

ATTRIBUTES OF BRAIN FUNCTIONAL NETWORK ARCHITECTURE
SUPPORTING SKILLED READING

By

Stephen K. Bailey

Dissertation

Submitted to the Faculty of the
Graduate School of Vanderbilt University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in

NEUROSCIENCE

December 15, 2018

Nashville, TN

Approved:

Date:

Professor Adam Anderson

Professor Laurie Cutting

Professor Zhaohua Ding

Professor Gavin Price

DEDICATION

This work – and especially the years of learning it is built upon – is dedicated to my parents, Dan and Janine Bailey, who taught me to learn something from everything: novels, newspapers, comics, classes, car rides, restaurants, sports, sermons, trivia, movies, games, work, success and failure.

Thank you for making the world a place full of meaning.

ACKNOWLEDGMENTS

It is wrong for me to ascribe myself as the sole author of this dissertation. The work described in the following pages is the result of the efforts of dozens of people, most notably my colleagues in Vanderbilt's Education and Brain Sciences Research Laboratory and the participants who lent their time, energy and brains to each of the studies. Julie Delheimer, Lanier Sachs, Laura Barquero, Angela Emerson, Hannah Rowland and Scott Burns worked relentlessly, year upon year, to keep the operations of our busy and growing lab humming along. Their efforts insulated myself and the rest of the research team from the everyday demands of running a high-performing lab, and they made it possible for me to focus almost exclusively on my own research and training.

I have been privileged to train at an institution rich in resources and funding. The staff at the Imaging Institute, Brain Institute, Kennedy Center and ACCRE have been wonderful colleagues. They were patient with my questions and fumblings as I attempted to play with just about every toy I could get my hands on these past five years. The National Institutes of Health has largely underwritten these experiences, through a variety of mechanisms. These include training grants (T32 MH064913, F31 HD090923), center grants (U54 HD083211), and the many research awards granted to Dr. Cutting (R01 HD044073, R01 HD067254, among others).

I am grateful for a supportive committee that gave me guidance at critical junctures and opened my eyes to a research domains I would not have otherwise seen. Dr. Gavin Price embodied for me the rigor and theoretical drive present in the best of cognitive psychology, and our conversations helped to give a pointed form to many of the ideas explored herein. (Any deviation from clarity is my own.) Dr. Adam Anderson gave me insight into the wider field of biomedical image analysis through his classes and lectures, and he also exposed me to a more programmatic approach to analysis. This move away from GUIs and toolboxes opened me up to new tools and techniques, and it has set me up to be a much

more innovative scientist. Finally, my collaborations with Dr. Zhaohua Ding gave me the unique experience of watching a scientific idea evolve from its infancy to its impact, as he chased, teased out, and trumpeted the existence of the BOLD signal in white matter tissue. His tenacity impressed upon me the role grit and sheer hard work play in pushing science forward.

To Dr. Laurie Cutting I owe a special debt. My experience as a graduate student was unusual: I had all the resources I needed, all the data I could want, all the opportunity I could ask for, from my first day as a student. Dr. Cutting has built a world-class training environment, and she gave me five years of freedom to play in it. What is most impressive to me, though, is that she has fostered a healthy, positive, and professional team culture that has persisted even as the team has turned over and grown. It has been a joy to be a part of this team. I am grateful for the gamble that Dr. Cutting took on me, a prospective student with no background in neuroscience, no experience with imaging, no knowledge of statistics or computing or special education. That I leave with all these things and more is a direct result of the guidance, opportunity and encouragement provided by Dr. Cutting.

I have made too many friends to count or acknowledge, but I will try. My cohort of graduate students – Mackenzie Catron, Eric Wilkey, David Simon, Dylan Morrow-Jones – were a great source of encouragement during our first years, as I was scrambling to recover the tiny amount of biochemistry I learned in college and perplexing over *t*-statistics and ANOVA designs. Later support came from my colleagues in the lab, especially Neena Hudson, Stephanie Del Tufo, Tin Nguyen, Mercedes Spencer and Laura Barquero. Then there were those who pulled me away from brains for refreshing moments: Alice Leach, Jake Benzing, Auvy Hossasin and Nausheen Karim. Finally, I must give a special acknowledgment to the very first person I met at Vanderbilt. Katherine Aboud has been a partner and friend in all of my research endeavors – and later, parenting efforts – as she pushed me to remember the “story” in all of my “process”. It has been a privilege to study, work and converse with these fine people, and I will miss it greatly.

The best analogy for the PhD is that of an odyssey: the destination is clear but the path is unknown and treacherous at times. For travelling with me and keeping me grounded, I am grateful for my wife, partner and best friend, Danielle. Our particular journey has been filled with classes and experiments and writing, of course. But it has also been filled with leaky houses, arduous job searches, and, most of all, children. It has only been through her conversation, support, love, and constant reminding of the important things that this odyssey has reached its happy ending.

TABLE OF CONTENTS

	Page
DEDICATION	ii
ACKNOWLEDGMENTS	iii
LIST OF TABLES	viii
LIST OF FIGURES	ix
LIST OF ABBREVIATIONS	xi
1 Introduction	1
1.1 Cognitive flexibility and network architecture	1
1.2 Reading is a whole-brain activity	4
1.3 Methods for characterizing brain networks	6
1.4 The role of network architecture in reading	10
1.5 Influence of development on network connectivity	16
1.6 Outstanding questions	19
2 Intrinsic network architecture and skilled reading	21
2.1 Motivation	21
2.2 Methods	23
2.3 Results	29
2.4 Discussion	32
3 Integration of resting-state networks during reading	37
3.1 Motivation	37
3.2 Methods	39
3.3 Results	44
3.4 Discussion	50
4 Network flexibility and consistency across tasks	56
4.1 Motivation	56
4.2 Methods	61
4.3 Results	64

4.4	Discussion	70
5	Modular networks throughout development	75
5.1	Motivation	75
5.2	Methods	77
5.3	Results	80
5.4	Discussion	85
6	Review and summary	89
6.1	The importance of attention in reading	92
6.2	Dynamic modeling of network activity	93
6.3	Individualized network assignments	95
6.4	High-resolution and multi-modal parcellations	97
6.5	Final word	99
	BIBLIOGRAPHY	100

LIST OF TABLES

Table	Page
2.1 Participant demographics for Study 1	24
2.2 List of resting-state networks	26
2.3 Comparison of global graph theory metrics to reading skill	32
3.1 Participant demographics for Study 2	39
3.2 Hub areas activated in reading	51
4.1 Participant demographics for Study 3	61
4.2 Correlation values between shared connectivity and cognitive skill	72
5.1 Participant demographics for Study 4	78
5.2 Statistical results for the effects of condition and group on modularity . .	82
6.1 Key findings in Studies 1 through 4	91

LIST OF FIGURES

Figure		Page
1.1	Network architecture at multiple scales	2
1.2	Examples of canonical resting-state networks	7
1.3	Schematic for a network with two modules	8
1.4	Reading areas are distributed across many resting-state networks	11
1.5	Dyslexia disproportionately impacts hub areas	16
1.6	Interactive specialization explains changes in activity	17
2.1	Schematic for connectome construction	25
2.2	Sampling of graph theory measures	28
2.3	Distribution and correlations between global graph theory measures	30
2.4	Relationships between network-level graph theory measures	31
2.5	Global modularity at rest is the best predictor of cognitive skills.	33
2.6	RSN modularity relationships with reading skill	34
3.1	Schematic of the reading comprehension task	41
3.2	Description of scan motion quality and task performance	44
3.3	A range of language-related areas were activated during reading comprehension	45
3.4	Distribution of reading-related activity among RSN nodes	46
3.5	Reading induces a more integrated global network architecture	47
3.6	RSN-level trends in task-evoked networks	48

3.7	Rewiring of RSNs during reading	49
3.8	Univariate activity is anti-correlated with participation coefficients	50
3.9	Higher modularity in reading is also related to reading skill	52
4.1	Common core architecture for reading and listening	57
4.2	Methods for measuring similarity between whole-brain connectomes . .	63
4.3	Large overlap between listening and reading activation	65
4.4	Activation differences due to modality of presentation among RSNs . .	66
4.5	Reading induces a more integrated network architecture than listening .	67
4.6	Network similarity across subjects in listening and reading.	69
4.7	Network similarity between listening and reading predicts word efficiency	70
4.8	RSNs share a large degree of similarity	71
5.1	Adults have lower modularity but undergo the same task effects as younger readers	81
5.2	Connection-level changes in the reading network	83
5.3	Developmental shifts in RSN interactivity	84
5.4	Modularity is related to reading skill in younger readers	85
5.5	Older subjects show less similarity between in reading-evoked networks .	86
6.1	Correlations between brain regions fluctuate over time	94
6.2	Individualized networks in a highly sampled individual brain	96
6.3	Multi-modal parcellation of the human brain	98

LIST OF ABBREVIATIONS

- AUD Auditory network
CON Cingulo-opercular network
DAN Dorsal attention network
DMN Default mode network
DWI Diffusion-weighted magnetic resonance imaging
fMRI Functional magnetic resonance imaging
FPN Fronto-parietal network
GLM Generalized linear model
MEM Memory retrieval network
MRI Magnetic resonance imaging
ROI Region of interest
RS Resting state
RSN Resting-state network
SOH Somato-motor (hand) network
SOM Somato-motor (mouth) network
SUB Subcortical network
VAN Ventral attention network
VIS Visual network
VWFA Visual word form area

CHAPTER 1

Introduction

Learning to read is probably the most difficult and revolutionary thing that happens to the human brain, and if you don't believe that, watch an illiterate adult try to do it.

John Steinbeck

1.1 Cognitive flexibility and network architecture

The human brain is remarkable for its flexibility: a person can interpret physical sensations, coordinate complex movements, interpret subtle social cues, construct meaning from sounds, embolden a person with courage or freeze them with embarrassment. And people can perform all of these incredible calculations at the same time without becoming confused or dismayed. This arsenal of skills, which is rivaled by few if any other species in the animal kingdom, is only possible through an efficient neural infrastructure. Neural areas responsible for sensory processing, executive decision-making, top-down attention and intrinsic motivation must all be able to interact quickly to react to changing environmental demands.

The organizing structures and mechanisms that facilitate the brain's activity are collectively referred to as its *network architecture*. The brain's network architecture has been studied on many scales – from molecules and synapses to brain systems – and with many techniques – from electron microscopy to electroencephalography. More recently, advances in magnetic resonance imaging (MRI) have allowed researchers to investigate the brain's structural connectivity as well as its more fluid functional connectivity (Betzel et al., 2013). These two domains of inquiry can be thought of as the patterns of wiring

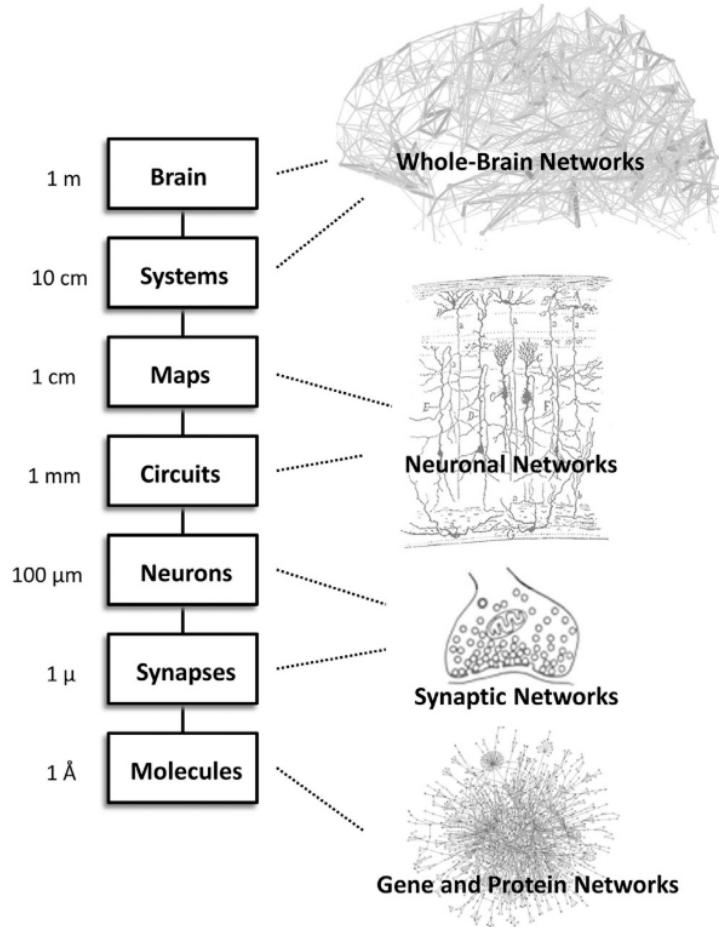


Figure 1.1: Network architecture at multiple scales of inquiry. The brain is organized in a manner that optimizes the trade-off between connectivity and metabolic efficiency. This results in small-world properties, including modularity, at multiple scales. In this dissertation, we focus on these properties in whole-brain networks. Figure adapted from Petersen and Sporns (2015).

and engagement between large patches of cortex, respectively. While our understanding of these patterns is becoming increasingly refined, there remain important questions, especially around the extent to which differences in network architecture are responsible for differences in individual behavior and development (Petersen and Sporns, 2015).

One of the challenges is that the body of knowledge surrounding large-scale network architecture have only recently begun to reach a consensus about fundamental points. This stands in contrast to the work mapping cognitive skills to specific parts of the brain con-

ducted by the neuroscience community for the past several decades (Yarkoni et al., 2011). To understand how individual variability in brain *network* structure and function drive individual differences in behavior and cognition, it will be critical to bridge the mature literature on specific neuro-cognitive processes with the nascent literature on whole-brain network architecture. This will provide a more holistic perspective on the underlying neurobiological mechanisms, including the relationship between localized neural processing and its integration into the global network.

Comparing findings between the two approaches with a well-understood model system can be a powerful way to synthesize results. The act of reading is a potent candidate: reading requires the tuning of specific and localized neuronal systems such as the VWFA (McCandliss and Noble, 2003), as well as global systems that integrate information across sensory, associative and motor systems (Price, 2012). It is a learned skill, as well, so the effects of education and development are ripe for study (Saygin et al., 2016).

In this dissertation, we flesh out a description of the network-level processes important for reading comprehension, how they form a basis for individual differences, and how aspects of functional network architecture change throughout the lifespan. This chapter lays the theoretical groundwork. First, we describe reading and our rationale for selecting it as a candidate cognitive process. We then describe metrics for measuring different aspects of network architecture and their potential significance to cognitive models. Next, we connect principal aspects of a network perspective (especially RSNs and hubs) to reading processes and dyslexia. We discuss how development influences network architecture and its relationship to reading skill. Finally, we outline the four studies undertaken to establish the importance of this network approach to reading comprehension, and more broadly, cognitive flexibility.

1.2 Reading is a whole-brain activity

Reading is a complex cognitive act. To read, individuals must precisely control visual attention, map symbols to sounds, extract meaning from words, maintain and update a mental model of the text events, inhibit unimportant associations, and make appropriate inferences. Consequently, reading difficulty can arise from many sources (Pennington and Bishop, 2009; van der Lely and Marshall, 2010). To further complicate matters, people who struggle with reading also commonly struggle with other learning and developmental disorders, such as specific language impairment and attention deficit / hyperactivity disorder (Pennington, 2006; Margari et al., 2013).

Despite these complexities, the most common aim of reading instruction and intervention is to build fast and efficient orthographic-phonological mapping. That is because teaching these skills is concrete and effective (Correro et al., 2000). Decoding is also a bottleneck to semantic processes: if an individual cannot decipher individual words, they will not be able to understand blocks of text. However, there are many individuals who struggle primarily with reading comprehension, but understanding the specific causes of their struggle is difficult (Cain and Oakhill, 2006). One issue is that the component skills in comprehension are less mechanical and accessible than those for word reading. For example, although vocabulary size is often used as a proxy for the ability to comprehend speech (Spencer et al., 2014), it does not account for important executive and attention skills. Passage comprehension measures, on the other hand, are highly variable in their administration, skills assessed and resulting measures (Cutting et al., 2009).

Neuroimaging provides an alternative way of assessing what makes good readers successful, and its use has yielded valuable insights into the neural mechanisms of typical and atypical reading. Researchers have shown that reading co-opts the brain's visual system to introduce a new input pathway into existing language comprehension circuitry (Jobard et al., 2007). As text complexity increases, a larger demand is made on support systems, and activation becomes more bilateral and widespread (Xu et al., 2005). Meta-analyses

show that individuals with reading difficulty typically exhibit underactivation in areas responsible for recognizing symbol units, parsing acoustic sounds into phonological units, and binding letters to sounds (Maisog et al., 2008; Richlan et al., 2009; Paulesu et al., 2014). Some initial studies even suggest that individuals who struggle with comprehension have separate neurobiological profiles than typical or dyslexic children (Bailey et al., 2016). However, many questions remain regarding the root causes of dyslexia, how to best identify children at risk, and the reasons for its high comorbidity with other developmental disorders.

Connectivity-based neuroimaging methods provide an alternative framework to examine reading difficulties. Whereas traditional approaches focus on identifying focal regions of deficit, many learning and psychiatric disorders are characterized, in part, by how brain networks behave and interact. In particular, connectome analyses have shown that the brain exhibits a network configuration which allows for rapid transfer of information at minimal cost, i.e. a small-world network architecture (Bullmore and Sporns, 2012). Two attributes of brain organization have been of special interest: the presence of densely intra-connected *modules*, often called resting-state networks (RSNs) (Sporns and Betzel, 2016); and the existence of a core group of *hub areas* that play an outsize role in conveying information between RSNs (van den Heuvel and Sporns, 2011).

Since reading requires rapid interaction and manipulation of disparate cognitive processes, the network framework is an appealing avenue of investigation. Previous research has suggested that the areas responsible for reading do not form a single network, but are instead distributed across multiple RSNs (Vogel et al., 2013). There is evidence that the constitution of these RSNs (e.g. the default mode network) could be predictive of disorders, including attention deficits (Uddin et al., 2008). Furthermore, damage to hub areas can cause devastating behavioral effects (Warren et al., 2014) and may be degenerated in psychiatric and developmental disorders such as schizophrenia, Alzheimer's disease and ADHD (Stam, 2014). Graph theory measures of connectivity within and between RSNs

may consequently be related to differences in reading skill. However, while a small number of papers indicate that they may be affected in dyslexia (Qi et al., 2016; Finn et al., 2014), its application in the reading domain has been relatively sparse, with few emergent themes thus far (Cao et al., 2016). This is surprising because connectomics data can be procured without using cognitive tasks (which represent a confounding variable) and because they provide a common neurobiological framework for understanding cognitive disorders. One reason for its slow adoption, however, is that the field is still settling on best practices (and best targets) in the analysis of brain networks.

1.3 Methods for characterizing brain networks

In the early 2000s, after initial findings of connectivity between distinct brain areas at rest (Biswal et al., 1995), researchers began to characterize several prominent brain networks observed at rest and in task (van den Heuvel and Hulshoff Pol, 2010). A seminal paper then characterized the entire brain in terms of its RSNs (Yeo et al., 2011), and since then, scientists have pushed the resolution of these parcellations to higher and higher resolutions. The major utility of characterizing these RSNs is that they generally correspond to bundles of cognitive functions, including language (Cordes et al., 2000; Hampson et al., 2002), visual perception (Simmons and Martin, 2012), motor functioning (Biswal et al., 1995) and executive control (Seeley et al., 2007).

A major advance in the quantitative analysis of RSNs came with the introduction of graph theory techniques to the field. One of the major early findings was that the brain is organized in a complex but efficient small-world architecture. That is, a set of hub areas have disproportionate influence in connecting disparate brain areas. The concept has implications for cognitive models and neurology: for example, lesions on areas that are not densely connected showed less extended impairments than regions which are hub-like in RS-fMRI analyses (Warren et al., 2014). Even less severe disorders appear to have disrupted network architecture: researchers observed a reorganization of RSNs and decrease

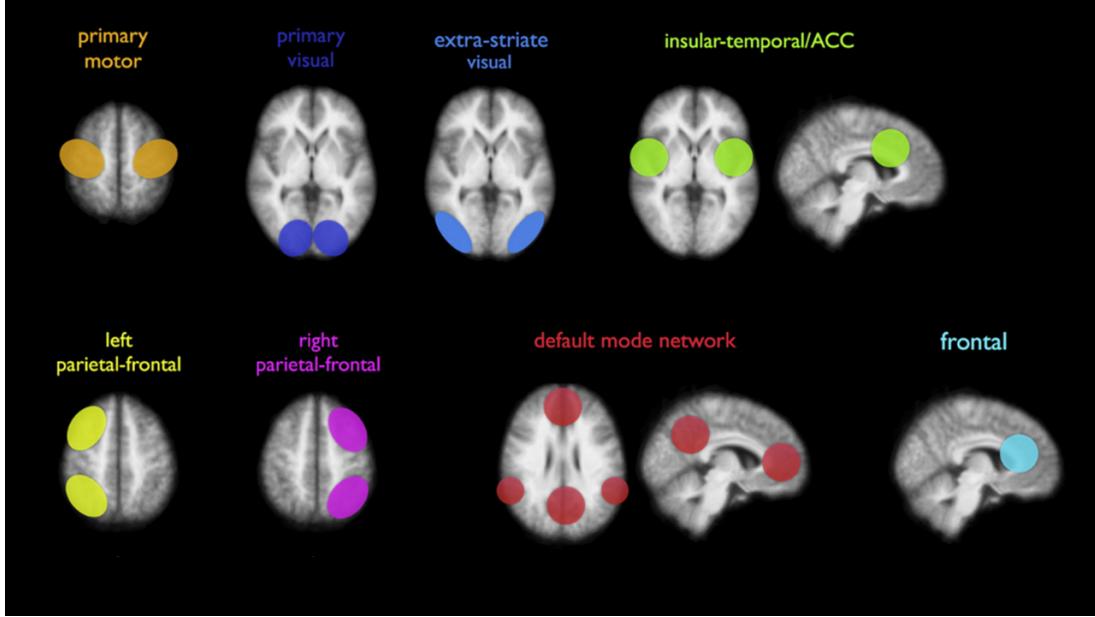


Figure 1.2: Examples of a few canonical resting-state networks observed in multiple studies with multiple methodologies from 1995 to 2010 (Biswal et al., 1995; Beckmann and Smith, 2005; De Luca et al., 2006; van den Heuvel et al., 2009). Subsequent parcellations such as that of Yeo and colleagues in 2011 formalized the notion that all brain areas are associated with an intrinsic network (Yeo et al., 2011). Figure adapted from van den Heuvel and Hulshoff Pol (2010).

of modularity in individuals with depression (Lord et al., 2012). Thus network properties may be important for explaining individual differences in neuropsychiatric disorders or cognitive skill, such as comprehension.

In the graph model of the brain, the brain is modeled as a set of *nodes* connected by *edges*. Typically, one of several approaches has been used to identify nodes: anatomical parcellations based on an atlas (Supekar et al., 2008; Liu et al., 2008; Lynall et al., 2010); individual voxels (Fair et al., 2007); functional ROIs from either *a priori* hypotheses or task-based activation (van den Heuvel and Hulshoff Pol, 2010); or an algorithm that parcellates the brain independent of function or anatomy (Goni et al., 2014). Differences in these methods can affect the RSNs identified. At high resolutions (e.g. voxel-level correlations), there is a greater chance of spurious correlations causing noise in the data; at lower resolutions, the average signal may blend multiple functional regions, creating a composite

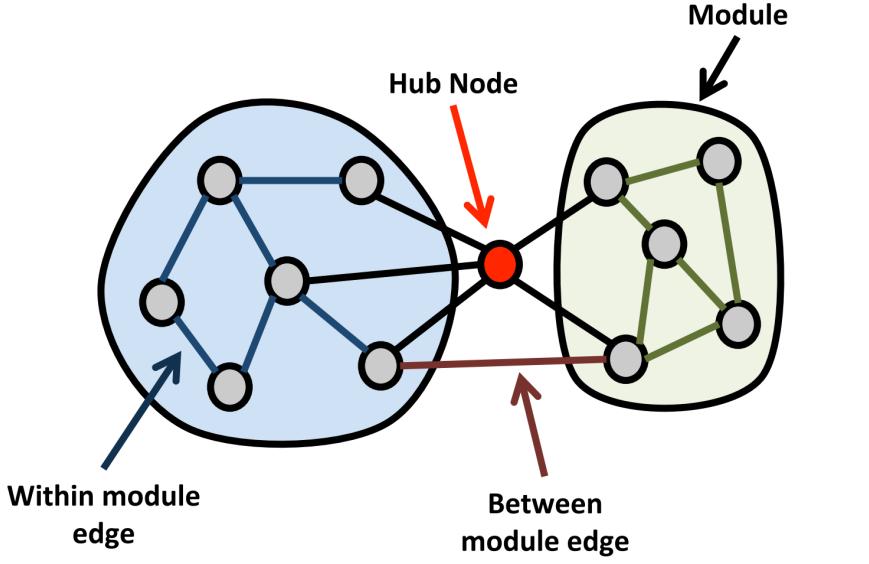


Figure 1.3: Schematic for a network with two modules, or resting-state networks. A high proportion of within-module edges leads to high modularity; a large proportion of between-module edges leads to high participation coefficient. Figure credit to Godwin (2016)

that does not truly reflect any of the underlying areas.

The edges connecting each node can be binary or weighted, in which case areas that are more highly correlated carry a greater connectivity value. The decision of how many and what type of edges to include is crucial because many of the most interesting characteristics, including modularity and small-worldness, only emerge when the graph has been thresholded to a certain level of sparsity (Moussa et al., 2012). It is now common to sweep analyses across a number of edge-forming thresholds in order to ensure that arbitrary selection of edges is not unduly influencing observed measures.

A major question is how best to model RSN properties so that they are both sensitive to network composition (e.g. default mode, fronto-parietal) and globally representative. In some of the initial and influential connectomics studies, whole-brain measures such as the “efficiency” or “characteristic path length” were used to show a relationship between intelligence and network architecture (Stam, 2014). On the other hand, other studies have investigated the roles of individual nodes in the whole-brain network – to identify individual hub regions, for example (Betzel et al., 2013). Although useful, neither of these sets of

measures model the composition of *functional systems*, i.e. RSNs. Connectivity measures related to a specific region such as the visual word form area, might be sensitive to differences in auditory-visual processing, but do not reflect the organization of the visual system at large (Rubinov and Sporns, 2010). Employing measures that are sensitive to regional variation, such as modularity and the participation coefficient, could better clarify drivers of individual differences in specific cognitive domains such as reading (Cao et al., 2016). One limitation is that these measures require a definite parcellation of the brain into RSNs, which has only become possible as the initial exploratory and descriptive studies have been done.

In the following studies, we focus on three (Rubinov and Sporns, 2010). *Modularity* is the degree to which a whole-brain network segregates into densely intra-connected sub-networks. Modularity is high in networks where nodes within the same module (oftentimes an RSN) are highly connected to each other but not elsewhere (Sporns, 2013). *Participation coefficient* is the degree to which a node participates in networks other than its primary one. The *shortest path length*, or simply *path length*, is the minimum number of edges that must be traversed to connect one node to any other. Small-world networks like the brain utilize hubs to maintain a relatively short path length from any one node to another.

While hundreds of studies have been published utilizing graph theory, the neurobiological basis of these metrics is still under investigation. While these connections do appear to be plastic and mediated by experience, they are not necessarily caused by new synapses. Several studies using diffusion-weighted MRI suggest that functional connectivity represents more than simply direct synaptic connections. Diffusion MRI uses water movement to model the white matter tracts within the brain. At high resolutions, it provides a coarse approximation of the human connectome, i.e. the total connections in the human brain (Sporns et al., 2005). another study investigated whether functional connectivity can be predicted from structural connectivity and found that, while structurally connected areas are typically functionally connected as well, the inverse is not true (Honey et al., 2009).

Areas that were closer together were also more highly functionally connected, possibly due to structural cortico-cortical projections.

1.4 The role of network architecture in reading

While reading researchers in the past decade have begun to acknowledge the contributions of domain-general skills (e.g. attention, working memory, planning and organizing) to reading, it remains a secondary concern in much neuroimaging literature. (This is not the case for all language research but specifically reading.) To illustrate the widespread distribution of activity, Bailey and colleagues compared the meta-analytic activations maps from NeuroSynth, a platform for automated meta-analysis of function imaging studies, with the 2011 Yeo resting-state network parcellation, one of the most widely-used RSN parcellations (Bailey et al., 2018; Speer et al., 2006; Yeo et al., 2011).

The results, shown in Figure 1.4, show attention networks combined to make up 37 percent of the NeuroSynth activations, while the visual and somatomotor-auditory RSNs constituted only about one quarter (17.5 and 8.2 percent, respectively). The fronto-parietal (19.3 percent) and default mode (17.8 percent) networks were also highly represented. The limbic network was the only RSN which did not meaningfully overlap with the reading network. The results makes clear what is implicitly understood: reading areas are well-distributed across different networks and load highly onto attention and executive networks. It is also notable that several important reading areas, including the inferior frontal gyrus and temporo-parietal junction, sit at points where multiple networks converge, i.e. likely hub areas.

In the next few sections, we survey possible roles these RSNs and the hub network might play during reading and in dyslexia.

The visual word form area as part of the dorsal attention network

The visual word form area (VWFA) performs an important role in orthographic processing, namely processing lexical and sublexical stimuli. Activity in the VWFA is thought to

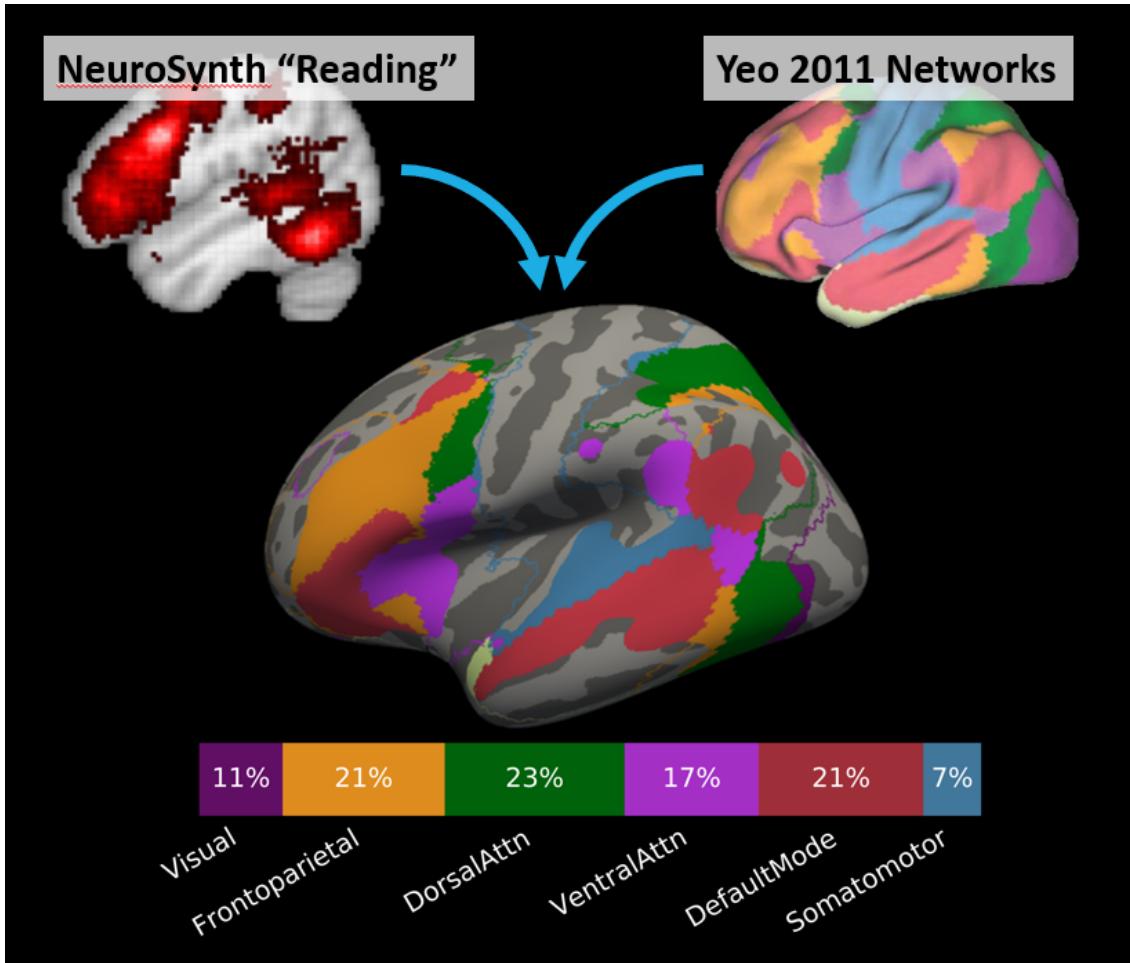


Figure 1.4: Reading areas are distributed across many resting-state networks. On the left is the volumetric breakdown of the “reading” network, pulled from a NeuroSynth automated meta-analysis (forward-inference: $p < 0.01$, FDR-corrected) (Yarkoni et al., 2011), according to the 7-network cortical parcellation from Yeo et al. (2011).

be insensitive to letter size, font and other orthographic attributes (Cohen et al., 2002). However, its alleged specificity to language has been a source of controversy over the past decade, and some have argued that its importance in reading is directly linked to its membership in the dorsal attention network (DAN) (Vogel et al., 2012), which supports the parsing of appropriate textual features and suppression of distracting information (Corbetta and Shulman, 2002). At issue is how important visual attention deficits are to dyslexia (Vogel et al., 2014). Although several studies of dyslexia have reported decreased activation in the VWFA to text relative to typically developing participants, these differences could

be due to more general visuo-spatial deficits (Richlan et al., 2009). For example, fluent reading requires accurate and precise eye movements (Rayner, 1978), and a key node in the DAN is the frontal eye fields which help coordinate saccadic activity (Connolly et al., 2002). In fact, a number of studies report deficits in visual attention, rather than word recognition, in children with reading disorders (Vidyasagar and Pammer, 2010). Whatever the true cause, it is clear that the DAN provides critical support for reading, above and beyond simply processing stimuli.

