Localization of Phonological and Semantic Contributions to Reading

J. Vivian Dickens,¹ Mackenzie E. Fama,^{1,3} Andrew T. DeMarco,¹ Elizabeth H. Lacey,^{1,2} Rhonda B. Friedman,¹ and Peter E. Turkeltaub^{1,2}

¹Department of Neurology, Georgetown University Medical Center, Washington, District of Columbia 20007, ²Research Division, MedStar National Rehabilitation Hospital, Washington, District of Columbia 20010, and ³Department of Speech-Language Pathology and Audiology, Towson University, Towson, Maryland 21252

Reading involves the rapid extraction of sound and meaning from print through a cooperative division of labor between phonological and lexical–semantic processes. Whereas lesion studies of patients with stereotyped acquired reading deficits contributed to the notion of a dissociation between phonological and lexical–semantic reading, the neuroanatomical basis for effects of lexicality (word vs pseudo-word), orthographic regularity (regular vs irregular spelling–sound correspondences), and concreteness (concrete vs abstract meaning) on reading is underspecified, particularly outside the context of strong behavioral dissociations. Support vector regression lesion–symptom mapping (LSM) of 73 left hemisphere stroke survivors (male and female human subjects) not preselected for stereotyped dissociations revealed the differential contributions of specific cortical regions to reading pseudowords (ventral precentral gyrus), regular words (planum temporale, supramarginal gyrus, ventral precentral and postcentral gyrus, and insula), and concrete words (pars orbitalis and pars triangularis). Consistent with the primary systems view of reading being parasitic on language-general circuitry, our multivariate LSM analyses revealed that phonological decoding depends on perisylvian areas subserving sound–motor integration and that semantic effects on reading depend on frontal cortex subserving control over concrete semantic representations that aid phonological access from print. As the first study to localize the differential cortical contributions to reading pseudowords, regular words, and concrete words in stroke survivors with variable reading abilities, our results provide important information on the neurobiological basis of reading and highlight the insights attainable through multivariate, process-based approaches to alexia.

Key words: acquired dyslexia; alexia; lesion–symptom mapping; reading; stroke

Significance Statement

Whereas fMRI evidence for neuroanatomical dissociations between phonological and lexical–semantic reading is abundant, evidence from modern lesion studies establishing the differential contributions of specific brain regions to specific reading processes is lacking. Our application of multivariate lesion–symptom mapping revealed that effects of lexicality, orthographic regularity, and concreteness on reading differentially depend on areas subserving auditory–motor integration and semantic control. Phonological decoding of print relies on a dorsal perisylvian network supporting auditory and articulatory representations, with unfamiliar words relying especially on articulatory mapping. In tandem with this dorsal decoding system, anterior inferior frontal gyrus may coordinate control over concrete semantic representations that support mapping of print to sound, which is a novel potential mechanism for semantic influences on reading.

Introduction

Localization of components of the reading network is a matter of longstanding investigation (Dejerine, 1892). Seminal studies of

patients with alexia, an acquired disorder of reading, contributed to the positing of at least two reading mechanisms: a phonologi-

Received Oct. 18, 2018; revised April 8, 2019; accepted April 29, 2019.

Author contributions: J.V.D., A.T.D., and P.E.T. analyzed data; J.V.D. wrote the first draft of the paper; J.V.D., A.T.D., and P.E.T. wrote the paper; M.E.F. and E.H.L. performed research; M.E.F., E.H.L., and R.B.F. edited the paper; E.H.L., R.B.F., and P.E.T. designed research.

This work was supported by the National Institute on Deafness and Other Communication Disorders (NIDCD)—National Institutes of Health (NIH) (Grants R01DC014960 and R03DC014310 to P.E.T., Grant F31 DC014875 to M.E.F., and Grant F30DC018215 to J.V.D.), Georgetown–Howard Universities Center for Clinical and Translational Sciences

(Grant KL2TR000102 to P.E.T. and Grant TL1TR001431 to A.T.D.), the Doris Duke Charitable Foundation (Grant 2012062 to P.E.T.). We thank Laura Skipper-Kallal for training the first author in lesion segmentation and SVR-LSM; Zainab Anbari for contributions to data collection and organization; and our participants for their commitment to furthering work on the neurobiology of reading and language.

The authors declare no competing financial interests.

Correspondence should be addressed to J. Vivian Dickens at jmd345@georgetown.edu.

<https://doi.org/10.1523/JNEUROSCI.2707-18.2019>

Copyright © 2019 the authors

Table 1. Participant demographic and clinical data

Analysis group	Age	Education	Gender	Chronicity	PNT	WAB Yes/No	MLU*
Lexicality ($n = 73$)	59.38 (9.67)	16.05 (2.98)	32 F, 41 M	44.46 (46.76)	34.1 (21.2)	54.9 (6.3)	4.3 (2.4)
Regularity and concreteness ($n = 48$)	60.10 (9.77)	16.42 (3.09)	16 F, 32 M	51.54 (50.67)	33.4 (21.5)	55.1 (5.4)	4.2 (2.6)

Values are shown as means (SD). The lexicality group completed the word/pseudoword reading task. The regularity and concreteness group completed the regular/irregular and concrete/abstract reading tasks. Age and education are in years. Poststroke chronicity is in months. PNT is the Philadelphia Naming Test raw score out of 60 (Roach et al., 1996). WAB Yes/No represents the raw score out of 60 on the Yes/No Questions Auditory Verbal Comprehension subtest of the Western Aphasia Battery–Revised (Kertesz, 2006). MLU is the mean length of utterance on a picture description task.

