Environmental Influences on the Neural Basis of Reading and Language Development

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Environmental Influences on the Neural Basis of Reading and Language Development

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Abstract

Children's environments early in life can have a profound influence on brain development, which provides the foundation for language and cognition. These environments include broad, distant factors such as one's socioeconomic status (SES), as well as more immediate influences, such as how many words a parent speaks to a child. In this thesis, I describe two studies investigating specific brain-environment relationships, progressing from distal to proximal influences on children's language and literacy development.

The first study (chapter 2) examines how SES relates to reading and cortical structure in 6-9 year-old children with reading disability (RD), before and after an intensive summer intervention. At baseline, SES was correlated with children's vocabulary and cortical thickness in bilateral perisylvian and supramarginal regions. Furthermore, SES uniquely predicted reading improvement and cortical growth, with lower-SES children exhibiting the greatest behavioral and neuroanatomical changes. These findings contribute to the literature on socioeconomic effects on neuroanatomy and neuroplasticity by investigating these relationships in a developmentally atypical population.

The second study (chapters 3 and 4) explores how the real-world language exposure of younger children (ages 4-6 years) relates to their oral language skills and both structural and functional brain development, independent of SES. While the sheer amount of adult speech was unrelated to neural measures, the amount of adult-child conversational turns was strongly related to Broca’s area activation during language processing, as well as the coherence of left hemisphere white matter tracts connecting Broca’s area to auditory regions. Both neural measures in turn predicted children’s verbal skills, suggesting that conversational experience impacts language development via these neural mechanisms. This is the first evidence directly relating children’s immediate language environments with brain development.

The combined results of both studies expand on the well-documented socioeconomic differences in linguistic skill (the “achievement gap”) and concomitant brain development and suggest that these differences may arise as a result of variance in children’s interactive language experiences early in life. Implications for social, educational, and clinical practices are discussed.

Table of Contents

Dedication

This dissertation is dedicated in part to my mother, Diane Partee Romeo, for talking to me incessantly when I was a child (and as an adult). Given my findings, I am certain this contributed greatly to my neural and cognitive development. Your encouragement and unfailing support is undoubtedly the reason I am where I am today.

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Chapter 1: General Introduction

Individual Differences in Language and Literacy Development

Over the last several decades, research in developmental psychology has reinforced findings that individual children vary widely in their developmental trajectories of language and literacy (for review see Bates, Dale, & Thal, 1995; Kidd, Donnelly, & Christiansen, 2018; Nelson, 1981). While early nativists theorized that language acquisition was an innate attribute (e.g., Chomsky, 1965, 1968, 1976; Lenneberg, 1969; McNeil, 1966, 1970; Pinker, 1994) that developed similarly across all children with little variation, other developmental psycholinguists acknowledged undeniable individual differences in children's language development (Bloom, 1970; Bloom, Lightbrown, & Hood, 1975; Fenson et al., 1994; Fillmore, Kempler, & Wang, 1979; Nelson, 1973; Snow, 1972, 1977). These researchers presumed that the observed individual differences might be attributed to child-level factors, such as personality, motivation, and cognitive styles, and/or to various environmental influences (Nelson, 1981).

Half a century later, it is widely accepted that there exist both genetic ("nature") and experiential ("nurture") contributions to children's language and literacy acquisition (Chapman, 2000; Elman et al., 1996; Hirsh-Pasek & Golinkoff 1996). Meta-analyses of the heritability of language abilities reveal that genetic factors may account for over half of the variance in the spoken and written skills of individuals with language and literacy disorders (Grigorenko, 2004; Olson, 2002; Plomin & Kovas, 2005; Stromswold, 2001), but genes explain a substantially smaller portion of the variance in typically-developing children's language skills (Stromswold, 2001). The remainder of variance in both populations is due to individual differences in children's environments, such as sociocultural (e.g. parenting practices), educational (e.g., school quality), and even physical (e.g., head injury) influences. However, genes and environment do not act in isolation; the burgeoning field of epigenetics stipulates that gene expression can be controlled by environmental circumstances, and these interactions give rise to a variety of cognitive phenotypes (Gottlieb, 2007). Thus, the role of the environment during early childhood development is likely to be profound.

This thesis examines environmental contributions to the neural and cognitive development of children's language and literacy skills. Specifically, I begin by exploring the broad influence of socioeconomic status, which is widely documented to contribute to variation in children's linguistic skills. I then investigate more proximal aspects of children's immediate language environments, which might drive the pervasive individual differences observed across socioeconomic strata.

Socioeconomic Status: A Definition

While seemingly intuitive, the concept of socioeconomic status, or SES, has proven surprisingly difficult to define. White (1982) wrote "even though "everybody knows" what is meant by SES, … standard, widely accepted definitions of SES are difficult to find" (pp. 462). Farah (2017) describes SES as a dimension from those who are "worst off" to "best off" in a given society, in terms of both material (i.e., "economic") and non-material (i.e., "social") resources. This encompasses both the relative nature of an individual's "status" compared to their peers, as well as a reference to the types of resources that give rise to these differences. The terms social class, social status, and socioeconomic position are often used interchangeably with SES depending on the field of study (e.g., economics, sociology, public health, etc.); however, SES is the preferred term in psychology, and will be used throughout this thesis.

The measurement of SES is equally complex and multifaceted. Modern objective measurement is typically a three-pronged assessment of an individual's educational attainment, income, and occupation (Bradley & Corwyn, 2002; Duncan & Magnuson, 2012; Ensminger & Fothergill, 2003; Green, 1970; U.S. Bureau of the Census, 1963; White, 1982); however, occasional measures include neighborhood SES (Minh, Muhajarine, Janus, Brownell, & Guhn, 2017) and subjective assessments of social status (Adler, Epel, Castellazzo, & Ickovics, 2000). For children who have not completed schooling and have no occupation/income, the education, income, and occupation of parents, guardians, or primary caregivers are typically substituted. Correlations amongst these three factors are typically moderate (Braveman et al., 2005; Duncan & Magnuson, 2003), prompting many researchers to combine two or three into a single composite index. Individual SES measures, however, are often independently related to academic and health outcomes (Geyer, Hemstrom, Peter, & Vagero, 2006; Liberatos, Link, & Kelsey, 1988), suggesting that social and economic capital may influence development via separate, and perhaps multiplicative, mechanisms (Evans, 2004). Additionally, individual components of SES may change dynamically throughout the lifespan (Duncan, 1988; Magnuson, 2007) and are susceptible to different forms of intervention. As such, many researchers advocate for a comprehensive but separate analysis of various indices of SES (Braveman et al., 2005; Duncan & Magnuson, 2003, 2012; Entwisle & Astone, 1994; Kingston, 2000; Krieger, Williams, & Moss, 1997) when investigating SES effects on child outcomes.

Socioeconomic Status and the Achievement Gap

The "achievement gap" refers to the disparity in academic performance and/or educational attainment between students from disparate backgrounds, typically by either racial or socioeconomic determinants (Reardon, 2011). The achievement gap has been of great interest to researchers since the 1966 Coleman Report, a sweeping review of American education that was produced in response to the Civil Rights Act of 1964 (Coleman et al., 1966). Coleman and colleagues found that the biggest determinant of a child's educational success was his/her family background, rather than the physical and economic attributes of his/her school. Specifically, the report highlighted gaps in academic performance, such that white and higher-income students performed several grade levels higher in both reading and math than black and lower-income students (Coleman et al., 1966).

In the decades following the Coleman report, the black-white achievement gap began to shrink as a result of targeted educational policy. On the other hand, the income achievement gap more than doubled, such that by the year 2000, wealthier students on average scored 1.25 standard deviations higher on standardized tests (Reardon, 2011; U.S. Department of Education). Although the income achievement gap has modestly narrowed in the 1998–2010 period, the large gap and glacial pace of improvement would require another 60 to 110 years to ameliorate the gap in math and reading scores at Kindergarten entry (Reardon & Portilla, 2016). Furthermore, the achievement gap is not limited to standardized test scores, and extends IQ measures (Gottfried, Gottfried, Bathurst, Guerin, & Parramore, 2003; Mercy & Steelman, 1982; Smith, Brooks-Gunn, & Klevanov, 1997; von Stumm & Plomin, 2015), grade point averages (White, 1982), subject-specific academic achievement (Burchinal, Peisner-Feinberg, Pianta, & Howes, 2002; Sirin, 2005), high school completion rates (Brooks-Gunn & Duncan, 1997; Duncan & Magnuson, 2011), college entry and completion (Bailey & Dynarski, 2011), educational expectations (Farkas, 2011), and longer-term outcomes such as ultimate educational attainment, occupation and lifetime income, which contribute to a perpetuating cycle of poverty (Duncan, Telle, Ziol-Guest, & Kalil, 2010; Entwisle, Alexander, & Olson, 2005).

Despite its wide-reaching consequences across educational outcomes, the impact of SES is not uniform across all cognitive domains. In effort to determine which domains are most affected, Farah and colleagues conducted a series of studies directly comparing relationships between children's SES background and skills in language, executive functioning/cognitive control, visuospatial cognition, memory, working memory, and reward processing (Farah et al., 2006; Noble, McCandliss, & Farah, 2007; Noble, Norman, & Farah, 2005). While several domains exhibited significant relationships with SES, language skills were disproportionately affected, with lower-SES kindergarteners (Noble et al., 2005) and middle-school children (Farah et al., 2006) scoring a full standard deviation below middle-SES children on assessments of receptive vocabulary, grammar, and phonological awareness (a precursor to reading) skills—more than double the effect size of the next most affected domains, executive functioning and memory. When treating SES as a continuous variable, SES explained nearly a third (32%) of the variance in the language skills of first graders, which was significantly more than in any other cognitive domain (Noble et al., 2007).

Socioeconomic disparities in language and literacy skills are also evident before children reach school age (Ginsborg, 2006; Lee & Burkam, 2002; Ramey & Ramey, 2004). For example, a nationally representative study of over 20,000 children beginning Kindergarten in 1998 revealed that before they even entered school, children from the highest SES quintile scored 1.2 standard deviations higher on assessments of reading and language than children from the lowest quintile (Lee & Burkam, 2002). Further research suggests that children might be *most* susceptible to the negative consequences of low SES during the earliest years of life. Comparing long-term outcomes of children who experienced transient poverty at different ages reveals that experiencing poverty in the first five years of life, before school entry, affects cognitive outcomes more than experiencing poverty later in childhood or adolescence (Duncan, Yeung, Brooks-Gunn, & Smith, 1998; McLoyd, 1998). These frequently replicated findings have spurred research into the years preceding school entry, in effort to characterize the earliest SES disparities in language skill and potential causes.

The most studied language capacity in the years before school entry is vocabulary size. In a landmark study, Hart and Risley (1992, 1995) followed 42 socioeconomically diverse children from 7-36 months of age. While all children began speaking at similar ages, those from higher-SES families quickly developed larger vocabularies (as measured by the number of different words spoken), such that by age 3, higher-SES children had double the vocabulary size of lower-SES children (Hart & Risley, 1995). A decade later, analysis of a large, nationally representative sample of children revealed that the majority of the SES disparity in vocabulary was evident by 36 months of age, and that this gap widened throughout the remainder of the pre-school years before remaining stable upon Kindergarten entry (Farkas & Beron, 2004). Because it is difficult to reliably assess children's vocabulary before age 3, other researchers have relied on parent report of children's word knowledge (Arriaga, Fenson, Cronan, & Pethick, 1998), as well as empirical measures that do not require child responses, such as tracking infants' gaze while they listen to speech (Fernald, Marchman, & Weisleder, 2013). Using both techniques, Fernald and colleagues found significant SES disparities in children's vocabulary and online language processing efficiency as early as 18 months of age, and by 2 years of age, lower-SES children were 6 months behind their higher-SES peers in language skills (Fernald et al., 2013).

Socioeconomic disparities in other language skills are evident even earlier in infancy. Utilizing standardized language measures designed for infants and young children, Noble and colleagues found SES disparities in children's expressive language skills (e.g., verbally expressing needs and responding to questions) by 21 months, and differences in receptive languages skills (e.g., direction following, vocabulary knowledge, and spatial understanding) as early as 15 months (Noble, Engelhardt, et al., 2015). Furthermore, analysis of the Early Childhood Longitudinal Study, Birth Cohort (ECLS-B), a nationally representative longitudinal study of nearly 11,000 children born in 2001, revealed SES disparities in early pre-linguistic skills—such as babbling—as early as 9 months of age, with gaps widening through 24 months of age (Halle et al., 2009).

Unfortunately, socioeconomic disparities do not stop in early childhood. Upon school entry, gaps in oral language skills often persist and transform into gaps in literacy acquisition. Several studies have demonstrated socioeconomic disparities in young children's phonological awareness (Bowey, 1995; Lonigan, Burgess, Anthony, & Barker, 1998; McDowell, Lonigan, & Goldstein, 2007), and effective reading relies on this knowledge of the phonological sound structure of language along with comprehension of the written information (Lonigan, Burgess, & Anthony, 2000; NICHD Early Child Care Research Network, 2005; Whitehurst & Lonigan, 1998, 2001). In a longitudinal assessment of a subset of the children from the study by Hart and Risley (1992; 1995), Walker and colleagues found that socioeconomic disparities in early childhood verbal skills predicted not only children's third grade receptive and expressive language skills, but also their achievement in reading and spelling (Walker, Greenwood, Hart, & Carta, 1994). More recently it has been shown that the SES gap in oral language skills at kindergarten entry explains the majority of the achievement gap in both reading *and* math in 2nd through 4th grades (Durham, Farkas, Hammer, Bruce Tomblin, & Catts, 2007), and that vocabulary levels as early as 24-25 months of age can predict later academic achievement (Morgan, Farkas, Hillemeier, Hammer, & Maczuga, 2015) and IQ (Marchman & Fernald, 2008), independent of SES.

In sum, these studies suggest that the socioeconomic achievement gap is particularly pervasive in language and literacy skills, and that the precursors to these disparities arise long before children arrive at school. This raises the question of how SES differences in children's language skills arise in the first several years of life, which has been a topic of intense study for many decades. Setting aside the potential for genetic difference in language capacities, we must examine aspects of children's early environments.

The Effects of Children's Early Language Environments

In the late 1960s, in effort to refute the hypothesis that language acquisition was an innate process occurring independent of environmental influence, developmental psycholinguists began to examine the characteristics of speech directed to children, primarily by mothers (Snow, 1977). These early studies noted specific acoustic, semantic and grammatical characteristics of adults' speech to children, originally termed "baby-talk," and subsequently rebranded first as motherese/parentese and most recently as infant/child-directed speech (for review, see Golinkoff, Can, Soderstrom, & Hirsh-Pasek, 2015; Newport, 1977; Saint-Georges et al., 2013; Soderstrom, 2007). According to the "motherese hypothesis," mothers modify and simplify their speech to children in order to help foster language development (Gleitman, Newport, & Gleitman, 1984; Snow, 1972; Snow & Ferguson, 1977). Researchers then began to systematically investigate whether children's language input influenced their language skills.

Such investigations took the form of both observational studies, in which investigators looked for correlated, naturally occurring variability in parental speech and child speech, and experimental studies, in which investigators manipulated children's language input in some way and then looked for effects in children's output (Hoff-Ginsberg & Shatz, 1982). Early observational studies revealed many significant relationships between children's linguistic input (i.e., frequency of specific syntactic structures or semantic categories) and their language development, both in terms of raw skill and acquisition rate (Cross, 1978; Furrow, Nelson, & Benedict, 1979; Gleitman et al., 1984; Hoff-Ginsberg, 1985, 1986; Moerk, 1972; Nelson, 1973; Newport, Gleitman, & Gleitman, 1977; Shatz, 1979). Similarly, experimental studies provided young children with repeated, structured responses to their natural utterances, for example, in the form of recasts, in which the semantic content of the child's utterance is repeated with an alternate syntactic structure (Nelson, 1977; Nelson, Carskaddon, & Bonvillian, 1973). Children selectively acquired the words and structures relevant to the targeted input, demonstrating a causal relationship between children's language exposure and language development.

Shortly after researchers linked language input to output, they began to investigate systematic individual differences in language input. One of the most pervasive findings concerned socioeconomic status. Specifically, multiple studies revealed that lower-SES children were exposed to a significantly smaller quantity of language in early childhood than their higher-SES peers (Hart & Risley, 1992, 1995; Hoff-Ginsberg, 1991; Huttenlocher, Vasilyeva, Waterfall, Vevea, & Hedges, 2007; Pan, Rowe, Singer, & Snow, 2005; Rowe, 2008). In the seminal study described above, Hart and Risley found that children from families with the lowest SES heard half as many words per hour as middle-SES children, and fewer than a third of the words heard by higher-SES children. When extrapolated over the first four years of life, this aggregates to a thirty million word gap in experience between children from the highest and lowest SES backgrounds (Hart & Risley, 1995).

Hart and Risley, however, were not only concerned with the *quantity* of linguistic input, but also the *quality*. They noted that higher-SES parents not only spoke more to their children overall, but also used more diverse vocabulary, more affirmatives and fewer prohibitions, more questions, and more linguistically beneficial responses such as repetitions, expansions, and extensions of child utterances, and they were generally more responsive, affirmative, and encouraging (Hart & Risley, 1995). The combination of these qualitative variables explained over 60% of the variance in children's IQs at 3 years of age.