Attention networks drive and suppress sensory integration

Attention underlies skilled reading at all levels: it is critical for identifying only the salient words in a large block of text, for suppressing environmental distractions and for maintaining focus for extended periods of time. In a common framework for attention, the DAN and ventral attention network (VAN) play collaborative roles for guiding activity. (A third salience network is sometimes differentiated from the VAN.) Simplistically, the DAN exerts top-down control of sensory processes to keep a person on task, while the VAN acts as a “circuit breaker” to help reorient the person by detecting salient or unexpected stimuli (Corbetta and Shulman, 2002; Vossel et al., 2014). This relationship may be impaired in individuals with dyslexia that have sluggish attention-shifting between visual and auditory modalities (Harrar et al., 2014). Slow or inadequately rapid attention-shifting could undermine fluent reading by causing temporal-spatial misalignment in processing, e.g. letter sequence and arrangement (Lallier et al., 2009). This deficit is argued to further characterize dyslexic readers’ rapid temporal and low spatial frequency processing (Witton et al., 1998), and asynchronicity within this system may be characteristic of dyslexia (Lallier et al., 2009). Active interaction between the DAN and VAN during reading may be key to understanding attention-switching problems observed in some struggling readers.

Executive networks coordinate other cognitive processes

Executive functions play an important role in predicting reading outcomes, especially at the level of comprehension (Cutting et al., 2009). Although the variety of cognitive processes that fall under the executive function construct do not map cleanly onto a single brain region or network, they are closely associated with the “central executive” system. This in turn is mapped on to the fronto-parietal and cingulo-opercular network (FPN and CON) (Fedorenko, 2014; Cocchi et al., 2013). Unlike many other RSNs, the FPN has components which are not neighboring, spanning portions of the frontal and parietal lobes (Yeo et al., 2011). Interestingly, the FPN has recently been hypothesized to act as a neural mediator of other brain systems by using wide-spread cortical connections to facilitate efficient processing of other networks, and in particular assist when areas are not functioning adequately (Menon and Uddin, 2010; Cole et al., 2014). According to this coordinator model of the FPN, greater symptoms of dyslexia may correspond with reduced functional and structural integrity of the FPN. Researchers have found de-activation and de-coupling of the FPN during a word rhyme judgment task in double deficit dyslexics (Norton et al., 2014), and in one of the only functional connectomics paper on young readers with dyslexia, another group found that whole-brain connectivity during a word/non-word rhyming task, and found that individuals with dyslexia showed de-coupling of fronto-parietal areas (Finn et al., 2014).

In addition to coordinating other RSNs, the FPN may play a role in directly supporting stressed cognitive systems (Cole et al., 2014). In the first study to explicitly examine executive network interactions influenced by reading intervention, Aboud and colleagues found that, prior to intervention, readers who were responsive to the intervention mediated reading network connectivity via a key region in the FPN, the dorsolateral prefrontal cortex (Aboud et al., 2018). Other studies have had similar findings, albeit with a less coherent network perspective. In a study by Horowitz-Kraus and colleagues, readers with and without dyslexia underwent a reading intervention. After intervention, readers with dyslexia had increased connectivity between a visual component and bilateral regions in the FPN

(notably, as in many studies on reading, the latter component was not identified as an FPN component, but instead discussed as a language network) (Horowitz-Kraus et al., 2015b). Another group examined resting state connectivity in dyslexic readers with variable remediation status, and found that children with a historical diagnosis of dyslexia had persistent de-coupling of frontoparietal areas compared to typical readers, regardless of remediation status (Koyama et al., 2013). Taken together, these findings support the hypothesis that executive areas in the FPN might act to facilitate the functional coherence of other systems necessary for reading.

Default mode network engagement and disengagement

Since its original discovery, the default mode network (DMN) has since been found to support a wide range of cognitive processes often classified under internal mentation (Buckner et al., 2008), including theory of mind, narrative processing, and autobiographical recall (AbdulSabur et al., 2014). The DMN spans the medial prefrontal cortex, bilateral inferior parietal lobules, and posterior cingulate cortex (Raichle et al., 2001). The DMN has a large amount of overlap with traditional language areas, including comprehension-related regions such as the angular gyrus and anterior temporal pole. However, the DMN also has antagonistic relationship with attention networks and the FPN, where the activation of one network necessarily comes at the suppression of the other. This relationship appears to be important for performance on a variety of cognitive processes (Fox et al., 2005; Keller et al., 2015). Consequently, appropriate FPN involvement may be best achieved by suppression of the DMN. Several studies point to over-involvement of the DMN in readers with dyslexia, including higher internal correlations of the DMN during reading (Finn et al., 2014) and greater correlations between the DMN and reading areas during reading and at rest (Schurz et al., 2014). An alternative theory is that the DMN dis-integrates within itself during language comprehension in order to re-integrate information into the active global workspace (Spreng et al., 2013). Given that activity in both the FPN and DMN are crit-

ical for reading comprehension, understanding the dynamics of this relationship could be illuminating.

Hub areas show abnnormalities in dyslexia

A particularly intriguing hypothesis is that dyslexia may be associated with differences in the brain's hub network, which is responsible for integrating information across many different RSNs. To determine whether there was any pattern related to network architecture in dyslexia-related areas, Bailey and colleagues compared clusters from three meta-analyses comparing fMRI activation for individuals with dyslexia to typical readers with measures of hubness across the brain from a connectomics study (Maisog et al., 2008; Richlan et al., 2009; Paulesu et al., 2014; Power et al., 2013). The Power and colleagues study reports the *participation coefficient* for each of 264 nodes previously described. As discussed, the participation coefficient reflects the diversity of a node's connectivity to different RSNs, where a higher value indicates that the node is correlated with many different RSNs.

The results, shown in Figure 1.5, shows that the node-by-node distribution of participation coefficients is not normal, with a large group of areas having low participation coefficients (i.e. affiliated with few RSNs) and a smaller hub-like group. Comparing nodes affected in dyslexia with those unaffected reveals that dyslexia loads onto brain areas with higher participation coefficients than would otherwise be expected, supporting the hypothesis that a network architecture perspective on reading skill is likely to yield new insights.

The finding that hubs areas are key in dyslexia are not surprising: dyslexia has often been thought to be a disorder of combining information across different functional systems, and in the context of connectomics, hub areas play a privileged role in mediating information flow between RSNs. For example, the posterior temporal sulcus connects visual and auditory networks by binding letters to sounds (Blau et al., 2010; van Atteveldt et al., 2009) and the inferior frontal gyrus has many different subdivisions supporting language parsing and manipulation (Hagoort, 2005). However, casting dyslexia dysfunction into a connec-

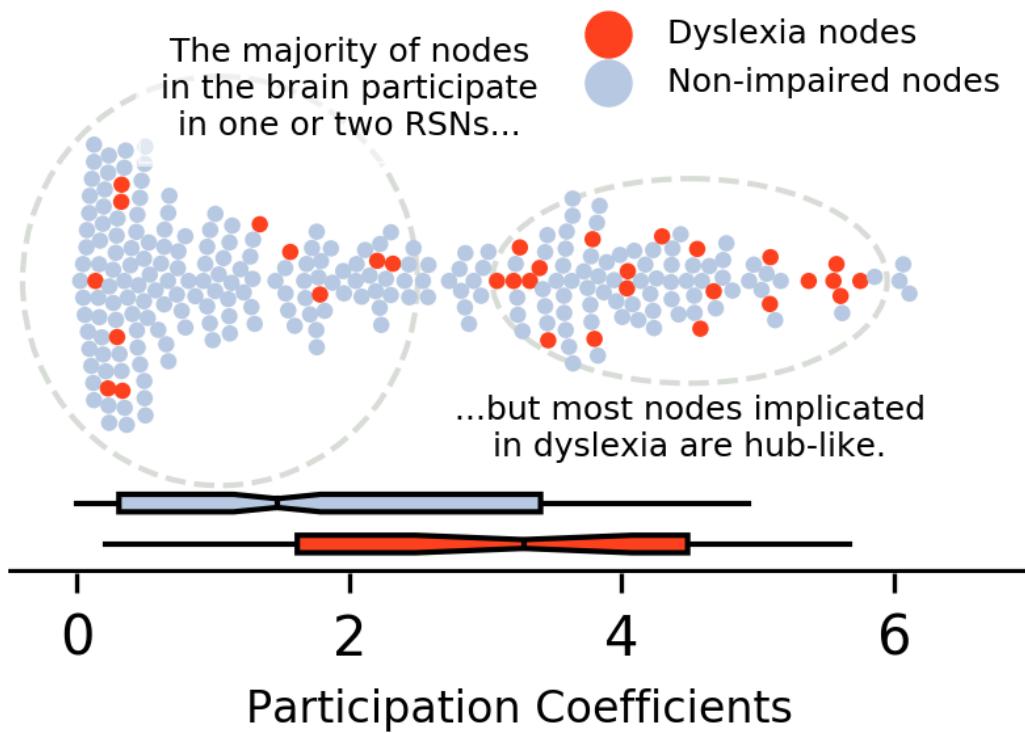


Figure 1.5: Dyslexia disproportionately impacts hub areas. Among the brain areas examined in Power and colleagues (2013), nodes implicated in dyslexia have higher participation coefficients (32 nodes) compared to the rest of the brain (232 nodes). Figure adapted from Bailey et al. (2018).

omics perspective opens up new hypotheses and research avenues. For example, the brain areas of interest and neuroimaging metrics can be unified across other developmental disorders, including ADHD, specific language impairment and autism (Stam, 2014). Another benefit is that it opens up many more avenues for investigating dyslexia using functional and diffusion MRI, which can be performed in younger children and without administering a cognitive task.

1.5 Influence of development on network connectivity

Children are taught to decode words between the ages of four and nine. This is a time of major developmental changes in the brain, with extensive synaptic pruning and myelina-

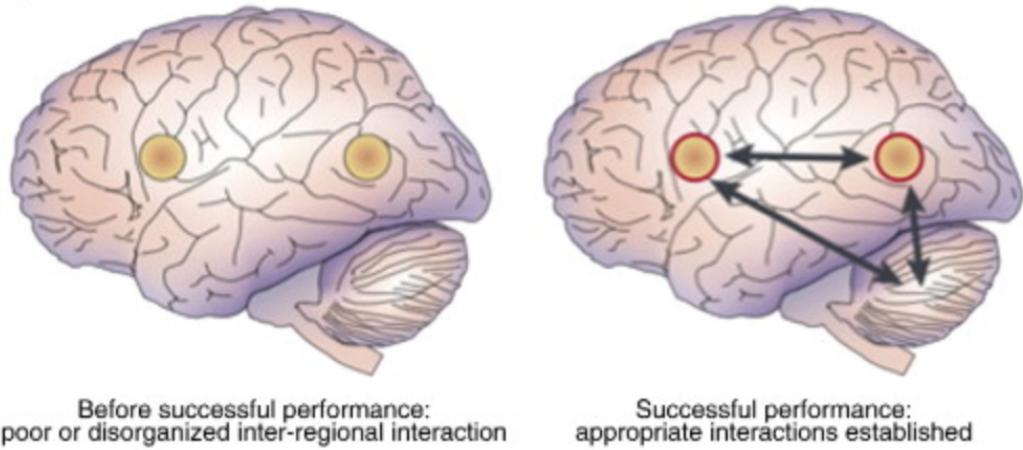


Figure 1.6: Interactive specialization posits that repeated co-activation of distant brain areas will create a network of regions important for performance of a given task. Figure adapted from Gaffrey et al. (2013).

tion of white matter tracts (Wandell and Yeatman, 2013). The brain areas responsible for fast and efficient word decoding may become specialized through a process of *interactive specialization*, in which intrinsic developmental processes and experience collaborate to form the mature, skilled reading system (Johnson, 2011; Klingberg, 2014). The theory is an extension of the Hebbian maxim that “neurons that fire together, wire together”, with the brain being considerably more plastic during this developmental period than it is later in life (Attneave et al., 1950).

Interactive specialization accommodates the observations that learning to read creates changes to connectivity that persist even at rest. In a series of studies led by Maki Koyama, it was found that individual connections between reading-related nodes was indicative of reading performance improvement. They first found that many reading-related nodes had overlapping connectivity with the left inferior frontal gyrus and left middle temporal gyrus, nodes that are important for skilled language use (Koyama et al., 2010). A follow-up study comparing IQ-matched children and adults found similar patterns: better readers in both groups showed increased connectivity between the inferior frontal gyrus and the middle and superior temporal gyri, as well as between the precentral gyrus and motor areas (Koyama

et al., 2011). In adults, positive correlations were found between reading ability and connectivity between the VWFA and phonological processing areas. In children, however, this correlation was weaker and negative, suggesting that the VWFA becomes more integrated with experience as well as skill. Reading intervention also exerts an effect on connectivity patterns. Dyslexic adolescents who received reading remediation had higher correlations between the VWFA and the right middle occipital gyrus than did control participants (Koyama et al., 2013). Connectivity values also correlated with spelling and single-word reading scores.

Despite the changes in connectivity between areas, reading-related regions do not create one distinct network but are members of separate RSNs (Vogel et al., 2013). These RSNs exhibit increasing functional correlation across the lifespan (Kesler et al., 2013; Uddin, 2010). Their properties, including density of connections, along with their locations and changes with development are a major area of interest, but their study is difficult due to differences in motion across the populations (Power et al., 2013). Nevertheless, the general understanding is that RSNs in children are more greatly constrained by proximity than in adults but are nonetheless functionally organized. Visual system regions, for example, form their own community, as do auditory regions and executive control regions (Seeley et al., 2007). This small-world architecture reaches peak efficiency in young adulthood, with younger children exhibiting fewer long-range RSNs and older adults showing a decrease in modularity, especially in higher-order RSNs like the DMN (Cao et al., 2016). However, the relationships between development, expertise and network architecture have not yet been disentangled.

According to the view of interactive specialization, an integrative ability like reading comprehension would induce a transient, highly connected brain state. Repeatedly activating this network over time would result in the common pathways becoming more tightly connected. Individuals who can more easily access these widespread resources, i.e. who have more integrated connectomes, may be more likely to read well; older readers, too,

would be expected to be more fine-tuned for comprehension. And because comprehension is a shared process between different regions, this network model may be even more telling than localized measures of brain function and activity.

1.6 Outstanding questions

We have established that the network model of cognition has particular bearing in the case of reading and that graph theory methods provide a framework with which to investigate the interactions between reading sub-processes. Furthermore, development of cognitive skills is facilitated by the *interactions* between regions, rather than solely by themselves – but the study of these processes have not been investigated extensively. These higher level processes are important for longer forms of reading, including passage reading, which is more common in older readers. Although disentangling the contributions from other skills (working memory, attention, planning/organization) during reading is difficult for behavioral research (Cain and Oakhill, 2006), it is a question that is well-suited to neuroimaging studies.

In this dissertation, we present four studies that investigate network properties as they relate to reading comprehension and reading success. The common thread is that reading requires the integration of many different brain networks (even moreso than listening) and that better readers are more able to meet these demands from a young age.

- *Study 1* investigates individual differences in “intrinsic” network architecture and its relationship to reading skill using resting-state fMRI data from older children (ages 10 to 11). We establish a set of methods for analyzing variability in connectomes and use their attributes to predict individual differences in reading skill.
- *Study 2* describes how network architecture changes *during* reading. We examine changes within and between RSNs and attempt to localize these differences to specific RSNs, such as the visual, dorsal attention and default mode networks. We also

elaborate on the results of Study 1, testing whether the relationship between network architecture and reading skill changes in the task-evoked connectome.

- *Study 3* moves beyond looking only at reading-evoked activity by comparing reading-evoked networks to listening-evoked ones, then between several other activities. The key questions this study addresses are whether greater variability between task-evoked networks is a beneficial attribute, and whether any particular RSNs (such as the fronto-parietal network) are more responsible for the reconfiguration of the whole-brain network.
- *Study 4* follows up on the modality results by analyzing network topology during reading comprehension across development. These analyses serve as a replication and extension of each of the previous studies: we test whether the relationship between reading and network architecture changes in more mature individuals and how task-evoked activity differs along the lifespan. While there is strong evidence that learning to decode creates persistent changes to the neural systems utilized in language (Schlaggar and McCandliss, 2007), there have been no studies investigating the trajectory of brain modularity and its relationship to reading over time.

Overall, these studies will use reading-related brain activity and behavior as a model for understanding how individual differences in network architecture form a basis for individual differences in cognitive processing. We combine inferences from several different methodological approaches, including resting-state network analysis, task-based activation analyses, and the combination of the two. Through this systematic approach, we strive to make a meaningful contribution to our understanding of brain modularity and its relationship to cognition.

CHAPTER 2

Intrinsic network architecture and skilled reading

2.1 Motivation

In the functional connectivity literature, researchers generally refer to two types of connectivity: intrinsic (or resting-state) connectivity and task-evoked connectivity. Network organization at rest is thought to be highly similar across people (Damoiseaux et al., 2006), and the pattern of connectivity within an individual is consistent over periods of time in excess of three years (Choe et al., 2015). It is thought that this stability may reflect a history of co-activation among brain regions that occurs over time (Power et al., 2010), and it is closely tied to patterns of white matter anatomical connectivity (Honey et al., 2009). As discussed in the introduction, a major feature of intrinsic network architecture is that of resting-state networks (RSNs). RSNs can be identified on an individual basis (Laumann et al., 2015) and are composed of brain regions that tend to function as a unit (De Luca et al., 2006; Smith and Nichols, 2009). This functional subdivision of the whole-brain network is hypothesized to provide a neural substrate for the diversity of cognitive functions in which people engage (Yeo et al., 2014).

Despite the overall stability across individuals, variations in network architecture have been noted. For example, differences have been observed in individuals who exhibit variation in executive functions (Reineberg et al., 2015; Tian et al., 2015) and in individuals with genetic susceptibility to Alzheimers disease (Trachtenberg et al., 2012). Consequently, variation in RSNs are likely to be stable measures of individual differences. To date, however, their relationship to other cognitive domains, and in particular reading, is not well understood. Given that large-scale networks underlie a variety of cognitive functions, it follows that individual variation within certain reading-related networks and the interaction among RSNs could be linked to varying reading abilities. The existence of these associ-

ations can be used to not only predict cognitive and academic functioning at the level of the individual, but also to allocate treatments, model developmental trajectories, or predict responses to intervention (Mattfeld et al., 2014; Crowther et al., 2015; Whitfield-Gabrieli et al., 2016).

We hope to better understand how variations in connectivity within and between RSNs is related to individual differences in reading skill. In general, skilled reading is associated with left hemisphere language and word recognition regions (left inferior frontal, supramarginal and occipito-temporal regions), and fronto-parietal regions supporting attention (Paulesu et al., 2014). The brain regions supporting reading do not, however, form a unique, fundamental network. Instead, reading appears to rely on the reconfiguration and integration of multiple, more fundamental brain networks (Koyama et al., 2010; Vogel et al., 2013). Indeed, emerging research suggests that functional connectivity indices are associated with differences in reading skill. Struggling readers, such as those with dyslexia, exhibit decreased connectivity between visual association areas and prefrontal attention areas, increased right hemisphere connectivity, and reduced connectivity to occipito-temporal cortex compared to non-impaired readers (Finn et al., 2014). In typically developing readers, Koyama and colleagues found increased positive connectivity among language regions was associated with increased word reading ability (Koyama et al., 2011), and recent studies suggest that interventions designed to enhance reading skill can increase the correlations between visual and frontal executive areas (Horowitz-Kraus et al., 2015a).

Although most cognitive functions are relevant to reading in some way, the RSNs most associated with primary reading subprocesses are the fronto-parietal, ventral attention, and visual RSNs. In addition to the intensity and composition of these networks, coordination between these brain areas and others are also likely to play a role in differentiating higher from lower performing readers. A separate study by Koyama and colleagues found that increased reading ability was associated with increased negative connectivity between reading regions and regions of the default mode network (Koyama et al., 2013), a network

typically implicated in internally-directed thinking (Andrews-Hanna et al., 2014). This negative relationship between the default and reading networks echoes work showing that increased anti-correlated activity between the default network and regions specialized for cognitive function, such as those involved in attention, inhibitory control, and working memory is associated with individuals who display higher performance. We expect, then, that there will be both regional and global effects of network architecture on reading skill.

Because of its stability and close ties to structure, understanding the degree of variability in intrinsic network architecture will serve as an excellent starting point for our aims. An in depth examination of how behavioral indices of reading relate to various properties of RSNs has not been previously reported, except within our own group (Bailey et al., 2018). First, we validate the existence of a small-world architecture in these subjects, and that the network parcellation is appropriate for them. Second, we determine whether global measures of network architecture, including modularity, participation coefficient and path length, are related to reading skill. Finally, we determine which RSNs drive the relationship between connectivity and reading skill. To address each of these questions, we analyze resting-state fMRI in developing readers, which has the further potential benefit of being able to be performed before children even start reading.

2.2 Methods

The following methods detail the current study's protocol and analytic approach. Because the following chapters borrow heavily from the methods described below, they are explained here in detail.

Participants

Participants were drawn from the fourth wave of a larger, longitudinal study investigating the neurobiological bases of reading comprehension. In total, 52 children completed scans and a subset of these met the motion and attention thresholds described below.

All participants were native English speakers with normal hearing and normal or cor-

Measure	Value
Subjects	44
Mean age	10.51 (0.33)
Sex	21 M, 23 F
WASI Full-Scale IQ, Vocabulary	52.91 (9.38)
Test of Word Reading Efficiency	104.66 (18.07)
Woodcock-Johnson Basic Reading	101.63 (12.79)

Table 2.1: Demographics and mean test scores for Study 1 participants are described here. For continuous data, the standard deviation is enclosed in parentheses.

rected vision, and no history of major psychiatric illness or traumatic brain injury/epilepsy. Subjects had no history of a developmental disability or contra-indication to MRI. Each participant gave written consent at the beginning of the study, with procedures carried out in accordance with Vanderbilt Universitys Institutional Review Board.

In addition to having an MRI scan, participants completed cognitive tests, including the Wechsler Abbreviated Scale of Intelligence (WASI) (Kaplan et al., 1999), the Test of Word Reading Efficiency (TOWRE) (Torgesen et al., 2012), the Woodcock Reading Master Tests (WRMT) (Woodcock, 1998), and the Gates-MacGinitie Reading Comprehension test (MacGinitie et al., 2000), among others. Demographics and selected test data are summarized in Table 2.1.

MRI acquisition and preprocessing

Imaging was performed on a Philips Achieva 3T MR scanner with a 32-channel head coil. Functional images were acquired using a gradient echo planar imaging sequence with 40 (3 mm thick) slices with no gap. Resting-state fMRI scans consisted of 190 dynamic volumes. Slices were parallel to the anterior-posterior commissure plane. Imaging parameters for functional images included: TE = 30 ms; FOV = 240 x 240 x 120 mm³; flip angle = 75°; TR = 2200 ms; and 3 mm³ isotropic voxels.

Whole-brain fMRI analyses were performed using tools from the FMRIB Software Library (version 5.0.9). For each session, the following pre-processing steps were performed:

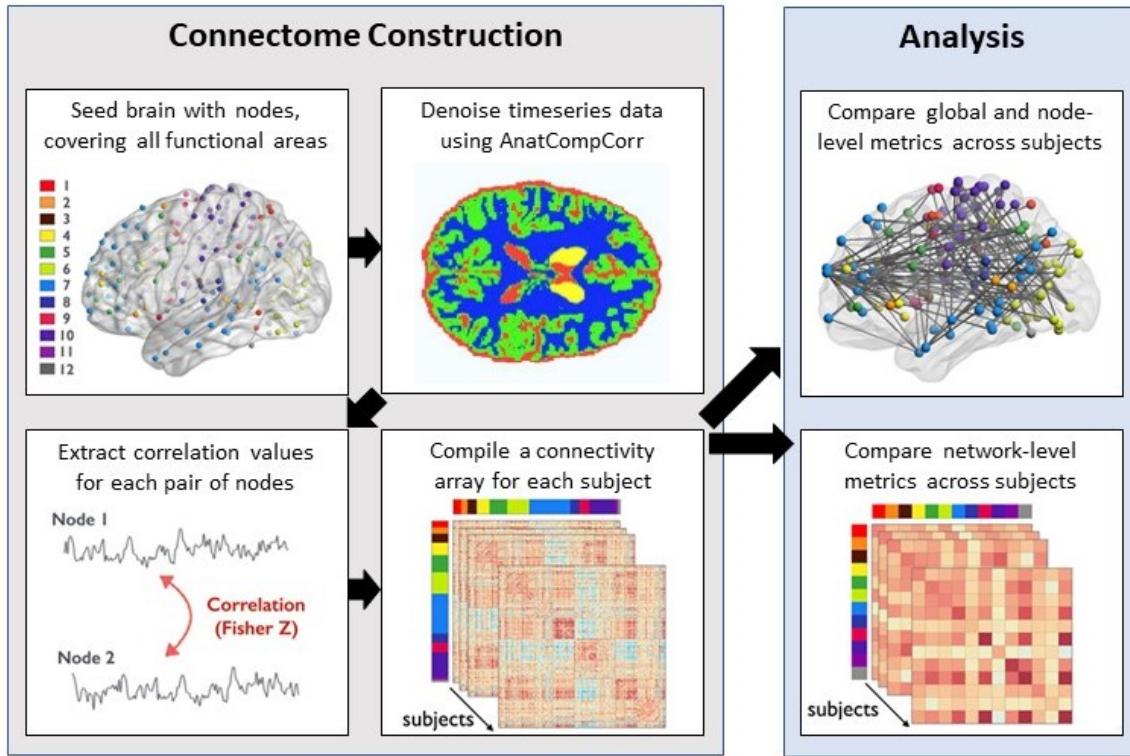


Figure 2.1: Connectomes are constructed from resting-state fMRI in the following steps: slice-timing correction, rigid-body motion correction, boundary-based registration to a T1-weighted anatomical image, and normalization to MNI 152 template. The timseries for 264 nodes are then extracted and denoised using signal from non-neural tissue, continuous motion parameters and outliers. A pair-wise connectivity matrix is then calculated and thresholded at multiple different thresholds, then analyzed at the global-, RSN-, or node-level. Figure adapted from (Yang et al., 2018).

slice-time correction, motion correction to the initial fMRI volume, boundary-based registration to the subject's structural image, and normalization to 2 mm MNI 152 standard space. To mitigate the effects of motion on our analyses, we regressed out 6 continuous motion parameters and scrubbed out outlier volumes. We defined an outlier volume as any in which the root-mean-square framewise displacement exceeded 0.7 mm. Because head motion can be a major confound for connectivity analyses, we removed scan runs where more than 20 percent of the fMRI volumes were outliers.

Suggested RSN	Abbreviation	Nodes
<i>Sensory</i>		
Auditory	AUD	13
Somatomotor (Hand)	SOH	30
Somatomotor (Mouth)	SOM	5
Visual	VIS	31
<i>Attention</i>		
Dorsal attention	DAN	11
Salience	SAL	18
Ventral attention	VAN	9
<i>Executive / Associative</i>		
Cingulo-opercular	CON	14
Default mode	DMN	58
Fronto-parietal	FPN	25
Memory retrieval	MEM	5
<i>Other</i>		
Cerebellar	CER	4
Subcortical	SUB	13
Not assigned	UNC	28

Table 2.2: List of networks used in connectivity analyses and the number of nodes affiliated with each. Although alternative parcellations of the node set are possible, we elected to use those network assignments suggested in (Power et al., 2013).

Network construction

To investigate whole-brain patterns of connectivity with minimal investigator bias, we selected 264 nodes *a priori* whose connectivity properties have been extensively analyzed in previous works (Power et al., 2011, 2013; Cole et al., 2014). The node set samples the entire brain, and nodes were selected based on their involvement in a diversity of cognitive tasks. Each node was assigned to one of 13 RSNs based on a previous study (Power et al., 2013). Approximately 10 percent of the nodes did not have a stable assignment in the original paper; for the present analyses, these nodes were excluded from graph theory calculations but included in network formation. A description of the 13 networks and their sizes is provided in Table 2.2.

Connectivity analysis was performed in the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Resting-state fMRI data were high-pass filtered at 0.008 Hz, motion-

corrected, co-registered to a structural image, normalized to MNI space and smoothed by a 5 mm FWHM spherical kernel. BOLD signal timeseries were corrected using “anatCompCorr”, which uses signal from white matter tissue and cerebrospinal fluid areas to reduce noise not related to brain activity (Chai et al., 2012). We also regressed out 12 continuous measures of motion and all outlier timepoints. The timeseries was then high-pass filtered at 0.01 Hz. fMRI timeseries correlations were calculated between each of the 264 nodes, resulting in a single connectivity array for each subject at each time point. Matrices were then thresholded into binary maps by keeping the top 5 percent of connections. (To confirm that this particular threshold did not unduly influence results, we also swept results between thresholds at the top 2 percent to the top 10 percent of connections.)

Network analyses

The metrics of interest were network *modularity*, *participation coefficient* and *path length* (Rubinov and Sporns, 2010). Modularity is high in networks where nodes within the same RSN are highly connected to each other but not elsewhere. The participation coefficient, on the other hand, is high when many nodes are connected to several different RSNs. Both of these metrics relate to the integration of information between RSNs. Path length describes the distance between any two nodes on the graph. This was calculated between every node, then summed up by RSN to create a measure of network distance. These properties, and their changes within our task, were investigated at the level of connectomes, RSNs and nodes.

First, we establish the validity of the parcellation for evaluating network properties in this sample. At rest, we expect to see high modularity (greater than 0.1), low participation (less than 0.9), and a lower path length within RSNs than between them. We also expect to see moderate-sized correlations between measures, since each is measuring an aspect of network architecture related to distance between nodes.

