S Dehaene, 2004; Vinckier F et al., 2007). Evidence of the ability of the putative VWFA to process stimuli in groups of varying sizes can also be found in the lesion literature. Typically, alexic patients have not lost the ability to read entirely. Rather, they have lost the ability to read words as a whole or in groups larger than single letters (Cohen L et al., 2003). Starrfelt and colleagues tested such patients, whose alexia arose from damage to the putative VWFA, on tasks designed to measure simultaneous processing of both letters and digits. They found alexic patients to be impaired on both types of items (Starrfelt R et al., 2009).

It is notable that activity in the putative VWFA is most commonly seen in response to highly complex, high frequency, high contrast visual stimuli. Words are composed of individual components (i.e. letters, bigrams) with a number of features (i.e. conjunctions of lines) arranged in a complex order. Line drawn objects, one of the other most common stimulus types shown to elicit activity in the putative VWFA (Bar M et al., 2001; Ben-Shachar M et al., 2001; Ploran EJ et al., 2007; Price CJ and JT Devlin, 2003; Starrfelt R and C Gerlach, 2007; Van Doren L et al., 2010) share this characteristic of complex conjunctions of many visual features. Relatedly, alexics have more difficulty processing complex visual stimuli (Behrmann M et al., 1998). When activity for high spatial frequency and low spatial frequency visual stimuli is compared directly, the left fusiform cortex around the putative VWFA shows more activity for the high spatial frequency stimuli (Kveraga K et al., 2007), consistent with the parvocelluar/ventral and magnocellular/dorsal processing stream distinction (Mishkin M et al., 1983).

Given what is known about the putative VWFA, in this study we aim to further explore the role of this region in reading by investigating both the specificity of its activation in reading and the particular processing characteristics that make it useful for reading. Dehaene and Cohen (2007) have proposed that with experience, neural regions, like the putative VWFA, can become so well “trained” or “adapted” for use in a particular task so as to become effectively specialized for that task. We test for such specialization in the putative VWFA in Study 1. The results presented in that study argue against such specialization. After failing to find specificity, we further explore what processing characteristics of the putative VWFA might make it particularly suitable for use in reading and other visual processing tasks in Study 2.

STUDY 1

Introduction

The aforementioned processing characteristics of the putative VWFA – its sensitivity to visual perceptual training, its differential responses to variably-sized “groups” of visual features, and its contribution to the processing of high contrast, high spatial frequency visually complex stimuli – certainly render plausible the notion that this region of cortex is “co-opted” for use in reading through training as proposed by Dehaene and Cohen (2007). On the other hand, the putative VWFA may indeed be ideally situated to perform the type of visual processing used in reading while continuing to be more generally recruited for the visual processing of other non-letter and non-word stimuli. In other words, this region could, through long-term use, come to be used predominantly in reading, or it could be a more generic visual processor that is used in reading in addition to a number of other tasks.

Here we will attempt to adjudicate between these two hypotheses by determining whether the putative VWFA is predominantly a “reading region” with preferential activity for words and letters or if it is a general visual processor that responds to words, letters, and other visual stimuli that have similar properties. To this end, we directly compare the BOLD activity elicited by a matching task involving six classes of stimuli: words, pseudowords composed of legal letter combinations, nonwords composed of orthographically illegal letter combinations, consonant strings, line drawn objects, and Amharic character strings. Amharic characters are used in the Ethiopian writing system. Because they are visually similar to Roman letters, yet have no meaning to the Amharic-naïve, English-speaking subjects in the present study, Amharic characters should not elicit strong activity in a region used predominantly for reading. As such, they are a useful stimulus class for querying the specificity of processing in the putative VWFA.

Methods

Participants

Subjects included 27 (13 male) right-handed, native, monolingual English speakers, ages 21-26 years old. All were screened for neurologic and psychiatric diagnoses and for use of chronic medications by telephone interview and questionnaire. The majority of subjects were from the Washington University or Saint Louis University communities and all were either college students or college graduates. All gave written informed consent and were reimbursed for their time per Washington University Human Studies Committee guidelines. All subjects were tested for IQ using the Wechsler Abbreviated Scale of Intelligence (Wechsler D, 1999) and for reading level using three subtests of the Woodcock-Johnson III (Letter-Word ID, Passage Comprehension, and Word Attack) (Woodcock RW and MB Johnson, 2002). All subjects were determined to have above average IQ (average 127, standard deviation 7.7) and reading level (average ≥ college graduates, estimated by a composite of the three Woodcock-Johnson III subtests).

Stimuli

Stimuli consisted of pairs of either line drawn pictures or 4 character strings. Strings were of 5 types: real words (e.g. ROAD), pseudowords with legal letter combinations (e.g. PRET), nonwords with orthographically illegal letter combinations (e.g. PPID), consonant strings (e.g. FGRT), or strings of Amharic characters (for more examples of all stimuli see Figure 2.1). Letter strings were presented in all uppercase letters to eliminate the possibility of matching on ascender/descender patterns. Words, pseudowords, and nonwords were matched for letter frequency, and consonant strings were screened to ensure none made an easily recognizable abbreviation. Each pair of items consisted of only one stimulus type. Pairs were presented with one string/picture above the fixation crosshair and one string/picture below. Each string or picture subtended approximately 0.5 degrees visual angle, and was presented 0.5 degrees from the central fixation cross, in white on a black background. Stimuli were presented using Psyscope X (Cohen JD et al., 1993).

Subjects saw a single run of each stimulus type, with the ordering of the runs counterbalanced across participants. Sixty pairs of letter or Amharic character strings were presented in each run. In half of these pairs the strings were identical. Of the remaining 30 pairs per run, half (15 pairs) were easy pairs, different in all 4 character positions, and half were hard pairs, different in only 2 character positions (for examples see Figure 2.1). The positions of the character substitutions were matched across string type. Each string was presented for 1500 msec. Forty-eight pairs of line drawn pictures were presented in a single run, half (24) of which were identical. Of the 24 remaining pairs, half (12 pairs) were hard pairs, different but in the same semantically related category (i.e. both animals, articles of clothing or man-made manipulable objects), and half were easy pairs, different and not in the same semantic category. Each picture pair was presented for 750 msec. Four separate pseudorandom orders (constrained such that subjects never saw more than 3 identical or 3 different pairs in a row) were generated for each run/stimulus type.

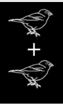
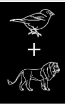
	Same	Different-Hard (differs in only 2 character positions)	Different-Easy (differs in all 4 character positions)
Words	DEER + DEER	DEER + WEAR	DEER + MOON
Legal pseudowords	HEAK + HEAK	HEAK + HINK	HEAK + GOOT
Illegal nonwords	PPID + PPID	HRET + NLET	RAPL + GOCV
Consonant strings	PWKS + PWKS	PWKS + PHBS	PWKS + CZHG
Amharic strings	አደጠጸ + አደጠጸ	አደጠጸ + አደፌጸ	አደጠጸ + ጸሸሠቀ
Line drawn pictures			

Figure 2.1. Examples of stimulus pairs

Six types of stimulus pairs were used. Half of the pairs presented were the same (as seen in the second column), one-quarter were different-hard (as seen in the third column), and one-quarter were different-easy (as seen in the fourth column). In the picture matching run (bottom row), pictures were drawn from the same semantically related category for the different-hard condition and from different semantic categories for the different-easy condition.

Task Design

Subjects were asked to make a visual matching judgment on each pair of strings/pictures. Each subject was instructed to press a button with the index finger of one hand if the stimuli looked the same and with the index finger of the opposite hand if the stimuli looked different in any way. The hand assignment was counterbalanced across subjects.

In all runs the stimulus trials were intermixed with an equal number of 2.5 second null frames, in which only a fixation crosshair was present on the screen. Stimuli were intermixed with null frames such that pairs could appear in consecutive frames, or with 1 or 2 null frames between stimulus presentations. As the strings were presented for 1.5 seconds within a 2.5 second TR; this organization resulted in a 1, 3.5, or 6 second interstimulus interval. Pictures were presented for only 750 msec, resulting in a 1.75, 4.25, or 6.75 second interstimulus interval. Jittered spacing such as this allows for a deconvolution of the hemodynamic response for individual trials (Miezin FM et al., 2000). Twenty-four separate lists with different combinations of stimulus trials and null frames were generated for the string matching runs while 12 separate lists were generated for the picture matching runs.

Of note, the matching tasks were embedded within a longer study consisting of a series of tasks including single-letter matching, single-letter and picture naming, word and nonword reading, and rhyme and picture-sound judgment. In total, each subject performed 16 runs split over 2 scanning sessions held 1-28 days apart. All tasks were intermixed, and the order of the runs was counterbalanced within and across scanning sessions.

Behavioral Data Acquisition and Analysis

Behavioral data were collected via a Psyscope compatible optical button box. Accuracy and response time were analyzed. A 5-level repeated measures analysis of variance (ANOVA) was used to determine whether the accuracy and response time varied by stimulus type. In the case of a significant effect of stimulus-type, we planned an additional set of post-hoc paired t-tests comparing each stimulus type with every other type.

MR Data Acquisition and Preprocessing

A Siemens 3T Trio scanner (Erlanger, Germany), with a Siemens 12-channel Matrix head coil was used to collect all functional and anatomical scans. A single high-resolution structural scan was acquired using a sagittal magnetization-prepared rapid gradient echo (MP-RAGE) sequence (slice time echo= 3.08 ms, TR= 2.4 s, inversion time= 1 s, flip angle= 8 degrees, 176 slices, 1 x 1 x 1 mm voxels). All functional runs were acquired parallel to the anterior-posterior commissure plane using an asymmetric spin-echo echo-planar pulse sequence (TR= 2.5 s, T2* evolution time 27 msec, flip angle 90 degrees). Complete brain coverage was achieved by collecting 32 contiguous interleaved 4mm axial slices (4 x 4 mm in-plane resolution).

Preliminary image processing included removal of a single pixel spike caused by signal offset, whole brain normalization of signal intensity across frames, movement correction within and across runs, and slice by slice normalization to correct for differences in signal intensity due to collecting interleaved slices (for detailed description see Miezin et al. 2000).

After preprocessing, data was transformed into a common stereotactic space based on Talairach and Tournoux (1988) but using an in-house atlas composed of the average anatomy of 12 healthy young adults ages 21-29 years old and 12 healthy children ages 7-8 years old (see (Brown TT et al., 2005; Lancaster JL et al., 1995; Snyder AZ, 1996 for methods). As part of the atlas transformation the data were resampled isotropically at 2 mm x 2 mm x 2 mm. Registration was accomplished via a 12 parameter affine warping of each individual's MP-RAGE to the atlas target, using difference image variance minimization as the objective function. The atlas-transformed images were checked against a reference average to ensure appropriate registration.

Participant motion was corrected and quantified using an analysis of head position based on rigid body translation and rotation. In-scanner movement was relatively low, as subjects were both instructed to hold as still as possible during each run and were custom-fitted with a thermoplastic mask to minimize head movement during the scan session. However, frame-by-frame movement correction data from the rotation and translation in the x, y, and z planes was computed for each subject for each run, to ensure there were no runs with overall movement greater than 1.5 mm rms. No runs were removed, as the maximum movement was .755 mm rms (average .254 mm rms).

fMRI Processing and Data Analysis

Stimulus-type by Timecourse Analyses

Statistical analyses of event-related fMRI data were based on the general linear model (GLM) conducted using in-house software programmed in the interactive data language

(Research Systems, Inc., Boulder, CO) as previously described (Brown TT et al., 2005; Miezin FM et al., 2000; Schlaggar BL et al., 2002). The GLM for each subject included time as a 7-level factor made up of 7 MR frames (17.5 s, 2.5s/frame) following the presentation of the stimulus, stimulus-type as a 6-level factor (pictures, Amharic character strings, consonant strings, nonwords, pseudowords, and words), and pair-type as a 3-level factor (same pairs, hard/2-character different (or same semantic category) pairs, and easy/4-character different (or different semantic category) pairs). No assumptions were made regarding the shape of the hemodynamic response function. Only correct trials were included in the analysis; errors were coded separately in the GLM.

First, a 6 stimulus-type (pictures vs Amharic strings vs consonant strings vs nonwords vs pseudowords vs words) by 7 timecourse (7 timepoints) voxel-wise whole brain repeated measures ANOVA was conducted. A Monte Carlo correction was used to guard against false positives resulting from conducting a large number of statistical comparisons over many images (Forman SD et al., 1995; McAvoy MP et al., 2001). To achieve a $p < 0.05$ corrected for multiple comparisons, a threshold of 24 contiguous voxels with a $Z > 3.5$ was applied.

This voxel-wise analysis produced an image containing voxels showing a stimulus-type by timecourse interaction (i.e. activity that both varies across the 7 timepoints and is different between the 6 stimulus conditions). Regions were extracted from this image using an in-house peak-finding algorithm (courtesy of Avi Snyder) that locates activity peaks within the Monte Carlo corrected images, by first smoothing with a 4 mm kernel, then extracting only peaks with a Z-score > 3.5, containing 24 contiguous voxels and located at least 10mm from other peaks.

The directionality of the statistical effect was demonstrated by extracting the timecourse (percent BOLD signal change at each of the 7 timepoints) in every individual subject for each stimulus type in each of the regions defined from the ANOVAs described above. Percent BOLD signal change at each timepoint was averaged across all subjects, and these average timecourses were plotted for each stimulus type.

Region of Interest Analyses

A similar analysis was performed on predefined regions of interest, including the putative VWFA coordinates from Cohen and Dehaene (2004) (left anterior VWFA: -43, -48, -12, left classic VWFA: -43, -54, -12, left posterior VWFA: -43, -68, -12 in Talaraich coordinates). For this literature-derived region of interest analysis, we first converted the Talariach coordinates to our in-house atlas coordinates and then built an 8mm sphere around each peak. The same ANOVA described above was applied to these regions looking for stimulus-type by timecourse interactions. The percent BOLD signal change was extracted for each of the 7 timepoints for each stimulus type for each subject and then averaged for each timepoint to produce the group timecourses shown in Figure 2.3.

Regressing Out Response Time

To ensure the effects reported here were not largely due to response time (RT) differences between the stimulus types, a separate set of GLMs similar to the stimulus-type by timecourse GLMs described above was generated for each subject. These GLMs not only included separate terms for errors, stimulus-type, and pair-type (as above) but also coded the RT for each individual trial. Thus RT could be used as a continuous regressor, and effects most related to RT alone would be assigned to that variable.

Results

Behavioral Results

All subjects performed the visual matching task with high accuracy, though they were statistically significantly less accurate when matching the Amharic character strings than any other stimuli ($p < 0.0001$). Subjects were also significantly slower to match Amharic character strings than any of the other stimulus classes ($p < 0.0001$ for all post-hoc t-tests) and were significantly faster to match pictures than any of the other stimuli ($p < 0.0001$ for all post-hoc t-tests). Subjects were also statistically slower to match consonant strings than all other letter strings ($p \leq 0.001$ for all post-hoc t-tests) and slower to match nonwords than pseudowords (p =

0.037), though there was no difference between consonant strings and nonwords, nonwords and words or pseduowords and words. The average, range and standard deviation of accuracy and response time for each type of stimulus pair is reported in Table 2.1.

Stimulus Type	**Accuracy**			**Response time**		
	Average	**Range**	**Std Dev**	**Average**	**Range**	**Std Dev**
Pictures	98%	89.5-100%	2.9%	797	618-1289	145
Amharic strings	94.3%	88.3-100%	3.3%	1373	907-1996	271
Consonant strings	98.1%	81-100%	3.4%	1011	760-1706	224
Nonwords	97.9%	73-100%	5.1%	919	771-1483	164
Pseudowords	98.3%	90-100%	2.5%	886	701-1325	138
Words	98.6%	95-100%	1.8%	898	705-1253	139

Table 2.1. Behavioral results for the visual matching task

Imaging Results

Stimulus-type by Timecourse Interactions

A whole brain analysis was performed first, in search of regions showing differential activity for the 6 stimulus types: pictures, Amharic character strings, consonant strings, nonwords, pseudowords, and words. A voxelwise 6 (stimulus-type) by 7 (timepoints), whole-brain repeated measures ANOVA produced the set of regions shown in Figure 2.2B and detailed in Table 2.2. In all of these regions, the interaction was driven by the Amharic character strings, pictures, or both the Amharic character strings and pictures producing a more substantial change in BOLD signal than the letter strings. None of these regions showed more substantial changes in BOLD activity for words, or even letter strings in general, than Amharic character strings and pictures.

The general pattern of Amharic character strings and pictures resulting in greater activity than letter strings held even in regions identified in the left fusiform cortex (Figure 2.2A), including those closest to the putative VWFA (Figure 2.2C-D). Post-hoc comparisons of the timecourses for each stimulus type in the two extracted left fusiform regions show significantly more activity for Amharic character strings than pictures ($p < 0.001$), and more activity for pictures ($p < 0.001$ for all) and Amharic character strings ($p < 0.001$ for all) than for every kind of letter strings. There was also slightly less activity for pseudowords than consonant strings in both regions ($p = 0.006$)

and less activity for pseudowords than nonwords in the posterior fusiform region (Figure 2.2C, p = 0.03). No other statistical differences were identified between letter strings in either region.

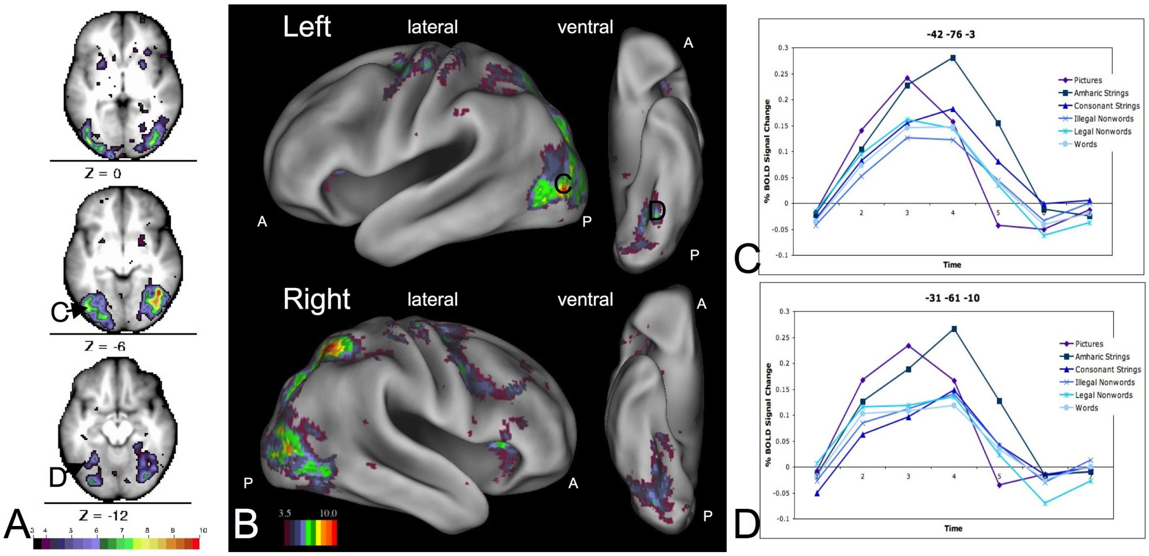


Figure 2.2. Left fusiform regions showing a stimulus-type by timecourse interaction

A. Whole brain analysis image showing all voxels with a significant stimulus-type by timecourse interaction in occipital and fusiform cortices. Letter labels indicate regions for which timecourses are shown in panels C and D.

B. Whole brain analysis image showing all voxels with a significant stimulus-type by timecourse interaction projected to the surface of semi-inflated brain surfaces rendered with CARET (Van Essen DC et al., 2001; http://brainmap.wustl.edu/caret). Letter labels indicate regions for which timecourses are shown in panels C and D.

C. Timecourses for all 6 stimulus types in a left fusiform region posterior and superior to the classically described VWFA (-42 -76 -2 in MNI coordinates). Further ANOVAs show this interaction is due to more activity for Amharic characters than pictures ($p < 0.001$) and letter strings ($p < 0.001$ for all) and more activity for pictures than letter strings ($p < 0.001$ for all).

D. Timecourses for all 6 stimulus types in a left fusiform region anterior and medial to the classically described VWFA (-31 -41 -10 in MNI coordinates). Further ANOVAs show this *interaction is due to more activity for Amharic characters than pictures ($p < 0.001$) and letter strings ($p < 0.001$ for all) and more activity for pictures than letter strings ($p < 0.001$ for all).*

Regions showing a stimulus-type by timecourse interaction

MNI Coordinates			Anatomic Label	Stimulus-type by Timecourse Z-score	Number of voxels
X	Y	Z			
-31	-61	-10	L fusiform	8.58	309
30	-53	-15	R fusiform	7.44	270
-30	-83	-7	L fusiform	8.51	384
11	-83	-11	R fusiform	5.51	47
44	-59	-8	R fusiform	8.72	325
41	-69	-6	R fusiform	8.89	395
-42	-76	-3	L fusiform	9.46	334
-15	-101	5	L occipital	8.18	291
21	-95	3	R occipital	6.31	145
35	-86	3	R occipital	8.58	275
-39	-86	5	L occipital	9.55	241
-1	-91	6	medial occipital	5.14	100
-28	-95	8	L occipital	9.11	323
26	-96	13	R occipital	5.93	90
-29	-75	11	L occipital	5.76	96
10	-86	6	R occipital	5.42	84
42	-78	5	R occipital	8.84	298
-44	-78	14	L occipital	6.5	269
49	-65	12	R occipital	5.45	167
-18	-66	14	L occipital	4.75	75
12	-72	16	R occipital	5.62	158
-3	-76	18	medial occipital	5.31	202
2	-84	16	medial occipital	4.92	111
3	-79	30	medial occipital	4.82	106
-28	-89	21	L occipito-parietal	8.74	397
38	-83	15	R occipital	7.92	289
-25	-79	32	L occipito-parietal	6.92	302
-30	-65	18	L occipito-temporal	5.41	82
-24	-64	49	L occipito-parietal	7.7	417
30	-72	40	R occipito-parietal	8.36	454
1	-71	56	medial parietal	7.33	283
-16	-75	54	L parietal	5.47	101
16	-69	58	R parietal	7.13	278
6	-48	48	Precuneus	4.82	82
2	-50	73	Precuneus	6.46	123
-39	-44	47	L parietal	5.51	207

37	-37	42	R parietal	5.37	153
3	-35	27	Posterior Cingulate	5.06	104
46	-34	46	R parietal	6.37	211
-34	-28	60	L parietal	6.85	284
34	-30	66	R parietal	5.59	78
28	-57	53	R parietal	9.39	468
-41	-20	57	L post-central gyrus	6.84	243
38	-22	56	R post-central gyrus	6.54	246
-29	29	2	L insula	4.84	221
18	26	2	R insula	5.8	177
-32	19	7	L insula	5.16	84
32	20	4	R insula	6.88	337
23	41	3	R frontal	5.13	236
50	29	6	R frontal	6.68	42
2	45	12	Anterior Cingulate	4.69	124
-7	14	41	Anterior Cingulate	4.88	61
6	27	36	Anterior Cingulate	6.32	244
49	31	24	R frontal	5.65	46
18	45	30	R frontal	5.62	157
29	23	32	R frontal	5.04	70
24	60	-9	R frontal	5.11	109
30	36	39	R fontal	5.15	281
-42	-8	49	L pre-central gyrus	6.85	108
35	-14	63	R pre-central gyrus	6.69	52
0	-14	54	medial pre-central gyrus	4.81	60
48	5	36	R pre-central gyrus	7.39	46
42	11	28	L pre-central gyrus	6.22	56
-26	-5	52	L pre-central gyrus	6.67	167
40	0	51	R pre-central gyrus	6.4	266
27	-5	56	R pre-central gyrus	7.07	354
15	-8	69	R pre-central gyrus	5.86	64
-6	-2	59	medial pre-central gyrus	6.05	142
-4	29	59	medial superior frontal	4.87	68
2	17	53	medial superior frontal	7.08	295
6	-2	65	medial pre-central gyrus	5.3	122
1	-8	10	thalamus	4.65	46
-12	-22	14	L thalamus	5.04	44
28	-11	8	R thalamus	4.38	24
11	-15	7	R thalamus	4.8	107
15	-6	18	R basal ganglia	4.95	95

-11	16	0	L basal ganglia	5.16	90
11	16	3	R basal ganglia	5.78	169
-25	6	-5	L basal ganglia	6.05	133
24	9	-5	R basal ganglia	5.48	153
-9	5	3	L basal ganglia	5.26	68
-20	7	8	L basal ganglia	5.96	150
18	4	8	R basal ganglia	6.01	257
-33	-55	-26	L Cerebellum	6.44	132
-43	-71	-24	L Cerebellum	4.54	50
-1	-81	-20	medial Cerebellum	5.77	135
26	-84	-20	R Cerebellum	6.31	211

Table 2.2. Regions showing a stimulus-type by timecourse interaction
All coordinates are reported in MNI coordinates, listed by anatomic location. All show greater deflection from baseline for Amharic characters, pictures or both Amharic characters and pictures than letter strings.

Region of Interest Analysis

None of the regions identified in the whole brain analysis was an exact match to the classically described putative VWFA. Therefore, we applied regions of interest at the coordinates described by Cohen and Dehaene (2004): anterior VWFA -43 -48 -12, classic VWFA -43 -54 -12, and posterior VWFA -43 -68 -12 (all in Talaraich coordinates, which were transformed into our in-house atlas coordinates for the purpose of this analysis). A 6 (stimulus-type) by 7 (timepoints) repeated measures ANOVA was performed on 8mm diameter spherical regions centered on the aforementioned coordinates. The anterior and classic VWFA regions did not show a stimulus-type by timecourse interaction, and all stimuli, including pictures and Amharic character strings, showed significantly positive BOLD activity in these regions (Figure 2.3B-C). The posterior VWFA did show a stimulus-type by timecourse interaction (Figure 2.3D). The pattern of activity was similar to that described for the closest fusiform regions identified in the whole brain analysis, with a trend towards greater activity for Amharic characters than consonants, pseudowords, and words (all $p < 0.10$), and significantly more activity for pictures than pseudowords, nonwords, and words (all $p < 0.04$).

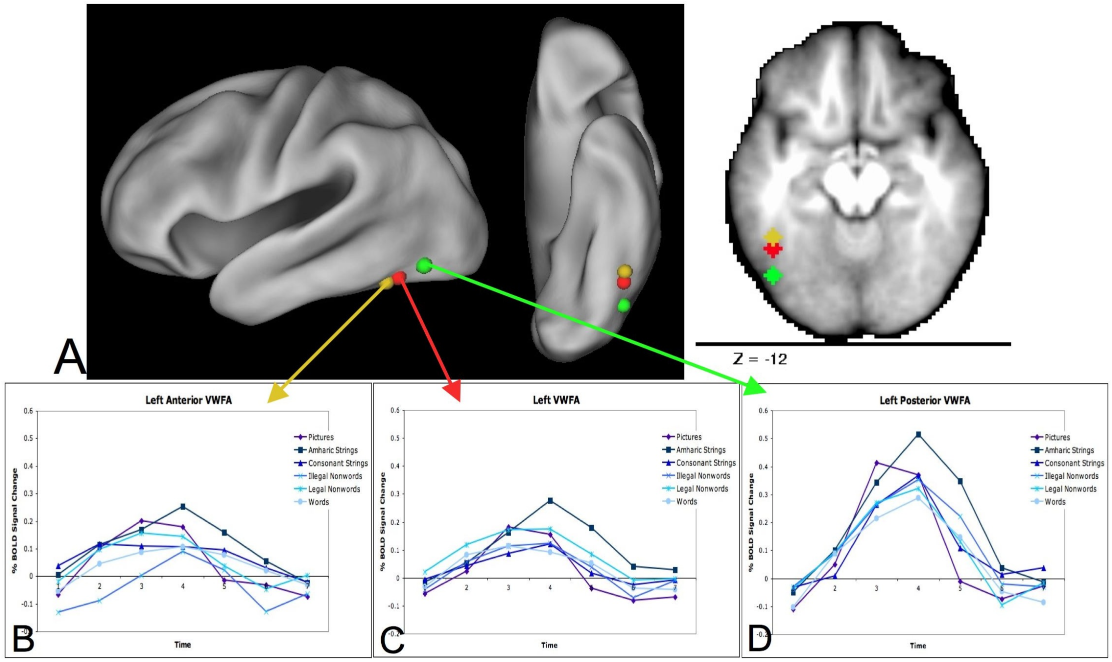


Figure 2.3. Stimulus effects in literature-derived putative VWFA regions

A. Location of applied putative visual word form area regions from Cohen and Dehaene (2004), displayed on a semi-inflated CARET surface and on a transverse section through fusiform cortex.

B. Timecourses for all 6 stimulus types in the left anterior VWFA. There was no stimulus-type by timecourse interaction in this region.

C. Timecourses for all 6 stimulus types in the classic left VWFA. There was no stimulus-type by timecourse interaction in this region.

D. Timecourses for all 6 stimulus types in the left posterior VWFA. There is a significant stimulus-type by timecourse interaction in this region ($p < 0.05$), which post-hoc ANOVAs show is due to trend-level greater activity for Amharic characters than consonants, pseudowords, and words (all $p < 0.10$) and significantly greater activity for pictures than nonwords, pseudowords, and words (all $p < 0.04$).

Effect of Response Time

It is difficult to envision how response time would drive the results of the present study, as the RT for matching pictures is significantly faster than the RT for matching letter strings, which is in turn significantly faster than the RT for matching Amharic character strings, a pattern that is inconsistent with the observed BOLD activity (letter strings < pictures < Amharic strings). Also, the pictures were presented for a shorter duration than the letter and Amharic strings, which should, if anything, decrease BOLD activity in visual processing regions, though the opposite is observed. Nonetheless, we addressed the question of whether any of the imaging results were due to the significantly longer RTs for matching Amharic character strings as compared to all other stimulus types by performing a second 6 (stimulus-type) by 7 (timepoints) whole-brain repeated measures ANOVA with GLMs that included RT as a continuous regressor. Even with RT regressed out, the regions near the putative VWFA identified in the whole brain analysis continue to show a significant stimulus-type by timecourse interaction with more activity for Amharic characters than pictures, and more activity for both Amharic characters and pictures than for letter strings. Similarly, when RT is regressed out there is still no effect of stimulus-type in the anterior and classic VWFA applied regions, while the stimulus-type by timecourse interaction (Amharic > pictures > letter strings) in the left posterior VWFA remains significant.

