EXPLORING FUNCTIONAL SPECIALIZATION WITHIN CEREBRO-CEREBELLAR CIRCUITS FOR READING

by

Travis A. Alvarez

Bachelor of Arts, Brooklyn College, 2011

Master of Science, University of Pittsburgh, 2015

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This dissertation was presented

by

Travis A. Alvarez

It was defended on

April 4th, 2019

and approved by

Tessa Warren, Associate Professor, Department of Psychology

Marc N. Coutanche, Assistant Professor, Department of Psychology

Michael W. Dickey, Associate Professor, Department of Communication Science & Disorders

Dissertation Advisor: Julie A. Fiez, Professor, Department of Psychology

Exploring Functional Specialization within Cerebro-cerebellar Circuits for Reading

Travis A. Alvarez, PhD

University of Pittsburgh, 2019

According to the cerebellar deficit hypothesis [CDH; (Nicolson, Fawcett, & Dean, 2001)], cerebellar dysfunction can place children at risk for developmental dyslexia. In a recent meta-analytic review, Alvarez and Fiez (2018) proposed a neural model for how the cerebellum interfaces with the cerebral reading network (CDHn). This model posits that two regions in the cerebellum, one in lobule HVIIB and one in lobule Crus1, are interconnected with the cerebral cortex to form a dorsal fronto-parietal and a ventral fronto-temporal circuit, respectively. Moreover, the CDHn model asserts that these circuits are functionally specialized, with the dorsal circuit biased towards phonological processing and the ventral circuit biased towards semantic processing. This dissertation employs functional connectivity and neural activation measures obtained with magnetic resonance imaging to empirically test the CDHn model, with an *a priori* focus on the five regions proposed as constituents of its dorsal and ventral circuits. Resting-state analyses tested for patterns of functional connectivity between the predefined constituents, with a special interest in circuit specialization within an inferior frontal junction region that is part of both circuits. Univariate and multivariate methods were used to characterize the predicted phonological versus semantic task biases between the dorsal and ventral circuit, respectively. Finally, the products of these analyses were used to test whether activation in cerebellar regions VIIB and Crus1 modulate neural representation in the cerebral constituents of the dorsal and ventral circuits, respectively. Conventional connectivity analyses revealed stronger evidence supporting the ventral circuit. However, success in our more unique connectivity approach to find circuit specialization within the frontal region implicated the presence of dissociative dorsal and ventral networks. As predicted, the parietal region successfully characterized a task-bias for phonological processing; no biased effect within the frontal region; and a trend towards a semantic bias within the temporal region. All cerebral regions succeeded in the multivariate task-dissociation. Although the cerebellar regions did not exhibit predicted functional specialization, the univariate analyses did uncover interactions of tasks, and Crus1 engagement was successful in modulating the semantically related properties of the temporal region. Overall, we found encouraging but incomplete support for the recently proposed CDHn model.

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PREFACE

Firstly, I cannot express enough of my gratitude and thanks to all of my mentors, friends and family for their support in what felt like the quickest long experience of my life.

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I want to thank my Community Forge friends/family. I have to say that my final years as a graduate student really meant a lot to me. What never gets old are the shocking expressions I receive whenever I tell people about how eight of us crazy millennials purchased an elementary school building to create a special community center in Pittsburgh. This part of my life has really kept me grounded as a scholar and human being. The people I’ve met have really grown to feel like family; even helping me during the many tough writing and analysis times.

Finally, I will always give the most praise to my family. Everything I do is for them. Having to leave my mother, sister, and then 2-year-old brother in Brooklyn was one of the hardest decisions I’ve ever made. Missing my baby brother’s youthful growth as a toddler has always been at the forefront of my mind. At graduation, witnessing their pride and genuine excitement in me accomplishing what my mother always believed I could achieve, was almost overwhelming. I could never thank my mother enough for everything she’s done for me, but I hope this achievement is at least a start.

1.0 INTRODUCTION

Literacy is one of the most important skills that humans acquire because it allows an individual to competently navigate through life. To better understand this skill and its development, considerable research has focused on localizing the neural constituents of the reading network and understanding how these brain regions may interact during the development of reading skills (Taylor, Rastle, & Davis, 2012; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Much of the reading literature claims that the neural constituents of reading can be fractionated into processing streams (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Kellmeyer et al., 2013; Vigneau et al., 2006). This distinction can be mapped onto models of reading processing that posits a dorsal phonological network playing a critical role in orthographic to phonologic mapping (i.e., decoding the pronunciation of the printed word), and a ventral semantic network involved in the representation of meaning and knowledge at the level of phrases, situation or context. Interestingly, the major neural models of reading rarely include the cerebellum, a sub-cortical brain structure traditionally known as a fundamental learning structure in the motor domain (Llinas, Hillman, & Precht, 1973; Marr, 1969; Thach, Goodkin, & Keating, 1992) and more recently in non-motor domains (e.g., Fiez, Petersen, Cheney, & Raichle, 1992; Strick, Dum, & Fiez, 2009). As a consequence of this gap, the field remains vulnerable in its ability to comprehensively understand the brain regions that contribute to reading. This dissertation focuses on investigating a theoretical model of cerebro-cerebellar interactions that support reading and its development.

1.1 MAKING A CASE FOR THE CEREBELLUM AND READING

1.1.1 Traditional cerebellar role

For decades, neuroscientists have appreciated the cerebellum's enormous computational power. This brain structure alone possesses a neuronal population that is more than double that of the cerebral cortex, yet this mass of neural architecture only comprises a miniscule 10% of the brain's total structural volume (Kim, Ugurbil, & Strick, 1994; Marr, 1969). The cerebellum also has more fiber connections to the cerebral cortex than any other structure of the nervous system (Llinas et al., 1973). Moreover, this structure produces some of the largest and most distinguishable neurons in the brain, known as Purkinje cells. These cells receive more synaptic inputs than any other neuron in the brain, allowing them to produce efficient responses to those inputs that require a rapid reaction. Marr (1969) suggested that the synaptic connections within the cerebellum could be modified by experience through an elaborate feedback system involving fiber pathways that carry sensory and motor information from the cerebral cortex (and other brain regions) into the cerebellum. He proposed that these fiber pathways combine to provide the computational elements needed to fine-tune motor functions that require both rapid responses and the ability to correct performance errors. Subsequently, other investigators have drawn upon the same line of reasoning to argue that the cerebellum may similarly contribute to the fine-tuning of cognitive functions (Alvarez & Fiez, 2018; Fernandez et al., 2015; Nicolson et al., 2001).

The cerebellum is known to have distinct regions that contribution to different types of motor coordination and timing (Ivry, 1997; Ivry, Spencer, Zelaznik, & Diedrichsen, 2002). This specialization is not because of differences in cytoarchitecture; rather, it is because there is segregated connectivity into and out of the cerebellum (Middleton & Strick, 1994; Middleton &

Strick, 1998). Within the motor domain, cerebro-cerebellar circuitry has been analyzed quite extensively, with an emphasis on cerebellar output and function. The focal sources of output for the cerebellum are five bilateral nuclei located within the deep white matter of the cerebellum or brainstem (i.e., the fastigii, emboliform, globose, dentate, vestibular nuclei). Each nucleus interconnects with different parts of the brain, and together they are the main output structures of the cerebellum. The outputs to the cerebral cortex (hereto referred as cerebro-cortical) are mediated by the dentate nucleus and historically they were thought to exclusively project, via the thalamus, to cerebro-cortical motor areas.

With the use of new tracer technology within monkeys, investigators found that there are multiple segregated circuits between the cerebellum and the cerebral cortex, and these circuits extend beyond motor areas (Hoover & Strick, 1999; Kelly & Strick, 2003). These recently identified connections from the cerebellum provide strong support for the hypothesis that the cerebellum contributes to non-motor functions. This divergence from the classical view of cerebro-cerebellar functionality is relatively new and is important for understanding both anatomic and functional specialization within the brain in its entirety.

The advancement of neuroimaging techniques offers the field a potentially powerful method for better understanding the involvement of the human cerebellum in the non-motor domain. A popular approach is based upon measuring variations in the blood-oxygen-level-dependent (BOLD) signal while participants are in a resting-state. By measuring the degree to which fluctuations in this functional signal are correlated across brain regions, it is possible to draw inferences about the strength of the connection pathway between two regions (Biswal, Yetkin, Haughton, & Hyde, 1995; for review see Fox & Raichle, 2007). Within the motor domain, cerebellar focused studies that involve the use of functional connectivity magnetic resonance imaging (fc-MRI) are consistent with earlier established anatomical evidence of cerebro-cerebellar circuitry (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Krienen & Buckner, 2009; O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010). These findings helped establish fc-MRI as a valid and reliable approach for investigating cerebro-cerebellar connectivity. In addition, these relatively recent functional connectivity investigations have found distinct cerebellar connections with cerebro-cortical regions implicated in higher cognitive functions (Buckner et al., 2011; Habas et al., 2009). These findings suggest that the lateral cerebellar hemispheres form parallel cortico-cerebellar loops with regions involved in executive control, memory, and salience detection (i.e., prefrontal, parietal, and temporal cortical regions).

Findings within the literature have driven the field towards questions about the role of the cerebellum in reading. Alvarez and Fiez (2018) provided a comprehensive review of this topic, for which we highlight some of their key examples across the neuroimaging and clinical domain. Task-based functional magnetic resonance imaging (fMRI) investigations have reported frequent observations of cerebellar activation during language and reading-related tasks (for reviews see Stoodley & Schmahmann, 2009; Vlachos, Papathanasiou, & Andreou, 2007). Clinical neuroimaging investigations have also disclosed evidence in support of cerebellar involvement in reading processes. For instance, Ben-Yehudah and Fiez (2008) found that individuals with cerebellar lesions performed more poorly on a rhyme judgment and verbal working memory task as compared to a non-lesion control group, and no other significant reading-related impairment between groups. Moreover, there is an abundant amount of work comparing individuals with or without dyslexia--a developmental reading disorder--that report aberrant cerebellar activation during reading-related tasks (Feng et al., 2017; Kronschnabel, Schmid, Maurer, & Brandeis, 2013; Menghini, Hagberg, Caltagirone, Petrosini, & Vicari, 2006; Yang, Bi, Long, & Tao, 2013), although there is some evidence that run counter to these reports (Cao, Bitan, Chou, Burman, & Booth, 2006; Georgiewa et al., 1999). One notable meta-analysis sought to identify differences in cerebellar cortical volume between controls and individuals with dyslexia, autism spectrum disorder, and attention deficit hyperactivity disorder (Stoodley, 2014). Importantly, this analysis found a deficiency of localized cerebellar grey matter within bilateral cerebellar lobule VI and right Crus2 that was specific to individuals with dyslexia. Collectively, the cerebellum's frequent associations with reading and reading-related processes pushes the literature towards questions about the theoretical underpinnings of this brain structure's contribution to the development of reading.

1.1.2 The CDH model

Although the evidence for cerebellar involvement in reading continues to emerge within the literature, there remains scant empirical investigation into mechanistic accounts of this structure's role in reading processes. A notable exception is the model proposed by Nicolson, Fawcett, and Dean (2001). These authors argued persuasively that readers with dyslexia frequently exhibit impairments in motor and perceptual functioning that implicate brain regions involved in procedural learning in the etiology of developmental dyslexia. With evidence grounded heavily in behavioral data, their "cerebellar deficit hypothesis" (CDH model) posits that the cerebellum, a region strongly associated with procedural learning processes (Marr, 1969; Wolpert, Miall, & Kawato, 1998), may contribute to reading skills via two indirect processes: articulatory fluency and skill automatisation (Figure 1). An important limitation of the CDH model is that it is largely a behavioral rather than a neural account. The CDH model thus suffers from a lack of integration with what is known about the cerebral reading network. As a consequence of this gap, the field remains vulnerable in its ability to comprehensively understand the brain regions that contribute to reading.

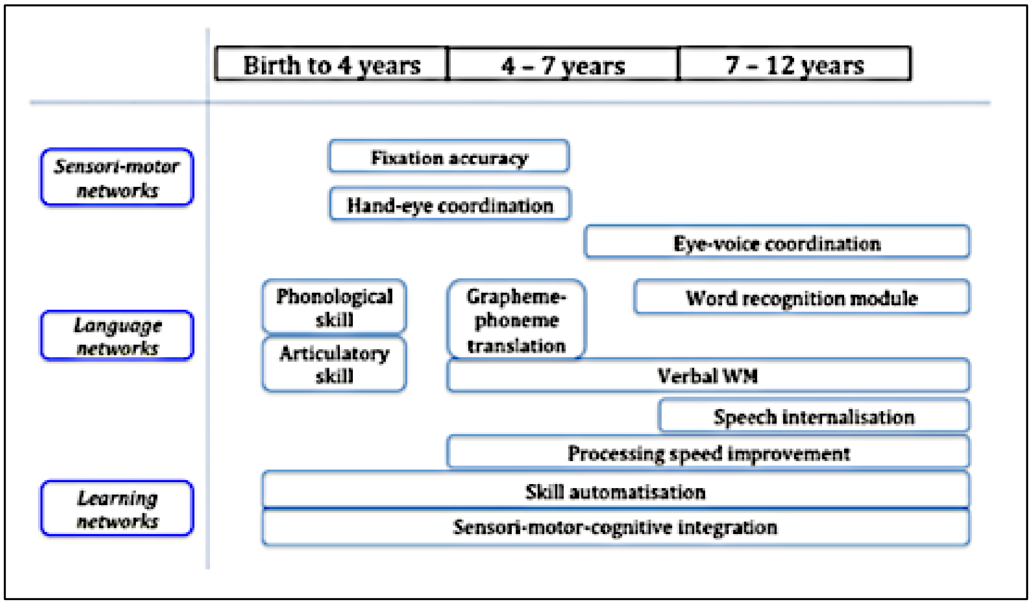


Figure 1. Theoretical schematic of cerebellar components for reading development

Illustrative review of the proposed CDH model as originally proposed and developed by Nicolson and Fawcett. Figure is reprinted from "Consensus paper: Language and the cerebellum: An ongoing enigma" by P. Marien et al., 2014, *Cerebellum*, 13, p. 399 (Permission not obtained).

This dissertation focuses on a neural account of the CDH model (namely, the CDHn model). The CDHn model arose from a previous meta-analytic review that investigated the cerebro-cerebellar networks involved in reading and reading-related processes (Alvarez & Fiez, 2018). This review involved the integration of multiple online meta-analytic tools [e.g., GingerALE (Eickhoff et al., 2009; Turkeltaub et al., 2012), Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011)] to take a data-driven approach towards elucidating potential cerebro-cerebellar pathways for reading within the literature broadly. Briefly, for this meta-analysis, the authors comprehensively compiled contrastive maps for previous neuroimaging meta-reviews. This included assembling coordinates of task-biased activation using GingerALE's activation likelihood estimates of the coordinates for three principal levels of contrasting phonological versus semantic processing (Figure 2), and a general reading map using Neurosynth's reverse inference maps for the term *reading* (Figure 3).