Next, we break each global measure down by RSN to determine how sub-systems differ

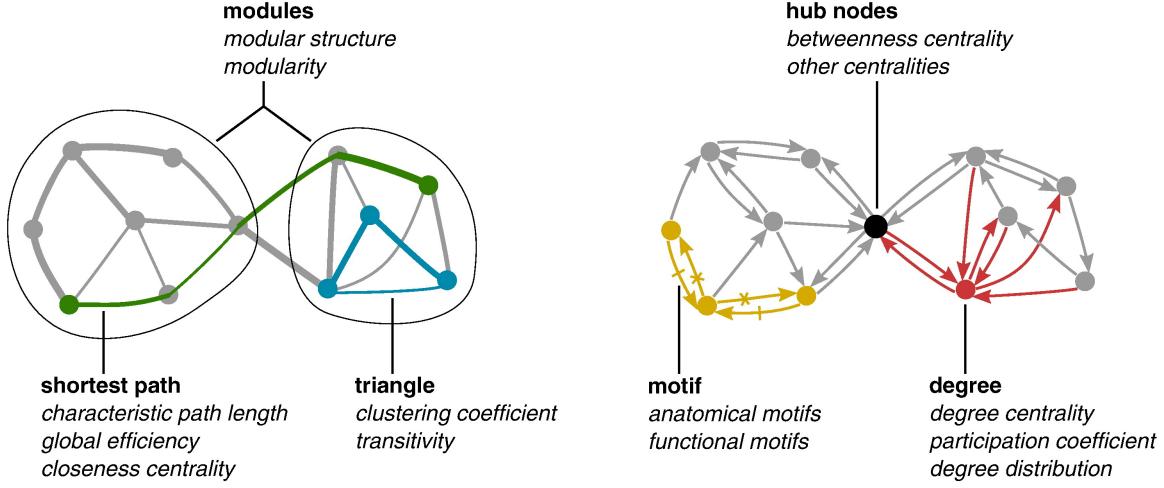


Figure 2.2: Sampling of graph theory measures, including those of present interest. Modularity (left, circular regions) is high in networks where nodes within the same RSN are highly connected to each other but not elsewhere. Path length describes the distance between any two nodes on the graph (left, green line). The participation coefficient, on the other hand, is high when many nodes are connected to several different RSNs (right, center node). Figure is reprinted from (Rubinov and Sporns, 2010).

in their network roles. For modularity, we report the total modularity contribution for each network. For participation coefficient and path length, we report the mean value within each network. We also investigate the measures obtained across the whole range of network-forming thresholds (retaining the top 2 to 10 percent of connections). We expect to see changes in the measures across thresholds, but ranked in a relatively stable order among the different RSNs.

To determine the relationship between network measures and individual performance on cognitive assessments, we input each global metric into a general linear model with the Test of Word Reading Efficiency (TOWRE, total word efficiency (TWE) standard score). Models containing measures of mean framewise-displacement (motion) and the WASI Vocabulary measure were also assessed to ensure that effects were not driven by motion confounds or global measures of cognitive skill. We also examined whether there were differences in the modularity relationship between TOWRE subtests (sight word efficiency and phonemic decoding efficiency).

To assess whether there was an RSN-level trend in the modularity-to-reading relationship, post-hoc analyses comparing network-level modularity values to TOWRE scores were also investigated. For each node, a correlation value was calculated between its modularity contribution and TOWRE TWE scores. To evaluate significance, RSN correlations were compared to a bootstrapped distribution of 5000 correlation values generated by sampling and totaling the modularities for a random set of nodes equal in size to the selected RSN. (For example, summing modularity contributions for 31 random nodes for comparison to the visual network.)

2.3 Results

Of the 52 subjects who completed resting-state fMRI scans, 44 met the scan quality criteria for inclusion. Connectome parcellations at the 5 percent threshold exhibited small-world properties: the mean global modularity value was 0.264 (SD = 0.037), and the mean participation coefficient was 0.599 (0.052). Furthermore, the path length within RSNs was significantly lower than those between: within-community nodes took an average of 2.49 (0.141) steps to reach each other, whereas between-community nodes took an average of 3.06 (0.207) steps ($p < 0.001$, two-sample t -test). Furthermore, a comparison of each metric against the others shows that, while there is overlap between the measures at the global level, there is substantial variability as well (Table 2.3).

Figure 2.4 highlights the contributions of each RSN to the graph theory measures. The visual, somatomotor, and default mode were the most modular RSNs, in part reflecting their larger size relative to others. The dorsal attention, auditory and cingulo-opercular networks were the most participatory RSNs at rest. The fronto-parietal RSN occupied an interesting place, possessing relatively high global modularity but also one of the higher participation coefficients and lower global path lengths. The effect of changing thresholds had consistent effects on each measure: as more connections were included, the modularity decreased, participation coefficient increased, and path length decreased (Fig. 2.4, bottom).

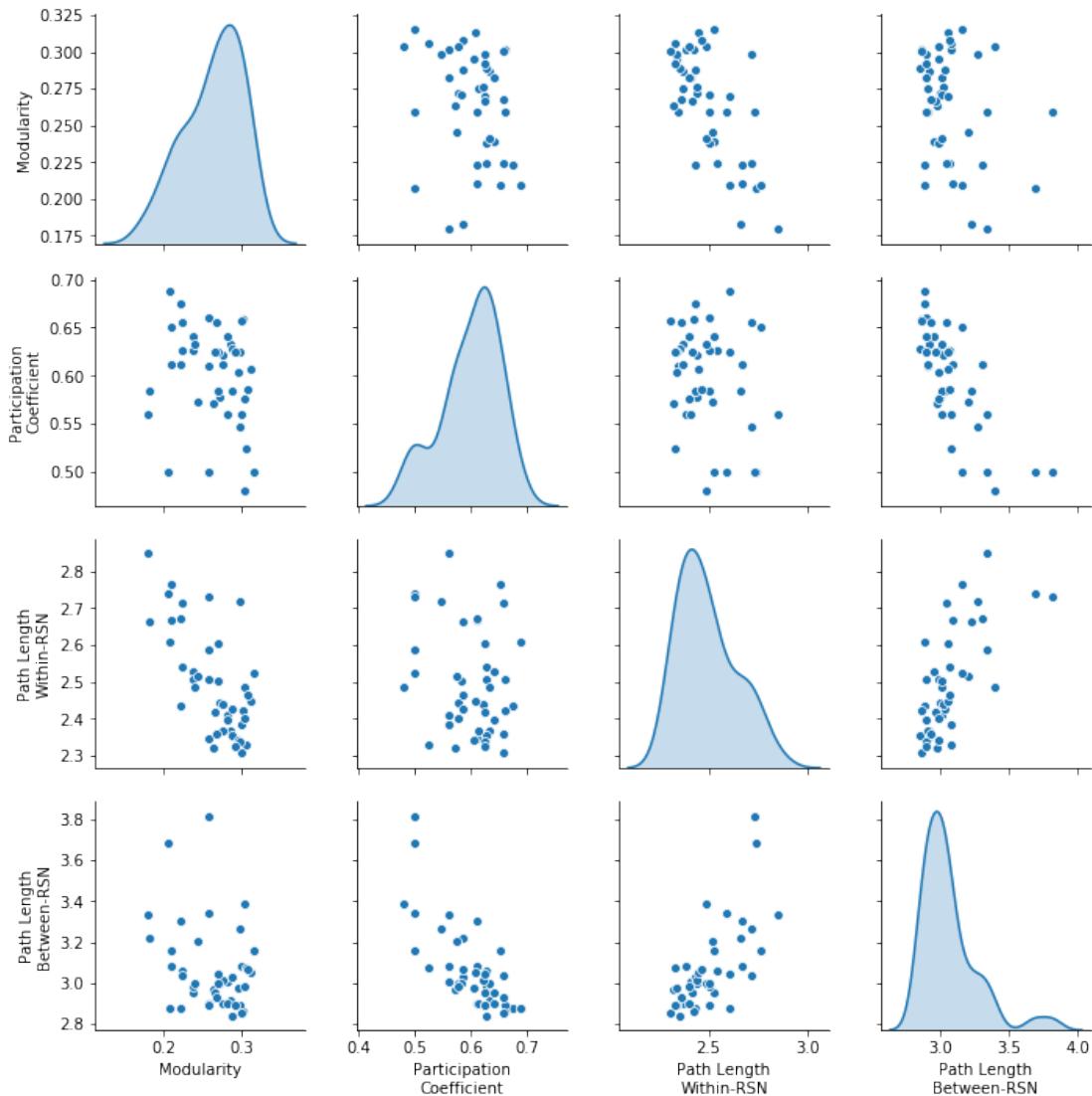


Figure 2.3: Distribution and correlations between the global modularity, participation coefficient and path length. Each attribute may be interpreted as a measure of connectedness between RSNs, but there is substantial variability between them.

The relationships between each graph theory metric to TOWRE Total Word Efficiency scores are summarized in Table 2.3. Global modularity, but not participation coefficient or path length, was predictive of reading skill even after controlling for mean frame-wise displacement (motion) and verbal intelligence ($Z_{TWE} = 2.536$). The direction of the relationship was positive, and it was higher for the Sight Word Efficiency subtest ($Z_{SWE} = 2.779$) than for Phonemic Decoding Efficiency ($Z_{PDE} = 2.138$), which did not reach significance

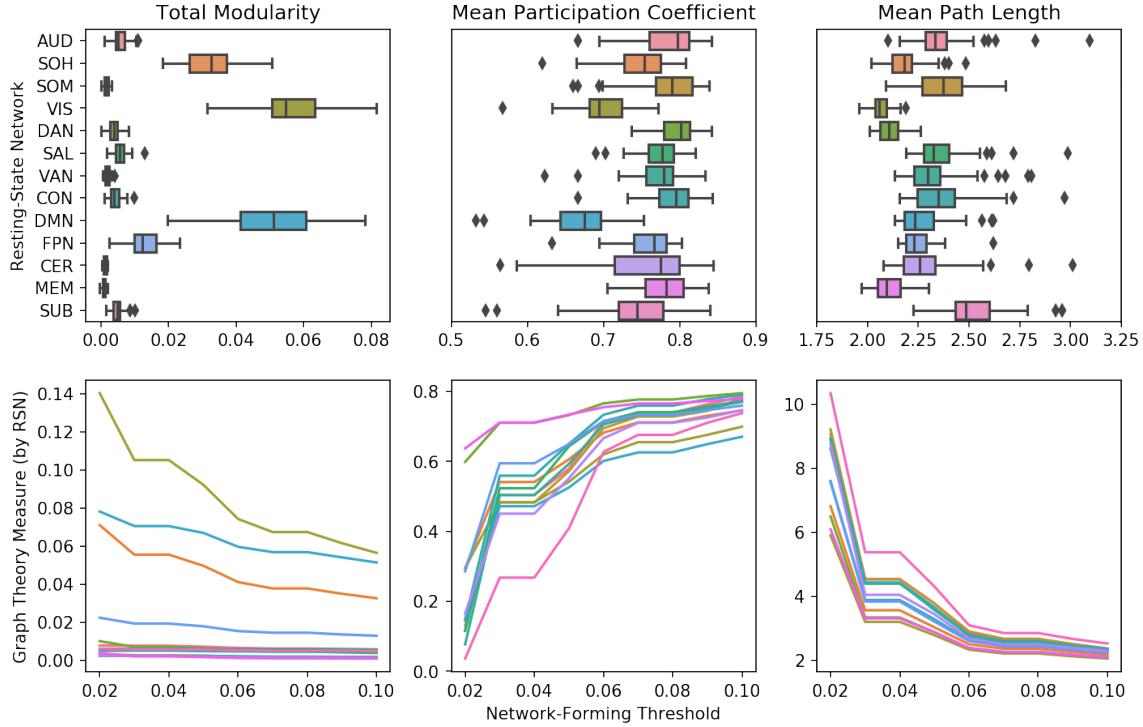


Figure 2.4: Relationships between network-level graph theory measures. Shown above are the network-level distributions of the graph theory measures when graphs are thresholded for the top 10 percent of connections (top row), and the network means as the network-forming thresholds are swept from 2 percent to 10 percent (bottom row).

when confounds were controlled.

The relationship between global modularity and TOWRE is stable across multiple thresholds (Fig. 2.5). In fact, when graph theory measures were compared to other language-related assessments, there was a trend towards a significant positive relationship between modularity and cognitive performance that was more stable than those of either the participation coefficient or global path length.

Finally, we investigated the correlation between each individual RSN’s modularity contribution and TOWRE scores (Fig. 2.6). Overall, no RSN reached the strength of correlation of the whole-brain measure (i.e., $r = 0.378$). The default mode RSN had the highest correlation with the TOWRE ($r_{DMN} = 0.350$), with the memory retrieval ($r_{MEM} = 0.303$) and attention ($r_{DAN} = 0.236$, $r_{VAN} = 0.248$) RSNs ranking next. Surprisingly, the relation-

Predictor	Z-statistic	p-value
TEST OF WORD READING EFFICIENCY		
<i>Total Word Efficiency</i>		
Modularity	2.536	0.011*
Part. Coefficient	-0.339	0.505
Path Length	-0.763	0.484
Modularity (cont. motion + verbal IQ)	2.025	0.045*
<i>Phonemic Decoding Efficiency</i>		
Modularity	2.138	0.033*
Part. Coefficient	-0.268	0.479
Path Length	-0.697	0.561
Modularity (cont. motion + verbal IQ)	1.433	0.167
<i>Sight Word Efficiency</i>		
Modularity	2.779	0.006**
Part. Coefficient	-0.418	0.547
Path Length	-0.750	0.459
Modularity (cont. motion + verbal IQ)	2.301	0.023*

Table 2.3: Results for analyses comparing global graph theory metrics to reading skill.

ship was significantly different in the auditory and cingulo-opercular RSNs: lower RSN modularity was associated with better reading skill ($r_{AUD} = -0.178$, $r_{CON} = -0.127$), potentially reflecting literacy-induced differences.

2.4 Discussion

Our aim for Study 1 was to establish whether network measures of resting-state fMRI data were related to reading skill. We established a series of methods and measures for summarizing the global and RSN-level network architecture, and showed that of all metrics, global modularity was most robustly able to index reading skill in our sample. We also explored how variations of this measure among RSNs is associated with individual differences in reading ability. This demonstrated that modularity within the default mode network is most similar to the whole-brain modularity, and it also revealed significant negative correlations between the modularity of the auditory and cingulo-opercular networks and reading skill.

One advantage to our approach is that we used an *a priori* defined set of nodes and net-

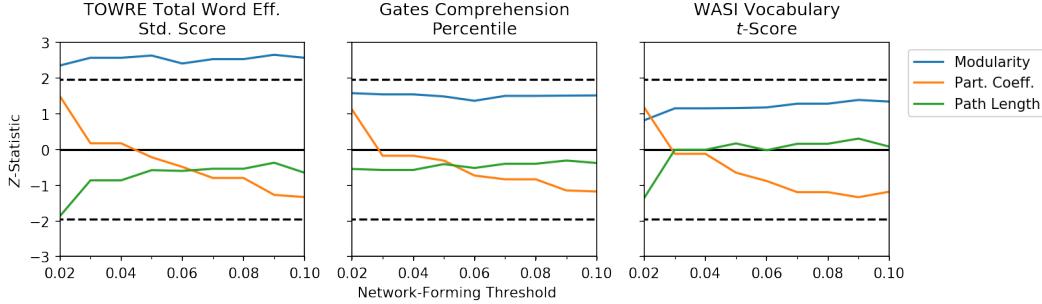


Figure 2.5: Global Modularity at rest is the most stable and predictive network measure for predicting language-related skills, although it only reached significance thresholds for the TOWRE.

work parcellation (Power et al., 2013). We then employed standard global measures that are sensitive to RSN properties: modularity, participation coefficient and path length. Although adjusting the network-forming threshold had a sizable impact on the values yielded for each metric, the relative contributions of each RSN to each metric were fairly stable. That is, there was a global and not local trend in the effect of thresholds, with a few exceptions for very small RSNs (for example, the memory retrieval network). Modularity, in particular, was relatively stable across thresholds, as indicated by its consistent relationship to cognitive metrics (Fig. 2.5).

Global modularity was the most effective measure for predicting individual differences, especially in reading but more broadly in verbal skill. Modularity is a measure of network segregation: the more different each RSN behaves during rest, the higher the modularity will be. One possible explanation is that modularity is an essential component to the entire network organization, whereas participation coefficient and path length are more regionally variable throughout the network (Bullmore and Sporns, 2012). Furthermore, this finding is consistent with previous literature showing that anti-correlations between the default mode network and the fronto-parietal network index cognitive skills (Anticevic et al., 2012).

The regional variability in correlation strength was also notable. We were surprised to find an anti-correlation between RSN modularity in the auditory and cingulo-opercular networks and reading skill, given the global trend of positive correlations. (The boot-

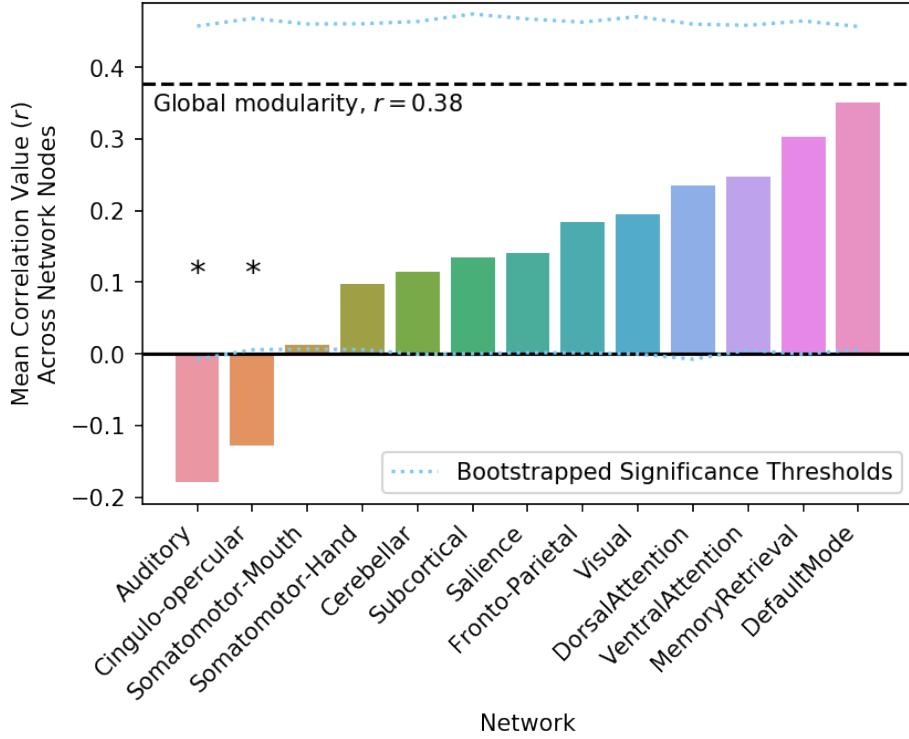


Figure 2.6: RSN modularity relationships with TOWRE. Although no individual RSN matched the strength of correlation of the global modularity measure, the default mode and memory retrieval RSNs had significant positive correlations with the TOWRE. The auditory and cingulo-opercular RSNs, on the other hand, had significant negative correlations.

strapped distribution yielded a range of correlation values spanning approximately $r = 0.0$ to $r = 0.4$. See Fig 2.6.) The localization of these differences onto the auditory network support a hypothesis that, in better readers, auditory networks are more integrated with other networks, such as visual networks. Although the modularity measure cannot support this directly, follow-up studies investigating task differences may be able to do. On the other end, we found that the default mode network was most highly correlated with reading and most closely approximated the global correlation. The DMN supports a wide range of cognitive processes important for comprehension, including theory of mind, narrative processing, and autobiographical recall (Buckner et al., 2008; AbdulSabur et al., 2014), and its cohesiveness during resting-state has been used to investigate other disorders (Uddin et al.,

2008).

Modularity in biological systems is an important feature from an evolutionary standpoint. It increases adaptability and robustness and thus increases the system's evolvability (Sporns and Betzel, 2016). Although no consensus interpretation exists, one could speculate that increased modularity indexes segregation of functions. This interpretation stems from a wide range of studies showing opposing activation in externally directed cognitive tasks for the fronto-parietal and default RSNs, during which functions of the two networks ought to be segregated to prevent interference (Reineberg et al., 2018). That is, an increase in global modularity indicates that each RSN is more capable of functioning independently, without the participation of external regions. Future studies will have to investigate this directly.

While this study is one of the first to examine the relationship between reading skills and intrinsic network architecture, there are a few limitations. One limitation is the extent of inference we can make about specific behavioral skills. We used a composite measure of reading that accounts for phonological decoding and sight-word reading skill, but reading skill relies on a number of other processes (e.g. semantic processing). Due to shared variance between these measures – and even domain-general ones – it is difficult to pinpoint which cognitive process is most closely associated with modularity. However, the finding that modularity was more closely associated with Sight Word Efficiency (which requires no decoding) than Phonemic Decoding Efficiency provides some evidence that modularity is related to speed of transfer of information between different systems, rather than environmental tuning. Another limitation is that, because we examined these relationships in relatively mature readers, it is possible that other relationships might be observed in developing readers. Such processes explain less and less variance in reading skill as texts become more difficult and reading starts to reach mature levels (Cutting et al., 2006).

Overall, the current results demonstrate that global modularity is an important indicator of successful reading skill, and there appear to be regional variations which influence it.

Future work will need to examine not just the internal connectivity, but the relationships between these networks during reading and at rest. The default mode network, for example, is typically anti-correlated with “task-positive” networks such as the fronto-parietal network. A high degree of anti-correlation has been reported to be important for performance on a variety of cognitive processes (Fox et al., 2005; Keller et al., 2015), but recent work suggests that high modularity and connectivity of the default mode during higher-level cognition is fundamental to processes relying on self-referential and memory retrieval processes, such as those found in language (Vatansever et al., 2015). How this modular architecture changes during the reading process is an important question that we will tackle in the following chapter.

CHAPTER 3

Integration of resting-state networks during reading

3.1 Motivation

In Study 1, we began building an argument that the brain compartmentalizes its cognitive functions because this improves cognitive efficiency, both for specific tasks and for integrating across the whole-brain network. We found this to be true in the case of reading fluency: global modularity is positively related to reading skill, even when controlling for verbal intelligence and motion. However, the brain network is not static but rather changes in response to the demands made upon it. Therefore, evaluating the brain *while* it is reading is critical for understanding how its organization supports fluency.

While resting-state functional connectivity is thought to provide insights into a relatively stable intrinsic architecture, *task-evoked* functional connectivity measures network organization in response to an environmental demand. The degree of reconfiguration is physiologically limited: the BOLD signal change during a task is only about 1 percent (Fox and Raichle, 2007), and there are underlying structural constraints such as white matter connectivity (Sui et al., 2014). Nevertheless, there is a large degree of flexibility to reconfigure the functional network based on the demands of the task. One study, for example, compared a finger-tapping to working memory task. Using measures of modularity and participation coefficient, they found that within-network communication was critical for the motor task, whereas between-network communication was important for working memory (Cohen and D’Esposito, 2016). This supports a hypothesis that tasks can operate on multiple levels: high connectivity within-module for sensorimotor tasks, and distributed for ones that require higher-order skills. The ability to flexibly switch between high- and low-modularity states may thus be an important trait.

Reading, and especially reading comprehension, spans both levels of cognitive activity.

On the one hand, readers continuously receive visual stimuli and transform them into auditory and semantic representations. These representations must then be kept in memory, evaluated for relevance and updated when necessary (Maguire et al., 1999). In general, task-evoked network architecture induces a decrease in modularity (Cole et al., 2014), and this decrease is associated with active engagement and awareness of the task at hand (Godwin et al., 2015). Other studies have shown that the extent of the modularity is related to the novelty and expertise at the task (Bassett et al., 2015). This has not, however, been related to individual differences in those broader cognitive skills.

A complementary question is whether the relationship between reading skill and network modularity *while reading* should remain the same. One hypothesis is that, if cross-network communication is critical to reading, better readers should exhibit a much less modular organization while reading than poor readers. However, there is evidence from univariate analyses of brain activation that would suggest the opposite: compared to poor readers, expert readers show *less* activation in many reading-related areas during reading tasks (Christodoulou et al., 2014). In the context of interactive specialization, this is explained by the increased efficiency of information transfer within an established network. If the resting-state network architecture represents an efficient baseline, then expert readers may be expected to deviate from it less.

It has been well-established that during reading, brain activity patterns span a wide range of networks and both hemispheres, especially as texts become longer and more complex (Rimrodt et al., 2009; Xu et al., 2005). However, less understood is the relationship between task-activity and changes to an area’s role in the network. Although hub regions of the brain are known to be important for cognitive functioning, implicated in a wide variety of processes and localize predominantly onto association cortices, we are not aware of any studies that have directly compared their hub role to their BOLD response in a specific task. That is, does the “activation” of a hub node correspond to its connecting of more areas, or does it reflect a specific in the traditional sense corresponds to increased engagement with

Measure	Value
Subjects	47
Total scan runs	88
Mean age	10.51 (0.31)
Sex	24 M, 23 F
WASI Full-Scale IQ, Vocabulary	53.15 (8.69)
Test of Word Reading Efficiency	105.00 (18.09)

Table 3.1: Participant demographics for Study 2. Subjects include all of those from Study 1, and three additional ones who had sufficiently high quality task-fMRI scans.

many areas, or if it reflects primarily local processing. The answer may be region- and task-dependent: visual areas may performing local processing, whereas activation of FPN areas may indicate the linking of two networks.

Reading comprehension is thus an excellent model task for understanding how task-evoked changes to network architecture vary throughout the brain and along reading skill. First, we validate our task with a traditional univariate analysis. Next, we describe the global changes to different aspects of network architecture during each condition. Then, we pinpoint which brain areas and RSNs that drive the changes to network architecture, and investigate the relationship between these changes and individual differences in reading skill.

3.2 Methods

Participants

Participants were drawn from the same cohort of subjects included in Study 1, and identical inclusion criteria for both demographic and scan motion were applied. However, additional measures related to the performance of the task were levied as described below. A total of 47 unique subjects and 88 scan sessions were included in the analysis. Their demographics are described in Table 3.1.

MRI acquisition and task design

Participants performed up to four runs of a language comprehension task, which was crossed on two conditions: the modality of presentation (listening or reading) and the passage genre (expository or narrative). Functional MRI acquisition parameters were identical to Study 1 with the exception of scan duration, which was increased to a total of 250 dynamic volumes for each run.

For the present analysis, only the “reading” scans were considered, and the effects of genre on brain activation were ignored, as they are balanced out within the majority of subjects. (6 subjects had only a single genre used for analysis.) In the following paragraphs, however, we will describe the experiment design in its entirety, as it will be relevant to subsequent analyses.

Each fMRI run had two baseline conditions: a modality-specific baseline task and a resting-state block with a fixation cross. At the conclusion of the comprehension portion of each experiment, two images were presented, and subjects were asked to decide if the image was related to the passage. (e.g., Is a picture of a cake with candles related to a story about a birthday party?) The order and duration for each block varied slightly across runs but was approximately: paragraph 1 (60 s), baseline 1 (60 s), paragraph 2 (60 s), baseline 2 (60 s), and resting-state (270 s). Total scan time was 550 s for each run. See Fig. 3.1 for a schematic describing the visual task.

To create a more naturalistic reading experience than single word presentation (Rayner, 1997), passages were presented in syntactic phrases ranging from 1-7 words in length. The interval between each stimulus was jittered to allow for event-related analyses (range: 275-4000 ms), although these effects were not examined here.

The sensory baseline condition was altered according to modality. For the reading runs, three non-alphanumeric symbols were displayed horizontally (two types), and their presentation time was matched to the passage phrases. Spacing between symbols was randomly alternated to replicate the variable phrase lengths in the passage condition. For

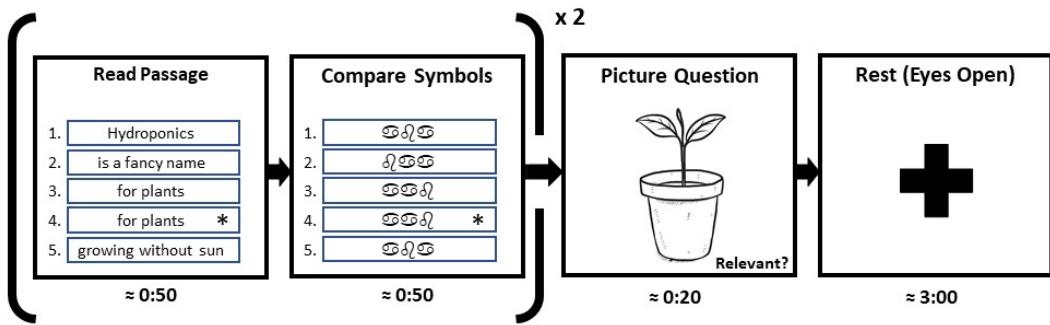


Figure 3.1: Schematic of the reading comprehension task. Subjects were presented two blocks of passage reading and a symbol comparison tasks, which were followed by a brief comprehension question and a resting block. Starred stimuli in the reading and symbols conditions represent “repeat” stimuli, and a participant is asked to click a button when they detect one. The total duration of each scan run was 550 seconds.

the listening runs, three tones (two frequencies) were played in sequence, with a new set of tones beginning at the same intervals as the corresponding passage presentation.

To monitor attention, 4 to 8 percent of the stimuli within each passage or symbols block were randomly repeated on two consecutive screens. Participants pressed a button with their right thumb when they detected a repeated phrase, symbol or tone configuration. Additionally, at the conclusion of each passage, a picture was presented on the screen, and subjects were asked to identify whether the picture had any relationship to the passage (e.g., a picture of a mushroom for a passage about fungi).

To assess performance, we analyzed three measures: in-scanner attention, in-scanner comprehension, and post-scan recall. To assess attention for the “repeated stimulus” task, we used the D' summary measure. It is calculated as:

$$D' = Z_{\text{true positive}} - Z_{\text{false positive}}$$

Individual scan runs with a D' value less than 2 were excluded from analysis. The in-scanner comprehension measure was the number (either 0, 1, or 2) of questions correctly

answered. To assess recall after the scan, each child was asked to recite as much of the passage as they could remember, and their answers were mapped to actual phrases present in the chapter.

In total, there were 4 passages (2 listening and 2 reading), each leveled to a third grade difficulty level and balanced on word measures such as concreteness and cohesiveness. All subjects were trained on the task in a mock scanner prior to the actual scan.

Activation analyses

Whole-brain fMRI analyses were performed using tools from the FMRIB Software Library (version 5.0.9). For each session, the following pre-processing steps were performed: slice-time correction, motion correction to the initial fMRI volume, high-pass filtering at 0.08 Hz, boundary-based registration to the subject's structural image, and normalization to 2 mm MNI 152 standard space. To mitigate the effects of motion on our analyses, we regressed out 6 continuous motion parameters and scrubbed out outlier volumes. We defined an outlier volume as any in which the root-mean-square framewise displacement exceeded 0.7 mm. We removed scan runs where more than 20 percent of the fMRI volumes were considered outliers.

All task conditions were convolved with the double-gamma hemodynamic response function to generate design matrices for each fMRI run. Two first-level contrasts were of interest: the main effect of passage comprehension ("reading vs. rest"), and the contrast of passage comprehension vs. the sensory baseline ("reading vs. symbols"). Repeated stimuli and the picture comprehension task were modelled out.

Reading effects were estimated at the subject-level using fixed effects analysis. These were carried over into group-level analyses using non-parametric methods implemented in FSLs *randomise* tool with threshold-free cluster enhancement. For each group-level analysis, we performed 5000 permutations and report results with $p < 0.05$.

To understand our univariate results as a function of system-level activation, we also

extracted activation values from each of the 264 connectome nodes, and summarized the activity of each intrinsic RSN.

Network analyses

For graph theory analyses, network estimation was performed in the *Conn: Functional Connectivity Toolbox* (version 17f) (Whitfield-Gabrieli and Nieto-Castanon, 2012). As in Study 1, for each scan run, the BOLD activity at each node was denoised using the anatomical CompCorr method, which regresses out background noise from white matter and cerebrospinal fluid tissue. We also regressed out 12 continuous measures of motion were also included, all outlier timepoints, and the effect of all task conditions (i.e., reading, symbols, and rest). The timeseries was then high-pass filtered at 0.01 Hz.