Discussion

To adjudicate between the competing hypotheses that 1) the putative VWFA is predominately used in reading, as the visual region most closely related to the processing of letters and words and 2) the putative VWFA is a more general region used in the visual processing of letters, words, and other stimuli that share visual processing demands, we compared BOLD activity elicited by a matching task involving 6 classes of stimuli: words, pseudowords composed of legal letter combinations, nonwords composed of orthographically illegal letter combinations, consonant strings, line drawn objects, and Amharic character strings. As there was equivalent or greater activity for matching Amharic character strings and line drawn objects as compared to letter strings in left occipto-temporal fusiform regions, we argue that the putative VWFA is a general visual processor that is indeed recruited for reading, among other tasks rather than to the exclusion of other tasks involving visual processing. That is, the results of this study refute the notion that the role of the VWFA in reading precludes its involvement in other tasks that involve similar types of processing.

No preferential activity for words and letter strings exists in the putative VWFA.

In this matching task, no brain regions were identified as showing more activity for words or letter strings than Amharic character strings and pictures, even when coordinates from the putative VWFA (Cohen L and S Dehaene, 2004) were applied directly. In applied VWFA regions we found either no difference between letter strings and Amharic character strings and pictures (anterior and classic VWFA) or more activity for Amharic character strings and pictures than letter strings (posterior VWFA). While we, like Vinckier et al. (2007), see differences between the posterior putative VWFA and more anterior regions, our results do not in any way suggest preference for words.

Our results are consistent with several previous studies that observed no preferential BOLD activity in the putative VWFA for letters or words (see Price CJ and JT Devlin, 2003 for an early review, Brem S et al., 2010; Van Doren L et al., 2010; Xue G et al., 2006; Xue G and RA Poldrack, 2007). A possible explanation for the discrepancy between our results and those that do show such preferential activity (Cohen L et al., 2002; Vinckier F et al., 2007) may be found in the task design. Our study utilized both a visual matching task and a long presentation time (1500 msec). Tagamets MA et al. (2001), Xue G et al. (2006) and Xue G and RA Poldrack (2007), which all showed more activity for false fonts than letters, used matching tasks with subsequently, rather than simultaneously presented stimuli. This design requires subjects to keep some representation of the stimuli online throughout the presentation set. Van Doren L et al. (2010), which also showed equivalent activity for pictures and letters, used a recognition memory task that presumably requires deeper processing than the passive viewing (Cohen L et al., 2002) or simple ascender judgment (Vinckier F et al., 2007) tasks that show more activity for letter strings than consonant strings and false fonts. Additionally, both (Cohen L et al., 2002) and (Vinckier F et al., 2007) use short presentation times (200 msec and 100 msec respectively). When presentation time is increased for passive viewing (to 1700 msec), the effect is reversed and more activity is seen for consonant strings than letters (Cohen L et al., 2003).

Recently, Brem et al. (2010) demonstrated that even when there was no preferential activity for words in the putative VWFA as measured by BOLD activity, there was preferential ERP activity in the N200 response for words relative to false fonts. The authors hypothesize that this difference may be related to the timescale of the preferential response – words are processed faster than false fonts in the putative VWFA, but overall activity is relatively equivalent between the stimulus types. This “fast processing” advantage could account for the observed specialization for words in tasks with very fast presentation rates and minimal processing requirements (i.e. Cohen L et al. 2002), relative to slower presentation rates (Cohen L et al., 2003; this study), increased memory requirements (Xue G et al., 2006) or deeper processing (Van Doren L et al., 2010). Thus, it seems that “preferential” activity for words and letter strings relative to other visual stimuli may only be seen when the task or presentation time does not allow for or does not encourage more than superficial processing of non-word or -letter stimuli.

Notably, a direct comparison of BOLD activity for matching and reading aloud the words, pseudowords and nonwords used in the task presented here showed no differences in the left fusiform cortex (Chapter 5). This observed similarity between matching and reading processing in fusiform regions argues that the matching task presented here is more reflective of how the fusiform cortex is used in single word reading than the faster and easier tasks sometimes used to study orthographic processing.

STUDY 2

Introduction

As discussed in the general introduction, the literature points to several processing characteristics that have been identified in the putative VWFA and that should be features of any reading-related visual processor. Any visual region used for reading should respond to high spatial frequency, high contrast stimuli with complex (multi-component) features, exactly those visual features that characterize letters. Additionally, reading requires being able to group stimuli into the appropriate visual "chunks" since fluent reading entails putting letters into combinations that form large chunks or even whole words. This grouping likely underlies the ability of fluent readers to read high frequency words of any length in about the same amount of time (Cohen L et al., 2003; Weekes BS, 1997).

In Study 2 we directly test for neural regions with activity related to visual complexity and the ability to group visual stimuli. To this end, we took advantage of various dimensions of the non-object stimuli presented in the visual matching experiment described in Study 1. Changizi and Shimojo (2005) proposed that the visual complexity of a writing system can be measured by the number of brush strokes per character. We adapted this measure of visual complexity as a way of characterizing the string pairs described in Study 1 in order to identify brain regions exhibiting sensitivity to visual complexity. We additionally leveraged the fact that stimulus pairs differed by either 2 or 4 characters, as a means of querying for cortical regions that demonstrate visual "chunking" or "grouping."

Comparing BOLD activity for stimuli that are processed in a group versus those that must be processed as individual components potentially allows us to identify regions used in grouped visual processing. Stimuli processed as individual components, or characters, should elicit increased response time and increased BOLD activity for pairs that are all the same relative to pairs that are two characters different, which in turn should require greater processing time and greater BOLD activity than pairs that are all different. Such increases in RT and BOLD activity reflect the fact that stimuli processed sequentially require comparing only one character when the strings are all different, 1, 2 or 3 characters when the strings are 2 characters different, and all 4 characters when the strings are identical. If, in contrast, the strings can be processed in chunks or as a whole, there should be similar activity for at least the identical and 4 character difference pairs. We hypothesized that real words should be able to be processed as a group, as discussed above. However, stimuli very different from real words, like Amharic strings, are not expected to be processed as singular groups. To test this hypothesis we compared RT and BOLD activity for the different pair types (identical, hard/2- and easy/4- character different pairs), and tested for RT and BOLD activity differences for pair types that differed between stimulus types.

Methods

All subjects, stimuli, task design, imaging acquisition and preprocessing were identical to that described in Study 1. Data analysis, however, utilized two different sets of statistical analyses described below.

Complexity by Timecourse Analysis

A set of GLMs was created for only the string stimuli to look at the effect of visual complexity. In these GLMs each trial was coded by stimulus type (Amharic character strings, consonant strings, nonwords, pseudowords, and words) and visual complexity as measured by the number of brushstrokes per character (criteria defined in Changizi MA and S Shimojo, 2005). Each pair was given a single complexity value by adding together the number of brushstrokes per character for each character in each pair. Complexity was used as a categorical variable by dividing the set of 60 pairs of each stimulus type into thirds. The 20 pairs with the highest complexity values were labeled “most complex”, the 20 pairs with the lowest complexity values “least complex”, and the middle 20 were modeled as a separate category in the GLM but not included in subsequent analyses. A whole brain 2 (most vs least visually complex) by 7 (timepoints) repeated measures ANOVA that collapsed complexity across all stimulus types was used to identify voxels showing a significant effect of visual complexity. The same methods described above were used to correct for multiple comparisons, extract peaks of activity and identify regions of interest. The timecourse of BOLD signal change was extracted for each subject for the identified regions and averaged together to create group timecourses.

Pair-Type by Timecourse Analysis

Behavioral Analysis

A pair-type (same, hard/4 character different pairs, easy/2 character different pairs) by stimulus-type (Amharic, consonants, nonwords, pseudowords, words) repeated measures ANOVA was performed. As the pair-type by stimulus-type interaction was found to be significant, we subsequently performed single-factor repeated measures ANOVAs of pair-type (with 3 levels) for each stimulus type individually. For any stimulus showing a significant effect of pair-type, we performed paired t-tests comparing each pair-type against every other pair-type within that stimulus.

Imaging Analysis

Another set of GLMs, identical to the stimulus-type by timecourse GLMs described in Study 1 but excluding pictures was generated. A 3 (pair-type: same vs hard vs easy) by 7 (timepoints) whole brain repeated measures ANOVA that collapsed across all stimulus types was used to identify voxels that showed an effect of pair-type. The same methods previously described for multiple comparison correction, peak-extraction and ROI identification were used. Timecourses of BOLD signal change for the 3 separate pair-types were extracted for each subject for the identified regions and averaged together to create group timecourses.

A separate region-based repeated measures ANOVA was also performed on the "pair-type by timecourse" regions identified in the above-described analysis. This 5 (stimulus-type: Amharic vs consonants vs nonwords vs pseudowords vs words) by 3 (pair-type: same vs hard vs easy) by 7 (timepoints) repeated measures ANOVA was used to look for effects of pair-type that varied with stimulus type. Timecourses of BOLD signal change were extracted for each pair type for each stimulus type. Additionally, separate ANOVAs were run for each stimulus type to determine the effect of pair-type on each stimulus type individually.

Regressing Out Response Time

In this analysis, the response time effects mimicked the BOLD effects; thus a separate set of GLMs was generated for each subject to ensure the effects reported were not simply due to these RT differences. Separate GLMs including RT as a trial-wise regressor were generated for both the complexity by timecourse and pair-type by timecourse GLMs described above.

Conjunction of Interactions

To determine whether the stimulus by timecourse, complexity by timecourse and pair-type by timecourse interactions described above were identified within overlapping regions we performed a conjunction analysis of the three interactions. For each interaction we first created a thresholded image, including only voxels showing an interaction Z-score > 3. We then converted these thresholded images to a positive mask, where every voxel present (i.e. every voxel> 3) was labeled as “active” (with a value of 1) and every other voxel given a value of 0. These 3 thresholded, masked images were then summed, so that voxels showing all interactions would have a value of 3. The same peak-finding algorithm described above was used to identify the peak coordinates of any region showing all effects.

Results

Complexity by Timecourse interactions

The effect of complexity was analyzed in a 2 (most/top 20 versus least/bottom 20 complex pairs) by 7 (timepoints) whole-brain repeated measures ANOVA. The complexity by timecourse ANOVA identified two groups of voxels showing an effect of visual complexity: one near the OT border (-40 -64 -4 in MNI coordinates, shown in Figure 2.4) and one in right posterior occipital cortex (28, -95, 0 in MNI coordinates). In both cases there was more BOLD activity for the most complex stimuli relative to the least complex stimuli. There was no complexity by stimulus-type by timecourse interaction (i.e. the effect of complexity did not depend on the type of stimulus), and in all stimulus types the most complex pairs produced more activity than the least complex pairs. Of note, Amharic characters were more visually complex than all of the letter strings (see Table 2.3), which could be contributing to the increased activity for Amharic characters relative to letter strings in the stimulus-type by timecourse analyses presented in Study 1.

Stimulus Type	Average Complexity of all pairs	Average Complexity of least complex pairs	Average Complexity of most complex pairs
Amharic strings	33.53	27.78	39.15
Consonant strings	20.4	17.0	23.7
Nonwords	20.2	15.95	24.05
Pseudowords	20.2	16.45	23.9
Words	20.2	16.35	24.5

Table 2.3. Average complexity values for stimulus pairs.

Complexity for each pair was computed as the summed value of brushstrokes/character (Changizi MA and S Shimojo, 2005) for all 8 characters in each pair. The 20 pairs with the highest complexity values for each stimulus type were labeled "most complex" and the 20 pairs with the lowest complexity values for each stimulus type were labeled "least complex".

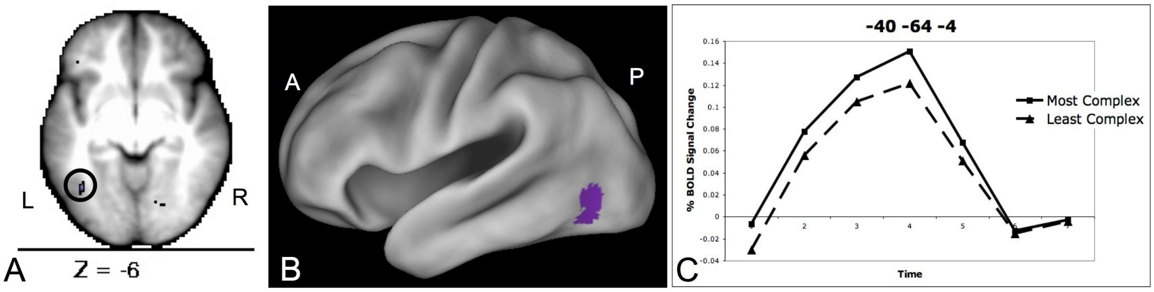


Figure 2.4. Left OT fusiform region showing a complexity by timecourse interaction

A. Location of voxels showing a visual complexity by timecourse interaction Z-score > 3.5 in a transverse slice through fusiform cortex. The circled OT region (-40 -64 -4 in MNI coordinates) was the only left hemisphere region identified.

B. Location of the left OT region showing a visual complexity by timecourse interaction on a semi-inflated CARET surface.

C. Timecourses for the most and least visually complex pairs (all stimulus types averaged together) in the left OT region identified from the whole brain complexity by timecourse analysis. This region shows more activity for the most complex relative to least complex pairs (p = 0.013)

Pair-type by Stimulus-type Interactions

We have hypothesized that fluent reading requires processing visual stimuli in “groups” or “chunks”. Making same/different judgments on strings of all different items should be easy regardless of whether those stimuli are processed as groups or in chunks, while making such judgments on strings with only 2-character differences should take longer and entail more processing. Making a same/different judgment on identical strings should take even longer than matching 2-character substitution strings if each character must be evaluated individually, but should be done very quickly if all items are processed together. Evaluating the overall pattern of response times to make such decisions shows a mixed set of effects in the present study. There is an effect of pair-type on RT ($p < 0.001$) with the fastest RT for the easy judgments, which is significantly faster than the hard/2-different pairs ($p < 0.001$), which is significantly faster than the same pairs ($p < 0.001$). However, our stimuli were designed so that some obeyed the rules and statistical regularities of real words (words and pseudowords) while others did not follow such rules and regularities (consonant strings and Amharic characters). Thus we performed a second repeated measures ANOVA on the RTs, taking into account not only pair-type, but stimulus-type as well. There is a pair-type by stimulus-type interaction on RT, indicating the effect of pair-type differs by stimulus-type.

Response times to match the consonant and Amharic character strings increased with the number of characters that must be evaluated sequentially to make a same/different judgment (see Figure 2.5). Subjects were fastest to match the easy stimuli different in all 4 character positions ($p < 0.001$ for both stimulus types). Matching hard pairs with 2-character differences was somewhat slower ($p < 0.001$ for both stimulus types), and the slowest RTs were found when matching pairs that were all the same ($p \leq 0.001$ for both stimulus types). As described in the introduction to this section, this pattern is expected if subjects have to “look at” each character sequentially to make the same/different judgment. Henceforth, we will refer to the Amharic and consonant strings as “ungroupable”.

In contrast, subjects are as fast to make a same/different judgment on the same pairs as the easy pairs ($p \geq 0.08$) for stimuli that follow the rules and regularities of real words (words and pseudowords), indicating these stimuli are processed as "groups" (see Figure 2.5). The increased RT for hard pairs ($p \leq 0.02$ for all contrasts in both stimulus types) in the words and pseudowords could be due to the shared letters between the pairs. Such shared letters could cause the activation of overlapping representations, resulting in increased processing time to resolve the discrepancy. Henceforth, we will refer to words and pseudowords as "groupable".

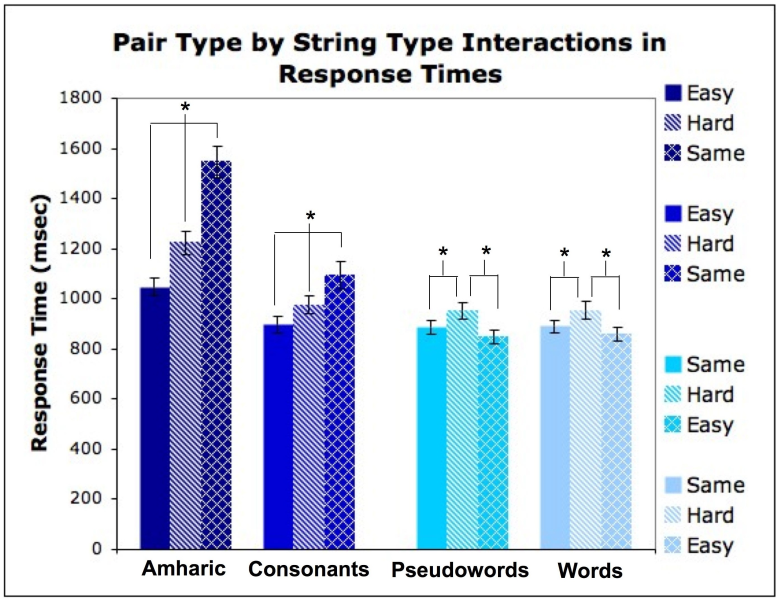


Figure 2.5. Response time to match various pair types for each stimulus type

Response time to match Amharic character and consonant strings increases with the number of characters that must be evaluated to make the matching decision. The RTs are significantly different for all pair types in these stimuli. Response times to match pseudowords and words are equivalent for the same and easy pairs, which are faster to match than hard pairs. All statistical effects are denoted with asterisks. Error bars indicate the standard error of the mean.

A brain region related to the grouping of visual stimuli should have a similar pattern of results as the response times. We first compared the BOLD response for the three different pair types, as done for RT, in a 3 (pair-type: easy vs hard vs same) by 7 (timepoints) whole brain repeated measures ANOVA. This whole brain ANOVA identified a number of regions in frontal and parietal cortex (left lateral hemisphere regions shown in Figure 2.6B, all detailed in Table 2.4) as well as a single left occipito-temporal (OT) region (-44 -67 -4 in MNI coordinates, shown in pink in Figure 2.6B). The left OT region (and all lavender regions in Figure 2.6B) showed a similar pattern as the RTs - more activity when pairs are identical or differed in only 2 characters than when the pairs differed in all 4 character positions (Figure 2.6C).

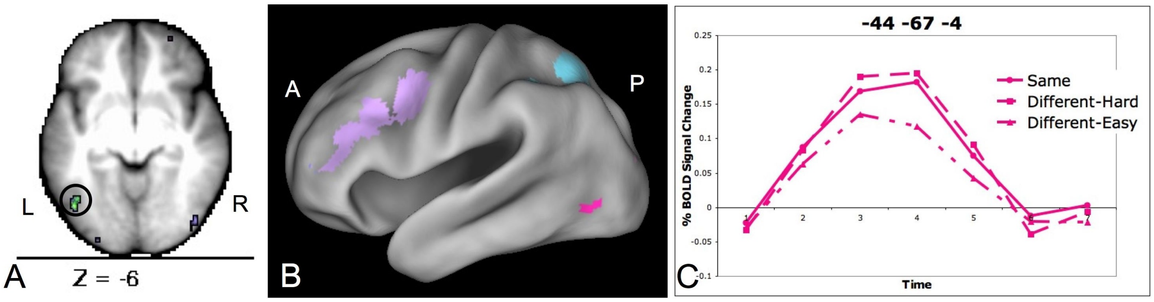


Figure 2.6. Left OT fusiform region showing a pair-type by timecourse interacton

A. Location of voxels showing a pair-type by timecourse interaction Z-score > 3.5 in a transverse slice through fusiform cortex. The peak of the circled left OT region is located at -44 -67 -4 in MNI coordinates.

B. All left lateral hemisphere regions showing a pair-type by timecourse interaction on a semi-inflated CARET surface. In pink is the OT region circled in panel A. Lavender regions show a similar pattern of effects as the pink region (BOLD activity for same pairs = hard pairs > easy pairs), blue region shows BOLD activity for hard pairs > same pairs = easy pairs.

C. Timecourse for the 3 types of stimulus pairs (pairs of the same strings, hard pairs, easy pairs, BOLD activity from all stimulus types averaged together) in the left OT region identified from the whole brain difficulty by timecourse region circled in panel A and shown in pink in panel B.

Regions showing a pair-type by timecourse interaction

Anatomical Location	MNI coordinates			Number of Voxels	Pair-Type Z-score	Pair-Type Effects	3-way Interaction Z-Score
	X	Y	Z				
L fusiform	-44	-67	-4	31	3.42	H = S > E	0.0013
R fusiform	41	-84	10	30	3.29	H = S > E	0.022
R parietal	33	-58	53	431	6.30	H = S > E	0.00149
L occipital	-30	-93	19	56	4.12	H = S > E	0.034
R precentral gyrus	27	-7	53	48	4.30	H = S > E	0.074
L occipital	-5	-82	-13	31	3.66	H = S > E	0.749
R occipital	31	-88	12	78	3.79	H = S > E	0.226
R basal ganglia	11	2	5	49	3.48	H = S > E	0.724
R basal ganglia	10	-16	13	46	3.70	H = S > E	> 0.75
L basal ganglia	-9	-18	14	41	3.81	H = S > E	0.987
L basal ganglia	-14	-4	14	96	4.18	H = S > E	0.771
R basal ganglia	17	-4	18	92	4.03	H = S > E	> 0.75
L cerebellum	-29	-58	-28	71	3.77	H = S > E	0.24
L parietal	-28	-62	50	458	6.28	H > S > E	0.0000449
Anterior cingulate	-3	15	52	346	5.81	H > S > E	0.021
R precentral gyrus	42	6	33	369	5.57	H > S > E	0.033
L anterior cingulate	-11	16	43	85	3.61	H > S > E	0.658
R frontal	50	25	24	149	4.59	H > S > E	0.16
R frontal	43	30	28	237	5.07	H > S > E	0.9325
L lateral parietal	-43	-60	48	83	3.07	H > S = E	0.00059
L lateral parietal	-47	-48	49	228	5.19	H > S = E	0.000198
L precentral gyrus	-44	3	35	447	7.29	H > S = E	0.000119
L frontal	-46	32	20	178	5.38	H > S = E	0.0215
L frontal	-39	10	48	46	3.02	H > S = E	0.334
L frontal	-43	20	28	278	5.33	H > S = E	0.374

R occipital	19	-97	0	66	4.47	S > H > E	0.617

Table 2.4. Pair-type by timecourse ROIs

Regions are listed by pattern of pair-type by timecourse effects. 3-way interaction refers to the pair-type by stimulus-type by timecourse interaction; those regions showing significant pair-type by stimulus-type by timecourse interactions are detailed in Table 2.5. The left OT region depicted in Figure 2.6 is shown in the top line.

Clearly, the more informative analysis for determining whether the “groupability” of the stimuli seen in response time is reflected in the BOLD activity is the search for a pair-type by stimulus-type interaction. In other words, for a region processing visual stimuli in “groups” to be useful in reading, it only needs to be able to “group” stimuli that look like words, as seen in the RT pair-type by stimulus-type interaction. Such a region should show the same pair-type by stimulus-type interaction as the RTs, where there is less activity for processing the easy/all-different and same pairs than the hard pairs in “groupable” stimuli and more activity for the same pairs relative to hard relative to easy pairs in “ungroupable” stimuli, as described above. In fact, our 3 (pair-type: easy vs hard vs same) by 5 (stimulus-type: Amharic strings vs consonant strings vs nonwords vs pseudowords vs words) by 7 (timepoints) repeated measures ANOVA performed on all of the regions identified from the pair-type by timecourse analysis revealed about half of the pair-type by timecourse regions showing an additional interaction with stimulus-type (the full report of which can be found in Table 2.6). Here the will focus will be on the left OT region shown in Figure 2.6.

In the left OT fusiform region identified as showing a pair-type by stimulus-type by timecourse interaction the timecourses generally followed the pattern seen in the RTs. When subjects made a matching decision on “ungroupable” stimulus pairs (consonant and Amharic character strings), the left OT fusiform region showed a pattern of activity consistent with letter-by-letter (or character-by-character) processing (exemplified in Figure 2.7D). When matching consonant strings, subjects showed the least activity when shown easy pairs, somewhat more activity for the hard pairs, and even more activity for identical pairs (Figure 2.7E). Subjects matching Amharic character strings showed less activity for the easy pairs than for both the hard and identical pairs, which produced equivalent activity (Figure 2.7F). As with RT, the magnitude of activity increased relative to the average number of characters that must be studied to make a same/different judgment for the consonant and Amharic character strings, suggesting that the subjects were looking at each letter (character) position sequentially.

In contrast, when viewing ”groupable” stimulus pairs (words and pseudowords), the OT fusiform region showed more activity for the hard decision than for the easy and identical decisions, which produced equivalent activity (Figure 2.7C and 2.7D). The similar BOLD response to completely identical and completely different pairs suggests that subjects did not need to look through each position to ensure the two letter strings were identical. The lower level of processing needed to make a correct “same” judgment indicates an ability to process these visual forms as a group. Again, the increased activity for the hard pairs likely reflects activation of partially overlapping representations due to the shared letters in the pairs, which takes increased processing to resolve.

To ensure the imaging results did not arise simply from response time differences, which in this case did mimic the BOLD data, we performed the same repeated measures ANOVAs but included RT as a trial-wise regressor (as described in the methods section). The pair-type by stimulus-type by timecourse interaction remained significant in the described OT fusiform region ($p < 0.05$, corrected for multiple comparisons) with RT regressed out. The pattern of hard > easy = same BOLD activity also remained significant for both words and pseudowords with RT regressed out, as did the same > hard > easy pattern for consonant strings and the same = hard > easy pattern for Amharic strings.

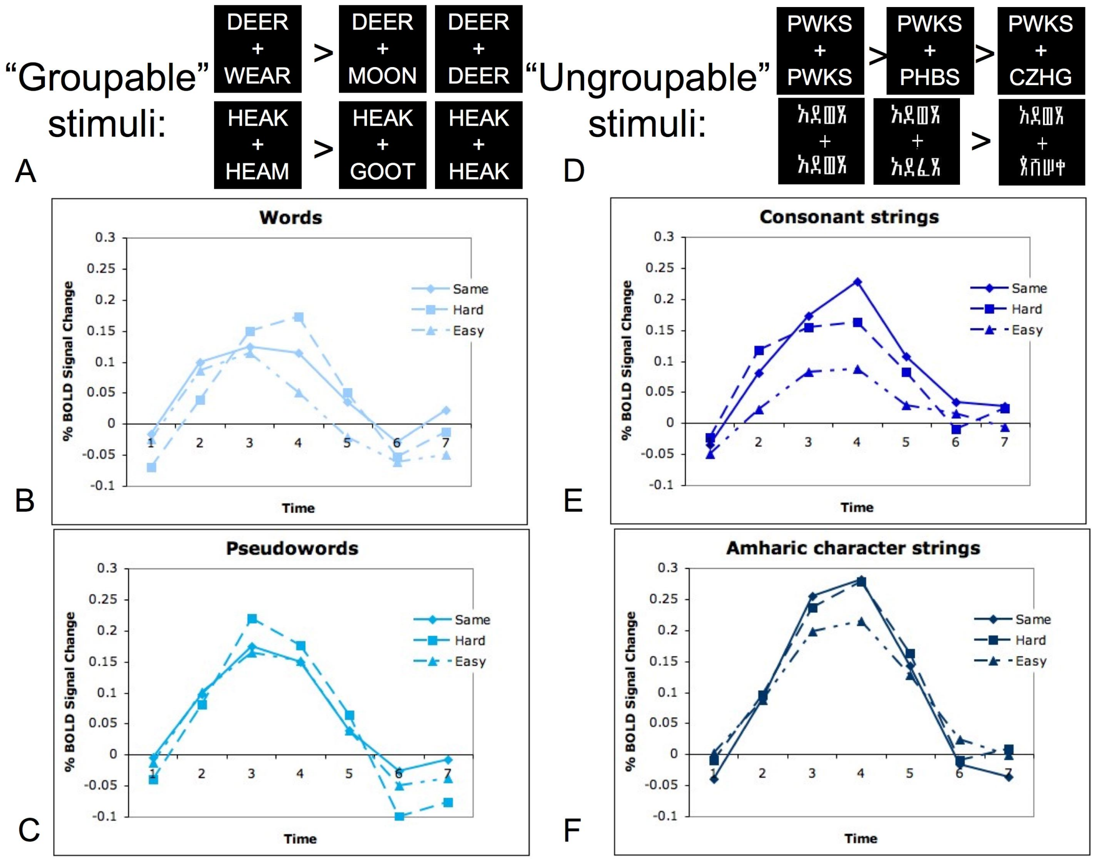


Figure 2.7. Difficulty by stimulus-type by timecourse interactions in the left occipito-temporal fusiform region

The left OT fusiform region was identified in the whole brain pair-type by timecourse analysis (-44 -67 -4 MNI). Note that all imaging effects in this region remain significant even when response time is regressed out.

A. Depiction of significant pair-type by timecourse BOLD interaction for “groupable” strings (words and pseudowords).

B. BOLD group-average timecourses for the 3 pair types of words: hard > easy = same pairs.

C. BOLD group-average timecourses for the 3 pair types of pseudowords: hard > easy = same pairs.

D. Depiction of significant pair-type by timecourse BOLD interaction for “ungroupable” stimuli (consonant strings and Amharic character strings).

E. BOLD group-average timecourses for the 3 pair types of consonant strings: same pairs > hard pairs > easy pairs.

F. BOLD group-average timecourses for the 3 pair types of Amharic character strings: identical = hard pairs > easy pairs.

Regions showing a pair-type by stimulus-type by timecourse interaction									
Anatomic Location	MNI coordinates			3-way Interaction Z-Score	Amharic	Cons.	Non-words	Pseudo-words	Words
	X	Y	Z						
L fusiform	-44	-67	-4	0.0013	H=S>E	S>H>E	ns	H>S=E	H>S=E
R fusiform	41	-84	10	0.022	S>H=E	S>H>E	ns	ns	H=S>E
R parietal	33	-58	53	0.00149	H=S>E	H=S>E	H=S>E	H>S=E	H>S>E
L occipital	-30	-93	19	0.034	S>E	S>H>E	ns	H>S=E	H>E
L parietal	-28	-62	50	0.0000449	H>E=S	ns	H>S>E	H>S=E	H>S=E
Anterior cingulate	-3	15	52	0.021	H=S>E	H=S>E	H=S>E	H>S=E	H>E
R precentral gyrus	42	6	33	0.033	H=S>E	H>S>E	ns	H>S=E	H=S>E
L lateral parietal	-43	-60	48	0.00059	H=S>E	ns	ns	H>E=S	H>S>E
L lateral parietal	-47	-48	49	0.000198	H=E>S	H=E>S	H>S>E	H>E=S	H>E=S
L precentral gyrus	-44	3	35	0.000119	ns	H=S>E	H>S=E	H>S=E	H>S>E
L frontal	-46	32	20	0.0215	ns	ns	ns	H>S=E	H>S=E

Table 2.5. Pair-type by Stimulus-type by timecourse interactions

All regions from the pair-type by timecourse analysis showing a 3-way pair-type by stimulus-type by timecourse interaction. The pattern of statistically significant effects is shown for each stimulus type. S denotes the same pairs, H denotes the hard/2-character different pairs, and E denotes the easy/4-character different pairs. The left OT region detailed in Figure 2.7 is shown in the top row.