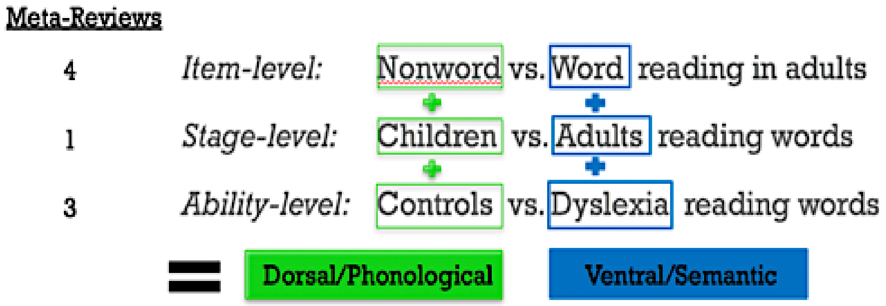
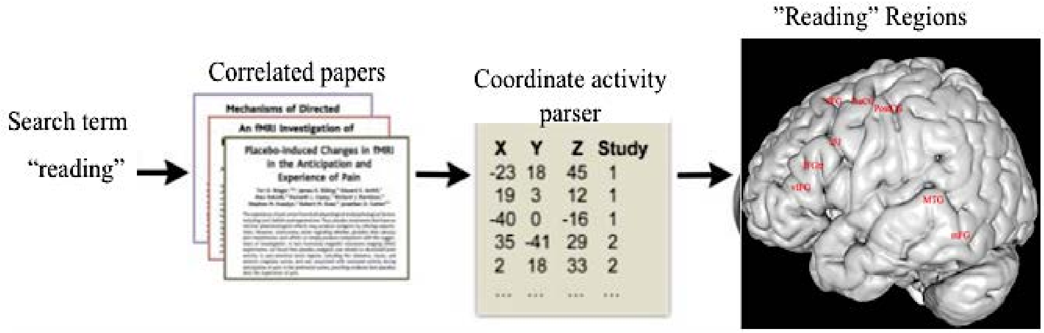


Figure 2. CDHn model's cerebro-cortical identification method using GingerALE

The CDHn model's systematic process for relevant meta-analytical literature using three principal contrasts that function as a means toward classifying differences in reading, namely phonological versus semantic processing. Coordinates of contrast-specific interest were extracted and statistically tested using GingerALE's voxel-by-voxel 3D gaussian activation likelihood estimate analysis to generate probabilistic imaging maps of the phonological versus semantic contrast.



X	Y	Z	Study
-23	18	45	1
19	3	12	1
-40	0	-16	1
35	-41	29	2
2	18	33	2
...	...	...	...

Figure 3. CDHn model's cerebro-cortical identification method using Neurosynth

The CDHn model leveraged Neurosynth's reverse inference map to localize the neural constituents of the term "reading."

The subsequent process leveraged Neurosynth's functional connectivity map to search for evidence of cerebellar engagement to and from each centroid coordinate extracted from their meta-reviews. Results from these efforts prompted the authors to propose: 1) a dorsal circuit with functional interconnectivity between the left inferior frontal junction, and the left inferior parietal lobe that converges to right cerebellar hemisphere VIIB/Crus2, and 2) a ventral circuit with functional interconnectivity between the left inferior frontal junction and the left middle temporal gyrus that converges at or near right cerebellar hemisphere Crus1/Crus2. The left inferior frontal junction's surprising emergence as the common node between the two circuits raised important issues about the degree to which these circuits are conceptually considered as separate without overlap. In their review, Alvarez and Fiez (2008) evaluated this finding from two competing perspectives within the literature. One perspective posits specialized sub-zones within the inferior frontal junction that are dedicated to phonological versus semantic processing (Bookheimer, 2002; Shalom & Poeppel, 2008; Vigneau et al., 2006). The other perspective posits a more domain-general top-down control over orthographic processing (Vogel, Miezin, Petersen, & Schlaggar, 2012; Vogel, Petersen, & Schlaggar, 2012). Importantly, Alvarez and Fiez argued that their data-driven approach towards identifying reading-related seed-regions across the literature provided stronger evidence in support of specialized sub-pathways within the inferior frontal junction. In the current dissertation study, we also expect to find sub-divisional segregation within the inferior frontal junction for the dorsal versus ventral pathways of reading.

In addition to identifying cerebro-cerebellar dorsal and ventral circuits for reading, Alvarez and Fiez (2018) also considered the potential of a functional role for these circuits. Specifically, they used Neurosynth's term-based analysis to examine overlapping cognitive terms associated with the regions within each respective circuit. This analysis revealed evidence that the neural constituents of the dorsal circuit shared the common term "phonological," whereas the constituents of the ventral circuit shared the term "semantic." Based on these findings, the CDHn model proposed that the cerebro-cerebellar dorsal and ventral circuits possess strong functional biases towards phonological and semantic processing, respectively.

Finally, Alvarez and Fiez (2018) also speculated about the specific functional contributions of the cerebellum within these circuits. The authors reasoned that the cerebellum could fine-tune the performance of the fronto-parietal pathway to improve the accuracy of orthographic-to-phonologic decoding during novel visual word recognition (i.e., phonological decoding). Similarly, the cerebellum could modulate the performance of the fronto-temporal pathway to improve the shift towards a more lexicalized decoding during reading (i.e., novel word recognition that is based upon previously learned word knowledge). Collectively, the cerebellum's fine-tuning of the information held within the bidirectionally connected cerebral regions for reading could be what lays the groundwork for its indirect influence in supporting the development of fluent visual word recognition. However, the authors also underscored an alternative domain-general account regarding the cerebellum' modulatory role in reading development. This perspective positions the cerebellum as an attentional modulator of visuo-sensory representations. In this manner, the cerebellum can restrict selective processing within the inferior frontal junction, thus constraining the information for a particular task to relevant lower-level spatial properties while also limiting irrelevant spatial properties.

Alvarez and Fiez (2018) concluded that more empirical work is needed to disentangle competing perspectives on the functional role of the cerebellum. The current study tests for evidence of a cerebellar role in fine-tuning the dorsal and ventral pathways. We expect to find evidence that reveals an improved performance of the phonological mappings in the dorsal circuit dependent upon the functionally connected cerebellar region, and similarly improved performance of the semantic mappings in the ventral circuit as modulated by the functionally connected cerebellar region.

Overall, the CDHn model situates the cerebellum within the broader literature on the neural basis of reading, which has strongly claimed evidence of two cerebro-cortical processing streams for reading (e.g, Gold et al., 2005; Price et al., 1997). The first is a dorsal stream dedicated to phonological processing, and the second is a ventral stream dedicated to lexical-semantic processing. However, traditionally these neuronal pathways for reading have not included or considered the cerebellum, and so there is a need for further empirical work to test the CDHn model and its claims about the involvement of the cerebellum in reading.

The overarching goal of this dissertation is to empirically test the CDHn model. The work focuses upon a set of *a priori* ROIs that correspond to the constituents of the CDHn model developed by Alvarez and Fiez (2018). As shown in Figure 4, the centers of these ROIs are located in the left inferior frontal junction (IFJ), left inferior parietal lobule (IPL), left middle temporal gyrus (MTG), right cerebellar hemisphere VIIB (HVIIB), and right cerebellar hemisphere Crus1 (Crus1). Functional magnetic resonance neuroimaging is used to acquire task-related and resting-state functional data (rs-fMRI). The acquired data is used to address three aims: 1) empirically confirm whether there are segregated cerebro-cerebellar dorsal and ventral circuits, with convergence in the inferior frontal junction and bimodal circuit specificity that is topographically distinguishable within the inferior frontal junction, 2) determine whether the cerebro-cerebellar dorsal and ventral circuits are functionally biased towards phonological and semantic processing, respectively, 3) examine whether the cerebellum exerts a modulatory role in developing more precise quality of representations within each cerebro-cerebellar circuit.

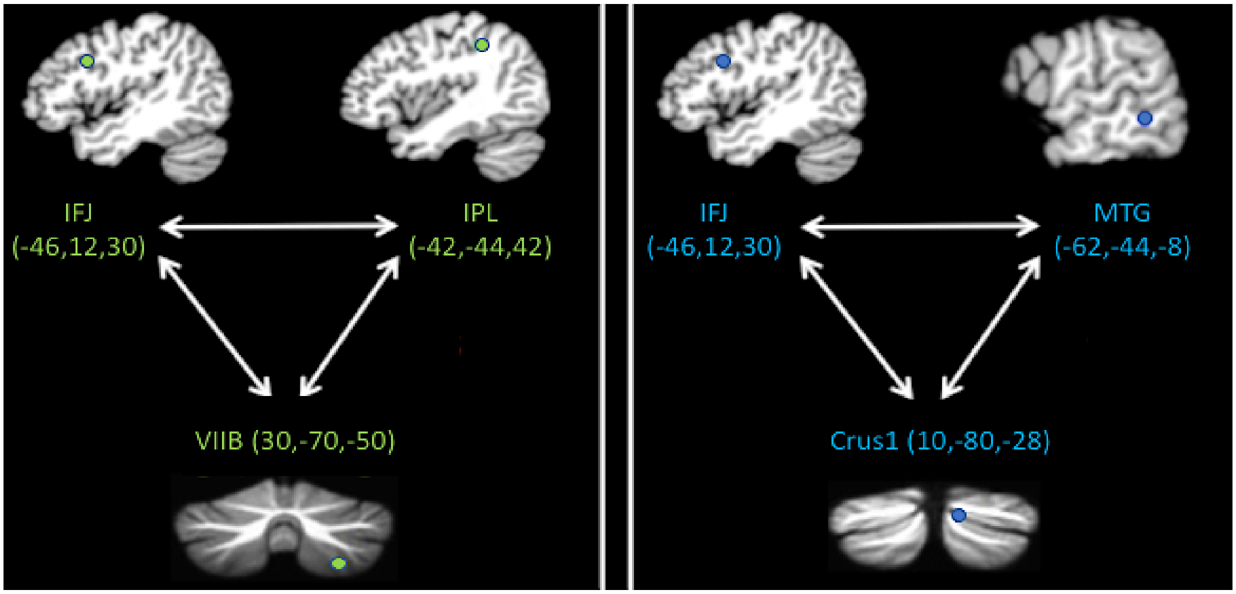


Figure 4. A priori circuit regions as extracted from the CDHn model

The identified coordinates of the CDHn model's dorsal phonologically biased (green) circuit and ventral lexico-semantically biased circuit (blue) were used as a center locus for each territory to generate our five regions-of-interests for all subsequent analyses. Importantly, the inferior frontal junction was the only convergent node, however it was not clear as to the potential for circuit division within this convergent territory. IFJ = inferior frontal junction, IPL = inferior parietal lobe, MTG = middle temporal gyrus. Figure is borrowed and modified from "Current perspectives on the cerebellum and reading development" by Alvarez and Fiez, 2018, *Neuroscience and Biobehavioral Reviews*, 92, p. 60. Permission not obtained.

In tackling these aims, we use an experimental neuroimaging design that represents an advance from the past work. The behavioral tasks' design allows for within-subject cross comparisons of well-matched phonological and semantic tasks. There is also the manipulation of difficulty within the tasks that grants an opportunity to examine task-dependent engagement as potentially modulated by effort. A major concern in analyzing resting-state neuroimaging data is its inherent susceptibility to physiological artifact. To account for this, we acquire heart-rate and pulse monitoring data during the imaging scan to be regressed out of the analyses. We also assess within-subjects' results across multiple neuroimaging analyses. In this manner, we are able to link the proposed functionally connected circuits to the proposed specialization of the circuits. Finally, we prioritize complete cerebellar coverage during all task-related scans, with slice orientation parameters adjusted for each participant.

2.0 CEREBRO-CEREBELLAR READING CIRCUITS

Motivation for the current dissertation arose from a previous meta-analytical review that provided new insights into cerebro-cerebellar networks involved in reading and reading-related processes (Alvarez & Fiez, 2018). The meta-analytic review developed a neural variant of the CDH model (the CDHn model). Specifically, this review provided evidence for two cerebro-cerebellar reading circuits: 1) a dorsal circuit in which there is functional interconnectivity between left inferior frontal junction (IFJ) and left inferior parietal lobule (IPL) that converges to right cerebellar hemisphere HVIIB, and 2) a ventral circuit with functional interconnectivity between left IFJ and left middle temporal gyrus (MTG) that converges at or near right cerebellar hemisphere Crus1. Their review also revealed that these dorsal and ventral circuits may possess functional biases towards phonological and semantic processing, respectively, thereby situating the cerebellum within the broader literature on the neural basis of reading, which has strongly claimed evidence of two cerebral processing streams for reading (Fiez, 1997; Gold et al., 2005; Price et al., 1997). Although Alvarez and Fiez's meta-analytic approach began with an idea of defining dorsal versus ventral circuits for reading as traditionally conceptualized within the literature, it also revealed the inferior frontal junction as a surprising convergent node across both circuits. This is interesting, especially given the debate within the literature about whether the inferior frontal junction plays a domain-general processing role (Derrfuss, Brass, Neumann, & Von Cramon, 2005; LaBar, Gitelman, Parrish, & Mesulam, 1999) or whether it contributes to more specific aspects of reading, such as phonological processing (Cao et al., 2006; J. S. H. Taylor, Plunkett, & Nation, 2011; Thompson-Schill et al., 1998). Overall, Alvarez and Fiez's review led them to posit dissociable functionally connected cerebro-cerebellar dorsal and ventral circuits, with dual involvement of the inferior frontal junction territory, as part of the reading network. However, their findings leave unclear whether or not these projections are to overlapping or segregated neuronal pools within the inferior frontal junction.

The current study provides an empirical evaluation of separable cerebellar connectivity into the dorsal and ventral routes for reading, which has become a predominant framework for understanding the role of cerebro-cortical regions involved in reading. It will also shed new light on the organization of the inferior frontal junction territory, a key region that is considered to play a crucial role in executive functioning, language, and reading processes. To broadly test for replicability of the dorsal (left inferior frontal junction, parietal lobule, and right cerebellar VIIB) and ventral (left inferior frontal junction, middle temporal gyrus, and right cerebellar Crus1) circuits in the CDHn model, we will conduct within-subjects functional connectivity analyses of resting-state magnetic resonance imaging (rs-fMRI) data at the region level (broad approach). To test for sub-divisional connectivity specialization within the inferior frontal junction -- a frontal tissue territory that has been postulated to possibly encompass subdivisions for separable processing pathways (Bookheimer, 2002; Shalom & Poeppel, 2008) -- we use a more precise approach with the same rs-FC data, but in this case probe for circuits at the voxel level. Using our broad approach, we predict significant functional connectivity between the VIIB ROI in the cerebellum and the dorsal circuit constituents (the left inferior frontal junction and inferior parietal lobule), and significant functional connectivity between the right Crus1 ROI in the cerebellum and the ventral circuit constituents (the left inferior frontal junction and middle temporal gyrus). Conversely, we do not expect to see significant between-circuit connectivity (e.g., ROIs exclusively in the dorsal circuit should not have significant connectivity with ROIs exclusively in the ventral circuit), with the possible exception of cross-circuit functional convergence in the inferior frontal junction ROI. We are especially interested whether the voxels within the inferior frontal junction ROI show full connectivity with both circuits, or if instead the voxels exhibit connectivity to one but not the other circuit. The former result would be consistent with more domain-general interpretations of the inferior frontal junction while the latter would suggest that this territory contains separable processing streams for the dorsal and ventral circuit. Collectively, we expect these results to empirically confirm and situate distinct sectors of the cerebellum as part of the dorsal and ventral processing streams for reading identified in the previous meta-analytical review, and determine the nature of intersection within the inferior frontal junction.