*MLU data not available for two participants in regularity/concreteness group and for nine in the lexicality group.

cal procedure through which sound is decoded from print and a lexical–semantic procedure through which whole-word knowledge is accessed (Marshall and Newcombe, 1973; Coltheart et al., 1980; Patterson et al., 1985). Impairments in phonological and lexical–semantic reading processes manifest as dissociable deficits observed in alexia syndromes, which are defined by the type of words the patient reads inaccurately. In the case of the nonvisual “central” alexias (i.e., phonological, surface, and deep alexia; Coslett and Turkeltaub, 2016), the dimensions of lexicality (word vs pseudoword), orthographic regularity (regular vs irregular grapheme–phoneme correspondences), and concreteness (concrete vs abstract meaning) are defining. Localization of neural contributions to phonological and lexical–semantic reading remain unclear, especially outside the context of strong alexic dissociations, and the degree to which reading depends on the more general, or “primary,” systems of phonology and semantics is debated (Woollams, 2014).

An effect of lexicality in which pseudowords are read less accurately than real words defines phonological alexia (Beauvois and Dérouesné, 1979). Whereas phonological and lexical–semantic processing support real words, novel letter strings (e.g., “t–w–u–v”) lack lexical–semantic support and rely on direct phonological decoding. Attempts to identify a critical lesion site for phonological alexia have yielded inconsistent results throughout perisylvian cortex (Lambon Ralph and Graham, 2000; Rapsak et al., 2009; Ripamonti et al., 2014).

Deep alexia may be thought of as a severe form of phonological alexia with concomitant semantic impairment (Friedman, 1996). An effect of concreteness in which words with abstract meanings are read less accurately than words with referents highly available to the senses is thus characteristic of deep alexia and, in some cases, phonological alexia (Friedman, 2002). Examination of acquired concreteness effects in reading are limited to lesion–syndrome studies of phonological/deep alexia, with lesioned left insula being implicated in a nonstatistical subtraction analysis of 10 phonological alexics (Ripamonti et al., 2014). Within the broader semantic cognition literature, EEG (Adorni and Proverbio, 2012), fMRI (Binder et al., 2009; Wang et al., 2010), PET (Binder et al., 2009; Wang et al., 2010), and lesion studies (Warrington, 1981; Loiselle et al., 2012; Joubert et al., 2017) suggest dissociable systems for abstract and concrete concepts, with abstract and concrete concepts perhaps relying more on verbal perisylvian and perceptual extrasyllabic regions, respectively (Binder et al., 2009). Importantly, for the goals of the current study, the neural basis for the concrete word advantage in reading is unknown.

Surface alexia is defined by an effect of regularity in which words with irregular grapheme–phoneme correspondences (e.g., “yacht”) are read less accurately than words with regular correspondences and pseudowords (Marshall and Newcombe, 1973). Typical grapheme–phoneme correspondences yield incorrect pronunciations of irregular words (i.e., regularization errors). Thus, access to whole-word knowledge either at the level of the orthographic word form or lexical semantics is thought of as

being especially critical for reading irregular words. Surface alexia is associated with semantic dementia, a disorder characterized by gradual temporal lobe atrophy (Woollams et al., 2007), and is less common in individuals with focal lesions. Whereas there is lesion evidence for lexical–semantic processing contributing more to reading irregular words (Woollams et al., 2007), there is no complementary lesion evidence for phonological decoding contributing more to reading regular words.

Overall, previous lesion studies of alexia have pursued syndrome-based localization in which lesions are analyzed in relation to categorical diagnoses based on clustering of behavioral deficits. Despite its merits, this approach precludes examination of the full spectrum of reading performance and lesion–behavior associations in the broader patient population. This study aimed to identify the differential contributions of brain areas to reading words that vary in lexicality, regularity, and concreteness through multivariate lesion–symptom mapping (LSM) in left hemisphere stroke survivors not preselected for alexia.

Materials and Methods

Participants

Participants were 73 native English-speaking adults (spoken since age ≤ 5) with chronic left hemisphere ischemic or hemorrhagic stroke (Table 1). All participants were drawn from a larger study investigating the brain basis of aphasia recovery and had at least 10 years of education and adequate vision with correction and hearing. Exclusion criteria were a history of stroke outside the left hemisphere, significant brain injury, or other significant neurological and psychiatric disorder. All participants performed the pseudoword reading task and a subset of 48 also performed the regular/irregular and concrete/abstract word reading tasks. In order to characterize the general language abilities of participants, Table 1 also provides performance on the Philadelphia Naming Test (Roach et al., 1996), the Yes/No Questions Auditory Verbal Comprehension subtest of the Western Aphasia Battery–Revised (Kertesz, 2006), and the mean length of utterance (MLU) on a picture description task. The Georgetown University Institutional Review Board approved the study protocol and all participants gave written informed consent.

Experimental design and statistical analysis

Oral reading battery. Participants completed a battery in which they read aloud words that varied along the dimensions of lexicality, orthographic regularity, and concreteness. There were three pairs of matched lists: pseudowords and regularly spelled real words, regular words and irregular words, and concrete words and abstract words (Table 2). The word/pseudoword list consisted of 20 pairs of monosyllabic strings of three or four letters to minimize articulatory complexity, with pseudowords differing from the matched regular words by one letter. The regular/irregular word list consisted of 15 word pairs selected from PALPA 35 (Kay et al., 1996) and matched on letter length, CELEX log10 word form frequency (Baayen et al., 1995), bigram frequency (Medler and Binder, 2005), and concreteness (Brysbaert et al., 2014). The concrete/abstract word list consisted of 30 word pairs matched on letter length, log10 frequency, and bigram frequency. Each pair of matched lists constituted its own block in the session. Within a block, an item from the matched lists was presented pseudorandomly at the center of fixation on a computer screen in Calibri font (size 44) via PowerPoint. Each item was cued by a beep and participants had 10 s to read the item aloud and end the

Table 2. Reading battery characteristics

<i>n</i>	Word 20	Pseudoword 20	Regular 15	Irregular 15	Concrete 30	Abstract 30
Letter Length	3.5 (0.51)	3.5 (0.51)	5.2 (1.37)	5.13 (1.25)	5.53 (1.38)	5.53 (1.38)
Log10 Freq	1.48 (0.69)	N/A	1.27 (0.53)	1.44 (0.55)	1.74 (0.35)	1.94 (0.46)
Bigram Freq	19.57 (15.80)	16.02 (13.39)	15.58 (8.90)	18.74 (9.26)	21.96 (10.66)	23.83 (12.27)
Concreteness	4.33 (0.64)	N/A	3.68 (1.21)	4.24 (0.83)	4.76 (0.20)	2.24 (0.55)