Overlap of Interactions

If there is a region particularly adaptable for reading due to its processing of visually complex stimuli in groups, that region should demonstrate all of the previously described interactions: stimulus-type by timecourse, complexity by timecourse and pair-type by timecourse interactions (following the "grouping" pattern). Using a conjunction analysis (as described in the methods), we found only one region showing all 3 effects (Figure 2.8). This region was centered very near the left OT fusiform region described in the previous three sections (-41, -66, -4 in MNI coordinates) and also showed the aforementioned pair-type by stimulus-type by timecourse interaction.

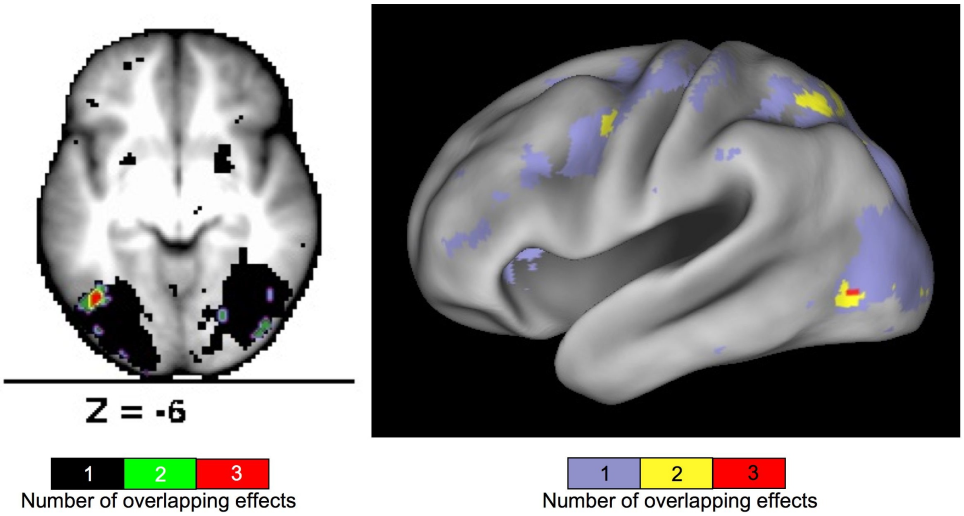


Figure 2.8. A single left fusiform region shows all previously described interactions

Location of the occipital-temporal region (-41 -66 -4 MNI) showing all three (stimulus-type by timecourse, complexity by timecourse and pair-type by timecourse) interactions. Voxels showing a significant interaction in all 3 ANOVAs are shown in red in both a transverse slice through fusiform cortex (left panel) and projected to the surface of a semi-inflated CARET surface (right panel). This region also had a significant pair-type by stimulus-type by timecourse interaction.

Discussion

We hypothesized that a visual processing region useful for reading (such as the putative VWFA) would process high contrast, high spatial frequency, visually complex stimuli in groups. A whole brain analysis of the effect of visual complexity revealed a region in the left occipito-temporal fusiform cortex showing more activity for the most visually complex stimuli relative to the least complex. A whole brain analysis of pair-type found a similar left occipito-temporal fusiform region that also showed a pair-type by stimulus-type by timecourse interaction. This interaction was driven by differences in “grouping”, whereby stimuli following the rules and statistical regularities of real words (words and pseudowords) showed RTs and BOLD activity indicative of similar processing for pairs that were all the same and all different, while stimuli that did not follow these rules and regularities (consonant and Amharic strings) showed RTs and BOLD activity indicative of character-by-character processing. The location of the complexity by timecourse, pair-type by timecourse, and pair-type by stimulus-type by timecourse effects, as well at the stimulus-type by timecourse effect described in Study 1, were co-localized to a single region in left occipito-temporal fusiform cortex.

Role of complexity in putative VWFA processing

Our finding of increased activity in the left occipito-temporal cortex for stimuli with increased visual complexity could explain some discrepant results in the putative VWFA literature. For example, while some groups show more activity for letters than digits in this region, digits tend to be less visually complex as measured by the brushstrokes/character criteria (Changizi MA and S Shimojo, 2005). Also, many line drawn pictures are more visually complex than letters (on this metric), possibly resulting in increased BOLD activity for pictures relative to letter strings.

Role of “grouping” in putative VWFA processing

The finding that a region in left occipito-temporal fusiform cortex is related to “grouping” of word-like stimuli was expected. As described in the introduction, acquired alexia, potentially caused by lesions to the left occipito-temporal fusiform cortex or to its connections to parietal cortex, is characterized by the inability to read words as a “whole” (Cohen L et al., 2003; Gaillard R et al., 2006), and at least some alexics show deficits in simultaneous processing of multiple stimuli (Starrfelt R et al., 2009). Also, Schurz et al. (2010) demonstrated the left fusiform cortex is responsive to both whole words and smaller segments of pseudowords.

Role of high contrast, high frequency visual processing in the putative VWFA

Unfortunately, we were unable to test the specificity of the left occipito-temporal fusiform cortex response to high spatial frequency, high contrast stimuli, as all of our stimuli possessed these properties. However, previous results (Kveraga K *et al.*, 2007) show that left fusiform cortex is more responsive to line drawn objects filtered to retain only high spatial frequency information relative to those filtered to retain low spatial frequency information.

General Discussion

The results presented here refute the notion that words or letters are processed exclusively or even preferentially in the left occipito-temporal fusiform cortex in general and in the putative VWFA in particular. These studies also directly tested several properties that should be characteristic of a visual processor used in reading, particularly the ability to process visually complex stimuli in groups. A region that seems to show both properties -- increased activity for more visually complex stimuli and activity reflective of grouped processing for stimuli following the rules and statistical regularities of real words -- was found in left occipito-temporal fusiform cortex. Together, these results not only argue against portraying the putative VWFA as a skill-specific region, but also inform our understanding of the type of processing actually done in this region. Moreover, by characterizing this left occipito-temporal fusiform region as a complex visual processor that has the capacity to group stimuli, we are able resolve disparate results from the literature.

Resolving disputes in orthographic neuroimaging studies

First, these results nicely account for the numerous reports of positive BOLD activity in the putative VWFA region in response to non-letter and non-word stimuli (Bar M et al., 2001; Ben-Shachar M et al., 2007; Kherif et al., 2010; Mei et al., 2010; Ploran EJ et al., 2007; Price CJ and JT Devlin, 2003; Starrfelt R and C Gerlach, 2007; Tagamets MA et al., 2000; Van Doren L et al., 2010; Xue G et al., 2006; Xue G and RA Poldrack, 2007). If, as we suggest, the putative VWFA is a relatively general-use visual region that processes visually complex stimuli in groups during reading and other tasks, there should be activity in this region for pictures and other non-letter stimuli.

More importantly, the ability of the putative VWFA to “group” stimuli, as demonstrated by the present results, may underlie reports of reduced activity for words relative to other visual items in this region. Specifically, the increased processing efficiency afforded by the ”grouped” processing of the putative VWFA may be driving the decreased activity for words relative to pseudowords (see Mechelli A et al., 2003 for a review), as well as the negative relationship between word frequency and putative VWFA activity (Graves WW et al., 2010; Kronbichler M et al., 2004). Experience-dependent grouping could also account for the decreased activity for non-word stimuli seen after visual training (Xue G et al., 2006). This “grouped” processing advantage may even be the basis for the preferential activity for words relative to consonant strings and false font stimuli observed exclusively at fast presentation times, as such “grouping” presumably facilitates efficiency of processing (see Study 1 discussion). Yet, as mentioned previously, this “grouped” processing does not supersede the ability of the putative VWFA to process the individual components of a greater whole, hence the activity for false fonts and objects, and the reported responsiveness to both whole words and smaller components (Schurz M et al., 2010).

Resolving disparate results in occipito-temporal lesion studies

The present characterization of the left occipito-temporal fusiform cortex may also be able to account for conflicting results reported in lesion studies (i.e. Cohen L et al., 2003; Gaillard R et al., 2006; Warrington ET and T Shallice, 1980 versus Behrmann M et al., 1998; Hillis AE et al., 2005; Starrfelt R et al., 2009). If this region processes word-like stimuli in groups, lesions should cause disruption to fluent reading, which requires the letters of words to be processed as a group.

Yet as a general visual processor, simultaneous processing problems may also extend to other stimuli with which patients have had significant experience, such as digits (as seen in Starrfelt R et al., 2009). However, more studies are needed to characterize the extent of disruption for non-word stimuli that may be processed as a "group" in patients with lesions to this region.

On the other hand, studies that aim to identify the core lesion location producing alexia by defining a large group of patients with acquired alexia, have not found the putative VWFA to be central to this deficit (Chen R et al., 2008; Hillis AE et al., 2005). The failure to identify a particular lesion site for acquired alexia is not inconsistent with the putative VWFA being a general use visual region that processes complex stimuli in groups, since it is possible that similar visual information is able to be transferred to "higher level" reading processors via a different route such as the lingual gyrus (Petersen SE et al., 1988) or the right occipito-temporal fusiform cortex. Studies of the activation profiles of patients with lesions to this region that do not show acquired alexia will be essential for understanding such compensation.

Understanding semantic effects in the putative VWFA

The present results, and the characterization of an occipito-temporal fusiform region as processing visually complex stimuli in groups, is not consistent with a primary role for the putative VWFA in semantic processing, as proposed by some (Devlin JT et al., 2006; Van Doren L et al., 2010). For example, increased activity for Amharic characters or false fonts relative to words is inconsistent with a semantic processing role.

However, a visual region used in reading is likely both to feed information into and to receive feedback from phonologic and semantic processors. Feedback from a semantic processor onto multiple representations of words and/or pictures located in a visual processing region such as that described here may produce some of the priming effects described in the putative VWFA (Devlin JT et al., 2006; Kherif F et al., 2010). In fact, some level of top-down feedback has been demonstrated in left fusiform regions (Bar M et al., 2006). Also, a visual region that groups complex stimuli is likely to be very useful in gathering enough information to identify an item. Thus, this region may be related to conscious awareness and recognition memory (as shown in Van Doren L et al., 2010) and accumulation of visual information (Ploran EJ et al., 2007), due to its role in visual processing, not semantics per se.

Location of the putative VWFA

The various effects seen in the present study – a stimulus-type by timecourse interaction, a complexity by timecourse interaction, and a pair-type by timecourse interaction – were all co-localized to a single region of occipito-temporal fusiform cortex centered on -41, -66, -4 (MNI coordinates). This region also showed the previously described pair-type by stimulus-type by timecourse interaction dependent on "groupablity". However, while this region, like the putative VWFA, is in the left occipito-temporal fusiform cortex, it is about 10 mm Euclidean distance from the Cohen and Dehaene (2004) VWFA region when they are both considered in the same atlas space. Our conjunction analysis-derived region is closer (in Euclidean distance) to regions defined by cue-related activity in spatial cueing tasks (see Corbetta M and G Shulman, 2002 for a review) and activity in visual search related tasks (Egner T et al., 2008; Fairhall SL et al., 2009; Leonards U et al., 2000). These regions, while often reported as being near the middle temporal region (MT+ in humans), are consistently inferior to MT+ regions found in motion localizer tasks (i.e. Sarkheil P et al., 2008; Tootell RB et al., 1995; Zacks JM et al., 2006).

It is unclear whether the region identified by the present analysis is functionally more similar to the putative VWFA or to the cue-related region described above. There is also the possibility that the putative VWFA and cue-related region are functionally the same, or that our described region is distinct from both. The relationship between these three regions should be studied further. However, the differences in tasks used for region definition, lack of clear coordinate locations in some studies, and differences in data acquisition properties and atlas transformations make simply applying our described statistical tests of literature-based VWFA and cue region coordinates less than satisfying. We anticipate that a more specific method of region definition, such as the combination of resting state functional connectivity and functional-based region definition described in Nelson, Cohen et al., (2010) (partly based on methods described in Cohen AL, DA Fair, NU Dosenbach et al., 2008), will prove very helpful in adjudicating whether regions from different studies and/or tasks converge anatomically.

Conclusions

Using a visual matching task on pictures, strings of Amharic characters, and letter strings of varying levels of orthographic regularity, we have shown that the putative visual word form area is not predominantly used for reading and should not be ascribed to “reading” alone. Rather the putative VWFA likely performs more general visual processing, such as the processing of high spatial frequency, high contrast, visually complex stimuli in groups. Direct tests of visual complexity and visual grouping relative to stimulus type shows a single region in left occipito-temporal fusiform cortex demonstrating both these processing properties and increased activity for pictures and Amharic characters relative to words and letter strings.

CHAPTER 3. THE PUTATIVE VWFA IS FUNCTIONALLY CONNECTED TO THE DORSAL ATTENTION NETWORK

Introduction

Functional neuroimaging has helped make great strides in understanding the neural underpinnings of reading. Single studies and meta-analyses have led to a general consensus regarding the brain regions used in reading processes. For example, regions in the left supramarginal gyrus (SMG, Church JA, DA Balota et al., 2010; Church JA et al., 2008; Graves WW et al., 2010) and inferior frontal gyrus (IFG, Fiez J and S Petersen, 1998; Mechelli A et al., 2003) have been reported in a number of studies involving phonological processing on visual words. Regions in the left angular gyrus (AG, Binder JR et al., 2009; Binder JR et al., 2005) are thought by some to relate to semantic processing. A region in the left fusiform cortex at the occipito-temporal junction is purported to be involved in orthographic processing (see details below) and has come to be called by some the visual word form area (VWFA).

The role of the putative VWFA in reading is a matter of considerable debate. The putative VWFA is one of the most consistently reported regions in reading meta-analyses (Jobard G et al., 2003; Mechelli A et al., 2003; Turkeltaub PE et al., 2003; Vigneau M et al., 2006). This region has been found to show activity for words that is case, size and font invariant *(Cohen L et al.*, 2002), and some studies report more activity in the region for words than for consonant strings (Cohen L et al., 2002; McCandliss BD et al., 2003), digits (Polk TA et al., 2002) or false fonts (Vinckier F et al., 2007). However, a number of studies have shown the putative VWFA is also active when processing visual stimuli other than words, including pictures (Ben-Shachar M et al., 2007; Kherif F et al., 2010; Ploran EJ et al., 2007; Price CJ and JT Devlin, 2003; Starrfelt R and C Gerlach, 2007; Van Doren L et al., 2010), faces (Mei L et al., 2010) and false fonts (Xue G et al., 2006; Xue G and RA Poldrack, 2007). Moreover, while damage to this region can sometimes result in acquired alexia, or letter by letter reading (Cohen L et al., 2003; Dejerine J, 1892; Gaillard R et al., 2006), there is some evidence that such lesions do not produce alexia exclusively (Behrmann M et al., 1990; Behrmann M et al., 1998; Price CJ and JT Devlin, 2003), and may instead cause a more general deficit in simultaneous visual processing (Starrfelt R et al., 2009).

Despite this controversy, it seems likely that the putative VWFA is in involved in reading in some way, leaving two possibilities. First, the putative VWFA could be used specifically or predominantly for reading, either by design or extensive training (as described in Dehaene S and L Cohen, 2007). Second, the putative VWFA could be a more general visual processor used in reading and other visual tasks. Here, we use resting state functional connectivity MRI (rs-fcMRI) to adjudicate between these two possibilities.

rs-fcMRI uses correlations in low frequency (approximately 0.01 to 0.1 Hz) fluctuations of the BOLD signal present at rest to define functional relationships between regions. rs-fcMRI has been used previously to study functional networks including the default mode network (Fox MD et al.; Greicius M et al., 2003), attentional control networks (Dosenbach NUF et al., 2007; Fox MD et al., 2005; Seeley WW et al., 2007) and reading networks (Koyama MS et al., 2010), among others. It seems the resting state correlations reflect a long history of co-activation (Dosenbach NUF et al., 2006; Fair DA et al., 2009; Fair DA, NU Dosenbach et al., 2007) that is somewhat malleable with short-term experience (Lewis CM et al., 2009; Stevens WD et al., 2010; Tambini A et al., 2010). By determining which regions have a history of co-activity with the putative VWFA, we should be able to gain insight into whether it is predominantly used in reading or is a more general visual processor.

If the putative VWFA is used predominately for orthographic processing in reading it should have functional connections to not only other visual regions but also to phonological processors such as the left SMG and left IFG, semantic processors such as the left AG or left middle temporal gyrus (Binder JR et al., 2009; Booth JR et al., 2007; Simmons WK et al., 2010), and possibly even supplementary motor area (Alario FX et al., 2006), mouth pre- and motor cortex, and auditory association cortex. If, on the other hand, the VWFA is a visual processor that is not used preferentially for words or word-like stimuli but is also used more generally for other visual processing demands, we might instead expect to see functional connections to other visual and visual attention regions in the absence of preferential functional connections to putative reading-related regions.

Even if the putative VWFA is a more general visual processor and is not functionally correlated with reading-related regions (as we purport in this chapter and the last), its pattern of functional connections should still inform our understanding of the type of processing done in this region. As the putative VWFA is consistently activated during reading, it must have some properties that make it particularly useful for this task. We have demonstrated that one such property is the ability to group visual stimuli that follow the rules and statistical regularities of real words into chunks of various sizes (see Chapter 2). In reading, the ability to "group" stimuli into various sized "chunks" is useful. Computing grapheme to phoneme correspondences used in the phonologic decoding of pseudowords or new words requires grouping letters into small "chunks", such as bigrams or trigrams. However, when adults read familiar words fluently, they seem to process the words as a whole and have minimal variability in their response latencies to name words that range in length from 3-7 letters (e.g. Cohen L et al., 2003; Weekes BS, 1997). In keeping with this hypothesis, Schurz and colleagues have shown that BOLD activity in the putative VWFA also has a length by lexicality effect, whereby activity increases with length when reading pseudowords but not real words (Schurz M et al., 2010). Additionally, activity in this region is modulated by bigram frequency (Graves WW et al., 2010; Kronbichler M et al., 2004), and is responsive to whole words (Schurz M et al., 2010; Vinckier F et al., 2007). Activity in the putative VWFA is generally increased for pseudowords relative to words (Binder JR et al., 2005; Church JA, DA Balota et al., 2010; Mechelli A, et al., 2003), possibly due to differences in the absolute size of "groups" represented in the putative VWFA for these stimuli.

A a region capable of visual "chunking" of the type used in reading, as described above, ought to develop preferentially strong functional connections with regions that direct attention to the appropriate group of features or spatial location. Since regions in the dorsal attention network direct attention to the appropriate spatial or feature "chunk" (Corbetta M and G Shulman, 2002), we hypothesize there should be functional relationships between the putative VWFA and dorsal attention regions. To further elaborate, this relationship should exist because it would be useless for the putative VWFA to process words in large chunks if attention could only be directed to single letters. Likewise, directing attention to the whole of an object (e.g. a string of Amharic characters) is not useful if its components must be processed individually. As the ability to process words in larger "groups" is related to age and/or reading ability (Backman J et al., 1984; Bijeljac-babic R et al., 2004; Defior S et al., 1996; Martens VEG and PF de Jong, 2008; Sandak R et al., 2004), this relationship between the putative VWFA and dorsal attention regions may also be related to age or reading level.

Methods

Subjects

Main analysis*:* Subjects included 25 children (8 male) ages 6-9 years and 23 adults (11 male) ages 21-26 years. All subjects were right handed, native mono-lingual English speakers. All were screened for neurologic and psychiatric diagnoses and use of chronic medications by telephone interview and questionnaire. All gave written informed consent and were reimbursed for their time per the Washington University Human Studies Committee guidelines. Subjects were tested for IQ using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler D, 1999) and for reading age using three subtests of the Woodcock-Johnson III (Letter-Word ID, Passage Comprehension, and Word Attack) (Woodcock RW and MB Johnson, 2002). Further information about the standard reading age and IQ for the adult subjects can be found in Table 3.1.

After further study, 3 children were excluded from the final analysis. As correlations with standard reading age were an analysis of interest, the 2 children with reading ages above 2 standard deviations from the mean (reading ages of 17.6 and 18.5 years old) were excluded. One other child was excluded for showing a majority of outlier rs-fcMRI correlation values in region-wise analyses (falling more than 2 standard deviations from the mean). Thus the final child data set included 22 children (7 male) age 6-9 years with an average age of 8.2 years. Behavioral data for this final analysis group is presented in Table 3.1.

Movement matched analysis: As seen in Table 3.1, the children used in the main analysis moved significantly more than the adults. Increased movement increases the noise in the rs-fcMRI signal, potentially making it more difficult to detect rs-fcMRI correlations and leading to spurious group differences. Therefore, we repeated the developmental analyses with groups of movement-matched children and adults, making use of some subject data obtained from additional datasets from our laboratory. The 23 children (age 7-10 years, mean 8.5) and 23 adults (age 21-26 years, mean 24.0 years) were also right-handed, native, mono-lingual English speakers screened for neurologic and psychiatric diagnosis similar to the main group. This movement-matched group included 13 children and 6 adults from the main analysis. Unfortunately, not all of the remaining subjects in this group were tested for reading level and IQ; the number of subjects contributing to each measurement are listed in Table 3.1. Age and movement measures are also reported for this group in Table 3.1.

	Chronological Age		**Movement (mm rms)**		**Full Scale IQ**		**Reading Age**	
Subject Group	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
Children (n=22)	8.15	0.84	0.70	0.31	117	15.7	9.5	3.3
Adults (n=23)	24.2	1.65	0.26	0.10	127	7.8	24.4	0.58
Children (n=23)	8.5	1.0	0.41	0.18	119 n=23	15	10 n=13	2.8
Adults (n=23)	24.0	1.4	0.39	0.12	132 n=12	4.8	24.6 n=6	0

Table 3.1 Subject characteristics
IQ was computed from the 2 subtest version of the Wechsler Abbreviated Scale of Intelligence.

Estimated reading ages were computed from 3 Woodcock-Johnson III subtests (Letter-Word ID, *Passage Comprehension, and Word Attack). IQ and reading level were only collected on a portion of the movement-matched group; the number of subjects contributing to each measurement is noted.*

Region Definition

The coordinates of the putative visual word form area (-45, -62, -8), left inferior frontal gyrus (-53, 27, 16), left supramarginal gyrus (-49, -57, 28) and left angular gyrus (-56, -43, 31) regions were defined from an in-house meta-analysis of 5 adult single word reading studies. This meta-analysis is reported in detail in Vogel AC et al., 2008; Vogel AC et al., 2009; and Chapter 4. Unfortunately, this meta-analysis did not show a region in the middle temporal gyrus, where semantic effects are often found (Binder JR et al., 2009). Therefore we have used the closest region identified in the meta-analysis, an inferior temporal gyrus (ITG) region (-61, -33, -15). This region does overlap with the large swath of activity in a meta-analysis of semantics (Binder JR et al., 2009), but is slightly inferior to the main portion of that reported region. All coordinates have been converted to MNI space.

The coordinates of the dorsal attention network regions, fusiform face area (FFA, 35, -49, -14), and extrastriate body area (EBA, 51, -69, 2 and -53, 27, 16), were obtained from the literature (see below). Coordinates for regions in the dorsal attention network were obtained from a meta-analysis of a 4 published studies, reported in the supplementary material of Carter AR et al., (2010). Coordinates for the putative FFA were obtained from a published literature-based meta-analysis (Berman MG et al., 2010). For the purpose of this meta-analysis the peak coordinates for the face localizer from the 50 listed studies were transformed into our in-house atlas space and averaged. This average coordinate was then converted back into MNI space for reporting purposes. Putative EBA coordinates were obtained from a literature search of papers that reported exact coordinates of a body localizer task. In order to most stringently compare the functional relationships of the putative VWFA and EBA, we used the left hemisphere EBA regions, as these are located quite close to the putative VWFA. All coordinates were transformed into our in house atlas space and then averaged. The average region coordinates were then converted back to MNI space for reporting purposes. The 12 papers used in the meta-analysis, the localizer that was used and the reported coordinates can all be found in Table 3.2.

Citation	**Coordinates**			**Localizer Contrast**
	x	**y**	**z**	
(Downing PE et al., 2001)	-51	-72	8	body parts > objects
(Astafiev SV et al., 2004)	-50	-69	9	body parts > objects
(Chan AW et al., 2004)	-45-47	-76	8	bodies > tools
(Spiridon M et al., 2006)	-58	-72	5	bodies > objects
(Morris JP et al., 2006)	-42	-82	9	bodies
(Saxe R et al., 2006)	-45	-72	3	bodies and body parts > objects
(Peelen MV et al., 2007)	-49	-74	7	body parts > tools
(Myers A and PT Sowden, 2008)	-52	-64	14	bodies > objects
	-50	-63	17	bodies > objects
(Pinsk MA et al., 2009)	-52	-72	14	body parts > objects
(Bracci S et al., 2010)	-48	-70	4	bodies and body parts > chairs
(Calvo-Merino B et al., 2010)	-55	-75	8	bodies > scrambles
(Aleong R and T Paus, 2010)	-43	-70	4	bodies > scrambles
Average coordinates	-49	-72	8	
Standard deviation	4.8	5.1	4.5	

Table 3.2. Literature-based meta-analysis of extrastriate body area (EBA) coordinates

All coordinates have been converted to MNI space using icbm2tal found on brainmap.org

MR Data Acquisition and Preprocessing

Each subject performed 1-4 functional resting runs, composed of 132 or 133 continuous frames with a 2.5 second TR. During the scans subjects looked at a black screen with a white central fixation cross. The subjects were instructed to look at the crosshair and relax, but to remain still with their eyes open. All subjects were fitted with a thermoplastic mask to facilitate their efforts to remain still.

A Siemens 3T Trio scanner (Erlanger, Germany) with a 12-channel Siemens Matrix head coil was used to collect all functional and anatomical scans. A single high-resolution structural scan was acquired using a sagittal magnetization-prepared rapid gradient echo (MP-RAGE) sequence (slice time echo= 3.08 ms, TR= 2.4 s, inversion time= 1 s, flip angle= 8 degrees, 176 slices, 1 x 1 x 1 mm voxels). All functional runs were acquired parallel to the anterior-posterior commissure plane using an asymmetric spin-echo echo-planar pulse sequence (TR= 2.5 s, T2* evolution time 27 msec, flip angle 90 degrees). Complete brain coverage was achieved by collecting 32 contiguous interleaved 4mm axial slices (4 x 4 mm in-plane resolution).

Preliminary image processing included removal of a single pixel spike caused by signal offset, whole brain normalization of signal intensity across frames, movement correction within and across runs, and slice by slice normalization to correct for differences in signal intensity due to collecting interleaved slices. For detailed description see Miezin FM et al., (2000).

After preprocessing, data was transformed into a common stereotactic space based on Talairach and Tournoux (1988), but using an in-house atlas composed of the average anatomy of 12 healthy young adults ages 21-29 years old and 12 healthy children ages 7-8 years old (see Brown TT et al., 2005; Lancaster JL et al., 1995; Snyder AZ, 1996 for methods). As part of the atlas transformation the data were resampled isotropically at 3 mm x 3 mm x 3 mm. Registration was accomplished via a 12 parameter affine warping of each individual's MP-RAGE to the atlas target using difference image variance minimization as the objective function. The atlas-transformed images were checked against a reference average to ensure appropriate registration.

Several additional steps (also described in Fair DA, NUF Dosenbach et al., 2007; Fox MD et al., 2005; Fox MD et al., 2009) were taken in processing the rs-fcMRI data in an attempt to reduce the likelihood that the relationships between regions were due to sources such as heart rate or respiration. To mitigate such effects the data were band-pass filtered for frequencies between 0.009 Hz and 0.08 Hz and spatially smoothed (6 mm full width, half max). Additionally, motion correction was performed via regression of the six parameters obtained from the rigid body head motion correction, regression of the signal derived from averaging across the whole brain, regression of signal from ventricular regions of interest (ROIs), and regression of signal from white matter ROIs.

Extraction of rs-fcMRI timecourses and generation of seed maps

A resting state timecourse was extracted for 10 mm spheres centered on the putative VWFA, FFA and EBA coordinates on an individual subject basis. The regional timecourse was composed of the average timecourse of all voxels within the 10 mm sphere. These timecourses were then correlated with the rs-fcMRI timecourse of all other voxels in the brain to create individual subject seed maps. These maps were then averaged together for the children and adults separately. The average maps were projected on the brain surface using CARET (Van Essen DC et al., 2001; http://brainmap.wustl.edu/CARET), thresholded at= 3.5.

Comparison of putative VWFA rs-fcMRI correlations to reading-related and dorsal attention network regions

The resting state timecourse was also extracted for 10 mm spheres centered on the coordinates of each reading-related region (left IFG, SMG, AG and ITG) and dorsal attention network region (bilateral MT+, anterior IPS, FEF, left posterior IPS, and right ventral IPS) described above. The correlation between each of these regions and the putative VWFA are plotted in Figure 3.4. To directly compare whether the putative VWFA is more closely related to reading-related or dorsal attention regions, we calculated the average rs-fcMRI correlation between the putative VWFA and all reading-related regions and the average rs-fcMRI correlation between the VWFA and all dorsal attention regions. A one-tailed, paired t-test was then performed on these average values for the 23 adults.

Comparison of putative VWFA seed maps with FFA and EBA seed maps

The adult average seed map for the putative VWFA was compared with the average seed maps of the putative FFA and EBA. This comparison was done by performing a t-test contrasting the average correlation value for each voxel with the putative VWFA versus the average correlation value for voxel with the FFA and EBA separately, each t-test corrected for multiple comparisons using false discovery rate (FDR). Those voxels showing a difference with> 3.5 were projected onto the surface of the brain using CARET.

Developmental analysis of VWFA rs-fcMRI relationships

Child and adult seed maps for the putative VWFA region were compared directly, by performing a voxel-wise t-test similar to that described above. A t-test was performed for each voxel to determine whether there was a significant difference in the average adult correlation value versus the average child correlation value, correcting for multiple comparisons using FDR. Voxels showing a difference with> 2.5 ($p < 0.01$) were projected on the brain surface using CARET.