Whole-brain connectomes for each condition were created by estimating the functional connectivity between each node using a weighted general linear model. For connection-level analyses, these values were compared directly across subjects and conditions. For graph theory analyses, the array of all node connections was thresholded to keep the top 5 percent of connections, resulting in a much sparser representation. This threshold was also tested at ranges from 2 percent to 10 percent. These arrays were then characterized using the previously described graph theory measures: modularity, participation coefficient, and path length.

To investigate the rewiring of the network at the RSN-level, we compared the number of connections across each RSN relationship at each condition. For each pair of networks, we computed a paired *t*-test between the total number of connections between the networks to determine whether there were more in one or the other condition. This resulted in a 13 by 13 RSN-level connectivity array. Connectivity changes were performed at each of the 9 thresholds, and relationships that showed significant changes ($p < 0.05$, uncorrected) in at least 7 of the 9 thresholds were included in the rewiring diagram.

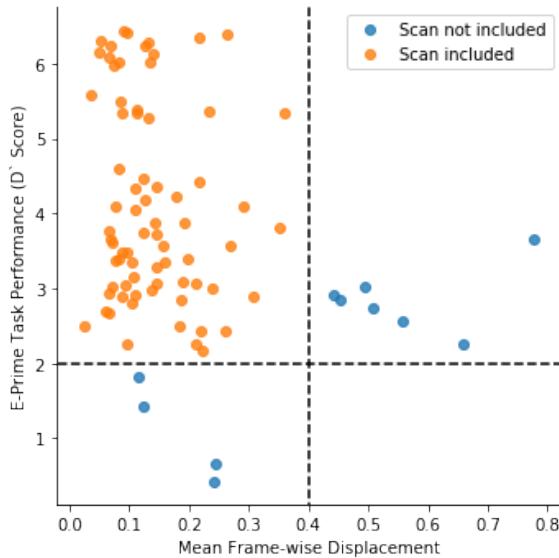


Figure 3.2: Scatterplot summarizing the relationship between scan motion quality and task performance. The D' score measures performance based on both active (correctly identifies repeats) and passive (few false alarm clicks) metrics. The frame-wise displacement measure also accounts for outlier volumes which are regressed out during analysis.

3.3 Results

Behavioral results

47 subjects (88 scan runs) met the attention and motion criteria for inclusion in the analysis. (5 subjects and 15 scan runs were excluded.) The distribution of performance and motion criteria are illustrated in Figure 3.2.

Activation results

Figure 3.3 demonstrates the range of language-related areas were activated during reading comprehension. Compared to the symbols baseline, reading-related activation spanned the inferior frontal gyrus, angular gyrus, premotor cortex, middle temporal gyrus and the superior frontal gyrus. Activation patterns were robustly present on both hemispheres but extended further and with greater intensity on the left hemisphere. There were also a number of areas that were more active in the sensory and resting state, particularly in the dorsal attention network and anterior dorsolateral prefrontal cortex.

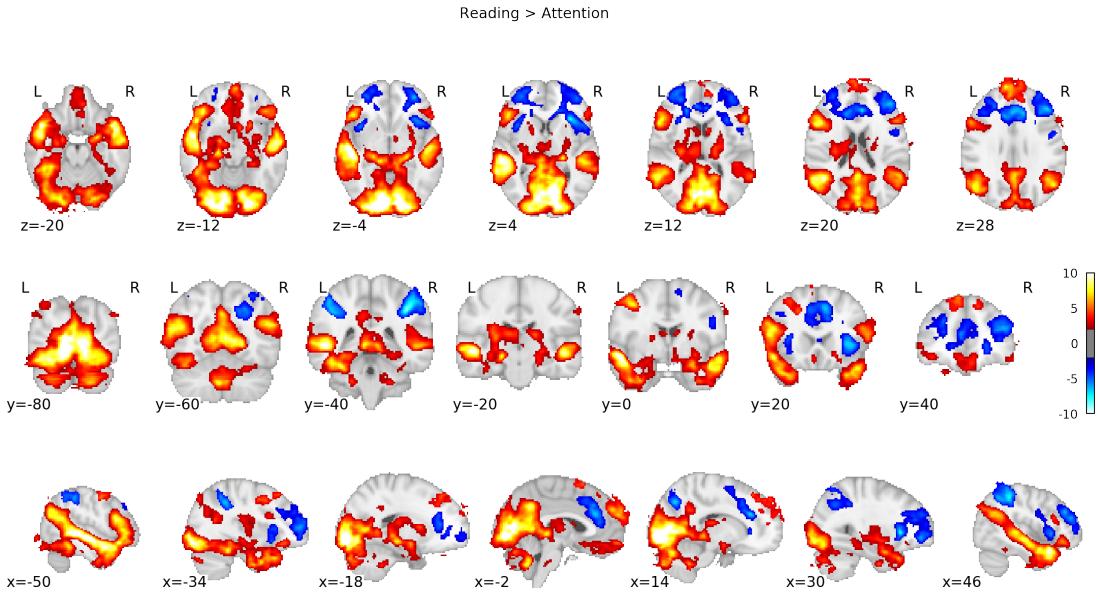


Figure 3.3: A range of language-related areas were activated during reading comprehension. The above figures show axial, coronal and sagittal views of the “reading vs. symbols” activation contrast. Reading-related activations span expected areas, including left fusiform, middle temporal and inferior frontal gyri, but also extend into right hemisphere homologues and the cerebellum. Results are thresholded at $p < 0.05$ using threshold-free cluster enhancement (5000 permutations).

To understand RSN-level trends in activation, we also examined the results when projected onto the 264 nodes in the connectome parcellation. Compared to the resting baseline, the ventral attention, visual and default mode networks had the greatest number of “active” nodes. It is also notable that the “uncertain” nodes were highly engaged. These nodes had variable activity that made them impossible to classify consistently in the original paper (Power et al., 2011). Their engagement may reflect the important role of functionally diverse regions in the execution of reading comprehension. On the other end, the memory retrieval, salience and cingulo-opercular networks exhibited decreased activity compared to rest. See Figure 3.4 for a diagram of these activations by RSN.

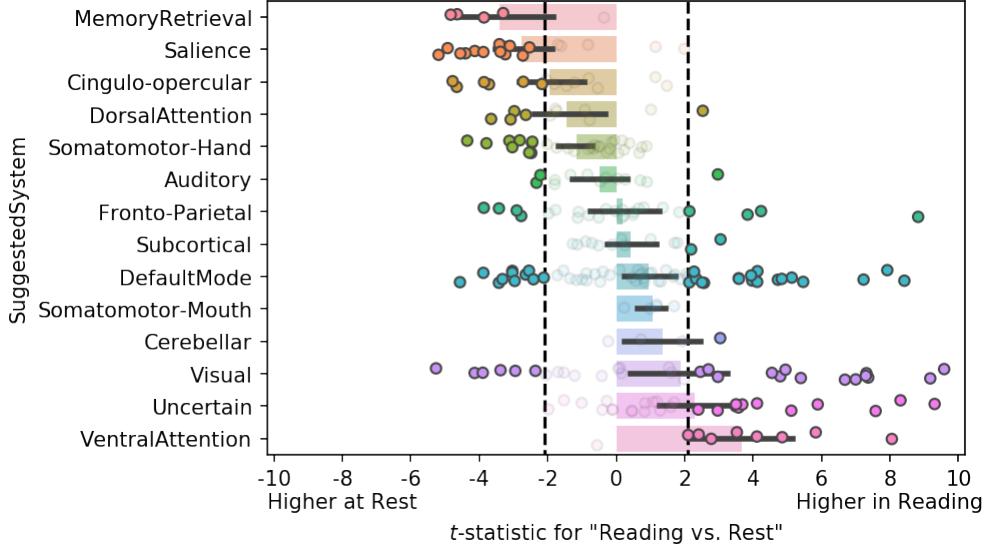


Figure 3.4: Distribution of reading-related activity among connectome nodes, grouped by RSN. Each point represents a single node, while bars represent the aggregate mean for each RSN. Visual and ventral attention networks showed the most network-level activity in reading, although large portions of the default mode and fronto-parietal network were also robustly related. Cingulo-opercular, memory retrieval and salience networks showed decreases. Dashed lines represent $p < 0.05$, uncorrected.

Network results

Next, we examined changes to global network architecture. Figure 3.5 summarizes the subject-level changes (as well as significance values) in modularity, participation coefficient, and path length. Overall, the effect was one of increased integration across RSNs during reading comprehension. Relative to rest, both reading comprehension reduced the global modularity and increased the participation coefficient. The magnitude of the effect in reading comprehension was also greater than that of the sensory condition. The path length within each RSN did not significantly change across condition, suggesting that the modular organization of the brain was not disrupted. However, there were significant increases in the between-RSN path length corresponding to greater efficiency of transferring information between these disparate systems.

Network-level trends in task-evoked differences, presented in Figure 3.6, were largely consistent with global effects. However, a few findings are worth noting: compared to rest,

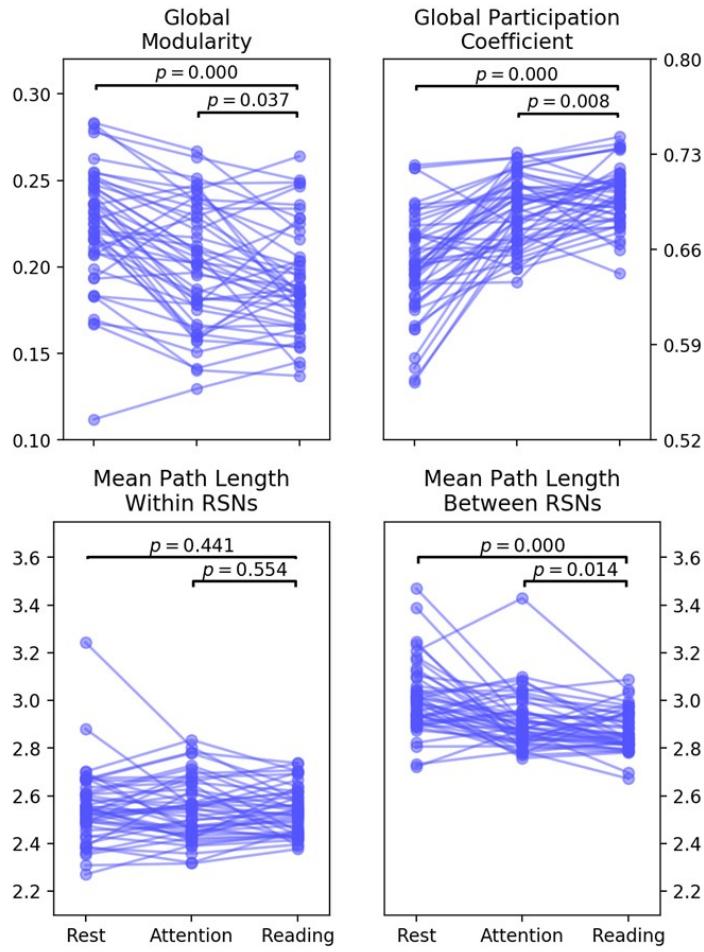


Figure 3.5: Reading induces a more integrated global network architecture. Each set of connected points represents a single subject. Compared to rest and the baseline symbols task, reading comprehension increased global measures related to RSN integration. Notably, the only measure not significantly changed during task was the within-RSN path length.

reading was marked by large decreases in modularity of the visual, dorsal attention and default mode networks. However, the increases to participation coefficient were global. Compared to the symbols task, network-level changes were modest, and the global differences were driven by reduced modularity in the default mode and fronto-parietal networks and increased participation of memory retrieval and default mode networks.

Specific relationships between RSNs are made apparent when comparing when examining the “rewiring” diagram comparing rest and reading (Figure 3.7). During rest, there

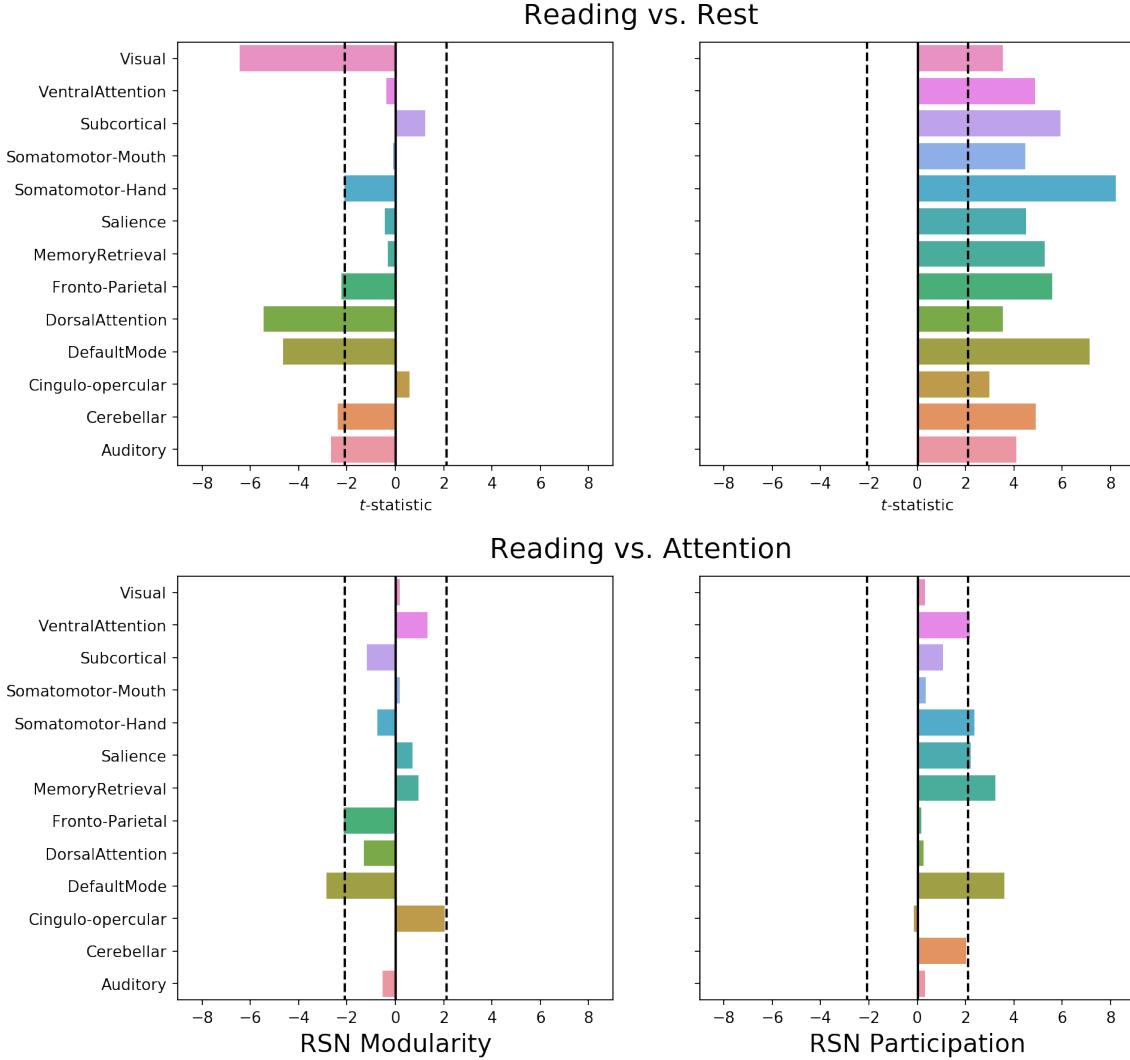


Figure 3.6: RSN-level trends in task-evoked networks. Changes to modularity were driven by the de-clustering of the visual, dorsal attention and default mode networks. For the participation coefficient, network-level trends in task-evoked differences to graph theory measures were largely related to global trends. There were many fewer significant changes in the “reading vs. symbols” contrast. Dashed lines represent uncorrected significance thresholds of $p < 0.05$.

are many more within-module connections in the sensory systems, dorsal attention and default mode networks. When reading, however, between-network connections increase across many between-network relationships and none within-network relationships. There is a modest breakdown of the modularity during reading, in which there is a global increase in integration across RSNs.

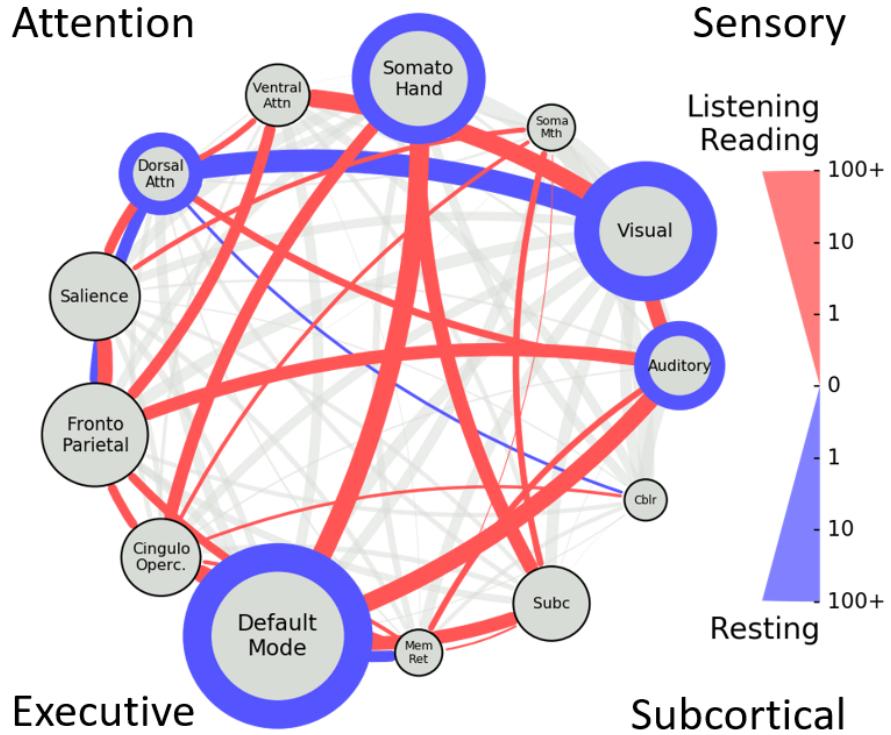


Figure 3.7: Rewiring diagram showing the changes in connectivity between networks during reading. During rest, there are many more within-module connections in the sensory systems, dorsal attention and default mode networks. During reading, however, between-network connections increase across many between-network relationships and none within-network relationships. That is, the brain becomes more integrated.

Decreases in modularity are coupled by increases in the participation of specific nodes. To address whether the areas that are activated during reading (in the traditional univariate sense) are also the areas driving integration, we correlated the two variables at the node level. Interestingly, we found that nodes that were more activated in reading tended to be those with lower participation coefficients ($r = -0.434, p < 0.001$). Nodes with high participation coefficients tended to be deactivated relative to rest, although a few of these hub-like areas were also activated. (This effect can be seen in Figure 3.8).

There were a few noteworthy hub areas that were active during reading. These areas spanned the left and right posterior temporal lobes, as well as the right inferior frontal gyrus. Nodes and their coordinates are listed in Table 3.2.

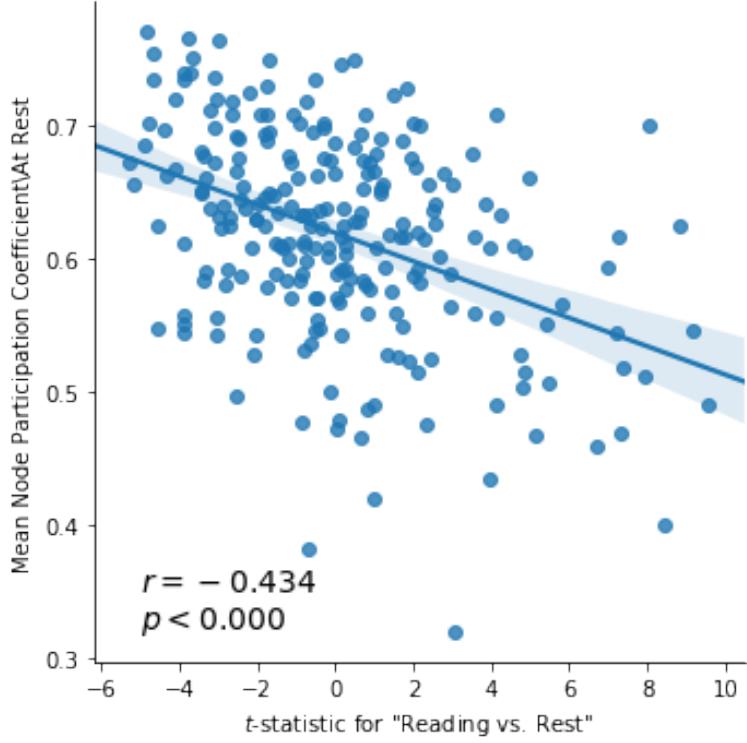


Figure 3.8: Univariate activity is anti-correlated with participation coefficients. Nodes with high participation coefficients tended to be deactivated relative to rest, although a few of these hub-like areas were also activated.

Finally, we sought to replicate our previous finding relating resting-state modularity with reading, and to determine whether this relationship would change in the task-evoked network. For the reading and rest task conditions, we regressed the global modularity against the TOWRE Total Word Efficiency standard score. We replicated the results of Study 1 using the shorter rest condition from our task ($r_{rest} = 0.432, p < 0.01$), and we also found that the relationship held in the reading condition ($r_{read} = 0.494, p < 0.01$) (Figure 3.9). There was no relationship between reading skill and the *change* in modularity between reading and rest, however.

3.4 Discussion

The primary purpose of the current study was to determine the ways in which task-evoked network architecture during reading differs from its baseline architecture, and whether

Brain region	MNI			PC	t_{read}	RSN
	X	Y	Z			
L superior temporal	-55	-39	13	0.680	3.527	Ventral attention
R superior temporal	51	-32	8	0.664	2.779	Ventral attention
R inferior frontal	52	32	0	0.655	2.412	Ventral attention
L inferior frontal	-46	10	23	0.633	4.233	Fronto-parietal
R middle temporal	51	-28	-4	0.565	5.831	Ventral attention

Table 3.2: Hub areas activated in reading. Five areas were both active during reading ($t_{read>rest} > 2.10$) and in the top 70th percentile or higher for participation coefficient (PC) at rest.

changes in modularity are good predictors of better reading skill. As expected, we found that reading activated areas throughout the brain, especially in the visual, ventral attention and default mode networks. Reading also increased measures of integration throughout the brain compared to rest and a simple visual task. This integration was primarily driven by the de-clustering of sensory, dorsal attention and default RSNs, and global increases to the participation coefficients. Interestingly, we also found that hub areas – those with the highest participation coefficients – tended to be deactivated. Finally, we found that the positive direction of the relationship between modularity and reading skill was unchanged at rest and in task.

One feature of the present connectomics approach is the disregard for laterality effects. There has traditionally been a major focus on laterality in reading and language (Martin et al., 2015). However, a systems-based approach aggregates across the RSN instead, providing a more comprehensive summary of the network’s performance, but also making it less sensitive to task effects in processes that are strongly lateralized. However, there is much to be gained by prioritizing systems of the brain over sides. First, these right hemisphere regions are homologues of important left hemisphere language areas, and complement major processing areas such as the temporoparietal junction and angular gyrus (Price, 2012; Jung-Beeman, 2005). Secondly, the domain-general functions subserved by attention, executive and default networks are thought to be more global and less lateralized, so

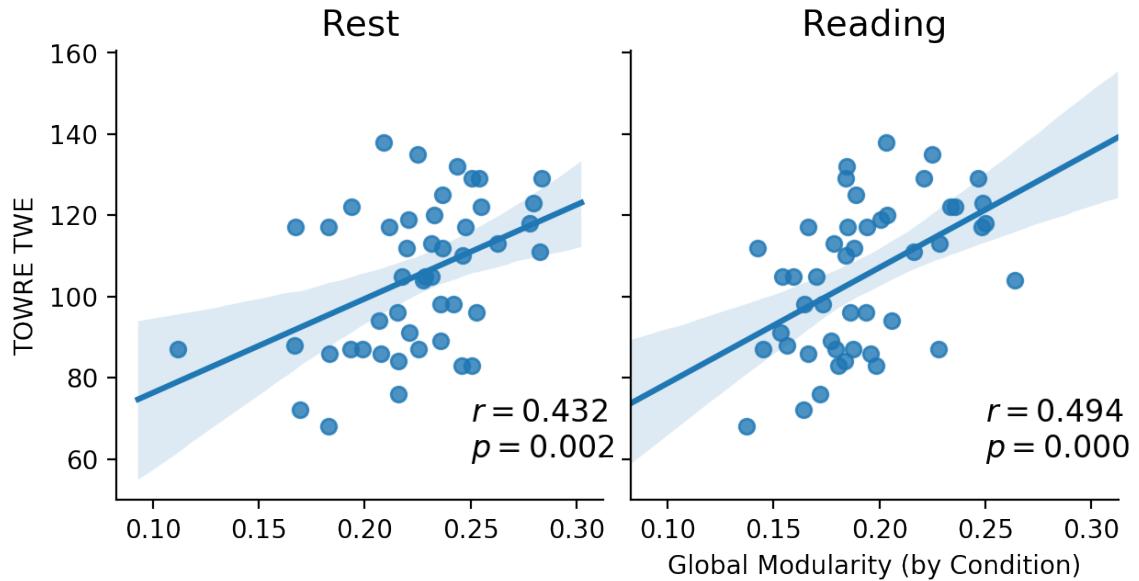


Figure 3.9: Higher modularity in reading is also related to reading skill. Although the global modularity significantly decreased for each subject, there was still a positive relationship between global modularity and reading skill.

the broader scope is more appropriate when treating reading holistically (with less focus on decoding or semantics, for example) (Yeo et al., 2011).

One insight gained in this study is that much of the “reading network” falls predominantly in visual, default and ventral attention networks. The heavy engagement of “un-classifiable” border nodes is also indicative of the integrative nature of reading. While the visual and default mode networks are commonly discussed in reading comprehension as the seats of decoding and semantic processing, respectively, the attention networks have received less attention. The ventral attention network, which was the most comprehensively activated RSN in reading, plays a key role in integrating information from the environment, and regulating top-down attention. It has a push-pull relationship with the dorsal attention and salience networks. This can be seen in Figure 3.4, where the VAN and DAN are activated in an opposing manner. This relationship is important for reading: the dorsal attention network encompasses the visual word form area, which was the only activated DAN node and an area that has been the subject of much interest and debate in reading

and dyslexia research (McCandliss and Noble, 2003). It is probable that this area is so important in reading not only because it is connected to language areas (Bouhali et al., 2014), but also because it is tightly tied to other areas that control goal-directed attention (Vogel et al., 2014). Vogel and colleagues found that reading ability in typical children and adults (including decoding and passage comprehension ability) predicted increased correlations between the visual word form area and the DAN (Vogel et al., 2012). The nesting of this orthographic-processing area within the attention systems is further evidence of how fundamental global systems of attention are to the reading process.

In terms of global network effects, we found that tasks reduced global measures of modularity and increased measures of between-RSN communication, including participation coefficient and path length. Relative to rest, this was most apparent in the visual RSN, which was characterized by a massive decrease in modularity compared to rest. These findings support a model in which the modular architecture of the brain is highly maintained between tasks, with global and some regional changes. It is not yet possible to say whether modularity within these specific RSNs correlates most highly with reading because of their functional roles in reading processes or whether they simply capture global trends better than other networks (because they are larger, for example). There is some reason to suspect specificity, however. In studies of remediation-induced changes to connectivity, increased connectivity within the visual network (Koyama et al., 2013) and cingulo-opercular network (Horowitz-Kraus et al., 2015b) have predicted reading improvement in dyslexic children.

Previous research has also noted that brain regions that have been found to be abnormal in dyslexia localize on high-hub regions (Bailey et al., 2018). Overall, however, we found that nodes with high participation coefficients tended not to be activated during reading. One explanation is that, in most cases, the nodes responsible for integrating information throughout the brain are not “taxed” in the same way that nodes performing specific computational processes are. The fronto-parietal network, for example, showed no RSN-level

changes in activity, although it is known to play an important role in task-switching and coordinating neural systems (Cole et al., 2013).

One implication of this finding is that it appears nodes of the hub network may work in two ways. The first is to play a network-level role in integrating information across the whole brain, facilitating the small-world architecture at a global level (van den Heuvel and Hulshoff Pol, 2010). The second role is a more active local-level role that is functionally specific, such as binding orthography to phonology in reading. The five hub-like regions identified in Table 3.2 are examples of areas that are typical hub regions when studied at rest but serve critical visual, semantic and procedural functions during reading comprehension (Price, 2012). These posterior temporal regions are also identified in meta-analyses of abnormal functional activity in reading disability (e.g. Maisog et al. (2008); Richlan et al. (2009). There could be potentially be two ties to reading disability, then: in one case, individual differences in global network architecture (observable at rest) leads to less efficient cognitive processing. This results in a garden-variety reading struggles, where the individual struggles to attend to and integrate sensory information rapidly into the system and struggles as a result, and which could also spill over into other cognitive domains such as attention (Paulesu et al., 2014). In the second case, there may be focal deficits in a specific process that give rise to reading struggles in children and adults which are caused by a gap in a specific learned skill such as phonological processing (Achal et al., 2016; Goswami, 2002).

Overall, the results suggest that the maintenance of an efficient network organization, i.e. one in which brain areas form clusters connected by hub regions, is important for skilled reading, even as between-network connectivity increases. To our knowledge, this is the first time the relationship between modularity and hubness to reading skill has been described during reading, adding to a foundation of work built on other connectivity methods. It also provides a replication of the resting-state findings described in Study 1. However, one limitation of the present approach is that effects were measured at a global level using

the a pre-defined RSN parcellation. While this allows for reproducibility and an interpretable RSN “rewiring” framework, it cannot capture or describe the presence of new communities (Power et al., 2011). Comparing the modularity or individual connections between conditions assumes a reference framework, but to what extent is *flexibility* in network connectivity important? Other analytical methods, such as investigating the number of shared connection between two connectomes may provide a more detailed insight into variability in task-evoked connectomes (Petersen and Sporns, 2015). In the next chapter, we will address this question of how individual networks reorganize across a wider variety of tasks.

CHAPTER 4

Network flexibility and consistency across tasks

4.1 Motivation

How does a modular architecture support cognitive flexibility? The results of Studies 1 and 2 suggest that a high degree of connectivity *within* RSNs leads to more efficient cognitive processes, even though communication *between* networks is critical for accomplishing specific tasks. As a biomarker, then, flexibility in functional networks across different tasks – at least those constructed using functional MRI – may not be related to efficiency of cognitive processing. Rather, better readers seem to have a shared and strong network “backbone” that is persistent throughout task reconfiguration.

The idea of similar activation between tasks reflecting a more efficient architecture is not novel. In fact, in the domain of language, it is a widely-held view is that reading and listening share the same core linguistic processes and differ primarily in the sensory transformations that feed into supra-model linguistic systems (Mattingly, 1971). Although the regions activated span the entire brain, it’s through a shared semantic processing core that language is abstracted from the domain of sensory experience into higher-level processes (Price, 2012). (see Figure 4.1 for a detailed mapping of these processes.) In this context, then, a high degree of similarity between task-evoked networks would likely indicate a system tuned for success in both listening and reading.