Values are shown as means (SD). Log10 freq represents the log10 of the CELEX word form frequency per million (Baayen et al., 1995). Bigram freq represents the unconstrained CELEX bigram frequency in thousands (Medler and Binder, 2005). Concreteness ratings range from 1–5 and are drawn from Brysbaert et al. (2014).

trial via a key press. Responses were recorded digitally, scored online, and rescored offline as either correct (1) or incorrect (0) based on the first complete response. Overall accuracy scores in reading aloud each of the six item categories served as the behavioral outcomes of interest.

Image acquisition. Participants completed a single scanning session in the Center for Functional and Molecular Imaging at Georgetown University. Images were acquired on a 3 T Siemens Trio scanner using a 12-channel head coil. For each patient, a high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was acquired with the following parameters: 176 sagittal slices; slice thickness = 1 mm, field of view (FOV) 250 × 250 mm; matrix = 256 × 256; repetition time (TR) = 1900 ms; echo time (TE) = 2.52 ms; inversion time (TI) = 900 ms; flip angle = 9°, voxel size = 1 × 1 × 1 mm. Additionally, a T2-weighted sampling perfection with application optimized contrasts using different flip angle evolution (SPACE) sequence was acquired with the following parameters: 176 sagittal slices; slice thickness = 1.25 mm, FOV = 240 × 240 mm; matrix = 384 × 384; TR = 3200 ms; echo train length = 145, variable TE; variable flip angle, voxel size = 0.625 × 0.625 × 1.25 mm.

Lesion tracing and normalization. Lesion masks were manually segmented on each participant's MPRAGE using ITK-SNAP software (Yushkevich et al., 2006; <http://www.itksnap.org/>) by P.E.T., a board-certified neurologist. T2-weighted structural images were referenced for additional sensitivity to white matter lesions within the vascular distribution of the stroke. Native space MPRAGEs and lesion tracings were warped to MNI space using the Clinical Toolbox Older Adult Template as the target template (Rorden et al., 2012) via a custom pipeline. First, brain parenchyma was extracted from each native space image by applying a mask intended to minimize the clipping of gray matter edges. The initial mask was generated by combining the lesion tracing image (binarized) with white and gray matter tissue probability maps generated by the unified segmentation procedure in SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) applied to the original native space image, cost function masked with the lesion tracing. The resulting mask was blurred and inverted to remove nonbrain tissue from the image. The resulting brain extracted image was then normalized using Advanced Normalization Tools software (ANTs; <http://stnava.github.io/ANTs/>; Avants et al., 2011). Lesion masking was used at each step of the ANTs process. After bias field correction was applied, normalization proceeded using a typical ANTs procedure, including a rigid transform step, an affine transform step, and a nonlinear SyN step. Next, the output of this initial ANTs warp was recursively submitted to three additional applications of the SyN step. Finally, the resulting linear (rigid and affine) and four nonlinear warp fields were concatenated and the original native space MPRAGE and lesion tracings were transformed to the template space using BSpline interpolation. This iterative application of nonlinear warping was intended to improve normalization of expanded ventricles and displaced deep structures in individuals with large lesions. The normalized lesion tracings were finally downsampled to 2.5 mm³.

Multivariate LSM. We applied a multivariate LSM technique called support vector regression LSM (SVR-LSM) (Zhang et al., 2014) to localize brain areas that contribute to phonological and lexical–semantic reading processes. Given the nonrandom nature of lesion distributions and the resultant autocorrelation of voxel lesion status, univariate methods such as voxel-based LSM (VLSM) (Bates et al., 2003) are vulnerable to mislocalization, especially when multiple brain areas support the process of interest (Mah et al., 2014). In this study, consideration of lesion covariance is particularly important because reading relies on a distrib-

uted network of coordinated regions (Turkeltaub et al., 2002; Price, 2012). SVR-LSM considers the lesion status of all voxels in a single regression model and is less vulnerable to lesion mislocalization and more sensitive to nonlinear relationships (Zhang et al., 2014). We applied SVR-LSM in MATLAB R2017b via a graphical user interface implementation developed in our laboratory (DeMarco and Turkeltaub, 2018; <https://github.com/atdemarco/svrlsmgui/>). Only voxels lesioned in at least 10% of participants were included in each analysis. We controlled for effects of lesion volume on reading accuracy by regressing lesion volume on both the lesion data and behavioral outcomes of interest, a method that eliminates lesion volume biases while maintaining sensitivity to lesion–behavior relationships (DeMarco and Turkeltaub, 2018). Six one-tailed (negative) SVR-LSM analyses were run to identify lesions associated with inaccurate reading of pseudowords, real words, regular words, irregular words, concrete words, and abstract words; accuracy on the word type of interest served as the dependent variable in each of these analyses. To isolate the effects of interest in the reading scores, accuracy on the corresponding control task was covaried with both the reading score of interest and the lesion data (e.g., for the analysis on concrete word reading, abstract word reading was included as a covariate to isolate the effects of high concreteness). Regardless of word type, reading engages similar visual, phonological, semantic, executive, and motor output processes. In a population of stroke survivors not preselected for alexia syndromes, strong dissociations across tasks are unlikely. Covarying performance on the matched reading task enables estimation of the typical poststroke relationship between reading pseudowords and real words, regular and irregular words, and concrete and abstract words and shows whether deviations from these typical relationships relate to lesion distribution. In other words, the lesion–symptom mapping analyses tested whether performance on the word type of interest was worse than is typical as determined through the relationship with the matched word type. This approach controls for all the shared processes across word types—for example, vision and speech production—and isolates the processes that are differentially important for reading each word type. Significance was determined using a permutation-based approach in which the behavioral scores were randomly reassigned to participants and SVR- β -value maps were generated for each of 10,000 permutations. SVR- β values were catalogued on a voxelwise basis and thresholded at $p < 0.005$ (one-tailed). To correct these maps for multiple comparisons, a cluster size threshold was applied to achieve a familywise error rate of 0.05 based on the largest cluster in each of the voxelwise thresholded permutation maps. This permutation approach minimizes the effects of lesion autocorrelation in LSM analyses (Kimberg et al., 2007). Overall, clusters identified through SVR-LSM represent lesions that account for additional variance in performance reading the word type of interest over and above the variance captured by performance on the control reading task.