A specific comparison of the VWFA to dorsal attention network correlations was also performed. The average rs-fcMRI timecourse for a 10 mm spherical ROI centered on the putative VWFA coordinate was correlated with the average rs-fcMRI timecourse for a 10 mm spherical ROI centered on each of the dorsal attention region coordinates. These correlation values were obtained for each region pair in each subject individually. Then a t-test was performed on each of these pairwise correlations, comparing children and adults. The pairwise comparisons were performed for both the original dataset and the movement matched dataset.

The correlations between reading age and VWFA/dorsal attention relationships were also investigated. A correlation between the standard reading age and VWFA/dorsal attention region rs-fcMRI correlations, as well as a partial correlation determining the relationship between standard reading age and VWFA/dorsal attention region rs-fcMRI correlation, controlling for chronological age and movement, was performed for each region of the dorsal attention network individually. These correlations and partial correlations were performed for all subjects together and for the children separately, as there was little variability in adult reading age.

Results

Whole brain analysis of putative VWFA rs-fcMRI correlations shows overlap with dorsal attention but not reading-related regions.

A seed map analysis of rs-fcMRI connections with the putative VWFA reveals a distributed pattern of activity in adults (Figure 3.1). The seed map represents those voxels whose rs-fcMRI timecourses were significantly correlated ($Z \leq -3.5$ or≥ 3.5) with the average timecourse of the putative VWFA seed region. The putative VWFA seed map does not overlap with most regions thought to be important in reading, including the left supramarginal gyrus (SMG), thought be involved in phonological processing (Church JA, DA Balota et al., 2010) and the left angular gyrus (AG) and inferior temporal gyrus (ITG) regions, purported to be involved in semantic processing (Binder JR et al., 2009) (Figure 3.2). As seen in Figure 3.2, there is a left MFG region showing significant correlations with the putative VWFA, though this region is about 10 mm Euclidean distance from our meta-analysis defined IFG region, generally thought to be related to phonological processing (Mechelli A et al., 2003). Moreover, the region identified from the putative VWFA seed map is even further from the opercular IFG region found in some reading meta-analyses (Fiez J and S Petersen, 1998; Jobard G et al., 2003). There is also no relationship with mouth sensorimotor cortex (note the lack of correlations with pre- and post central sulcus in Figure 3.1) or auditory cortex (note the lack of correlations with superior temporal gyrus regions in Figure 3.1).

In contrast, the putative VWFA seed map does overlap with regions from the dorsal attention network, as defined by a published meta-analysis (Carter AR et al., 2010) (Figure 3.3). A plot of the actual rs-fcMRI correlation values between the putative VWFA and reading-related relations (shown in blue in Figure 3.4) and dorsal attention network regions (shown in green in

Figure 3.4) shows the VWFA to dorsal attention region correlations are clearly stronger than the VWFA to reading-region correlations, which in some cases are even negative (Figure 3.4). A one-tailed paired t-test comparing the average correlation values between the putative VWFA and all reading regions to the average correlation value between the putative VWFA and all dorsal attention regions shows the latter to be significantly stronger ($p < 0.0001$). The difference in correlations between reading-related and dorsal attention regions remains significant ($p < 0.0001$) even when the bilateral MT+ regions, which are both very close to the putative VWFA region and should be considered visual processing regions, are removed.

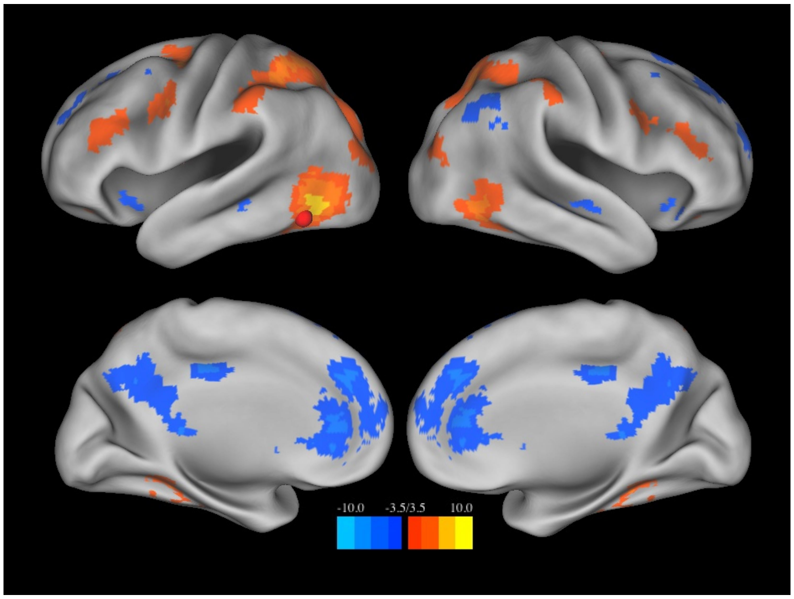


Figure 3.1. Putative VWFA seed map

Map displays voxels showing significant correlations ($Z \leq -3.5$ or ≥ 3.5) with the rs-fcMRI timecourse of the putative VWFA in 23 adults. The location of the putative VWFA seed is shown in red.

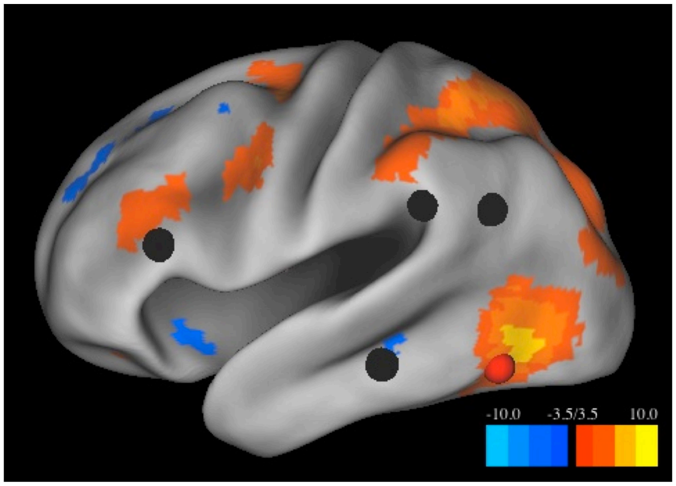


Figure 3.2. VWFA seed map with reading regions

The seed map shown in Figure 3.1 is overlaid with reading specific (left IFG, ITG, SMG and AG regions from anterior to posterior) in black and the location of the putative VWFA seed in red.

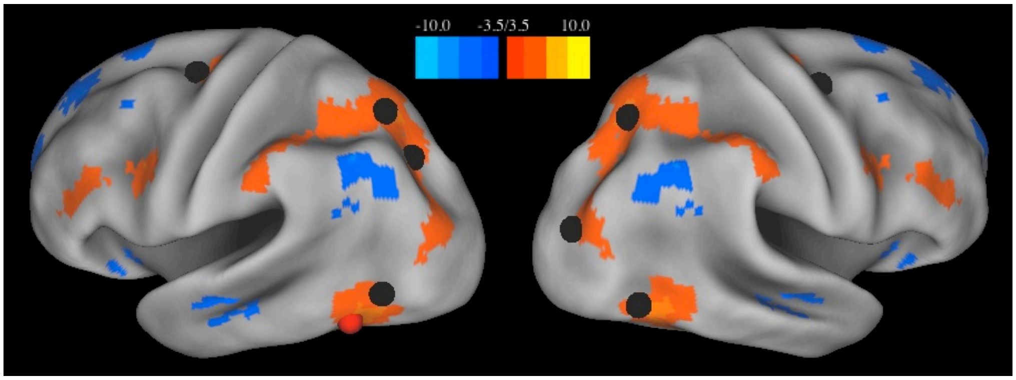


Figure 3.3. VWFA seed map with dorsal attention regions

The seed map shown in Figure 3.1 is overlaid with dorsal attention network regions in black, while the putative VWFA seed is shown in red.

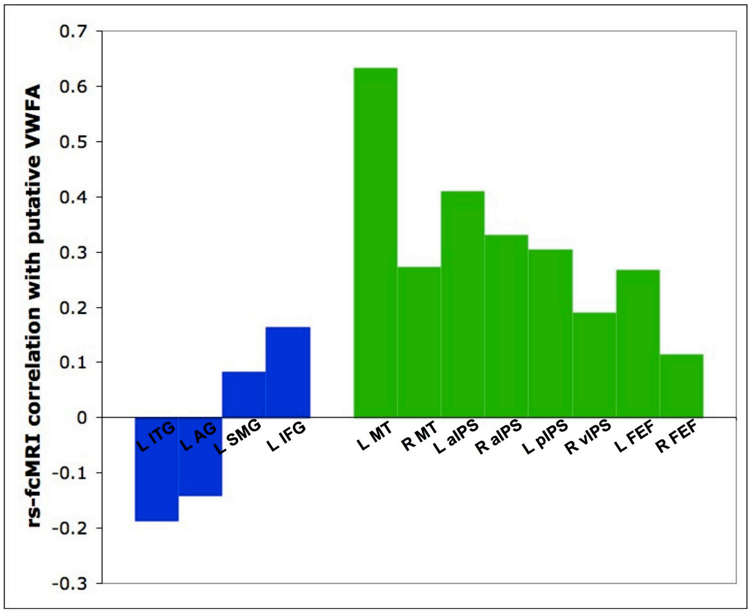


Figure 3.4. Comparison of putative VWFA relationships with reading-related and dorsal attention regions.

The correlations between the putative VWFA and reading-related regions in blue and dorsal attention regions in green. rs-fcMRI correlations to the dorsal attention regions are significantly stronger than correlations to the reading regions ($p < 0.00001$) when calculated as group averages. The statistical difference remains even when the bilateral MT+ regions are removed ($p < 0.00001$).

Correlations between the putative VWFA and dorsal attention network regions do not generalize to all fusiform regions.

To test whether the relationship between the putative VWFA and the dorsal attention network is a specific relationship or a general property of fusiform processing regions, we made seed maps showing all voxels significantly correlated with the rs-fcMRI timecourse of 2 other purportedly specialized fusiform regions- the right fusiform face area (FFA) and the left extrastriate body area (EBA). These seed maps were then directly compared with the putative VWFA seed maps (Figure 3.5).

A seed placed on the putative right FFA shows some correlations with the right parietal dorsal attention network in adults (top panel Figure 3.5A). However, directly comparing the seed maps for the putative VWFA and putative FFA with a paired t-test of each voxel shows significantly stronger correlations between the putative VWFA and dorsal attention regions than between the putative FFA and dorsal attention regions (warm colors in bottom panel of Figure 3.5A).

A seed placed on the putative left extrastriate body area (EBA) also shows some correlation with the dorsal attention network in adults (top panel Figure 3.5B). However, a t-test of the putative VWFA and putative EBA seed maps showed putative VWFA to be significantly more correlated to the dorsal attention regions than is the EBA (warm colors in bottom panel of Figure 3.5B).

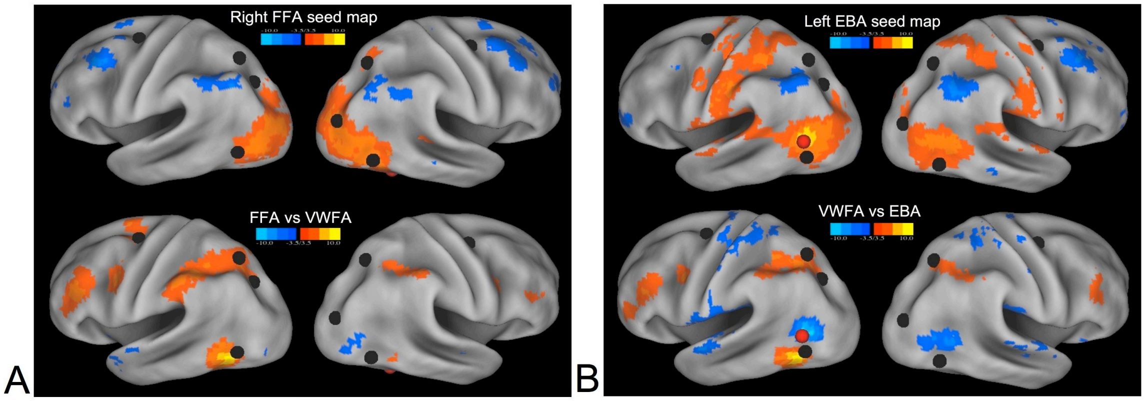


Figure 3.5. Specificity of rs-fcMRI correlations between the putative VWFA and dorsal attention network regions

A. Top panel shows the seed map of voxels significantly correlated (Z ≤ -3.5 or Z ≥ 3.5) with the right FFA rs-fcMRI timecourse in 23 adults. Bottom panel shows all voxels significantly different between the putative VWFA and FFA seed maps. Positive Z-scores (in warm colors) indicate those voxels with significantly stronger correlations with the putative VWFA; Negative Z-scores (in cool colors) indicate those voxels with significantly stronger correlations with the FFA. Both are overlaid with locations of dorsal attention network regions in black and the location of the FFA seed in red

B. Top panel shows the seed map of voxels significantly correlated ($Z \leq -3.5$ or $Z \geq 3.5$) with the left EBA rs-fcMRI timecourse in 23 adults. Bottom panel shows all voxels significantly different between the putative VWFA and EBA seed maps. Positive Z-scores (in warm colors) indicate those voxels with significantly stronger correlations with the putative VWFA; Negative Z-scores (in cool colors) indicate those voxels with significantly stronger correlations with the left EBA. Both are overlaid with locations of dorsal attention network regions in black and the location of the EBA seed in red.

Correlations between the putative VWFA and dorsal attention network may develop with age.

A seed map was also constructed for the putative VWFA in 22 children (age 7-9 years). The child putative VWFA seed map shows some overlap with the dorsal attention network (top panel, Figure 3.6). However, a direct comparison of the children and adults via a paired t-test of the two seed maps shows that adults have significantly stronger correlations between the putative VWFA and dorsal attention regions than children (bottom panel, Figure 3.6). Directly comparing the correlation values between the VWFA and each of the dorsal attention regions individually shows significant differences ($p < 0.05$) between correlations with the left and right FEF, left aIPS, and right aIPS regions. When a movement matched group of children and adults was used, only the age related differences in putative VWFA to left FEF correlations remained significant ($p = 0.023$), though the mean correlation value was still qualitatively increased in adults relative to children in the remaining regions and the VWFA/left aIPS correlation difference approached trend level ($p = 0.15$).

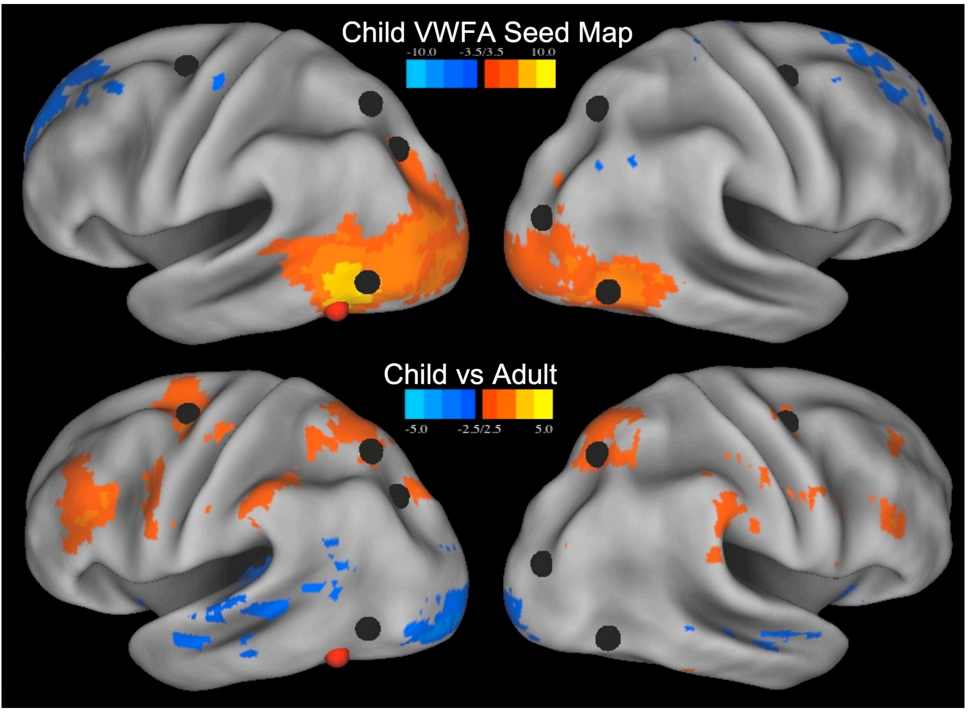


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Figure 3.6. Developmental differences in putative VWFA rs-fcMRI correlations

Top panel shows the seed map of all voxels correlated with the putative VWFA in 22 children (7-9 years old) with Z ≤ -3.5 and Z ≥ 3.5. Bottom panel shows the difference map of all voxels with a significant difference (Z ≤ -2.5 or Z ≥ 2.5, p < 0.01) in VWFA correlations between children (n = 22) and adults (n = 23). Correlations stronger in adults are shown in warm colors and those stronger in children in cool colors. The locations of the dorsal attention network regions are shown in black and the location of the putative VWFA seed in red.

The rs-fcMRI relationships between the VWFA and aIPS regions of the dorsal attention network are correlated with reading level.

Correlations between standard reading age and the correlations between the VWFA and dorsal attention regions were calculated across the combined group of children and adults. Only the putative VWFA to left and right aIPS correlations were significantly correlated with reading age in this combined group (Figure 3.7). The correlations between standardized reading age and left VWFA and left and right IPS across the age groups were 0.462 (p= 0.001) and 0.542 (p<

0.0001), respectively. When chronological age and movement were controlled for using partial correlations, these correlations were r= 0.185 (p= 0.234) for the VWFA/left aIPS correlation and r= 0.340 (p= 0.026) for the VWFA/right aIPS correlation.

Given the narrow range of adult reading ages, we repeated the above-described correlation analysis in the child only group. For children, only the putative VWFA/left and right aIPS correlations were significantly correlated with reading age. When the correlation between left VWFA and left aIPS was correlated directly with the reading age, a trend-level significance was obtained (r = 0.383, p = 0.079). When age and movement were controlled for in a partial correlation, the correlation between the VWFA/left aIPS correlation and reading age was 0.431 (p = 0.057). Similarly, when the putative VWFA/right aIPS correlation was directly correlated with reading age, the pearson's r was 0.460 (p= 0.031), and when age and movement were controlled for in a partial correlation the r was 0.526 (p= 0.017).

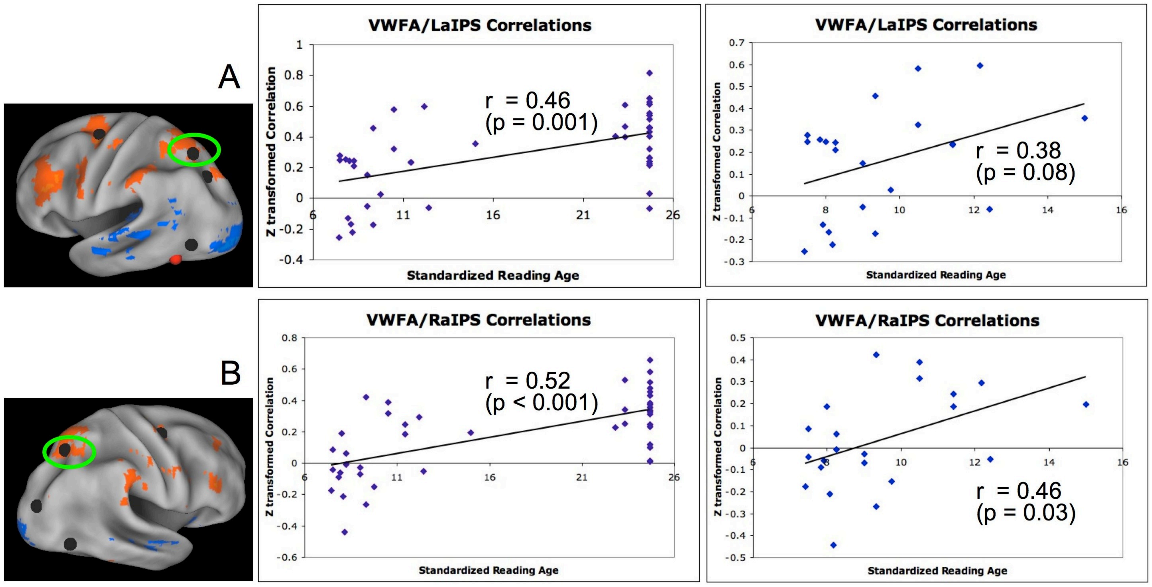


Figure 3.7. Relationship between reading age and putative VWFA functional correlations

A. Relationships between reading age and putative VWFA to left aIPS rs-fcMRI correlations. The location of the left aIPS region is shown on the left, the plot of all subjects (n = 23 adults and 22 children) and the line of best fit is shown in the middle panel and the plot of child subjects only with the line of best fit is shown on the right. Note that when a partial correlation controlling for *chronological age and movement is performed the correlation for the combined child/adult group drops to r= 0.19 (p = 0.23), but the correlation for the child only group increases to r= 0.43 (p= 0.06).*

B. Relationships between reading age and putative VWFA to right aIPS rs-fcMRI correlations. The location of the right aIPS region is shown on the left, the plot of all subjects (n = 23 adults and 22 children) and the line of best fit is shown in the middle panel and the plot of child subjects only with the line of best fit is shown on the right. Note that when a partial correlation controlling for chronological age and movement is performed the correlation for the combined child/adult group drops to r= 0.14 (p = 0.03), but the correlation for the child only group increases to r= 0.53 (p= 0.02).

Discussion

We have demonstrated that the putative visual word form area has resting state functional correlations with regions in the dorsal attention network (left and right aIPS, MT+, and FEF regions) and not predominantly with reading-related regions (left SMG, AG, and ITG regions). These putative VWFA to dorsal attention correlations are not a general property of all regions in the fusiform cortex or even of all specialized visual processing regions; neither the right FFA nor the left EBA (despite the latter's close proximity to left MT+) shows more significant connectivity with dorsal attention regions than that shown by the putative VWFA. The rs-fcMRI correlations between putative VWFA and some regions of the dorsal attention network appear to increase with age, and correlations between the putative VWFA and bilateral aIPS regions of the dorsal attention network also increase with reading age. Together, these results point to a role for the putative VWFA in processing visual stimuli in general, presumably a role shaped by its relationship with regions of dorsal attention network. Thus while the VWFA may be considered an important region for reading, the data clearly refute the notion that the processing of words is its preferred functional ascription.

The putative VWFA is not preferentially connected to reading-related regions

The seed map of regions showing voxels with rs-fcMRI timecourses significantly correlated to the putative VWFA does not overlap significantly with regions thought to be important specifically for reading, including left supramarginal gyrus (SMG), left angular gyrus (AG), and left inferior temporal gyrus (ITG) (Binder JR et al., 2009; Jobard G et al., 2003; Vigneau M et al., 2006). The putative VWFA seed map did contain a left middle frontal gyrus (MFG) region close to, but not overlapping the left IFG region identified in the reading meta-analysis performed in our laboratory (Vogel AC et al., 2009; Vogel AC et al., 2007). However, the identified left MFG region is even further from left IFG pars opercularis regions identified in other, previously published meta-analyses (Fiez J and S Petersen, 1998; Jobard G et al., 2003). Moreover, there are no correlations with regions in mouth sensorimotor or auditory cortices, which might be expected if the putative VWFA was commonly activated during reading aloud.

While this set of findings seems to rule out a strongly preferential role for the putative VWFA in reading, it does not at all rule out the possibility that the VWFA contributes to reading. rs-fcMRI correlations seem to reflect a history of co-activation (Dosenbach NUF et al., 2006; Fair DA, NUF Dosenbach et al., 2007; Lewis CM et al., 2009; Stevens WD et al., 2010; Tambini A et al., 2010). In our seed map analyses, we are potentially seeing the outcome of the strongest and most consistent of those co-activations. If the putative VWFA was sometimes activated with reading-related regions but oftentimes activated with other regions, the history of co-activation and thus "connection" strengths, would be spread among the region sets, minimizing the correlations between the putative VWFA and each individual region with which it is sometimes activated.

Rather, we show the putative VWFA has some of its strongest functional correlations with regions of the dorsal attention network, thought to be involved in spatial attention (Corbetta M and G Shulman, 2002). These functional correlations indicate that the processing done in the putative VWFA is likely somehow related to spatial attention. While we do not believe the VWFA is exclusively or even predominantly involved in reading, for the remainder of this discussion we will frame the significance of the functional connections between the putative VWFA and the dorsal attention network in the context of letter and word processing. While the same relationships could apply to other sets of visual stimuli, we feel using letters and words as examples will be most illuminating given the long history of studying the VWFA in reading, its likely involvement in reading at some level, and the ease of describing these effects on words, which are a well-defined type of visual stimulus.

Properties of the dorsal attention system

Previous studies have shown the dorsal attention network is involved in overt (Connolly JD et al., 2000; Petit L et al., 1997) and covert (Fairhall SL et al., 2009; Gitelman DR et al., 1999; Sylvester CM et al., 2007) spatial attention and orienting. These regions show increased activity in both the cue and preparatory period of cued spatial and feature-based attention tasks (see Corbetta M and G Shulman, 2002 for a review) and visual search tasks (Egner T et al., 2008; Fairhall SL et al., 2009; Leonards U et al., 2000). Concomitant with these dorsal attention responses, there are changes in BOLD activity in visual regions representing the attended spatial location (Sylvester CM et al., 2007) and suppression of BOLD activity in regions outside the attended spatial location (Sylvester CM et al., 2008). It is thought that the posterior parietal regions of the dorsal attention system are related to posterior parietal cortex regions in macaque, which contain cells responsive to spatial and feature attention cues that also modulate activity in visual processing regions like MT+ (Saalmann YB et al., 2007). Therefore, it has been hypothesized that the dorsal attention network plays a role in visual attention by amplifying the “lower level” visual responses to specific spatial locations and features and dampening the responses to locations and features outside of the attentional window (Corbetta M and G Shulman, 2002).

Role of the dorsal attention system in reading

As described in the introduction, we argue the putative VWFA “groups” letters (and other visual items) into appropriately sized chunks. This capacity for “chunking” results in preferentially strong functional connections with regions that direct attention to the appropriate “chunk” of features or spatial location. At the same time, if regions in the dorsal attention network direct attention to the appropriate spatial group, their activity should also be modulated by properties that affect letter “chunking”. As mentioned in the introduction, compared to reading words reading pseudowords requires processing letters in smaller “chunks” and so should require more changes in spatial attention. In fact, the bilateral aIPS regions of the dorsal attention network do show more activity for reading pseudowords than for reading words (Church JA, DA Balota et al., 2010). Furthermore, aIPS regions show a length effect, whereby longer words and nonwords, which should require more attention shifts, show more activity than shorter words and nonwords (Church JA, DA Balota et al., 2010; Schurz M et al., 2010).

Additionally, any manipulation that presents words in a format that decreases the ability of the visual system to “chunk” the letters or requires more shifts of spatial attention should increase parietal activity. Words presented in unusual formats of many kinds – including mixed-case stimuli (Mayall K et al., 2001), rotated words, words with many spaces between the letters, words presented to the left of fixation (Cohen L et al., 2008), and vertically presented words (Rosazza C et al., 2009) – have all been shown to increase lateral parietal activity. Pammer et al. (2006) uses MEG to determine the timecourse of activity for reading shifted-case stimuli (where every other letter is presented superior to the normal line of text), and report that there is mutual feedback between the parietal and fusiform regions when words are presented in this unique form. Moreover, while all of the manipulations described here increase the response time to read words, increased parietal activity was not seen when subject performed the same tasks on words with low visual contrast, even though the response time to process these stimuli was just as long as the mixed case stimuli (Mayall K et al., 2001).

Directed attention is not only important for reading single words; it is perhaps even more important for reading connected text. Data from eye-movement studies indicate that fluent reading is associated with a particular pattern of eye movements, whereby subjects land consistently to the left of center in a word and have generally one or fewer eye movements per word (see Rayner K, 1998 for a review). The dorsal attention network has been implicated in directing eye movements (Connolly JD et al., 2000; Petit L et al., 1997) and Lee and Newman (2010) recently found increased activity in inferior and superior parietal lobule regions during whole sentence presentation, which requires directed eye movements, relative to rapid serial visual presentation, in which words are presented one at a time.

Developmental changes in putative VWFA to dorsal attention system connectivity

Developmental changes have been reported for both within-word letter processing and the reading of connected text. Children rely more on making orthographic to phonological conversions of individual word "chunks" than adults. Unlike adults, children show response times to read words that are dependent on word length (Bijeljac-babic R et al., 2004; Defior S et al., 1996; Martens VEG and PF de Jong, 2008). Additionally, children are significantly slower to read words with irregular orthographic to phonologic conversions than words with regular mapping, a reflection of their increased use of assembled phonology (Backman J et al., 1984; Sandak R et al., 2004). Children also have shorter saccades and longer fixations, indicative of less fluent eye movements, when reading connected text (Rayner K, 1998). These effects could indicate a less efficient relationship between the putative VWFA and the dorsal attention system in early as compared to skilled readers. We see the development of this relationship, at least partially, in both the age-related increases in correlations between the putative VWFA and some dorsal attention regions and the reading-related increases in correlations between the putative VWFA and bilateral aIPS regions.

However, there were limitations in our ability to see developmental differences related to age or reading level in this study. First, the children in this study are already relatively good readers (average reading age 9.5 years), which restricts our ability to see the earliest developmental effects. Additionally, we have no direct measure of either process we purport to ascribe to the VWFA to dorsal attention relationship. We do not know to what extent the children are still reading with a phonological strategy, converting graphemes into phonemes rather than processing words as a whole. We also have no measure of connected text reading fluency. Standardized reading age can act as a surrogate of both, as both improve with increased reading ability, but further studies should be done to determine whether either of these measures relates to putative VWFA/dorsal attention network correlations specifically.