Further research has found associations between SES and a number of other qualitative aspects of language exposure, including the mean length of utterance (Hoff, 2003; Hoff & Naigles, 2002; Hoff-Ginsberg, 1991; Rowe, 2008), syntactic complexity and diversity (Huttenlocher, Vasilyeva, Cymerman, & Levine, 2002; Naigles & Hoff-Ginsberg, 1998), sentence types (Snow et al., 1976), vocabulary sophistication (Rowe, 2012; Weizman & Snow, 2001), topical contingency and connectedness (Conway et al., 2018; Goldstein, King, & West, 2003; Hirsh-Pasek et al., 2015; Hoff-Ginsberg, 1991; Hoff-Ginsberg, 1998; Reed, Hirsh-Pasek, & Golinkoff 2016; Smith et al., 2018; Tamis-LeMonda, Kuchirko, & Song, 2014), temporal contiguity/fluency (Conway et al., 2018; Hirsh-Pasek et al., 2015; Smith et al., 2018; Tamis-LeMonda et al., 2014), gesture (Iverson, Capirci, Longobardi, & Cristina Caselli, 1999; Pan et al., 2005; Rowe & Goldin-Meadow, 2009; Rowe, Özçalişkan, & Goldin-Meadow, 2008), decontextualized language (Rowe, 2012), referential transparency (Cartmill et al., 2013), and conversational turn-taking (Hirsh-Pasek et al., 2015; Zimmerman et al., 2009). Several studies have found that these qualitative aspects have varying importance at different points in children's developmental trajectories (Hirsh-Pasek et al., 2015; Hoff & Naigles, 2002; Rowe, 2012), and may be more important than the sheer quantity of input in predicting children's language outcomes (Jones & Rowland, 2017; Rowe, 2012; Rowe, Leech, & Cabrera, 2017). Furthermore, the quantity and/or quality of children's early language experience statistically explains the SES achievement gaps in language skills (Hoff, 2003; Huttenlocher et al., 2002; Rowe & Goldin-Meadow, 2009).

Recognizing that children's language development is linked to their language input, researchers have since turned from descriptive studies toward investigations into the mechanisms underlying this input-output relationship. A series of eye-tracking studies from Fernald and colleagues found that the quantity and quality of caregivers' child-directed speech predicted children's later efficiency in real-time spoken language comprehension (Hurtado, Marchman, & Fernald, 2008; Weisleder & Fernald, 2013). Mediation analyses revealed that lexical processing efficiency partially explained the relationship between child-directed speech and vocabulary size, suggesting that increased early language exposure bolsters children's language learning systems. These differences in real-time processing may in turn impact syntactic comprehension at older ages (Huang, Leech, & Rowe, 2017) and further acquisition of new vocabulary (Pace, Luo, Hirsh-Pasek, & Golinkoff, 2017). Thus, differences in early language exposure may have cascading effects, not only by providing increased input, but also by strengthening children's ability to process and "filter" this language; likewise, parents' awareness of children's increasing processing capabilities may further mold their linguistic practices, thereby creating a feedback loop supporting language development (Arunachalam, 2016). Such mechanistic insights into children's language processing suggests the existence of socioeconomic effects on the neural architecture underlying language acquisition and development.

Socioeconomic Effects on Brain Structure and Function Underlying Language and Literacy Development

Owing to ethical constraints, research on the neurodevelopmental effects of SES has largely been descriptive in nature, aiming to establish naturally occurring SES correlations and/or high-low SES group differences in neural measures. Many of these studies have focused on structural measures of gray and white matter, which allows for the analysis of more trait-like differences that are independent of temporary state shifts and potential confounds due to experimental circumstances and/or task demands. Reviews on the relationships between SES and brain development in children and adults (Brito & Noble, 2014; Farah, 2017; Hackman & Farah, 2009; Hackman, Farah, & Meaney, 2010; Holz, Laucht, & Meyer-Lindenberg, 2015; Johnson, Riis, & Noble, 2016; Nelson & Sheridan, 2011; Raizada & Kishiyama, 2010; Tomalski & Johnson,

2010) find strong associations between SES and measures of cortical gray matter (volume, thickness, and surface area) as well as both white matter macrostructure (e.g., volume) and microstructure (e.g., diffusivity as measured by diffusion weighted imaging). Nearly all studies yielded positive correlations, such that higher-SES was associated with thicker, more voluminous gray matter and more coherent white matter connections in both regional and global indices. These differences are presumably due to a process of "biological embedding," by which the adverse influences associated with low-SES environments during early childhood affect later life outcomes via brain development (Hertzman, 1999). More specifically, lower-SES environments theoretically accelerate synaptic pruning and reduce myelination (Fox, Levitt, & Nelson, 2010; McLaughlin, Sheridan, & Nelson, 2017), and conversely, the positive influences of an enriched environment increase dendritic branching, synapse formation and maintenance, and myelination during sensitive periods of development (Baroncelli et al., 2010; Mohammed et al., 2002).

Many structural studies have found developmental socioeconomic differences in the volume, thickness, and surface area of cortical gray matter, as measured by magnetic resonance imaging (MRI). These relationships start very early, such that positive SES correlations with total cortical volume are visible in 5-week-old newborns (Betancourt et al., 2016), 5-month-old infants to 4 year-old children (Hanson et al., 2013) and 6-to-12-year-old elementary school children (Luby et al., 2013). More specifically, SES has been linked to a number of regions known to be involved in language and reading processes, with some indicating neural mechanisms linking SES to behavioral outcomes. SES is positively correlated with the volume of bilateral middle temporal, left fusiform, and right inferior occipito-temporal regions in 8-10 year-old children (Jednorog et al., 2012); the volume of left inferior frontal regions in 5 year-old children (Raizada, Richards, Meltzoff, & Kuhl, 2008); the volume of frontal and temporal lobes broadly in 4-22 year-olds, which partially mediates the SES gap in verbal and non-verbal achievement (Hair, Hanson, Wolfe, & Pollak, 2015); the thickness of broad bilateral occipito-temporal regions in 13-15 year-old adolescents, which is associated with school achievement (Mackey et al., 2015); and the surface area of bilateral inferior frontal, fusiform, occipito-temporal regions in 3-20 year-olds, which in turn correlates with language and reading scores (Noble, Houston, et al., 2015). SES also augments the time course of cortical maturation in many of these regions, with evidence of age × SES interactions in left inferior frontal gyrus (Noble, Houston, Kan, & Sowell, 2012), left fusiform gyrus (Piccolo, Merz, He, Sowell, & Noble, 2016), left superior temporal gyrus (Noble et al., 2012; Piccolo et al., 2016), and fronto-parietal regions as a whole (Hanson et al., 2013), such that lower-SES children exhibit slower cortical growth during early childhood and accelerated cortical thinning during later childhood and adolescence, which in turn relate to lower language scores. Additional findings suggest that neuroanatomical measures predict language skills independent of SES (Eckert, Lombardino, & Leonard, 2001), but also that SES moderates the relationship between cortical thickness and language and reading scores such that SES predicts language skills more strongly in children with thinner cortices, suggesting that high SES may protect against such a neurobiological risk factor (Brito, Piccolo, & Noble, 2017).

Evidence on the relationships between SES and white matter development is more mixed. While one study found a significant relationship between SES and total white matter volume in elementary-aged children (Luby et al., 2013), the same was not found for newborns (Betancourt et al., 2016), infants and preschoolers (Hanson et al., 2013), or adolescents (Mackey et al., 2015), suggesting that SES may selectively influence white matter macrostructure at very specific periods in child development (barring a methodological differences explanation). Other studies have employed diffusion-weighted imaging to measure white matter microstructure, typically utilizing fractional anisotropy (FA)—a summary measure of the strength and directionality of the movement of water molecules that serves as a proxy for fiber organization and coherence (Lebel, Treit, & Beaulieu, 2017). While some studies have failed to find a relationship between SES and FA in a whole brain analysis with children (Jednorog et al., 2012) and adults (Chiang et al., 2011), others have identified significant associations between SES and FA in association fiber pathways known to underlie language development, most notably the left superior longitudinal fasciculus (SLF) (Dufford & Kim, 2017; Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2013; Noble, Korgaonkar, Grieve, & Brickman, 2013; Rosen, Sheridan, Sambrook, Meltzoff, & McLaughlin, 2018; Ursache, Noble, & PING Study, 2016) and the inferior longitudinal fasciculus (ILF) (Dufford & Kim, 2017; Gullick, Demir-Lira, & Booth, 2016), both of which have been linked to language and reading skills in adults and children (Dick, Bernal, & Tremblay, 2014). Furthermore, SES has been found to interact with the heritability of fiber integrity, such that the microstructure of lower-SES individuals is more environmentally determined (Chiang et al., 2011).

In addition to neuroanatomical differences, numerous studies of brain function have investigated relationships between SES and neurophysiology relevant to language processing and development. Studies with infants and young children often employ resting electroencephalography (EEG) to study relationships between SES and frequency band power spectra (a measure of neural oscillatory amplitude), because resting EEG does not require any sort of behavioral response to measure brain activity. Typical EEG maturation in childhood involves a developmental decrease in overall absolute power, accompanied by decreases in the relative power in low-frequency bands (i.e., theta and delta bands) and increases in the relative power in high-frequency bands (i.e., alpha, beta and gamma bands) (Matoušek & Petersén, 1973; Saby & Marshall, 2012). However, low SES children often exhibit oscillation patterns indicative of a maturational lag—higher levels of absolute power, in addition to higher percentages of low-frequency power and lower percentages of high-frequency power (Harmony, Marosi, Diaz de Leon, Becker, & Fernandez, 1990; Otero, 1994; Otero, 1997; Otero, Pliego-Rivero, Fernandez, & Ricardo, 2003), similar to patterns seen in children with learning/ neurodevelopmental disorders (Barry, Clarke, & Johnstone, 2003; Kinsbourne, 1973) and children experiencing severe deprivation and neglect (Marshall, Fox, & BEIP Core Group, 2004; McLaughlin et al., 2010). More recent studies indicate that SES differences in high-frequency gamma bands arise within the first year of life, such that there are no significant differences at birth (Brito, Fifer, Myers, Elliott, & Noble, 2016), yet disparities arise in frontal regions by the age of 6-9 months (Tomalski et al., 2013)—a pattern that has been linked to language development and impairments (Benasich, Gou, Choudhury, & Harris, 2008; Gou, Choudhury, & Benasich, 2011).

As children become older, it becomes more feasible to investigate socioeconomic differences in language related brain activity with task-based functional MRI (fMRI). In contrast to resting EEG, task-based fMRI requires the participants to execute a mental task while brain activation is quantified and compared across conditions and/or individuals. With reference to language and literacy development, the majority of SES-focused fMRI studies have utilized tasks related to reading and phonological awareness, including auditory and printed rhyming judgments (Demir, Prado, & Booth, 2015; Demir-Lira, Prado, & Booth, 2016; Raizada et al., 2008) and reading words and pseudowords (Monzalvo, Fluss, Billard, Dehaene, & Dehaene-Lambertz, 2012; Noble, Wolmetz, Ochs, Farah, & McCandliss, 2006). The rhyming studies have found significant correlations between SES and language-related activation in broad, left perisylvian regions in 8-13 year-olds (Demir et al., 2015; Demir-Lira et al., 2016) and the degree of left lateralization in inferior frontal regions in pre-reading 5 year-olds (Raizada et al., 2008). However, in a reading study with 6-9 year-olds, SES modulated the relationship between phonological awareness skills and brain activity in left fusiform and perisylvian regions during reading, such that lower-SES children exhibited a stronger brain-behavior relationship than their higher-SES peers, who exhibited higher fusiform activation and higher reading scores no matter their phonological awareness scores (Noble, Farah, & McCandliss, 2006; Noble, Wolmetz, et al., 2006). These results suggest that early environmental experiences, such as increased exposure to language and literacy practices, may have buffered the low phonological skill in higher-SES children, resulting in increased fusiform recruitment and better reading outcomes. Similarly, SES modulated the relation between phonemic discrimination and brain activation in left prefrontal regions, such that 7-12 year-old children with lower perceptual skills show tighter links between their environment and brain activation (Conant, Liebenthal, Desai, & Binder, 2017); this is commensurate with findings that lower SES may be associated with noisier, less efficient processing of speech (Skoe, Krizman, & Kraus, 2013), which may also be a result of diminished early linguistic exposure. However, neither of these hypotheses about the neural effects of early language exposure has yet been explored.

Present Research Questions

While the last decade has seen proliferation of studies on the functional and structural neural correlates of SES, many gaps remain. Given that SES has the greatest neurocognitive effects on the language domain (Farah et al., 2006; Noble et al., 2007; Noble et al., 2005), there are surprisingly few studies that specifically focus on SES relationships with the neuroanatomy, neurophysiology, and neuroplasticity that specifically underlie speech, language, and literacy development. The few that have been conducted have examined typically developing children within the average skill range; however, given the strong relationship between SES and language skills, children from lower-SES backgrounds are at increased risk of language and reading impairment. This may result in categorically different brain-behavior relationships across SES, which may in turn warrant different treatment methods. These hypotheses warrant a deeper investigation into the relationship between SES and neural development in children with language/reading impairments.

Additionally, multiple neuroimaging studies reviewed above hypothesize that the myriad SES differences in brain structure and function are likely the results of proximal differences in early language environments (Brito & Noble, 2014; Johnson et al., 2016; Noble et al., 2012; Perkins, Finegood, & Swain, 2013). Similarly, the psychological literature reviewed explains the links between systematic SES differences in children's early language experience and the gaps seen in their later language, reading, and academic skills; but, any causal model by which experience shapes behavior must also include how experience first shapes the brain.

Indeed, models of how SES shapes behavior include both proximal influences, such as language exposure and other forms of cognitive stimulation/deprivation, as well as neural mechanisms mediating the input-output relationship (Brito & Noble, 2014; Johnson et al., 2016; McLaughlin, Sheridan, & Lambert, 2014; Noble et al., 2012; Perkins et al., 2013; Sheridan & McLaughlin, 2014). However, there is currently no research on the neural mechanisms specifically relating children's early language environments to their language skills. Investigation of these mechanisms may better inform evidence-based interventions.

Thus, in this thesis I will investigate how SES relates specifically to neural measures underlying language and literacy development, and whether certain aspects of children's language environment drive this neural development independent of SES. More specifically, in study 1 (chapter 2), I ask how SES relates to neuroanatomy and neuroplasticity in children with reading and language difficulties. The findings of this study lead me to ask in study 2 (chapters 3 and 4) whether children's early language experience, *independent* of SES, relate to their brain structure and function, and if so, which aspects of the language environment are most important. After detailing the methods, results, and brief discussions for each of these studies, I conclude with a general discussion of the findings and how they fit into the wider body of literature on SES, language acquisition, and brain development. I also discuss the implications of this research for clinical and educational practice, and outstanding questions for future research.

Chapter 2: Relationship between Socioeconomic Status and Brain Structure and Plasticity in Children with Reading Disability

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Author Contributions

J. A. Christodoulou and J. D. E. Gabrieli developed the initial study. K. K. Halverson, J. Murtagh, A. B. Cyr, P. Chang, and J. A. Christodoulou collected the data. C. Schimmel conducted data quality assurance. R. R. Romeo developed the present hypotheses and performed the data analysis and interpretation under the supervision of J. D. E. Gabrieli and J. A. Christodoulou. R. R. Romeo, J. D. E. Gabrieli, and J. A. Christodoulou wrote the manuscript. All authors approved the final version of the published manuscript.

Abstract

Although reading disability (RD) and socioeconomic status (SES) are independently associated with variation in reading ability and brain structure/function, the joint influence of SES and RD on neuroanatomy and/or response to intervention is unknown. Sixty-five children with RD (ages 6 to 9) with diverse SES were assigned to an intensive, 6-week summer reading intervention (*n* = 40) or to a waiting-list control group (*n* = 25). Before and after the 6-week period, all children completed standardized reading assessments and magnetic resonance imaging (MRI) to measure cortical thickness. At baseline, higher SES correlated with greater vocabulary and greater cortical thickness in bilateral perisylvian and supramarginal regions—especially in left pars opercularis. Within the intervention group, lower SES was associated with both greater reading improvement and greater cortical thickening across broad, bilateral occipitotemporal and temporoparietal regions following the intervention. Additionally, treatment responders (*n* = 20), compared to treatment non-responders (*n* = 19), exhibited significantly greater cortical thickening within similar regions. The waiting control and non-responder groups exhibited developmentally-typical, non-significant cortical thinning during this time period. These findings indicate that effective summer reading intervention is coupled with cortical growth and is especially beneficial for children with RD who come from lower-SES home environments.

Introduction

Reading is the bedrock of early education, and difficulty in reading has widespread and long-term consequences. Two major factors associated with difficulty in learning to read are reading disability (RD) and socioeconomic status (SES). Reading disability (RD) is the most prevalent type of learning disability (Shaywitz, Morris, & Shaywitz, 2008), and is estimated to affect about 10% of school-age children (Shaywitz, 1998). Developmental dyslexia describes children with RD who demonstrate difficulty with single word reading accuracy or fluency in the context of intact cognitive skills and adequate educational opportunity (Lyon, Shaywitz, & Shaywitz, 2003). SES is a common conceptualization of the social and economic status of an individual or group that is often measured by some combination of parental educational attainment, income, and occupation. Higher SES is associated with better reading outcomes (Peterson & Pennington, 2015), but unlike RD, SES is associated with environmental factors such as home language environment (Hoff, Laursen, & Tardif, 2002) and quality of school instruction (Lee & Burkam, 2002). Here we asked whether there are neuroanatomical brain differences in young children (ages 6 to 9) with RD from varying SES backgrounds, and whether a reading intervention yields similar or dissimilar reading benefits and brain plasticity in children across the SES continuum.