From a cognitive standpoint, reading and listening comprehension processes overlap a lot more than reading and resting or reading and a simple working memory task. An important extension of this similarity principle, then, is how much variability in network architecture is there between dissimilar tasks? Our results thus far suggest that – as in the case of listening and reading – more consistency between task states would mean that fewer “new” systems need to be used, leading to greater efficiency. How do we reconcile

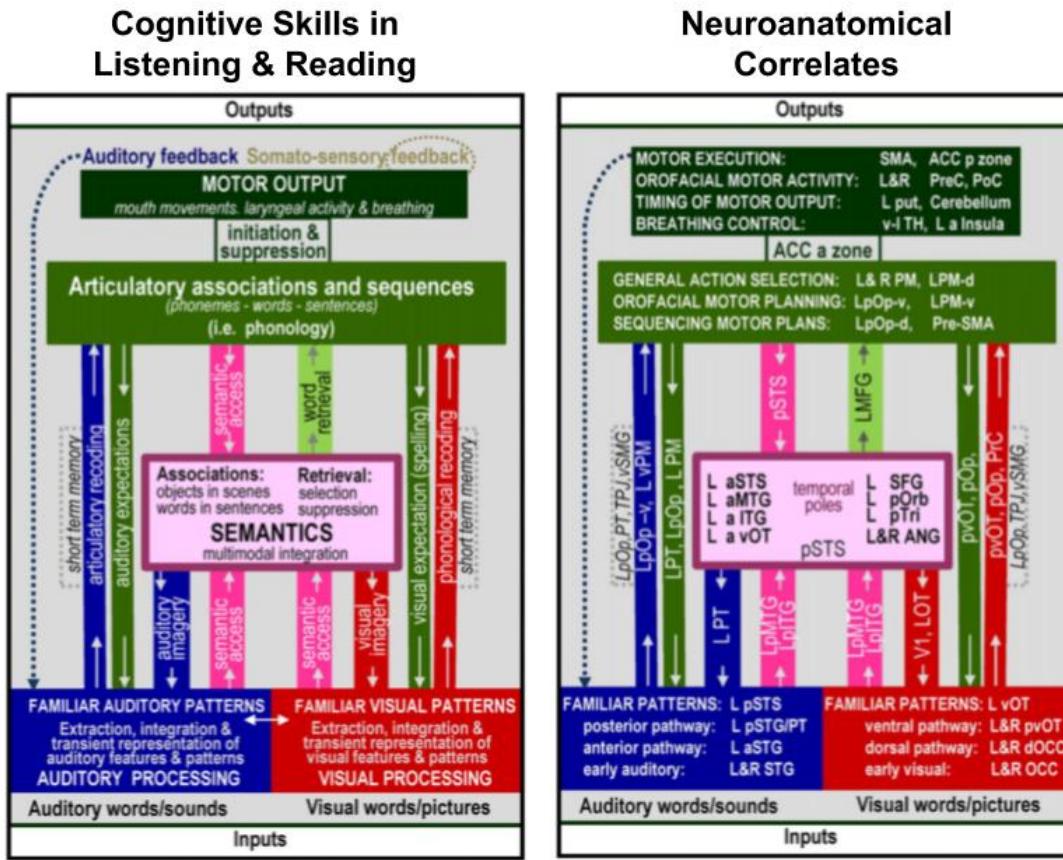


Figure 4.1: There exists a common core architecture for reading and listening. The models presented here contend that reading and listening share the same core processes, with the major differences being in the sensory processing functions. Figure adapted from (Price, 2012).

this with the diversity of activity patterns seen in thousands of fMRI studies? One potential answer may be the hub network that serves as a central role in integrating the whole-brain network.

In this third study, we seek to address two questions. First, do better readers have greater similarity between listening- and reading-evoked networks? Second, does this principle of a strong “network backbone” extend to other tasks, and if so, can we identify any network-level drivers of flexibility? To answer this, we expand our task scope and their analysis to include the auditory modality, and we also more closely examine network re-configuration of the sensory baseline tasks. Below, we review additional background on

relevant cognitive processes and network mechanisms.

The connectome in listening and reading comprehension

The *Simple View of Reading*, a widely-used and time-tested psychological model of reading, states that reading comprehension is the product of listening comprehension and decoding skills (Gough and Tunmer, 1986). This view has received support from large behavioral studies (Kirby and Savage, 2008) and neuroimaging investigations: many literacy-related changes are linked to visual or phonological systems, areas not directly related to semantic or comprehension processes (Schlaggar and McCandliss, 2007; Dehaene et al., 2015). These findings support a model in which inputs from auditory or visual domains are fed up into higher-order association areas that sequence, encode articulation plans, and extract semantic information (Price, 2012). These processes localize onto the similar areas regardless of language and writing system (Rueckl et al., 2015), and may even extend to inputs from somatosensory domains (Xu et al., 2005; Sood and Sereno, 2016). Neuroanatomical models of language, such as the one shown in Figure 4.1, illustrate that language is distributed throughout much of the brain with a high degree of overlap between listening and reading comprehension.

The supra-modal language core is largely left-lateralized and centers on the inferior frontal gyrus, anterior and posterior middle temporal gyrus and the angular gyrus. These areas are responsible for the construction of a mental representation that includes textual information and associated background knowledge, connected by some conscious and some unconscious executive processes (Kendeou et al., 2014). During comprehension, the relationship between areas is dynamic and the mental model of the text constantly being re-evaluated, and so attention and executive systems also play an important role (Spreng et al., 2013).

Despite the clear overlap between reading and listening, there is also evidence that the two skills are not directly equivalent. The pioneering researcher Alvin Liberman suggested

that reading is *parasitic* on listening: it requires the majority of the listening machinery, as well as an awareness of the linguistic act (Mattingly, 1971). There is also a subset of students who, despite adequate word decoding skills and vocabulary skills, struggle with reading comprehension (Pimperton and Nation, 2010; Spencer et al., 2014). From a neurobiological perspective, differences in core language systems are also observed: studies have found additional activation in left posterior temporal and parietal areas in reading (Constable et al., 2004), as well increased bi-laterality of activity in children (Berl et al., 2011). Altogether, there is substantial evidence that reading relies on existing speech comprehension circuitry, but that there may be meaningful differences even beyond sensory processing. A high degree of overall *convergence* in the evoked networks may therefore be an indicator of better reading, but certain key hubs or RSNs may play special roles in weaving the processes together.

The connectome across many tasks

If the brain preserves its modular architecture across tasks, how does it tie together the disparate processes that make each task unique? Strong candidates for this role are the brain's hub regions, which show flexibility across a number of tasks – not just listening and reading but other cognitive tasks as well (Cole et al., 2014).

The “flexible hub” theory asserts that a subset of regions in the brain are responsible for coordinating other brain systems in the accomplishment of internally-directed aims (Cole and Schneider, 2007). Hubs provide a way in which the brain might maintain its overall modular architecture while still increasing communication between regions. While there are a number of cognitive systems that may perform hub-like functions, including the salience, dorsal attention, ventral attention, and cingulo-opercular networks, several researchers have targeted the fronto-parietal network as a particularly important set of areas likely to perform hub-like functions (Cole et al., 2013; Niendam et al., 2012).

The fronto-parietal network is an assembly of brain regions encompassing the lateral

frontal and parietal cortices along with insular, anterior cingulate, and inferior temporal areas that have been broadly implicated in a variety of higher-level cognitive tasks (Fedorenko et al., 2013). One reason it has been targeted is that it encompasses the lateral prefrontal cortex, which has been seen to exert top-down control over other brain areas and which is often active in novel or difficult tasks (Duncan, 2010). Some have described the fronto-parietal network as supporting active and adaptive online control, initiating and adjusting goal-directed mental systems (Dosenbach et al., 2007), while others have proposed a more general superordinate role in directing cognition (Niendam et al., 2012). Furthermore, it has been found that variability in the connectivity of the fronto-parietal network is predictive of the severity of cognitive deficits in intelligence and symptoms of schizophrenia in a clinical population (Cole et al., 2011). Specifically, higher connectivity from the prefrontal cortex to areas outside of the fronto-parietal network was tied to worse psychiatric symptoms. Taken together, there is significant evidence for the importance of hub regions in supporting flexible cognition, and the fronto-parietal network may be particularly important.

Study aims

Overall, the aims of the present study were to determine to what extent flexibility across different tasks is predictive of individual differences in skilled reading and cognition. While global modularity can be an important metric that reflects network similarity – specifically, similarity to a pre-determined RSN partition – we here also employ a reference-free method for identifying similarity between networks. This will improve our ability to directly compare the architectures of listening and reading, and those between other tasks. First, we test *similarity* between listening and reading network architecture corresponds to higher reading skill. Second, we compare *similarity* between task-evoked networks across many conditions, and examine the variability at the level of individual RSNs. We specifically expect that attributes related to the fronto-parietal network will be important indicators of

Measure	Value
Subjects	42
Total scan runs	142
Mean age	10.54 (0.31)
Sex	21 M, 21 F
Test of Word Reading Efficiency	105.60 (17.16)
WASI Full-Scale IQ, Vocabulary	53.76 (8.20)

Table 4.1: Participant demographics for Study 3. Participants were a subset of those examined in Study 2, who had also completed a listening comprehension task with sufficiently high quality.

cognitive processing.

4.2 Methods

Participants

Participants were drawn from the same cohort of subjects included in Studies 1 and 2, and identical inclusion criteria for both demographic and scan motion were applied. However, additional measures related to the performance of the task were levied as described below. A total of 42 unique subjects and 142 scan sessions were included in the analysis. The demographics for these subjects are described in Table 4.1.

Functional MRI acquisition and processing

The task design for this study is described in detail in Chapter 3. Briefly, subjects were presented up to four separate runs of a language comprehension task. The task included two passage blocks (“reading” or “listening”), two sensory baseline blocks (“symbols” or “tones”) and a trailing resting-state block (“rest”). The four scan runs were crossed on two conditions: the modality of presentation (auditory or visual) and the genre of the passage (narrative or expository).

A scan session was excluded based on the following parameters: the number of high-motion volumes exceeding 20 percent, mean frame-wise displacement greater than 0.4, or

poor task performance ($D' < 2$). To control for the effects of genre, we matched all scans that met inclusion criteria with their opposing-modality counterpart, so that each subject had either 2 scans (same genre in listening and reading) or 4 scans (both genres in listening and reading). In total, 42 children (142 scans) met inclusion criteria.

Functional MRI acquisition and preprocessing procedures were equivalent to those described for Study 2. See the *Methods* section of Chapter 3 for a detailed description of these processes and their parameters.

Activation and network analyses

Our analysis was broken into two parts: first, comparing the similarities and differences in network organization for listening and reading, then across all available tasks.

For the modality comparisons, we used a fixed-effects subject-level model to estimate the shared activation for “listening and reading” and their differences “listening vs. reading”. We then used FSL’s *randomise* utility to estimate the main effects of modality across all subjects in our sample (5000 permutations, threshold-free cluster enhancement, $p < 0.05$). We also investigated these effects in “connectome space” by extracting the values at each of the 264 nodes used for connectivity analysis, then comparing the activity profile of each RSN during reading and listening.

Network similarity estimation

Global modularity estimates the similarity of a network to a reference partition, such that two networks with high modularity must be similar to the reference, but not necessarily to each other. This method, while useful, has the drawback of being biased towards the provided RSN parcellation: two networks could receive the same modularity score, but deviate in significant ways (i.e. both similar to partition but not to each other).

One similarity metric that is not biased towards a reference is the *intersection of the union* (IOU). To calculate the IOU of two binary matrices, one sums the total number of shared connections (intersection) and divides it by the total number of connections in

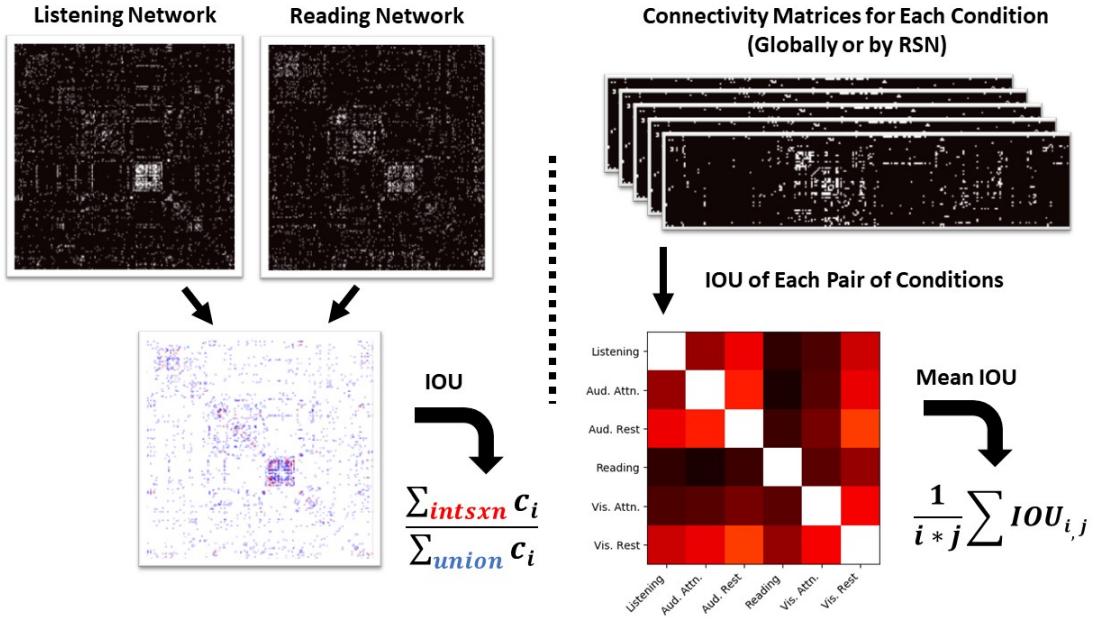


Figure 4.2: Schematic of methods for measuring similarity between whole-brain connectomes. The intersection of the union (IOU) can compare two connectivity arrays without reference to a pre-defined set of RSNs. On the left are methods for comparing listening to reading connectomes. On the right are methods for comparing, for each whole-brain network or RSN array, the similarity across all task and rest conditions.

either array (union), resulting in a value between 0 to 1, with 0 corresponding to no shared connections and 1 representing identical arrays. IOU provides two advantages compared to simply calculating the number of shared connections: it converts all comparisons to a common range, and it can compare arrays with different numbers of connections without being biased towards dense arrays (e.g. comparing an array with many connections to one with few connections). The IOU approach provides a complementary perspective to estimates of modularity.

We first compared the IOU of network arrays across individuals within the two linguistic conditions: listening to listening and reading to reading. We summarized the distributions of the IOU, with the expectation that there would be the most variability within the reading condition, since listening is more “natural”. Next, we tested whether the similarity between an individual’s reading and listening network arrays was related to reading skill.

Finally, we analyzed RSN-level patterns of similarity and difference between reading and listening.

Next, we broadened the scope of analysis to include comparisons between all task conditions: rest (x2), symbols, tones, listening and reading. For each subject, we calculated the IOU between each evoked network in all conditions. This resulted, for each subject, in 15 network comparison values, for each set of nodes examined. The question we were interested in was whether, within-subject, individuals who had fewer changes in network configuration were also better cognitive performers. We then sought to determine whether changes within a single RSN (e.g. the fronto-parietal network) were the key drivers of this.

4.3 Results

Behavioral results

In-scanner task performance measures were not related to modality of stimulus presentation. However, there was a trend towards difference in median FDRMS between scan modalities (paired t-test, $t = 1.904, p = 0.059$), so we also replicated analyses with a stricter motion threshold (no more than 10 percent outliers in a scan run). The main results from analysis of this 35 subject (116 scan runs) cohort were broadly consistent.

Activation results

As expected, reading and listening shared a common core of language-related activations. These included the bilateral middle temporal and inferior frontal gyri, as well as the anterior temporal poles. The differences related to modality fell into three categories: sensory processing areas, including the insula, superior temporal gyrus, and secondary visual processing areas; and hetero-modal association areas, most notably the inferior frontal gyrus and angular gyrus; and somato-motor regions, including the premotor cortex and lateral geniculate nucleus of the thalamus (Fig. 4.3). Areas showing greater activation in listening localized on primary auditory cortex and the dorsal attention network.

This result is more easily visualized when viewing it in terms of the 264 nodes of

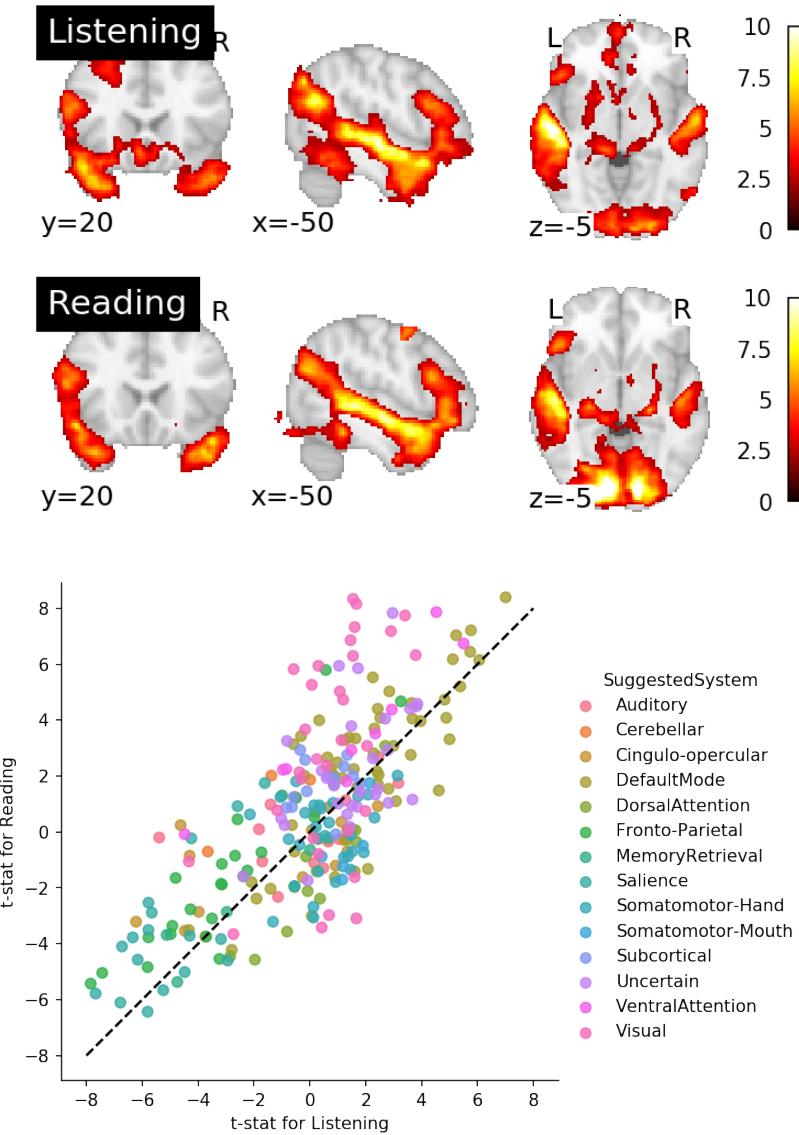


Figure 4.3: There was a large overlap in activation between the listening and reading comprehension tasks. Activation spanned a bilateral set of regions, especially around middle temporal, inferior frontal gyri. Activations shown for $p < 0.05$, threshold-free cluster enhancement (5000 permutations).

the connectome. There was a very high correlation coefficient between activation during reading and listening compared to the sensory baseline ($r = 0.748, p < 0.001$), reflecting the high degree of shared activity in the language network. Relative to rest, the variability was slightly higher ($r = 0.552, p < 0.001$), but still significant.

In general, areas that are active during listening are also active during reading, but

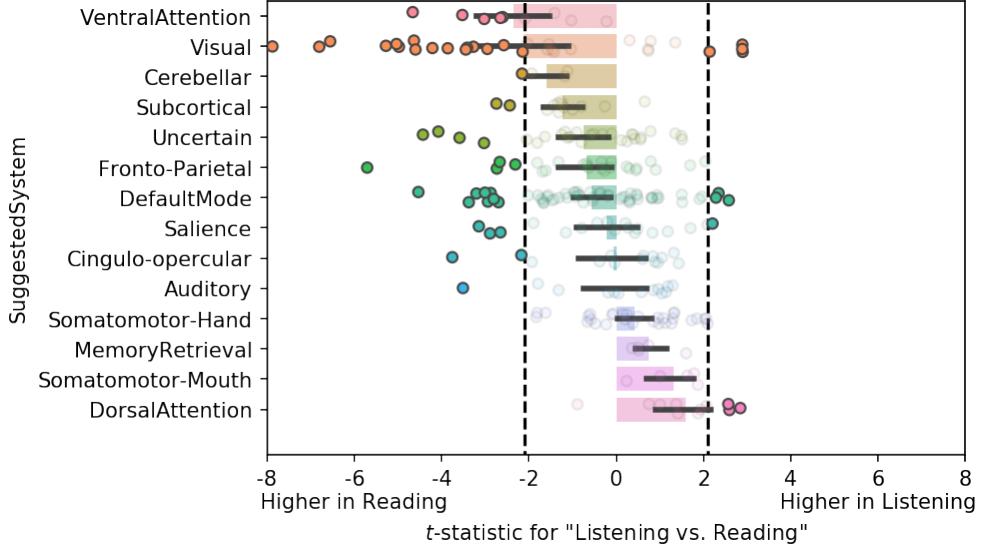


Figure 4.4: Activation differences due to modality of presentation among RSNs, when both tasks were compared to their sensory baseline. Each point represents a single node, while bars represent the aggregate mean for each RSN. Visual and ventral attention networks showed the most network-level activity in reading, although large portions of the default mode and fronto-parietal network were also robustly related. Cingulo-opercular, memory retrieval and salience networks showed decreases. Dashed lines represent $p < 0.05$, uncorrected.

there were differences in the intensity with which they were activated: many nodes were more strongly activated in reading compared to listening. Figure 4.4 displays these in connectome space. These fell predominantly into the ventral attention, visual, and default mode networks. Only a few areas were more active in listening than reading: areas in the dorsal attention network and a few in the default mode and salience networks.

Network results

In terms of graph theory measures, we found a significant decrease in global modularity ($t = 3.670, p < 0.001$) and a significant increase in participation coefficient ($t = -4.312, p < 0.001$) in reading compared to listening (top panel of Figure 4.5). Investigating the differences in path length between the two modalities provides a stronger sense of key drivers of this increased integration. The bottom panel of Figure 4.5 displays the node-level connections of nodes that get closer or further during the reorganization. The large

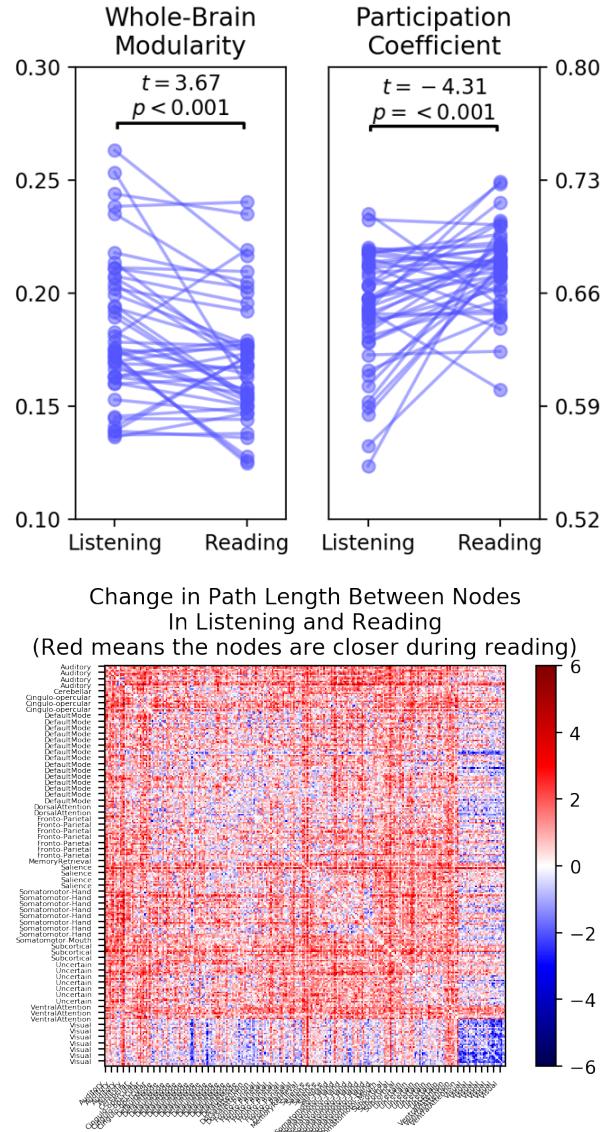


Figure 4.5: Reading induces a more integrated network architecture than listening. In terms of modularity and participation coefficient, there is greater integration during reading than listening. The bottom panel displays the changes to the number of steps connecting each node. The large amounts of red reflect the greater global integration seen in reading; the blue patches represent a reduction in modularity, especially within visual networks.

amounts of red reflect the greater global integration seen in reading. On the other side, the large blue patch showing a reduction in visual network connectivity is particularly salient.

Network similarity results

We next investigated whether there were individual differences in the task-evoked networks for listening and reading. For each pair of participants and modality of presentation, we calculated the IOU between their whole-brain networks (Fig. 4.2, left side). We found that listening-evoked networks had more overlap between subjects than reading-evoked networks ($t = 53.190$, $p < 0.001$). Additionally, we found a trend among subjects in which those with the highest mean similarity overall were also more similar to other high-similarity subjects. This suggests there is a common architecture that is approximated by each individual (see top panel of Figure 4.6).

As readers become more experienced, the expectation is that the task-evoked network architecture for reading would converge onto the listening comprehension system. To test this, we compared each subject's listening network with their reading network then correlated this measure with TOWRE scores (Fig. 4.7). Better readers had a higher degree of similarity between the listening and reading networks ($r = 0.408$, $p = 0.007$). Furthermore, we found that reading and listening networks *within* a subject were on average more similar than between subjects ($t = 26.123$, $p < 0.001$).

We next extended this question to encompass multiple task conditions and examined connectome variability at the level of individual RSNs. For each person, we created a similarity matrix describing the shared connections between each of these conditions. Then, we calculated the mean of the shared connections (Fig. 4.2, right side). Figure 4.8 shows the distribution of within-subject IOU values for each RSN. The global similarity was 0.364, meaning that within an individual subject, the evoked connectomes from the listening, reading, tone, symbol and resting conditions shared more than one third of connections on average. At the RSN-level, the highest similarities were among the visual, dorsal attention and memory retrieval conditions; the lowest were in the auditory, ventral attention, subcortical and somatomotor (mouth) regions.

We next correlated these measures with TOWRE scores. The mean within-subject IOU

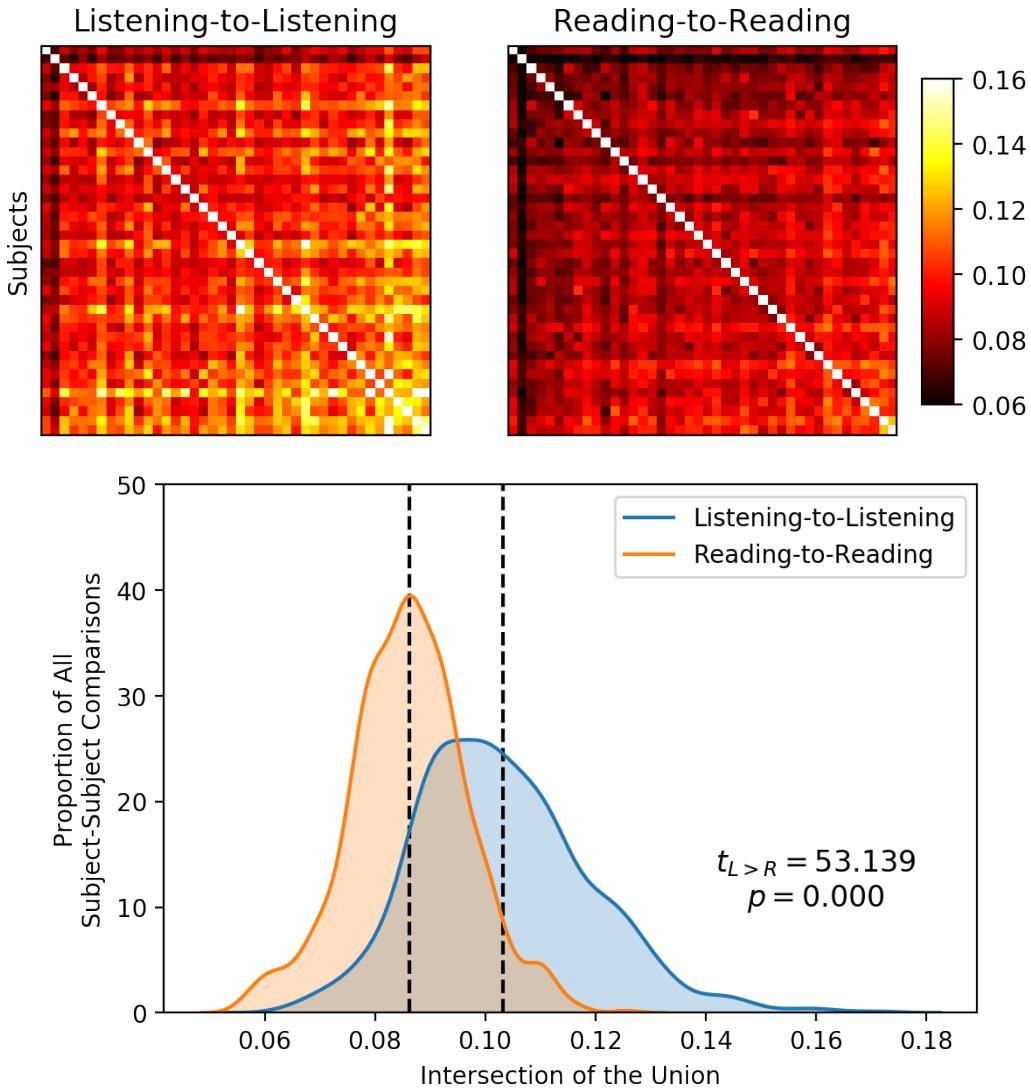


Figure 4.6: Distribution of subject similarity values in listening and reading. Top panel: each matrix represents the subject-to-subject similarity of task-evoked networks in the listening or reading conditions. Subjects with high mean similarity (brighter) also tended to be more similar to each other, suggesting they approximated a common network configuration. Bottom: When comparing the distributions of similarity scores, there is greater similarity between listening-evoked networks than reading-evoked ones. Dashed lines represent the mean subject-to-subject IOU for each condition.

for the entire connectome (264 nodes) was significantly correlated with the TOWRE Total Word Efficiency standard score ($r = 0.324$, $p = 0.033$). Individual RSNs generally followed this trend, although a few had higher correlations: the ventral attention ($r = 0.384$), fronto-parietal ($r = 0.370$), salience ($r = 0.352$) and default mode ($r = 0.346$) networks

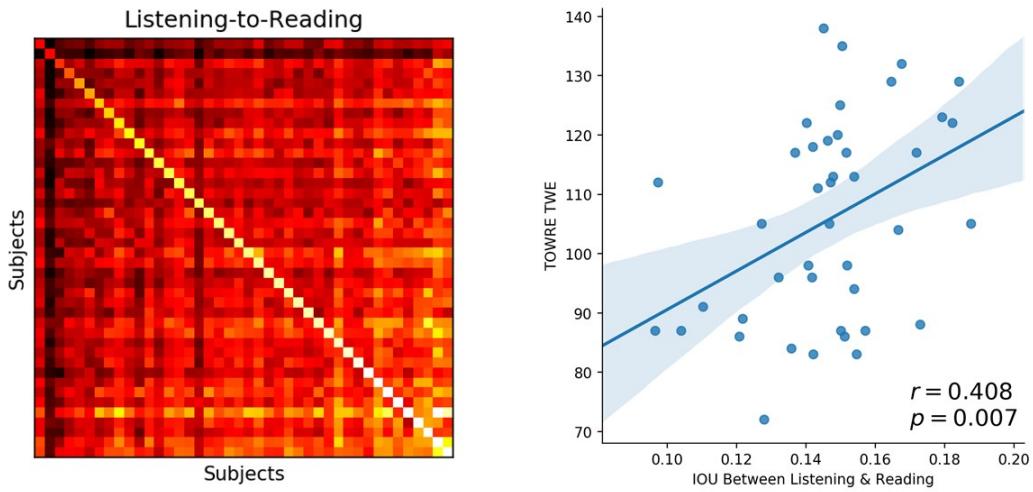


Figure 4.7: Network similarity between listening and reading predicts word efficiency. We compared the listening-evoked network to the reading-evoked networks within each subject and found that it, too, correlated with reading skill.

were slightly greater than the whole-brain IOU. To test whether this was specific to reading skill or more general, we performed the same correlation using the Vocabulary scores from the WASI intelligence test. We found an even stronger correlation between global similarity measures and vocabulary scores ($r = 0.481$, $p < 0.001$), with the trend continuing for the other RSNs.