2.1 METHODS

2.1.1 Participants

This study acquired an integrated imaging dataset from 21 right-handed native English speakers (M_{age} = 22.41 years, *SD* = 4.91 years, 11 females). Participants were recruited from postings around the University of Pittsburgh campus and a research-subject database maintained by reading and language researchers at the University. Exclusionary criteria during the initial prescreening process included a self-reported history of neurological injury, left-handedness, or any factor that precludes participation in a magnetic resonance imaging scan (e.g. ferrous metal in the body, pregnancy, claustrophobia). Post-imaging data from three participants with a maximum motion displacement exceeding 4 mm, 4 degrees were not included in any analyses. Therefore, a total of 18 participants' imaging and behavioral data were used for all analyses. Informed consent was provided using standard procedures approved by the University of Pittsburgh Institutional Review Board, and all participants received monetary compensation upon completion of the study.

2.1.2 Imaging and task protocol

2.1.2.1 Image acquisition

The complete experimental dataset for each participant included the acquisition of a high-resolution structural scan, four task-based functional magnetic resonance imaging (fMRI) scans with corresponding behavioral task data, and one resting-state functional magnetic resonance imaging (rs-fMRI) scan with pulse and heart-rate recordings.

Data acquisition were acquired at the Neuroscience Imaging Center (NIC, University of Pittsburgh) using a Siemens TIM Allegra 3.0 Telsa scanner with a 32-channel head coil. Upon entering the scanner, participants were situated with a pneumatic belt around their waist to collect cardiac pulse, and a pulse oximeter on one of their left fingers to measure heart-rate. These physiological monitoring data were acquired during the rs-fMRI scan. Foam pads were placed on both sides of the head to reduce movement. Magnetization-prepared rapid gradient echo (MPRAGE) structural images were first acquired (192 sagittal slices, 1 x 1 x 1 mm voxels, TR = 2300 ms, TE = 2.98 ms, flip angle = 9 degrees, TE = 2.98 ms, flip angle = 9 degrees). Next, four fMRI scans, described and analyzed in Chapter 3, were acquired using a single-shot EPI sequence with 3.1 x 3.1 x 3.2 mm voxel size in a 64 x 64 x 32 matrix, TR = 2000 ms, TE = 25 ms, FA = 70 degrees, AC-PC aligned. Finally, one rs-fMRI scan was collected with the same functional imaging acquisition parameters, with a total length of 5 minutes. All task stimuli was designed and performed using the E-prime software (Schneider & Zuccoloto, 2007), projected on a monitor situated behind the scanner and viewed through a mirror mounted on the radio frequency coil.

2.1.2.2 Resting-state functional connectivity

The current chapter focused on analyzing the data from the resting-state fMRI scan to explore patterns of functional connectivity between theorized cerebro-cerebellar circuits. This neuroimaging approach is based upon measuring variations in the blood-oxygen-level-dependent (BOLD) signal while participants are in a resting-state (i.e., not performing any particular task during the scan). By measuring the degree to which fluctuations in a seed-voxel's functional signal is correlated with other areas throughout the brain, it is possible to draw inferences about the connectional pathways between two regions (Biswal et al., 1995; Fair et al., 2007).

During the rs-fMRI scan, participants were instructed to stare directly at the centered crosshair on the monitor for the duration of the 5 minute scan. Stimuli and procedural descriptions of the behavioral tasks performed during the four task-based fMRI scans are described in Chapter 3.

2.1.3 Imaging analysis

2.1.3.1 Image preprocessing

Physiological noise data (cardio and heart-rate) were sampled using the BIOPACK Acqknowledge software (Pascual-Leone, 2000), and detection of peak to peak systole intervals was processed in Matlab (version 9.5; MathWorks) . The physiological data were then resampled as slice-based regressors matching the TR of the functional image using the RetroTS.py plugin in the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). White matter and ventricle masks were created from each participants' structural image using Freesurfer's automated segmentation program (Fischl et al., 2002). These physiological monitoring and anatomical parcellation data were then included in a slightly modified version of AFNI's suite of preprocessing scripts for resting-state data (*afni_proc.py*). To adjust for scanner equilibration, the first two volumes of imaging data were discarded from both the physiological and resting-state functional timeseries data (*1dcat and 3dTcat*, respectively). Removal of transient signal spikes from the functional timeseries were processed using an interpolation algorithm (*3dDespike*), followed by the removal of the physiological signal using retrospective image correction [RETRIOCOR, (Glover, Li, & Ress, 2000)]. Next, a Fourier timeseries phase-shifting algorithm was applied during image slice time correction to the middle slice (*3dTshift)*. The structural volumes were aligned to the base functional image (i.e., minimum outlier fraction) using a Local Pearson's Correlation cost function (align_epi_anat.py) and transformed into standard MNI space (MNI152_T1_2009c AFNI template, 1 mm^3) using a non-linear registration. Motion correction was conducted by registering all functional volumes to the minimum outlier volume (*3dvolreg)*. Functional timeseries were then normalized to MNI space and resampled into 3 mm^3 isotropic voxels using non-linear warp (*3dNwarpApply)*. The functional timeseries data were smoothed using a three-dimensional Gaussian filter with a full-width half maximum of 6 mm (*3dmerge)*, and scaled to an intensity mean of 100 with a maximum of 200 to facilitate group-level comparisons.

To address particular aspects of our research questions, we conducted two separate analyses on these pre-processed data (see below). Of note is the fact that we did not include any spatial smoothing of the functional data for the second analysis. All imaging analyses were conducted in standard stereotactic Montreal Neurological Institute (MNI) atlas space.

2.1.3.2 A-priori ROI identification

In their CDHn model of reading, Alvarez and Fiez (2018) reported the central coordinates for the constituents of both their dorsal [(inferior frontal junction (-46 12 30), inferior parietal lobule (-42, -44, 42)], cerebellar hemisphere VIIB (30, -70, -50)] and ventral circuits [inferior frontal junction (-46 12 30), middle temporal gyrus (-62, -44, -8), and cerebellar hemisphere Crus1 (10, 80, -28)]. We generated regions-of-interest (ROIs) using each of these as a center coordinate in AFNI (*3dUndump)* with a cube radius of 4 mm or 6 mm. The 4 mm ROIs were used in the broad test, and the 6 mm ROIs were used in the precise test.

2.1.3.3 Broad test of the CDHn model

Within the field of neuroimaging, the most commonly used method to examine functional connectivity between brain regions is to correlate the timeseries of a particular voxel or seed-ROI to that of each and every other voxel's timeseries of interest during a rest period. Co-activation of the spontaneous MRI signal during rest is suggestive of cross-regional network communication for information processing.

To test for replicability of the dorsal and ventral circuits in the CDHn model, we conducted an ROI-based functional connectivity analysis of the resting-state timeseries data. For each participant, we first ran AFNI's individual-level regression analysis (*3dDeconvolve*) to extract the design matrix containing spurious signal of no interest (i.e., nuisance variables). This design matrix included the regressor weights for the following nuisance variables: 1) estimated regressors for the standard motion parameters (six demeaned and six derivatives), 2) linear and quadratic drift regressors, 3) local white-matter regressors, and 4) ventricle signal regressors. Using AFNI's unique linear regression model (*3dTproject)*, we then extracted the BOLD signal timeseries of the rs-fMRI data from each voxel while simultaneously applying a temporal bandpass filter (0.005 Hz < f < 0.10 Hz), censoring motion contaminated time points (frame-by-frame displacement > .2 mm), and projecting out nuisance variables' timeseries (Caballero-Gaudes & Reynolds, 2017). We then averaged the denoised (cleaned) resting-state BOLD signal timeseries for all of the voxels within each of our ROI cubes (*3dmaskave*) to generate seed-timeseries for our IFJ, IPL, MTG, VIIB, and Crus1 ROIs.

A voxelwise resting-state functional connectivity analysis was conducted for each of the five ROIs (*3dTcorr1D*). These analyses generated five maps of the correlation between the seed-timeseries for each ROI and the timeseries within every other voxel in the brain. The correlation maps were converted to z-score maps using Fisher's r-to-z transformation for group level testing (*3dcalc -expr 'atanh(a)')*. For each region's z-map, we extracted the average value of all the voxels within each of the other four ROIs to test the functional relationship between all regions using a one-sample t-test.

2.1.3.4 Precise test of the CDHn model

To test whether the dorsal and ventral circuit projections to the inferior frontal junction, as seen in the CDHn model, are to overlapping or segregated neuronal pools, we conducted a functional connectivity analysis of the rs-fMRI data at the voxel-level. For this test, imaging data were analyzed using the same preprocessing steps as applied in the broad test, except we did not apply any spatial blurring to the data. The denoised rs-fMRI timeseries map for each of the voxels within each of the five ROIs were produced using the same AFNI linear regression command as in the broad test (*3dTproject).*

Next, we conducted a stepwise functional connectivity analysis that considered every voxel within the dorsal circuit – i.e., the cumulative set of voxels in the inferior frontal junction, inferior parietal lobule, and VIIB ROIs. For each voxel within the inferior frontal junction ROI, we determined how many complete dorsal circuit connections, in which each pairwise connection was significant ($r > .25$, $p < .001$), could be found. Specifically, the timeseries of a given seed-voxel within the inferior frontal junction was searched for its correlation to the timeseries of each voxel within the inferior parietal lobule and VIIB. Each inferior parietal lobule and VIIB voxel that survived the inferior frontal junction connectivity significance threshold was then also tested for significant connectivity to each other. For example, seed-voxel 1 in the inferior frontal junction ROI might be connected with voxel 1 in the inferior parietal lobule ROI and voxel 1 in the VIIB ROI. However, voxel 1 in the inferior parietal lobule ROI must also exhibit connectivity with voxel 1 in the VIIB ROI for seed-voxel 1 in the inferior frontal junction to be counted as an instance of a complete dorsal loop circuit. This logic was iterated, to produce a count of the complete dorsal loop circuits detected for each voxel within the inferior frontal junction ROI. This computational process was also done using the middle temporal gyrus and Crus1 voxels to establish the ventral circuit count for each inferior frontal junction voxel. We then computed the ratio values between the count of the dorsal and ventral loops within each inferior frontal junction voxel, and finally extracted voxels with the strongest circuit bias to visually examine whether or not there is any spatial consistency as to where these potentially biased voxels are located within the inferior frontal junction.

2.2 RESULTS

2.2.1 Broad test of the CDHn model: Replicating the cerebro-cerebellar reading network

The first goal of this study was to explore experimental evidence in support of the CDHn model’s cerebro-cerebellar connectivity network. To test this hypothesis, we conducted multiple ROI-seed based functional connectivity analyses between all of the regions in the dorsal and ventral circuits reported in the meta-analysis. Specifically, for the dorsal cerebro-cerebellar network, it was hypothesized that there would be bidirectional significant functional connectivity between the left inferior frontal junction, left inferior parietal lobule and right cerebellar hemisphere VIIB. For the cerebral-cerebellar ventral network, it was expected to be significant bidirectional connections between the left inferior frontal junction, left middle temporal gyrus, and right cerebellar hemisphere Crus1.

The rs-fMRI temporal signal comparisons across each of our five ROIs were roughly in support of the CDHn model of reading (Figure 5). The cerebro-cerebellar ventral circuit ROIs (i.e., IFJ, MTG, and Crus1) revealed the most complete connectivity pathways between brain areas in support of the CDHn model. The cerebro-cerebellar dorsal circuit ROIs only partially confirmed the CDHn model, falling short of pathway connectivity within the cerebellar region VIIB. As expected, the strongest weighting of connectivity between regions derived from the cortical areas within the cerebral cortex. Notably, the only cross-circuit connections were again between the inferior frontal junction and the other areas within the dorsal and ventral routes.

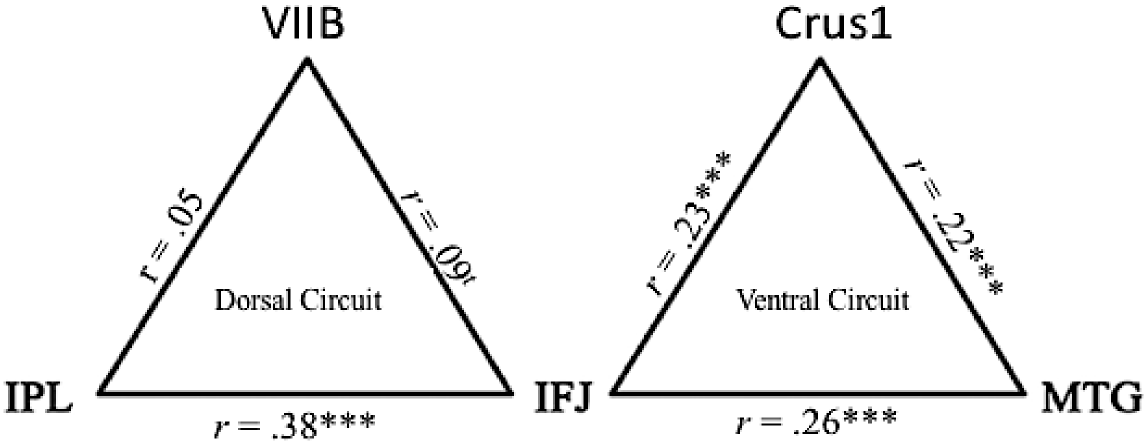


Figure 5. Results for the broad functional connectivity test of the CDH model

Statistically significant resting-state functional connectivity correlations are indicated by asterisks. Pattern connectivity most consistent with predictions of the CDHn model was observed for the ventral circuit. Partial support for the predicted dorsal circuit was observed, with no significant timeseries correlations generated for the right cerebellar VIIB ROI. IFJ = inferior frontal junction, IPL = inferior parietal lobule, MTG = middle temporal gyrus. $p < .001$***, $p < .10^t$.