Dorsal attention system processing and dyslexia

Dyslexia – or reading deficits that result in a reading level that is significantly reduced relative to IQ despite access to the opportunity to learn to read – has generally been thought of as a phonological processing deficit (see Shaywitz SE, 1998 for a review). However, there is increasing evidence that deficits in visual attention may also play a role in dyslexia (see Valdois S et al., 2004 and Vidyasagar TR and K Pammer, 2010 for reviews). Dyslexic children show impairments in matching symbol strings, a visual processing task that requires no lexical processing but does require processing spatial relationships (Pammer K et al., 2004). Dyslexic children with and without obvious phonological impairments also show deficits in simultaneous processing of consonant strings (Lassus-Sangosse D et al., 2008). More specific attentional deficits are seen in impairments in exogenous orienting tasks exhibited by a subset of dyslexic children (Facoetti A et al., 2010). However, the relationship between dyslexia and visual processing or attention is a matter of debate at present (i.e.Shovman MM and M Ahissar, 2006; Ziegler JC et al., 2010). The results presented here indicate a role for the dorsal attention system in visual specialization of the type used in fluent reading, and interrogating the putative VWFA/dorsal attention correlations in dyslexic subjects may shed light on whether visual attention impairments are contributing to some subjects' disordered reading.

Summary and Conclusions

This study demonstrates relatively weak rs-fcMRI relationships between the putative visual word form area, thought to be involved in visual processing of words and letters, and regions thought to be integral to reading, including the left supramarginal gyrus and angular gyrus and potentially the left inferior frontal gyrus. In contrast, we observed strong rs-fcMRI correlations between the putative VWFA and regions in the dorsal attention network. This pattern of functional connectivity indicates the putative VWFA is not predominantly used in reading, but instead, is likely to be a more general-use visual region that is able to process stimuli in "groups". The relationship between the putative VWFA and the dorsal attention network may be related to this ability of the putative VWFA to group stimuli, which, in turn, may be used to parse visual stimuli, like words, into appropriate visual components and interact with dorsal attention networks to direct eye movement to the appropriate spatial locations. Just as these skills develop with age and reading level, we see increased correlations between the putative VWFA and parts of the dorsal attention system with increases in age and reading level.

CHAPTER 4: RS-FCMRI DEFINED NETWORK STRUCTURE OF READING-RELATED REGIONS IN CHILDREN AND ADULTS

Introduction

Reading, as with many advanced human behaviors, is a complicated skill requiring a network of neural regions. Several meta-analyses (Fiez J and S Petersen, 1998; Jobard G et al., 2003; Turkeltaub PE et al., 2003; Vigneau M et al., 2006) of functional MRI (fMRI) neuroimaging studies have attempted to define regional components of a reading network. Together these meta-analyses have described a group of brain regions consistently used in single word reading tasks. One such region, the visual word form area (VWFA, Cohen L and S Dehaene, 2004) is in the fusiform cortex near the occipital-temporal border. The VWFA sometimes shows more activity for words than consonant strings (McCandliss BD et al., 2003; Vinckier F et al., 2007) and digits (Polk TA et al., 2002), though its specificity for processing words (and nonwords) is debated (Price CJ and JT Devlin, 2003). The meta-analyses have also identified regions in the supramarginal gyrus (SMG) and angular gyrus (AG) as important for reading. Other studies have implicated the SMG in phonological processing (Church JA, DA Balota et al., 2010; Church JA et al., 2008; Graves WW et al., 2010) and the AG in semantic processing (Chou TL et al., 2006; Graves WW et al., 2010). Finally, regions in the inferior frontal gyrus (IFG), most commonly localized to the pars opercularis, have been identified as important in phonological processing (Fiez J et al., 1999; Gitelman DR et al., 2005; Mechelli A et al., 2003; Pugh KR et al., 1996).

Yet reading is an ontologically and phylogenetically new trait and is still not universal. Thus, while functional neuroimaging studies have converged on a general set of neural regions used during reading, it is unclear whether these regions are dedicated to reading in particular or perform more general functions that, while particularly useful for reading, are not restricted to reading. If these regions are dedicated specifically to reading, they should compose a distinct network. However, if these regions perform some more general function, they may or may not have specific relationships to one another, depending on their general processing properties.

Here, we will adjudicate between these two hypotheses by determining the network structure of reading-related regions.

A large, distributed group of regions is used in single word reading.

In order to determine the network structure of reading-related regions we must first define what constitutes a reading-related region, a particularly important step in network analyses (Power JD et al., 2010). The aforementioned meta-analyses focused on regions identified by comparing reading to another task in an attempt to remove more “task general” processing. When the data are analyzed to identify all regions showing reading-related activity different from a baseline estimate or rest condition, many more regions are identified (Binder JR et al., 2005; Brown TT et al., 2005; Church JA, DA Balota et al., 2010; Graves WW et al., 2010). This abundance of neural activity reflects the use of visual, phonologic and semantic processing, articulatory and motor output processing, spatial processing to appropriately direct visual attention, task control processing to instantiate and maintain the reading task set, evaluate performance, and many other functions, all essential for fluent reading though not specific for it. As we are interested in the network structure of all regions used in the conversion of written, visual input into spoken output we have performed a meta-analysis of five single word reading studies (some previously published in Church JA, DA Balota et al., 2010; Palmer ED et al., 2004) and included all regions with significant BOLD activity in a majority of the studies in our analysis.

Additionally, while we are interested in the network structure of reading-related regions in adults, this organization likely undergoes developmental changes. Acquiring fluent reading requires considerable instruction and experience (see Schlaggar BL and BD McCandliss, 2007 for a review). Also, children show different functional activity for reading than adults in both ERP (Maurer U et al., 2005; Tarkiainen A et al., 1999) and fMRI studies (Booth JR et al., 2004; Brown TT et al., 2005; Church JA et al., 2008; Puce A et al., 1996; Schlaggar BL et al., 2002). Therefore, studying the network structure across development may give additional insight into the organization of reading-related regions and possible age or skill-related increases in skill specificity. However, studying the developing network structure requires a set of regions used for single word reading in both children and adults. Thus we added regions showing differential BOLD activity between children and adults in a task activation based fMRI study (Church JA et al., 2008) to our meta-analytic reading set.

rs-fcMRI allows for large scale network definition.

Resting state functional connectivity (rs-fcMRI) provides a way to define functional relationships between regions in the broader “reading network”. rs-fcMRI uses correlations in low frequency (approximately 0.01-0.1 Hz) blood oxygen dependent (BOLD) signal fluctuations to define relationships between regions. Regions that seem to be functionally related (i.e. often activate in the same tasks) have significantly correlated rs-fcMRI timecourses (Biswal B et al., 1995; Fox MD et al., 2005), and the presence of these correlations is thought to reflect the history of co-activation between the regions (Dosenbach NUF et al., 2007; Fair DA et al., 2009), that is somewhat malleable by short term experience (Lewis CM et al., 2009; Stevens MC et al., 2009; Tambini A et al., 2010). rs-fcMRI correlations have been used to study the interregional relationships of the default mode network (Fox MD et al., 2005; Greicius M et al., 2003), task control networks (Dosenbach NUF et al., 2007; Seeley WW et al., 2007), and attentional networks (Fox MD et al., 2006).

rs-fcMRI has recently been used to study the functional relationships of a limited number of reading-related regions. Koyama and colleagues determined the relationship between the small set of reading regions described above (VWFA, SMG/AG, IFG) as well as a few other regions of interest (ROIs) (Koyama MS et al., 2010). Hampson and colleagues used rs-fcMRI to study the relationship of IFG connectivity to reading ability (Hampson M et al., 2006). Yet neither of these studies has utilized the capability of rs-fcMRI to perform a true network analysis of a large numbers of regions (see Power JD et al., 2010 and Vogel AC et al., in press for reviews).

Here we utilize graph theoretic techniques and rs-fcMRI defined connections to study the large-scale network organization of all reading-related regions defined in our meta-analytic and developmental studies. Graph theory is a field of mathematics devoted to studying the structure of networks. Networks are collections of individual components (nodes) with relations between them (edges) (Sporns O et al., 2004). Here, the nodes are the meta-analytic and developmental reading-regions and the edges are the correlations in rs-fcMRI timecourses between each pair of these regions. We utilize two graph theoretic community detection methods, modularity optimization (Newman ME and M Girvan, 2004) and Infomap (Rosvall M and CT Bergstrom, 2008), to characterize the grouping of these reading-related regions based on the pattern of edges, or rs-fcMRI correlations, between the nodes, or regions. Again, if reading-related regions are dedicated to reading specifically these methods should find that these regions form a network, possibly a network that arises through development. However, if reading utilizes regions with a more general processing function, these methods are unlikely to detect such a network.

Methods

Definition of Regions

Reading-related regions were defined in two ways: a meta-analysis of studies in which adults read single words aloud and a single developmental study of reading single words aloud. By using both types of regions we were able to utilize well-characterized adult regions and regions showing developmental changes, which are likely important in considering the developmental trajectory of reading networks.

<u>Meta-analysis of adult reading-related regions</u>

The meta-analysis included 5 studies, briefly described in Table 4.1. In each of these studies typical adult readers spoke aloud a single word or pseudoword presented in the center of a screen. Several of these studies manipulated other lexical variables: 3 of the 5 studies manipulated frequency (the rate at which words appear in written English), 2 manipulated lexicality (whether the stimulus is a word or pseudoword), and 2 manipulated consistency (whether a word’s sounds correspond directly to its letter groups). All studies had an event related design and were performed in a 1.5 Tesla MAGNETOM Siemens Vision system (Erlanger, Germany).

Study Number	Stimuli	Effects obtained	Subject number
1	Verbs	ME	16
2	Words and Pseudowords	ME Lexicality Consistency	24
3	Words and Pseudowords	ME Lexicality Frequency	24
4	Words	ME Consistency Frequency	24
5	High frequency words	ME	28

Table 4.1. Description of studies included in the adult single word reading meta-analysis

A set of conjunction analyses was performed on the 5 reading studies. First, images were created for each study of only voxels with a Z-score greater than 7 for the ME. The 5 main effect images were summed and masked to include only voxels with activity in at least 4 of the 5 studies. A peak finding algorithm was run on this image to find the coordinates of highly consistent activations between the studies, while ensuring that peak coordinates were separated by at least 10 mm.

Regions showing an effect of any lexical manipulation were defined using a similar conjunction analysis approach. For example, voxels with a frequency by time interaction Z-score greater than 2 were calculated for each study manipulating frequency. These images were summed and masked for only voxels showing an effect in at least 2 of the 3 studies manipulating frequency and a peak-finding algorithm run on this image. The effect of lexicality and consistency were calculated similarly, with a required variable by time interaction Z-score greater than 2 and interactions in both of the studies manipulating each variable. However, all regions defined using lexical manipulations were compared to those showing a ME, and any regions closer than 10 mm were discarded in favor of the main effect region.

All regions were visualized on the average anatomy of the 2 groups of 30 subjects used in the resting-state functional connectivity analysis described below. A small number of regions that fell clearly in the white matter, ventricles, outside the brain or along the tentorium (as defined by either visual inspection or individual resting-state seed maps) were discarded.

Developmental reading-related regions

Regions were also obtained from a single study of reading development. In this study (characterized more extensively in Church JA et al., 2008), typical child and adult subjects were asked to read aloud single words (along with several other lexical manipulations that will not be addressed here). The analysis comprises a group of 24 adults (19-35 years old) and 24 children (7-10 years old), matched on accuracy and response time. Regions were defined as those with an age by time interaction Z-score ≥ 3.5. All developmental regions were visualized on the average anatomy described above and the small number of those lying in white matter, ventricles, or tentorium discarded. All remaining regions were compared to the meta-analytic regions and any regions within 10 mm were discarded in favor of the meta-analytic region.

Resting State Functional Connectivity Pre-processing

Subjects

Resting state subjects consisted of 2 groups of 30 subjects. These groups included 30 children age 7-10 years (average age 9.0 years) and 30 adults 21-29 years (average age 24.8 years). All subjects were recruited from Washington University and the surrounding community. All filled out questionnaires indicating no history of neurologic or psychiatric diagnosis or drug abuse. All subjects gave informed consent in accordance with the guidelines and approval of the Washington University Human Studies Research Committee. The groups were matched for movement and the amount of data collected, detailed in Table 4.2. All but 1 child and 15 of the 30 adults were tested for full scale IQ using the 2 subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler D, 1999); data from the tested subjects are included in Table 4.2.

Subject Group	Age (years)		IQ		Minutes of data collection		Movement (mm rms)	
	Avg	**Std Dev**	**Avg**	**Std Dev**	**Avg**	**Std Dev**	**Avg**	**Std Dev**
Children	9.0	1.26	118	15.3	11.22	3.48	0.412	0.192
Adults	24.8	2.04	124	14.8	12.66	3.30	0.389	0.105

Table 4.2. Subject characteristics

Child and adult groups do not differ statistically using a 2-tailed t-test in any of the listed variables (age, IQ, data collected, or movement). Note only 29 of the 30 children and 15 of the 30 adults were tested for IQ.

Data-acquisition and pre-processing

Each subject performed 1-4 functional resting runs, composed of 132 or 133 continuous frames with a 2.5 second TR (child and adult groups were matched for the amount of data collected, see Table 4.2). During the scans subjects looked at a black screen with a white central fixation cross. The subjects were instructed to look at the crosshair and relax but remain still. All subjects were fitted with a thermoplastic mask to facilitate their ability to remain still.

A Siemens 3T Trio scanner (Erlanger, Germany) with a 12-channel Siemens Matrix head coil was used to collect all functional and anatomical scans. A single high-resolution structural scan was acquired using a sagittal magnetization-prepared rapid gradient echo (MP-RAGE) sequence (slice time echo= 3.08 ms, TR= 2.4 s, inversion time= 1 s, flip angle= 8 degrees, 176 slices, 1 x 1 x 1 mm voxels). All functional runs were acquired parallel to the anterior-posterior commissure plane using an asymmetric spin-echo echo-planar pulse sequence (TR= 2.5 s, T2* evolution time 27 msec, flip angle 90 degrees). Complete brain coverage was achieved by collecting 32 contiguous interleaved 4mm axial slices (4 x 4 mm in-plane resolution).

Preliminary image processing included removal of a single pixel spike caused by signal offset, whole brain normalization of signal intensity across frames, movement correction within and across runs, and slice by slice normalization to correct for differences in signal intensity due to collecting interleaved slices. For detailed description see Miezin FM et al., 2000.

After preprocessing, data was transformed into a common stereotactic space based on Talairach and Tournoux (1988) using an in-house atlas composed of the average anatomy of 12 healthy young adults ages 21-29 years old and 12 healthy children ages 7-8 years old (see (Brown TT et al., 2005; Lancaster JL et al., 1995; Snyder AZ, 1996 for methods). As part of the atlas transformation the data were resampled isotropically at 3 mm x 3 mm x 3 mm. Registration was accomplished via a 12-parameter affine warping of each individual's MP-RAGE to the atlas target using difference image variance minimization as the objective function. The atlas-transformed images were checked against a reference average to ensure appropriate registration.

Several additional steps (also described in Fair DA, NUF Dosenbach et al., 2007; Fox MD et al., 2005; Fox MD et al., 2009) were taken in processing the rs-fcMRI data in an attempt to reduce the likelihood that the relationships between regions were due to sources such as heart rate or respiration. To mitigate such effects the data were band-pass filtered for frequencies between 0.009 Hz and 0.08 Hz and spatially smoothed (6 mm full width, half max). Additionally, we performed motion correction by regression of the six parameters obtained from the rigid body head motion correction, regression of the signal derived from averaging across the whole brain, regression of signal from ventricular regions of interest (ROIs), and signal from white matter ROIs. Care was taken to match the two groups for movement.

<u>Extraction of resting state timecourses and generation of correlation matrices</u>

A resting state timecourse was extracted for a 10 mm sphere centered on each of the 77 coordinates defined in the meta-analysis and developmental reading-region sections above. These timecourses were extracted separately in each of the 60 subjects described above. For each of the 60 subjects the correlation (r) between the timecourse of each region and every other region was calculated, yielding a 77 x 77 correlation matrix. These individual matrices were then averaged in the two groups of 30 subjects described above. A general overview of the resting state methods used here is shown in Figure 4.1.

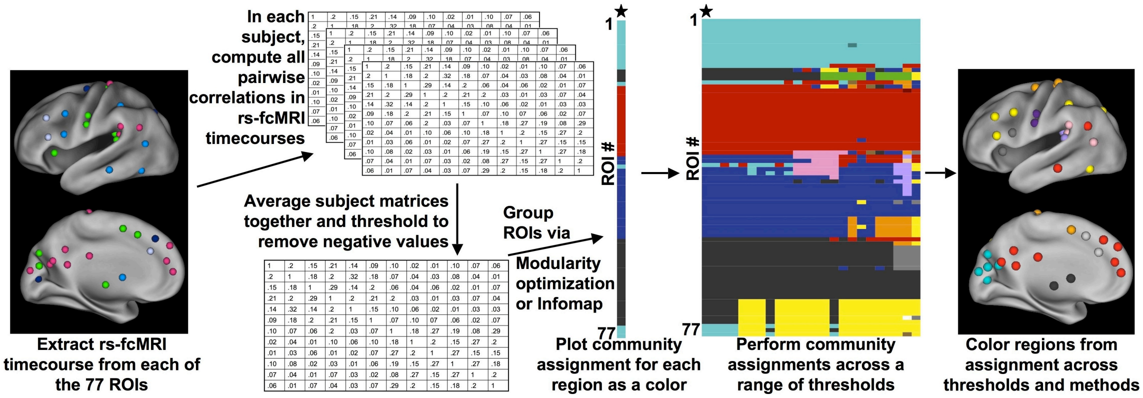


Figure 4.1. rs-fcMRI methods

Results will be shown as in the last two panels- a color chart with the ROIs presented as rows on the y-axis and the community assignment across thresholds on the x-axis for each method and a plot of the location of regions colored by community assignment on the brain.

Use of graph theoretic techniques in defining network structure

Graph theoretic techniques have been developed to describe the relationship between large numbers of nodes in networks, making them ideal to study the organization of networks of brain regions. In this section, nodes will refer to the 77 regions in the reading network described above. Edges will refer to rs-fcMRI correlations between those regions. A connection, or edge, occurs between two nodes, or regions, if the average correlation coefficient (r) between those regions is greater than the given threshold (i.e. if the threshold under analysis is $r = 0.10$, all region pairs with an $r \geq 0.10$ are considered to have an edge between them). All edges present above the given threshold are then weighted by their correlation coefficient.

Modularity optimization analysis

Communities of reading-related regions were detected using modularity optimization, a graph analysis method described in Newman ME, 2006). This method optimizes the value Q, also called modularity, and refers to the number of observed edges within communities in the given grouping relative to the number of expected edges predicted to be within communities in a random graph with an equal number of nodes and edges. Any grouping which has more observed edges than expected in a random graph will have a positive Q, and the modularity optimization algorithm attempts to maximize the value of Q. For a detailed description of the algorithm used see Fair DA et al., 2009 and Newman ME, 2006.

Modularity optimization was performed on the reading network in both age groups at all thresholds which passed two criteria: (1) the resulting communities showed a $Q > 0.4$ (Fortunato S, 2010), (2) the network was at least 80% connected. In a network that is 80% connected, there is a path by which 80% of the nodes can reach all other nodes. It is important to have such a highly interconnected network when starting modularity optimization to ensure that communities are not defined by artificial breaks caused by a few regions having no connections to the rest of the network. Final community assignment for each age group was made after visually inspecting the communities across the range of thresholds, and the whole range is presented below (as depicted in Figure 4.1 and shown in Figures 4.3 and 4.4).

Bootstrapping validation of modularity optimization assignments

To validate our community assignments a set of permutation type tests were performed on the 77 x 77 correlation matrix. For both children and adults, 25 of the 30 subjects were randomly drawn to make a new group, and this random draw was repeated 100 times. For each randomly drawn group modularity optimization was performed. In each of these permutations each node was compared to each other node to determine whether they were assigned to the same community. These “similarity assignment” counts were then entered into another 77 x 77 matrix, in which each cell contained the proportion of times in the 100 permutations the two nodes were assigned to the same community. Thus a high value means two nodes are often in the same community, and a low value means that they were rarely placed in the same community. Modularity optimization was then run on this matrix, only this time the edges were defined by the proportion of times the nodes were co-localized.

Modularity assignment using Infomap

Two general ways to group nodes into modules include maximizing the Q, as done in modularity optimization, and by minimizing the amount of information needed to describe a random walk through the graph, as done in Infomap (Rosvall M and CT Bergstrom, 2008). Infomap divides the network by calculating the amount of time the walker spends within a module versus the amount of time spent traveling between modules. Thus, it provides a second method for analyzing the network structure of our regions using an entirely different set of calculations that minimizes a different graph theoretic characteristic. Infomap was performed across the same range of thresholds used in modularity optimization in each age group.

Results

Meta-analysis and developmental studies find a large group of reading-related regions.

Combining the adult meta-analytic regions and the developmental reading regions resulted in 77 regions that were distributed across the brain (Table 4.3, Figure 4.2). Forty-nine regions were obtained from the adult meta-analysis: 25 from the main effect of time (green in Figure 4.2), 15 defined as showing an effect of lexicality by time (blue in Figure 4.2), 6 showing an effect of spelling to sound consistency by time (navy in Figure 4.2), and 3 showing an effect of frequency by time (light gray in Figure 4.2). Twenty-eight regions were defined in the developmental study, all of which showed more activity in children relative to adults (pink in Figure 4.2). Again, by including all regions showing significant BOLD activity during single word reading we are including both regions involved in many non-reading tasks (such as occipital and motor regions) and regions commonly described as important for reading specifically, such as the putative visual word form area (VWFA), regions in the left supramarginal (SMG) and angular gyri

(AG), a region in the left superior temporal sulcus (STS), and a region in the left inferior frontal gyrus (IFG).

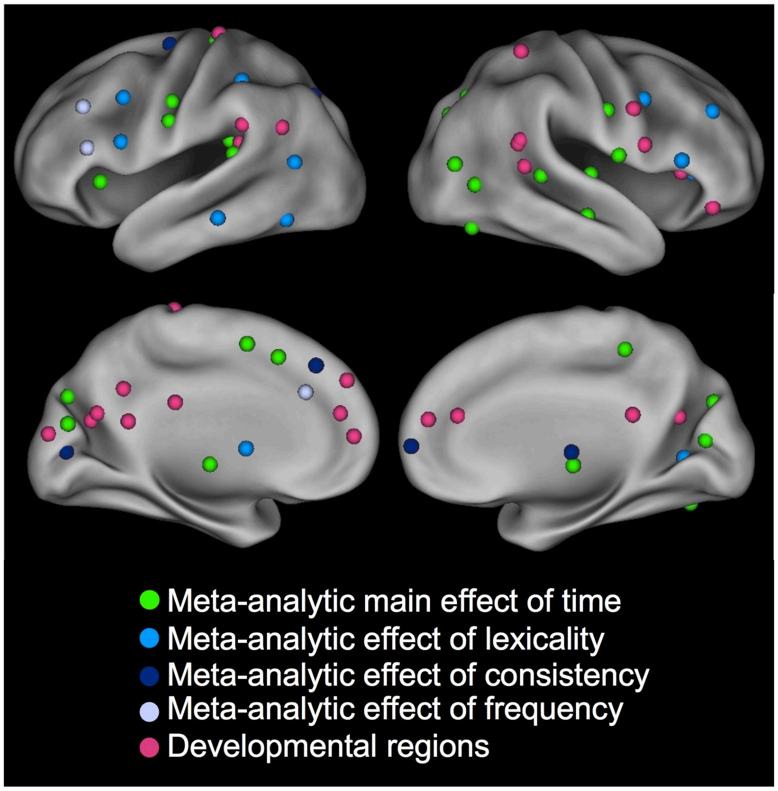


Figure 4.2. Reading-related regions

MNI Coord.			**Region Description**		**Community Definition**	
x	**y**	**z**	**Anatomic Location**	**Functional definition**	**Adults**	**Children**
-6	-92	6	Left medial occipital	DA	Visual	Visual
7	-74	10	Right medial occipital	ME	Visual	Visual
36	-73	12	Right mid occipital	ME	Visual	Visual
22	-73	28	Right medial occipito-parietal	ME	Visual	Visual

MNI Coord.			Region Description		Community Definition	
x	y	z	Anatomic Location	Functional definition	Adults	Children
-3	-81	14	Left medial occipital	ME	Visual	Visual
13	-78	23	Right medial occipito-parietal	ME	Visual	Visual
-18	-76	25	Left medial occipito-parietal	ME	Visual	Visual
16	-66	0	Right medial anterior occipital	ME	Visual	Visual
-8	-81	2	Left medial occipital	Consistency	Visual	Visual
41	-65	4	Right occipito-temporal	ME	Visual	Visual
34	-65	-9	Right occipito-temporal fusiform	ME	Visual	Visual
-17	-65	15	Left precuneus	DA	Visual	Default/Parietal
-20	-61	-32	Left cerebellum	Lexicality	Cerebellum	Cerebellum
12	-63	-18	Right cerebellum	ME	Cerebellum	Cerebellum
-16	65	-21	Left cerebellum	ME	Cerebellum	Cerebellum
8	-43	46	Right medial parietal	ME	Default	No assignment
-58	-34	-15	Left inferior temporal	Lexicality	Default	No assignment
42	28	-3	Right inferior frontal	DA	Default	No assignment
-2	24	44	Mesial superior frontal	Consistency	Default	Default/Frontal
-2	39	39	Mesial frontal	DA	Default	Default/Frontal
4	51	13	Right medial inferior frontal	Consistency	Default	Default/Frontal
7	40	25	Right anterior cingulate	DA	Default	Default/Frontal

MNI Coord.			Region Description		Community Definition	
x	y	z	Anatomic Location	Functional definition	Adults	Children
-9	32	24	Left anterior cingulate	DA	Default	Default/Frontal
-8	40	15	Left anterior cingulate	DA	Default	Default/Frontal
5	27	26	Right anterior cingulate	DA	Default	Default/Frontal
-11	-55	28	Left posterior cingulate	DA	Default	Default/Parietal
6	-48	22	Right posterior cingulate	DA	Default	Default/Parietal
-6	-54	16	Left posterior cingulate	DA	Default	Default/Parietal
10	-61	20	Right precuneus	DA	Default	Default/Parietal
-8	-36	25	Left mid cingulate	DA	Default	Default/Parietal
-7	-66	18	Left precuneus	DA	Default	Default/Parietal
-45	-58	22	Left angular gyrus	DA	Default	Temporal
49	-22	-6	Right middle temporal	DA	Default	Temporal
-38	-50	24	Left SMG gyrus	DA	Temporal	Temporal
-47	-63	9	Left superior temporal sulcus	Lexicality	Temporal	Temporal
39	-49	20	Right superior temporal	DA	Temporal	Temporal
49	-50	22	Right SMG gyrus	DA	Temporal	Temporal
38	-48	10	Right mid temporal	DA	Temporal	Temporal
46	-37	10	Right mid temporal	ME	Temporal	Temporal
-52	-45	26	Left SMG	DA	Temporal	Temporal

MNI Coord.			Region Description		Community Definition	
x	y	z	Anatomic Location	Functional definition	Adults	Children
-39	-39	15	Left anterior SMG gyrus	ME	Auditory Temporal	Auditory Temporal
-52	-41	11	Left ventral SMG gyrus	ME	Auditory Temporal	Auditory Temporal
52	-21	12	Right anterior temporal	ME	Auditory Temporal	Auditory Temporal
51	-13	19	Right posterior ventral frontal	ME	Motor	Motor
52	-2	38	Right premotor	DA	Motor	Motor
-46	-18	32	Left motor	ME	Motor	Motor
46	-14	33	Right motor	ME	Motor	Motor
-49	-15	24	Left motor	ME	Motor	Motor
-5	-7	49	Left supplementary motor area	ME	Superior Frontal & Parietal	dACC & SMA pair
30	-44	60	Right superior parietal	DA	Superior Frontal & Parietal	Superior Frontal & Parietal
-21	-18	53	Left superior frontal	ME	Superior Frontal & Parietal	Superior Frontal & Parietal
-20	-36	53	Left superior frontal	Consistency	Superior Frontal & Parietal	Superior Frontal & Parietal
-27	-35	63	Left superior parietal	DA	Superior Frontal & Parietal	Superior Frontal & Parietal
-8	17	31	Left medial frontal	Frequency	dACC & medial frontal	dACC & SMA pair

MNI Coord.			Region Description		Community Definition	
x	y	z	Anatomic Location	Functional definition	Adults	Children
-2	5	47	Dorsal anterior cingulate	ME	dACC & medial frontal	Cingulo-opercular
50	14	17	Right frontal operculum	Lexicality	Cingulo-opercular	Cingulo-opercular
-34	10	7	Left anterior insula/ frontal Operc.	Consistency	Cingulo-opercular	Cingulo-opercular
-42	2	17	Left frontal operculum	Lexicality	Cingulo-opercular	Cingulo-opercular
31	22	17	Right lateral IFG	Lexicality	Cingulo-opercular	Cingulo-opercular
40	12	12	Right lateral IFG	DA	Cingulo-opercular	Cingulo-opercular
51	2	21	Right premotor	DA	Cingulo-opercular	Cingulo-opercular
-12	-18	8	Left anterior thalamus	ME	Subcortical	Subcortical
9	-18	10	Right anterior thalamus	ME	Subcortical	Subcortical
0	-19	-10	Thalamus	Consistency	Subcortical	Subcortical
18	-5	12	Right putamen	Lexicality	Subcortical	Subcortical
-18	-4	12	Left putamen	Lexicality	Subcortical	Subcortical
-28	-18	2	Left putamen	ME	Subcortical	Subcortical
29	-18	4	Right putamen	ME	Subcortical	Subcortical
38	-2	38	Right frontal	Lexicality	Frontal-Parietal	Fronto-Parietal/Frontal
-40	-1	36	Left frontal	Lexicality	Frontal-Parietal	Fronto-Parietal/Frontal
35	25	26	Right lateral frontal	Lexicality	Frontal-Parietal	Fronto-Parietal/Frontal

MNI Coord.			Region Description		Community Definition	
x	y	z	Anatomic Location	Functional definition	Adults	Children
-42	17	35	Left dorsolateral prefrontal	Frequency	Frontal-Parietal	Fronto-Parietal/Frontal
-49	19	20	Left lateral inferior frontal gyrus	Frequency	Frontal-Parietal	Fronto-Parietal/Frontal
-41	-42	36	Left superior parietal	Lexicality	Frontal-Parietal	Superior Frontal & Parietal
-24	-68	34	Left inferior parietal sulcus	Consistency	Frontal-Parietal	Visual
28	-62	37	Right inferior parietal sulcus	ME	Frontal-Parietal	Visual
-41	-62	-10	Left occipito-temporal fusiform	Lexicality	Frontal-Parietal	Visual

Table 4.3. Reading-related regions

ME refers to main effect of reading regions, DA to regions identified in the developmental analysis.