4.4 Discussion

This study addressed two questions: how does task-evoked network architecture vary between two highly similar tasks, and how do individual differences in this variability relate to cognitive skills? We covered differences between reading and listening at the level of activation, global network measures and network similarity. At all levels, we found a high degree of similarity between listening and reading relative to the other conditions, but with reading eliciting more integration across RSNs and more variability between subjects. We found that the degree of similarity between listening and reading task-evoked networks

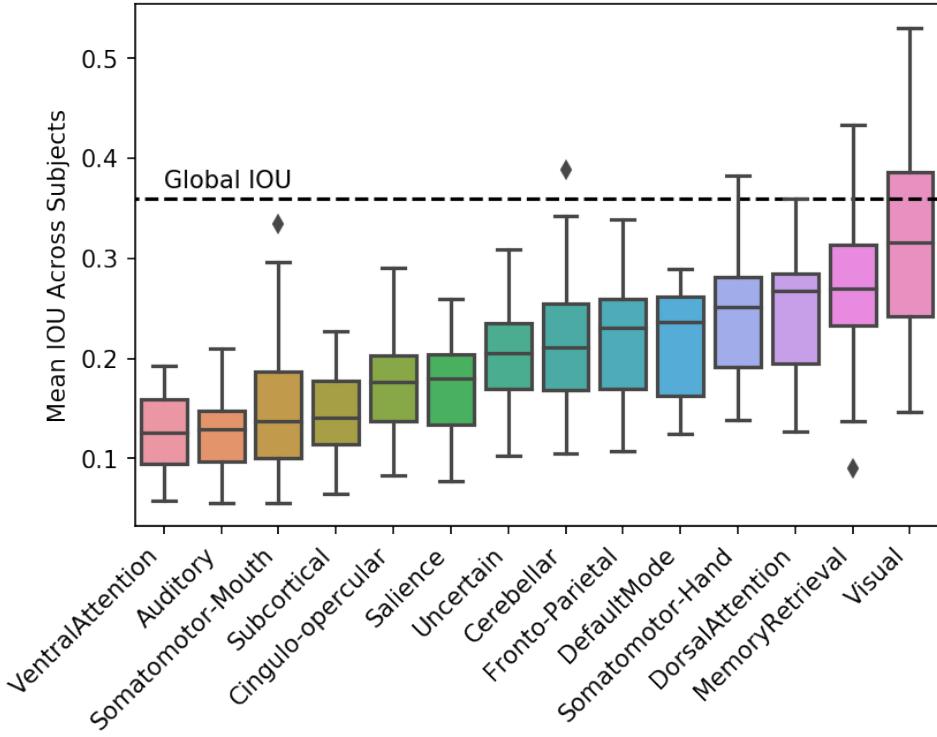


Figure 4.8: RSNs share a large degree of similarity. At the global level, the mean similarity among task-evoked networks was higher (0.362) than any individual RSN. Several of the language- and task-oriented RSNs had very low similarity (ventral attention, auditory, somatomotor).

was related to reading skill; the degree of similarity between all of the conditions, in fact, was related to reading skill. The results provide further support that variability in network architecture is not associated with increased cognitive performance. Rather, it seems to be the case that the “evoked” networks approximate a baseline architecture that is surprisingly stable across task demands.

Reading and listening elicited a similar activation profile with many overlapping areas. This is consistent with previous research and theoretical models suggesting that, after the act of word recognition, reading and listening share a common supramodal core set of processing areas (Rueckl et al., 2015; Hoover and Gough, 1990; Price, 2012). However, there were some important differences. The first was the finding of greater activity during reading along several shared language-related areas, including the temporo-parietal junc-

SET OF NODES	TOWRE - TWE		WASI VOCABULARY	
	Rank	r	Rank	r
Whole-Brain	–	0.324*	–	0.481**
Fronto-Parietal	2	0.370	2	0.498
<i>Sensory RSNs</i>				
Auditory	9	0.283	7	0.417
Somatomotor-Hand	14	0.119	12	0.285
Somatomotor-Mouth	6	0.322	9	0.402
Visual	7	0.316	5	0.456
<i>Attention RSNs</i>				
DorsalAttention	12	0.261	4	0.464
Salience	3	0.352	8	0.416
VentralAttention	1	0.384	6	0.453
<i>Associative RSNs</i>				
Cingulo-opercular	8	0.307	13	0.271
DefaultMode	4	0.346	1	0.509
MemoryRetrieval	10	0.277	3	0.469
<i>Other RSNs</i>				
Subcortical	5	0.327	11	0.325
Cerebellar	11	0.267	10	0.346
Uncertain	13	0.136	14	0.234

Table 4.2: Correlation values between shared connectivity and cognitive skills. Individual RSNs generally followed the global trend, with the exception of the unclassifiable and somatomotor (hand) RSNs. * = $p < 0.05$, unc.; ** = $p < 0.01$, unc.

tion and inferior frontal gyrus. The greater activation here likely represents more effortful processing: in developing readers, there is an elevated BOLD signal for reading compared to listening (Berl et al., 2011). This elevation is also true for individuals with dyslexia who will sometime exhibit greater activation in reading-related areas compared to typically developing children (Pugh et al., 2000).

The other meaningful difference is the deactivation of the dorsal attention network during reading, relative to listening. The dorsal attention network has a push-pull relationship with the ventral attention and salience networks. Because the ventral attention network is so heavily engaged during reading (viz. Chapter 3), it is likely that this reduction in DAN activity is a response to it. The DAN is closely connected to language areas including the

visual word form area (Bouhali et al., 2014), but also plays a major role in guiding top-down attention, and is closely related to other executive RSNs such as the fronto-parietal (Vogel et al., 2014). Vogel and colleagues found that reading ability in typical children and adults (including decoding and passage comprehension ability) predicted increased correlations between the visual word form area and the DAN (Vogel et al., 2012). That the deactivation of the DAN (and activation of the VAN) are present in a contrast of the two skills suggests that these attention processes are unique to reading and not general to language comprehension. To our knowledge, this is the first report of this.

Speech comprehension is “natural”, in the sense that most everyone learns to understand language regardless of their educational environment. The greater similarity values observed when comparing the listening-evoked networks across participants may reflect the more practiced nature of speech. On the other hand, the greater variability in the reading-evoked network might be indicative of the additional interactions necessary in reading: guided control of eye movements, visual processing, additional engagement of the attention systems (Mattingly, 1971; Rayner et al., 2006). There are also differences in what is encoded in speech and text. Speech contains overt clues about the speaker, such as tone and prosody, and these can convey additional non-linguistic meaning for the listener. Reading could be considered a more purely linguistic act. Reading may thus allow more room for self-generated situation models and more independent direction of thought.

As readers become more experienced, the expectation is that the task-evoked network architecture for reading would become more similar to that of the intrinsic listening comprehension system. It is thus expected that greater overlap between the two systems would be correlated with reading skill, as it was. Once again, each individual RSN was broadly representative of the global trend, but there were a few of particular note. Similarity of structure in the fronto-parietal and default mode networks were the only RSNs that outperformed the global IOU in both correlations with cognitive skills. It could be argued that these two represent the two core higher-order RSNs. High similarity in both implies

that they are anti-correlated, once again touching upon the segregation hypothesis. The two RSNs that had no correlation with either measure were the “uncertain” nodes – nodes whose connectivity profiles were too variable to assign to an RSN – and the somatomotor (hand) RSN, whose connectivity may have been strongly influenced by the tapping task throughout the scans.

The overarching result is that variability in task-evoked network architecture, whether it is between language tasks, simple sensory tasks or resting state, is anti-correlated with cognitive performance. Although alterations to the intrinsic organization are inevitable when performing a task, the degree of reorganization appears to be related to the task difficulty – or at least the extent of cognitive functions employed – with reading representing the most taxing model investigated by us. We have also seen that differences in the network architecture are robust within individuals: the correlations with reading have held across a number of different network measures. But how and when do they change? Does the relationship with reading hold true throughout the lifespan? We tackle these questions in the next chapter.

CHAPTER 5

Modular networks throughout development

5.1 Motivation

Childhood represents the ideal time window in which to study the relationship of brain network architecture on reading because of the rapid changes and growth. Over the first three studies, we found that whole-brain modularity was predictive of reading skill and conserved during reading comprehension but that there was an increase in integration among RSNs during reading. RSNs related to attention and internal thinking, including the dorsal attention, ventral attention and default mode networks were especially impacted. Reduced modularity was not unique to the reading process, however, and we found a high degree of similarity, on average, when comparing several different network structures within each individual – roughly one third of connections were conserved.

Despite the benefits of studying children, it is important to couch these findings in a developmental context: for example, does higher modularity and network consistency represent a more mature architecture, or is it tied to individual variability in organization? Although we are just beginning to understand how maturation changes the network architecture of the brain, there have been some consistent findings in the past several years. One of the earliest findings was that in children, short-range connections are strongest, whereas in adults, long-term connections increase in strength (Power et al., 2010; Chan et al., 2014). This is accompanied by decreases in functional network modularity and the coherence (fractional anisotropy) of white matter tracts, and in later life, decreases in the participation coefficients of hub areas (Betzel et al., 2014). It should be noted, however, that many of these lifespan studies have investigated the time period between early adulthood and senescence, with fewer studies having been done in childhood and adolescence (Cao et al., 2016).

One purported benefit of a modular brain architecture is “evolvability”: the capacity for a system to easily adapt to environmental circumstances because new modules can be added without drastically altering the other modules (Kashtan and Alon, 2005). Each one can work in parallel, sharing information when necessary, but without being too dependent on the success or failure of another system. This makes modularity not only efficient and robust to damage, but also capable of accommodating change over the lifespan. Cognition, too, has traditionally been considered to a large degree modular, with the pseudo-science of phrenology being the most extreme example, but more recent efforts coming from a deeper understanding of visual and sensory systems (Barrett and Kurzban, 2006). However, some higher-order cognitive functions such as working memory, attention and planning have not been localized to a discrete cortical area and are more likely to depend on a global workspace (Dehaene et al., 1998).

The degree of reorganization is likely to depend on the individual’s ability to respond to a given task. Although it is still an area of investigation, one group investigated how modularity changed over the course of learning a novel task. Bassett and colleagues scanned participants at four timepoints while they were learning a new finger-tapping task: before training, early in training, midway through training and at the end of training (Bassett et al., 2015). The authors empirically defined a visual and motor module, and investigated changes to it throughout training. They found two important trends: first, the two modules became increasingly segregated throughout training and practice; and second, the involvement of non-module nodes such as those in subcortical systems was reduced over time. A separate study found that that modules are more likely to re-organize at early stages in the training process (Bassett et al., 2010). Taken together, the findings suggest a model in which the early stages of training require a high degree of cross-module communication, whereas later stages rely on more automated, modular processes (i.e. efficient and segregated processing).

The cognitive processes in reading are also thought of in a modular sense: visual, au-

ditory, semantic and motor processes can each be taught or assessed separately. Phonics instruction focuses on letter-sound mapping, a process which engages both auditory and visual systems. Neuroimaging evidence from the past two decades suggest that this binding process localizes to specific areas, including the left temporo-parietal junction and visual word form area (Price, 2012). These areas have received a lot of focus because they serve as bottlenecks for reading efficiency which, if they have not been tuned properly, prevent fluent reading. However, there have also been efforts to characterize poor reading as a lower-level deficit in terms of more fundamental processes, including visuo-spatial attention (Vidyasagar and Pammer, 2010), cerebellar function (Pernet et al., 2009; Eckert et al., 2003), subcortical sensory processing (Stein and Walsh, 1997; Angelica and Fong, 2008), or some combination of these (Pernet et al., 2009). We suggest that global modularity in the context of reading skill is best interpreted as high efficiency in these more basic processes.

In this chapter, we seek to further develop our model of the relationship between network architecture and reading by investigating changes throughout development. We use task-based methods previously described (but with new stimuli) to attempt a replication of previous findings in a new cohort of subjects. We then explore the differences in network organization during reading comprehension. Finally, we use the reference-free methods of similarity described in Chapter 4 to investigate within- and between-subject flexibility of network architecture. The results will provide important context for our previous findings and help to flesh out a model of the advantages conferred to specific cognitive skills by the modular brain.

5.2 Methods

Participants

Participants in this study were drawn from several studies and age groups to represent a cross-section of the population at different points in development. They fell into three categories: a group of children (ages 8 to 10) were selected from the third wave of the

Measure	Group 1	Group 2	Group 3
Subjects	38	18	20
Total scan runs	118	64	72
Mean age	9.38 (0.31)	11.61 (1.33)	25.96 (4.49)
Sex	18 M, 20 F	5 M, 13 F	16 M, 4 F
WASI Full-Scale IQ, Vocabulary	55.37 (11.95)	55.89 (7.52)	—
Test of Word Reading Efficiency	109.95 (15.23)	101.33 (15.50)	—

Table 5.1: Participant demographics for Study 4. Participants were drawn from three samples: children from the third wave of the longitudinal study described in Studies 1 to 3; adolescents in a cross-sectional study of reading comprehension skill; and adult volunteers. Scan sessions followed the same task design as in Study 3 but stimuli were novel.

longitudinal study described in Study 1; a group of adolescents (ages 10 to 14) from a large, cross-sectional study on the cognitive components of reading; and a group of adults (ages 18 to 40), largely from a population of university research assistants and graduate students. In this final group, behavioral data was sparsely collected, so no analyses of reading-related skill are possible. Demographics for these subjects are described in Table 5.1.

Functional MRI acquisition and processing

The task design for this study is described in detail in Chapters 3 and 4. Briefly, subjects were presented up to four separate runs of a language comprehension task. The task included two passage blocks (“reading” or “listening”), two sensory baseline blocks (“symbols” or “tones”) and a trailing resting-state block (“rest”). The four scan runs were crossed on two conditions: the modality of presentation (auditory or visual) and the genre of the passage (narrative or expository). One difference, however, was that the contents of the passages presented to these participants differed from those previously described. While still balanced to a third-grade reading level using Coh-Metrix, the passages were novel.

Motion is a major confound in age-related connectivity analyses since, on average, children move much more during a given scan session than their older counterparts. To

combat this, we applied a stricter motion criteria for inclusion than previously: subjects needed to have no more than 10 percent outlier volumes across the entire scan. A total of 72 unique subjects and 256 scan sessions met this criteria.

Functional MRI acquisition and preprocessing procedures were equivalent to those described for Studies 2 and 3. See the *Methods* section of Chapter 3 for a detailed description of these processes and their parameters.

Network analyses

Analyses were broken into three parts. First, we sought to understand what effects development had on the modularity of the brain at rest and during reading. We assessed these changes by analyzing the task-evoked networks for each of our participants, and using the group (children, adolescents, adults) and task conditions (rest, symbols, reading) as the factors in a two-way ANOVA predicting network modularity. We then analyzed changes to connectivity strength at the connection- and RSN-level to summarize changes to reading-evoked activity across development. For these analyses, we created connectivity networks (thresholded to retain the top 5 percent of connections) for each subject's "reading" connectome, then we performed an independent two-sample *t*-test between younger readers (Group 1) and older readers (Groups 2 and 3) on each connection. For each RSN-RSN pair, we summed all connections that were significant at an uncorrected $p < 0.05$ to create a measure of net connectivity change between the two RSNs.

We also sought to replicate previous results showing a positive relationship between global modularity and reading. In particular, we sought to determine whether this relationship changed over time (for example, flattening out in older readers). For this study, we used the average modularity during the resting condition of the task. (Data could be drawn from either 2 or 4 sessions, or approximately 8 - 16 minutes of resting-state signal). The adult group had an inconsistent amount of data available, so this regression analysis was only able to be performed across Groups 1 and 2.

Finally, we built upon Study 3 by investigating how network similarity changes throughout development. We had two questions: first, whether between-subject similarity increases over time, and second, whether the mature network is more “flexible” and reorganizes itself to a greater degree during different tasks than younger individuals. To accomplish these two objectives, we calculated the intersection of the union for each subject’s reading-evoked network with each of their peers (Group 1 to Group 1, etc.). (We also did this for their resting-state network.) We then averaged this IOU metric and performed a *t*-test between the younger and older participants. To study within-subject variability, we followed the methods described in Chapter 4: for each of the six conditions that each subject (reading, listening, symbols, tones and rest in each modality), we calculated the pairwise similarity matrix, then averaged it. Higher mean values indicate a higher level of similarity between each evoked state. We then performed a *t*-test between younger and older subjects.

5.3 Results

In total, 76 subjects (254 scan runs) were analyzed. Despite our stricter criteria, motion does represent a potentially confounding variable for between-group comparisons, as there was significantly less motion in Group 3 (adults). As discussed in Study 1, however, we have attempted to address these differences through preprocessing techniques.

We first tested the effects of task condition and age on estimates of modularity on the reading comprehension task. We set up a two-way ANOVA with the three groups (young readers, adolescents, adults) as one factor and the three experimental conditions (rest, symbols, reading) as the other factor. Figure 5.1 displays the distribution of these data.

We found significant main effects for both group ($F = 11.376, p < 0.001$) and condition ($F = 60.4, p < 0.001$), but not their interaction ($F = 0.470, p = 0.758$). We then conducted post-hoc *t*-tests on the comparisons within each factor. With regard to group effects, adults had a lower modularity than the younger participants, but Groups 1 and 2 were not significant different. For experimental conditions, resting state had a higher global

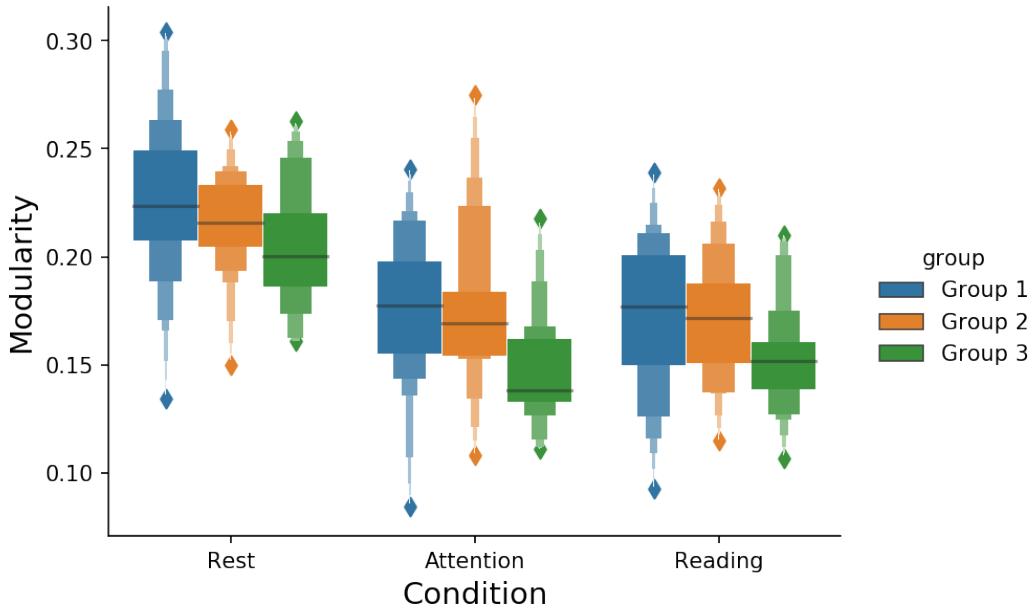


Figure 5.1: Adults have lower modularity but undergo the same task effects as younger readers. For the group factor, adults ('Group 3') had a lower modularity than the younger participants, but Groups 1 and 2 were not significant different. For experimental conditions, resting state had a higher modularity than both task conditions, which did not differ significantly.

modularity than both task conditions, which did not differ significantly. See Table 5.2 for complete results.

Next, we turned to individual differences in RSN connectivity to understand drivers of decreased modularity. We first examined changes at the connection-level by comparing the strength (i.e. correlation) between the younger and older groups. We noted two spatial trends: there is greater connectivity strength in posterior areas in the younger group, whereas the older group shows greater connectivity between anterior and bilateral areas. See Figure 5.2 for a diagram of these connections.

To summarize this at the RSN level, we grouped each significant connection by its originating and target RSN, then summed up the number of connections changed. The net results of this aggregated connectivity map are shown in Figure 5.3. This map reveals a few important trends: when children read, there is high connectivity within and between

Variable	SSq	df	F- / t-statistic	p-value
Two-WAY ANOVA				
Group	0.023	2	11.374	< 0.001
Condition	0.126	2	60.402	< 0.001
Group:Conditions	0.001	4	0.469	0.758
Residual	0.229	219		
POST-HOC <i>t</i>-TESTS				
<i>Conditions</i>				
Rest vs. Attention			13.341	< 0.001
Rest vs. Reading			14.279	< 0.001
Attention vs. Reading			0.437	0.663
<i>Groups</i>				
Group 1 vs. Group 2			0.604	0.546
Group 1 vs. Group 3			3.733	< 0.001
Group 2 vs. Group 3			2.869	0.005

Table 5.2: Two-way ANOVA table for the main effects of condition and group on modularity. Below are results for post-hoc *t*-tests conducted within each factor.

the dorsal attention, visual, somatomotor and executive networks. In older readers, the concentration of connections shifts towards higher-order areas such as the default mode and salience network, as well as the auditory and ventral attention areas. In the context of our previous findings, it would seem that mature readers have a reduced modularity due to decreased within-network connectivity of visual, somatomotor and dorsal attention networks.

We then attempted to replicate our findings that higher global modularity at rest was associated with higher reading skill. We were unable to test the relationship in the oldest readers (ages 15 and older), but did have access to TOWRE scores from participants in Group 2. When all subjects were included in the analysis ($n = 56$), there was a positive correlation that trended toward significance but did not quite reach it ($r = 0.256$, $p = 0.057$). When analyzed separately, we found that the correlation was higher in younger readers ($r = 0.280$, $p = 0.089$) than older readers ($r = 0.198$, $p = 0.432$).

We noticed that some of the poorest readers had more variability in their modularity

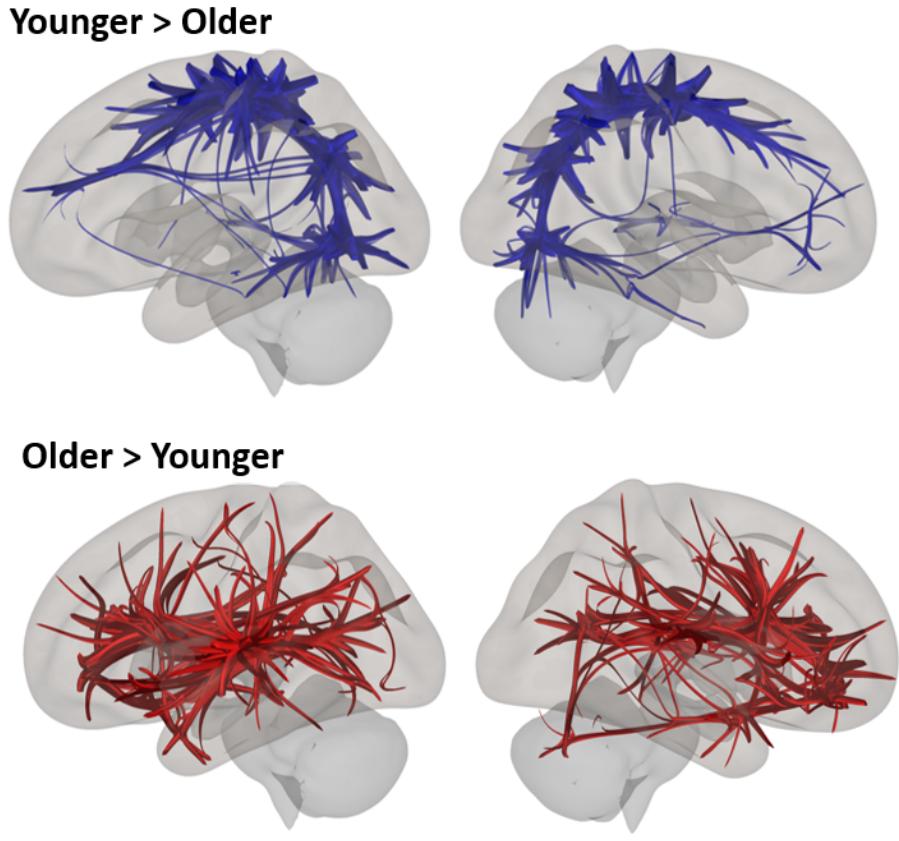


Figure 5.2: Connection-level changes to the reading network. Connections that showed significant differences between older and younger readers. Dorsal and posterior connections had higher connectivity strength in younger readers than anterior and bilateral connections. Connections shown here are significant at $p < 0.05$, FDR-corrected.

values. We re-ran the correlations excluding the 4 readers with standard scores of 85 or less (one standard deviation below average, or the bottom 16 percent). This adjustment made the correlation across the entire group ($r = 0.404$, $p = 0.003$) and the younger group ($r = 0.459$, $p = 0.006$). Although the correlation increased for the adolescent group, it did not reach significance either ($r = 0.292$, $p = 0.273$).

Finally, we investigated how subject “flexibility” differed across age groups. We first compared the degree of subject similarity between “developing readers” (Group 1) and “mature readers” (Groups 2 and 3) during reading and rest. Consistent with our findings of decreased modularity, we found that older participants had, on average, lower similarity to their peers than children did. This was true both during language comprehension ($t =$

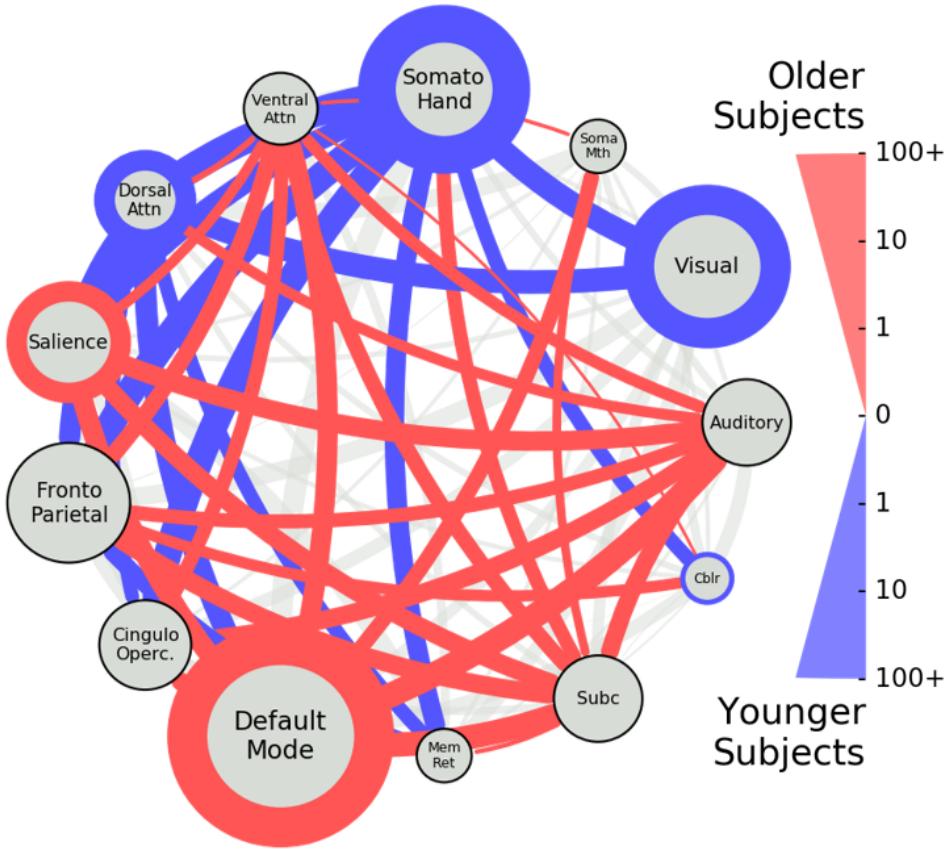


Figure 5.3: Developmental shifts in connectivity strength. When children read, there is greater connectivity within and between the dorsal attention, visual, somatomotor and executive networks. In older readers, the concentration of connectivity shifts towards ventral attention, salience and the default mode networks.

$13.829, p < 0.001$) and at rest ($t = 9.087, p < 0.001$). Figure 5.5 provides an example of this effect for the reading-evoked network.

Despite the findings of decreased modularity, we found no evidence that the within-subject IOU across conditions changed ($t = 0.239, p = 0.811$). This was also true of the comparison of the listening-evoked to reading-evoked networks, which were previously found to be correlated with reading skill. This level of similarity was consistent across all age groups and had a mean of 0.345 (standard deviation of 0.047), replicating the results from Chapter 4 (mean similarity of 0.364).

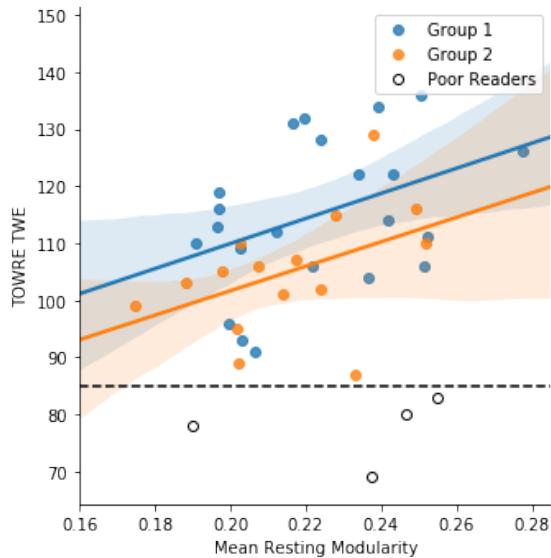


Figure 5.4: Modularity is related to reading skill in younger readers. Although including all developing readers resulted in a significant correlation, and both Groups 1 and 2 had positive correlations with reading skill, the relationships only reached significance in Group 1 when analyzed separately. It is also possible that this relationship is different in very poor readers (e.g. bottom 16 percent, as shown here).

5.4 Discussion

In this study, we sought to better understand how the maturation of the human brain affects functional network architecture and its reorganization during tasks. We build on our previous work showing that the modular organization of the brain decreases slightly throughout the lifespan but is similarly disrupted during tasks, no matter the age or expertise of the individual. We identified developmental shifts in network connectivity which show that an emphasis on sensorimotor and dorsal attention systems gives way to connectivity between default mode, auditory, ventral attention and salience systems. While the within-individual variation of task-evoked and resting-state architecture remained consistently high in mature participants, adult networks showed a greater amount of variability than in children. The results bolster the hypothesis that modularity is an adaptive trait which allows for growth and the support of cognitive functioning throughout the lifespan.