2.2.2 Precise test of the CDH^n model: Sub-divisional circuitry within the inferior frontal junction

The second goal of this study was to examine the possibility of subdivisions within the inferior frontal junction that are indicative of this territory's connectivity bias towards either the parieto-cerebellar dorsal pathway or a temporo-cerebellar ventral pathway of the CDHn model. To test this, we conducted a stepwise functional connectivity analysis counting the number of complete dorsal and ventral circuits within each of the voxels in our inferior frontal junction ROI. Sub-divisional specialization within this ROI was measured by weighting each inferior frontal junction voxel's bias towards the dorsal regions versus its bias towards the ventral regions, expressed as the ratio between the dorsal versus ventral circuit count, and examining the histograms of the inferior frontal junction's voxelwise circuit bias. Voxels with ratio values closer to 0.0 have more ventrally specialized circuity, and voxels with ratio values closer to 1.0 have more dorsally specialized circuitry. Voxels closer to the median (i.e., 0.5) represent inferior frontal junction voxels that have roughly equivalent connectivity to the dorsal and ventral circuits. It was hypothesized that, if there are dissociable dorsal and ventral processing streams within the inferior frontal junction, then there should be a topographical distinction in the location of inferior frontal junction voxels with a dorsal versus ventral circuit connectivity bias.

An examination of the individual voxel distributions revealed some participants with distinctively specialized dorsal versus ventral circuits within the IFJ (See Figure 6 for an example participant). Across all participants, we did not see a complete dorsal versus ventral dissociation of every voxel within the inferior frontal junction. However, the anatomical mappings of this distribution illustrate that these dissociated voxels have a topographical pattern, in line with predictions of separable processing pathways within the inferior frontal territory for reading (Figure 7). Specifically, voxels on the tail end of the distribution for greater dorsal circuitry bias primarily clustered towards the dorsal-posterior extent of the inferior frontal junction, whereas tail end voxel with a greater ventral circuitry bias positioned closer to the ventral-anterior extent of the inferior frontal junction. Overall, these findings are in line with hypotheses for a topographical division of dorsal versus ventral pathways within the inferior frontal junction.

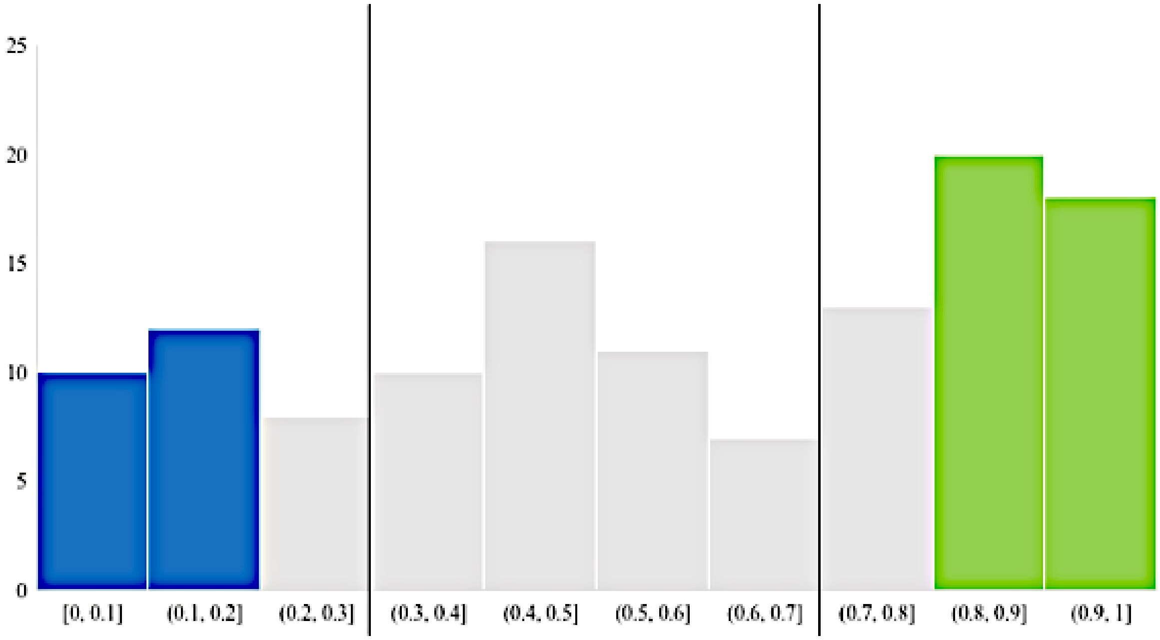


Figure 6. Voxelwise distribution of the dorsal and ventral circuity in the IFJ

Inferior frontal junction histogram of the voxelwise dorsal versus ventral circuit connectivity distribution ratios for an individual participant. Solid line denotes the near third split of voxel count between the total amount of voxels with either a stronger dorsal circuit bias (right), ventral bias (left), or no bias between the circuits (middle). Green bars highlight the top 20th percentile of inferior frontal junction voxels with greater dorsal than ventral circuit bias, and blue bars depict the 20th percentile voxels with greater ventral than dorsal circuit bias (right).,

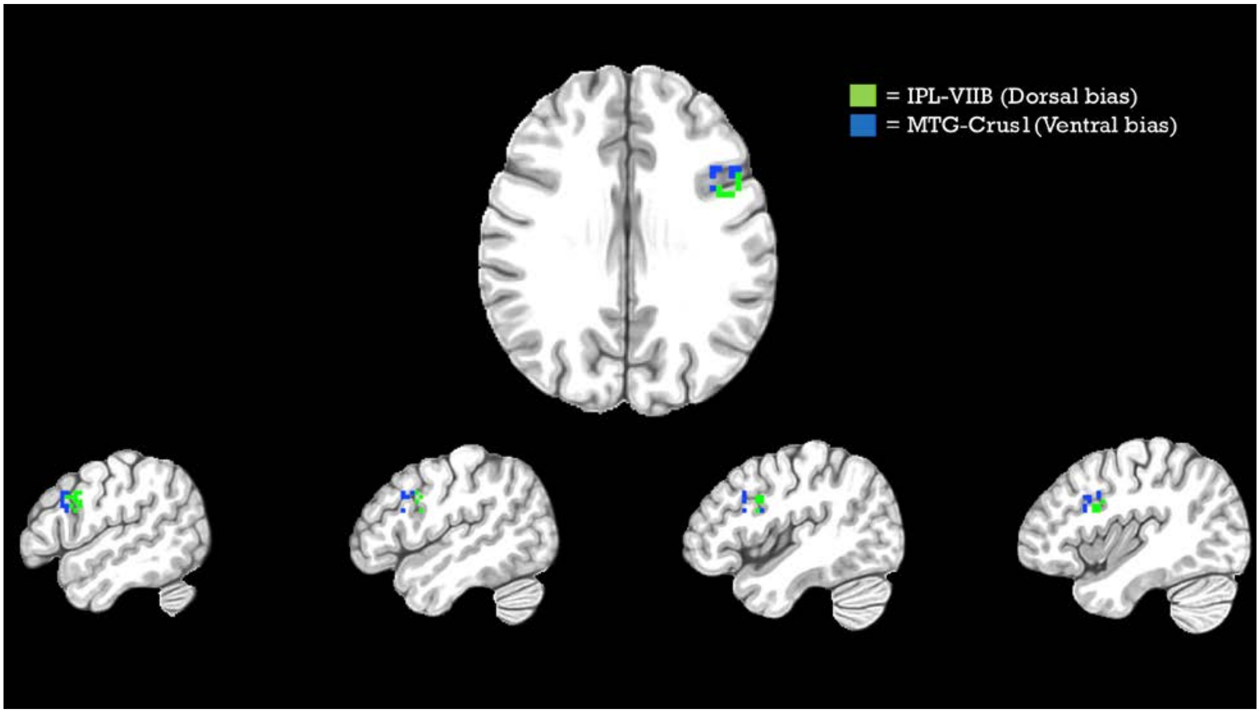


Figure 7. Dorsal versus ventral circuit topography within the IFJ

The neuroanatomical mapping of the inferior frontal junction voxels with the greatest dorsal versus ventral bias are plotted on axial (top row) and sagittal (bottom row, 3 mm gap between images) slices of the group distribution. These images implicate a sub-divisional topography within the inferior frontal junction, with more dorsal circuit voxels clustering at the posterior region (green voxels) and more ventral biased circuits clustering anteriorly (blue voxels). Numbers below each slice indicate the corresponding plane coordinate in MNI space (axial image=z-plane, sagittal images=x-plane).

2.3 DISCUSSION

It is oft understood that the temporal dependency of the BOLD signal between spatially distinct regions reflect how regions within the brain may be functionally communicating to process cognitive information across neural networks (Biswal et al., 1995; Friston, Frith, Liddle, &

Frackowiak, 1993; Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000). In a previous meta-review of the cerebellar involvement in reading-related networks, (Alvarez & Fiez, 2018) proposed a neural account of the CDH model partialy based on their findings of two spatially distint cerebro-cerebellar pathways for reading. In our effort to support these findings with empirical data, we examined the functional connections of participants' resting-state MRI data across five a priori ROIs derived from the prior meta-review, and further scrutinized the common node across these two networks (the inferior frontal junction ROI) for possible sub-node specialization.

The broad ROI-based approach did reveal the full interconnectivity that was expected amongst the constituents of the ventral circuit. Specifically, the predicted interconnectivity between the constituent ROIs of a ventral circuit (IFJ, MTG, Crus1) was observed. Surprisingly, this approach did not completely reveal the expected interconnectivity for the neural constituents of the dorsal circuit. Specifically, interconnectivity between the inferior frontal junction and inferior parietal lobule was observed, but significant connectivity between these regions and the cerebellar constituent of the circuit (VIIB) was not observed. Overall, findings using our ROI-based functional connectivity analysis revealed evidence of cerebellar interconnections with cerebro-cortical regions associated with reading, which were most strongly in support of the fronto-temporo-cerebellar ventral circuit.

Greater success was found using a precise voxel-by-voxel approach. This novel approach gave positive results for both the predicted cerebro-cerebellar dorsal and ventral circuits. Not only did this approach delineate a number of complete dorsal and ventral circuits within the inferior frontal junction, it also disclosed strong evidence that voxels within this frontal territory appear to have a consistent topographical circuit bias that holds across participants. To further support this evidence of functional subdivision within the inferior frontal junction, a future direction might be to extract the center-of-mass coordinate of the voxels within this territory that are more dorsally weighted and the center-of-mass coordinate for those that are more ventrally weighted. Using Neurosynth's term lists for these inferior frontal territory coordinates, terms could be compared to assess the frequency in which our biased coordinates support a model of sub-divisional specialization within the inferior frontal junction. Overall, findings using our voxel-based functional connectivity analysis give credit to the utility in designing a precise approach that can parcellate potential sub-neuronal populations within these reading pathways.

It is important to note the potential limitations of the study, especially as it pertains to the partial support of evidence using the broad ROI-based analysis. Notably, in the CDHn model, cerebellar hemisphere VIIB emerged as the smallest cluster of interconnectivity with cerebral-cortical reading regions, as compared to cerebral-cortical interconnectivity with cerebellar Crus1. This could explain the observed null results for VIIB, because our study might have included some voxels within the VIIB ROI cube that does not contribute to the dorsal circuit. It is also possible that the location of VIIB, it being the most inferior cerebellar region with voxels surrounding the edge of the brain, made it particularly susceptible to sources of artifact, thus degrading the signal-to-noise ratio within this ROI. Another limitation concerns some of the distinguishing features of the cerebellum as compared to the cerebral cortex. For instance, the cerebellum's largest and main efferent cells (Purkinje neurons) are inhibitory, whereas the equivalent cells in the cerebral-cortex (pyramidal neurons) are excitatory. Moreover, cerebral cortical connections with the cerebellum must first pass through the subcortical thalamic nuclei, therefore instituting an additional trans-neuronal pathway that can often present challenges in consistently establishing cerebro-cerebellar pathways (Hwang, Bertolero, Liu, & D'Esposito, 2017; Middleton & Strick, 1994). It is possible that one or more of these features could have impacted our ability to observe significant functional connectivity of the dorsal circuit. One avenue for future direction could involve constraining the size of the ROI cube to the magnitude of each cluster size in the CDHn model. This could increase the potential of honing-in on voxels that reliably contribute to bidirectional processing between cerebro-cerebellar regions and reducing voxels that do not contribute to this effect.

Although our broad ROI-level data revealed only partial replication of the CDHn model's proposed cerebro-cerebellar dorsal circuit, it seems premature to conclude that this circuit does not exist. One reason is due to the strength of the model's meta-analytic review, which provided strong qualitative and quantitative support for the dorsal circuit. Moreover, our alternative voxelwise precise analysis provided compelling evidence in support of both the dorsal and ventral circuits for reading. As a cautionary note, it is possible that our voxelwise precise method is susceptible to false positives and in need of a more stringent approach. We used an arbitrary p-value (< .001) commonly used for parametric clustering within AFNI processing protocols (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Taylor et al., 2018). As has been reported on numerous occasions, p-value thresholding involves some arbitrariness no matter how 'stringent' a particular test may be considered. Future studies may want to explore potential methods of iterative voxel-level region-of-interest comparisons to propose an optimal method that can lessen the potential of inflated false-positive rates in these types of analyses. While our arbitrary statistical threshold may have elevated the count of observed dorsal and ventral voxel-level circuits, it should not have systematically biased the findings towards one type of circuit or the other. Thus, we retain confidence in our current findings, as well as the potential in replicating these results with the use of a more stringent p-value. Overall, we conclude that our results support the CDHn model in its recognition of dissociable dorsal and ventral circuits for reading that include the cerebellum.

3.0 FUNCTIONAL SPECIFICITY OF THE CDH$_N$ MODEL

For decades, the predominant theories of developmental dyslexia have emphasized an underlying deficit in phonological (Liberman, 1973; Stanovich, 1988) or visual processing (Lovegrove, Bowling, Badcock, & Blackwood, 1980; Stein, 1991), with a presumed loci of brain tissue abnormality or dysfunction in regions within the cerebral cortex (for review see Richlan, 2012). The cerebellum, a subcortical brain structure recognized for its enormous computational processing power (Llinas et al., 1973; Marr, 1969), remains mostly detached as a region that maps on to any of the prominent neurobiological models of reading and developmental dyslexia. This is somewhat surprising given the growing number of studies that have associated measures of aberrant cerebellar processing with common symptoms of developmental dyslexia (Feng et al., 2017; Kronschnabel et al., 2013; Menghini et al., 2006; Yang et al., 2013). Further, from even the earliest uses of fMRI to study reading in healthy participants, evidence of cerebellar activation has been observed during cognitive tasks that engage dissimilar processes of reading (Fiez et al., 1996; Fulbright et al., 1999; Roskies, Fiez, Balota, Raichle, & Petersen, 2001). However, contrasting evidence can be found in the few meta-analytic neuroimaging reviews of disordered versus normal reading wherein no significant group difference arise for any region within the cerebellum (Pollack, Luk, & Christodoulou, 2015; Richlan, 2012; Richlan, Kronbichler, & Wimmer, 2009). As such, there remains a strong need to reconcile conflicting views regarding the functional link between the cerebellum and reading processes.