Results

Participants demonstrated a wide range of reading abilities, as indicated by the large variance relative to total points possible (Table 3). Figure 1 shows the relationship between paired tasks as estimated through linear regression. The best-fit lines (Fig. 1) and the mean difference in performance between paired tasks (Table 3) demonstrate that, on average, participants tended to perform equally well on regular and irregular words, whereas participants tended to perform slightly less well on abstract words compared

Table 3. Summary of participant performance on reading battery

Effect of interest	Word type	Mean accuracy (SD)	Mean difference (SD)	Range of difference
Lexicality	Word	67% (36)	32% (26)	–5 to +95%
	Pseudoword	35% (35)		
Regularity	Regular	63% (38)	0% (12)	–33 to +27%
	Irregular	63% (36)		
Concreteness	Concrete	67% (39)	2% (8)	–27 to +23%
	Abstract	65% (39)		

Mean difference indicates the average difference in accuracy between words and pseudowords, regular and irregular words, and concrete and abstract words. Range of difference indicates the minimum and maximum difference in accuracy between words and pseudowords, regular and irregular words, and concrete and abstract words. A total of 73 subjects completed the lexicality task; 48 completed the regularity and concreteness tasks.

with concrete words. Most subjects read pseudowords less accurately than the matched real words or were otherwise equally accurate on both. To determine how general decoding ability related to effects of regularity and concreteness on reading accuracy in the 48 subjects who completed all reading tasks, accuracy on pseudowords was correlated with the difference in accuracy between regular and irregular words and concrete and abstract words. Pseudoword reading accuracy correlated positively with the difference in accuracy between regular and irregular words ($r = 0.38$, $p = 0.008$). Thus, poorer decoding ability related to less of an advantage for regular words over irregular words. Pseudoword reading accuracy did not correlate with the difference in accuracy on concrete and abstract words ($r = 0.01$, $p = 0.935$).

Because the matched tasks were included as covariates for LSM, deviations from the relationship between paired tasks (i.e., the residuals from the best-fit lines; Fig. 1) reflect the individual variations in poststroke effects of lexicality, regularity, and concreteness. These residuals are the values that were tested for relationships with lesion distribution during LSM. Specifically, the SVR-LSM analyses tested whether lesion distribution systematically related to worse performance on the word type of interest given its typical relationship with the matched word type (Fig. 1).

Figure 2 shows the lesion overlap maps of the entire participant pool (Fig. 2A; $n = 73$) and of the subset who completed the full reading battery (Fig. 2B; $n = 48$). These lesion maps demonstrate broad coverage of frontal, parietal, and superior temporal areas involved in reading and language processing. Lesion coverage in ventral occipitotemporal areas important for reading was not adequate for inclusion in analyses.

No clusters survived correction for multiple comparisons for SVR-LSM analyses of inaccurate reading of real words relative to pseudowords, abstract words relative to concrete words, or irregular words relative to regular words. SVR-LSM analyses yielded significant clusters associated with less accurate reading of regular words and concrete words relative to their matched control word types, as well as a borderline significant cluster for pseudowords (Fig. 3). Lesions to left ventral precentral gyrus related to less accurate reading of pseudowords (cluster size = 4063 mm^3 , cluster $p = 0.051$). Lesions to left planum temporale, anterior supramarginal gyrus, ventral postcentral gyrus, central/posterior insula, and ventral precentral gyrus related to less accurate reading of regular words (cluster size = 18813 mm^3 , cluster $p = 0.004$); this cluster's extension into ventral precentral gyrus nearly fully encompassed the cluster associated with inaccurate pseudoword reading (note magenta in Fig. 3). The clusters associated with inaccurate reading of pseudowords and regular words extended into the underlying white matter. Lesions to pars orbitalis and pars triangularis of left inferior frontal gyrus and left anterior insula related to less accurate reading of concrete words

(cluster size = 4656 mm^3 , $p = 0.049$). Table 4 summarizes the size, location, and center of mass of the clusters identified through SVR-LSM, as well as the maximal amount of lesion overlap between subjects within each cluster.

Discussion

The neuroanatomical bases for phonological and semantic contributions to reading are underspecified. Our multivariate LSM analyses demonstrated the differential contributions of specific cortical regions to reading words that vary in lexicality, orthographic regularity, and concreteness. Building on activation studies suggesting that reading relies on a distributed network (Turkeltaub et al., 2002; Price, 2012; Martin et al., 2015), our application of SVR-LSM to a cohort of stroke survivors with variable reading impairments provides evidence for phonological decoding of print depending on dorsal perisylvian areas subserving sound–motor integration (Vigneau et al., 2006; Hickok and Poeppel, 2007) and for semantic influences on reading depending on frontal cortex subserving semantic control (Ralph et al., 2017). Consistent with the primary systems hypothesis that reading is instantiated within the general architecture of phonology and semantics (Patterson and Ralph, 1999), the perisylvian and frontal clusters correspond to cortex previously identified through SVR-LSM as critical for phonological working memory and word retrieval, respectively (Lacey et al., 2017).