Graph theoretic techniques reveal a reading network configuration similar to previous large network analyses.

Several techniques, including modularity optimization (Newman ME, 2006), Infomap (Rosvall M and CT Bergstrom, 2008), and modularity optimization of bootstrap similarity matrices, were used to define the network structure of reading-related regions in adults (21-29 years old). Using these three techniques to define the smallest parcellations, 11 communities were defined across a range of appropriate thresholds (as described in the methods), shown in Figure 4.3. The assignments included communities of visual and cerebellar regions (cyan and blue, respectively) and a group overlapping the previously described default network (red, Fox MD et al., 2005; Greicius M et al., 2003). Further inspection across thresholds also suggested a group of temporal regions (pink) that is sometimes assigned to the same community as a small group of auditory temporal regions (lavender) that, in turn, is sometimes assigned to the same community as a motor community (purple) and a community of superior frontal and parietal regions (orange). Additionally, the trio of methods defined a pair of regions in the dorsal anterior cingulate cortex (dACC) and mid frontal cortex (light gray), a cingulo-opercular community including members of the previously described cingulo-opercular control network (dark gray, Dosenbach NUF et al., 2007) and a group of all subcortical regions (black), all of which are sometimes assigned to the same community. Finally, a community that overlapped with the previously described fronto-parietal control network (yellow, Dosenbach NUF et al., 2007) was found. The modularity optimization and Infomap assignments from thresholds of r = 0.05 to 0.28 are shown in the top panel of Figure 4.3 (regions are presented in the order listed in Table 4.3), as are the bootstrapped modularity assignments thresholded at similarities from 0.50 to 0.75. The locations of the regions colored by community assignment are shown in the bottom panel of Figure 4.3. It is important to note that among the “reading specific regions” that the AG is assigned to the default community, the SMG and STS to the temporal community, and the IFG and VWFA to the fronto-parietal community. In other words, the regions consistently activated during reading do not form a separate community in this analysis.

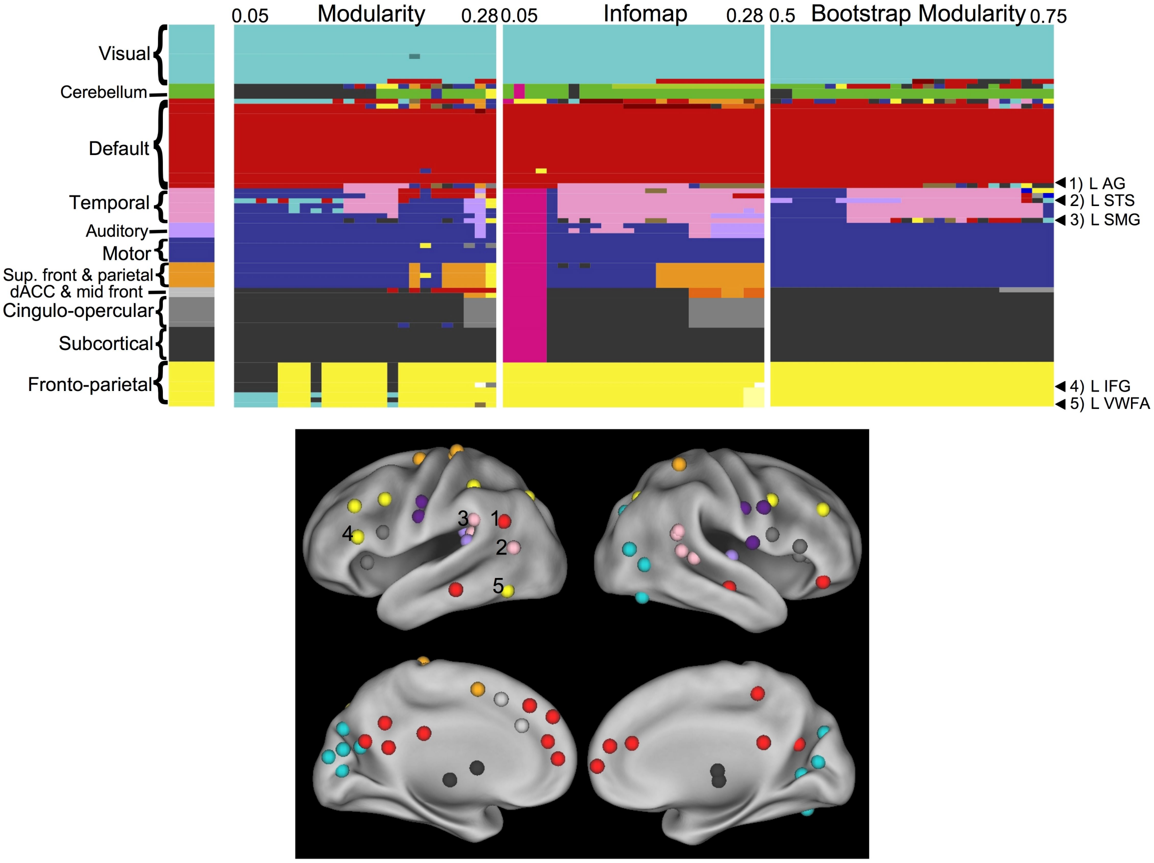


Figure 4.3. Network organization of reading-related regions in adults

Top panel depicts community assignment of reading-related regions in 30 adults. The leftmost color bar indicates the community assignment made by looking across all thresholds in all methods. To the right of the color bar the modularity optimization assignment from correlation values of 0.05 to 0.28, Infomap from correlation values of 0.05 to 0.28, and modularity optimization of the bootstrap similarity matrix from similarity values of 0.5 - 0.75 (assigned to the same group in 50% - 75% of the bootstrapped groups) are shown sequentially. In all, each region corresponds to a row in the color plot and each threshold corresponds to a column. Community assignments are depicted as colors in the color bar and bottom panel- visual regions in cyan, cerebellar regions in green, default regions in red, temporal regions in pink, presumptive auditory regions in lavender, motor regions in purple, superior frontal and parietal regions in *orange, the dACC & mid frontal pair in light gray, cingulo-opercular regions in dark gray, subcortical regions in black, and fronto-parietal regions in yellow. Numbered labels denote regions typically found in reading analyses.*

The developmental trajectory of the reading network follows a local to distributed pattern similar to other large brain networks.

Utilizing the same three methods (modularity optimization, Infomap, and bootstrapped modularity optimization) in children (ages 7-10 years) we find a different network structure than adults. In children communities are generally defined by anatomic proximity but "reorganize" into more anatomically distributed communities with age. The modularity optimization, Infomap, and bootstrapped modularity optimization assignments across thresholds in children are shown in the left panel of Figure 4.4A, presented in same order as Table 4.3, and the locations of these communities on the brain are shown in the right panel of Figure 4.4A.

Children also show 11 functional communities. As with the adults, these communities include visual and cerebellar groups (cyan and green, respectively), as well as temporal (pink) and auditory temporal communities (lavender) that are sometimes assigned to the community. In children we find a similar motor community as that defined in adults (purple), but these regions more often share community assignment with a subcortical community (black). A group of regions overlapping with the cingulo-opercular network (dark gray, Dosenbach NUF et al., 2007) also sometimes shares community assignments with the motor and subcortical regions in children. There are sometimes overlapping community assignments between these regions and the frontal regions from the fronto-parietal network (light yellow, Dosenbach NUF et al., 2007). In this group of children, the parietal regions from the fronto-parietal network are part of the visual community. Similarly, the default mode network is divided into separate frontal (bright red) and parietal (maroon) communities. The dACC and presumptive supplementary motor area form a pair (light gray). Finally, a few regions, including a right medial superior occipital region, a left inferior temporal and a right inferior frontal region, are very difficult to classify and are colored in brown, though they do not form a coherent community. In children, the putative VWFA is located in the visual community, while the AG, STS, and SMG are placed in the temporal community, and the IFG in the frontal/fronto-parietal community.

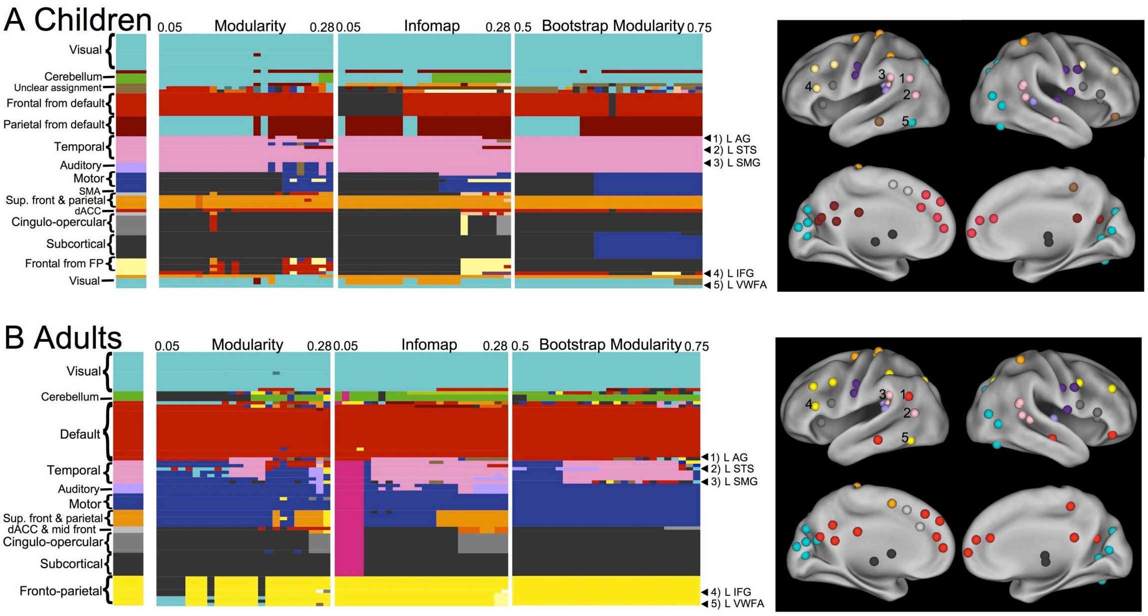


Figure 4.4. Development of reading-related network organization

A. Community assignment of reading-related regions in 30 children (7-10 years old) for modularity optimization, Infomap, and bootstrapped modularity analyses. A bar with the community assignment is shown to the left of the three thresholded assignment plots. Regions are presented vertically in the order listed in Table 4.3. The location of the regions on the brain, colored by community assignment can be found in the right panel. Note, the brown regions do not correspond to a true community but are rather a set of regions with no identifiable assignment. Numbered labels denote regions typically found in reading analyses.

B. Community assignment of reading-related regions in 30 adults (21-29 years old) for modularity optimization, Infomap, and bootstrapped modularity analyses as shown in Figure 4.3, with the location of the regions colored by community assignment in the left panel (as in Figure 4.3). Numbered region labels denote regions typically found in reading analyses.

Developmental changes in reading regions follow the principles of functional segregation and integration.

In addition to sharing the general property of local to distributed developmental changes, these networks also appear to make some changes via functional segregation and integration as described in previous work (Fair DA et al., 2009; Vogel AC et al., in press). Functional segregation is apparent when regions are ordered based on the child modularity assignments. In the left panel of Figure 4.5, child community assignments are shown as a colored bar on the left and adult assignments shown as a colored bar on the right. Regions assigned to the same community in children become assigned to disparate communities in adults. Most obviously, visual regions (cyan in children) divide into visual (cyan) and fronto-parietal (yellow) communities in adults.

Functional integration can be observed in the right panel of Figure 4.5, when regions are ordered by adult community assignment. Functional integration is seen by the different colors in the child plot that come together with age, or regions in disparate communities in children integrating into the same community in adults. This integration is most apparent in the default (red) and fronto-parietal (yellow) adult communities, which are formed from their frontal and parietal components in children.

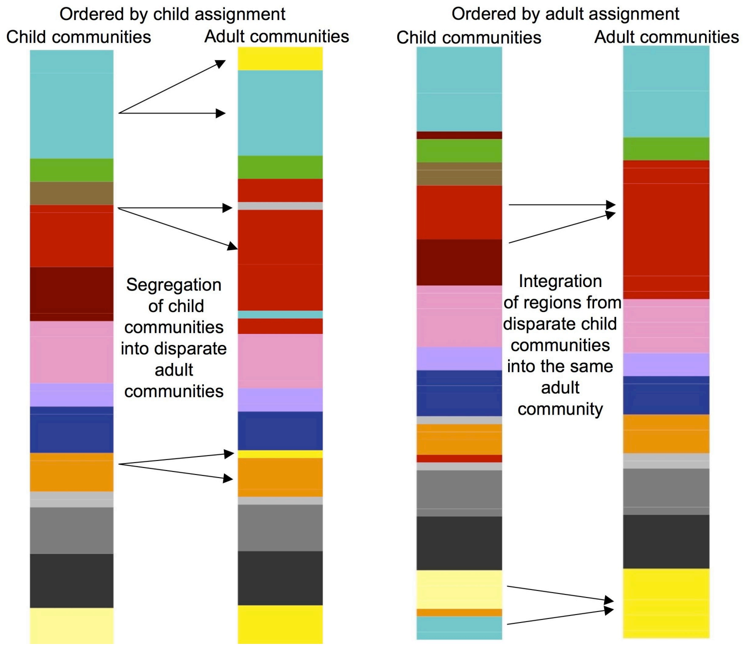


Figure 4.5. Development of network structure via segregation and integration

The left panel shows community assignments ordered by child communities. Regions that belong to a single community in the child analysis segregate into different communities in adults. The right panel shows community assignments ordered by adult communities. Regions that belong to separate communities in the child analysis integrate into a single community in adults.

Discussion

We have defined a group of 77 regions used in reading single words aloud, presumably encompassing a majority of the regions involved in transforming a set of printed characters into verbal output. Defining these regions as nodes and the resting state correlations between the regions as edges, we used graph theoretic techniques to define the network structure of reading-related regions. We find that there does not appear to be a distinct community specific to reading, but rather the structure of this network consists of communities similar to those previously described, such as the fronto-parietal and cingulo-opercular task control networks (Dosenbach NUF et al., 2007) and default mode network (Fox MD et al., 2005; Greicius M et al., 2003) as well as sensory and motor processing communities. The developmental structure of the reading network generally recapitulates previous descriptions of a more local community organization in children that develops into distributed adult communities through integration of previously unrelated regions and segregation of regions related in childhood (Fair DA et al., 2009; Vogel AC et al., in press). Overall these results support the hypothesis that the defined reading-related regions perform relatively general processing that is useful for, but not specific to, reading.

Mature network structure of reading-related regions

Unlike most reading meta-analyses (Fiez J and S Petersen, 1998; Jobard G et al., 2003; Turkeltaub PE et al., 2002; Vigneau M et al., 2006) our reading network includes regions not specific to reading tasks, such as primary motor and primary visual cortex. However, the analysis is not completely task-general as it also includes regions thought to be used predominantly in reading, such as the left visual word form area (VWFA, for review see Cohen L and S Dehaene, 2004), and regions in the left supramarginal gyrus (SMG, Church JA, DA Balota et al., 2010; Church JA et al., 2008; Sandak R et al., 2004), angular gyrus (AG, Binder JR et al., 2005; Graves WW et al., 2010), and left inferior frontal gyrus (IFG, Fiez J et al., 1999; Mechelli A et al., 2003). By using such a complete group of regions we had the possibility of describing the whole network used to perform overt word reading - from the original visual processing through the spoken output.

In this analysis, we were unable to identify a specific network for word reading. Using modularity optimization (Newman et al., 2006), Infomap (Rosvall M and CT Bergstrom, 2008), and modularity optimization of a bootstrapped consistency matrix a consistent network structure was identified; but rather than a reading network, per se, this structure seemed to replicate previously reported functional communities. For example, we identified communities that overlapped with the fronto-parietal and cingulo-opercular control networks (Dosenbach NUF et al., 2007), one overlapping the default mode network (Fox MD et al., 2005) and several communities seemingly related to sensorimotor processing (visual, motor, and temporal communities).

As discussed in the introduction, reading is a newly acquired skill in evolutionary terms (and still not a universal one), and it seems that rather than having developed neural regions preferentially dedicated to reading-related processing, these regions may, in fact, be used at least as much, or more, for many other tasks. As we believe resting state correlations reflect a long history of co-activation, regions that have relatively promiscuous activity patterns (i.e., are not used primarily or only during reading) will have rs-fcMRI correlations with multiple regions. Thus, if regions used in reading are also used in other tasks, they will have rs-fcMRI correlations with not only the other regions used predominantly during reading but also with regions used in any other task in which that given region is activated. This variety in correlational pattern seems to make the detection of a reading network using rs-fcMRI quite difficult.

While we used a graph theoretic approach to large-scale network analysis, the same lack of specificity in reading networks can be found in a seed map approach. In a seed map analysis, the rs-fcMRI timecourse from a given seed region is correlated with every other voxel in the brain. Those voxels showing significant correlations with the seed region are considered functionally related to the seed region. When Koyama and colleagues performed a seed map analysis on six potential “reading regions”, including the VWFA, SMG, AG, and IFG, they did find two regions of overlap in the SMG and IFG in 5 of the 6 maps; but the seed maps also contained a large number of non-overlapping regions (Koyama MS et al., 2010). While these seed map differences were not the focus of the study, they do support the idea that these regions are not part of one particular network but rather perform a function that is used in reading and other tasks as well.

It is important to note that the nature of the resting state correlations purportedly allows us to address regional relationships based on a history of co-activation across all tasks in which a region in active; this method cannot address how regions interact in one specific task. Methods such as effective connectivity, dynamic causal modeling (Friston KJ et al., 2003) and Granger causality (Eichler M, 2005; Granger CWJ, 1969), on the other hand, address how a small number of regions interact in a specific task. Previous effective connectivity studies of reading-related regions do show interactions between the VWFA, SMG/AG and IFG during orthographic and phonologic processing tasks (Bitan T et al., 2007).

Development of the network structure of reading-related regions

We also did not observe developmental changes indicative of a developing reading network or any type of reading specificity. In children, communities were generally composed of regions from the same basic anatomic neighborhood; for example, the fronto-parietal and default communities were broken into generally separate frontal and parietal components in children (see Figures 4.4 and 4.5). In part, this local to distributed functional organization recapitulates previously demonstrated developmental network changes (see Fair DA et al., 2009; Vogel AC et al., in press) in both its pattern and the method of achieving distributed connections. Like the smaller group of regions previously investigated, we see both segregation of regions located in the same community in children into new distributed communities, and integration of regions from disparate communities in children into a single functional community in adults. Overall, while reading is a learned skill that continues to improve greatly between the ages of 7-10 years and 21-29 years, no reading specific changes in the resting state functional connectivity networks were seen.

Again, the lack of reading specific network development is likely due to the nature of the signal used to define network relationships (i.e., resting state correlations). Previous work by Bitan T et al. (2007) shows developmental changes in effective connectivity with increasing age and reading skill in orthographic and phonologic processing tasks performed on written stimuli. But as described above, rs-fcMRI encompasses changes related to increasing age and skill across many tasks, not only reading. Thus, this is further evidence that though these regions may be used in reading, they are not used predominantly for reading.

However, while the regions typically described as reading-related (left VWFA, SMG, AG, IFG) do not form a single network through development, some of these regions do undergo interesting developmental changes. The left SMG and AG, for example, are both located in the temporal community in children. While the SMG retains its membership in the temporal community in adults, the AG becomes integrated into the default community. Previously, Church and colleagues have shown distinctions in the developmental trajectory of the functional timecourses in these regions (Church JA et al., 2008). The Church study demonstrated that while both the SMG and AG showed positive timecourses for reading words in children, only the SMG showed positive activity during word reading in adults. Additionally, the VWFA is the only non-parietal region to become separate from the visual community in children and integrate into the fronto-parietal community in adults. The relationships between these individual regional developmental changes and age or reading skill should be the subject of further study.

Summary and Conclusions

In this study, we first described a large group of reading-related regions that show consistent changes in BOLD activity when adults read single words aloud. We then demonstrated, using resting-state functional connectivity MRI and graph theoretic methods that there does not appear to be a specific network of reading-related regions. This observation does not mean that there are not special relationships between some of these regions during reading, but rather lends support to the idea that these regions are broadly used across many tasks, including reading. Consistent with this interpretation, we recapitulate previously defined rs-fcMRI functional networks including the default mode, fronto-parietal and cingulo-opercular control networks. We also demonstrate the general developmental patterns of functional segregation and integration in the change from relatively locally defined communities in childhood to more distributed communities in adults. Overall, we argue these results should encourage the investigation of the general types of processing performed in neural regions rather than attempts to ascribe particular brain regions to specific cognitive skills.

CHAPTER 5. MATCHING IS NOT NAMING: A DIRECT COMPARISON OF LEXICAL MANIPULATIONS IN EXPLICIT AND IMPLICIT READING TASKS

Introduction

The neurobiological underpinnings of reading have been studied since the advent of functional neuroimaging (i.e. Petersen SE et al., 1988) and interest in the neural processing systems contributing to fluent reading has grown considerably. A recent Pubmed search of the terms “reading”, “language”, and “fMRI” or “PET” returned 1147 results, of which 997 were published in the last 10 years. As a whole, this research has contributed much to our knowledge about the neuroscience of reading, including identification of regions consistently used in single word reading (see Bolger DJ et al., 2005; Fiez J and S Petersen, 1998; Jobard G et al., 2003; Turkeltaub PE et al., 2002; Vigneau M et al., 2006 for meta-analyses), how the neural systems for reading change with development (reviewed in Schlaggar BL and BD McCandliss, 2007), and how these systems may be disrupted in dyslexic readers (see Gabrieli JD, 2009; Shaywitz SE, 1998). However, due to the technical difficulties of imaging spoken output, including recording verbal responses (Nelles JL et al., 2003) and the possibility of movement related artifacts (Mehta S et al., 2006), many groups have used implicit reading tasks such as matching (i.e., Tagamets MA et al., 2000), ascender judgments (i.e., Price CJ et al., 1996), target string detection (i.e. Vinckier F et al., 2007), and silent reading (i.e., Dehaene S et al., 2001). In fact, only 90 of the aforementioned 1147 neuroimaging studies are found if “aloud” is added to the reading search terms described above.

The use of non-vocal tasks for studying reading-related processing has been justified by the proposition that the reading pathway is automatically activated whenever a word is viewed. Automaticity in reading has a long history, dating back at least to William James (James W, 1890). Behavioral studies of reading have provided some evidence for the automatic activation of reading pathways when viewing (or matching or scanning) words. For example, in the classic word-color Stroop effect, subjects are slower to report the ink color of words that name a color other than the ink color, an indication that the word itself has been read despite its lack of relevance to the task at hand (see MacLeod CM, 1991). Additionally, two influential models of word reading, a connectionist model in which orthographic, phonologic and semantic processors work together to produce a spoken word (e.g., Harm MW and MS Seidenberg, 2004), and the dual route connectionist model in which words are processed in distinct phonologic and orthographic pathways (e.g., Coltheart M et al., 2001), generally assume automatic activation of these neural components when a word is viewed.

Early functional neuroimaging studies also support the concept of "automatic activation". As described above, functional neuroimaging studies have generally converged on a set of left hemisphere regions used for single word reading (see Bolger DJ et al., 2005; Jobard G et al., 2003; Turkeltaub PE et al., 2002; Vigneau M et al., 2006 for meta-analyses), including a region near the left occipito-temporal border in the fusiform cortex termed the visual word form area by some (VWFA, see Cohen L and S Dehaene, 2004 for a review), regions near the left supramarginal gyrus (SMG) and angular gyrus (AG) which have been reported as phonologic and/or semantic processors (Binder JR et al., 2005; Church JA et al., 2008; Graves WW et al., 2010; Sandak R et al., 2004), and regions in the left inferior frontal gyrus (IFG) thought to be involved in phonological processing and/or articulation (Booth JR et al., 2007; Fiez J et al., 1999; Mechelli A et al., 2003). Many studies that do not require reading aloud (i.e., Cohen L et al., 2003; Dehaene S et al., 2001; Polk TA et al., 2002; Price CJ et al., 1996; Tagamets MA et al., 2000; Turkeltaub PE et al., 2003) show activity in these regions.

However, there is some evidence that task manipulation may alter reading-related neural processing in at least some brain regions. For example, activity differences, measured when contrasting the processing of letters and digits, are reduced in an orthographic processing region when subjects are asked to name the stimuli aloud relative to silent reading (Polk TA et al., 2002). Starrfeldt and Gerlach (2007) have also shown differential stimulus effects for color versus category naming in the VWFA. More regions with differential activation in dyslexic and typical readers are found when subjects read words aloud than when subjects perform an implicit reading task (Brunswick N et al., 1999). Tasks that emphasize specific processing components of reading, such as rhyme matching versus spelling, show clear distinctions in BOLD activity in regions such as the SMG, IFG and VWFA (Bitan T et al., 2007; Booth JR et al., 2004).

In the present study, we directly test for neural processing differences between subjects reading aloud and making a visual matching judgment on three classes of orthographic stimuli: words, pseudowords (defined as orthographically legal letter combinations), and nonwords (defined as orthographically illegal letter combinations). Variations of visual matching have been used as an implicit reading task (i.e., Tagamets MA et al., 2000), and we contend that this matching task involves a similar form of low level or implicit visual processing involved in tasks like ascender judgments or unique string detection. By using both word and non-word stimuli we are not only able to test for task effects (matching versus naming), but also effects of string type (word versus pseudowords versus nonwords) and interactions between task and string type.

String-type by task interactions are those most likely reflect processing differences between the two tasks. While activity may be generally reduced for the implicit task (matching) relative to the explicit task (reading), if there is truly automatic activation of the reading pathway, there should be similar effects of string-type in the two tasks. If, in contrast, the string types are processed differently in the two tasks, this likely reflects an effect of top-down control on reading-related processes, a result that would necessarily encourage caution when comparing implicit reading to reading aloud, or when assuming that implicit reading tasks act as surrogates for explicit reading.

Methods

Participants

Subjects included 22 (10 male) right-handed native English speakers ages 21-26 years old. All were screened for neurologic and psychiatric diagnoses and medications by telephone interview and questionnaire. The majority was from the Washington University or Saint Louis University communities, and all were either college students or college graduates. All gave informed, written consent and were reimbursed for their time per the Washington University Human Studies Committee approval. All subjects were tested for IQ using a 2-subtest versions of the Wechsler Abbreviated Scale of Intelligence (Wechsler D, 1999) and for reading level using 3 subtests of the Woodcock-Johnson III (Letter-Word ID, Passage Comprehension, and Word Attack) (Woodcock RW and MB Johnson, 2002). All subjects have above average IQ (mean = 127, range 115-138, standard deviation 6.4) and reading level (mean standard reading level 17.3 years education (college graduates), range 15.4-18 years education (the maximum estimated by the WJ-III), standard deviation .88).

Stimuli

All stimuli consisted of 4-letter strings. Letter strings were of 3 types: real words (e.g. ROAD), pseudowords with all orthographically legal letter combinations (e.g. PRET) or nonwords with orthographically illegal letter combinations in English (e.g. PPID). Each letter subtended approximately 0.5 degrees horizontal visual angle, and strings were presented in uppercase Verdana font in white on a black background.

In the single-item naming task, one string was presented foveally, replacing a central fixation crosshair. All strings were presented for 1 second. 45 strings (15 real words (e.g. FACE), 15 pseudowords (e.g. RALL), 15 nonwords (e.g. GOCV)) were presented in pseudorandom order in each of 4 runs per subject, resulting in a total of 180 stimuli. Stimuli were pseudorandomized within run with the constraint that no string type appear on more than 3 consecutive trials, and run order was counterbalanced across subjects.

In the string-matching task, 2 strings appeared parafoveally, one above the fixation crosshair and one below (each approximately 1.5 degrees vertical visual angle from the fixation cross). Each pair was presented for 1.5 seconds. The pairs were either both real words, both pseudowords, or both nonwords. Subjects saw a single run of each stimulus type, with 60 pairs per run. Within each run half of the pairs (30) were the same and half (30) were different, and half of those pairs that were different (15) differed in all 4 character positions, while half (15) different in only 2 character positions. A total of 4 separate pseudorandom orders were generated for each run/stimulus type. Examples of the matching stimuli can be seen in Table 5.1.

String Type	Same pairs	Different pairs	
		Easy (4 character difference)	Difficult (2 character difference)
Words	ROAD + ROAD	FACE + COAT	LAND + TEND
Legal Pseudowords	RALL + RALL	TARE + FLOY	KRIT + PRET
Illegal Nonwords	GOCV + GOCV	BAOO + NLES	FOCR + WECR

Table 5.1. Examples of string matching stimuli

Task Design

Two tasks were used in the present study; single word reading and letter string matching. Each subject performed both tasks. Of note, both tasks were embedded within a longer study consisting of single letter and picture matching tasks, single letter and picture naming tasks, and a rhyme judgment and picture-sound judgment task. All together, each subject performed 16 runs split over two scanning sessions held 1-28 days apart. The order of the runs was counterbalanced within and across scanning sessions.

For the single word reading task, the 45 stimuli (15 of each string type) were intermixed with 90 null frames where only a fixation crosshair was presented. The trials were arranged such that the words were presented sequentially or with 1, 2, or 3 null frames between strings. Each trial consisted of a single 2.5 second TR, thus the actual time between stimuli was 1.5s, 4s, 6.5s, or 9s. Such a jitter allows the event-related timecourse to be extracted (Miezin FM et al., 2000). Subjects were instructed to read aloud each item as accurately and quickly as possible.

In the matching task, each stimulus pair was presented for 1.5 seconds, within a 2.5s TR trial. 60 stimulus trials (of the same type, i.e. all real words) were intermixed with 60 null frames in each run such that the stimuli appeared either sequentially or with 1 or 2 null frames between pairs, resulting in a 1, 3.5 or 6 second interstimulus interval. Subjects were instructed to press a button with one index finger if the stimuli were the same and with the other index finger if they were different. The hands assigned to the "same" and "different" judgments were counterbalanced across subjects. Stimuli were pseudorandomized within each run so that no more than two consecutive correct responses ever required the same hand for a response.

Behavioral Measures

Behavioral data were collected with digital voice recording software for the naming task (described in Nelles JL et al., 2003) and with a Psyscope compatible optical button box for the matching task (Cohen JD et al., 1993). For the naming task, responses were scored as correct for pseudowords if the subject gave the correct sequence of orthographic to phonologic conversions. Responses to the nonwords were scored liberally; if the subject incorporated a sound associated with all letters or graphemes in the word in the correct order the response was scored as "correct". For example, correct responses to PPID included "pi-pid" and "pid".