A central challenge in reconciling this conflicting literature is the lack of understanding about how the contributions of the cerebellum relate to recognized functional specializations of cerebral regions involved in reading. Neuroscience investigations of the predominant models of visual word recognition -- the dual-route (Coltheart, 2008; Forster & Chambers, 1973; Marshall & Newcombe, 1973) and triangle model (Rumelhart & McClelland, 1982a, 1982b; Seidenberg & McClelland, 1989) -- have focused on mapping these models onto cerebral regions (for review see Taylor, Rastle, & Davis, 2012). Consequently, within the reading development literature, the cerebellum has been mostly detached as a region that maps onto any of the prominent models of reading, yet it is frequently engaged during tasks that involve reading.

The current work builds upon on a model of reading that implicates the cerebellum as a part of a learning system for reading. Nicolson and colleagues (2001) reasoned that the frequently exhibited behavioral impairment of motor and sensoriperceptual functioning in individuals with dyslexia is indicative of a more complex neural system for reading development. Their “cerebellar deficit hypothesis” (CDH) proposed a causal chain involving an indirect link between the cerebellum and the development of reading skills. However, the CDH model and its base of evidence suffers from a lack of integration between speculations about the cerebellum and how it is functionally integrated into what is known about the cerebral reading network.

Similar to Nicolson and colleagues' (2001) approach, much of the speculation about a cerebellar role in reading has drawn upon the motor literature; relating classic motor-based concepts (e.g., Llinas, Hillman, & Precht, 1973; Marr, 1969) to high-level cerebellar processes during reading. For example, one perspective of particular interests reasons that the involvement of the cerebellum reflects its role in error-driven learning (Ben-Yehudah & Fiez, 2008). The error-driven perspective posits a cerebellar internal articulatory monitoring process that involved possible feedback systems between synaptic connections from cerebro-cortical regions and the cerebellum during non-motor cognitive tasks (i.e., prediction, outcome, error-correction).

Although there seem to be emergent themes from the literature on the cerebellum and reading, core aspects of these theories remain untested. In our previous work, we conducted a meta-analytic review to develop a better understanding of the neural connectivity between the cerebellum and the reading network (Alvarez & Fiez, 2018). The result is a neural variant of the CDH model (the CDHn model) which revealed a functionally interconnected cerebro-cerebellar dorsal circuit [comprising the left inferior frontal junction, left inferior parietal lobule, and right cerebellar hemisphere VIIB/Crus2 (VIIB)], and a functionally interconnected cerebro-cerebellar ventral circuit [comprising the left inferior frontal junction, left middle temporal gyrus, and right cerebellar hemisphere Crus1]. Notably, in the CDHn model, both the dorsal and ventral circuits show a bias towards phonological versus semantic activation, respectively, with supposition about a cerebellar modulatory role of the phonological and lexico-semantic properties within the interconnected cerebro-cortical regions of these circuits. However, the functional biases attributed to these circuits were based on meta-analytic evidence and not a direct empirical test. Moreover, to our knowledge, this idea about the cerebellum's functional position within these reading circuits have yet to be considered, let alone empirically tested. The present study addresses these gaps, by investigating the functional responses of these regions during two tasks that differentially emphasize phonological versus semantic processing: a rhyme-judgment and a semantic-categorization task.

Phonological processing is generally understood to consist of three distinct yet overlapping abilities: 1) phonological awareness, which is an individual's ability to identify and discriminate a language's phonological structure of sound, 2) phonological memory, which is the ability to maintain the phonological information within short term memory, and 3) phonological recoding, which is an individual's capability of quickly and effectively retrieving the phonological unit associated with the written or orthographic symbol and translate them into words (Wagner & Torgesen, 1987). Previous study findings have found left cerebral cortical areas (e.g., precentral gyrus and the anterior insula) associated with phonological processing and speech production (Fiez, Raife, et al., 1996; Fiez, Raichle, Balota, Tallal, & Petersen, 1996; Vigneau et al., 2006). However, this phonological processing pathway has only recently begun to include the cerebellum as an integrated region. The CDHn model proposes that a portion of lobule VIIB is part of a dorsal phonological circuit, thus leading to the prediction that this region, as well as the inferior parietal constituent of the dorsal circuit (inferior parietal lobule) should be more engaged during a rhyme-judgment as compared to semantic-categorization task.

Semantic processing refers to a representation of meaning and knowledge at the level of phrases, situation or context. Studies investigating lexico-semantic processing in the cerebral cortex report findings of task-biased regions in left ventral-inferior frontal gyrus and the superior-temporal sulcus/middle temporal cortex (Demb et al., 1995; Gabrieli et al., 1996) . Roskies et al., (2001) identified a region in the right cerebellar hemisphere Crus1 that responded more strongly to the semantic task compared to the rhyme task, as well as semantic task-biased regions in left cerebral cortical areas that have been associated with lexico-semantic processing. This is consistent with the CDHn model, which proposes that a portion of right cerebellar lobule Crus1/Crus2 is part of a ventral semantic circuit. Thus, prior findings and the CDHn model lead to the prediction that this region, as well as the middle temporal constituent of the ventral circuit (middle temporal gyrus) should be more engaged during the semantic-categorization as compared to rhyme-judgment task.

Two different approaches are used to test for the predicted functional specializations across the rhyme-judgment and semantic-categorization tasks. A univariate approach focuses on characterizing the functional biases of regions within the dorsal and ventral circuit, based on overall differences in the magnitude of the functional response during each task. A multivariate approach employs machine learning methods to test whether the tasks are associated with differences in the pattern of activity within each region. This is of particular interest for the inferior frontal junction region, because this region is part of both circuits and the multivariate approach could reveal evidence of a functional subdivision that is not apparent at the regional level. Together, these analyses will test whether two cerebro-cerebellar circuits, which were primarily defined on the basis of functional connectivity patterns, have regional components that exhibit predicted biases for the phonological versus semantic processing of printed words.

Additionally, a third analysis combines univariate and multivariate measures to test for a modulatory role of the cerebellum on the quality of representation within interconnected cerebral regions. This analysis is inspired by considerations of how the cerebellum may functionally contribute to the cerebral reading network. As one possibility, Alvarez and Fiez (2018) drew upon the motor and non-motor literature on the cerebellum to propose that its role in reading may be to fine-tune the phonological and lexico-semantic representations within the dorsal and ventral circuits, respectively. If this idea is correct, then one expectation might be that stronger engagement of the cerebellum will track with greater representational quality in the cerebro-cortical regions that are connected with it. To test this idea, the trial-level data from the cerebellar constituents of the CDHn model are subdivided into high versus low activation trial, using the univariate BOLD data from the rhyme-judgment task for the VIIB ROI, and the semantic-categorization task for the Crus1 ROI. Then, for the cerebral constituents of the CDHn model, the classifier performance (a multivariate measure) is compared for high versus low trials. Based on ideas of Alverez and Fiez (2018), the prediction is that classifier performance within the inferior frontal junction and inferior parietal lobule will be significantly more accurate for trials with high versus low VIIB rhyme-judgment activation, and the inferior frontal junction and middle temporal gyrus will be more accurate for trials with high versus low Crus1 semantic-categorization activation.

3.1 METHODS

3.1.1 Participants

The participants in this study are the same as those described in Chapter 2.

3.1.2 Imaging and task protocol

3.1.2.1 Imaging acquisition

The imaging acquisition parameters for the structural and functional runs of this study are the same as described in Chapter 2. The current chapter focuses on the four fMRI runs that were included within the overall protocol. During each of these scans, participants performed one of two behavioral tasks that differentially emphasize phonological versus semantic processing: a rhyme-judgment and a semantic-categorization task, respectively. While in the scanner, participants performed each task twice, with the task order counterbalanced between participants, and the length of each functional run prescribed at 5.6 minutes. Task instructions were displayed at the beginning of each run until the participant pressed their thumb key to begin. All task instructions and stimuli appeared in a black 32-point bold capital letters on the center of the screen in a gray background setting. Before being placed in the scanner, participants completed five trials of practice for each task, using stimuli different from those in the actual experiment.

3.1.2.2 Phonological task: Rhyme-judgement stimuli and procedure

The stimuli for the rhyme-judgement task consisted of four sets of one-syllable word pairs, which were drawn from a previously unpublished undergraduate thesis (Raboy, 2010). The items across each set were matched in word length and frequency according to (Francis & Kucera, 1982), number of phonemes, and the number of phonologic and orthographic neighbors. The original list consisted of 160-word pairs of four different rhyme conditions. Pairs in the “hard-yes” condition are visually dissimilar but do indeed rhyme (e.g., MOOSE, JUICE). Rhyme “hard-no” condition share some orthographic similarities but do not rhyme (e.g., BOOT, FOOT). Rhyme “easy-yes” condition share some orthographic similarities and do rhyme (e.g., BLOT, CLOT). Rhyme “easy-no” word pairs share no orthographic similarities and do not rhyme (e.g., LIST, BRAN). For the purpose of the current study, this list was reduced to 48 total word pairs (12 pairs of words per condition) by constraining pairs within a reaction-time and accuracy rating of one standard deviation (Table 1). Within each of the two runs involving the rhyme task, 6-word pairs were selected from each of the four conditions, to give a total of 24 trials per run. The selection of the word pairs from each category and the order of their presentation within a run was randomly selected for each participant.

Each trial of the rhyme-judgement task consisted of a pair of words appearing together above and below a central crosshair for 600 ms. This was followed by a response screen with a central crosshair displayed for 13.4 seconds. Finally, a response screen (central crosshair) was displayed for 13.4 seconds. Participants were instructed to indicate as quickly and accurately as possible, during the response screen display, whether or not the two words on the screen rhyme by pressing their index finger for “yes” or their middle finger for “no.”

Table 1. Example of participant stimuli for the rhyme-judgment task

EASY				HARD			
No		Yes		No		Yes	
PIPE	FERN	COIL	BOIL	BONE	NONE	PAIN	LANE
GRANT	SHELL	SOUND	POUND	LONE	GONE	PHONE	KNOWN
SALT	JUMP	CREAM	DREAM	TOUR	SOUR	BATCH	LATCH
LIST	BRAN	BLOT	CLOT	CLOVE	GLOVE	SOLE	COAL
SNOW	THING	NUMB	DUMB	BOOT	FOOT	NEWS	LOSE
SLUG	SOUP	NOISE	POISE	DOUGH	ROUGH	MOOSE	JUICE

3.1.2.3 Semantic task: Semantic-categorization stimuli and procedure

The stimuli for the current study’s semantic-categorization task were drawn from a previous study that identified task-specific brain regions associated with semantic processing (Roskies et al., 2001). This past study involved 79 category words and 158 semantically related and 158 non-related words. Similar to rhyme-judgement task, the stimuli from the Roskies et al. study can be organized into word lists representing four conditions: “hard-yes”, Semantic ‘hard-no”, semantic “easy-yes”, and semantic “easy-no”. To generate word-pairs for each of the four conditions, each category word is paired with one semantically related or one non-related word, to give a maximum of 48 pairs without repetition of the category word. Thus, for each participant, the stimuli from the Roskies’ et al. study were reduced to 48 word-pairs (12 pairs of words per condition) by randomly selecting word pairings for a condition and replacing those trials that included a repeated word across any of the four conditions (Table 2). Within each of the two runs involving the semantic task, 6-word pairs were selected from each of the four conditions, to give a total of 24 trials per run. The selection of the word pairs from each category and the order of their presentation within a run was randomly determined for each participant.

The stimulus presentation parameters for the semantic-categorization task were identical to those for the rhyme-decision paradigm, except that during the presentation of each word pair, the category word first appearing on the screen for 200 ms, then both words appeared together above and below a central crosshair for another 400 ms. All other semantic task procedures matched the rhyme task. Participants were instructed to indicate as quickly and accurately as possible whether or not the bottom word was an exemplar of the category word by pressing their index finger for “yes” or their middle finger for “no.”

Table 2. Example of participant stimuli for the semantic-categorization task

EASY				HARD			
No		Yes		No		Yes	
FISH	LAMP	HERB	MINT	SHOES	NYLON	GEM	JADE
CLOTH	MANGO	STONE	MARBLE	MEAT	LION	PLANT	GRASS
VIRUS	BLIMP	NUT	ALMOND	SPORT	WALTZ	BREAD	ROLL
REPTILE	CHANT	METAL	STEEL	MUSIC	RAIN	TOOL	STAPLER
VOLUME	PEPPER	WEIGHT	POUND	SHAPE	INCH	MONEY	CHECK
BUILDING	SHARK	GRAIN	WHEAT	COLOR	GRASS	RELATIVE	WIFE

3.1.3 Data analyses

3.1.3.1 Behavioral tasks

We examined the rhyme-judgment and semantic-categorization task behavioral data for task differences. Using the IBM’ Statistical Package for the Social Sciences program (SPSS), we implemented two 2 x 2 x 2 analysis of variance (ANOVA) models with Task (Rhyme, Semantic), Difficulty (Easy, Hard) and Expected-response (No, Yes) as factors. These factors allowed us to examine our eight task conditions (Easy-No, Easy-Yes, Hard-No, Hard-Yes, for each of our two tasks), testing for overall task differences, as well as influences of difficulty and type of expected-response that might affect task performance. One ANOVA was carried out using accuracy as the outcome measure, and the other with reaction time (RT) as the outcome measure.

3.1.3.2 Image preprocessing

Images were preprocessed using the AFNI software package (Cox, 1996) using nearly the same processing stream as in Chapter 2. For the current chapter, as a task-based fMRI protocol, we did not include a temporal bandpass-filter, or any of the nuisance parameters that are most relevant for the analysis of resting-state connectivity data (e.g., heart-rate and pulse data, and segmented white matter and ventricle parcellations).

To address particular aspects of our research questions, we utilized both univariate and multivariate analyses to characterize functional activity within each of five regions-of-interest (ROIs). Of note is that we did not apply any spatial smoothing of the functional data for the multivariate analysis.

3.1.3.3 A-priori ROI identification

All analyses in the current chapter used the same five 4 mm cube ROIs that were generated in Chapter 2 [i.e., left inferior frontal junction (IFJ), left inferior parietal lobule (IPL), left middle temporal gyrus (MTG), right cerebellar hemisphere VIIB, and right cerebellar hemisphere Crus1].

3.1.3.4 Univariate approach: Rhyme versus semantic

We employed a univariate approach to test whether the constituents of the CDHn model can be functionally characterized as part of either a dorsal or ventral circuit that preferentially contributes to phonological (rhyme-judgment task) or semantic (semantic-categorization task) processing demands, respectively.

Subject whole brain maps of the response amplitude and variability were generated by conducting a voxel-wise general linear model analysis using AFNI (i.e., modeling the maximum likelihood estimation of the finite impulse response at each voxel). Estimation of the hemodynamic response function (HRF) was modeled in using a TENTzero function beginning at trial onset and ending at the conclusion of an entire trial (14 seconds), with continuous independent piecewise linear impulse response functions (first and last basis function were constrained to an amplitude of zero). The timeseries of each condition's impulse response coefficient was generated using the AFNI flag -*iresp* in the general linear model (*3dDeconvolve*). This process led to a total of eight regressors-of-interest corresponding to the eight task conditions (four conditions each for both the rhyme and category tasks). As was done in Chapter 2, signal trend and motion parameters were also included as nuisance regressors. Each condition's estimated area under the curve (AUC) was generated by summing the timecourse of the impulse response at each estimated timepoint for a given voxel. Region specific hemodynamic response amplitudes were then generated by calculating the mean AUC value for of all voxels within each of our five ROIs, and these values were extracted for analysis outside of the AFNI program in SPSS.