An acquired deficit in reading pseudowords (i.e., phonological alexia) has been associated with circumscribed and expansive lesions throughout perisylvian regions (Lambon Ralph and Graham, 2000; Rapcsak et al., 2009; Ripamonti et al., 2014) that likely constitute a network subserving phonology (Vigneau et al., 2006). Whereas our results implicating cortex associated with pseudoword reading more than real word reading and regular word reading more than irregular word reading cannot speak to a nonlexical mapping procedure specialized for reading (Coltheart et al., 2001; Nickels et al., 2008), they are consistent with the primary systems view (Woollams, 2014) of phonological decoding relying on perisylvian circuits subserving articulatory (ventral precentral gyrus and insula), auditory (planum temporale), and somatosensory (ventral postcentral and supramarginal gyri) contributions to phonology. Moreover, the finding that lesions to these perisylvian areas related more to deficits in regular word reading than deficits in irregular word reading aligns with the proposal that direct phonological decoding best subserves regular words (Plaut, 1997). It would thus be expected that poor general decoding ability, as indexed through pseudoword reading accuracy, would correlate with less of an advantage of regular words over irregular words; this was indeed the case.

Consideration of the role that the implicated regions play in both reading and language may elucidate the functional organization of this dorsal decoding system. First, the relationship of lesioned ventral precentral gyrus (vPG) with deficits in pseudoword reading more than real word reading and in regular word reading more than irregular word reading supports an important role for articulatory mapping (Pulvermüller et al., 2006) during decoding. Involvement of vPG is unlikely to reflect articulatory complexity given our closely matched control words (Table 2). Compared with familiar words, pseudowords may tax this decoding system and require greater support from articulatory representations subserved by vPG. Indeed, pseudowords consistently activate left frontal operculum more than words during reading and spelling (Jobard et al., 2003; DeMarco et al., 2017). Additionally, real words tend to show no unique activations compared with pseudowords or show activations suggestive of se-

Figure 1. Relationship between accuracy on paired reading tasks as determined through linear regression. **A**, Matched real words and pseudowords ($n = 73$). Participants tended to read pseudowords less accurately than real words. **B**, Matched irregular and regular words ($n = 48$). On average, participants read regular words and irregular words equally well. **C**, Matched abstract and concrete words ($n = 48$). On average, participants read abstract words slightly less accurately than concrete words. The shaded region around the lines of best fit represent the 95% confidence curves.

Figure 2. Lesion overlap maps. **A**, Lesion overlap map of lexicality analysis group ($n = 73$). **B**, Lesion overlap map of orthographic regularity and concreteness analysis group ($n = 48$).

mantic engagement (Binder et al., 2009; Price, 2012; Taylor et al., 2013). Although insular contributions to decoding are unclear, our reported association of lesioned central/posterior insula with reduced regular word reading accuracy is consistent with insular involvement in articulatory control (Dronkers, 1996), sensorimotor integration (Chang et al., 2013), and reading (Ripamonti et al., 2014).

The implication of lesioned left planum temporale (PT) with reduced regular word reading accuracy suggests auditory representations contribute to decoding. PT activity relates to sublexical speech perception (Turkeltaub and Coslett, 2010; Schwartz et al., 2012; Mirman et al., 2015), letter and speech sound congruity (van Atteveldt et al., 2004), and literacy acquisition (Dehaene et al., 2010). PT may also be a substrate for sensory–motor integra-

Figure 3. SVR-LSM results at voxelwise $p < 0.005$ and clusterwise FWE $p < 0.05$, with lesion size regressed out of the behavioral and lesion data. **A**, Inaccurate pseudoword reading relative to real word reading localized to left ventral precentral gyrus, shown in red (clusterwise $p = 0.051$). **B**, Inaccurate regular word reading relative to irregular word reading localized to a cluster spanning left planum temporale, supramarginal gyrus, ventral postcentral gyrus, ventral precentral gyrus, and central/posterior insula, shown in blue (clusterwise $p = 0.004$). **C**, Inaccurate concrete word reading relative to abstract word reading localized to lesioned left pars orbitalis and pars triangularis and left anterior insula, shown in green (clusterwise $p = 0.049$). **D**, Combined cluster overlays, with magenta representing the overlap between the regular word and pseudoword clusters within left precentral gyrus. **E**, 3D rendering of SVR-LSM results. No clusters survived correction for multiple comparisons for inaccurate reading of real words, abstract words, and irregular words relative to their matched word types.

Table 4. Size and location of SVR-LSM clusters associated with inaccurate reading of pseudowords, regular words, and concrete words

Word type	Cluster volume (mm ³)	Center of mass	Anatomical sites	Maximal lesion overlap (n)
Pseudowords	4063	MNI = −38, −1, 16	Ventral precentral gyrus	35
Regular words	18813	MNI = −44, −11, 14	Planum temporale	30
			Supramarginal gyrus	
			Ventral postcentral gyrus	
			Ventral precentral gyrus	
			Central/posterior insula	
Concrete words	4656	MNI = −44, 28, −6	Pars triangularis	17
			Pars orbitalis	
			Anterior insula	

MNI, Montreal Neurological Institute coordinates. Cluster volume and center of mass were generated through our SVR-LSM GUI implementation (DeMarco and Turkeltaub, 2018; <https://github.com/atdemarco/svrlsmgui/>). The maximal lesion overlap column indicates the largest amount of lesion overlap between subjects within each cluster.

tion in auditory and speech processing (Hickok et al., 2009), with lesioned PT relating to phonological working memory deficits and conduction aphasia (Buchsbaum et al., 2011). Thus, PT may be an essential interface (Dehaene, 2009) between the occipito-temporal visual word recognition system (Vinckier et al., 2007) and the dorsal auditory–motor system (Hickok and Poeppel, 2007). The relationship of lesioned anterior supramarginal gyrus (SMG) with reduced regular word reading accuracy is consistent with the relationship of SMG density with reading aloud in central alexics (Aguilar et al., 2018) and SMG's role in phonemic (Turkeltaub and Coslett, 2010; Schwartz et al., 2012) and non-lexical (Papagno et al., 2017; Savill et al., 2019) order processing.