Neuroimaging studies of children and adults with RD have revealed both structural and functional differences as compared to typical readers (for review, see Norton, Beach, & Gabrieli, 2015). Structurally, RD is typically associated with cortical gray matter reductions in bilateral temporoparietal regions underlying phonological processing (Brown et al., 2001; Eckert, 2004; Hoeft et al., 2007; Silani et al., 2005; Vinckenbosch, Robichon, & Eliez, 2005) and left occipitotemporal regions underlying visual whole-word recognition (Eckert, 2004; Kronbichler et al., 2008; Silani et al., 2005; Steinbrink et al., 2008), as well as parts of the cerebellum bilaterally (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2003; Kronbichler et al., 2008; for meta-analyses, see Linkersdörfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Richlan, Kronbichler, & Wimmer, 2013). These gray matter disparities are evident even in young children with a family history of dyslexia who have yet to learn how to read (Raschle, Chang, & Gaab, 2011), suggesting that these differences are not purely a consequence of reading difficulty. Some studies have found additional gray matter reductions in canonical language regions, including left inferior frontal cortex (including Broca's area) and left superior temporal cortex (including Wernicke's area) in both children with RD (Eckert et al., 2003; Hoeft et al., 2007) and adults with RD (Brambati et al., 2004; Brown et al., 2001; Steinbrink et al., 2008). These neuroanatomical differences in left-hemisphere language areas are consistent with evidence that a weakness in a specific component of language, namely some aspects of phonological processing, is one of the most common pre-reading predictors and continuing correlates of RD (Melby-Lervåg, Lyster, & Hulme, 2012).

There is also evidence for brain plasticity following intervention in both children and adults with RD. Most neuroimaging studies examining intervention-induced plasticity have measured functional changes, and often report normalization of pre-intervention hypoactivation in left-hemisphere regions associated with reading and language, as well as increased activation in right-hemisphere homologues interpreted as compensatory plasticity (for reviews, see Barquero, Davis, & Cutting, 2014; Gabrieli, Christodoulou, O'Loughlin, & Eddy, 2010). The two studies examining intervention-induced structural plasticity have reported bilateral changes in the hippocampal region, left precuneus, and right cerebellum (Krafnick, Flowers, Napoliello, &

Eden, 2011) and in white-matter microstructure of the left anterior centrum semiovale that correlated with improvement in phonological decoding ability (Keller & Just, 2009).

Socioeconomic status is also strongly associated with reading skill (Bowey, 1995; Hecht, Burgess, Torgesen, Wagner, & Rashotte, 2000; White, 1982). The disproportionate influence of SES on reading and language skills, as compared to other cognitive domains (Farah et al., 2006; Noble et al., 2007; Noble et al., 2005) is thought to arise from variation in the quantity and complexity of early language exposure (for reviews, see Hoff, 2006; Perkins et al., 2013; Schwab & Lew-Williams, 2016). SES-related differences in brain structure are evident as early as one month of age (Betancourt et al., 2016), and appear to increase with age (Hanson et al., 2013; Noble et al., 2012). Specifically, lower SES is correlated with reduced activation in left perisylvian regions during language-related tasks (Raizada et al., 2008) and reduced gray matter in both left perisylvian regions (Noble, Houston, et al., 2015; Noble et al., 2012) and bilateral occipitotemporal regions (Jednorog et al., 2012; Mackey et al., 2015), among many other regions (for review, see Brito & Noble, 2014).

Although separate lines of evidence have revealed neuroanatomical differences in left-hemisphere language areas in relation to RD and SES, these two lines of evidence have yet to be integrated. This is an important gap in knowledge to address, because children from lower-SES backgrounds disproportionately meet RD criteria (Peterson & Pennington, 2015) and are diagnosed with specific learning disabilities at significantly higher rates than children from higher-SES backgrounds (Shifrer, Muller, & Callahan, 2011). In 2015, 4th and 8th grade students eligible for the National School Lunch Program (indicating low family income) were 2.5 times more likely to read at a “below proficient” level than students from higher-income families (U.S. Department of Education 2015). This may be related to gene × environment interactions, such that a genetic risk for RD is amplified by decreased access to reading/literary resources in lower-SES environments (Mascheretti et al., 2013), and/or that potentially typical-readers are not achieving their potential due to decreased resources (Friend, DeFries, & Olson, 2008). Therefore, it is important to understand whether RD arises from similar brain differences and responds similarly or differently to interventions for lower- and higher-SES students.

There are currently no studies examining RD and SES interactions in regard to brain structure, but two functional magnetic resonance imaging (fMRI) studies examining this interaction have yielded conflicting results. One study investigated the effects of SES on the relationship between phonological awareness, word decoding, and brain activation in children (Noble, Wolmetz, et al., 2006). Participants (6-9 years old) were recruited based on a history of reading difficulty and, on average, scored in the low- to below-average range on standardized assessments of pseudoword reading skills and phonological awareness. Among children with the lowest phonological awareness scores, higher-SES children exhibited an increased response, versus lower-SES children, in left fusiform and perisylvian regions while viewing pseudowords versus a fixation cross (Noble, Wolmetz, et al., 2006). The other study investigated the effects of SES on brain activation while both typical readers and children with a diagnosis of dyslexia (8-10 years old) viewed words (versus houses, faces, checkerboard, and blank screen) and listened to speech (versus foreign language and silence) (Monzalvo et al., 2012). Although there were SES-related activation differences for the speech task in right-hemisphere perisylvian regions, there were no SES-related differences during the visual word task (Monzalvo et al., 2012). These two functional studies reached conflicting conclusions about the relation between SES and functional activation in response to print, which could be explained by any number of methodological differences, including language (English vs. French), participant age (6-9 vs. 8-10 years), sample size (38 vs. 23 non-control children), inclusion criteria (history of reading difficulty vs. externally diagnosed dyslexia), SES measurement (continuous variable based on parental education, occupation, income-to-needs ratio vs. categorical variable based on school districts), and/or print stimuli (pseudowords vs. short familiar real words).

The most important goal of understanding RD is to help people overcome reading difficulties, to the extent possible, through educational intervention. Although SES is relatively easy to measure and known to be associated with reading skill, very few studies have asked whether participant response to an intervention varies in relation to SES. A review of 14 studies reported behavioral factors predicting responsiveness to literacy interventions (Lam & McMaster, 2014). Although the majority of studies collected some sort of SES information, only 4 studies analyzed SES as a predictive factor; of these, 2 found that higher SES predicted better treatment response on reading outcome measures (Hatcher et al., 2006; Morris et al., 2012). The other studies either treated SES as a nuisance variable or as a descriptive characterization of their overall sample. Similarly, neuroimaging studies examining brain plasticity associated with intervention rarely consider the SES of participants. In a review of functional neuroimaging studies of reading interventions (Barquero et al., 2014), only 4 of 22 studies reported participant SES information. Of these, only one study (Bach, Richardson, Brandeis, Martin, & Brem, 2013) examined the relationship between SES and intervention outcomes, albeit only in behavioral outcomes. Although this specific study of Swiss-German children did not reveal SES as predictive of intervention efficacy, relationships between SES and academic achievement appear to be stronger in individuals from the United States (Tucker-Drob & Bates, 2016), potentially due to greater SES variability in educational quality in the United States. Given how strong the effects of U.S. SES are on both children's reading ability and their neural architecture, it may be that SES is related to behavioral and neuroanatomical intervention response sensitivity in U.S. children.

In the present study, we recruited young children with RD from a broad SES range and assigned them either to an intensive reading intervention during the school summer break or to a waiting-list control group. First, we asked whether cortical thickness varied by SES at baseline, because it is unknown whether there is such a relation between RD and SES neuroanatomically. Based on the literature linking SES to brain structure in typically developing children (e.g., Brito & Noble, 2014), we hypothesized that higher-SES children with RD would exhibit thicker cortex, especially in inferior frontal and posterior temporal regions canonically associated with language and reading. Second, we asked whether SES was related to intervention efficacy in relation to reading outcomes and structural brain plasticity. While there is some evidence of structural brain plasticity associated with reading intervention (Keller & Just, 2009; Krafnick et al., 2011), the specific effect on cortical thickness and the relations of plasticity to SES and treatment response are unknown. Behaviorally, we hypothesized that higher-SES children would respond more positively to the intervention, based on previous intervention response findings (Hatcher et al., 2006; Morris et al., 2012; Torgesen et al., 1999). Furthermore, we predicted that the children who exhibited greater behavioral improvement would also exhibit greater gains in cortical thickness.

Materials and Methods

Participants

Children (*n* = 65, 22 female) with RD who were between the ages of 6 and 9 years (*M* = 7.75 years, *SD* = 0.64 years) and completing grade 1 or 2 were recruited from communities in an SES-diverse Northeast region around a major urban center. Specifically, children were recruited both from the community at-large (*n* = 50) and from a local partner school (*n* = 15), which was an SES-diverse urban charter school.

Inclusion criteria required participants to have a history of reading difficulty based on parental report, a current demonstration of reading difficulty, and no neurological or psychiatric impairments or associated medications with the exception of Attention Deficit Hyperactivity Disorder (ADHD). Eleven children carried a diagnosis of ADHD, a disorder highly co-morbid with reading disability (Germano, Gagliano, & Curatolo, 2010), and 6 of these children received daily medication. However, they did not differ from the remaining participants on any behavioral measures or demographic variables (all $p > 0.13$), so all 11 were included in the final sample. Additionally, all participants were native English speakers, although 6 participants were simultaneous bilinguals (natively acquired English and another language from birth), and 5 others had exposure to a second language outside of typical foreign language class at school. There was no relationship between bilingualism and any demographic variable, assessment score, group assignment, or intervention response (all $p > 0.05$). Behavioral findings from a subset of these children (*n* = 47) who participated in the first phase of the intervention study were previously reported (Christodoulou et al., 2017). Findings reported here are from all children who participated in the intervention study except for those whose neuroimaging data were problematic (described below). Written informed consent was obtained from parents, and written assent was obtained from all child participants. All procedures were approved by the Institutional Review Board at the Massachusetts Institute of Technology.

Demographics

Participants' SES was determined by a composite of maternal education and occupational prestige, as calculated by the *Barratt Simplified Measure of Social Status* (BSMSS; Barratt, 2006). Maternal factors were chosen because they are the most frequently used SES measure (Ensminger & Fothergill, 2003), are considered to have stronger relation than paternal factors to cognitive development in younger children (Mercy & Steelman, 1982), and because 13 participants lived in single-mother homes. For the 4 participants whose mothers were full-time homemakers, paternal occupation was substituted and combined with maternal education. The BSMSS scale yields possible scores ranging from 8 (lower SES) to 66 (higher SES); participants' scores ranged from 17 to 66 ($M = 47.35$, $SD = 11.75$). Maternal education and occupation scores were highly correlated (Pearson's $r = 0.76$, $p < 1^{-12}$), supporting their combination into a composite measure. Additionally, 48 participants (74%) optionally reported their annual gross family income, which ranged from \$15,000 to >\$120,000 (M = \$77,400, SD = \$33,550). Income was highly correlated with maternal education ($r = 0.53$, $p < 0.001$), maternal occupation ($r = 0.47$, $p < 0.001$), and total BSMSS scores ($r = 0.51$, $p < 0.001$); thus, BSMSS scores were judged to be a valid index of SES. Unless otherwise noted, SES was treated as a continuous variable for all analyses.

Behavioral Assessments

Screening Session

Participants were first invited to a screening session, at which they completed a battery of tests. Non-verbal cognition was assessed with the Matrices subtest of the *Kaufman Brief Intelligence Test, 2nd edition* (KBIT-2; Kaufman & Kaufman, 2004). Core reading subskills were assessed with the Elision and Nonword Repetition subtests of the *Comprehensive Test of Phonological Processing* (CTOPP; Wagner, Torgesen, & Rashotte, 1999), and the Objects, Letters, and 2-set Letters and Numbers subtests of the *Rapid Automatized Naming and Rapid Alternating Stimulus Tests* (RAN/RAS; Wolf & Denckla, 2005). Reading was assessed by the Oral Reading Fluency subtest of the *Dynamic Indicators of Basic Early Literacy Skills* (DIBELS; Good & Kaminski, 2002).

Participants were included in the final RD sample ($n = 65$) if they (1) scored 'At Risk' or 'Some Risk' on the DIBELS (Good & Kaminski, 2002), a criterion-referenced benchmark assessment ($n = 56$), and/or (2) scored below the 25th percentile on at least three of five phonological processing (CTOPP; Wagner et al., 1999) and rapid naming (RAN/RAS; Wolf & Denckla, 2005) subtests—skills that are highly associated with reading ability ($n = 32$). Twenty-three participants met both criteria, and there were no demographic differences between the two inclusion criteria (all $p > 0.23$). Additionally, all participants were required to score at or above the 16th percentile on a measure of non-verbal cognitive ability (Matrices subtest, KBIT-2; Kaufman & Kaufman, 2004). Twenty-four participants (37%) possessed an external diagnosis of dyslexia or a reading-based learning disability.

Pre-Intervention Characterization

After meeting inclusion criteria, participants completed additional assessments of language skills. Two additional CTOPP subtests (Blending Words and Memory for Digits) were administered to better characterize phonological processing (Wagner et al., 1999). Receptive vocabulary was assessed with the *Peabody Picture Vocabulary Test, 4th edition* (PPVT-4; Dunn & Dunn, 2007).

Pre- & Post-Intervention Outcome Measures

Four *a priori* outcome measures were administered before (pre-test) and after (post-test) the intervention/waiting period: untimed word reading [Word Identification subtest (Word ID), *Woodcock Reading Mastery Test, 3rd edition* (WRMT-3); Woodcock 2011], untimed pseudoword reading [Word Attack subtest (Word Attack), WRMT-3; Woodcock, 2011], timed word reading [Sight Word Efficiency subtest (SWE), *Test of Word Reading Efficiency, 2nd edition* (TOWRE-2); Torgesen, Wagner, & Rashotte, 2012], and timed pseudoword reading [Phonemic Decoding Efficiency subtest (PDE), TOWRE-2; Torgesen et al., 2012]. For all four subtests, Form A was administered at pre-test, and Form B was administered at post-test to avoid practice/familiarity effects. High alternate form reliability has been reported for standardized tests scores on both the WRMT-3 subtests (Word ID $r = 0.93$, Word Attack $r = 0.76$; Woodcock, 2011) and the TOWRE-2 subtests (SWE $r = 0.90$, PDE $r = 0.92$; Torgesen et al., 2012). Thus, we report changes in standard scores, because changes in raw scores are difficult to interpret. The primary outcome measure was a composite reading score obtained by averaging the standard scores from all four subtests.

Confirming inclusion criteria from screening, all participants either (1) scored below the 25th percentile on at least 2 of the 4 reading subtests ($n = 52$), and/or (2) possessed a discrepancy of 15 or more standard points between the reading composite score and the non-verbal cognitive ability score ($n = 43$). Thirty participants met both descriptions. There were no demographic differences (including age, grade, gender, bilingual status, diagnoses, and SES) between these two descriptions (all $|t| < 1.15$, all $\chi^2 < 1.71$, all $p > 0.17$).

Group Assignment

After all pre-test assessments were completed, the fifty children recruited from the community at-large were randomly assigned to either receive an intensive summer reading intervention ($n = 25$) or to a waiting-list control group ($n = 25$), who received equal access to services after post-test assessments. For the intervention-assigned participants in this community sample, intervention was based in Cambridge, MA in dedicated space at MIT ("Site 1"). Children recruited from the local partner school ($n = 15$), were all assigned to the intervention group as a condition of school participation, and instruction was delivered on-site at the school ("Site 2"). The overall intervention group was therefore oversubscribed with 15 non-randomly assigned students, which allowed for better investigation of individual differences in response to treatment. After pre-test, one participant from the community at-large who had been randomly assigned to the intervention did not continue study participation, leaving 39 participants in the intervention group.

Intervention and control groups did not differ significantly on any demographic or assessment measures, including age, grade, gender, portion with comorbid ADHD, bilingualism, SES, nonverbal cognition, vocabulary, and all reading skills (all $|t| < 0.76$, all $\chi^2 < 1.93$, all $p > 0.16$). Within the full treatment group ($n = 39$), there was a marginal difference in SES by site [$t(37) = 1.87$, $p = 0.07$], which was driven by one outlier from the partner school with an SES 2.6 standard deviations below the sample mean. If excluded, no significant SES difference remained between assignment sites [Site 1 $M = 48$, $SD = 12.6$, Site 2 $M = 42$, $SD = 11.4$, $t(36) < 1.50$, $p > 0.14$]. There were no differences between sites on any other demographics (age, grade, gender, ADHD, bilingualism), pre-test reading scores (all $|t| < 0.26$, all $\chi^2 < 0.83$, all $p > 0.36$), or intervention response (see Results below). Thus, participants from both sites who completed the intervention were combined into a single treatment group ($n = 39$).

Intervention

The intervention is described in detail in a prior publication (Christodoulou et al., 2017). In brief, intervention participants (at both sites) received an intensive version of the Lindamood-Bell *Seeing Stars: Symbol Imagery for Fluency, Orthography, Sight Words, and Spelling* (Bell, 2007) program in small groups (3-5 children) by trained Lindamood-Bell teaching staff. *Seeing Stars* is a multisensory remedial approach with a primary focus on training orthographic and phonological processing to improve reading accuracy, fluency, and comprehension. The program was held 4 hours per day, 5 days per week, for 6 weeks during the summer break from school, with a high rate of attendance ($M = 113$ total hours, $SD = 7.5$). Total number of hours of attendance was not correlated with any demographic variable, intervention site, pre-test or post-test assessment score, or treatment response (all $|r| < 0.23$, all $p > 0.20$).