Although the global differences between reading and rest remained the same throughout

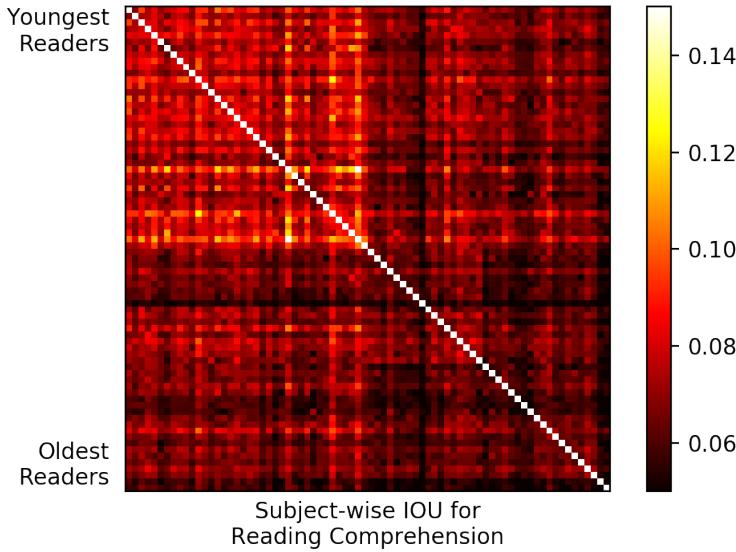


Figure 5.5: Older subjects show less similarity between in reading-evoked networks. Network similarity decreased in the older group, even as within-subject similarity stayed the same. This suggests that, while older subjects largely retain the modular architecture from early in life, they also develop a more individualized connectome.

development, there were major changes in the manner with which they reorganized. The adult connectivity network had fewer connections in visual, dorsal attention and somato-motor areas. This is consistent with previous findings of decreased modularity of visual, dorsal attention and control regions in later life (Betzel et al., 2014). One interpretation is that children were more sensory-laden: they used their top-down attention systems to focus more on the mechanics of reading. Adults, on the other hand, had a more anterior and bilateral network. The significant increases of connectivity within the default mode network certainly support the hypothesis that adults had richer internal mental activity during the stories (Spreng et al., 2013). That is, they may have been better able to focus on the content and integrate it with more of their personal experiences and background knowledge. We also note in particular the differences in connectivity between the dorsal attention and ventral attention networks. In Study 2, we saw that the ventral attention network is a critical reading-related RSN, and in adults we observe that it is connecting out to a number of higher-order processing areas. This supports the idea that adults have automated much

of the lower-level visual processing of reading such that the ventral attention network can feed it up to other systems (Twomey et al., 2011).

Some models of network development suggest that children have intact network architectures from early on in life and RSNs with long-range connections, such as those in the fronto-parietal and cingulo-opercular, strengthen later in life (Uddin, 2010; Cao et al., 2016). Our findings are compatible with such a model but extend it in two ways. First, the finding of greater modularity in children also means that younger subjects were more similar to the reference partition from Power and colleagues (Power et al., 2011). This reference partition is the result of finding a consensus parcellation across nearly 100 subjects, suggesting that children more closely resemble the “average” brain network than adults. Second, adults shared fewer similarities to other adults than children did to other children, but showed strong consistency within themselves. In effect, their within-person modularity was just as high as it was in children.

It thus appears that humans start life with an archetypal architecture and “tweak” it as they learn and grow. In fact, this is the evolutionary advantage of modularity: a system can easily adapt to its environmental circumstances because new modules can be added without drastically altering the other modules (Kashtan and Alon, 2005). Individuals can add new skills, such as recognizing a new alphabet, or rewire portions of cortex to perform new functions, as in stroke recovery, without having to re-build the system from the ground up. Indeed, this is what happens in the case of literacy: locations predisposed to be useful for connecting areas (e.g. fusiform gyrus) are recycled for more specific uses (Saygin et al., 2016). It’s likely that this process occurs consistently throughout development and even in less “revolutionary” skills than reading, as John Steinbeck puts it. This process of continual editing and adding results in a more individualized architecture in adulthood, even though the template remains the same.

Although this study boasts several major features, including the replication of previous results, multiple cross-sectional age groups and a large number of analyzed scans (254

scans totalling nearly 30 hours of scan time), there are a few limitations. First of all, the passages were balanced to a third grade reading level, meaning that the younger groups may have found them challenging while the older groups found them very easy. While this is likely, we do not believe this unduly influences the results. The passages were presented at a pace that was slow enough for the young readers to follow along without difficulty, and they were also presented phrase-by-phrase so that older readers would still have to engage with the text for the same amount of time and retain a mental model over the same period. More pernicious may be the differences in scan motion between the two groups. However, we have included a narrower portion of the young population and also performed several layers of preprocessing to account for these effects.

We were able to replicate our findings that higher global modularity is correlated with better reading skill, with two new findings. First, the strength of the connection seems to decrease as children get older and reach adolescence. This might reflect the individuation of their architecture, as discussed above, or it could be that the effects of experience begin to trump an intrinsic biological disposition. The relationship was greatly strengthened in the younger group when we excluded very poor readers from analysis. One possibility is that individuals who struggle may have focal differences, such as in phonological processing, that are not reflected in the global architecture. We interpret a highly modular brain as one with many very efficiently organized sub-systems. One potential intersection this model has with reading is that this may reflect the importance of the “building blocks” of reading. Rather than reading (and reading difficulty) being defined by the activity of a few important areas (for example, the occipito-temporal cortex, temporo-parietal junction, inferior frontal gyrus), the integrative process relies on finely tuned RSNs. These may correspond with cognitive skills such as visual attention and phonological awareness. Any inefficiencies in these basic skills will cascade into problems integrating into the larger network.

CHAPTER 6

Review and summary

The human brain is a remarkable and complex organ. Its small-world organization of the brain is an apparent paradox: to more efficiently integrate cognitive processes, it has to segregate their neural substrates into spatially and functionally distinct modules. Reading, a skill that combines almost every cognitive process humans have, is one of the brain's most remarkable capabilities and a prime example of the brain coordinating activity among distributed systems. Throughout this dissertation, we have investigated the influence of these organizational principles on individual differences in the ability to efficiently integrate brain systems during reading. We combined inferences from several different methodological approaches, including behavioral testing, resting-state network analysis, task-based activation analyses, and the combination of the two. We believe these results represent a contribution to the fields of macro-scale human connectomics, as well to those studying reading and its disabilities.

Over the course of the first three studies, we analyzed the network architecture of fourth grade readers under a variety of conditions. Using resting-state networks, we established a set of connectome-forming methods and descriptive metrics including modularity, participation coefficient and path length. We then compared individual differences in these attributes to reading skill, finding that better readers had greater global network modularity but reduced modularity in the auditory and cingulo-opercular RSNs. This suggests that this segregated network architecture is important for functioning but that literacy acquisition may impact the composition of specific networks.

We then sought to describe how network architecture changes *during* reading, and whether task-evoked networks had a different relationship to reading skill than those at rest. In Study 2, we observed that reading comprehension decreased global modularity,

especially in the visual, dorsal attention and default mode networks. Overall, it increased measures of integration between a wide-variety of RSNs, including sensory and attention systems. Furthermore, the positive relationship between reading skill and global modularity persisted during comprehension, suggesting that the maintenance of each module across tasks is an important attribute of an efficient connectome.

Does that mean that *more* similarity between task-evoked network architectures is indicative of a more efficient organization? If so, do some RSNs become more similar and other nodes less so? To answer these questions, Study 3 compared two related but different processes - reading and listening. We found that there was a common core of areas activated in the two network states, as well as a common network backbone. In fact, better readers had a greater degree of similarity between the two language conditions, suggesting that the two networks merge in more skilled readers. We then calculated network flexibility across many different architectures, including simple attention tasks and rest, and we found that the listening-to-reading similarity was not unique to language, but inherent to the individual: participants were generally more similar to themselves in different tasks than to others in the same task.

Finally, we investigated the effects of development on modularity and network organization. In Study 4, we replicated previous findings of a relationship between modularity and reading skill in younger readers using novel stimuli and a larger group size. We found that the modular organization of the brain – as determined by using a group average reference parcellation – decreases slightly throughout the lifespan but is similarly disrupted during tasks, no matter the age or expertise of the individual. We also identified developmental shifts in network connectivity which show that an emphasis on sensorimotor and dorsal attention systems gives way to connectivity between default mode, auditory, ventral attention and salience systems. Adults also showed greater differences between each other than children did, although their within-subject “flexibility” did not change.

Taken as a whole, the studies underscore the importance of functional network archi-

Figure Key Finding

STUDY 1

- 2.5 Global modularity was the graph theory measurement most predictive of reading skill.
- 2.6 Modularity in the auditory and cingulo-opercular networks was anti-correlated with reading skill.

STUDY 2

- 3.4 Reading comprehension induces system-level increases in the ventral attention, visual, somatomotor (mouth) and default mode networks.
- 3.7 Reading is especially characterized by decreased connectivity *within* sensory, dorsal attention and default mode and increased connectivity *between* many different RSNs.
- 3.9 The positive relationship between network modularity and reading persists during reading comprehension.

STUDY 3

- 4.5 Reading comprehension requires more integration across networks than listening.
- 4.7 Better readers have greater similarity between their listening and reading networks.
- 4.8 There is a relatively high level of mean similarity between network configurations across many tasks.

STUDY 4

- 5.1 Modularity decreases with age but exhibits similar task-evoked changes in all groups.
 - 5.4 Global modularity predicts reading skill in young readers better than adolescent ones.
 - 5.5 Adults showed less connectome similarity with their peers than children, although within-subject similarity remained the same.
-

Table 6.1: Key findings in Studies 1 through 4.

tecture in cognitive processing, as well as its stability over time and cognitive states. The results support a neurocognitive model in which efficiently segregated processes serve as a scaffolding for their integration during complex functions, and over time, the development of new connections and displacement of others individuates each person's connectome. The studies illustrate how a connectomics approach to reading illuminates – not displaces – previous neuroimaging research, much of which focused on localizing specific cognitive

processes. We made every attempt to be systematic in our methodology, and believe we have made a meaningful contribution to our understanding of brain modularity as it relates to cognitive processing. However, there is much left to be investigated, and many possible future directions for these research aims. Below, we outline a few of these.

6.1 The importance of attention in reading

One of the consistent findings across our studies was the engagement and disengagement of attention networks in reading. The ventral attention network was the RSN most engaged by reading in Study 2, and the dorsal attention network was one of the only RSNs to show lower activation in reading than in listening (Study 3). Furthermore, adults had greater connectivity between the ventral attention network and many other networks, whereas children had higher modularity with the dorsal attention network and higher connectivity between it and visual and somatosensory systems. Although it's widely recognized that reading relies heavily on attention (e.g. Vogel et al. (2012); Vidyasagar and Pammer (2010); Clifton et al. (2016)), it may warrant an even closer relationship to language processes than it currently bears. Popular models such as the Simple View of Reading, for example, don't account for attention explicitly, instead modeling reading ability as the product of word recognition and oral language comprehension (Gough and Tunmer, 1986).

One of the major benefits of prioritizing the attentional aspects of reading, as opposed to its visual or linguistic aspects, is the potential for identifying similarities across multiple cognitive processes. As we have seen, from a network standpoint, the reading-evoked network is less unique than might be expected. Apart from a few remarkable regions (the visual word form area, temporo-parietal junction), a great degree of the reading process appears to be the orchestration of pre-existing and highly efficient sensory processes, and attentional networks are key to this orchestration: they will help identify salient words in a large block of text, suppress environmental distractions and maintain focus for extended periods of time (Fedorenko and Thompson-Schill, 2014). Slow or inadequately

rapid attention-shifting could undermine fluent reading by causing temporal-spatial misalignment in processing, e.g. letter sequence and arrangement (Lallier et al., 2009). Attention issues such as these could affect performance in other cognitive domains such as specific language impairment and attention deficit / hyperactivity disorder, which are often comorbid with reading disorders (Pennington, 2006; Margari et al., 2013). One question ripe for investigation is how the push-pull relationship between the dorsal and ventral attention networks proceeds during reading, and whether it varies at different points during the comprehension process. New methods for modelling this dynamic relationship are described below.

6.2 Dynamic modeling of network activity

Brain networks are not static, even though they are often modelled as such. Connectivity patterns are constantly shifting, and changes in the configuration of networks across time (so-called dynamic connectivity) have become an increasingly important domain of research in the past several years. Work using sliding time windows have illustrated that during rest modules alternate between time periods of higher and lower levels of integration (e.g. global efficiency) over time (Zalesky et al., 2014). These changes are periodic and can be consistent throughout different parts of the brain (Handwerker et al., 2012). (See Figure 6.1 for an example.) Modelling this variability across subjects can be a challenge, since subjects states tend not to be locked in time with each other outside of tasks; however, many advances have been had by using wavelets and other techniques (Zalesky et al., 2014).

Answering this question is crucial to understanding our findings of high modularity in better readers. The networks we examined in these studies were averaged over a relatively long time period – the course of a few minutes. In that time, there could have been many transitions between low- and high-modularity states. The frequencies at which the brain cycles through these states could be driving the “average” global modularity observed in

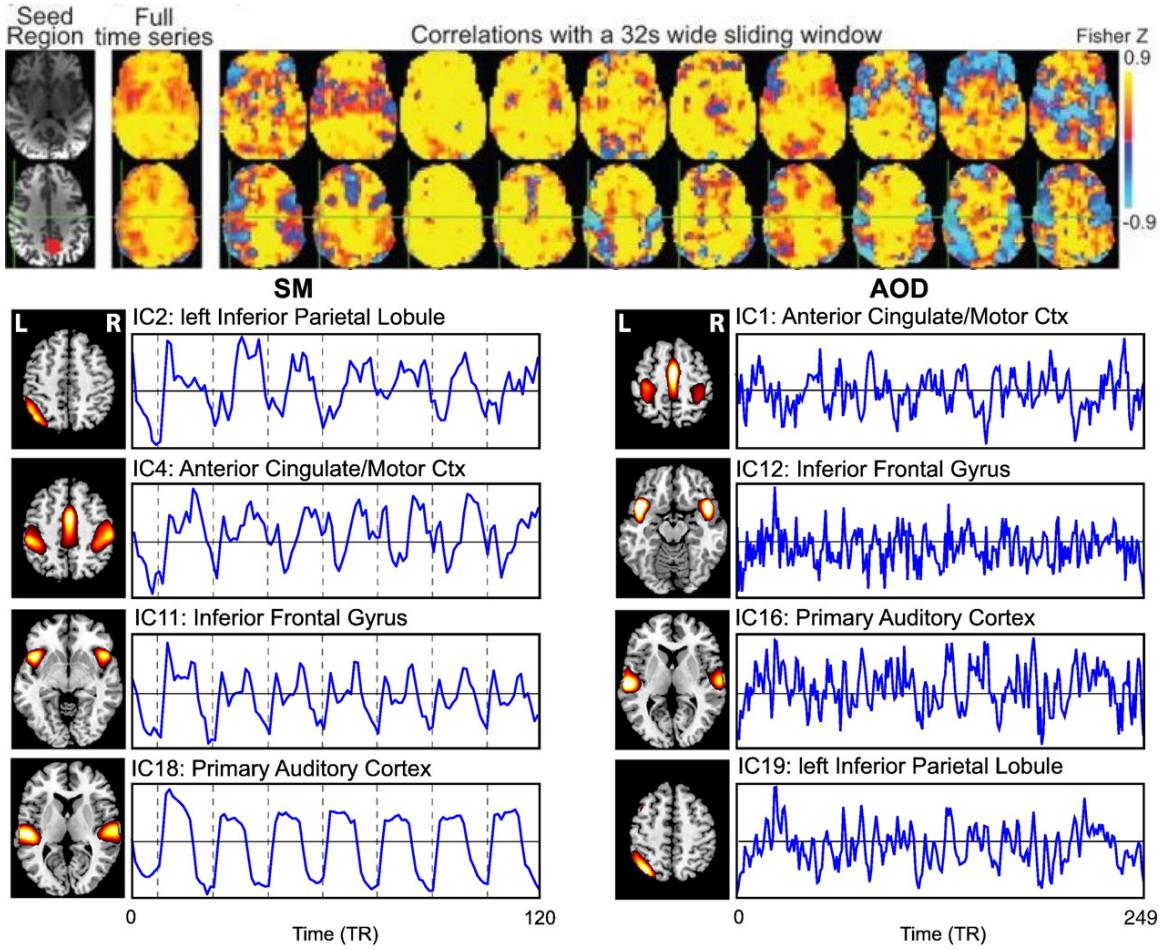


Figure 6.1: Correlations between brain regions fluctuate over time. Top panel, from left to right: the posterior cingulate seed region; the correlation map created from the seed using a 10 minute time series; correlation maps created over 32s temporal windows. The shorter correlation windows show how functional connectivity changes over time. The authors were able to parse brain regions based on the temporal frequency of these changes in connectivity. Bottom panel: relationships between different RSNs can be modelled and compared using methods such as Grainger causality. Figures adapted from Handwerker et al. (2012) and Havlicek et al. (2010).

our studies (Fries, 2005). Indeed, this oscillatory activity has been the subject of a number of studies and represents a promising new dimension to resting-state fMRI analyses (Hutchison et al., 2013). One intersection that these dynamics may address is the ubiquitous role of the default mode network across a number of tasks. In reading, for example, large portions of both the default mode and fronto-parietal networks are active, despite the well-established anti-correlation between them. One explanation could be that some areas

of the default mode network oscillate at higher frequencies in order to integrate information into the global workspace (Vatansever et al., 2015).

Another major question relates to the effects of task-switching during reading. Previous research demonstrating the flexibility of the fronto-parietal network in cognition used event-related connectivity measures in which subjects performed a task with rapid changes in instructions or event-related working memory tasks (Cole et al., 2013; Braun et al., 2015). The FPN may thus be critical for the initial switching action in connectivity patterns, after which the network becomes more settled. In the context of reading, individuals will spend time in various stages of the comprehension process: at some point extra attention will be paid to the decoding of the text, at others to the semantic processing, at others to the recall and integration of previous information (Spreng et al., 2013). Looking at the variations in activity at key junctures of the reading task would elucidate the roles of individual RSNs such as the FPN in the construction, maintenance and evaluation of the text (Sakai, 2008). The answers would help to identify whether the flexibility of certain RSNs and connections are an attribute of that connection or of the task.

6.3 Individualized network assignments

One caveat with connectomics analyses, including those presented here, are that results for the modularity analyses are often based on RSN parcellations from previous literature (e.g. Power et al. (2011)) and are applied indiscriminately across the entire group. This allows for a common reference partition and more interpretable results, but it neglects the fact that there may be important differences between individuals in the optimal community partition for an individual. Even within a given method, there can be a very large number of alternative community parcellations that may differ from the maximum in only a very slight way (Good et al., 2010). Community-agnostic measurements such as the intersection of the union, which we employed in the present analyses, or consensus-based clustering can address some of these concerns, but they are still essentially limited in their capacity to

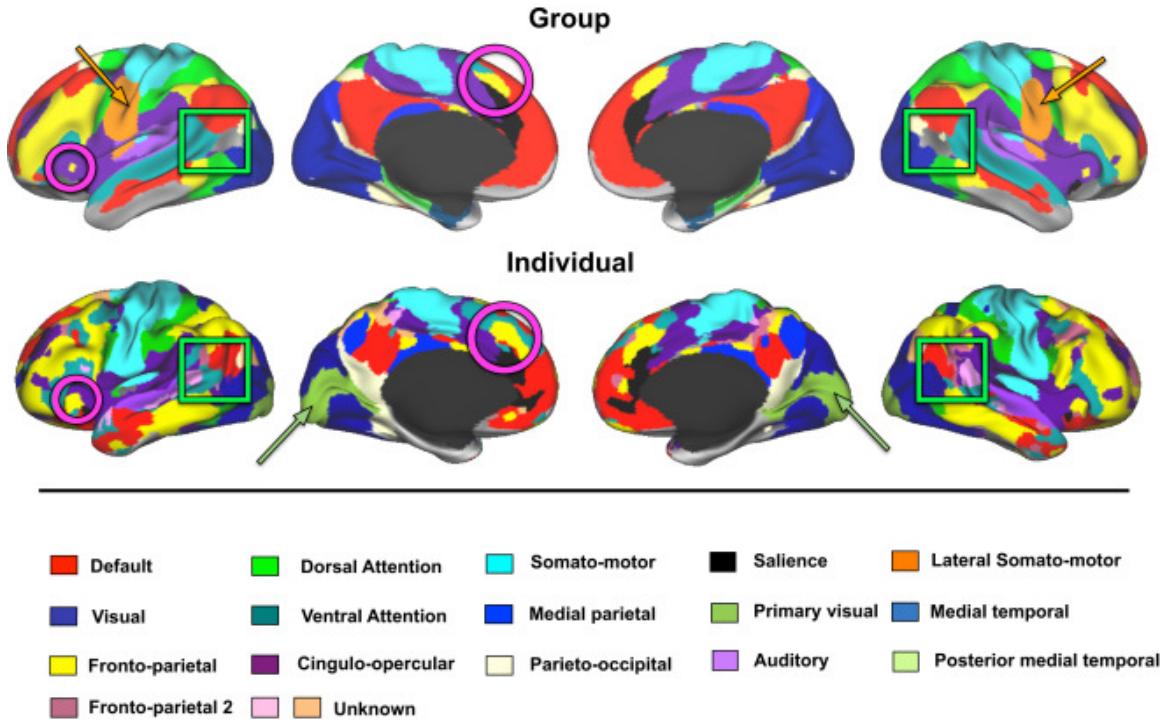


Figure 6.2: Individualized networks in a highly sampled individual brain. Although the individual's systems-level organization is broadly similar to the group, it demonstrates distinct network features. Annotations represent areas where the individual parcellation diverges meaningfully from the group. Figure from Laumann et al. (2015).

allow variability of possible partitions in the system.

The problem may be especially acute in the context of development. As we noted in Study 4, as children mature, the pattern of connectivity changes significantly, with modules becoming more segregated and long-range RSNs such as the fronto-parietal network becoming more robustly connected (Cao et al., 2016). In cases where there are actual differences in the architecture, comparison to the same reference partition will result in one group being considered lower modularity when in fact they are more appropriately deemed *different* modularity. One alternative methodology is to create a group average map for each group then assign communities (e.g. Chan et al. (2014)), but as we have seen, this neglects individual differences in the network architecture that may be important and interesting. One important way this can be controlled is by modelling subject's networks on an individual basis and measuring changes longitudinally, as in Bassett et al. (2015). This

allows for the accommodation of individual differences as well the condition effect.

6.4 High-resolution and multi-modal parcellations

One tension present in network analysis is that of resolution: using too coarse of a sampling of the brain and one risks losing important detail; too fine and one risks introducing extra noise and unneeded complexity. In these analyses we used 264 nodes that have been used in a number of other studies (e.g. Power et al. (2013); Cole et al. (2014)). These nodes cover a large range of brain systems and functional subdivisions (defined by meta-analytic techniques), and each node is separated by at least 10 mm, meaning there is less redundant information being measured. Functional MRI, however, represents only a narrow sliver of the possible methods for understanding the network architecture of the brain, and how it differs between individuals. Functional methods for human brain mapping can also be found in electroencephalography and magnetoencephalography, which offer much higher temporal resolution. Other whole-brain methods in MRI include white matter tractography and structural covariance. (See Sui et al. (2012) for a review of methods connecting different modalities.) In recent years, the combination of these techniques has resulted in a renaissance of brain mapping, and its impact is beginning to extend into the cognitive domain.

One of the more influential parcellations has been one developed by Glasser and colleagues using Human Connectome Project data (Glasser et al., 2016). This parcellation utilizes changes in cortical architecture, function, structural connectivity, and topography to delineate 180 cortical areas on each hemisphere of the brain. This large number of areas, and the amount of data it is built on, stands in stark contrast to the 52 Brodmann areas which have long formed the standard schema for analysis. However, this is hardly the only contender: there is also the multimodal Brainnetome (210 parcels), Gordon atlas (356), Shen atlas (213), and the ubiquitous Yeo (98), Brodman (52) and AAL (74) atlases, among others (Gordon et al., 2016; Fan et al., 2016; Shen et al., 2013; Yeo et al., 2011).

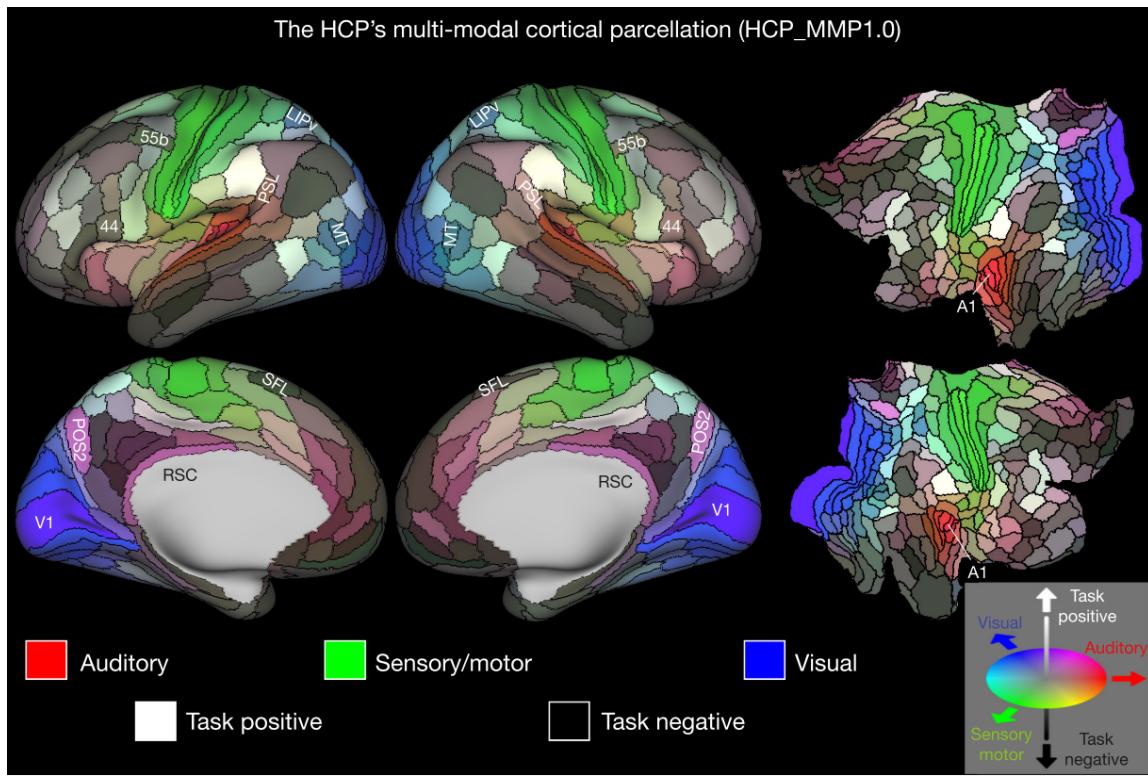


Figure 6.3: This high-resolution parcellation of the human brain is based on cortical anatomy, structural tractography and functional covariance. Each hemisphere has 180 regions of interest which can be projected onto a surface map. In this picture, black outlines indicate areal borders and colours indicate the extent to which each area is associated with the corresponding sensorimotor system. Figure from Glasser et al. (2016).

The challenges limiting the adoption of these advanced methods – especially in environments with a more specialized population such as pediatric imaging – is the amount and quality of data required (multiple modalities, little-to-no subject motion), as well as the steep learning curve associated with implementing them in practice (many pieces of software, advanced programming techniques, many different file types). The number of parcellations can also be overwhelming: although there is a high degree of similarity between each of them, it will be useful for the field to converge on an accepted standard for researchers seeking to bridge the latest advances in network science to their more specific fields. However, as more tutorials become available and software becomes more accessible, future research is likely to reap incredible benefit from these more detailed methods.

(Poldrack and Farah, 2015).

6.5 Final word

Reading is a remarkable ability that requires the efficient coordination of information between distributed brain systems. Mastering it is, in John Steinbeck's words, one of "the most difficult and revolutionary thing that happens to the human brain." Why might some children find it easy, even natural, to read, whereas others find it a grueling or impossible chore? One piece of the puzzle is likely to be the brain's network architecture: the scaffold developed from the first moments of life through birth and childhood and into adulthood. The ongoing tuning and shaping of this architecture forms a basis for the myriad cognitive tasks in which people engage, including reading.

BIBLIOGRAPHY

- AbdulSabur, N. Y., Xu, Y., Liu, S., Chow, H. M., Baxter, M., Carson, J., and Braun, A. R. (2014). Neural correlates and network connectivity underlying narrative production and comprehension: A combined fMRI and PET study. *Cortex*, 57:107–127.
- Aboud, K. S., Barquero, L. A., and Cutting, L. E. (2018). Prefrontal mediation of the reading network predicts intervention response in dyslexia. *Cortex*, 101:96–106.
- Achal, S., Hoeft, F., and Bray, S. (2016). Individual Differences in Adult Reading Are Associated with Left Temporo-parietal to Dorsal Striatal Functional Connectivity. *Cerebral Cortex*, 26(10):4069–4081.
- Andrews-Hanna, J. R., Smallwood, J., and Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, 1316(1):29–52.
- Angelica, M. D. and Fong, Y. (2008). Structural Connectivity Patterns of the Visual Word Form Area and Children’s Reading Ability. *Brain Research*, 141(4):520–529.
- Anticevic, A., Cole, M. W., Murray, J. D., Corlett, P. R., Wang, X. J., and Krystal, J. H. (2012). The role of default network deactivation in cognition and disease. *Trends in Cognitive Sciences*, 16(12):584–592.
- Attneave, F., B., M., and Hebb, D. O. (1950). *The Organization of Behavior; A Neuropsychological Theory*. John Wiley & Sons, Inc., New York.
- Bailey, S., Hoeft, F., Aboud, K., and Cutting, L. (2016). Anomalous gray matter patterns in specific reading comprehension deficit are independent of dyslexia. *Annals of Dyslexia*, 66(3):256–274.
- Bailey, S. K., Aboud, K. S., Nguyen, T. Q., and Cutting, L. E. (2018). Applying a network framework to the neurobiology of reading and dyslexia. *Journal of Neurodevelopmental Disabilities*.
- Barrett, H. C. and Kurzban, R. (2006). Modularity in cognition: Framing the debate. *Psychological Review*, 113(3):628–647.
- Bassett, D. S., Wymbs, N. F., Porter, M. A., Mucha, P. J., Carlson, J. M., and Grafton, S. T. (2010). Dynamic reconfiguration of human brain networks during learning. *Proceedings of the National Academy of Sciences*, 108(18).
- Bassett, D. S., Yang, M., Wymbs, N. F., and Grafton, S. T. (2015). Learning-induced autonomy of sensorimotor systems. *Nature Neuroscience*, 18(5):744–751.
- Beckmann, C. F. and Smith, S. M. (2005). Tensorial extensions of independent component analysis for multisubject FMRI analysis. *NeuroImage*, 25(1):294–311.

- Berl, M. M., Duke, E. S., Mayo, J., Rosenberger, L. R., Erin, N., Vanmeter, J., Ratner, N. B., Vaidya, C. J., and Gaillard, D. (2011). Functional anatomy of listening and reading during development. *Brain and Language*, 114(2):115–125.
- Betzel, R. F., Avena-Koenigsberger, A., Goñi, J., Sporns, O., Griffa, A., Thiran, J. P., and Hagmann, P. (2013). Multi-scale community organization of the human structural connectome and its relationship with resting-state functional connectivity. *Network Science*, 1(3):353–373.
- Betzel, R. F., Byrge, L., He, Y., Goñi, J., Zuo, X. N., and Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage*, 102(P2):345–357.
- Biswal, B., FZ, Y., VM, H., and JS, H. (1995). - Functional connectivity in the motor cortex of resting human brain using. *Magn Reson Med*, 34(9):537–541.
- Blau, V., Reithler, J., Van Atteveldt, N., Seitz, J., Gerretsen, P., Goebel, R., and Blomert, L. (2010). Deviant processing of letters and speech sounds as proximate cause of reading failure: A functional magnetic resonance imaging study of dyslexic children. *Brain*, 133(3):868–879.
- Bouhali, F., Thiebaut de Schotten, M., Pinel, P., Poupon, C., Mangin, J.-F., Dehaene, S., and Cohen, L. (2014). Anatomical Connections of the Visual Word Form Area. *Journal of Neuroscience*, 34(46):15402–15414.
- Braun, U., Schäfer, A., Walter, H., Erk, S., Romanczuk-Seiferth, N., Haddad, L., Schweiger, J. I., Grimm, O., Heinz, A., Tost, H., Meyer-Lindenberg, A., and Bassett, D. S. (2015). Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proceedings of the National Academy of Sciences*, 112(37):11678–11683.
- Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, 1124:1–38.
- Bullmore, E. and Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, 13(5):336–49.
- Cain, K. and Oakhill, J. (2006). Profiles of children with specific reading comprehension difficulties. *British Journal of Educational Psychology*, 76(4):683–696.
- Cao, M., Huang, H., Peng, Y., Dong, Q., and He, Y. (2016). Toward Developmental Connectomics of the Human Brain. *Frontiers in Neuroanatomy*, 10(March):1–17.
- Chai, X. J., Castañán, A. N., Öngür, D., and Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage*, 59(2):1420–1428.