Together with ventral postcentral gyrus, SMG may underlie somatosensory contributions to phonology (Hickok, 2012). Overall, these findings point to a decoding procedure emergent from interactions between left-lateralized auditory, somatosensory, and articulatory cortex.

The lexical–semantic route is probably the less understood of the two hypothesized reading pathways. In particular, semantic influences on reading aloud are controversial (Taylor et al., 2015), with dual route models holding that the semantic system is inconsequential for mapping orthography to phonology (Coltheart et al., 2001; Perry et al., 2007). Previous studies of normal reading demonstrated an imageability by regularity interaction (Strain et al., 1995, 2002; Cortese et al., 1997) such that mappings to highly imageable concepts support phonological access from poorly decodable words. Our SVR-LSM result implicating lesioned left anterior inferior frontal gyrus (IFG), an area critical for semantic control (Ralph et al., 2017), with reduced concrete word reading accuracy suggests that semantic effects on reading aloud depend on an intact semantic control network. The support afforded by high imageability in accessing lexical phonological representations (Cortese et al., 1997) may thus at least partially depend on the ability for a semantic control system centered in left anterior IFG (Ralph et al., 2017) to select the appropriate concrete semantic representation. The implication of lesioned IFG with reduced accuracy on concrete words contrasts somewhat with fMRI evidence suggesting that abstract words tax the semantic control system (Hoffman et al., 2015a). However, our results complement studies implicating temporal damage with selec-

tive impairment of processing concrete concepts, namely in patients with anterior temporal atrophy (Bonner et al., 2009; Joubert et al., 2017) and selective anterior temporal lobe resection (Loiselle et al., 2012). Such patients are impaired at the level of semantic representation, whereas stroke survivors are often impaired in semantic access (Jefferies and Lambon Ralph, 2006). Our identification of a lesion site critical for semantic control as opposed to representation (e.g., anterior temporal cortex) is expected. Our results suggest that computational models of reading could benefit from incorporating a cognitive control system to better account for variability in naming words of differing semantic content.

It is notable that we did not identify lesions related to the reading of abstract words more than concrete words. Impaired reading of abstract words has been noted in the context of significant phonological processing deficits due to left perisylvian damage. Impaired phonological decoding may force the patient to rely on a lexical–semantic route that is ill fitted for supporting phonological access from words connected to concepts sparsely represented in extrasylvian association cortex (Friedman, 2002; Binder et al., 2009). Thus, one might expect that lesions similar to those identified for regular word and pseudoword reading would relate to abstract word reading, but we did not find such a relationship. The null result for abstract words may suggest that, although the decoding system supports the reading of both abstract and concrete words, the semantic system provides stronger support for concrete words. Given that we covaried accuracy on concrete words in the SVR-LSM analysis of abstract words, performance on abstract words may not capture additional unique variance in lesion–behavior associations. It is important to note that concrete word reading was modestly affected by anterior inferior frontal lesions (Fig. 1C, Table 3). This finding is thus of scientific interest because of implications for the neurobiology of reading, but may be of limited practical significance to patients or clinicians.

That lesioned IFG was not associated with inaccurate reading of irregular words is surprising given fMRI evidence for irregular words strongly engaging frontal cortex (Mechelli et al., 2005). However, our null result is consistent with a previous LSM study of a similar stroke population, which also found no cortex associated with accuracy reading irregular words (Binder et al., 2016). Rather, Binder et al. (2016) implicated posterior middle temporal gyrus with regularization errors specifically. Within connectionist models, low-frequency irregular words are understood as reliant on semantics because the phonological route is not adequately trained to support their pronunciation (Plaut, 1997). The lack of convergence between fMRI and lesion studies of irregular word reading is notable and future lesion work examining interactions among frequency, regularity, and individual differences in semantic reliance (Hoffman et al., 2015b) is necessary to clarify the anatomical basis of the lexical–semantic route and surface alexia. Importantly, our lesion coverage of middle temporal gyrus was modest and coverage of the so-called visual word form area (Cohen et al., 2002) was not adequate for inclusion in analyses (Fig. 2).

By localizing brain areas that support reading words differentially dependent on phonological and lexical–semantic processing, we aimed to identify brain structures underlying these reading mechanisms. Our multivariate LSM analyses implicate a phonological decoding process dependent on dorsal perisylvian areas subserving sound–motor integration and a semantic control process dependent on frontal areas that leverage concrete semantic representations to access phonology from print. Fur-

thermore, our results highlight the promise of process-based (Binder et al., 2016) as opposed to syndrome-based analyses of alexia.