Neuroimaging Data Acquisition

Participants completed neuroimaging sessions at pre-test and post-test. First, children were acclimated to the MRI environment and practiced lying still in a mock MRI scanner. Data were then acquired on a 3 Tesla Siemens MAGNETOM Trio Tim scanner equipped for echo planar imaging (EPI; Siemens, Erlangen, Germany) with a 32-channel phased array head coil. First, an automated scout image was acquired, and shimming procedures were performed to optimize field homogeneity. Then a whole-head, high-resolution T1-weighted multi-echo MPRAGE (van der Kouwe, Benner, Salat, & Fischl, 2008) structural image was acquired using a protocol optimized for movement-prone pediatric populations (TR = 2530 ms, TE = 1.64 ms, FoV = 220mm, and flip angle = 7°) yielding 176 slices with 1-mm isotropic resolution (Tisdall et al., 2012). All neuroimaging took place at the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research, at the Massachusetts Institute of Technology.

Assessment Timeline

Behavioral testing and MRI scanning took place on two separate days to avoid child fatigue. All pre-test behavioral assessments occurred within the 5 weeks prior to the start of the intervention (M = 18 days prior to start of intervention, SD = 12 days). Given constraints of MRI availability during early summer, baseline neuroimaging occurred over a longer timespan within the 10 weeks prior to the start of intervention (M = 39 days prior to start of intervention, SD = 19 days). There were no differences in the timing of pre-test assessments or scanning between intervention and control groups [$t(59) = 0.82$, $p > 0.4$] nor was there a relationship with any demographic variable (all $|r| < 0.19$, all $p > 0.14$). Similarly, all post-test assessments (both behavioral and MRI scanning) occurred within the 6 weeks immediately following the conclusion of the intervention (behavioral: $M = 15$ days after intervention conclusion, $SD = 8$ days; MRI: $M = 11$ days after intervention conclusion, $SD = 8$ days). The average time difference between pre and post behavioral assessments was 2.16 months ($SD = 0.32$), and the average time difference between pre and post MRI scanning was 2.71 months ($SD = 0.69$). Again, there was no relationship between date of post-testing and any demographic variable (all $|r| < 0.13$, all $p > 0.3$). Unintentionally, intervention and control groups differed marginally in the timespan between intervention conclusion and post-test MRI scanning [$t(56) = 1.99$, $p = 0.052$], although the average difference between groups was only 4.3 days (intervention group $M = 11.4$ days after conclusion; control group $M = 15.7$ days after conclusion), which is a negligible amount of time for confounding cortical changes to occur. However, to ensure correction for potential timing differences, the time interval between intervention conclusion and post-scanning was added as a nuisance variable to between group longitudinal cortical thickness analysis, which did not affect results.

Behavioral Analyses

Change scores were computed individually for each of the four assessments chosen *a priori* as outcome measures. Additionally, a composite change score was computed subtracting the average pre-test standard score from the average post-test standard score. Repeated measures ANOVAs were used to determine the group effect of the reading intervention, and multiple regressions were used to determine which participant-level factors were associated with treatment response.

Structural Image Analyses

T1-weighted images were visually inspected for image quality. Two trained observers, who were blind to participant SES and behavioral measures, rated each image on a scale of 1 (perfect) to 5 (unusable) based on a visual guide of artifacts associated with motion created in-house. If ratings differed, the two observers discussed their ratings until a consensus was reached. Three participants were excluded from pre-test neuroimaging analyses because of poor image quality (pre-test $n = 62$), and six additional participants (3 from each assigned group) had unusable images at post-test. The remaining 55 participants [19 waiting control, 36 intervention (18 each treatment responders/non-responders)] had images of equivalent quality at both time points, which is necessary for accurate measurement of cortical changes. Quality ratings were not correlated with SES, any behavioral measures, or intervention group (all $p > 0.2$).

Cortical reconstruction was conducted with FreeSurfer Version 5.3.0 (Fischl, 2012). First, a semi-automated processing stream (recon-all) with default parameters completed motion and intensity correction, surface-based registration, spatial smoothing, subcortical segmentation, and parcellation of cortical white and gray matter boundaries. Pial and white matter surfaces were then manually edited as needed. An observer blind to participant SES and behavioral measures confirmed the accuracy of the final surfaces.

All T1 images from both time points were resampled to a standard brain (fsaverage) and smoothed with a 10-mm full-width half-maximum kernel. Cortical thickness was defined at each location as the distance between the white and pial surfaces (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). To examine cross-sectional differences at the pre-test time point, general linear models were constructed to test the whole brain for correlations between cortical thickness and SES, with participant gender and age as nuisance variables. Whole-brain analyses were corrected for multiple comparisons using a Monte Carlo simulation with 10,000 repetitions and Bonferroni adjusted for both hemispheres (cluster-forming $p < .05$, cluster-wise $p < .05$; Hagler, Saygin, & Sereno, 2006). Volumetric analyses were conducted on the 35 parcellations of the Desikan-Killiany Atlas (Desikan et al., 2006) automatically segmented in FreeSurfer. All volumetric analyses were controlled for gender, age, and estimated intracranial volume (ICV; Buckner et al., 2004) and Bonferroni-corrected for multiple comparisons.

Both T1 images from all participants with two useable images were processed with FreeSurfer's longitudinal stream (Reuter, Schmansky, Rosas, & Fischl, 2012). This process estimates average participant anatomy by creating an unbiased within-participant template space (Reuter & Fischl, 2011) using a robust, inverse consistent registration (Reuter, Rosas, & Fischl, 2010). After all templates were manually edited and checked (as above), information from both the templates and individual T1 images were combined to calculate longitudinal changes in individual anatomy, and surfaces were again resampled to a standard brain and smoothed with a 10-mm full-width half-maximum kernel. General linear models were constructed with symmetrized percent change (SPC) as the dependent variable and controlled for gender. SPC is the rate of change at each location with respect to the average thickness across both time points. This approach is more robust than rate of change or simple percent change, which refer to change only in terms of the first measurement. Whole-brain analyses were cluster-corrected for multiple comparisons using a Monte Carlo simulation with 10,000 repetitions and were Bonferroni adjusted for both hemispheres (cluster-forming $p < .05$, cluster-wise $p < .05$; Hagler et al., 2006).

Results

Relation of SES to Behavioral Measures at Pre-Test

At pre-test, participants' scores on tests of phonological awareness, phonological memory, and rapid naming ranged from average to below-average (Table 2.1). Single word and pseudoword reading skills clustered at borderline low average to below average scores. Higher SES correlated significantly with higher scores on vocabulary (PPVT-4, Pearson's $r = 0.37$, $p = 0.002$) and marginally with higher nonverbal cognitive ability scores (KBIT-2, $r = .023$, $p = 0.065$), despite these mean standard scores being within or above the average range. SES was not correlated with scores on any subtests assessing phonological awareness, phonological memory, or rapid naming (all $|r| < 0.08$, all $p > 0.50$). Higher SES was only correlated with higher scores on one of the four single-word reading subtests (WRMT-3 Word Attack: $r = 0.26$, $p = 0.036$; all other reading subtests $r < 0.17$, $p > 0.2$), and consequently was marginally correlated with higher reading-composite scores ($r = 0.24$, $p = 0.05$). Neither of these SES-reading relationships retained significance when controlling for KBIT-2 scores (both $r < 0.2$, both $p > 0.1$). In contrast, when controlling for reading scores, SES and vocabulary maintained a relationship as strong as the zero-order correlation ($r = 0.36$, $p = 0.003$).

Table 2.1. Participant Test Scores and Relation to Socioeconomic Status.

List of standardized assessments administered before intervention, participants' average standard scores, and correlations with SES. Partial correlations between SES and reading scores control for standardized KBIT-2 scores.

Assessment	*M* (*SD*)	Zero-order Correlation with SES	Partial Correlation with SES
Nonverbal Cognition			
KBIT-2 Matrices	103.09 (14.05)	$r = 0.23^{\dagger}$	*N/A*
Oral Language			
PPVT-4 (Receptive Vocabulary)	107.03 (12.50)	$r = 0.37^{**}$	$r = 0.32^{**}$
Phonological Awareness			
CTOPP Elision	8.49 (2.02)	$r = 0.02$	$r = -0.02$
CTOPP Blending Words	10.12 (2.27)	$r = -0.08$	$r = -0.13$
Phonological Memory			
CTOPP Nonword Repetition	7.92 (1.18)	$r = -0.02$	$r = -0.07$
CTOPP Memory for Digits	9.23 (2.33)	$r = 0.05$	$r = 0.02$
Rapid Automatized Naming			
RAN/RAS Objects	89.79 (13.65)	$r = 0.02$	$r = 0.07$
RAN/RAS Letters	95.33 (11.49)	$r = 0.08$	$r = 0.09$
RAN/RAS 2-Set Letters and Numbers	23 (11.90)	$r = -0.03$	$r = -0.04$
Single Word/Nonword Reading Accuracy			
WRMT-3 Word Identification	85.11 (9.82)	$r = 0.13$	$r = 0.04$
WRMT-3 Word Attack	86.72 (11.69)	$r = 0.26^{*}$	$r = 0.15$
Single Word/Nonword Reading Fluency			
TOWRE-2 Sight Word Efficiency	84.54 (10.67)	$r = 0.09$	$r = 0.05$
TOWRE-2 Phonemic Decoding Efficiency	80.80 (9.89)	$r = 0.17$	$r = 0.11$
Reading Composite	84.08 (8.71)	$r = 0.24^{\dagger}$	$r = 0.19$

$^{\dagger}p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$

Table 2.1 (Continued)

Note: KBIT-2 = *Kaufman Brief Intelligence Test, 2nd edition*, PPVT-4 = *Peabody Picture Vocabulary Test, 4th edition*, CTOPP = *Comprehensive Test of Phonological Processing*, RAN/RAS = *Rapid Automatized Naming and Rapid Alternating Stimulus Tests*, WRMT-3 = *Woodcock Reading Mastery Test, 3rd edition*, TOWRE-2 = *Test of Word Reading Efficiency, 2nd edition. All assessments have a mean standard score of 100, with a standard deviation of 15, except CTOPP which has a mean scaled score of 10 and a standard deviation of 3.*

Relation of SES to Cortical Thickness and Reading Scores at Pre-Test

Confirming our hypothesis, higher SES correlated significantly with greater pre-test cortical thickness in several clusters spanning both hemispheres (Figure 2.1, Table 2.2). In the left hemisphere, these clusters included parts of (1) pars opercularis (the posterior portion of Broca's area), (2) supramarginal and postcentral regions, and (3) insula, transverse temporal gyrus, and superior and middle temporal regions. In the right hemisphere, significant clusters included (1) middle and superior temporal regions, (2) surpramarginal and postcentral regions, (3) lateral occipital/fusiform regions, and (4) paracentral regions (see Supplementary Figure S2.1 for scatterplots by region). Nearly identical clusters emerged when additionally controlling for composite reading score. While cortical thickness and SES showed significant associations, cortical thickness was not correlated with any individual reading assessment scores or the reading composite score.

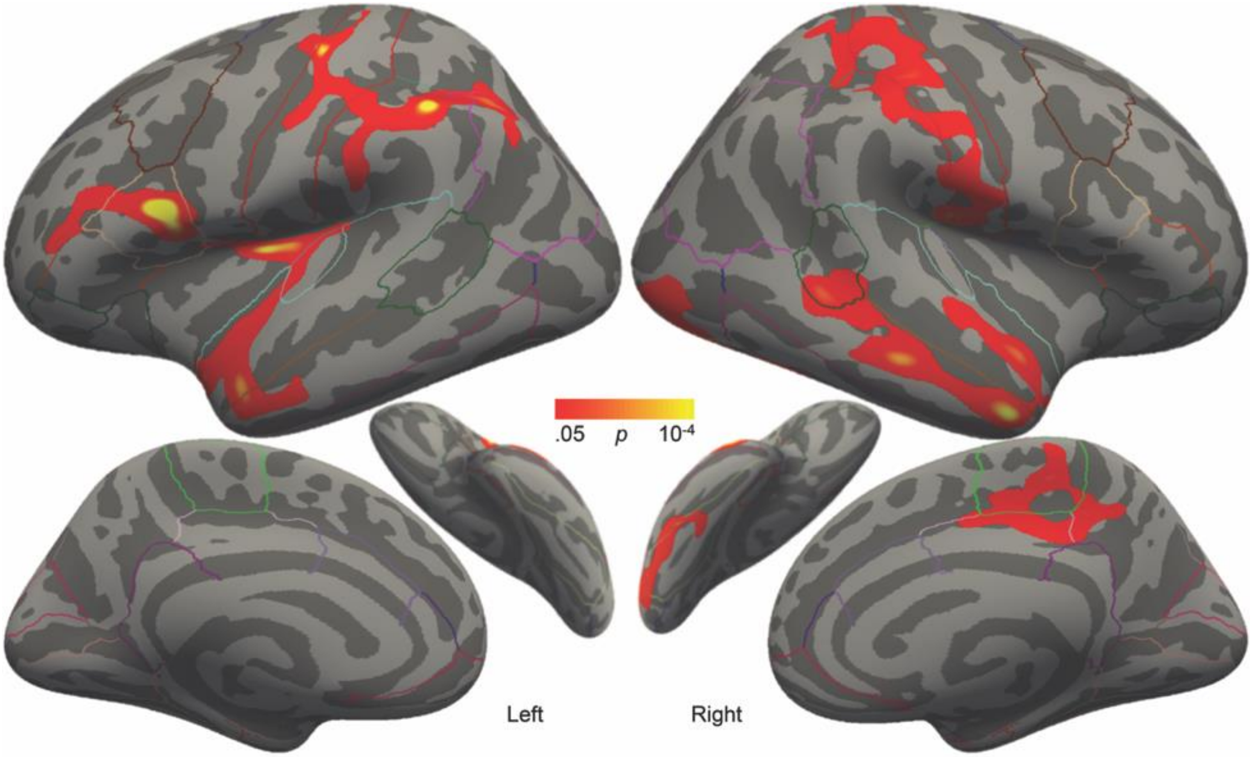

Figure 2.1 Correlation between SES and cortical thickness, controlling for age and gender. Colored regions exhibited significantly thicker cortex with higher SES at baseline. Outlines represent the cortical parcellations from the Desikan-Killiany gyral-based atlas.

Table 2.2. Pre-test Correlations between Socioeconomic Status and Cortical Thickness

Regions where SES was significantly correlated with cortical thickness, controlling for age and gender. Note: MNI = Montreal Neurological Institute.

Region of Cluster	Approximate Brodmann Areas	Area of cluster (mm^2)	Peak Significance ($-\log_{10} p$)	Peak MNI Coordinates x	y	z	Cluster-wise p
Left pars opercularis	44	916.13	6.262	-46.9	12.0	18.2	0.04547
Left supramarginal + postcentral	40, 3, 1, 2	2581.86	4.782	-53.5	-42.4	45.6	0.00020
Left insula + superior/ middle temporal	41, 42, 21, 22	1710.62	4.056	-36.1	-15.6	11.3	0.00020
Right middle/superior temporal	21, 22	1927.57	4.134	56.0	1.1	-29.4	0.00020
Right supramarginal + postcentral	40, 3, 1, 2	2486.63	3.388	44.7	-17.7	20.0	0.00020
Right lateral occipital + fusiform	18, 19, 37	1526.07	3.042	35.2	-80.2	-12.0	0.00080
Right paracentral	4, 3, 1, 2	139722	2.951	9.4	-32.3	51.4	0.02504

Although the smallest by area, the left opercular cluster's cortical thickness exhibited the strongest correlation with SES ($p = 10^{-6}$). Using the pre-defined cortical parcellations, higher SES also correlated significantly with greater volume of the entire left pars opercularis (lpOp, partial $r = 0.33$, $p = 0.005$). Given that SES was also strongly correlated with receptive vocabulary scores, we undertook a mediation analysis (Figure 2.2). By adding lpOp to the regression model, the relationship between SES and vocabulary scores was rendered insignificant, indicating a full mediation. To confirm, a bootstrapping method with 10,000 iterations (Hayes 2013) was employed. There was a significant indirect effect of SES on vocabulary score through lpOp volume, [indirect effect = 0.15, bootstrapped 95% CI (0.06, 0.29), indirect/total effect = 0.37]. This indicates that the volume of the left pars opercularis could account for 37% of the total effect of SES on vocabulary scores.

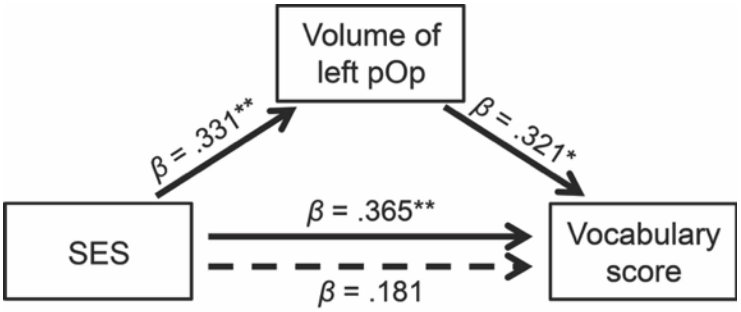

Figure 2.2. Mediation model showing the effect of SES on vocabulary scores as mediated by the volume of the left pars opercularis. Solid arrows represent direct paths, whereas the dotted arrow represents the indirect (mediated) path. β coefficients represent standardized regression coefficients. Each regression controls for participant age and gender, and all models involving the left pars opercularis (lpOp) also control for head size (estimated intracranial volume). Thus, vocabulary is represented by raw scores on the *Peabody Picture Vocabulary Test, 4th edition* (PPVT-4), to avoid adjusting for age twice. *$p < 0.05$, **$p < 0.01$.