MR Data Acquisition and Preprocessing

A Siemens 3T Trio scanner (Erlanger, Germany) with as 12-channel Siemens Matrix head coil was used to collect all functional and anatomical scans. A single high-resolution structural scan was acquired using a sagittal magnetization-prepared rapid gradient echo (MP-RAGE) sequence (slice time echo= 3.08 ms, TR= 2.4 s, inversion time= 1 s, flip angle= 8 degrees, 176 slices, 1 x 1 x 1 mm voxels). All functional runs were acquired parallel to the anterior-posterior commissure plane using an asymmetric spin-echo echo-planar pulse sequence (TR= 2.5 s, T2* evolution time 27 msec, flip angle 90 degrees). Complete brain coverage was achieved by collecting 32 contiguous interleaved 4mm axial slices (4 x 4 mm in-plane resolution).

Preliminary image processing included removal of a single pixel spike caused by signal offset, whole brain normalization of signal intensity across frames, movement correction within and across runs, and slice by slice normalization to correct for differences in signal intensity due to collecting interleaved slices. For a detailed description see Miezin FM et al., 2000.

After preprocessing, data was transformed into a common stereotactic space based on Talairach and Tournoux (1988) using an in-house atlas composed of the average anatomy of 12 healthy young adults age 21-29 years old and 12 healthy children age 7-8 years old (see Brown TT et al., 2005; Lancaster JL et al., 1995; Snyder AZ, 1996 for methods). As part of the atlas transformation, the data were resampled isotropically at 2 mm x 2 mm x 2 mm. Registration was accomplished via a 12 parameter affine warping of each individual's MP-RAGE to the atlas target using difference image variance minimization as the objective function. The atlas-transformed images were also checked qualitatively against a reference average to ensure appropriate registration.

Participant motion was corrected and quantified using an analysis of head position based on rigid body translation and rotation. In-scanner movement was relatively low as subjects were both instructed to hold as still as possible during each run and were custom fitted with a thermoplastic. However, frame-by-frame movement correction data from the rotation and translation in the x, y, and z planes were compiled to ensure there were no runs with overall movement greater than 1.5 mm rms, which there was not (mean movement = 0.273 mm rms, standard deviation = 0.120 mm). The difference in movement between the matching (mean = 0.262 mm rms, standard deviation = 0.127 mm) and naming (mean = 0.284 mm rms, standard deviation = 0.114 mm) tasks was not significant.

fMRI Processing and Data Analysis

Statistical analyses of event-related fMRI data were based on the general linear model (GLM) conducted using in-house software programmed in the interactive data language (IDL, Research Systems, Inc., Boulder, CO) as previously described (Brown TT et al., 2005; Miezin FM et al., 2000; Schlaggar BL et al., 2002). The GLM for each subject included time as a 9 level factor made up of 9 MR frames (22.5 s, 2.5s/frame) following the presentation of the stimulus, task as a 2 level factor (matching and naming) and string type as a 3 level factor (words, pseudowords, nonwords). No assumptions were made regarding the shape of the hemodynamic response function. Only correct trials were included in the analysis; errors were coded separately in the GLM but were not analyzed.

First, a 2 task (matching vs naming) by 3 string-type (words vs pseudowords vs nonwords) by 9 (timepoints) voxel-wise whole brain repeated measures ANOVA was conducted. A Monte Carlo correction was used to guard against false positives resulting from conducting a large number of statistical comparisons over many images (Forman SD et al., 1995; McAvoy MP et al., 2001). To achieve a $p < 0.05$ corrected for multiple comparisons, a threshold of 24 contiguous voxels with a $Z > 3.5$ was applied.

This voxel-wise ANOVA produced 4 images: voxels with a main effect of timecourse (activity that showed differences among the 9 timepoints collapsing across task and string-type), voxels with a task by timecourse interaction (activity that shows timecourse differences between the matching and naming tasks), voxels with a string-type by timecourse interaction (activity that shows timecourse differences between the three string types, collapsed across the 2 tasks), and voxels with a string-type by task by timecourse interaction (activity that shows timecourse differences between the 3 string types dependent on the 2 task conditions).

Regions were extracted from these images using an in-house peak-finding algorithm (courtesy of Avi Snyder) that located activity peaks within the Monte Carlo corrected contiguous voxels images, by first smoothing with a 4 mm kernel, then extracting only peaks with a Z score > 3.5, containing 24 contiguous voxels and located at least 10mm from other peaks.

The nature of the statistical effects was demonstrated by extracting the timecourse (percent BOLD signal change at each of the 9 timepoints) in every individual subject for each stimulus type in each task in each of the regions defined from the ANOVAs described above. Percent BOLD signal change at each timepoint was averaged across all subjects and these average timecourses plotted for each stimulus type in each task.

To ensure the effects were not due to response time differences between the two tasks, a second set of GLMs was generated for each subject as described above but with an additional regressor coding the response time for each individual trial. Thus response time was used as a continuous regressor and unique variance related to response time should be assigned to that variable.

Results

Behavioral Results

Subjects showed high accuracy in both the naming (average 98.3%) and matching (average 98.0%) tasks. A 3 (string-type: words, pseudowords, nonwords) by 2 (task-type: matching and naming) repeated measures ANOVA indicated no difference between the tasks (p = 0.770) or the string-types (p = 0.17), and no string-type by task interaction (p= 0.98).

An analysis of response time with a 3 (string-type: words, pseudowords, nonwords) by 2 (task-type: matching and naming) repeated measures ANOVA demonstrated a string type by task interaction (p < 0.0001), and though there was no effect of task (p = 0.289), there was a significant effect of string type (p < 0.0001). Post-hoc 3 level (string-type) ANOVAs performed for the matching and naming tasks individually showed that the task by string-type interaction was driven by an effect of string-type on RTs for the naming task (p < 0.0001, post-hoc paired t-tests indicated nonwords > pseudowords > words) that was not present in the matching task (p = 0.46). See Table 5.2 for details.

	Accuracy			**Response Time (in msec)**		
Naming	**Average**	**Range**	**sd**	**Average**	**Range**	**sd**
Words	99.0%	95.0-100%	1.6%	837	647-1032	100
Pseudowords	98.2%	91.7-100%	2.3%	932	752-1102	100
Nonwords	97.5%	93.3-100%	2.5%	1038	851-1270	120
Average	98.3%	95.5-100%	1.3%	955	741-1103	100
Statistical effects:	No effect of string type			Nonwords > Pseudowords > Words		
Matching						

	Accuracy			Response Time (in msec)		
Naming	**Average**	**Range**	**sd**	**Average**	**Range**	**sd**
Words	98.6%	95.0-100%	1.8%	914	705-1253	139
Pseudowords	98.3%	90.0-100%	2.5%	889	701-1325	138
Nonwords	97.9%	73.3-100%	5.1%	910	771-1483	164
Average	98.0%	88.9%-100%	2.5%	904	735-1331	147
Statistical effects:	No effect of string type			No effect of string type		

Table 5.2. Behavioral results

Imaging Results

Regions Common to Both Matching and Naming Tasks

Many regions show statistically and presumably biologically significant (BOLD signal change > 0.10%) activity in both the matching and naming tasks, as seen in Figure 5.1 (detailed in Table 5.3). These regions are in locations thought to be important for reading, including the left VWFA, IFG, and posterior AG, as described in the introduction. However, there are also significant changes in activity throughout bilateral primary visual and fusiform cortex, and in regions thought to be involved in spatial attention (such as the left and right superior parietal cortex) or control processes (such as bilateral intraparietal sulcus and frontal operculum).

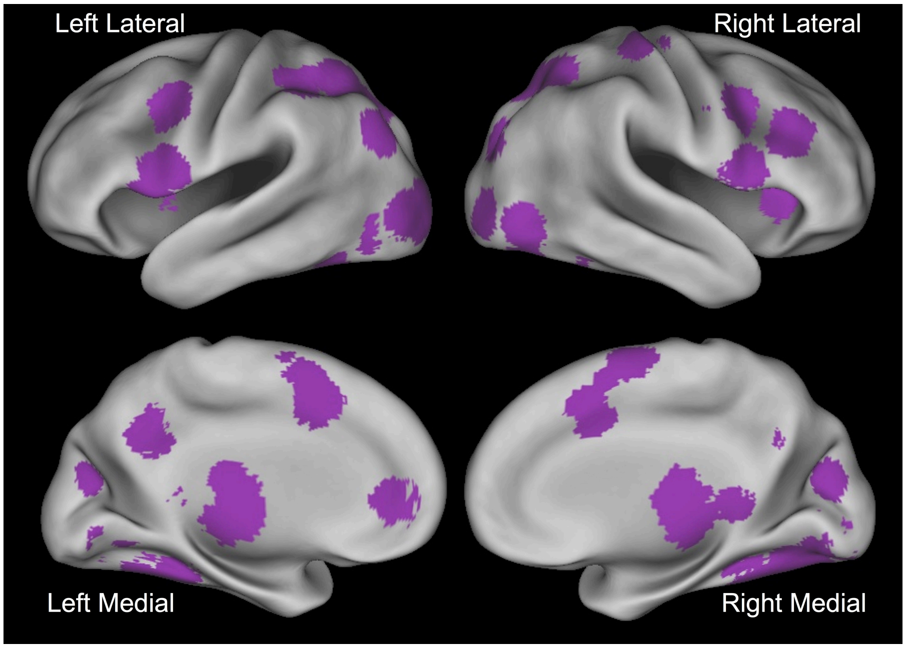


Figure 5.1. Main effect of timecourse

Regions showing a main effect of time and at least 0.10% peak BOLD signal change in both the string matching and string naming tasks.

Task by Timecourse effects

Many regions show a task (matching vs naming) by timecourse effect (Figure 5.2, Table 5.3). Of these regions, only bilateral finger sensorimotor cortex and a single left occipital region show more activity for matching relative to naming (regions shown in blue in Figure 5.2A, timecourses for left finger motor cortex in Figure 5.2B). Many more regions, including bilateral mouth sensorimotor cortex and auditory cortex, show statistically ($p < 0.05$) and biologically significant (BOLD signal change > 0.10% from baseline) activity only during the naming task (regions shown in red in Figure 5.2A, timecourses for a representative region in auditory cortex in Figure 5.2C). A third set of regions, including the left IFG, shows activity in both matching and naming tasks but significantly more activity in the naming task (regions shown in purple in Figure 5.2A, timecourses for a representative left IFG region in Figure 5.2D).

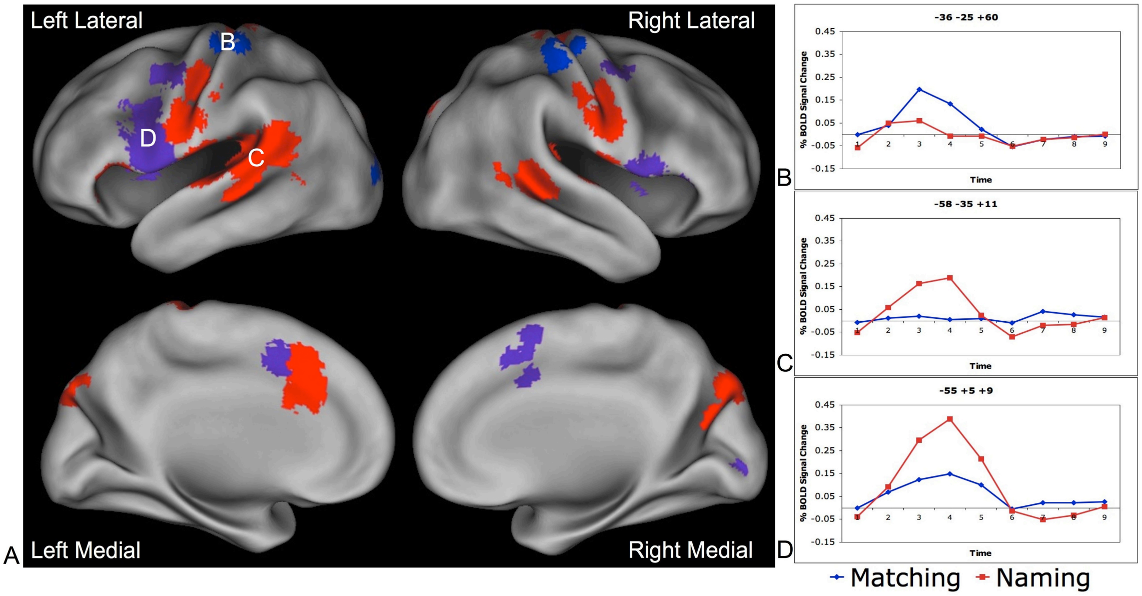


Figure 5.2. Task by Timecourse effects

A. Regions obtained from a whole brain task (matching vs naming) by timecourse repeated measures ANOVA. Blue regions show more activity for matching than naming. Red regions show activity in the naming task but have no biologically significant activity in the matching task (either no main effect of time or < 0.10% BOLD signal change). Purple regions are active in both tasks, but have more activity in the naming relative to matching tasks. Note the general lack of task by timecourse effects in occipital and fusiform regions.

B. Timecourses for an exemplar blue (matching > naming) region (left finger sensorimotor region: -36 , -28, 57). Timecourse for matching is shown in blue and for naming in red.

C. Timecourses for an exemplar red (naming only) region (left auditory cortex: -56, -26, 10). Timecourses for matching shown in blue and naming in red.

D. Timecourses for an exemplar purple (naming > matching) region (left IFG: -52, 2, 10). Timecourses for matching shown in blue) and naming in red.

MNI Coordinates			Anatomical location
x	y	z	
String Matching > String Naming			
Main effect of time in naming and matching tasks (Fig 5.2A blue)			
-27	-97	10	Left occipital
Main effect of time in matching, no main effect or < 0.10% signal change in naming (fig 2a, blue)			
-36	-25	60	Left finger sensorimotor
37	-22	58	Right finger sensorimotor
46	-25	54	Right finger sensorimotor
String Naming > String Matching			
Main effect of time in naming and matching tasks (Fig 5.2A, purple)			
17	-88	0	Right occipital
-46	2	46	Left premotor
45	2	54	Right premotor
11	11	52	Right anterior cingulate
-15	9	43	Left anterior cingulate
3	15	42	Right anterior cingulate
-55	5	9	Left inferior frontal gyrus
58	12	3	RIght inferior frontal gyrus
-54	10	19	Left inferior frontal gyrus
-46	12	28	Left inferior frontal gyrus
-40	6	7	Left mid insula
47	11	5	Right mid insula
53	22	-3	Right anterior insula
Main effect of time in naming, no main effect or < 0.10% signal change in matching (Fig 5.2A, red)			

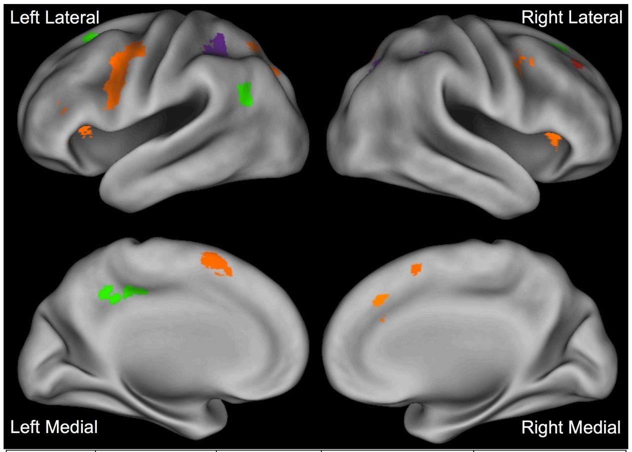
MNI Coordinates			Anatomical location
x	y	z	
-10	-84	34	Left medial parietal/occipital junction
10	-83	41	Right medial parietal/occipital junction
17	-80	34	Right medial parietal/occipital junction
-58	-66	7	Left superior temporal sulcus
63	-53	9	Right superior temporal sulcus
-56	-49	18	Left supramarginal gyrus
-41	-40	18	Left supramarginal gyrus
25	-64	-21	Right superior temporal sulcus
-58	-35	11	Left superior temporal gyrus
55	-34	3	RIght superior temporal gyrus
-48	-32	-1	Left superior temporal gyrus
-44	-29	13	Left superior temporal gyrus
43	-29	13	Right superior temporal gyrus
-15	-32	70	Left superior parietal
18	-28	63	Right superior parietal
-57	-17	7	Left mouth sensorimotor
56	-10	8	Right mouth sensorimotor
-45	-16	40	Left mouth sensorimotor
50	-11	35	Right mouth sensorimotor
-57	-7	25	Left mouth sensorimotor
57	-6	25	Left mouth sensorimotor
-43	21	-1	Left anterior insula
-84	22	27	Left anterior cingulate
-10	22	41	Left anterior cingulate

Table 5.3 Task by Timecourse Regions

Regions defined in a whole brain task (matching vs naming) by timecourse repeated measures ANOVA (reported in MNI coordinates, depicted on the brain in Figure 5.2)

String Type by Task by Timecourse effects

Perhaps most important for evaluating implicit versus explicit reading tasks are the regions showing a task (matching vs naming) by string type (word vs pseudowords vs nonwords) by timecourse (timepoints 1-9) interaction (Figure 5.3, Table 5.4), as it is this interaction that most likely reveals lexical processing differences between the two tasks. Regions identified in this analysis do not simply show different overall levels of activity between tasks, but show differing effects of string-type dependent on the task demands.



Region Color	Direction of timecourse deflection from baseline	Task x Timecourse effect	String Naming: String Type x Timecourse effect	String Matching: String Type x Timecourse effect
Orange	Positive	Naming > Matching	effect of lexicality: nonwords = pseudowords > words	None
Purple	Positive	None	effect of string type: nonwords > pseudowords > words	None
Green	Negative	None	effect of lexicality: nonwords = pseudowords < words	None
Red	Positive	Naming > Matching	effect of lexicality: nonwords = pseudowords < words	< 0.10% BOLD signal change

Figure 5.3. String-Type by Task by Timecourse effects

Regions identified in a whole brain string-type (words vs pseudowords vs nonwords) by task (matching vs naming) by timecourse repeated measures ANOVA. Region colors described in the legend are elaborated upon in the text as effect types 1, 2 and 3.

Planned post-hoc comparisons were done on each of these 3-way interaction regions to explore the separate task by timecourse and string-type by timecourse effects; the timecourses showed 3 general patterns:

1) One group of regions shows positive timecourses with an effect of lexicality in the naming task (pseudowords and nonwords > words) but no such effect in the matching task. These regions also show a task by timecourse effect, with significantly more BOLD activity for nonword naming and much lower BOLD activity for all string types in the matching task (which are instead qualitatively similar in activity level to the word naming). Regions showing these effects are shown in orange in Figure 5.3 and timecourses from a representative left IFG region are shown in Figure 5.4B.

2) The second group of regions also shows positive timecourses and a string-type (nonwords > pseudowords > words) by timecourse (timepoints 1-9) interaction in the naming but not matching task (purple in Figure 5.3, timecourses from a representative left lateral parietal region in Figure 5.4C). However, in these regions there is no task by timecourse effect, as the average level of matching activity is equivalent to the average BOLD activity in the naming task. Of note, in the representative left lateral parietal region depicted in Figure 5.4C, there may be an effect of lexicality in addition to the string type effect, as there is much larger increase in the BOLD activity for naming pseudowords than words compared to the activity difference between reading pseudowords and nonwords. However, the other regions in this category show an equivalent increase in the amount of activity for reading pseudowords relative to words and nonwords relative to pseudowords.

3) A third group contains regions with negative BOLD timecourses that also have an effect of string-type by timecourse in the naming task (nonwords < pseudowords < words) but not

the matching task. As in group 2, there is no task by timecourse interaction, as the magnitude of negative deflection in the matching task is similar to the negative deflection of nonword naming (which are all more negative than word naming). These regions are depicted in green in Figure 5.3 and timecourses for a representative left AG region are shown in Figure 5.4D. Notably, these regions show similar effects to those described for group 2, only with a negative range of BOLD activity change.

In addition to these general patterns, there is a single region with dissimilar effects from those described above. A right posterior frontal region (shown in red in Figure 5.3) shows positive timecourses and a string-type by timecourse effect in the naming task (nonwords > pseudowords and words) but no statistically or biologically significant activity in the matching task.

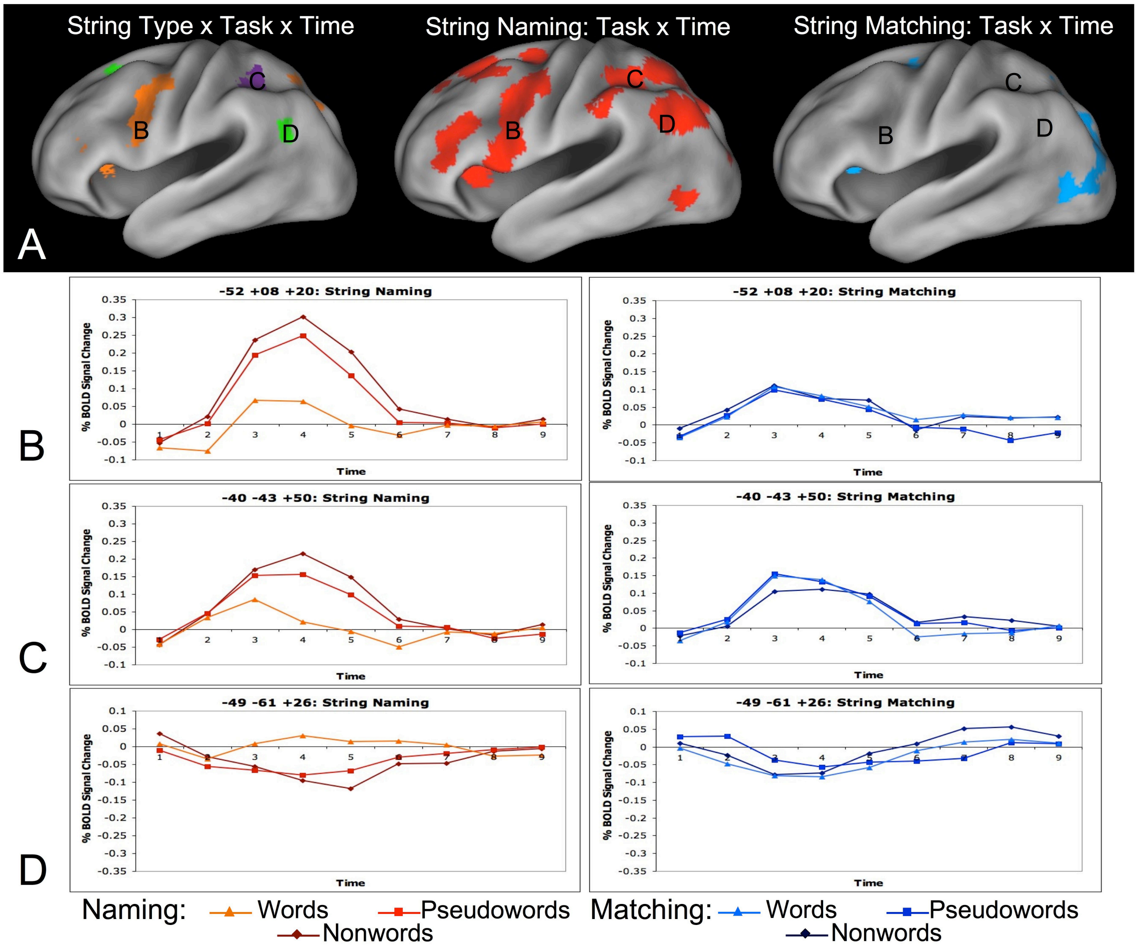


Figure 5.4. Examples of regions showing 3 types of string type by task by timecourse effects

A. Left lateral views of regions showing a string-type (nonwords vs pseudowords vs words) by task (matching vs naming) by timecourse interaction in left panel (colored as described in Figure 5.3), of regions showing a string-type by timecourse interaction in the string naming task in the center panel, and of regions showing a string-type by time interaction in the string matching task in the right panel. Note that while there is an effect of string-type in occipito-temporal regions in both the matching and naming tasks, these effects do not result in a task by string-type by timecourse interaction (do not differ in pattern between the two tasks).

B. Timecourses from an exemplar orange region (left lateral IFG: -5, 4, 21) in the string naming task in the left panel and string matching task in the right panel. While there is positive activity in both the naming and matching tasks, there is also a task by timecourse interaction in this region. Moreover, there is an effect of lexicality (pseudowords and nonwords > words) in the naming but not the matching task.

C. Timecourses from an exemplar purple region (left lateral parietal: -40, -45, 47) in the string naming task on the left and string matching task on the right. There is no task by timecourse interaction in these regions and the string-type by task by timecourse interaction is driven by an effect of string-type (nonwords > pseudowords > words) in the naming task while there is no such effect in the matching task.

D. Timecourses from an exemplar green region (left AG: -47, -61, 23) in the string naming task on the left and string matching task on the right. There is no task by timecourse interaction in the green regions, and the string-type by task by timecourse interaction is driven by a lexicality effect (pseudowords and nonwords < words) in the string naming task but no lexicality or string-type by timecourse effect in the string matching task.

x	y	z	Anatomical location	p value String Type x Time String Matching	p value String Type x Time String Naming	p value Task x Time
Orange regions in figure 3						
-22	-74	39	Left superior occipital	p > .05	p < .001	p < .01
-23	-60	46	Left posterior parietal	p > .05	p < .001	p < .01
22	-70	52	Right posterior parietal	p > .05	p < .001	p < .01
-42	1	39	Left MFG	p > .05	p < .001	p < .001
46	6	37	Right MFG	p < .01 (nonwords < pseudowords)	p < .001	p < .001
-49	-3	49	Left superior posterior frontal	p > .05	p < .001	p < .001
-42	3	27	Left IFG	p > .05	p < .001	p < .001
-52	8	20	Left IFG	p > .05	p < .001	p < .001
-46	39	14	Left anterior IFG	p > .05	p < .001	p < .001
-34	21	4	Left insula	p > .05	p < .001	p < .001
32	22	4	Right insula	p > .05 (p = .02 with RT regressed)	p < .001	p < .01
-3	13	54	medial superior frontal	p > .05	p < .001	p < .001
Purple regions in figure 3						
28	-64	41	Right occipito-parietal	p > .05	p < .001	p > .05 (p = .01 with RT regressed)
-41	-43	50	Left lateral parietal	p > .05	p < .001	p > .05
44	-37	48	Right lateral parietal	p < .01 (p = .06 with RT regressed)	p < .001	p > .05
Green regions in figure 3						
-49	-61	26	Left AG	p < .03 (words/nonwords < pseudowords)	p < .001	p > .05

x	y	z	Anatomical location	p value String Type x Time String Matching	p value String Type x Time String Naming	p value Task x Time
-10	-35	38	Left posterior cingulate	p > .05	p < .001	p < .05 (matching < naming)
-8	-47	39	Left precuneus	p > .05	p < .001	p > .05
3	-37	47	Right precuneus	p > .05	p < .001	p < .001 (matching < naming)
-23	18	46	Left superior frontal	p > .05	p < .001	p < .05 (naming < matching)
20	31	46	Right superior frontal	p > .05	p < .001	p < .01 (naming < matching)
Red regions in figure 3						
29	35	39	Right MFG	BOLD activity < 5%	p < .01	p < .01

Table 5.4 Task by String-type by timecourse regions

Regions defined in a whole brain string type (illegal vs legal pseudowords vs words) by task (matching vs naming) by time repeated measures ANOVA (in MNI coordinates), with a Z ≥ 3.5 (p < 0.05 corrected for multiple comparisons). Colors reflect those used in Figure 5.3. Regions with statistical effects that do not strictly conform to the grouping described in the text are noted and effect direction is described in the table. Any changes in effect significance for individual regions when response time is regressed are noted.

While there is a task by string-type interaction in response time that mimics the imaging effects (nonwords RT > pseudowords RT > words RT), the imaging results described above are not dependent on response time. When RT was added as an individual trial regressor to the GLM, all regions with string-type by task by timecourse interactions described above continue to show that interaction. One right occipital parietal region (purple in Figure 5.3A) changes from a non-significant to significant task by timecourse interaction when RT is regressed. One region in the right insula (orange in Figure 5.3A) has a significant string-type by timecourse interaction in the string matching task once RT is regressed out, though this effect was non-significant before RT regression.

Occipital and Fusiform Regions Show a Lack of Task Based Interactions

As noted above, presumptive visual processing regions in occipital and fusiform cortex do show positive activity during both matching and naming (Figure 5.1). Activity in these regions generally does not differ between the tasks, with the exception of a left posterior occipital region and a right medial occipital region. The left occipital region showing a task by timecourse interaction has more activity for matching than naming, but is strongly positive in both tasks (see Figure 5.2, left lateral view, blue region in posterior occipital cortex). The right medial occipital region also shows positive activity in both the string matching and naming tasks and does not show a string-type by task by timecourse interaction (see Figure 5.2, right medial view, purple region in the calcarine sulcus). In fact no regions occipital or fusiform regions show a string-type by task by timecourse interaction (see lack of occipital and fusiform regions in Figure 5.3).

Discussion

Here we have demonstrated that while there are similarities in BOLD activity for reading aloud and matching words, pseudowords and nonwords, there are also considerable differences between these two tasks in the level of evoked activity and in the effects of lexical manipulation in reading-related regions. Many classically described reading-related regions, including the left inferior frontal gyrus (IFG) and angular gyrus (AG), show an effect of lexicality only in the naming task. On the other hand, regions in occipital and fusiform cortex do not show differential task effects, as seen by a lack of string-type by task by timecourse interactions. The task by stimulus-type interactions provide an argument for reconsidering the general automaticity of reading-related processing, offer grist for further insights into the neural processing underlying the matching and naming tasks, and give reason for careful consideration of study design that uses implicit reading tasks as a surrogate for explicit reading.

Task by stimulus-type by timecourse interactions indicate matching and reading tasks do not automatically activate similar processing in reading-related pathways.

Due to the difficulties of collecting and analyzing fMRI data while subjects are speaking aloud (detailed in the introduction), some investigators have substituted implicit reading tasks for aloud word reading, assuming that there is automatic activation of the reading pathway, a point also critiqued in Schlaggar BL and BD McCandliss, 2007. While there is BOLD activity in the traditionally described “reading” pathway during the implicit reading (visual matching) task, this activity fails to distinguish between strings with different lexical properties -- words, pseudowords, and nonwords -- while reading aloud does produce this distinction. A critical point, then, is that while there is activity in some classically described reading regions in implicit reading, there is not general equivalence in the way these classically described reading regions process items during explicit and implicit reading tasks. In fact, if one were to have analyzed only the data from the matching experiment detailed here, one would reach the erroneous conclusion that there are few regions that differentiate between real words versus pseudo- and nonwords.