References

- Adorni R, Proverbio AM (2012) The neural manifestation of the word concreteness effect: an electrical neuroimaging study. *Neuropsychologia* 50:880–891.
- Aguilar OM, Kerry SJ, Crinion JT, Callaghan MF, Woodhead ZVJ, Leff AP (2018) Dorsal and ventral visual stream contributions to preserved reading ability in patients with central alexia. *Cortex* 106:200–212.
- Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2011) A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage* 54:2033–2044.
- Baayen RH, Piepenbrock R, Gulikers L (1995) The CELEX lexical database (CD-ROM). Philadelphia: Linguistic Data Consortium, University of Pennsylvania.
- Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, Dronkers NF (2003) Voxel-based lesion–symptom mapping. *Nat Neurosci* 6:448–450.
- Beauvois MF, Dérouesné J (1979) Phonological dyslexia: three dissociations. *J Neurol Neurosurg Psychiatry* 42:1115–1124.
- Binder JR, Desai RH, Graves WW, Conant LL (2009) Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex* 19:2767–2796.
- Binder JR, Pillay SB, Humphries CJ, Gross WL, Graves WW, Book DS (2016) Surface errors without semantic impairment in acquired dyslexia: a voxel-based lesion–symptom mapping study. *Brain* 139:1517–1526.
- Bonner MF, Vesely L, Price C, Anderson C, Richmond L, Farag C, Avants B, Grossman M (2009) Reversal of the concreteness effect in semantic dementia. *Cogn Neuropsychol* 26:568–579.
- Brysbaert M, Warriner AB, Kuperman V (2014) Concreteness ratings for 40 thousand generally known English word lemmas. *Behav Res Methods* 46:904–911.
- Buchsbaum BR, Baldo J, Okada K, Berman KF, Dronkers N, D'Esposito M, Hickok G (2011) Conduction aphasia, sensory-motor integration, and phonological short-term memory: an aggregate analysis of lesion and fMRI data. *Brain Lang* 119:119–128.
- Chang LJ, Yarkoni T, Khaw MW, Sanfey AG (2013) Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. *Cereb Cortex* 23:739–749.
- Cohen L, Lehericy S, Chochon F, Lemer C, Rivaud S, Dehaene S (2002) Language-specific tuning of visual cortex? Functional properties of the visual word form area. *Brain* 125:1054–1069.
- Coltheart M, Rastle K, Perry C, Langdon R, Ziegler J (2001) DRC: a dual route cascaded model of visual word recognition and reading aloud. *Psychol Rev* 108:204–256.
- Coltheart M, Patterson K, Marshall JC (1980) Deep dyslexia. London: Routledge and Kegan Paul.
- Cortese MJ, Simpson GB, Woolsey S (1997) Effects of association and imageability on phonological mapping. *Psychon Bull Rev* 4:226–231.
- Coslett HB, Turkeltaub PE (2016) Acquired dyslexia. In: *Neurobiology of language* (Hickok G, Small S, eds), pp 791–804. London: Academic.
- Dehaene S (2009) Reading in the brain: the new science of how we read. New York: Penguin.
- Dehaene S, Pegado F, Braga LW, Ventura P, Nunes Filho G, Jobert A, Dehaene-Lambertz G, Kolinsky R, Morais J, Cohen L (2010) How learning to read changes the cortical networks for vision and language. *Science* 330:1359–1364.
- Dejerine JJ (1892) Contribution à l'étude anatomo-pathologique et clinique des différentes variétés de cécité verbale. *C R Seances Soc Biol Fil* 44:61–90.
- DeMarco AT, Turkeltaub PE (2018) A multivariate lesion symptom mapping toolbox and examination of lesion-volume biases and correction methods in lesion–symptom mapping. *Hum Brain Mapp* 39:4169–4182.
- DeMarco AT, Wilson SM, Rising K, Rapcsak SZ, Beeson PM (2017) Neural substrates of sublexical processing for spelling. *Brain Lang* 164:118–128.
- Dronkers NF (1996) A new brain region for coordinating speech articulation. *Nature* 384:159–161.
- Friedman RB (1996) Recovery from deep alexia to phonological alexia: points on a continuum. *Brain Lang* 52:114–128.
- Friedman RB (2002) Alexia. In: *Encyclopedia of the human brain*, four-