Effect of Remediation Program on Reading Scores

When examining changes on behavioral assessments (i.e., response to intervention), repeated measures ANOVAs revealed group by time-point interactions on the composite reading score [$F(62,1) = 21.87$, $p < 0.001$] and on 3 of the 4 reading subtests (meeting a Bonferroni-adjusted significance criterion), indicating a benefit of the intervention (Figure 2.3, Table 2.3). These included untimed word reading [WRMT-3 Word Identification, $F(62,1) = 8.00$, $p = 0.006$], untimed pseudoword reading [WRMT-3 Word Attack, $F(61,1) = 10.97$, $p = 0.002$], and timed pseudoword reading [TOWRE-2 Phonemic Decoding Efficiency, $F(56,1) = 12.27$, $p = 0.001$]. Post-hoc paired t-tests for all significant interactions revealed that children with RD who received intervention maintained their scores across time points (all $p > 0.6$), while children with RD in the waiting control group significantly declined (all $p < 0.001$). Both groups declined on the TOWRE-2 Sight Word Efficiency subtest (both $p < 0.005$). Overall, the relative benefit of the intervention was expressed as maintenance of scores for the intervention group relative to a loss of skills for the control group (see Christodoulou et al. 2017 for further information).

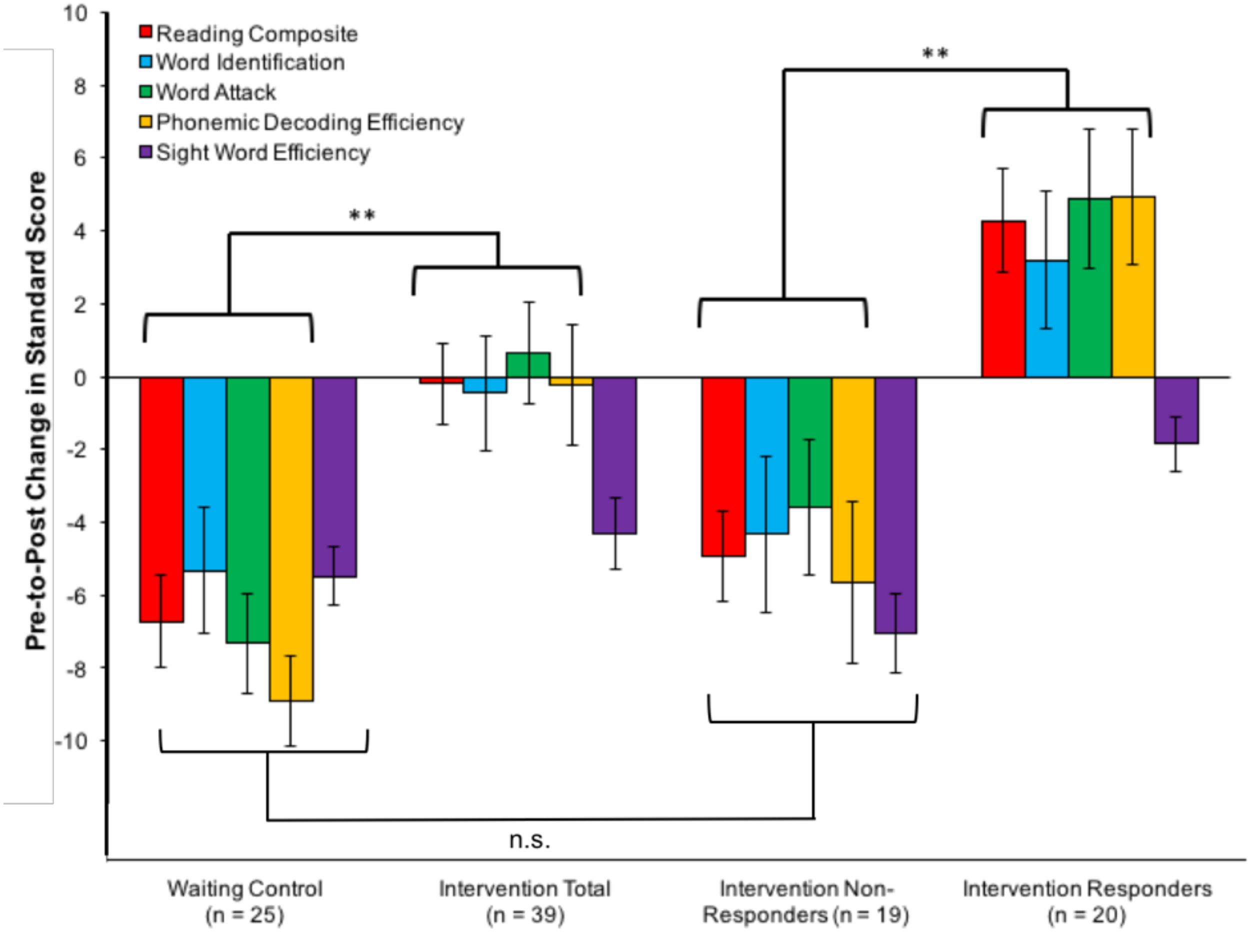

Figure 2.3. Pre-to-post changes in standard scores on reading composite and subtests and composite by group. Positive scores indicate a score increase, while negative scores indicate a score decrease. "Intervention Total" combines Intervention Non-Responders and Intervention Responders. Reading Composite is the average of standard scores on all four subtests. Word Identification and Word Attack are subtests of the *Woodcock Reading Mastery Test, 3rd edition* (WRMT-3). Sight Word Efficiency and Phonemic Decoding Efficiency are subtests of the *Test of Word Reading Efficiency, 2nd edition* (TOWRE-2). Error bars represent standard errors. **$p < 0.01$, n.s. = not significant

Table 2.3. Post-Test Reading Scores

Group means (and standard deviations) of reading assessment standard scores at post-test. All assessments have a mean standard score of 100, with a standard deviation of 15. Change scores are post-test minus pre-test scores, averaged across participants, with indicated significance from paired t-tests. Word Identification and Word Attack are subtests of the *Woodcock Reading Mastery Test, 3rd edition* (WRMT-3). Sight Word Efficiency and Phonemic Decoding Efficiency are subtests of the *Test of Word Reading Efficiency, 2nd edition* (TOWRE-2). Reading Composite is the average of standard scores on all four subtests.

Post-Test Assessment	Waiting Control (*n* = 25)	Intervention Total (n=39)	Intervention Non-Responders (n=19)	Intervention Responders (n=20)
Word Identification	80.08 (8.22)	84.69 (9.76)	84.32 (10.22)	85.05 (9.55)
Change Score	*-5.32 (6.26)****	*-0.46 (6.97)*	*-4.32 (5.38)***	*3.20 (6.39)**
Word Attack	79.96 (9.83)	87.67 (9.79)	87.16 (10.07)	88.15 (9.75)
Change Score	*-7.32 (8.61)****	*0.66 (9.81)*	*-3.58 (9.34)*	*4.89 (8.52)**
Sight Word Efficiency	79.16 (11.28)	80.34 (12.79)	79.44 (14.09)	81.15 (11.81)
Change Score	*-5.48 (6.88)****	*-4.32 (8.63)***	*-7.06 (8.17)***	*-1.85 (8.48)*
Phonemic Decoding Eff.	73.35 (9.36)	79.87 (8.81)	78.44 (9.90)	81.15 (7.73)
Change Score	*-8.90 (6.12) ****	*-0.22 (10.37)*	*-5.67 (9.66)**	*4.95 (8.30)**
Reading Composite	78.13 (8.53)	83.62 (8.55)	82.63 (9.33)	84.56 (7.86)
Change Score	*-6.72 (4.02) ****	*-0.20 (6.17)*	*-4.91 (4.74)****	*4.28 (3.41)****

*$p < 0.05$, **$p < 0.01$, *** $p < 0.001$

Differences Between Children Who Responded More or Less to Intervention

To examine variation within the intervention group, we classified participants based on the change in composite scores (Figure 2.4). Of the 39 participants who completed the intervention, approximately half had positive composite change scores (“responders”: $n = 20$, $M = 4.28$, $SD = 3.41$), indicating pre-to-post improvement, and half had negative composite change scores (“non-responders”: $n = 19$, $M = -4.91$, $SD = 4.74$). For comparison, the waiting control group had a mean change score of -6.72 ($SD = 4.02$). Independent t-tests revealed that non-responders did not differ from waiting controls on pre-to-post change scores for the composite or any subtest (all $p > 0.17$), whereas responders differed from both non-responders and waiting controls on all pre-to-post change scores with exception of the Sight Word Efficiency subtest from the TOWRE-2 (all $p < 0.006$; Table 2.3 and Figure 2.3).

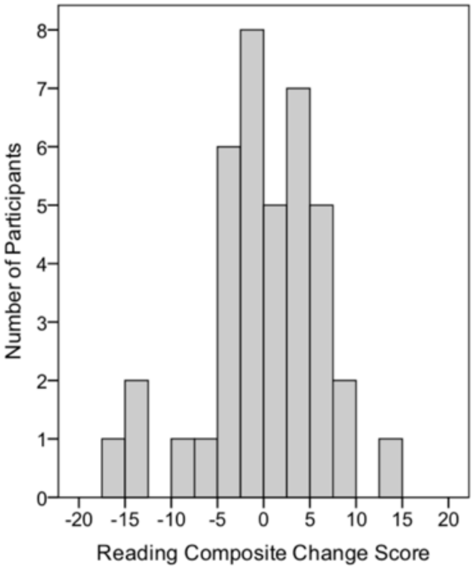

Figure 2.4. Histogram of pre-to-post changes in the composite reading score for all participants in the intervention group only ($n = 39$). Positive scores indicate a score increase and classification as an intervention “Responder,” while negative scores indicate a score decrease and classification as an intervention “Non-Responder.”

Contrary to our hypothesis, responders had a significantly *lower* SES (*M* = 39.9, *SD* = 12.7) than non-responders [*M* = 51.2, *SD* = 11.1; *t*(37) = 2.96, *p* = 0.005; Figure 2.5a]. When children were divided by median SES, 14 of the 20 responders were in the lower-SES half, and 13 of the 19 non-responders were in the higher-SES half [$\chi^2(1, n = 39) = 5.76, p = .016$]. Treatment response was not significantly related to any other demographic variable, including age, grade, gender, bilingualism, presence of an ADHD diagnosis and/or use of ADHD medication, vocabulary scores, non-verbal cognitive ability scores, hours of intervention attendance, timing of pre-test or post-test assessments, or whether participants met a low score or discrepancy inclusion criterion (all $|t| < 1.4$, all $p > 0.17$).

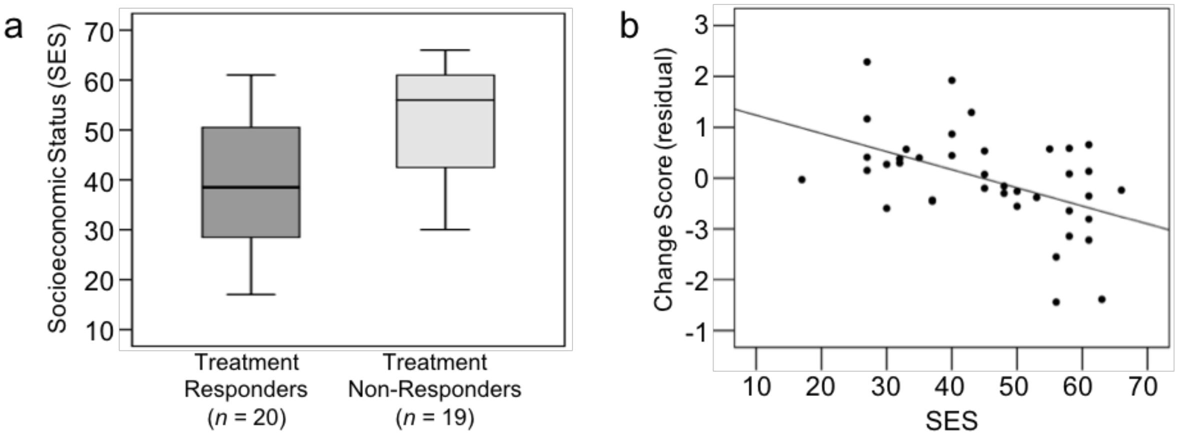

Figure 2.5. Relation between SES and response to treatment. (a) Boxplot of SES as a factor of treatment response. Intervention response (improvement) was operationalized as a positive change score when averaging standard scores on four reading subtests: WRMT-3 Word Identification and Word Attack, and TOWRE-2 Sight Word Efficiency and Phonemic Decoding Efficiency. (b) Partial residual plot showing the amount of improvement (change in composite reading score, controlled for baseline score) as a function of SES.

At baseline, responders also had significantly lower composite reading scores than non-responders [responders: $M = 80.28$, $SD = 6.64$; non-responders: $M = 87.54$, $SD = 10.01$; $t(37) = 2.68$, $p = 0.01$]. To control for the effect of baseline scores, a regression analysis was performed to examine the relative relations of all potential predictive variables to intervention response. A model including age, grade, gender, bilingual status, ADHD diagnosis, ADHD medication, which inclusion criterion was met, total hours of intervention attendance, intervention site, SES, and RD severity (reverse of pre-test composite score) revealed that only SES and RD severity were significant predictors of binary-coded improvement, with SES explaining 26% of the variance in improvement ($\beta = -0.019$, $p < 0.003$;) and RD severity explaining 14% of the variance in improvement ($\beta = 0.022$, $p < 0.05$). Removing all non-significant predictors yielded the same pattern (SES: $\beta = -0.015$, $p = 0.01$, $R^2 = 0.17$; RD severity: $\beta = 0.019$, $p = 0.02$, $R^2 = 0.14$), and these results held when using change scores as the dependent variable instead (Figure 2.5b; SES: $\beta = -0.164$, $p = 0.02$, $R^2 = 0.14$; RD severity: $\beta = 0.248$, $p = 0.01$, $R^2 = 0.16$). These findings indicate that both more severe RD and lower SES, two risk factors, were independently associated with greater response to intervention.

Analogous results were seen in pre-to-post cortical thickness changes. On average, there were no significant differences in thickness changes between the intervention and waiting control groups. However, there were large differences in thickness changes within the intervention group. Responders exhibited significantly greater thickening than non-responders bilaterally in several large clusters spanning (1) middle/inferior temporal regions (extending into fusiform region on the right), (2) supramarginal/angular regions, (3) precentral regions, and (4) paracentral/posterior cingulate regions (Figure 2.6, Table 2.4, see Supplementary Figure S2.2 for group differences by region). An additional cluster spanned a large portion of the right superior temporal gyrus extending into insula. The greatest longitudinal between-group difference occurred in the left middle temporal cluster, where responders' cortices *thickened* by an average of 31 micrometers (µm) per month (1% gain), and non-responders' cortices *thinned* by an average of 11 µm per month (0.37% loss). For comparison, the waiting control group on average exhibited 7 µm of thinning per month (0.26% loss) in this region, although this thinning was not statistically significant. There were no clusters in which non-responders exhibited greater thickening or thinning than the waiting-control group. When the three participant groups (responders, non-responders, and controls) were analyzed separately, responders exhibited significant thickening over most of the cortical surface, whereas non-responders and controls exhibited no regions of significant thickening or thinning.

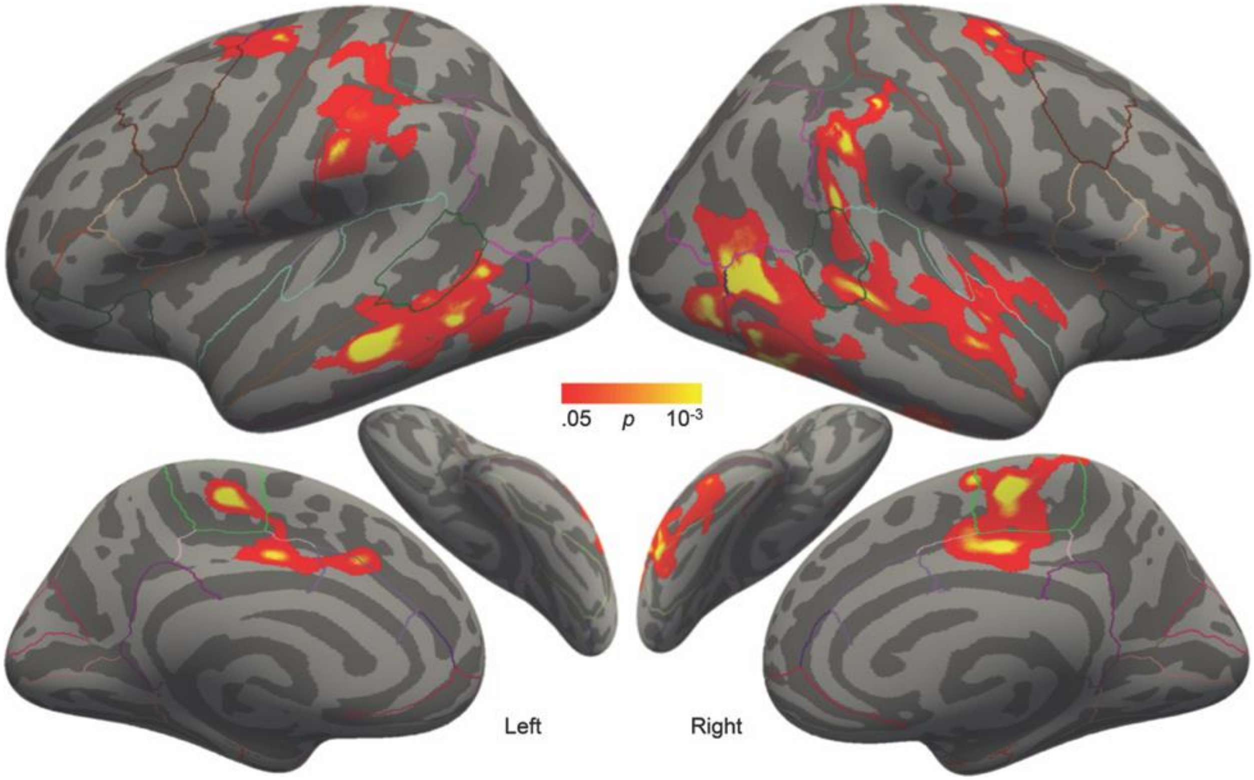

Figure 2.6. Regions where treatment responders exhibited significantly greater cortical thickening versus treatment non-responders following an intensive summer intervention, controlling for gender.