For each of our five ROIs, we ran a 2 x 2 x 2 ANOVA with Task (Rhyme, Semantic), Difficulty (Easy, Hard) and Expected-answer (No, Yes) as within-group factors. We expected to find evidence compatible with the predictions of the CDHn model. Specifically, we hypothesized that inferior parietal lobule and VIIB ROIs would show a significant task effect with greater activation for rhyme than semantic trials. We also expected the middle temporal gyrus and Crus1 ROIs would exhibit a task effect, but in the opposite direction (i.e., greater engagement for the semantic than rhyme trials). We did not expect the inferior frontal junction ROI to exhibit any significant between-task effects because the CDHn model proposes this region is common to both the dorsal-phonological and ventral-semantic circuits.

3.1.3.5 Multivariate approach: Rhyme and semantic classification

We employed a multivariate pattern-information analysis (MVPA) to test how well the neural spatial patterns within each of the five ROIs provide sufficient information to classify rhyme-judgment versus semantic-categorization task trials. Trial-specific regressors of the BOLD response were modeled using a GAM function with the *-stim_times_IM* flag in AFNI's GLM toolbox (*3dDeconvolve*). These trial-level estimated HRF data were used as dependent measures in the subsequent MVPA classifier approach using the Princeton Multi-Voxel Pattern Analysis toolbox (Detre et al., 2006). Task classification training for ROI spheres employed a leave-two-halfruns-out cross-validation procedure (i.e., select half of the trials from one rhyme and one semantic run to test the model, and use all of the other trials to train the model). Classification training computed pattern decoding maps for classifying a trial as either the rhyme-judgment or semantic-categorization task. This process was done for all trials within one of the rhyme-judgement runs and one of the semantic-categorization runs (a total of 48 randomly sequenced trials). The trained model's decoding map was then used on the other rhyme and semantic runs to test the model's classification accuracy for the trials in this held-out data. This procedure underwent multiple iterations, until each iteration had been tested. The classifier performance accuracies were averaged across iterations to represent the mean classifier accuracy value for a given ROI, for each participant. The mean classification percentages were then aggregated across participants and subjected to group-level statistical analyses to test whether the voxel patterns from a given ROI can be used to classify the trials as the rhyme or semantic task with better than chance accuracy, using a one-sample t-test in SPSS (i.e., greater than 50%). Based on the CDHn model, above-chance classifier performance was predicted for the four ROIs that are constituents of only one circuit (dorsal or ventral; IPL, MTG, VIIB, Crus1 ROIs). No prediction was made for the IFJ ROI, which is a constituent of both circuits. If this region contributes to domain-general processing, then one might expect to observe near-chance classifier performance. Alternatively, if this region has functionally specialized neuronal pools within it (either randomly dispersed or topographically organized) then one might expect above-chance classifier performance.

3.1.3.6 Testing for a cerebellar modulatory role of the reading network

To test for a cerebellar modulatory role on the dorsal and ventral circuits within the CDHn model, we extracted the participants' trial-level HRF data to catalogue each participant's rhyme-judgment and semantic-categorization trials' activation. Cerebellar VIIB trial-level estimated HRF data were then split into high versus low rhyme trials (i.e., trials for which this region, a proposed constituent of the dorsal-phonological circuit, is most active during the rhyme task and trials for which it is least active). It is possible that the four conditions within each task (i.e., Easy-No, Easy-Yes, Hard-No, Hard-Yes) could be disproportionately distributed between the high and low trials. To limit the potential of confounding the data results, extraction of the high and low trials was subdivided within each of the four condition types (i.e., six high and six low cerebellar activation trials per condition). This process ensured an even distribution of the condition types within the high versus low activation trial subsets. This process was repeated, but using the data from the cerebellar Crus1 ROI and the semantic-categorization task trials to create the high versus low activation subsets (i.e., trials for which the Crus I ROI, a proposed constituent of the ventral-semantic circuit, is most active during the semantic task and trials for which it is least active). The catalogued trials were used as trials-of-interest in the multivariate classifier to examine the compare the classification performance for the dorsal (IFJ and IPL) and ventral (IFJ, and MTG) ROIs for trials that exhibited high versus low activity in the cerebellar VIIB and Crus1 ROIs, respectively. For each cerebral-cortical ROI cube, we calculated the rhyme-judgement classifier accuracy during high versus low cerebellar rhyme trials to yield a ratio measure for each cerebral-cortical ROI for each participant (i.e., how accurate was the classifier model for a given ROI for trials with high versus low activation in the right cerebellar VIIB ROI). Likewise, we calculated the semantic-categorization classifier accuracy during high versus low cerebellar categorization trials to yield a ratio measure for each cerebral-cortical ROI for each participant (i.e., how accurate was the classifier model for a given ROI for trials with high versus low activation in the right cerebellar Crus1 ROI). A classifier ratio accuracy was thus generated comparing both the rhyme and semantic high versus low activation trials. These ratio values were analyzed using group-level statistics to test whether each cerebral ROI showed significant differences in performance accuracy between high versus low cerebellar rhyme trials, or between high versus low cerebellar semantic trials. It was hypothesized that greater cerebellar engagement would predict better classifier accuracy in the functionally connected cerebral regions in the CDHn model. Specifically, the middle temporal gyrus classifier would make fewer mistakes in classifying the semantic task for trials with high as compared to low activation in the right cerebellar Crus 1 ROI, while the inferior parietal lobule classifier would make fewer mistakes on the phonological task for trials with high as compared to low activation in the right cerebellar VIIB ROI, and the inferior frontal junction classifier would make fewer mistakes on both tasks for the corresponding trials with the relevant high versus low cerebellar activation.

3.2 RESULTS

3.2.1 Behavioral tasks

An initial 2 x 2 x 2 ANOVA with Task (Rhyme, Semantic), Difficulty (Easy, Hard) and Expected-response (No, Yes) was conducted on the two behavioral tasks to assess behavioral performance differences, with accuracy and RT as outcome measures. Importantly, based on prior results (Raboy, 2010; Roskies et al., 2001), we expected no significant difference in the overall performance accuracy between the rhyme and semantic tasks. We did anticipate a significant difference between tasks for RT, with slower performance for the semantic-categorization as compared to rhyme-judgment task.

The full ANOVA results are listed in Appendix A and visually plotted in Figure 8. Generally, our results are comparatively consistent with predictions. Notably, when examining participants' accuracy in performing the rhyme-judgment (*M* = .90, *SE* = .02) and semantic-categorization tasks (*M* = .87, *SE* = .02), we found no significant difference, as well as no interaction between task and difficulty. This indicates that participants can achieve comparable success in accurately performing the rhyme-judgment and semantic-categorization tasks. Analysis of RT revealed that participants were significantly slower to perform the semantic-categorization (*M* = 877, *SE*= 93) as compared to the rhyme judgment task (*M* = 718, *SE* = 93). However, importantly there was no interaction between task and difficulty. For the main effect of difficulty, participants displayed better accuracy during the easy (*M* = .96, *SE*= .01) than hard trials (*M* = .81, *SE* = .02), and slower responses for hard (*M* = 904, *SE* = 103) than easy trials (*M* = 691, *SE*= 67). For the main effect of expected-outcome, participants displayed better accuracy during the yes (*M* = .90, *SE* = .01) than no trials (*M* = .87, *SE* = .02), and slower responses for no (*M* = 860, *SE* = 99) than easy trials (*M* = 734, *SE* = 76). There was also a significant interaction between difficulty and expect-outcome in participants' overall accuracy, as well as a 3-way interaction (task by difficulty by expected-outcome) for participant's reaction-time.

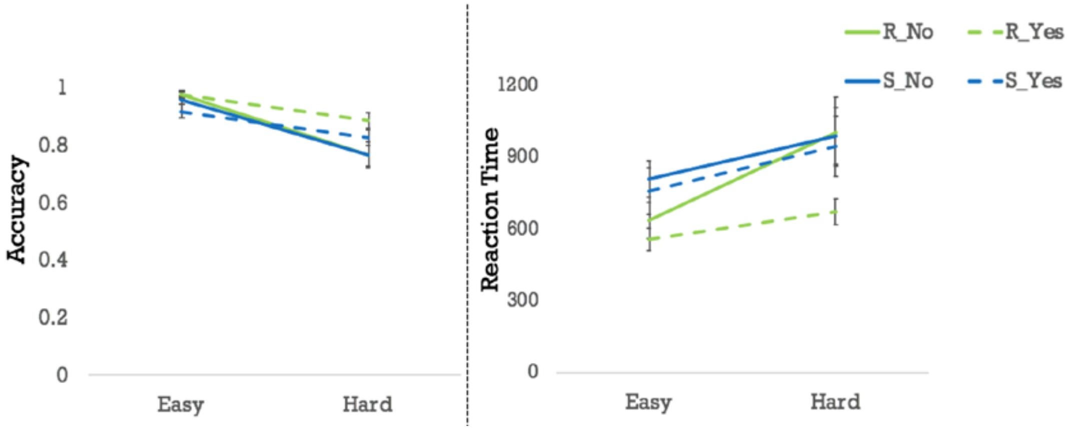


Figure 8. Behavioral tasks' accuracy and reaction-time results

Results for the 2 (Task) x 2 (Difficulty) x 2 (Expected-response) ANOVAs are plotted for the mean accuracy (left) and reaction time (right). Line color indicate the type of task, with green representing the rhyme task and blue representing semantic task. Solid lines represent the no trials, and dashed lines represent the yes trials. Error bars reflect the standard error of the mean.

3.2.2 Univariate analysis of fMRI data

We applied a classic univariate method to test for functional specificity using the five centroid coordinates identified in the CDHn model as a priori ROIs representing the proposed dorsal (IFJ, IPL, VIIB ROIs) and ventral (IFJ, MTG, Crus1 ROIs) circuit constituents. The full ANOVA results for each of the ROIs are enumerated in Appendix B.

3.2.2.1 Left inferior frontal junction

Within the left inferior frontal junction, there were significant main effects of the difficulty, expected-response, and an interaction between task and difficulty (Table 4). Specifically, for the main effect of difficulty, there was significantly greater IFJ activation for the hard (*M* = 1.47, *SE*

= .146) than easy trials (*M* = .89, *SE* = .105). For the main effect of expected-response, there was significantly greater activation during the no (*M* = 1.31, *SE* = .123) than yes trials (*M* = 1.05, *SE* = .126). The effect of difficulty was larger in the rhyme-judgment task than in the semantic-categorization task, as indicated by the significant interaction between task and difficulty (Figure 9); post-hoc pairwise comparisons revealed significant activation differences between difficulty for both the rhyme task, *t* (17) = 5.01, *p* < .001, and the semantic task *t* (17) = 2.52, *p* < .05 (Bonferroni corrected). Most notably, our primary prediction for this region was supported. That is, the left inferior frontal junction did not exhibit a significant difference in task-evoked activation between the rhyme and semantic tasks or any of the other factors.

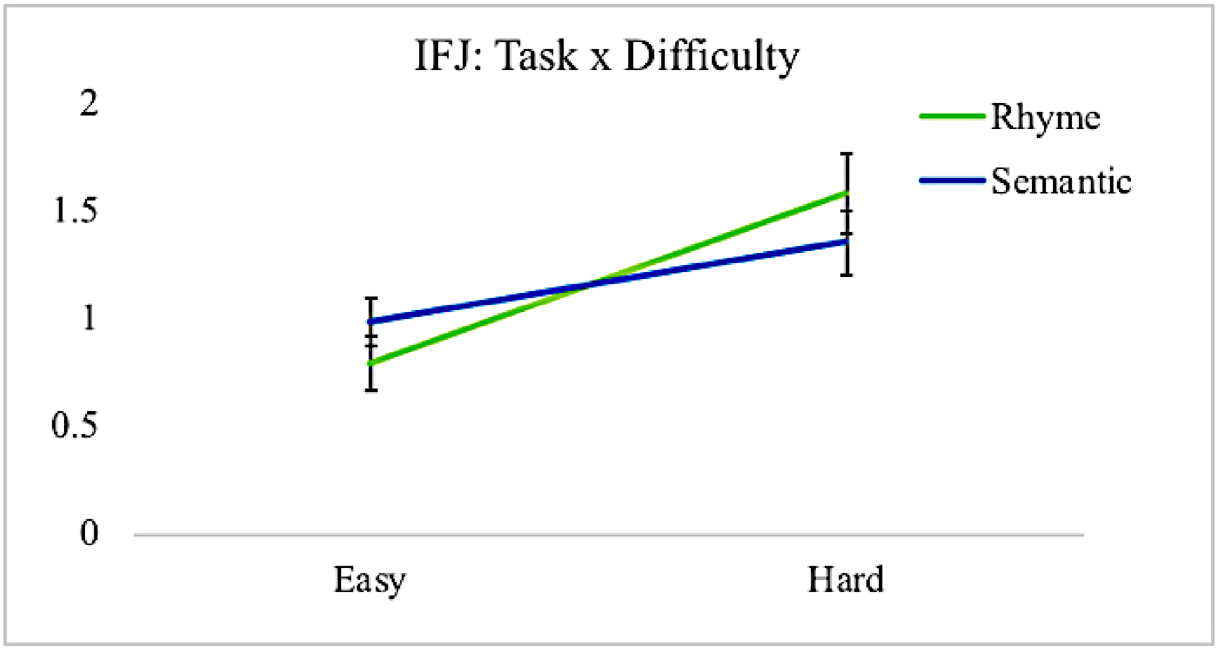


Figure 9. Univariate: Task by difficulty interaction within IFJ

Group-level activity in the inferior frontal junction plotted for the interaction between the task and difficulty factors. The y-axis is the scale for mean group BOLD activity within the inferior frontal junction ROI. Error bars reflect the standard error of the mean.

3.2.2.2 Left inferior parietal lobule

Within the left inferior parietal lobule, there were significant main effects of task and difficulty; no significant interactions were observed (Table 5). Importantly, support for the predicted task-biased effect of inferior parietal lobule was revealed with greater activation within this region for the rhyme-judgement trials (*M* = .84, *SE* = .12) than for the semantic-categorization trials (*M* = .42, *SE* = .13). For the unpredicted main effect of difficulty, engagement of the left inferior parietal lobule was greater for the hard trials (*M* = .74, *SE* = .11) as compared to the easy trials (*M* = .52, *SE* = .14). There were no other significant differences in any of the other factors.

3.2.2.3 Left middle temporal gyrus

Within the middle temporal gyrus, results revealed a main effect of difficulty (Table 6), with greater activation within this region for hard trials (*M* = .38, *SE* = .12) than easy trials (*M* = .17, *SE* = .11). Contrary to our predictions, there was a null effect of task, although greater middle temporal gyrus engagement during the semantic-categorization (*M* = .39, *SE* = .13) than rhyme-judgement trials (*M* = .15, *SE* = .13) did trend in the expected direction, *(p* = .089). The middle temporal gyrus did not reveal a significant difference in any of the other factors or interactions.