- volume set (Ramachandran V, ed), pp 111–117. New York: Elsevier Science.
- Hickok G (2012) Computational neuroanatomy of speech production. *Nat Rev Neurosci* 13:135–145.
- Hickok G, Poeppel D (2007) The cortical organization of speech processing. *Nat Rev Neurosci* 8:393–402.
- Hickok G, Okada K, Serences JT (2009) Area spt in the human planum temporale supports sensory-motor integration for speech processing. *J Neurophysiol* 101:2725–2732.
- Hoffman P, Binney RJ, Lambon Ralph MA (2015a) Differing contributions of inferior prefrontal and anterior temporal cortex to concrete and abstract conceptual knowledge. *Cortex* 63:250–266.
- Hoffman P, Lambon Ralph MA, Woollams AM (2015b) Triangulation of the neurocomputational architecture underpinning reading aloud. *Proc Natl Acad Sci U S A* 112:E3719–E3728.
- Jefferies E, Lambon Ralph MA (2006) Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain* 129: 2132–2147.
- Jobard G, Crivello F, Tzourio-Mazoyer N (2003) Evaluation of the dual route theory of reading: a metaanalysis of 35 neuroimaging studies. *Neuroimage* 20:693–712.
- Joubert S, Vallet GT, Montembeault M, Boukadi M, Wilson MA, Laforce RJ, Rouleau I, Brambati SM (2017) Comprehension of concrete and abstract words in semantic variant primary progressive aphasia and Alzheimer's disease: a behavioral and neuroimaging study. *Brain Lang* 170: 93–102.
- Kay J, Lesser R, Coltheart M (1996) Psycholinguistic assessments of language processing in aphasia (PALPA): an introduction. *Aphasiology* 10:159–180.
- Kertesz A (2006) Western aphasia battery, revised. San Antonio, TX: Pearson.
- Kimberg DY, Coslett HB, Schwartz MF (2007) Power in voxel-based lesion: symptom mapping. *J Cogn Neurosci* 19:1067–1080.
- Lacey EH, Skipper-Kallal LM, Xing S, Fama ME, Turkeltaub PE (2017) Mapping common aphasia assessments to underlying cognitive processes and their neural substrates. *Neurorehabil Neural Repair* 31:442–450.
- Lambon Ralph MA, Graham NL (2000) Acquired phonological and deep dyslexia. *Neurocase* 6:141–178.
- Loiselle M, Rouleau I, Nguyen DK, Dubeau F, Macoir J, Whatmough C, Lepore F, Joubert S (2012) Comprehension of concrete and abstract words in patients with selective anterior temporal lobe resection and in patients with selective amygdalo-hippocampectomy. *Neuropsychologia* 50:630–639.
- Mah YH, Husain M, Rees G, Nachev P (2014) Human brain lesion-deficit inference remapped. *Brain* 137:2522–2531.
- Marshall JC, Newcombe F (1973) Patterns of paralexia: a psycholinguistic approach. *J Psycholinguist Res* 2:175–199.
- Martin A, Schurz M, Kronbichler M, Richlan F (2015) Reading in the brain of children and adults: a meta-analysis of 40 functional magnetic resonance imaging studies. *Hum Brain Mapp* 36:1963–1981.
- Mechelli A, Crinion JT, Long S, Friston KJ, Lambon Ralph MA, Patterson K, McClelland JL, Price CJ (2005) Dissociating reading processes on the basis of neuronal interactions. *J Cogn Neurosci* 17:1753–1765.
- Medler DA, Binder JR (2005) MCWord: An On-Line Orthographic Database of the English Language. Available at <http://www.neuro.mcw.edu/mcword/>.
- Mirman D, Chen Q, Zhang Y, Wang Z, Faseyitan OK, Coslett HB, Schwartz MF (2015) Neural organization of spoken language revealed by lesion-symptom mapping. *Nat Commun* 6:6762.
- Nickels L, Biedermann B, Coltheart M, Saunders S, Tree JJ (2008) Computational modelling of phonological dyslexia: how does the DRC model fare? *Cogn Neuropsychol* 25:165–193.
- Papagno C, Comi A, Riva M, Bizzi A, Vernice M, Casarotti A, Fava E, Bello L (2017) Mapping the brain network of the phonological loop. *Hum Brain Mapp* 38:3011–3024.
- Patterson KE, Marshall JC, Coltheart M (1985) Surface dyslexia: cognitive and neuropsychological studies of phonological reading. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Patterson K, Ralph MA (1999) Selective disorders of reading? *Curr Opin Neurobiol* 9:235–239.
- Perry C, Ziegler JC, Zorzi M (2007) Nested incremental modeling in the development of computational theories: the CDP+ model of reading aloud. *Psychol Rev* 114:273–315.
- Plaut DC (1997) Structure and function in the lexical system: insights from distributed models of word reading and lexical decision. *Lang Cogn Process* 12:765–806.
- Price CJ (2012) A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage* 62:816–847.
- Pulvermüller F, Huss M, Kherif F, Moscoso del Prado Martin F, Hauk O, Shtyrov Y (2006) Motor cortex maps articulatory features of speech sounds. *Proc Natl Acad Sci U S A* 103:7865–7870.
- Ralph MA, Jefferies E, Patterson K, Rogers TT (2017) The neural and computational bases of semantic cognition. *Nat Rev Neurosci* 18:42–55.
- Rapcsak SZ, Beeson PM, Henry ML, Leyden A, Kim E, Rising K, Andersen S, Cho H (2009) Phonological dyslexia and dysgraphia: cognitive mechanisms and neural substrates. *Cortex* 45:575–591.
- Ripamonti E, Aggajaro S, Molteni F, Zonca G, Frustaci M, Luzzatti C (2014) The anatomical foundations of acquired reading disorders: a neuropsychological verification of the dual-route model of reading. *Brain Lang* 134:44–67.
- Roach A, Schwartz M, Martin N, Grewal R, Brecher A (1996) The Philadelphia naming test: scoring and rationale. *Clin Aphasiology* 24:121–133.
- Rorden C, Bonilha L, Fridriksson J, Bender B, Karnath HO (2012) Age-specific CT and MRI templates for spatial normalization. *Neuroimage* 61:957–965.
- Savill NJ, Cornelissen P, Pahor A, Jefferies E (2019) rTMS evidence for a dissociation in short-term memory for spoken words and nonwords. *Cortex* 112:5–22.
- Schwartz MF, Faseyitan O, Kim J, Coslett HB (2012) The dorsal stream contribution to phonological retrieval in object naming. *Brain* 135: 3799–3814.
- Strain E, Patterson K, Seidenberg MS (1995) Semantic effects in single word naming. *J Exp Psychol Learn Mem Cogn* 21:1140–1154.
- Strain E, Patterson K, Seidenberg MS (2002) Theories of word naming interact with spelling-sound consistency. *J Exp Psychol Learn Mem Cogn* 28:207–214; discussion 215–220.
- Taylor JS, Rastle K, Davis MH (2013) Can cognitive models explain brain activation during word and pseudoword reading? A meta-analysis of 36 neuroimaging studies. *Psychol Bull* 139:766–791.
- Taylor JSH, Duff FJ, Woollams AM, Monaghan P, Ricketts J (2015) How word meaning influences word reading. *Curr Dir Psychol Sci* 24:322–328.
- Turkeltaub PE, Coslett HB (2010) Localization of sublexical speech perception components. *Brain Lang* 114:1–15.
- Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA (2002) Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* 16:765–780.
- van Atteveldt N, Formisano E, Goebel R, Blomert L (2004) Integration of letters and speech sounds in the human brain. *Neuron* 43:271–282.
- Vigneau M, Beaucois V, Hervé PY, Duffau H, Crivello F, Houdé O, Mazoyer B, Tzourio-Mazoyer N (2006) Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage* 30:1414–1432.
- Vinckier F, Dehaene S, Jobert A, Dubus JP, Sigman M, Cohen L (2007) Hierarchical coding of letter strings in the ventral stream: dissecting the inner organization of the visual word-form system. *Neuron* 55:143–156.
- Wang J, Conder JA, Blitzer DN, Shinkareva SV (2010) Neural representation of abstract and concrete concepts: a meta-analysis of neuroimaging studies. *Hum Brain Mapp* 31:1459–1468.
- Warrington EK (1981) Concrete word dyslexia. *Br J Psychol* 72:175–196.
- Woollams AM (2014) Connectionist neuropsychology: uncovering ultimate causes of acquired dyslexia. *Philos Trans R Soc Lond B Biol Sci* 369:20120398.
- Woollams AM, Ralph MA, Plaut DC, Patterson K (2007) SD-squared: on the associated between semantic dementia and surface dyslexia. *Psychol Rev* 114:316–339.
- Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G (2006) User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage* 31:1116–1128.
- Zhang Y, Kimberg DY, Coslett HB, Schwartz MF, Wang Z (2014) Multivariate lesion-symptom mapping using support vector regression. *Hum Brain Mapp* 35:5861–5876.