Table 2.4. Cortical Thickness Changes in Treatment Responders vs. Non-Responders

Regions exhibiting significant differences in cortical thickness changes between children whose reading scores improved after intervention versus children whose scores did not improve. Comparisons are controlled for age and gender. Note: MNI = Montreal Neurological Institute.

Region of Cluster	Approximate Brodmann Areas	Area of cluster (mm^2)	Peak Significance ($-\log_{10} p$)	Peak MNI Coordinates x	y	z	Cluster-wise *p*
Left middle/inferior temporal	21, 37	1548.41	5.359	-60.1	-29.2	-12.2	0.00020
Left supramarginal	40	1401.52	3.035	-56.3	-24.6	27.5	0.00020
Left precentral	4	691.94	3.070	-31.7	-12.9	57.6	0.01514
Left paracentral + cingulate	4, 3, 1, 2, 31, 24	773.27	3.857	-7.5	-27.0	53.4	0.00619
Right middle/inferior temporal + fusiform	21, 37, 19	3302.67	4.546	47.8	-59.7	3.1	0.00020
Right supramarginal + angular	39, 40	926.53	3.490	59.0	-42.5	17.1	0.00140
Right superior temporal + insula	22	1836.93	3.239	44.0	-33.7	-0.8	0.00020
Right precentral	4	730.29	3.095	22.1	-10.1	53.0	0.01236
Right paracentral + posterior cingulate	4, 3, 1, 2, 31	1544.20	4.753	7.4	-20.1	56.3	0.00020

Also commensurate with behavioral results, lower SES and greater RD severity were independently correlated with cortical thickening in neighboring but non-overlapping regions. Lower SES (controlling for RD severity) correlated with greater thickening in the bilateral middle temporal and paracentral/cingulate regions, as well as left precentral and right lateral orbitofrontal/pars orbitalis regions (Figure 2.7 cool colors, Table 2.5). Greater RD severity (controlling for SES) correlated with greater thickening in a right lateral occipital cluster (Figure 2.7 warm colors, Table 2.5). To further evaluate whether the apparent neuroanatomical dissociations in cortical thickening related to lower SES and greater RD severity were independent as opposed to being secondary to statistical thresholding, we examined in several main clusters the correlations between changes in cortical thickness and both baseline SES and RD. These analyses supported the conclusion that regional changes in cortical thickness were related distinctly to either SES or RD (Supplementary Figure S2.3). There were no significant correlations between thickness changes and SES or RD severity in the waiting control group.

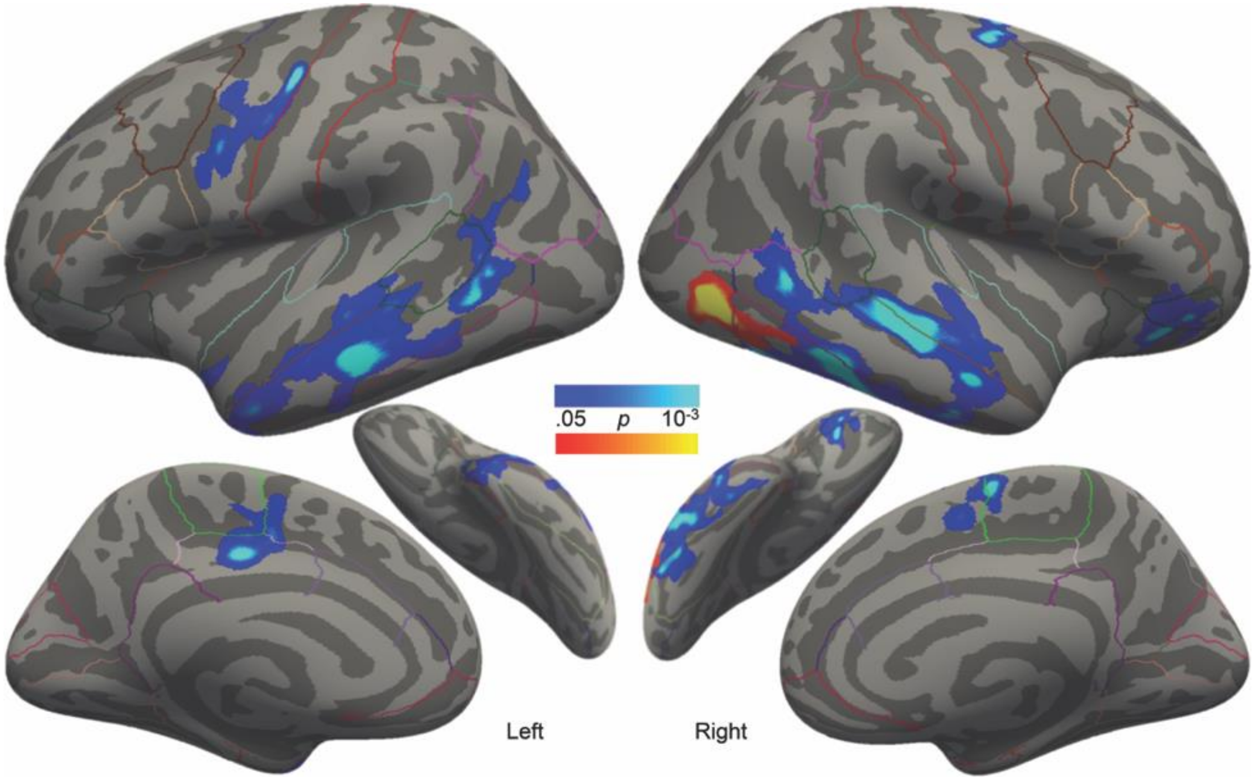

Figure 2.7. Regions exhibiting significant correlations between changes in cortical thickness and SES (cool colors) or RD severity (warm colors) among all children who received intervention, controlling for gender.

Table 2.5. Cortical Thickness Changes Associated with SES and RD Severity

Regions exhibiting significant correlations between changes in cortical thickness and SES (controlling for RD severity and gender) or with RD severity (controlling for SES and gender) among all children who received intervention. Note: MNI = Montreal Neurological Institute.

Region of Cluster	Approximate Brodmann Areas	Area of cluster (mm^2)	Peak Significance (–log$_{10}$ *p*)	Peak MNI Coordinates			Cluster-wise *p*
				x	y	z	
Correlation with SES, controlling for RD severity							
Left middle temporal (anterior)	21, 20	2705.29	-3.755	-64.5	-26.4	-14.8	0.00020
Left middle temporal (posterior)	21, 20	623.14	-3.311	-60.6	-54.9	0.0	0.03017
Left precentral	4	774.27	-3.783	-33.0	-18.2	39.3	0.00619
Left posterior cingulate + paracentral	31, 4, 5, 3, 1, 2	611.57	-3.345	-6.4	-17.7	39.1	0.03469
Right middle/superior temporal	21, 22	3913.28	-5.150	52.4	-24.5	-12.8	0.00020
Right paracentral	11, 47	963.37	-3.770	8.4	-10.6	61.3	0.00060
Right pars orbitalis + lateral orbitofrontal	4, 3, 1, 2	704.96	-3.671	37.5	30.0	-14.5	0.01732
Correlation with RD severity, controlling for SES							
Right lateral occipital	18, 19	726.64	-5.205	41.2	-73.2	-1.5	0.01276

Discussion

The present study yielded three novel discoveries about the relations between SES and RD, including behavioral and neuroanatomical responses to reading intervention. First, among a group of children with RD, higher SES was associated with thicker cortex in multiple neocortical regions, including bilateral perisylvian and supramarginal regions associated with language and reading; this extends, for the first time, the well-documented SES-neuroanatomy relationship to children with RD. Moreover, the strongest correlation occurred in Broca's area in left inferior frontal cortex, the volume of which fully mediated the relationship between SES and vocabulary, commonly known as the "vocabulary gap." Second, whereas children who did not receive intervention or who did not respond to intervention exhibited no significant cortical changes, children who responded to intervention (i.e., whose reading improved) exhibited pre-to-post thickening of cortex across broad bilateral occipitotemporal and temporoparietal regions, most notably in the middle temporal gyri. Third, children from lower-SES families and children with more severe RD were more likely to benefit from the intervention than children from higher-SES families or children with less severe RD, both behaviorally and neurally.

Relation of SES, Cortical Thickness, and Vocabulary in Children with RD

In accordance with our hypothesis, higher SES (independent of RD severity) was associated with thicker cortex in bilateral perisylvian and supramarginal regions at pre-test, with the strongest association in left pars opercularis (posterior portion of Broca's area). Prior studies have reported similar relations between SES and neuroanatomical characteristics of language cortex in typically developing children (for review, see Brito & Noble, 2014). However, this is the first study to demonstrate the same relationship among children with RD. The combined influences of RD and lower SES on neuroanatomy may make children especially vulnerable for academic challenges in reading.

Further, there was a strong relation between higher SES and larger vocabulary, a finding consistent with many studies reporting striking relations between SES, home language environment, and vocabulary (e.g., Hart & Risley, 1995; Hoff, 2003; Weisleder & Fernald, 2013). The present study offers an initial insight into a brain mechanism that may be involved in the relation of childhood SES to vocabulary, albeit specifically in children with RD. A mediation model revealed that the volume of the left pars opercularis (the posterior portion of the canonical Broca's area) fully mediated the strong correlation between SES and vocabulary size, accounting for over a third of the relation between SES and vocabulary.

The present findings are consistent with prior evidence associating SES, neuroanatomy, and performance on a measure of verbal academic achievement (Hair et al., 2015). That study reported that lobar gray matter volumes mediated the relation between growing up near or below the federal poverty line and broader linguistic achievement in children and young adults, with frontal-lobe volume explaining 11% of the income-related differences in language scores. The authors suggested that their results might underestimate the true effects of SES because of strict exclusion criteria that selected for a typical sample of participants and little variation in the other socio-educational domains comprising SES (Hair et al., 2015). Indeed, by defining SES continuously and more broadly within a sample of young children with RD, the present study found that a more specific portion of the left frontal lobe (pars opercularis) explained 37% of the effect of SES on children's vocabulary knowledge. This relation between Broca's area and vocabulary is consistent with the known major role of Broca's area to language development (Grodzinsky & Santi, 2008; Hagoort, 2005, 2014). This not only proposes a more focal locus for the previous study's whole-brain global effects, but also suggests an even tighter relationship between SES, brain, and achievement in a group of children with RD.

Despite notable SES-related variation in vocabulary and the neural structure of core language regions, there were little SES-related behavioral differences in children's reading profiles, including word and pseudoword reading accuracy and fluency, as well as reading-related phonological processing and rapid naming skills. This may in part reflect a restricted range of poor reading ability for all of the children, who all had to have evidence for substantial RD regardless of SES. The similarity of reading scores across SES makes more salient the differences in vocabulary and in neuroanatomy.

Individual Differences in Intervention Response and Brain Plasticity

We found considerable variation in response to intervention, with about half of the children with RD exhibiting significant gains in reading after intervention, and about half exhibiting essentially no gains (i.e., they did not differ significantly from the children with RD who received no intervention). Although intervention programs are typically evaluated on the basis of an average, overall response, frequently some portion of children with RD (anywhere from 3-80%, depending on response criteria) fail to respond to intervention programs that are effective for other children (for reviews, see Al Otaiba & Fuchs, 2002; Lam & McMaster, 2014; Nelson, Benner, & Gonzalez, 2003). The present finding of 50% non-response is consistent with previous studies of similar-age children with persistent reading difficulties (Al Otaiba & Fuchs, 2002; Lam & McMaster, 2014).

There were striking developmental differences in brain plasticity between the children with RD who did respond to the intervention versus the other two groups of children with RD who either did not respond to the intervention or who received no intervention. Responders exhibited greater cortical thickening across broad bilateral occipitotemporal and temporoparietal regions. The greatest group difference was evident in the middle temporal gyrus, where responders' cortices *thickened* by an average of 31 µm/month, and non-responders' and waiting controls' cortices *thinned* by 11 and 7 µm/month, respectively. For reference, this region thins by an average of 5 µm/month in typically developing, similarly aged children (Sowell et al., 2004). This suggests that non-responders and waiting controls exhibited a typical cortical trajectory of developmental thinning during this study, whereas children with RD who responded by improving their reading exhibited a noteworthy thickening of cortex.

Two other studies have examined neuroanatomical plasticity, one in gray matter and one in white matter, following reading intervention with children. Our left hemisphere findings are consistent with a study that used the same *Seeing Stars* intervention in 11 children ages 7-11 years and found increased gray matter volume in left occipitotemporal and medial parietal regions (Krafnick et al., 2011). Another study reported intervention related changes in white matter microstructure in children ages 8-12 (Keller & Just, 2009). A difference between the prior and present studies is that only the present study reports a specific relation between individual differences in treatment response and structural plasticity.

Several prior studies have reported functional brain differences between individuals with RD who did or did not respond to intervention at either a single pre-intervention (Davis et al., 2011; Farris et al., 2011; Molfese, Fletcher, & Denton, 2013; Odegard, Ring, Smith, Biggan, & Black, 2008) or post-intervention time point (Rezaie et al., 2011a, 2011b), although few have reported longitudinal neural changes. One study using magnetic source imaging (MSI) found that responders, but not non-responders, exhibited increased duration of activity and a shift in activation timing in a broad left temporoparietal region during a phonological decoding task, such that their neural profiles matched typical readers post-intervention (Simos et al., 2007). Another study used evoked response potentials (ERPs) during a German phonological lexical decision task to compare functional plasticity between responders and non-responders (Hasko, Groth, Bruder, Bartling, & Schulte-Korne, 2014). Treatment responders, but not non-responders, exhibited an increase in the post-test amplitude of the N400 component, thought to underlie orthographic processing. Although locating the source of ERP components is difficult, the N400 is thought to arise from bilateral superior/middle temporal gyri and temporoparietal regions (Kutas & Federmeier, 2011). Thus, the prior functional studies align with the present structural study in suggesting that plasticity in temporoparietal regions distinguishes children with RD who do versus do not respond to specific interventions.

Relation of SES and RD Severity to Intervention Response and Plasticity

Contrary to our hypotheses, both lower SES and greater RD severity at baseline were independently associated with *greater* response to intervention in regard to both reading ability and brain plasticity. Importantly, because analysis models controlled for baseline reading scores, this result cannot solely be attributed to a regression-to-the-mean explanation. SES and RD severity, however, appeared to have differential relations between reading gains and structural plasticity, suggesting that the two factors influenced treatment response via cortical growth in different brain regions. Children from lower SES families exhibited greater thickening across broad bilateral occipitotemporal regions, largely corresponding with the left hemisphere reading network and its right hemisphere homologues. Children with more severe RD exhibited greater thickening in a right lateral occipital region that may provide compensatory support for the visual component of reading.

The finding that children with lower SES and more severe RD responded more strongly to this specific intervention is a notable difference from prior studies. Most reading intervention studies examining these factors have largely found that lower-SES children (Hatcher et al., 2006; Morris et al., 2012; Torgesen et al., 1999) and children with lower word-reading and decoding skills (Compton et al., 2012; Hatcher et al., 2006; Vellutino, Scanlon, Zhang, & Schatschneider, 2007) tended to exhibit a *worse* response to interventions. However, these studies largely utilized in-school remediation programs focused on phonological awareness with short instructional sessions distributed across many weeks during the academic year, whereas the present study employed an intensive, short-term intervention with a small teacher to student ratio (1:3-5) during the non-academic summer.

Several interpretations are possible for the greater effect of the intervention on lower-SES than higher-SES children with RD. One possibility concerns the nature of the present intervention; specifically, the pronounced focus on visual and orthographic imagery. Given that lower-SES, above-average readers exhibit greater white matter tract coherence in the right inferior longitudinal fasciculus (Gullick et al., 2016), which supports visuospatial processing, it is possible that this visual approach stimulated greater neural plasticity in right hemisphere areas, and, in turn, a more positive treatment response. Another possibility is that the combination of intervention intensity, duration, and small group size, all of which predict greater response frequency (Denton, 2012), was particularly potent for lower-SES children. A limitation on interpretation of these findings is that the waiting-control group served as a passive control condition, thus precluding the separation of effects of intensive, small-group attention and interaction from the specific academic content of the intervention.

In any case, another possible explanation concerns the timing of the intervention. The particular benefits of the reading intervention during summer for the lower-SES children with RD may be related to evidence that lower-SES children in general are vulnerable to academic regression during the summer, a phenomenon known as “summer slump” or “summer slide.” During the summer months, lower-SES students tend to regress in their reading skills, while higher-SES students tend to maintain or gain reading skills (Alexander, Entwisle, & Olson, 2007; Cooper, Nye, Charlton, Lindsay, & Greathouse, 1996; McCoach, O'Connell, Reis, & Levitt, 2006). This is frequently attributed to decreased access to books and reduced experiences with or emphasis on literacy in the homes of lower-SES children. Thus, it is plausible that the present access to an intensive reading program provided the lower-SES children with precisely the literacy access they would otherwise be missing, and presumably had missed in previous summers.