3.2.2.4 Right cerebellar hemisphere VIIB

Within the right cerebellar hemisphere VIIB, there was a significant main effect of difficulty and an interaction between task and difficulty (Table 7). For the main effect of difficulty, there was significantly greater activation during the hard (*M* = .63, *SE* = .08) than easy trials (*M* = .35, *SE* = .09). Regarding our primary prediction for VIIB, contrary to our hypothesis, the results did not reveal greater VIIB activation for the rhyme-judgment trials as compared to the semantic-categorization trials. However, we did find the anticipated significant task-by-difficulty interaction

(Figure 10). Post-hoc analyses revealed significantly greater engagement of VIIB during rhyme-judgment hard versus easy trials, *t* (17) = 5.07, *p* < .001, but equivalent activation for semantic-categorization hard versus easy trials, *t* (17) = 1.03, *p* = .32 (Bonferroni corrected). There were no other significant differences in any of the other factors or interactions.

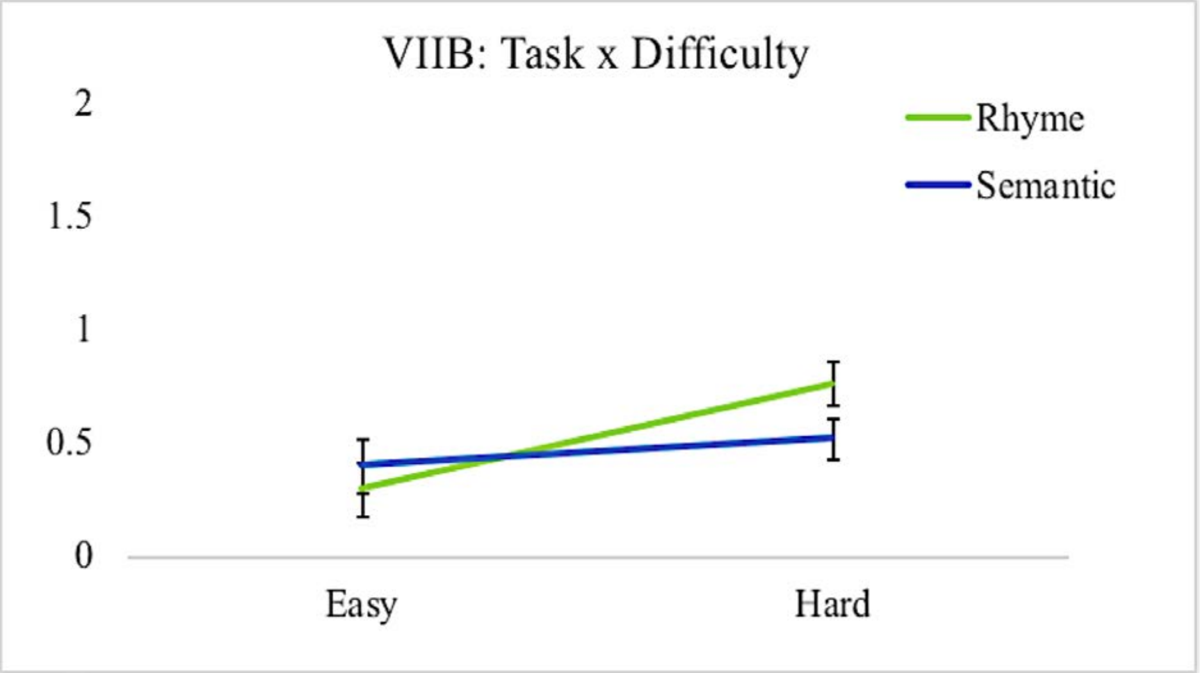


Figure 10. Univariate: Task by difficulty interaction within VIIB

Group-level activity in the right cerebellar hemisphere VIIB plotted for the interaction between the task and difficulty factors. The y-axis is the scale for the mean group BOLD activity within the VIIB ROI. Error bars reflect the standard error of the mean.

3.2.2.5 Right cerebellar hemisphere Crus1

Within the right cerebellar hemisphere Crus1, there was a significant main effect of difficulty and a surprising interaction between task and expected-response (Table 8). For the main effect of difficulty, there was significantly greater activation during the hard (*M* = .70, *SE* = .11) than easy trials (*M* = .31, *SE* = .09). The interaction between task and expected-response was not predicted (Figure 11). Follow-up analyses indicate that this interaction does not reflect significant differences between trials with *yes* versus *no* expected responses, for either the rhyme-judgment, *t* (17) = 1.68, *p* = .11, or the semantic-categorization task, *t* (17) = 1.74, *p* = .10, (Bonferroni corrected), but since these effects trend in opposite directions the interaction with task reaches significance. Contrary to our prediction, we did not reveal a Crus1 task effect, or a task-by-difficulty interaction. There were no other significant differences in any of the other factors or interactions.

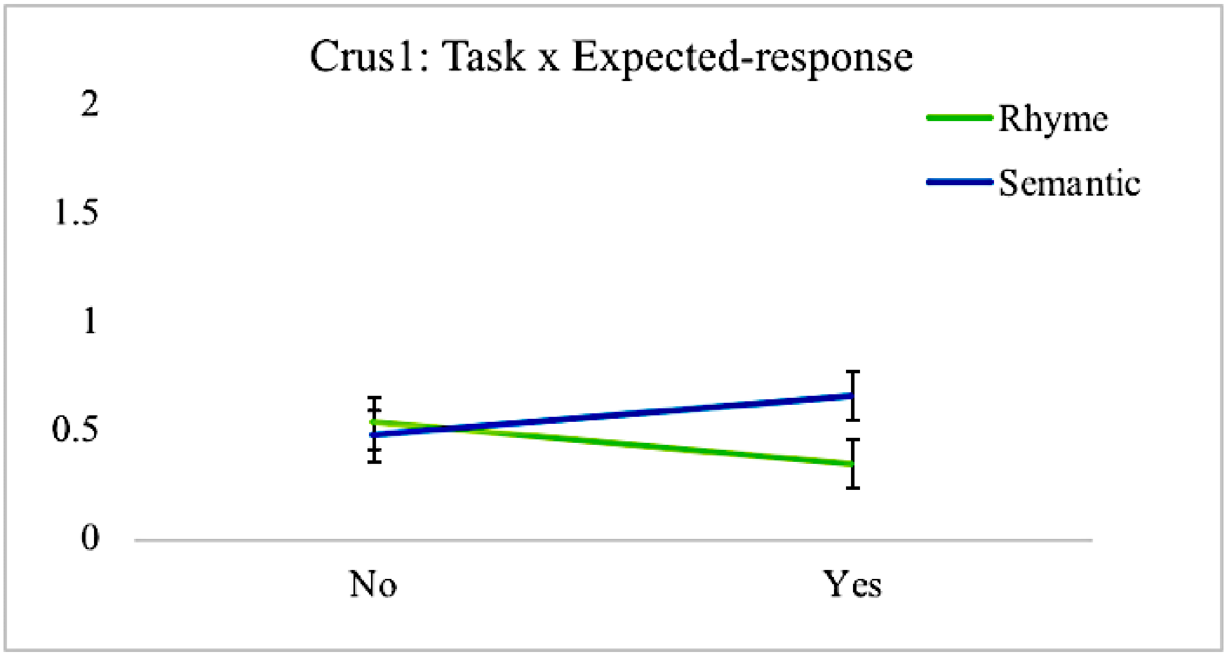


Figure 11. Univariate: Task by expected-response interaction within Crus1

Group-level activity in the right cerebellar hemisphere Crus 1 plotted for the interaction between the task and expected-response factors. The y-axis is the scale for the mean group BOLD activity within the Crus1 ROI. Error bars reflect the standard error of the mean.

3.2.3 Multivariate analysis of the fMRI data

Using a multivariate analysis approach, we tested how accurately a classifier for each ROI could determine whether one a given trial the participant was performing the rhyme-judgment or semantic-categorization. Each region's classifier performance was measured and tested using a one-sample t-test against chance (50 %) and plotted in Figure 12. Successful above chance classifier performance was found for the IFJ [M = 55.15; t (17) = 2.97, p < .01], the IPL [M = 56.60; t (17) = 4.68, p < .001], and the MTG [M = 56.42; t (17) = 4.24, p < .001] ROIs. Classifier performance for the cerebellar VIIB and Crus1 ROIs did not differ from chance [M = 51.74; t (17) = 1.10, p = .288, and M = 52.14; t (17) = 1.56, p = .138, respectively]. Collectively, these MVPA results support our hypotheses for the cerebral but not the cerebellar constituents of the CDHn model.

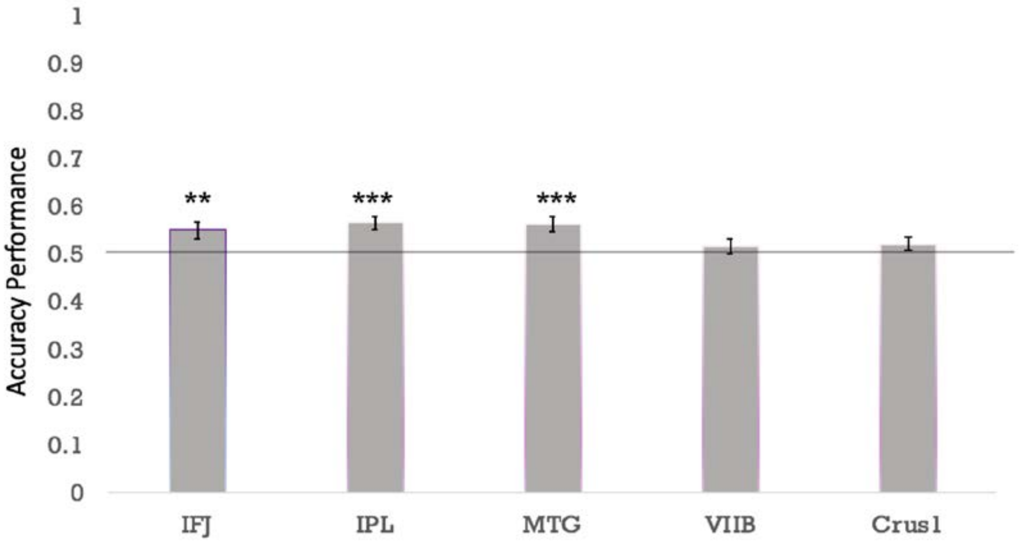


Figure 12. Multivariate: Task classifier performance within each region-of-interest

Group-level classifier performed significantly above chance for within IFJ, IPL, and MTG regions. Chance level accuracy was at 50% (solid line). IFJ = inferior frontal junction, IPL = inferior parietal lobule, MTG = middle temporal gyrus. p < .001***, p < .01**. Error bars reflect the standard error of the mean.

3.2.4 Modulatory role of the cerebellum

Finally, we attempted to use a combination of univariate and multivariate measures to test whether the engagement of the cerebellar constituents of the CDHn model influences the quality of representation in the cerebral constituents of the model. We did so by examining the MVPA classifier performance for the rhyme and semantic trials as a function of the corresponding activation strength in the relevant cerebellar ROIs.

For the classifier performance in the IFJ ROI, there was no significant difference between the trials catalogued as high VIIB rhyme-task BOLD activity (*M* = .55, *SE* = .03) versus low rhyme task activity [(*M* = .55, *SE* = .02), *F* (1,17) = .003, *p* = .959]. Similarly, there was no significant difference between the trials catalogued as high Crus1 semantic-task BOLD activity (*M* = .59, *SE* = .04) versus low semantic-task activity [(*M* = .52, *SE* = .04), *F* (1,17) = 1.74, *p* = .205]. Neither of these results for the inferior frontal junction support our predictions.

For the classifier performance in the inferior parietal lobule, there was no significant difference between the trials catalogued as high VIIB rhyme-task BOLD activity (*M* = .60, *SE* = .03) versus low rhyme task activity [(*M* = .55, *SE* = .02), *F* (1,17) = 2.16, *p* = .160]. This finding does not support our prediction for this parietal region.

For the classifier performance in the middle temporal gyrus, there was a significant difference between the trials catalogued as high Crus1 semantic-task BOLD activity (*M* = .57, *SE* = .03) versus low Crus1 semantic-task activity [(*M* = .46, *SE* = .03); *F* (1,17) = 6.68, *p* < .05]. This finding does support our hypothesis for this ventral circuit region.

3.3 DISCUSSION

In this study, we investigated the functional properties of two newly proposed cerebro-cerebellar circuits for reading: a fronto-parieto-cerebellar dorsal circuit, and a fronto-temporo-cerebellar ventral circuit. Using two behavioral tasks designed to measure phonological (via rhyme-judgement) and semantic processing (semantic-categorization), multiple analyses were used to: 1) test for a phonological bias within the dorsal circuit and a semantic bias within the ventral circuit using a univariate approach, 2) examine whether there are voxel-wise patterns within each of the dorsal and ventral circuit regions that can discriminate between the phonological and semantic tasks using a multivariate approach, and 3) test whether the quality of representations within the cerebral-cortical regions of the networks are modulated by cerebellar engagement using results from both the univariate and multivariate analyses. It is important to note that in testing for a modulatory role of the cerebellum, alternative analyses may provide dissimilar results.

Comparisons across the univariate and multivariate analyses revealed noteworthy results for the cerebral regions. As anticipated, using a univariate approach the inferior frontal junction failed to reveal any bias towards phonological versus semantic processing. However, using a multivariate approach pattern-decoding in this region was attained. Focusing on the middle temporal gyrus, functional activity within this region trended toward a semantic-bias, and this region attained significant voxel-pattern dissociations between the tasks using a multivariate test. The univariate and multivariate approaches were able to generate task-biased and task dissociative effects within the inferior parietal lobule, respectively. These findings, especially in regards to the inferior frontal junction and middle temporal gyrus, are of special interest in the area of neuroimaging methodology, as much of the field is moving towards utilizing multivariate approaches as opposed to traditional univariate analyses due to multivariate method's possessing greater sensitivity for stimulus pattern recognition (Haxby, 2012; Haxby et al., 2001).

It is important to examine the inherent limitations and strengths within this study. Regarding the cross-comparisons between the two behavioral tasks, we did attempt to match the two tasks in terms of their behavioral characteristics. However, the four conditions (EasyNo, EasyYes, HardNo, HardYes,) within the rhyme and semantic tasks do not have conflicting information that conceptually aligns in the same way (i.e., judgements for these are not exactly parallel). For the semantic task, it is designed for an individual to make a connection between a category and an exemplar (e.g., bird -> bat versus bird -> penguin). Therefore, lexical-semantic retrieval for the words are a core feature in this task. In contrast, the rhyming task requires conversion of the orthographic features to its phonological form. In some accounts, the rhyme judgment task pits phonological representations determined through the assembly of sub-lexical grapheme-phoneme correspondences against lexical-phonological representations retrieved from memory (e.g., (Johnston & McDermott, 1986; Kramer & Donchin, 1987; McPherson, Ackerman, & Dykman, 1997). This is especially true in the hard-no condition, where individuals must reconcile competing results from these two different procedures. This is unlike the semantic task, which does not have a sub-lexical component. Our findings of reaction time differences between the rhyme and semantic task support this notion. An avenue for future research could include reaction time as a covariate with brain activation patterns during trials.