Task by string-type by timecourse interactions inform the understanding of different components of lexical processing.

The pattern of BOLD activity during the matching and naming tasks may inform our understanding of the type of neural processing performed in regions involved in the two tasks. The left supramarginal (SMG) and angular gyrus (AG) have sometimes been treated as a single region performing phonological and/or semantic processing (Booth JR et al., 2002). However, regions in these two locations show very different effects in the present study. The SMG does not show biologically significant activity during the matching task and also shows no task by timecourse interaction or task by stimulus-type by timecourse interaction. On the other hand, the AG, which has been purported to be involved in semantic processing (Binder JR et al., 2005; Graves WW et al., 2010), shows a negative range of BOLD activity. In both the naming and matching tasks the BOLD signal shows a negative deflection from baseline, though this deflection is only around -0.10% signal change. In the matching task, this activity is equivalently negative for all 3 stimulus types (see a lack of stimulus-type by timecourse interaction in the matching task, Figure 5.4A), and the percent signal change is equivalent to the negative deflection for naming nonwords (see Figure 5.4D). There is also a negative deflection of BOLD activity from baseline for naming pseudowords and nonwords, but no change in BOLD activity from baseline when reading words, consistent with previous reports (Bolger DJ et al., 2008; Church JA, DA Balota et al., 2010; Church JA et al., 2008; Graves WW et al., 2010). Interestingly, this pattern is also present in other members of the default mode network (green regions in Figure 5.3, see Raichle ME et al., 2001 for a further description of the default mode network).

A near inverse pattern of BOLD activity can be observed in left and right anterior superior parietal lobule (SPL) regions, where there is very little activity for reading words but stronger activity for reading pseudo- and nonwords that is equivalent to the activity produced by matching all string types (purple regions in Figure 5.3). In the case of the SPL regions, these differences may be related to task difficulty, as these regions are near left IPS regions in the dorsal attention network (Corbetta M et al., 2000), and left lateral parietal regions in the fronto-parietal control network (Dosenbach NUF et al., 2006). Likewise, the negative deflections in default mode regions (including the AG) may be related to the level of difficulty in performing the tasks on the particular stimuli, not necessarily due to a generally high level of semantic processing ongoing at rest that continues when reading words but decreases when naming pseudo- and nonwords or matching words, pseudowords, and nonwords. When considered together, the pattern of activity in the AG and lateral parietal regions indicates a reduced need for task level control or attentional processing when reading words relative to reading pseudo- and nonwords or matching letter strings.

Notably, visual regions (occipital cortex and fusiform cortex) are largely excluded from the widespread task related differences. As shown in the two right panels of Figure 5.4A, there are regions with string-type by timecourse interactions in occipital cortex and fusiform cortex in both the matching and naming tasks individually (including a region near the left occipito-temporal fusiform cortex commonly referred to as the visual word form area (see Cohen L and S Dehaene, 2004 for a review). Yet none of these visual regions demonstrate a task by string-type by timecourse effect (leftmost panel of Figure 5.4A). Moreover, as seen in Figure 5.2A, there is only a single left occipital region and a single right medial occipital region with a task (matching vs naming) by timecourse effect. The left posterior occipital region (blue in Figure 5.2A) has a strong BOLD response for both tasks and is one of only four regions to show more activity for matching than naming. The right medial occipital region (purple in Figure 5.2A) also shows positive activity for both tasks, though slightly more in the naming task. Therefore, it seems that while there are task differences in “higher level” reading regions, matching and naming tasks appear to show equivalent demands on visual processing regions, and the matching task, which emphasizes visual processing, activates similar processing in the two tasks.

Implications for study design

Given the described patterns of task related differences, we suggest a careful consideration of task design when attempting to draw conclusions about neural activity related to reading. We particularly promote the use of a truly explicit reading task. Reading silently may not suffice, in part because it is impossible for the investigator to ensure subjects are performing the task or to monitor errors during silent reading. For example, if the subject becomes inattentive or drowsy the experimenter has no way to remove responses made during that state. As many stimulus related differences appear as reduced activity for reading words, inattention or failure to perform the task may reduce stimulus related differences. There is also increasing evidence that even if the subject is performing the task adequately, error responses change BOLD activity in many brain regions (Dosenbach NUF et al., 2006; Garavan H et al., 2002). If experimenters are not able to detect and either remove or control for error responses, those responses may artificially contribute to differences in BOLD activity.

Similarly, making a low level vocal response such as “yes” to a word, nonword or non-letter string is also unlikely to be equivalent to reading. The task control demands of reading and making a single, repetitive response are disparate, and we have shown here that varying task demand does have an effect on the BOLD activity in reading regions. In fact, when the task is so basic, it may even result in visual processing differences not being seen, as the implicit matching task used here stresses visual processing.

We recognize the inability to use non-naming tasks makes studying reading related specialization for words in comparison to non-letter stimuli difficult. By the very nature of the stimuli, there is no way to “read” non-letter or consonant strings, which makes a true “reading” study impossible when using such stimuli. However, it may be possible to use such stimuli to study certain aspects of reading. For example, we have demonstrated that there are no task related differences in visual processing for these particular matching and naming tasks. An extension of this point is that while visual tasks may be used to study visual processing, tasks that emphasize other reading related processes may be used to study the specific type of processing emphasized. However, unless these tasks are directly contrasted with explicit reading, one cannot know whether any effects observed are similar to actually reading.

Finally, these task considerations may be particularly important when comparing different subjects groups such as children (early readers) to adults or dyslexic to typical fluent readers. When making group based comparisons not only can the task potentially confound lexical processing (as demonstrated here), but subject group comparisons assuming equivalent performance in the two groups may also confound results (a problematic point expanded upon in Church JA, SE Petersen et al., 2010; Schlaggar BL and BD McCandliss, 2007).

Summary and Conclusions

There are task related differences in BOLD responses to words, pseudowords and nonwords when directly comparing adults performing an implicit (visual matching) and explicit reading task. String-type (words vs pseudowords vs nonwords) by timecourse effects are only present during an explicit naming task in most putative reading regions. The pattern of such effects indicates an automaticity or decreased difficulty in reading words during the naming task only. We suggest that these task related differences should be considered when designing studies for the purpose of understanding neural activity related to reading processes.

CHAPTER 6: CONCLUSIONS

Reading, while an incredibly important skill for many, does not seem to be instantiated by specialized neural processors. The data presented here indicate orthographic processing is accomplished via more general visual processing mechanisms. However, even if other components of reading, such as those used in phonologic or semantic processing, are more specialized, there does not seem to be any preferential functional connections between orthographic processing and these regions. Moreover, there is no specific "reading network" on a large, brain-wide scale. It should be noted that this does not mean there is not functional specialization in reading-related regions, nor does it mean there are not any functional relationships between the general (or potentially specialized) processors. What the findings presented here do indicate, is that at least for orthography, reading co-opts visual processing that is also used more generally and that the relationships between reading regions are not the predominant or strongest ones.

Summary of results

In Chapter 2 we defined the functional specificity of the putative visual word form area (VWFA) and studied the particular processing performed in the occipito-temporal fusiform cortex that would be useful for reading. While it seems clear that the putative VWFA is used in fluent reading (Jobard G et al., 2003; Turkeltaub PE et al.; Vigneau M et al., 2006), it was unclear whether this region becomes functionally adapted to be used predominantly in reading (Dehaene S and L Cohen, 2007) or whether it is a general visual processor used in reading and many other visual tasks. By asking fluent adult readers to match words, pseudowords with all legal letter combinations, nonwords with illegal letter combinations, consonant and Amharic character strings, and line drawn pictures, we demonstrated that the putative VWFA does not show preferential processing for words or even letter strings, relative to pictures or Amharic character strings.

Moreover, in Chapter 2 we directly tested what visual processing properties made regions in occipito-temporal fusiform cortex particularly useful in reading. We hypothesized that a visual processor useful in reading would process high spatial frequency, high contrast, complex (i.e. multi-feature) visual stimuli in groups. By comparing the most visually complex letter and Amharic character string pairs to the least complex pairs, we found a specific region in left occipito-temporal fusiform cortex responsive to visual complexity. By studying the interaction between string-type and pair-type (comparing identical pairs to pairs with 2- and 4-character differences), we demonstrated that a region in occipito-temporal fusiform cortex was able to process stimuli that followed the rules or statistical regularities of real words, including words and pseudowords, as a group. In contrast, stimuli that do not follow such rules or statistical regularities, like consonant and Amharic character strings, were processed character-by-character. Importantly, the regions showing the aforementioned interactions – more activity for more visually complex stimuli, grouping dependent on stimulus type and increased activity for Amharic character strings and pictures relative to letter strings – overlapped in only the left occipito-temporal fusiform cortex. Unfortunately, our study design did not allow us to test whether this region specifically responds to high spatial frequency, high contrast stimuli, though other studies (Kveraga et al., 2007) have shown increased activity for high versus low spatial frequency images in the left fusiform cortex.

We investigated the functional connectivity of the putative VWFA, defined by a reading meta-analysis, in Chapter 3. A seed map analysis searching for regions that significantly correlated with the putative VWFA rs-fcMRI timecourse demonstrated this region is not functionally connected to other regions typically used in reading such as regions in the left supramarginal gyrus (SMG), angular gyrus (AG) and inferior frontal gyrus (IFG) (Jobard G et al., 2003; Turkeltaub PE et al., 2002; Vigneau M et al., 2006). Rather, we made the novel observation that the putative VWFA is functionally related to regions in the dorsal attention network, including regions in the bilateral anterior intraparietal sulcus (aIPS), middle temporal area (MT+), and frontal eye fields (FEF). Also, the functional connections between the putative VWFA and aIPS regions increase with age and reading level. These functional connections may be related to the role of the putative VWFA in grouping visual stimuli, information that would conceivably both inform and be influenced by regions used for directing spatial and feature-based attention.

Together, the task based fMRI and rs-fcMRI connectivity results from Chapters 2 and 3 indicate the putative VWFA is not specific for reading or even predominantly used in reading. Rather, it seems to be a general visual processor used in processing complex visual stimuli in groups that is utilized when reading.

In Chapter 4, we extend this finding to a network of reading-regions located across the brain. We performed a meta-analysis of five studies of single-word reading in adults and a single developmental reading study. This meta-analysis found both regions classically described as “reading-related”, such as the putative VWFA, left SMG, AG, and IFG (Jobard G et al., 2003; Turkeltaub PE et al., 2002; Vigneau M et al., 2006), and general processing regions used in the complete transformation of visual information into spoken output, such as primary visual and motor regions, task control and spatial attention regions. We used graph theoretic methods on rs-fcMRI correlations to define the network structure of all of these reading-related regions. Rather than finding a specific “reading” community composed of those regions typically thought to be used predominantly in reading, we found a network structure composed of previously defined communities, including the default mode network (Greicius et al., 2003; Fox MD et al., 2005) and fronto-parietal and cingulo-opercular task control networks (Dosenbach NUF et al., 2007). Studying the network structure in children shows a similar absence of reading specific community structure. Development proceeds via segregation of generally local child communities into integrated communities of regions distributed more widely across the cortex in adults. Again, these non-specific developmental changes indicate there is no specific functional network organization for reading that develops with reading skill or experience.

Finally, in Chapter 5, the activity differences between an implicit visual matching task and an explicit naming task were compared. While many “reading” studies use implicit tasks in order to avoid the complications of collecting fMRI data during overt vocalizations, we demonstrate differences in processing nonwords, pseudowords, and words in matching and naming tasks. These stimulus-type by task by timecourse interactions indicate implicit reading tasks should not be considered equivalent to explicit reading. Not only do these findings have implications for study design, but the finding that changing task design can have such a profound effect on neural processing in reading-related regions supports the proposition that these regions serve some more general purpose that also makes them useful for reading.

Implications for cognitive psychology and neuroscience

Our finding that the occipito-temporal fusiform cortex in general, and the putative VWFA in particular, is not specifically tuned for reading as a cognitive skill may have implications for cognitive psychology. These data call into question the practice of ascribing categorical specificity to visual processing regions. We have shown that despite the use of the putative VWFA in processing letters and words, it retains general processing characteristics as well. Similarly, other “category specific” processors such as the extrastriate body area (EBA) or extrastriate tool area (for other examples see Kanwisher N, 2010), may have more general processing characteristics that make them particularly amenable to processing these types of stimuli while still not being in any way specific to these stimuli. For example, the location of the EBA is very near MT+. It is possible that this visual region is particularly useful for processing things that move (as bodies typically do), but not body parts per se. Of course, the type of processing actually performed in these regions should be specifically tested.

The data presented throughout this dissertation also call into question the practice of ascribing brain regions to particular cognitive domains or skills, such as “reading”. Attempting to describe the actual processing performed in regions and networks is likely to be more informative for understanding the brain at both the level of individual functional areas and functional networks.

By not describing brain regions by a single, cognitive domain or skill, we are not asserting that some functional areas are not used predominantly in certain cognitive skills or domains. For example, regions in the middle temporal lobe (MT+), anterior intra-parietal sulcus (aIPS) and the frontal eye fields (FEF) all seem to be used predominantly in spatial attention processing, and they have strong “functional connections” with each other. Yet, just describing these regions as serving “attention” is a coarse distinction given how their underlying processing properties diverge. It is more informative to know that the MT+ region shows activity modulation based on the presence and direction of motion (i.e., Maunsell JHR and DC Van Essen, 1983), while activity in the aIPS and FEF is modulated during a preparatory period when directing “attention” to specific locations (i.e., Murphey DK and JH Maunsell, 2008; Shulman GL et al., 2001; Snyder LH et al., 1997).

Similarly, while the left SMG and IFG may both be “phonology” regions, they show different fMRI responses (see Chapter 5, Graves WW et al., 2010), and a fuller understanding of these regions may be gained by studying not only which “phonology” tasks drive these regions but whether they are active in other tasks with potentially overlapping processing characteristics. For example, if the SMG really performs an orthographic to phonologic conversion, it could generally be used when pairing visual and auditory stimuli, or when parsing auditory stimuli into “chunks” — both testable hypotheses.

However, moving beyond such domain or skill level descriptions requires a move to reconsider the general way in which most cognitive psychologists and neuroscientists interact with each other and the literature (see Nelson SM, NUF Dosenbach et al., 2010 for another discussion). Currently, many researchers working in a specific domain predominantly read the literature oriented toward that domain and attend conferences and talks in that domain. For example, there are some conferences devoted to only the study of reading or memory (i.e., the Society for the Scientific Studies of Reading Conference or Memory Disorders Research

Meeting), and/or devoted to cognitive control or language (i.e., the Attention and Performance conference and the Annual Neurobiology of Language Conference). If regions are used in multiple tasks, many researchers may not be aware of this cross-functionality, as they are not able to scour the journals for all mention of locations near their (potentially multiple) regions of interest. Thankfully, several new databases, including SUMSdb (http://sumsdb.wustl.edu/sums; Van Essen DC, 2005; Van Essen DC et al., 2001), designed by David Van Essen and colleagues, and Brain Map (http://www.brainmap.org; Fox PT and JL Lancaster, 2002; Laird AR et al., 2005), designed by Peter Fox and colleagues allow for a wider-scale search of individual brain coordinates. Russ Poldrack and colleagues have also attempted to build a database describing studies by the processes tested, rather than the cognitive domain (http://www.cognitiveatlas.org/).

Yet, being able to find information about a given region across many fields of study also requires quality information about the location of a region. While reporting the stereotactic coordinates of activations is increasingly common, it is still not universal. Coordinates are incredibly important, as anatomical descriptions can apply to large swaths of cortex, and clearly distinct functional areas are given similar anatomical descriptions (Devlin JT and RA Poldrack, 2007; Nelson SM, NUF Dosenbach et al. 2010). Brodmann Areas are not a useful descriptor, as there are numerous cytoarchitectonic and anatomical connectivity distinctions within a single Brodmann area (i.e., Ongur D et al., 2003). Additionally, even reported coordinates can differ depending on the atlas (and atlas transformation) used (Devlin JT and RA Poldrack, 2007), so special care should be taken to transform the coordinates into the same atlas space when making comparisons (see Devlin JT and RA Poldrack, 2007 for a discussion and brainmap.org, Eickhoff SB et al., 2009 for transformation algorithms).

Future Directions

Anatomic specificity of the putative VWFA

The type of anatomic specificity discussed above is particularly important for our description of the occipito-temporal fusiform cortex. The location of the left occipito-temporal fusiform visual processing region described in Chapter 2 is not exactly the same as reported putative VWFA coordinates. Rather, this region is located somewhat closer to a fusiform region often found in cued-attention (i.e., Corbetta M and G Shulman, 2002) and search (i.e., Fairhall SL et al., 2009) studies. However, due to the types of anatomical limitations detailed above, resolving this issue is not simply a matter of determining whether “our” region is located closer to one region or another listed in the literature. This is especially true given the possibility that these two regions, the VWFA and the cued attention region, are themselves the same. Thus, as described in Chapter 2, an important next step is developing a better anatomic description of the left fusiform cortex in general and area around the putative VWFA and MT+ in particular.

We plan to address the question of fusiform anatomy using methods similar to those described in Nelson SM, AL Cohen, et al., 2010. This paper, based on methods developed in Cohen et al., 2008, uses changing patterns of rs-fcMRI correlations to divide functional areas. Functional areas are defined by performing a distinct function, or set of processes, and having a distinct pattern of anatomical connections (Felleman DJ and DC Van Essen, 1991). For both of the aforementioned reasons, all voxels located within a given functional area should have a very similar pattern of functional connectivity with the rest of the brain. Neighboring functional areas, on the other hand, will have a somewhat different pattern of functional connectivity. By looking for locations where the pattern of rs-fcMRI correlations changes dramatically, we can define the borders between functional areas; and by looking for locations where the pattern of rs-fcMRI correlations is very consistent, we can define the basic centers of functional areas (for detailed methods and descriptions see (Cohen AL et al., 2008).

After dividing the left fusiform cortex into presumptive functional areas, we can better determine what types of processing are performed in these regions. Functional or processing determinations can be made in two ways—first by looking at similarities and differences in tasks using fMRI, and second by looking at similarities and differences in these regions’ strongest rs-fcMRI defined neighbors (Nelson SM, AL Cohen et al., 2010). As the regions in left occipito-temporal fusiform cortex are reportedly related to visual processing of words, letters, and other visual stimuli (see Chapter 2), cued attention (see Corbetta M and G Shulman, 2002 for a review), and may even relate to evidence accumulation (Ploran EJ et al., 2007) and recognizing or remembering pictures (Van Doren L *et al.*, 2010), we will attempt to discriminate the rs-fcMRI defined regions based on functional timecourses from these types of tasks. We will apply our rs-fcMRI defined regions to the task design used in Chapter 2, along with the naming task described in Chapter 5. These regions can also be applied to cued attention tasks and visual recognition tasks (i.e., Ploran EJ et al., 2007). Moreover, knowing what other regions have the strongest functional relationships with each presumptive fusiform area (i.e., the regions' functional neighbors) will allow us to further describe the regions by their functional networks. The location of these "functional neighbors" and pattern of overlap between them can give insight into both the type of processing done in the putative fusiform regions and the relationships between them (Nelson SM, AL Cohen et al., 2010). This may be especially true as we have a prototype of the relationships expected for the VWFA (see Chapter 3).

Further inquires into the functional properties of a visual processing region used in reading

Regardless of the exact location of the functional area defined in Chapter 2 relative to the putative VWFA, the nature of the processing performed could be further investigated.

Dependence of "grouping" on statistical regularities

We have defined a region in occipito-temporal fusiform cortex that seems to process visually complex stimuli in groups, if the visual properties of the stimuli follow the rules or statistical regularities of real words. The "groupability" of these stimuli is presumably due to experience with those rules and regularities. If the region's ability to group visual stimuli is really dependent on experience with the item, it should show two other properties: the strength of this "grouping" effect should develop with age, and providing visual training should induce grouping of non-letter stimuli with which adult subjects have no experience.

The first hypothesis, that the grouping of word-like stimuli develops with age, would be relatively easy to test. If "grouped" processing of words and letter groups develops with experience, early readers should lack this experience and show a similar pattern of response times and activity for matching words, pseudowords, consonant strings and Amharic character strings. However, to truly test this hypothesis, the experimental design described in Chapter 2 should be modified slightly. Children are significantly slower to match words and letter strings in general (Burgund ED et al., 2006; Hale S, 1990) and in this task (Vogel AC et al., 2007). Accuracy and response time data indicate that, at least inside the MRI, a child's ability to correctly perform the matching task is somewhat compromised as they do not have sufficient time to compare each character in one string to the same position in the other string (unpublished data). Thus, a developmental study would require either a longer presentation time or a shorter string length than the study described in Chapter 2. Moreover, as currently implemented, the subjects saw only 15 pairs of the "all different" and "two character different" conditions. Even if subjects were performing with 100% accuracy, which children did not (unpublished data), this is near the minimal number of measurements needed to get an accurate estimation of the BOLD signal using our GLM approach. Ideally, such modifications would also allow very early readers (i.e. those in kindergarten to first grade) to perform the task, as this is the age most children begin reading.

If the "grouping" observed is the root of specialization in orthographic processing, it should relate to other measurements of specialized orthographic processing. As stated previously, children's response times to name words are dependent on the length of the words (Bijeljac-babic R et al., 2004; Defior S et al., 1996; Martens VEG and PF de Jong, 2008), but as they become better readers response times to name words become relatively independent of length (Cohen L et al., 2003; Weekes BS, 1997). Additionally, children show increased response times to name inconsistent words relative to consistent words (Backman J et al., 1984; Sandak R et al., 2004), whereas adults show no effect of consistency on response time. Along with these behavioral effects there is a decrease in the use of putative phonological processors, such as the left SMG, with age (Church JA et al., 2008; Schlaggar BL and BD McCandliss, 2007). These behavioral and activity measurements indicating the ability to group words into larger chunks should correlate with behavioral and activity measurements of “grouping” words and pseudowords described in Chapter 2.

Additionally, if “grouping” is truly due to experience with the specific rules or statistical regularities of words, increasing experience with a set of non-letter stimuli in adults should promote processing these characters in “groups”. Testing this hypothesis could utilize the same task design described in Chapter 2. If the hypothesis is correct, adults given visual training on Amharic stimuli, such as practice on a matching task, should begin to show behavioral and activity patterns indicative of “grouping” for the trained Amharic strings.

Presentation rate effects on BOLD activity for viewing words

It was also proposed in Chapter 2 that “grouped” processing in occipito-temporal fusiform cortex may underlie the potential advantage for words seen at fast presentation times (i.e., Cohen L et al., 2002; Cohen L et al., 2003; Vinckier F et al., 2007) or in the N200 ERP response (Brem S et al., 2010). To test this theory, one would first have to establish that such visual specialization for words did exist at fast presentation times, even though specialization does not exist at slower presentation rates. To this end, a target detection task could be performed on the stimuli presented here (words, pseudowords, consonant strings and Amharic strings) at various presentation times (i.e. 100, 300, 500, 1000 ms). Early processing specialization would be demonstrated by a presentation-time by string-type by time interaction, whereby words and pseudowords would show more activity than consonant and Amharic strings at the fast presentation times but less activity than the consonant and Amharic strings at slow presentation times. If such a fast processing advantage exists, it could be due to the “grouped” processing of word and pseudoword stimuli. Such a hypothesis would be supported by a finding that visual training with Amharic stimuli decreases the differences in BOLD activity between words and Amharic strings at all presentation times (i.e. at the fastest presentation times the activity for processing Amharic characters is would increase relative to words and at the slower presentation times, the activity would decrease relative to words).

Top-down influences on visual processing of word and letter forms

While we showed the predominant functional connections of the putative VWFA are with spatial attention regions rather than “reading” regions, there must be some feedforward mechanism by which visual information about words and letters is passed to phonologic and semantic processors and by which those processes feedback onto this visual component. Some evidence for such feedback effects does exist. There are semantic priming effects in the putative VWFA (Devlin JT et al., 2006), yet it is unlikely to be a semantic processor, as there is more activity for meaningless visual stimuli such as consonant strings and Amharic character strings than meaningful stimuli such as words. Also, phonologic and semantic training of non-letter stimuli increases BOLD activity in this region (Xue G et al., 2006). Furthermore, Bar and colleagues have shown top down influences of frontal cortex on similar left fusiform regions during object processing (Bar M et al., 2006).

While we were unable to detect the influence of phonologic and semantic processing on the putative VWFA due to methodological confounds, these are testable effects. Tasks that emphasize phonologic or semantic processing should increase activity in this region relative to simple visual matching tasks. For example, having subjects make a rhyme judgment on two words, pseudowords, or pictures should increase activity in the putative VWFA if there is an effect of phonological processing. Similarly, having subjects make a semantic categorization judgment on two words or pictures should increase putative VWFA activity relative to simple visual matching, if semantic activity has an effect on putative VWFA processing.

Unfortunately fMRI does not have the temporal resolution to fully demonstrate the feedback or feedforward nature of these effects—though MEG does have such capability. By defining the neural locations of regions responding to phonologic and semantic manipulations in fMRI task studies, one should be better able to interpret the less spatially distinct MEG activity. Then, MEG timecourses can be used to determine the relative timing of phonologic and semantic effects in the putative VWFA (similar to the technique used in Bar M et al., 2006).

Use of functional relationships to inform the specialization of other reading-related regions

Thus far, I have predominantly focused on how these results can inform orthographic processing, but the large reading network study in Chapter 4 also gives tantalizing hints about the possible specialization of other regions thought to be predominantly used in reading. Our network level analysis showed that while regions in the SMG and AG are localized to the same functional community in children, they belong to two separate functional communities, the auditory temporal community and default community, in adults (see Chapter 4). These results mimic the developmental functional distinction between these regions seen in Church et al., 2008. In this study, Church and colleagues demonstrate that both the SMG and AG show positive activity for reading words in children, while only the SMG has positive activity when reading words in adults (Church JA et al., 2008).

A specific analysis of the functional relationships of the SMG and AG may inform our understanding of both the role of these regions in reading and how that role changes with age. For example, the SMG seems to have a functional relationship with both auditory regions and the left IFG in adults, while the AG does not (unpublished data). These results indicate a potential primary role for the SMG but not the AG in reading or language. Studying correlations from the rs-fcMRI correlations between SMG and AG and other reading, auditory, and motor regions to reading level and age (similar to the developmental analysis performed on putative VWFA functional connections in Chapter 3), may inform our understanding of whether this functional divergence is related to developing reading skill or some other process.

Informing the underlying etiology of reading disorders

While dyslexia has typically been characterized as resulting from problems with phonological processing, there is strong evidence for at least some disruption in visual processing. Dyslexic subjects show decreased BOLD activity in the putative VWFA when reading words (Shaywitz BA et al., 2002; Shaywitz BA et al., 2007). A subset of dyslexic subjects also show impairments in matching symbol strings (Pammer K et al., 2004) and simultaneous processing of consonant strings (Lassus-Sangosse D et al., 2008). It is unclear whether these orthographic processing deficits are separate from or are caused by phonological processing deficits (Gabrieli JD, 2009), but, regardless, they exist.

Visual processing deficits in dyslexia could be related to a possible deficit in “grouping” words and letter strings into the appropriate chunks, though this has not been tested directly. The methods described in Chapter 2 provide a potential mechanism to test for disruption of “grouping” in dyslexia. If such disruption exists, it should manifest as a reduced pair-type by string-type interaction in dyslexic subjects relative to fluent readers, or in other words, less differences between stimuli that have word-like features relative to stimuli that do not. Moreover, studying the ability of dyslexic subjects to group visual stimuli with and without phonological referents may give insight into the primacy of visual deficits in dyslexia. If a disruption in “grouped” processing exists in dyslexics and if visual training with Amharic stimuli increases “grouping” of Amharic characters in fluent readers but not dyslexics, one could argue that part of the dysfunction observed in dyslexia is due to a primary deficit in the capacity for visual “grouping”.

Additionally, some dyslexic subjects seem to show a specific deficit in visual attention (Valdois S et al., 2004; Vidyasagar TR and K Pammer, 2010). This deficit could be related to impaired ability to group stimuli, which in turn could result in (or result from) impaired connectivity between the putative VWFA and aIPS regions related to spatial attention (Corbetta M and G Shulman, 2002). As mentioned in the discussion of Chapter 3, comparing the functional connectivity of the putative VWFA in fluent and dyslexic readers could give insight into whether spatial attention plays a role in this disorder.

If fluent reading is related to specific visual processing characteristics such as grouping and relationships to the dorsal attention network, this not only identifies another possible process and set of neural regions that may be dysfunctional in dyslexia, but a potential way to discriminate between dyslexic or delayed readers who may differentially responsive to various treatments. Additionally, if these visual processing characteristics do related to impaired reading, they may also offer new potential remediation or early intervention techniques such as increasing visual experience with words and letters, potentially in ways that encourage readers to group the letters into chunks of various sizes.

Conclusions

Reading, though an important skill for most adults in the developed world, is not subserved by a network of regions specifically devoted to reading-related processing. Orthographic processing is done by a general visual processor that happens to be used in reading. Functional activation and functional connectivity results indicate this region is involved in the processing of complex visual stimuli in groups. Moreover, not only does the “orthographic processing region” lack specific functional connections to other regions thought to be predominantly used in reading, these other regions do not have preferential functional connections to each other. These results, and the finding that changing task demands can change the processing performed in these regions for visual stimuli with varied lexical properties, indicates a lack of specificity for “reading” in the brain. Thus, rather than the acquisition of fluent reading fundamentally reshaping neural areas (as argued in Dehaene and Cohen, 2007), reading seems to utilize but not co-opt phylogenetically older processes and networks.

I argue the results presented here challenge three dominant themes in cognitive psychology and neuroscience. First, it should be understood that changing task demands can change functional processing. Therefore task design, in reading and other domains, should be carefully considered. Second, the ascription of particular stimulus categories to visual processing regions should be re-thought. At the very least, the VWFA should be understood not as a visual word form area but as at least a visual word, object, and squiggly line area- a cumbersome abbreviation that indicates that a better description would be anatomically, and specifically coordinate, based. Third, functional regions and networks are perhaps better ascribed to particular processes than cognitive domains or skills.

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