Finally, the better intervention response for lower-SES participants could be related to variations in RD etiology. Reading deficits can occur for many reasons, and it is possible that the origins of

RDs could vary in relation to SES. Differences in environmental factors, such as home literacy, access to reading material, and school quality may be responsible for systematic heterogeneity in the root cause of RD across children from varying SES (Ursache & Noble, 2016). Consistent with this possibility is the finding that higher-SES and lower-SES environments interact differently with genetic factors related to RD (Friend et al., 2008; Mascheretti et al., 2013). A large study of twins with reading difficulty revealed differences in the heritability of reading disability across SES, such that environmental factors accounted for more of the variance in reading deficits in children from lower-SES families than higher-SES families (Friend et al., 2008; but see Kirkpatrick, Legrand, Iacono, & McGue, 2011 for conflicting findings). This raises the possibility that the neurobiological bases of RD could vary with SES. In such a case, environmentally-driven neurobiological differences in children from lower-SES families may be more amenable to an (environmental) treatment intervention. In contrast, genetically-driven neurobiological differences in children from higher-SES families may be more resistant to treatment intervention. By this view, children with RD of varying SES could respond differently to interventions due to variation in environmental versus genetic contributions to the etiologies of their behaviorally similar RD.

Several limitations of the present study are noted. One limitation involves the non-random treatment group assignment of 15 participants, as a condition of school participation. Ideally all participants would have been randomly assigned to the treatment or control group, so that the post-intervention response can only be explained by the intervention itself. It is, however, unlikely that alternative participant characteristics (such as school or intervention site) contributed to either between-group or within-group treatment differences, because participants were similar across sites in their demographics, assessment scores, and treatment response. A second limitation is that we lacked information to characterize the quality of school reading instruction for all participants. On average, it is likely that lower-SES children may receive less high-quality instruction in lower performing schools, though this was not evaluated in our current study. In order to promote SES diversity of children in this study, the children attended a wide variety of public, private, and public-charter schools from a large metro region. Future studies may attempt to control for this by enrolling participants from a single school with a SES-diverse population, or by characterizing the quality of reading instruction in diverse schools. Third, we could not dissociate potentially separable effects of SES dimensions of parental education, parental occupation, and income on any outcomes. There is evidence for dissociations among these dimensions on both behavioral (e.g., Duncan & Magnuson, 2012) and neural (e.g., Brito & Noble, 2014) child outcomes. In our sample, parental education, parental occupation, and parental income were highly correlated, which precluded any dissociations. Future research with larger, more diverse participant samples will be required to untangle these correlated dimensions of SES when considering treatment response in children with RD.

In summary, this study investigated how the brain structure of young students with RD varies by SES and explored SES-related differences in their behavioral and neural response to intervention. Despite reduced cortical thickness in canonical language regions at baseline, lower-SES children responded more favorably to an intensive summer reading invention than their higher-SES peers, both in terms of reading scores and structural plasticity throughout the neural reading networks. Taken as a whole, this suggests that intensive summer reading intervention might be even more effective for these dually at-risk children.

Chapter 3: Relationship between Language Exposure and Language-Related Brain Function in Young, Typically-Developing Children

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Author Contributions

R. R. Romeo and J. D. E. Gabrieli developed the study concept. R. R. Romeo, J. A. Leonard, A. P. Mackey, M. L. Rowe, and J. D. E. Gabrieli designed the study. R. R. Romeo, J. A. Leonard, and S. T. Robinson collected the data. R. R. Romeo performed the data analysis and interpretation under the supervision of J. D. E. Gabrieli and M. L. Rowe. R. R. Romeo and J. D. E. Gabrieli wrote the manuscript. All authors approved the final version of the published manuscript.

Abstract

Children’s early language exposure impacts their later linguistic skills, cognitive abilities, and academic achievement, and large disparities in language exposure are associated with family socioeconomic status (SES). However, there is little evidence about the neural mechanism(s) underlying the relation between language experience and linguistic/cognitive development. Here, language experience was measured from home audio recordings of 36 SES-diverse 4-6 year-old children. During a story-listening fMRI task, children who had experienced more conversational turns with adults—independent of SES, IQ, and adult/child utterances alone—exhibited greater left inferior frontal (Broca’s area) activation, which significantly explained the relation between children’s language exposure and verbal skill. This is the first evidence directly relating children’s language environments with neural language processing, specifying both environmental and neural mechanisms underlying SES disparities in children’s language skills. Furthermore, results suggest that conversational experience impacts neural language processing over and above SES and/or the sheer quantity of words heard.

Introduction

Children’s early life experiences during sensitive periods of neural plasticity shape the brain structures and functions underlying their cognitive aptitudes. One critical experience is language exposure. Specifically, the language quantity (e.g., number of words) and quality (e.g., sentence complexity, lexical diversity) that young children hear are the foundation of later language and literacy skills (Hirsh-Pasek et al., 2015; Rodriguez & Tamis-LeMonda, 2011; Rowe, 2012) and non-verbal capacities including executive functioning (Sarsour et al., 2011), math ability (Levine, Suriyakham, Rowe, Huttenlocher, & Gunderson, 2010), and social skills (Connell & Prinz, 2002).

Children’s language exposure varies substantially in relation to their socioeconomic status (SES). SES represents the social and economic resources of an individual or group, and children from lower-SES backgrounds on average hear fewer and less complex utterances than their more advantaged peers (Hart & Risley, 1995; Rowe, 2008). In a landmark study, Hart and Risley (1995) estimated that by age 3, children from higher-SES backgrounds had heard 30 million more words than children from lower-SES backgrounds, and other studies report similar trends (Hoff, 2006). Until recently, such studies required time-consuming transcription of parent-child exchanges that limited the amount of data that could be collected. Technological advances now allow for longer, more comprehensive, and less intrusive recordings of naturalistic language exposure. One device, Language Environment Analysis (LENA), records 16-hour days from the child’s perspective and automatically characterizes children’s language environments. Studies using LENA have confirmed substantial variation in the amount of language children experience in association with SES (Gilkerson, Richards, Warren, et al., 2017).

This broad or *distal* association between SES and children's language development must be distinguished from the direct or *proximal* association between language exposure and language development (Bronfenbrenner & Morris, 2007). SES is a broad characterization of many correlated factors including income, educational access, other environmental resources, stress, health, and nutrition. Development, however, depends upon specific, proximal factors that directly affect the child, such as immediate language exposure. Indeed, the separability of distal SES from proximal language experience is evident in the considerable variation in early language exposure within each SES band (Gilkerson, Richards, Warren, et al., 2017; Hirsh-Pasek et al., 2015; Rowe, Pan, & Ayoub, 2005; Weisleder & Fernald, 2013). When SES is controlled, children's language exposure remains strongly associated with variation in their language abilities (Rowe, 2012; Weisleder & Fernald, 2013), and differences in exposure partially or fully explain the SES-related gap in language skills (Hoff, 2006).

Despite considerable behavioral research linking children's language exposure to their language abilities, there is currently no evidence about the neural mechanisms underlying this relationship. There is, however, a growing body of evidence that SES disproportionately affects language ability and language neural systems compared to other neurocognitive domains (Farah, 2017). Structurally, lower SES is associated with reduced gray matter in left perisylvian regions underlying phonological, semantic, and syntactic components of language comprehension and production (Noble, Houston, et al., 2015; Noble et al., 2012), as well as with bilateral occipitotemporal regions involved in reading (Jednorog et al., 2012; Mackey et al., 2015). Additionally, functional neuroimaging studies that deploy language tasks has revealed SES-related differences in left inferior frontal (Raizada et al., 2008), superior temporal, and fusiform regions (Noble, Wolmetz, et al., 2006).

Although these studies provide valuable insight on the relation between brain development and SES, they have not aimed to relate brain measures directly to children's language environments—the proximal factor presumed to directly influence children's linguistic abilities (Noble et al., 2012; Perkins et al., 2013). Relating specific and objectively measurable language experiences to brain development is of particular interest because such experiences can become practical and efficacious targets for intervention (Roberts & Kaiser, 2011). Only two neuroimaging studies have related home language experiences to brain functions. One study using fMRI with children ages 8-12 reported a relation between videotaped home language and right prefrontal activation on a complex nonverbal task (Sheridan, Sarsour, Jutte, D'Esposito, & Boyce, 2012). Another study with infants reported a relation between LENA-measured adult word counts and event related potentials (ERPs) to phonetic contrasts in left frontal electrodes (Garcia-Sierra, Ramírez-Esparza, & Kuhl, 2016). However, neither study examined the joint roles of SES and language input in relation to linguistic brain functions.

The present study aims to elucidate how variation in children's natural language experience relates to brain function underlying language processing, and in turn to linguistic abilities. Specifically, we hypothesized that LENA measures of language exposure—over and above SES—would be associated with children's language skills and language-related brain activation, especially in left perisylvian neocortices known to support language.

Method

Participants

Thirty-six children (22 male) aged 4 years, 6 months to 6 years, 10 months (*M* = 5.8 years, *SD* = 0.63 years) and their parents completed this study (see Supplement for justification of sample size). Boys and girls did not significantly differ on any behavioral (all $p > 0.15$), demographic (all $p > 0.33$), language exposure (all $p > 0.76$), or neural measure (maximum $z = 1.2$). Children were native English speakers and typically developing, with no history of premature birth, neurological disorders, developmental delay, speech/language therapy, or grade repetition, and all bilaterally passed a 4 pure-tone hearing screening (0.5 KHz, 1 KHz, 2 KHz, 4KHz) on the day of assessment. Nineteen children were initially assessed and excluded for not meeting these inclusion criteria.

Twenty of the 36 participants additionally participated in a larger randomized controlled intervention study on parenting practices; only their baseline data (before learning of group assignment) was used here. Twenty-seven other children participated but did not have complete data sets, either because they did not complete the home recordings ($n = 6$), did not participate in the fMRI scan ($n = 11$), fell asleep during the fMRI scan ($n = 3$, details below), or exhibited excessive movement during the fMRI scan ($n = 7$, details below). These participants did not differ from the included sample on any behavioral scores, language exposure measures, or SES. All procedures were approved by the Institutional Review Board at the Massachusetts Institute of Technology, and written informed consent was obtained from parents.

Behavioral and Demographic Assessments

Children completed standardized behavioral assessments to characterize verbal and nonverbal cognitive skills (see Supplement for additional info on executive function assessments). These included the Matrix Reasoning, Picture Memory, and Bug Search subtests of the *Wechsler Preschool and Primary Scale of Intelligence* (WPPSI-IV; Wechsler, 2012), the *Peabody Picture Vocabulary Test* (PPVT-4; Dunn & Dunn, 2007), and the Sentence Comprehension, Word Structure, Formulated Sentences, and Recalling Sentences subtests of the *Clinical Evaluation of Language Fundamentals* (CELF-5; Wiig, Semel, & Secord, 2013), which together form the CELF-5 Core Language Score (CLS). Age-normed scaled scores from the three WPPSI-IV subtests were averaged to create a "nonverbal composite score." Inclusion criteria required all participants to have nonverbal composite score, PPVT-4 standard score, and CELF-5 CLS greater than or equal to one standard deviation below the mean (16th percentile). Because the CELF-5 only provides age-based norms for children aged 5 years or more, four-year-olds were required to score greater than or equal to the age equivalent for their raw scores on each of the four subtests. Composite Verbal Scores were created by averaging the PPVT-4 standard score and the CELF-5 CLS.

Additionally, parent(s) filled out questionnaires about the child's developmental history and family demographics, including highest level of education obtained by both parents and annual household income. When a father was present in the home, maternal and paternal years of education were averaged to create a parental education metric (1 = high school or less, 2 = some college/associate's degree, 3 = bachelor's degree, 4 = master's/professional degree, 5 = doctoral level degree).

Neuroimaging Data Acquisition

Neuroimaging took place at the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research, at the Massachusetts Institute of Technology. First, children were acclimated to the MRI environment and practiced lying still in a mock MRI scanner. Data were then acquired on a 3 Tesla Siemens MAGNETOM Trio Tim scanner equipped for echo planar imaging (EPI; Siemens, Erlangen, Germany) with a 32-channel phased array head coil. An automated scout image was acquired, and shimming procedures were performed to optimize field homogeneity. A whole-head, high-resolution T1-weighted multi-echo MPRAGE structural image was acquired using a protocol optimized for movement-prone pediatric populations (TR = 2530 ms, TE = 1.64 ms/3.5 ms/5.36 ms/7.22 ms, TI = 1400 ms, flip angle = 7°, resolution = 1-mm isotropic). Whole-brain functional images were acquired with a continuous gradient echoplanar T2*-weighted sequence (T2*-weighted images, TR = 2500 ms, TE = 30 ms, flip angle = 90°, bandwidth=2298 Hz/Px, echo spacing= 0.5 ms, 41 transverse slices with FoV = 192 × 192, in-plane resolution of 3 mm × 3 mm). Before each scan, six dummy volumes were acquired and discarded to reach equilibrium, and online prospective acquisition correction (PACE) was applied to the echo planar image sequence throughout the scan.

Functional MRI Task

Children passively listened to short, simple stories derived from the Narrative Language Measures (Petersen & Spencer, 2012), the content of which includes events that young children are likely to be familiar with (e.g., playing games, getting hurt). All stories had consistent narrative structure, word count, and language complexity, and were recorded by a female native-English speaker. A block design paradigm presented fifteen-second long trials consisting of a single story either played normally or played in reverse (backward speech), followed by 5 seconds of silent rest. A third condition (not analyzed here) involved dichotic speech with a different story played in each ear. One run consisted of 6 trials of each condition (18 trials total), such that the run lasted 6 minutes, with condition order pseudo-randomized such that the same condition never repeated twice in a row. Participants were randomly assigned to hear one of two stimulus lists containing all different stories with equal story interest ratings. A female stick figure appeared on a gray screen throughout auditory stimulation to remind children to listen. During the scan, an experimenter stood at the foot of the bore and monitored participants' attentiveness. If the participant closed their eyes for more than 5 seconds, they were considered asleep and their data was discarded (*n* = 2, mentioned above). Before entering the scanner, children completed a short practice with stories not heard in the scanner and were required to correctly answer 2 of 4 free-response comprehension questions to ensure familiarity with the task. In the scanner, participants were reminded to listen carefully to the stories to earn prizes upon task completion. Participants were not instructed to memorize the passages, because the goal was to record brain responses during natural language comprehension. Pilot data from children and adults indicated that participants had very low levels of incidental memory for the passages; as such, no post-MRI comprehension/retention test was administered to avoid burdensome additional testing that would be uninformative. All stimuli and scripts are available for download at http://dx.doi.org/10.7910/DVN/DIDBMQ.

Neuroimaging Analysis

Functional MRI data preprocessing and analysis was executed with Nipype (Gorgolewski et al., 2011), utilizing FSL version 5.0.9 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) and FreeSurfer version 5.3.0 (Fischl, 2012). Functional images were re-aligned to the first volume of the run, co-registered to the corresponding anatomical image (which had been processed and manually edited as necessary in FreeSurfer to ensure correct gray and white matter boundaries), and then to a standard MNI152 template. Functional time-series outliers (global mean intensity > 3 standard deviations, or volume-to-volume motion > 2 mm) were identified by ART and removed from the analysis by adding one regressor per outlier to subject-level general linear models (GLMs). Participants with outliers in more than 20% of volumes were excluded from the study ($n = 7$, mentioned above). Time-series data were high-pass filtered at 120 seconds, spatially smoothed using 6 mm FWHM Gaussian kernel, and convolved with the canonical double-gamma hemodynamic response function (HRF) in FSL, and GLMs were used to create contrast maps for each subject. Subject-level results were combined in mixed effects models using FSL's FEAT with FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1. Results were corrected for multiple comparisons using a conservative cluster-forming threshold of $p < 0.001$, connectivity of 26 (voxels must be connected by at least a point), and a family-wise error rate of $p < 0.05$, and fractionally projected orthogonally to the surface for visualization purposes. Average activations were extracted from subject-level cortical parcellations according the Desikan-Killiany gyral-based atlas (Desikan et al., 2006) for mediation analysis.

Home Audio Recordings

Parents were given two LENA Pro digital language processors (DLPs), which are 2-ounce digital recorders that fit in a child's shirt pocket and store up to 16 hours of digitally recorded audio. Parents were instructed to collect full-day recordings from a consecutive Saturday and Sunday, beginning when the child woke up. The average number of days between assessment/MRI and

LENA recording was 8.97 (*SD* = 5.81), with a maximum of 21 intervening days. Upon return of the DLPs, the LENA Pro processing system automatically analyzed the audio and provided estimates of the total number of adult words spoken in the recording (i.e. word tokens), the total number of child utterances, and the total number of adult-child conversational turns, defined as a discrete pair of an adult utterance followed by a child utterance, or vice versa, with no more than 5 seconds pause between the two. Whereas adult words and child utterances are simple linguistic measures, conversational turns incorporate both linguistic information and non-verbal communicative aspects such as temporal contiguity, adult responsiveness, joint social attention, and exchange of communicative information. As such, conversational turns may represent a more holistic measure of interpersonal conversational engagement.

LENA speech-identification algorithms have been determined to be highly reliable, yielding measures approximately 82% accurate for adult speech and 76% accurate for the speech of infants and young children up to 3 years old (Gilkerson, Richards, Warren, et al., 2017; Oller et al., 2010; Zimmerman et al., 2009). Although primarily designed to analyze speech of children younger than four years old, the same algorithms were applied to recordings from all participants, such that any potential inaccuracies would be consistent. Running totals for each speech category were calculated for each consecutive 60 minutes across the two days in 5 minute increments (e.g., 7:00 AM – 8:00 AM, 7:05 AM – 8:05 AM, etc.), and the per-participant highest hourly total of adult words, child utterances, and conversational turns were separately extracted for further analysis. This metric helped minimize differences in daily totals due solely to different recording lengths and/or loud activities that may have masked speech and misrepresented language input. It also attempted to reduce the amount of “overheard speech” that was not child-directed, since peak language periods are shown to be more similar to engaged structured play situations (Tamis-LeMonda, Kuchirko, Luo, Escobar, & Bornstein, 2017). Such measures of peak naturalistic observations are consistent with other studies utilizing LENA (Garcia-Sierra et al., 2016; Ramírez-Esparza, García-Sierra, & Kuhl, 2014).