Another caveat in the study can be found in comparisons between the rhyme and sematic tasks used for our experiment. The behavioral tasks used to extract the dorsal and ventral networks in the CDHn model are not completely parallel to the behavioral tasks used in our study. Notably, the inferior parietal lobule and middle temporal gyrus in particular came from a contrast of word naming and lexical decision under conditions expected to theoretically rely more upon a dorsal versus ventral processing route. Therefore, the task was the same, but the characteristics of the stimuli (e.g., words versus nonwords) or participants (e.g., skilled versus unskilled readers) was the source of difference. Consistent with the CDHn model, much of the literature reports the middle temporal gyrus as the most reliable region with greater activation for words than pseudowords (Booth et al., 2004). However, our study did not utilize such a particular task, which may account for why there were inconsistent results for the middle temporal gyrus across our univariate and multivariate analyses. Finally, it is important to note that our modulatory analysis did not take into account behavioral covariates, such as trial accuracy. This is an important consideration because if the cerebellum is fine-tuning the cerebral pathways, it might be expected that better trial accuracy would be modulated by greater cerebellar activation.

4.0 OVERALL DISCUSSION

In the CDHn model, Alvarez and Fiez (2018) proposed a fronto-parieto-cerebellar dorsal circuit and fronto-temporo-cerebellar ventral circuit for reading development, with connectivity between the territories within both of these circuits converging at the inferior frontal junction. Additionally, the model purports that these circuits are biased towards phonological versus semantic activation, respectively. Finally, the model posits a potential modulatory role of the cerebellum in improving phonological processing within the dorsal circuit, and lexicalized-decoding in the ventral circuit. This dissertation sought to empirically test this model using multiple neuroimaging and statistical analyses. In the first experiment (Chapter 2), we used resting-state functional connectivity methods at the ROI-level to test for replication of the dorsal and ventral reading circuits. We then conducted a functional connectivity analysis at the voxel-level to look for neuroanatomical circuit specialization within inferior frontal junction. In the second experiment (Chapter 3), we first conducted a univariate analysis to test whether the dorsal and ventral circuits exhibit functional biases for behavioral tasks that engage phonological versus semantic processing, respectively. We then conducted a multivariate analysis to test the dissociative properties of these circuit regions in distinguishing between the tasks. Finally, results from the multivariate analyses were used to test if peak levels of cerebellar engagement predict a higher quality of the representations within the cerebro-cortical dorsal and ventral regions.

Overall, we found encouraging but incomplete support for the recently proposed CDHn model. Resting-state functional connectivity analyses at the broad level disclosed stronger support for the ventral circuit, with partial support for the dorsal circuit. However, the more precise resting-state functional connectivity analyses did reveal the evidence of topographical subpopulations within the inferior frontal junction, with more dorsal circuit voxels clustering at the posterior sector of the inferior frontal junction and more ventral biased circuits clustering anteriorly. Therefore, in addition to observing segregated neuronal pools of dorsal versus ventral circuits within the inferior frontal junction, the more precise functional connectivity approach implicated voxels within cerebellar regions VIIB and Crus1 that are part of the dorsal and ventral circuits, respectively. It is possible that observing these patterns of connectivity using the broad ROI connectivity approach could result in lesser power by averaging out the connectivity that existed within a specific subset of voxels. Results from our more precise approach marks a promising way to look at circuit biases within regions, especially in regions where there is high individual variability such as the cerebellum (Marek et al., 2018), or when there is uncertainty about the exact locus of the key tissue within a circuit.

The task-based univariate and multivariate designs also provided partial support of the CDHn model for reading. As expected, univariate task contrasts revealed significant functional specialization for the phonological task within the inferior parietal lobule, with a trend towards a semantic bias in the middle temporal gyrus, and no bias in the inferior frontal junction. Using the multivariate approach, each of these cerebral ROIs were able to successfully dissociate between the phonological and semantic tasks, further indicating their involvement in tasks that engage reading-related processes.

Both of the cerebellar ROIs failed to exhibit the predicted task specialization, as assessed using either the univariate or multivariate analysis approach. However, the univariate analyses did uncover interactions of task for each of these two regions. In line with this notion, although these interactions were not specifically predicted, Alvarez and Fiez (2018) did describe the potential importance of difficulty and the need for error correction in the recruitment of the cerebellum. This is in line with prior evidence that more difficult trials may yield stronger cerebellar activation due to its possible involvement in error-based learning or monitoring during more demanding trials (Ben-Yehudah & Fiez, 2008). This previous suggestion was supported for the VIIB ROI, with greater engagement of this region during the rhyme hard condition than the rhyme easy condition. Interestingly, the Crus1 ROI did not exhibit a task by difficulty interaction, rather, a task by expected-response interaction was observed, with greater activation during semantic yes trials than semantic no trials. These cerebellar results suggest that there is some kind of specificity for these regions, but that specificity might be most observable under more demanding conditions.

Finally, the results for testing the CDHn model's proposal of a cerebellar mechanism that modulates the phonological and semantic representations of the dorsal and ventral circuit ROIs were encouraging but in need of further investigation. Although we were unable to support our predicted inferior frontal junction and inferior parietal lobule effects, we were able to confirm a cerebellar modulatory effect of the middle temporal gyrus. As it relates to the CDHn model, much of the work on cerebellar processes for reading primarily speaks on its role in phonological processing, with not much work emphasizing a role in semantic processing. However, the relationship between Crus1 activation and the middle temporal gyrus classifier accuracy was consistent with the strength of interconnectivity between these regions. This is interesting, as it highlights a need for greater effort towards exploring exactly how the cerebellum's contribution to semantic processing can support reading development.

As one avenue for further study, Alvarez and Fiez (2018) touched upon a potential answer based on Share's (1995)'s model of reading development. Briefly, Share's model argued that during learning, less skilled readers rely mostly on phonological decoding, and as this skill develops, it shifts from a sub-lexical phonological process to one that relies more on comparisons of unfamiliar words to previously learned and visually similar words (i.e., lexicalized decoding). Alvarez and Fiez argued that this lexicalized decoding might be a function of the ventral pathway, whereas the sub-lexical phonological decoding is processed in the dorsal pathway. This is very interesting, especially given the technical differences between our study and the meta-analytical review by Alvarez and Fiez. In our study, we recruited skilled adult readers and operationally defined phonological versus semantic processing via two behavioral tasks. Contrastingly, Alvarez and Fiez used three distinct levels of contrast to operationally define these concepts, two of which included population contrasts that were not included in our study [i.e., stage-level – children (phonological) vs. adults (semantic) and ability-level – control (phonological) vs. dyslexic (semantic)]. As such, we argue that the strong pattern of results found for the semantic circuit in our study could be a product of this technical difference in the studies. That is, our skilled adult readers could be less reliant upon the dorsal circuit due to their developed skill in recognizing novel words via lexicalized decoding, which theoretically is processed in the ventral pathway. Overall, our findings present an opportunity for researchers to further develop methodological approaches for examining speculated cerebellar mechanisms within the reading network.

One of the major aims in this study was to provide an empirical test of the neural circuits proposed in the CDHn model for reading. In considering the design of the study, it is important to highlight some key differences between our study design and the meta-analytic approach used by to develop the CDHn model. As a meta-analytical report, Alvarez and Fiez (2018) necessarily compiled information drawn from a variety of studies in which reading and reading-related processes were studied in different ways. For instance, the inferior parietal lobule and middle temporal gyrus reported in their meta-analysis, and used center coordinates in our a-priori ROIs, arose from a compilation of meta-analyses that include participants whom varied in age, reading ability, and other individual differences that inherently permeate meta-analytic research. The meta-analytical focus on phonological versus semantic processing was not based on contrasting tasks with differing explicit demands, as in the current study. Rather, the meta-review systematically compiled results obtained using only lexical-decision and word-naming tasks, pitting against each other contrasts that should favor the reliance on a dorsal versus ventral circuit (e.g., reading of pronounceable nonwords versus real words). Furthermore, labeling of the circuits as phonological versus semantic came from a meta-analytic database of fMRI studies that links a given coordinate to the words that have been most often associated when reported as a significant cluster of activation. The resulting term lists thus combine across many different papers that have used many different tasks. It is also important to note the way in which the coordinates of a priori clusters were selected. The CDHn model opted to select the centroid coordinate of each cluster. However, it is possible that the difference between peak to centroid coordinate is smaller in the ventral circuit clusters than the difference in the difference between the two within the dorsal circuit clusters. If that were the case, then it is possible that our study introduced a greater amount of noise in the data by averaging voxels that surround the centroid coordinate rather than the peak coordinate. Therefore, this could lead to a difference in results as reported in the current study. Generally, there is ample reason to believe that the experiments in this dissertation represent a different and more narrow approach for examining dorsal and ventral circuits in reading, as compared to the meta-analytic approach of Alvarez and Fiez, and so it is not surprising that the results do not fully confirm the predictions of the CDHn model.

Collectively, our systematic investigation of the recently proposed CDHn model of cerebro-cerebellar circuits for reading provide partial support for this model, and give traction to this sparse literature as the first empirical test of this model. In general, there was stronger support for the model’s proposed ventral circuit. However, partial success in supporting the model’s supposition about a dorsal circuit was also observed. These results reinforce the need for continued efforts towards understanding how the cerebellum relates to acknowledged brain networks for reading. In particular, the idea that the cerebellar plays a modulatory role in phonological and lexical-semantic processing remains extremely novel and in need of further testing. As has been asserted in the CDH model, dysfunction in cerebellar regions that may involve particular cognitive processes -- such as those tested in this study -- have the potential to put an individual at risk for developing a reading disorder (Nicolson & Fawcett, 1995, 2007). Accordingly, delineating not only the cerebral neural constituents but also the cerebellar neuronal populations that underlie reading development is essential for theoretical advancement that could lead to more effective remediation.

APPENDIX A FULL ANOVA TABLE FOR BEHAVIORAL RHYME AND SEMANTIC TASKS

Table 3. Behavioral statistics for accuracy and reaction-time ANOVAs Task

Outcome Measure	Effect	*F*	*p*	η_p^2	
Accuracy					
	Task	2.44	0.137	0.13	
	Difficulty	48.17	< 0.001	0.74	***
	Expected-response	5.10	< 0.05	0.23	*
	Task * Difficulty	0.06	0.82	0.01	
	Task * Expected-response	2.50	0.13	0.13	
	Difficulty * Expected-response	12.75	< 0.01	0.43	**
	Task * Difficulty * Expected-response	0.09	0.77	0.01	
Reaction-time					
	Task	34.14	< 0.001	0.67	***
	Difficulty	26.33	< 0.001	0.61	***
	Expected-response	5.62	< 0.05	0.25	*
	Task * Difficulty	3.73	0.07	0.18	
	Task * Expected-response	1.87	0.19	0.10	
	Difficulty * Expected-response	4.20	0.06	0.10	
	Task * Difficulty * Expected-response	6.49	< 0.05	0.28	*

APPENDIX B FULL ANOVA TABLES FOR THE FIVE ROIS USING A UNIVARIATE APPROACH

B.1 INFERIOR FRONTAL JUNCTION

Table 4. Univariate statistics for task-biased engagement of the IFJ

ROI	Effect	*F*	*p*	η_p^2	
Inferior frontal junction					
	Task	.047	0.83	0.01	
	Difficulty	23.79	< 0.001	0.58	***
	Expected-response	5.93	< 0.05	0.26	*
	Task * Difficulty	4.89	< 0.05	0.22	*
	Task * Expected-response	0.58	0.46	0.03	
	Difficulty * Expected-response	2.18	0.16	0.11	
	Task * Difficulty * Expected-response	2.36	0.14	0.12	

$p < .001$***, $p < .01$**, $p < .05$*, trending^t ($p < .10$),

B.2 INFERIOR PARIETAL LOBULE

Table 5. Univariate statistics for task-biased engagement of the IPL

ROI	Effect	*F*	*p*	η_p^2	
Inferior Parietal Lobule					
	Task	19.36	< 0.001	0.53	***
	Difficulty	6.78	< 0.05	0.29	*
	Expected-response	2.04	0.17	0.11	
	Task * Difficulty	3.67	0.07	0.18	
	Task * Expected-response	0.15	0.71	0.01	
	Difficulty * Expected-response	2.95	0.10	0.15	
	Task * Difficulty * Expected-response	0.02	0.88	0.01	

$p < .001$***, $p < .01$**, $p < .05$*, trending^t ($p < .10$),

B.3 MIDDLE TEMPORAL GYRUS

Table 6. Univariate statistics for task-biased engagement of the MTG

ROI	Effect	*F*	*p*	η_p^2	
Middle Temporal Gyrus					
	Task	3.24	0.09	0.16	
	Difficulty	6.58	< 0.05	0.28	*
	Expected-response	3.80	0.07	0.18	t
	Task * Difficulty	1.50	0.24	0.08	
	Task * Expected-response	2.00	0.18	0.10	
	Difficulty * Expected-response	1.05	0.32	0.06	
	Task * Difficulty * Expected-response	1.01	0.33	0.06	

$p < .001$***, $p < .01$**, $p < .05$*, trending^{t} ($p < .10$),

B.4 CEREBELLAR VIIB

Table 7. Univariate statistics for task-biased engagement of VIIB

ROI	Effect	*F*	*p*	η_p^2	
Cerebellar VIIB					
	Task	0.38	0.55	0.02	
	Difficulty	13.12	< 0.005	0.44	**
	Expected-response	1.15	0.30	0.06	
	Task * Difficulty	7.14	< 0.05	0.30	*
	Task * Expected-response	0.96	0.34	0.05	
	Difficulty * Expected-response	0.37	0.55	0.02	
	Task * Difficulty * Expected-response	0.70	0.42	0.04	

$p < .001$***, $p < .01$**, $p < .05$*, trending^t ($p < .10$),

B.5 CEREBELLAR CRUS1

Table 8. Univariate statistics for task-biased engagement of Crus1

ROI	Effect	*F*	*p*	η_p^2	
Cerebellar Crus1					
	Task	2.07	0.17	0.13	
	Difficulty	21.17	< 0.001	0.56	***
	Expected-response	0.01	0.99	0.01	
	Task * Difficulty	0.80	0.80	0.05	
	Task * Expected-response	5.17	< 0.05	0.23	*
	Difficulty * Expected-response	0.13	0.25	0.08	
	Task * Difficulty * Expected-response	0.09	0.73	0.01	

$p < .001$***, $p < .01$**, $p < .05$*, trending^t ($p < .10$),

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