- Chan, M. Y., Park, D. C., Savalia, N. K., Petersen, S. E., and Wig, G. S. (2014). Decreased segregation of brain systems across the healthy adult lifespan. *Proceedings of the National Academy of Sciences*, 111(46):E4997–E5006.
- Choe, A. S., Jones, C. K., Joel, S. E., Muschelli, J., Belegu, V., Caffo, B. S., Lindquist, M. A., Van Zijl, P. C., and Pekar, J. J. (2015). Reproducibility and temporal structure in weekly resting-state fMRI over a period of 3.5 years. *PLoS ONE*, 10(10):1–29.
- Christodoulou, J. A., Del Tufo, S. N., Lymberis, J., Saxler, P. K., Ghosh, S. S., Triantafyllou, C., Whitfield-Gabrieli, S., and Gabrieli, J. D. E. (2014). Brain bases of reading fluency in typical reading and impaired fluency in dyslexia. *PLoS ONE*, 9(7):e100552.
- Clifton, C., Ferreira, F., Henderson, J. M., Inhoff, A. W., Liversedge, S. P., Reichle, E. D., and Schotter, E. R. (2016). Eye movements in reading and information processing: Keith Rayner's 40 year legacy. *Journal of Memory and Language*, 86:1–19.
- Cocchi, L., Zalesky, A., Fornito, A., and Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. *Trends in Cognitive Sciences*, 17(10):493–501.
- Cohen, J. R. and D'Esposito, M. (2016). The Segregation and Integration of Distinct Brain Networks and Their Relationship to Cognition. *Journal of Neuroscience*, 36(48):12083–12094.
- Cohen, L., Lehéricy, S., Chochon, F., Lemé, C., Rivaud, S., and Dehaene, S. (2002). Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area. *Brain*, 125(5):1054–1069.
- Cole, M. W., Anticevic, A., Repovs, G., and Barch, D. (2011). Variable global dysconnectivity and individual differences in schizophrenia. *Biological Psychiatry*, 70(1):43–50.
- Cole, M. W., Bassett, D. S., Power, J. D., Braver, T. S., and Petersen, S. E. (2014). Intrinsic and task-evoked network architectures of the human brain. *Neuron*, 83(1):238–251.
- Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., and Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, 16(9):1348–1355.
- Cole, M. W. and Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, 37(1):343–360.
- Connolly, J. D., Goodale, M. A., Menon, R. S., and Munoz, D. P. (2002). Human fMRI evidence for the neural correlates of preparatory set. *Nature Neuroscience*, 5(12):1345–1352.
- Constable, R. T., Pugh, K. R., Berroya, E., Mencl, W. E., Westerveld, M., Ni, W., and Shankweiler, D. (2004). Sentence complexity and input modality effects in sentence comprehension: An fMRI study. *NeuroImage*, 22(1):11–21.

- Corbetta, M. and Shulman, G. L. (2002). Control of Goal-Directed and Stimulus-Driven Attention in the Brain. *Nature Reviews Neuroscience*, 3(3):215–229.
- Cordes, D., Haughton, V. M., Arfanakis, K., Wendt, G. J., Turski, P. A., Moritz, C. H., Quigley, M. A., and Meyerand, M. E. (2000). Mapping functionally related regions of brain with functional connectivity MR imaging. *American Journal of Neuroradiology*, 21(9):1636–1644.
- Correro, G., Linnea Ehri, P., Gwenette Ferguson, M., Norma Garza, C., Michael L. Kamil, P., Cora Bagley Marrett, P., S.J. Samuels, E., Timothy Shanahan, P., Sally E. Shaywitz, M., Thomas Trabasso, P., Joanna Williams, P., Dale Willows, P., and Joanne Yatvin, P. (2000). *Teaching children to read: An evidence-based assessment of the scientific research literature on reading and its implications for reading instruction*, volume 7. National Institutes of Health.
- Crowther, A., Smoski, M. J., Minkel, J., Moore, T., Gibbs, D., Petty, C., Bizzell, J., Schiller, C. E., Sideris, J., Carl, H., and Dichter, G. S. (2015). Resting-state connectivity predictors of response to psychotherapy in major depressive disorder. *Neuropsychopharmacology*, 40(7):1659–1663.
- Cutting, L. E., Clements, A. M., Courtney, S., Rimrodt, S. L., Schafer, J. G., Bisesi, J., Pekar, J. J., and Pugh, K. R. (2006). Differential components of sentence comprehension: Beyond single word reading and memory. *NeuroImage*, 29(2):429–438.
- Cutting, L. E., Materek, A., Cole, C. A., Levine, T. M., and Mahone, E. M. (2009). Effects of fluency, oral language, and executive function on reading comprehension performance. *Annals of Dyslexia*, 59(1):34–54.
- Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., and Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, 103(37):13848–13853.
- De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., and Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage*, 29(4):1359–1367.
- Dehaene, S., Cohen, L., Morais, J., and Kolinsky, R. (2015). Illiterate to literate: behavioural and cerebral changes induced by reading acquisition. *Nature Reviews Neuroscience*, 16(4):234–244.
- Dehaene, S., Kerszberg, M., and Changeux, J.-P. (1998). A neuronal model of a global workspace in effortful cognitive tasks. *Proceedings of the National Academy of Sciences*, 95(24):14529–14534.
- Dosenbach, N. U. F., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A. T., Fox, M. D., Snyder, A. Z., Vincent, J. L., Raichle, M. E., Schlaggar, B. L., and Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences*, 104(26):11073–11078.

- Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends in Cognitive Sciences*, 14(4):172–179.
- Eckert, M. A., Leonard, C. M., Richards, T. L., Aylward, E. H., Thomson, J., and Berninger, V. W. (2003). Anatomical correlates of dyslexia: Frontal and cerebellar findings. *Brain*, 126(2):482–494.
- Fair, D. A., Dosenbach, N. U. F., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., and Schlaggar, B. L. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences*, 104(33):13507–13512.
- Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P. T., Eickhoff, S. B., Yu, C., and Jiang, T. (2016). The Human Brain-Netome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cerebral Cortex*, 26(8):3508–3526.
- Fedorenko, E. (2014). The role of domain-general cognitive control in language comprehension. *Frontiers in Psychology*, 5(APR):1–17.
- Fedorenko, E., Duncan, J., and Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, 110(41):16616–16621.
- Fedorenko, E. and Thompson-Schill, S. L. (2014). Reworking the language network. *Trends in Cognitive Sciences*, 18(3):120–127.
- Finn, A. S., Kraft, M. A., West, M. R., Leonard, J. A., Bish, C. E., Martin, R. E., Sheridan, M. A., Gabrieli, C. F. O., and Gabrieli, J. D. E. (2014). Cognitive Skills, Student Achievement Tests, and Schools. *Psychological Science*, 25(3):736–744.
- Fox, M. D. and Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, 8(9):700–711.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, 102(27):9673–9678.
- Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends in Cognitive Sciences*, 9(10):474–480.
- Gaffrey, M. S., Luby, J. L., and Barch, D. M. (2013). Towards the study of functional brain development in depression: An Interactive Specialization approach. *Neurobiology of Disease*, 52:38–48.

- Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkinson, M., Smith, S. M., and Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. *Nature*, 536(7615):171–178.
- Godwin, D., Barry, R. L., and Marois, R. (2015). Breakdown of the brain’s functional network modularity with awareness. *Proceedings of the National Academy of Sciences*, 10(36):201414466.
- Godwin, F. D. (2016). *Investigations of the global network properties of attention and awareness*. Dissertation, Vanderbilt University.
- Goni, J., van den Heuvel, M. P., Avena-Koenigsberger, A., Velez de Mendizabal, N., Betzel, R. F., Griffa, A., Hagmann, P., Corominas-Murtra, B., Thiran, J.-P., and Sporns, O. (2014). Resting-brain functional connectivity predicted by analytic measures of network communication. *Proceedings of the National Academy of Sciences*, 111(2):833–838.
- Good, B. H., De Montjoye, Y. A., and Clauset, A. (2010). Performance of modularity maximization in practical contexts. *Physical Review E - Statistical, Nonlinear, and Soft Matter Physics*, 81(4):1–20.
- Gordon, E. M., Laumann, T. O., Adeyemo, B., Huckins, J. F., Kelley, W. M., and Petersen, S. E. (2016). Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cerebral Cortex*, 26(1):288–303.
- Goswami, U. (2002). Phonology, Reading Development, and Dyslexia: A Cross-linguistic Perspective. *Annals of Dyslexia*, 52(1):141–163.
- Gough, P. B. and Tunmer, W. E. (1986). Decoding, Reading, and Reading Disability. *Remedial and Special Education*, 7(1):6–10.
- Hagoort, P. (2005). On Broca, brain, and binding: A new framework. *Trends in Cognitive Sciences*, 9(9):416–423.
- Hampson, M., Peterson, B. S., Skudlarski, P., Gatenby, J. C., and Gore, J. C. (2002). Detection of functional connectivity using temporal correlations in MR images. *Human Brain Mapping*, 15(4):247–262.
- Handwerker, D. A., Roopchansingh, V., Gonzalez-Castillo, J., and Bandettini, P. A. (2012). Periodic changes in fMRI connectivity. *NeuroImage*, 63(3):1712–1719.
- Harrar, V., Tammam, J., Pérez-Bellido, A., Pitt, A., Stein, J., and Spence, C. (2014). Multisensory integration and attention in developmental dyslexia. *Current Biology*, 24(5):531–535.
- Havlicek, M., Jan, J., Brazdil, M., and Calhoun, V. D. (2010). Dynamic Granger causality based on Kalman filter for evaluation of functional network connectivity in fMRI data. *NeuroImage*, 53(1):65–77.

- Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., and Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences of the United States of America*, 106(6):2035–40.
- Hoover, W. A. and Gough, P. B. (1990). The simple view of reading. *Reading and Writing*, 2(2):127–160.
- Horowitz-Kraus, T., Difrancesco, M., Kay, B., Wang, Y., and Holland, S. K. (2015a). Increased resting-state functional connectivity of visual- and cognitive-control brain networks after training in children with reading difficulties. *NeuroImage: Clinical*, 8:619–630.
- Horowitz-Kraus, T., Toro-Serey, C., and Difrancesco, M. (2015b). Increased resting-state functional connectivity in the cingulo-opercular cognitive-control network after intervention in children with reading difficulties. *PLoS ONE*, 10(7):e0133762.
- Hutchison, R. M., Womelsdorf, T., Allen, E. A., Bandettini, P. A., Calhoun, V. D., Corbetta, M., Della Penna, S., Duyn, J. H., Glover, G. H., Gonzalez-Castillo, J., Handwerker, D. A., Keilholz, S., Kiviniemi, V., Leopold, D. A., de Pasquale, F., Sporns, O., Walter, M., and Chang, C. (2013). Dynamic functional connectivity: Promise, issues, and interpretations. *NeuroImage*, 80:360–378.
- Jobard, G., Vigneau, M., Mazoyer, B., and Tzourio-Mazoyer, N. (2007). Impact of modality and linguistic complexity during reading and listening tasks. *NeuroImage*, 34(2):784–800.
- Johnson, M. H. (2011). Interactive Specialization: A domain-general framework for human functional brain development? *Developmental Cognitive Neuroscience*, 1(1):7–21.
- Jung-Beeman, M. (2005). Bilateral brain processes for comprehending natural language. *Trends in Cognitive Sciences*, 9(11):512–518.
- Kaplan, E., Fein, D., Kramer, J., Delis, D., and Morris, R. (1999). Wechsler Individual Intelligence Scale, Third Edition.
- Kashtan, N. and Alon, U. (2005). Spontaneous evolution of modularity and network motifs. *Proceedings of the National Academy of Sciences*, 102(39):13773–13778.
- Keller, J. B., Hedden, T., Thompson, T. W., Anteraper, S. A., Gabrieli, J. D., and Whitfield-Gabrieli, S. (2015). Resting-state anticorrelations between medial and lateral prefrontal cortex: Association with working memory, aging, and individual differences. *Cortex*, 64(0):271–280.
- Kendeou, P., Van Den Broek, P., Helder, A., and Karlsson, J. (2014). A cognitive view of reading comprehension: Implications for reading difficulties. *Learning Disabilities Research and Practice*, 29(1):10–16.

- Kesler, S. R., Wefel, J. S., Hosseini, S. M. H., Cheung, M., Watson, C. L., and Hoeft, F. (2013). Default mode network connectivity distinguishes chemotherapy-treated breast cancer survivors from controls. *Proceedings of the National Academy of Sciences*, 110(28):11600–11605.
- Kirby, J. R. and Savage, R. S. (2008). Can the simple view deal with the complexities of reading? *Literacy*, 42(2):75–82.
- Klingberg, T. (2014). Childhood cognitive development as a skill. *Trends in Cognitive Sciences*, 18(11):573–79.
- Koyama, M. S., Di Martino, A., Kelly, C., Jutagir, D. R., Sunshine, J., Schwartz, S. J., Castellanos, F. X., and Milham, M. P. (2013). Cortical Signatures of Dyslexia and Remediation: An Intrinsic Functional Connectivity Approach. *PLoS ONE*, 8(2):e55454.
- Koyama, M. S., Di Martino, A., Zuo, X.-N., Kelly, C., Mennes, M., Jutagir, D. R., Castellanos, F. X., and Milham, M. P. (2011). Resting-State Functional Connectivity Indexes Reading Competence in Children and Adults. *Journal of Neuroscience*, 31(23):8617–8624.
- Koyama, M. S., Kelly, C., Shehzad, Z., Penesetti, D., Castellanos, F. X., and Milham, M. P. (2010). Reading networks at rest. *Cerebral Cortex*, 20(11):2549–2559.
- Lallier, M., Thierry, G., Tainturier, M. J., Donnadieu, S., Peyrin, C., Billard, C., and Valdois, S. (2009). Auditory and visual stream segregation in children and adults: An assessment of the amodality assumption of the 'sluggish attentional shifting' theory of dyslexia. *Brain Research*, 1302:132–147.
- Laumann, T. O., Gordon, E. M., Adeyemo, B., Snyder, A. Z., Joo, S. J., Chen, M. Y., Gilmore, A. W., McDermott, K. B., Nelson, S. M., Dosenbach, N. U., Schlaggar, B. L., Mumford, J. A., Poldrack, R. A., and Petersen, S. E. (2015). Functional System and Areal Organization of a Highly Sampled Individual Human Brain. *Neuron*, 87(3):658–671.
- Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., Yu, C., Liu, H., Liu, Z., and Jiang, T. (2008). Disrupted small-world networks in schizophrenia. *Brain*, 131(4):945–961.
- Lord, A., Horn, D., Breakspear, M., and Walter, M. (2012). Changes in community structure of resting state functional connectivity in unipolar depression. *PLoS ONE*, 7(8).
- Lynall, M.-E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., and Bullmore, E. (2010). Functional Connectivity and Brain Networks in Schizophrenia. *Journal of Neuroscience*, 30(28):9477–9487.
- MacGinitie, W., MacGinitie, R., Maria, K., and Dreyer, L. (2000). Gates-MacGinitie Reading Tests, Fourth Edition.

- Maguire, E. A., Frith, C. D., and Morris, R. G. (1999). The functional neuroanatomy of comprehension and memory: The importance of prior knowledge. *Brain*, 122(10):1839–1850.
- Maisog, J. M., Einbinder, E. R., Flowers, D. L., Turkeltaub, P. E., and Eden, G. F. (2008). A meta-analysis of functional neuroimaging studies of dyslexia. *Annals of the New York Academy of Sciences*, 1145:237–259.
- Margari, L., Buttiglione, M., Craig, F., Cristella, A., de Giambattista, C., Matera, E., Operato, F., and Simone, M. (2013). Neuropsychopathological comorbidities in learning disorders. *BMC Neurology*, 13(1):198.
- Martin, A., Schurz, M., Kronbichler, M., and Richlan, F. (2015). Reading in the brain of children and adults: A meta-analysis of 40 functional magnetic resonance imaging studies. *Human Brain Mapping*, 36(5):1963–1981.
- Mattfeld, A. T., Gabrieli, J. D., Biederman, J., Spencer, T., Brown, A., Kotte, A., Kagan, E., and Whitfield-Gabrieli, S. (2014). Brain differences between persistent and remitted attention deficit hyperactivity disorder. *Brain*, 137(9):2423–2428.
- Mattingly, I. (1971). Reading, the Linguistic Process, and Linguistic Awareness. *Status Report on Speech Research*, pages 23–34.
- McCandliss, B. D. and Noble, K. G. (2003). The development of reading impairment: A cognitive neuroscience model. *Mental Retardation and Developmental Disabilities Research Reviews*, 9(3):196–204.
- Menon, V. and Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain structure & function*, 214(5-6):655–667.
- Moussa, M. N., Steen, M. R., Laurienti, P. J., and Hayasaka, S. (2012). Consistency of Network Modules in Resting-State fMRI Connectome Data. *PLoS ONE*, 7(8):e44428.
- Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., and Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective and Behavioral Neuroscience*, 12(2):241–268.
- Norton, E. S., Black, J. M., Stanley, L. M., Tanaka, H., Gabrieli, J. D., Sawyer, C., and Hoeft, F. (2014). Functional neuroanatomical evidence for the double-deficit hypothesis of developmental dyslexia. *Neuropsychologia*, 61(1):235–246.
- Paulesu, E., Danelli, L., and Berlingeri, M. (2014). Reading the dyslexic brain: multiple dysfunctional routes revealed by a new meta-analysis of PET and fMRI activation studies. *Frontiers in Human Neuroscience*, 8(November):1–20.
- Pennington, B. F. (2006). From single to multiple deficit models of developmental disorders. *Cognition*, 101(2):385–413.

- Pennington, B. F. and Bishop, D. V. (2009). Relations Among Speech, Language, and Reading Disorders. *Annual Review of Psychology*, 60(1):283–306.
- Pernet, C., Andersson, J., Paulesu, E., and Demonet, J. F. (2009). When all hypotheses are right: A multifocal account of dyslexia. *Human Brain Mapping*, 30(7):2278–2292.
- Petersen, S. E. and Sporns, O. (2015). Brain Networks and Cognitive Architectures. *Neuron*, 88(1):207–219.
- Pimperton, H. and Nation, K. (2010). Suppressing irrelevant information from working memory: Evidence for domain-specific deficits in poor comprehenders. *Journal of Memory and Language*, 62(4):380–391.
- Poldrack, R. A. and Farah, M. J. (2015). Progress and challenges in probing the human brain. *Nature*, 526(7573):371–379.
- Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., Vogel, A. C., Laumann, T. O., Miezin, F. M., Schlaggar, B. L., and Petersen, S. E. (2011). Functional Network Organization of the Human Brain. *Neuron*, 72(4):665–678.
- Power, J. D., Fair, D. A., Schlaggar, B. L., and Petersen, S. E. (2010). The Development of Human Functional Brain Networks. *Neuron*, 67(5):735–748.
- Power, J. D., Schlaggar, B. L., Lessov-Schlaggar, C. N., and Petersen, S. E. (2013). Evidence for hubs in human functional brain networks. *Neuron*, 79(4):798–813.
- Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *NeuroImage*, 62(2):816–847.
- Pugh, K. R., Mencl, W. E., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Constable, R. T., Skudlarski, P., Marchione, K. E., Jenner, A. R., Fletcher, J. M., Liberman, A. M., Shankweiler, D. P., Katz, L., Lacadie, C., and Gore, J. C. (2000). The Angular Gyrus in Developmental Dyslexia: Task-Specific Differences in Functional Connectivity Within Posterior Cortex. *Psychological Science*, 11(1):51–56.
- Qi, T., Gu, B., Ding, G., Gong, G., Lu, C., Peng, D., Malins, J. G., and Liu, L. (2016). More bilateral, more anterior: Alterations of brain organization in the large-scale structural network in Chinese dyslexia. *NeuroImage*, 124:63–74.
- Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, 98(2):676–682.
- Rayner, K. (1978). Eye movements in reading and information processing. *Psychological Bulletin*, 85(3):618–660.
- Rayner, K. (1997). Eye movements in reading and information processing: 20 years of research. *Psychological Bulletin*, 124(3):372–422.

- Rayner, K., Chace, K. H., Slattery, T. J., and Ashby, J. (2006). Eye Movements as Reflections of Comprehension Processes in Reading. *Scientific Studies of Reading*, 10(3):241–255.
- Reineberg, A. E., Andrews-Hanna, J. R., Depue, B. E., Friedman, N. P., and Banich, M. T. (2015). Resting-state networks predict individual differences in common and specific aspects of executive function. *NeuroImage*, 104:69–78.
- Reineberg, A. E., Gustavson, D. E., Benca, C., Banich, M. T., and Friedman, N. P. (2018). The Relationship Between Resting State Network Connectivity and Individual Differences in Executive Functions. *Frontiers in Psychology*, 9(September):1–14.
- Richlan, F., Kronbichler, M., and Wimmer, H. (2009). Functional abnormalities in the dyslexic brain: A quantitative meta-analysis of neuroimaging studies. *Human Brain Mapping*, 30(10):3299–3308.
- Rimrodt, S. L., Clements-Stephens, A. M., Pugh, K. R., Courtney, S. M., Gaur, P., Pekar, J. J., and Cutting, L. E. (2009). Functional MRI of sentence comprehension in children with dyslexia: Beyond word recognition. *Cerebral Cortex*, 19(2):402–413.
- Rubinov, M. and Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3):1059–1069.
- Rueckl, J. G., Paz-Alonso, P. M., Molfese, P. J., Kuo, W.-J., Bick, A., Frost, S. J., Hancock, R., Wu, D. H., Mencl, W. E., Duñabeitia, J. A., Lee, J.-R., Oliver, M., Zevin, J. D., Hoeft, F., Carreiras, M., Tzeng, O. J. L., Pugh, K. R., and Frost, R. (2015). Universal brain signature of proficient reading: Evidence from four contrasting languages. *Proceedings of the National Academy of Sciences*, 112(50):15510–15515.
- Sakai, K. (2008). Task Set and Prefrontal Cortex. *Annual Review of Neuroscience*, 31(1):219–245.
- Saygin, Z. M., Osher, D. E., Norton, E. S., Youssoufian, D. A., Beach, S. D., Feather, J., Gaab, N., Gabrieli, J. D. E., and Kanwisher, N. (2016). Connectivity precedes function in the development of the visual word form area. *Nature Neuroscience*, 19(9):1250–1255.
- Schlaggar, B. L. and McCandliss, B. D. (2007). Development of Neural Systems for Reading. *Annual Review of Neuroscience*, 30(1):475–503.
- Schurz, M., Kronbichler, M., Crone, J., Richlan, F., Klackl, J., and Wimmer, H. (2014). Top-down and bottom-up influences on the left ventral occipito-temporal cortex during visual word recognition: An analysis of effective connectivity. *Human Brain Mapping*, 35(4):1668–1680.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., and Greicius, M. D. (2007). Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neuroscience*, 27(9):2349–2356.

- Shen, X., Tokoglu, F., Papademetris, X., and Constable, R. T. (2013). Groupwise whole-brain parcellation from resting-state fMRI data for network node identification. *NeuroImage*, 82:403–415.
- Simmons, W. K. and Martin, A. (2012). Spontaneous resting-state BOLD fluctuations reveal persistent domain-specific neural networks. *Social Cognitive and Affective Neuroscience*, 7(4):467–475.
- Smith, S. M. and Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, 44(1):83–98.
- Sood, M. R. and Sereno, M. I. (2016). Areas activated during naturalistic reading comprehension overlap topological visual, auditory, and somatotomotor maps. *Human Brain Mapping*, 37(8):2784–2810.
- Speer, N. K., Yarkoni, T., and Zacks, J. M. (2006). Neural correlates of narrative comprehension and memory. *NeuroImage*, 41(4):1408–1425.
- Spencer, M., Quinn, J. M., and Wagner, R. K. (2014). Specific reading comprehension disability: Major problem, myth, or misnomer? *Learning Disabilities Research and Practice*, 29(1):3–9.
- Sporns, O. (2013). The human connectome: Origins and challenges. *NeuroImage*, 80:53–61.
- Sporns, O. and Betzel, R. F. (2016). Modular Brain Networks. *Annual Review of Psychology*, 67(1):613–640.
- Sporns, O., Tononi, G., and Kötter, R. (2005). The human connectome: A structural description of the human brain. *PLoS Computational Biology*, 1(4):0245–0251.
- Spreng, R. N., Sepulcre, J., Turner, G. R., Stevens, W. D., and Schacter, D. L. (2013). Intrinsic Architecture Underlying the Relations among the Default, Dorsal Attention, and Frontoparietal Control Networks of the Human Brain. *Journal of Cognitive Neuroscience*, 25(1):74–86.
- Stam, C. J. (2014). Modern network science of neurological disorders. *Nature Reviews Neuroscience*, 15(10):683–695.
- Stein, J. and Walsh, V. (1997). To see but not to read; the magnocellular theory of dyslexia. *Trends in Neurosciences*, 20(4):147–152.
- Sui, J., Adali, T., Yu, Q., Chen, J., and Calhoun, V. D. (2012). A review of multivariate methods for multimodal fusion of brain imaging data. *Journal of Neuroscience Methods*, 204(1):68–81.
- Sui, J., Huster, R., Yu, Q., Segall, J. M., and Calhoun, V. D. (2014). Function-structure associations of the brain: Evidence from multimodal connectivity and covariance studies. *NeuroImage*, 102(P1):11–23.

- Supekar, K., Menon, V., Rubin, D., Musen, M., and Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*, 4(6).
- Tian, H., Lu, C., Yang, J., Banger, K., Huntzinger, D. N., Schwalm, C. R., Michalak, A. M., Cook, R., Ciais, P., Hayes, D., Huang, M., Ito, A., Jain, A. K., Lei, H., Mao, J., Pan, S., Post, W. M., Peng, S., Poulter, B., Ren, W., Ricciuto, D., Schaefer, K., Shi, X., Tao, B., Wang, W., Wei, Y., Yang, Q., Zhang, B., and Zeng, N. (2015). Global patterns and controls of soil organic carbon dynamics as simulated by multiple terrestrial biosphere models: Current status and future directions.
- Torgesen, J. K., Wagner, R. K., and Rashotte, C. A. (2012). Test of Word Reading Efficiency, Second Edition.
- Trachtenberg, A. J., Filippini, N., Ebmeier, K. P., Smith, S. M., Karpe, F., and Mackay, C. E. (2012). The effects of APOE on the functional architecture of the resting brain. *NeuroImage*, 59(1):565–572.
- Twomey, T., Kawabata Duncan, K. J., Price, C. J., and Devlin, J. T. (2011). Top-down modulation of ventral occipito-temporal responses during visual word recognition. *NeuroImage*, 55(3):1242–1251.
- Uddin, L. Q. (2010). Typical and atypical development of functional human brain networks: insights from resting-state fMRI. *Frontiers in Systems Neuroscience*, 4:1–12.
- Uddin, L. Q., Kelly, A. M. C., Biswal, B. B., Margulies, D. S., Shehzad, Z., Shaw, D., Ghaffari, M., Rotrosen, J., Adler, L. A., Castellanos, F. X., and Milham, M. P. (2008). Network homogeneity reveals decreased integrity of default-mode network in ADHD. *Journal of Neuroscience Methods*, 169(1):249–254.
- van Atteveldt, N., Roebroeck, A., and Goebel, R. (2009). Interaction of speech and script in human auditory cortex: Insights from neuro-imaging and effective connectivity. *Hearing Research*, 258(1-2):152–164.
- van den Heuvel, M. P. and Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, 20(8):519–534.
- van den Heuvel, M. P. and Sporns, O. (2011). Rich-Club Organization of the Human Connectome. *Journal of Neuroscience*, 31(44):15775–15786.
- van den Heuvel, M. P., Stam, C. J., Kahn, R. S., and Hulshoff Pol, H. E. (2009). Efficiency of Functional Brain Networks and Intellectual Performance. *Journal of Neuroscience*, 29(23):7619–7624.
- van der Lely, H. K. J. and Marshall, C. R. (2010). Assessing Component Language Deficits in the Early Detection of Reading Difficulty Risk. *Journal of Learning Disabilities*, 43(4):357–368.

- Vatansever, D., Menon, D. K., Manktelow, A. E., Sahakian, B. J., and Stamatakis, E. A. (2015). Default Mode Dynamics for Global Functional Integration. *Journal of Neuroscience*, 35(46):15254–15262.
- Vidyasagar, T. R. and Pammer, K. (2010). Dyslexia: a deficit in visuo-spatial attention, not in phonological processing. *Trends in Cognitive Sciences*, 14(2):57–63.
- Vogel, A. C., Church, J. A., Power, J. D., Miezin, F. M., Petersen, S. E., and Schlaggar, B. L. (2013). Functional network architecture of reading-related regions across development. *Brain and Language*, 125(2):231–243.
- Vogel, A. C., Miezin, F. M., Petersen, S. E., and Schlaggar, B. L. (2012). The putative visual word form area is functionally connected to the dorsal attention network. *Cerebral Cortex*, 22(3):537–549.
- Vogel, A. C., Petersen, S. E., and Schlaggar, B. L. (2014). The VWFA: it's not just for words anymore. *Frontiers in Human Neuroscience*, 8(March):1–10.
- Vossel, S., Geng, J. J., and Fink, G. R. (2014). Dorsal and Ventral Attention Systems. *The Neuroscientist*, 20(2):150–159.
- Wandell, B. A. and Yeatman, J. D. (2013). Biological development of reading circuits. *Current Opinion in Neurobiology*, 23(2):261–268.
- Warren, D. E., Power, J. D., Bruss, J., Denburg, N. L., Waldron, E. J., Sun, H., Petersen, S. E., and Tranel, D. (2014). Network measures predict neuropsychological outcome after brain injury. *Proceedings of the National Academy of Sciences*, 111(39):14247–14252.
- Whitfield-Gabrieli, S., Ghosh, S. S., Nieto-Castanon, A., Saygin, Z., Doehrmann, O., Chai, X. J., Reynolds, G. O., Hofmann, S. G., Pollack, M. H., and Gabrieli, J. D. (2016). Brain connectomics predict response to treatment in social anxiety disorder. *Molecular Psychiatry*, 21(5):680–685.
- Whitfield-Gabrieli, S. and Nieto-Castanon, A. (2012). Conn : A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity*, 2(3):125–141.
- Witton, C., Talcott, J. B., Hansen, P. C., Richardson, A. J., Griffiths, T. D., Rees, A., Stein, J. F., and Green, G. G. (1998). Sensitivity to dynamic auditory and visual stimuli predicts nonword reading ability in both dyslexic and normal readers. *Current Biology*, 8(14):791–797.
- Woodcock, R. W. (1998). Woodcock Reading Mastery Tests-Revised (WRMT-R).
- Xu, J., Kemeny, S., Park, G., Frattali, C., and Braun, A. (2005). Language in context: Emergent features of word, sentence, and narrative comprehension. *NeuroImage*, 25(3):1002–1015.

- Yang, F.-C., Chou, K.-H., Hsu, A.-L., Fuh, J.-L., Lirng, J.-F., Kao, H.-W., Lin, C.-P., and Wang, S.-J. (2018). Altered Brain Functional Connectome in Migraine with and without Restless Legs Syndrome: A Resting-State Functional MRI Study. *Frontiers in Neurology*, 9(January):1–10.
- Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., and Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, 8(8):665–670.
- Yeo, B. T., Krienen, F. M., Chee, M. W., and Buckner, R. L. (2014). Estimates of segregation and overlap of functional connectivity networks in the human cerebral cortex. *NeuroImage*, 88:212–227.
- Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zollei, L., Polimeni, J. R., Fischl, B., Liu, H., and Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of neurophysiology*, 106:1125–1165.
- Zalesky, A., Fornito, A., Cocchi, L., Gollo, L. L., and Breakspear, M. (2014). Time-resolved resting-state brain networks. *Proceedings of the National Academy of Sciences*, 111(28):10341–10346.