Results

Behavioral Results

All data (to the extent that they may ethically be shared) are freely available for download at http://dx.doi.org/10.7910/DVN/DIDBMQ. Children's verbal and nonverbal ability, according to standardized assessments, ranged from low average to above average (verbal composite standard score: Range = 86-139, $M = 114$, $SD = 15$; nonverbal composite scaled score: Range = 7.3-14.7, $M = 10.6$, $SD = 2.1$). Parental education ranged from partial high school to doctorate level degrees (M = some college), and familial income ranged from $6,000 to $250,000 per year, with median of $85,500 per year, consistent with the median familial income in Massachusetts of $90,590. Parental education, but not income, was positively correlated with children's nonverbal ability (education: $r = 0.34$, 95% CI = [.02, .67], $p < 0.05$; income: $r = 0.11$, p = n.s.; Figure 3.1a). Although both education and income were correlated with children's verbal ability (education: $r = 0.69$, 95% CI = [.44, .94], $p < 0.00001$; income: $r = 0.48$, 95% CI = [.17, .79], $p < 0.01$; Figure 3.1b), linear regression revealed that income predicted no unique variance in child verbal ability after accounting for parental education (education: $\beta = 8.25$, 95% CI = [4.07, 12.44], $p < 0.001$, income: $\beta = < .01$, p = n.s.).

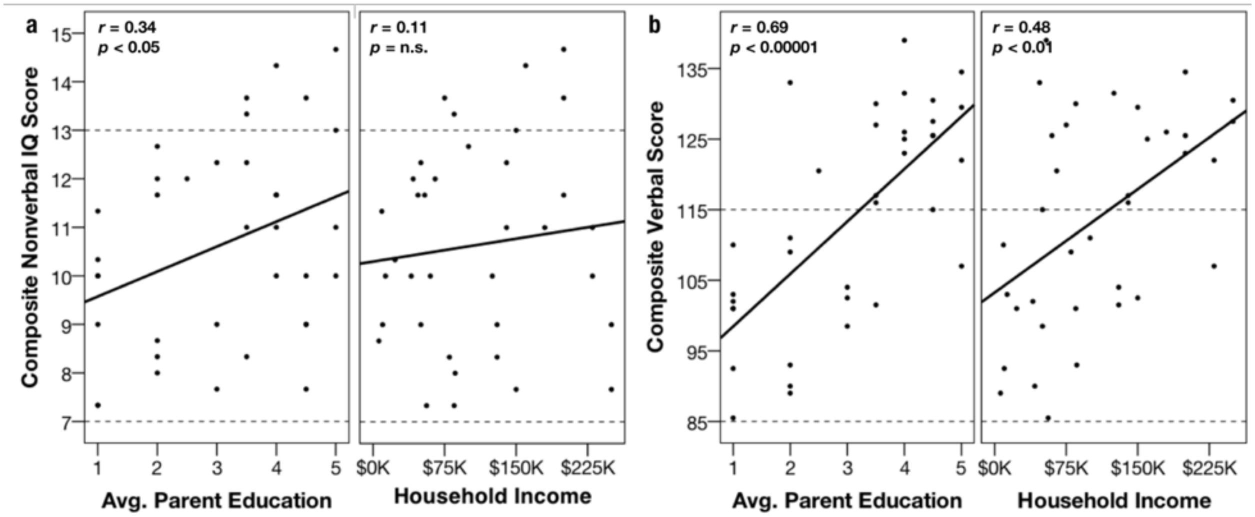


Figure 3.1. Scatterplots of composite (a) nonverbal and (b) verbal scores as functions of parent education level (mother and father averaged) and household income. Standardized nonverbal assessments evaluated fluid reasoning, nonverbal working memory, and processing speed. Standardized verbal assessments evaluated vocabulary, receptive and expressive morphosyntax, and verbal working memory skill. Dotted lines indicate the average range of scores (within 1 standard deviation of population mean).

There was great individual variability in language exposure measures, including the number of adult words per peak hour (*M* = 4260, *SD* = 1225, range = 1953-6991), the number of child utterances per hour (*M* = 743, *SD* = 261, range = 300-1275), and the number of conversational turns per hour (*M* = 181, *SD* = 56, range = 86-317). Higher parental education and income correlated significantly with more adult words (education: $r = 0.41$, 95% CI = [.09, .73], $p < 0.05$; income: $r = 0.39$, 95% CI = [.06, .71], $p < 0.05$) and more conversational turns (education: $r = 0.34$, 95% CI = [.02, .67], $p < 0.05$; income: $r = 0.37$, 95% CI = [.04, .69], $p < 0.05$; Figure 3.2), but neither SES measure was significantly correlated with child utterances (education: $r = 0.25$, p = n.s.; income: $r = 0.24$, p = n.s.). If these peak-hour measures are extrapolated, children in the top and bottom SES quartiles would experience an annual adult word gap of 5 million words, which could accumulate to approximately 30 million words by age of enrollment in this study, similar to the gap originally reported by Hart and Risley (1995). However, SES only explained a moderate share of the variability in language exposure (11-17%), indicating that there was wide variability of language exposure within families of similar SES.

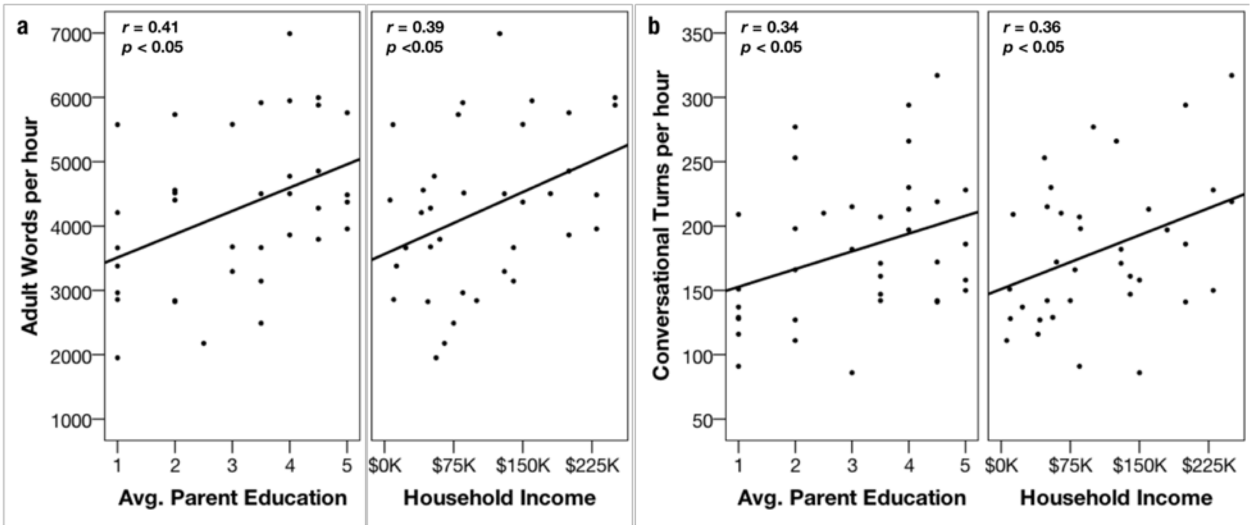


Figure 3.2. Scatterplots of peak hourly (a) adult words and (b) conversational turns as functions of parent education level (mother and father averaged) and household income.

All three measures of language experience correlated with children's scores on behavioral language assessments, although conversational turns most strongly predicted the verbal composite score (conversational turns: $r = 0.51$, 95% CI = [.21, .81], $p < 0.001$; adult words: $r = 0.36$, 95% CI = [.04, .69], $p < 0.05$; child utterances: $r = 0.34$, 95% CI = [.01, .66], $p < 0.05$). Multiple regression models were constructed to predict verbal composite scores as a function of parental education, family income, and each of the three language experience measures. In all three models, parental education significantly predicted verbal scores [all $\beta > 7.70$, $p < 0.001$, partial $r > 0.55$] whereas income did not [all $\beta < 0.1$]. Only conversational turns significantly predicted additional variance in verbal scores after education and income were partialled out (β = 0.09, 95% CI = [.02, .16], $p = 0.01$, partial $r = 0.43$, R^2 change = 0.10; Figure 3.3). Thus, children's composite verbal score increased by one point for every additional 11 conversational turns experienced per hour*,* independent of SES. The relation between conversational turns and verbal scores remained significant (all $\beta > 0.08$, $p < 0.05$) when adult words and/or child utterances was added to the model, suggesting that conversational turns was not just a proxy for adult speech or child talkativeness. Furthermore, a bootstrap mediation analysis revealed that the number of conversational turns significantly mediated the relationship between parental education and verbal composite scores (indirect effect = 1.16, 95% CI = [0.22, 2.92], indirect/total effect = 0.16), such that variation in conversational turns could account for 16% of the total relationship between parental education and children's verbal scores.

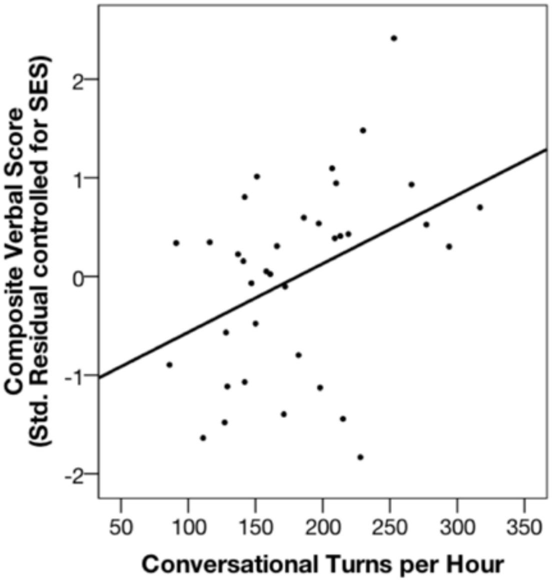


Figure 3.3. Relationship between children's composite verbal score (controlled for parent education level and income) and the number of hourly conversational turns.

Neuroimaging Results

The contrast of interest was activation during the comprehensible forward speech condition versus the incomprehensible backward speech condition, which yields activation specific to higher-level language processing involved in comprehending heard stories, roughly controlling for auditory characteristics. As a group, this task yielded significant activation along bilateral superior temporal sulci (STS), with a leftward lateralization (Figure 3.4, Table 3.1); in the left hemisphere, a cluster extended from the temporal pole to supramarginal/angular gyri, while in the right hemisphere, a cluster was restricted to the anterior portion of the STS.

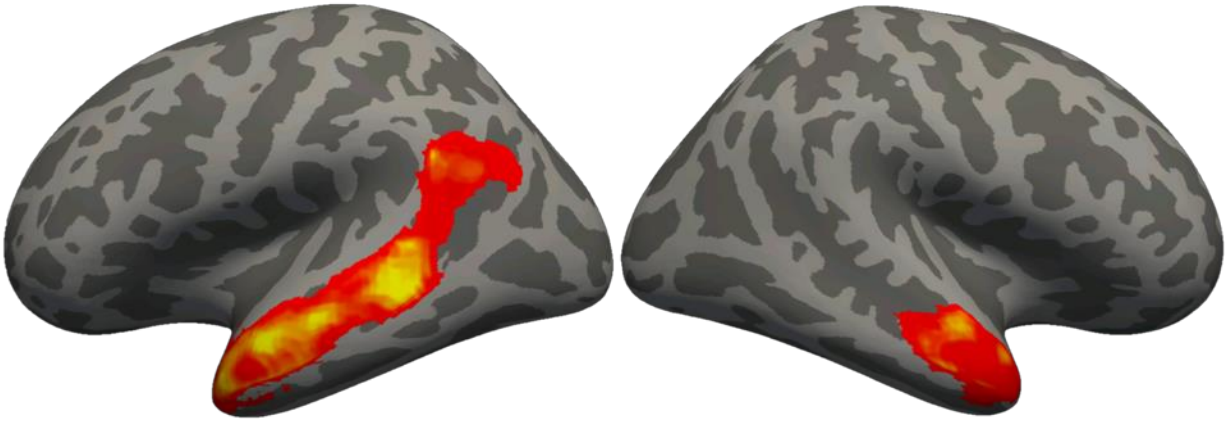


Figure 3.4. Regions where activation was significantly greater while listening to forward speech versus backward speech, averaged across all participants. Clusters include the whole of the left superior temporal sulcus and the anterior portion of the right superior temporal sulcus.

Table 3.1. Group Mean Task Activations for Forward > Backward Speech

Coordinates and anatomical descriptions of local peak activations for the forward > backward speech contrast, averaged over the entire sample (n = 36). Analyses revealed two significant clusters, one in each hemisphere, visualized in Figure 3.4.

	MNI coordinates			
Z-value	x	y	z	Anatomical Description
Left Hemisphere Cluster (3552 voxels)				
6.40	-52	-7	-12	Anterior superior temporal sulcus
6.39	-55	-39	4	Posterior superior temporal sulcus
6.11	-50	9	-22	Temporal pole
5.81	-57	-51	30	Supramarginal gyrus
Right Hemisphere Cluster (1418 voxels)				
5.93	54	-4	-13	Anterior superior temporal sulcus
5.47	51	13	-20	Temporal pole

Whole brain correlations with the three LENA measures were conducted to detect individual differences in activation related to language exposure. While there were no significant correlations with the number of adult words or child utterances, the number of conversational turns correlated positively with activation in a single cluster (Figure 3.5a, Table 3.2, 766 total voxels) spanning left pars triangularis (Brodmann area 45) extending into pars opercularis (Brodmann area 44), which together comprise "Broca's area." This cluster remained significantly correlated with conversational turns after controlling for parental education and income (Figure 3.5b), verbal and nonverbal composite scores (Figure 3.5c), adult words and child utterances counts (Figure 3.5d), or all of these covariates together (Figure 3.5e), indicating that this relationship was not driven simply by any of these factors. In other words, the more conversational turns a child experienced, the greater their activation in Broca's area during language processing, independent of the child's SES, cognitive ability, or sheer numbers of adult words and child utterances. There were no clusters exhibiting significant correlations with any demographic variables (age, gender, parent education, income) or cognitive (verbal, nonverbal scores) variables.

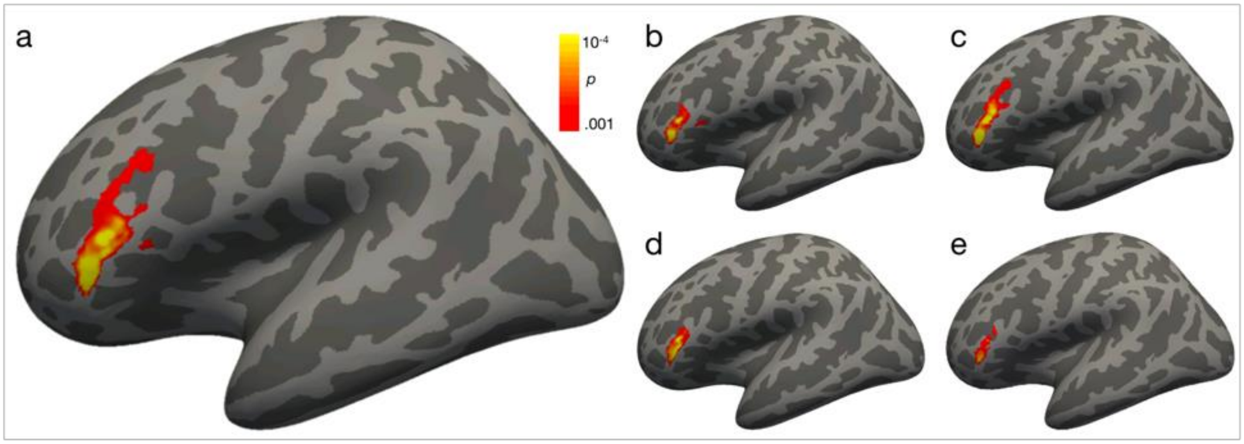


Figure 3.5 Correlations between activation during language processing and the number of hourly conversational turns children experienced. **(a)** Zero-order correlation between the number of conversational turns and activation in the forward > backward speech contrast. Correlations remained significant when controlling for **(b)** parental education and income, **(c)** verbal and nonverbal assessment scores, **(d)** individual numbers of adult words and child utterances, or **(e)** all of these covariates.

Table 3.2. Correlation Between Conversational Turns and Forward > Backward Activation

Coordinates and anatomical descriptions of local peak activations in a single cluster (Figure 3.5a, 766 voxels) exhibiting a significant correlation between the number of conversational turns children experienced per hour and activation in the forward > backward speech contrast.

	MNI coordinates			
Z-value	x	y	z	Anatomical Description
4.59	-48	33	15	Left posterior pars triangularis
4.18	-56	33	10	Left anterior pars triangularis
3.55	-43	13	15	Left anterior pars opercularis

We then asked if Broca's area activation helped explain the relation between children's language exposure and verbal scores. The magnitudes of children's Broca's area activations, (averaged over anatomically-defined opercular and triangular regions, as shown in Figure 3.6) significantly mediated the relation between the number of conversational turns and verbal composite scores (indirect effect = 0.065, 95% CI = [0.02, 0.11], indirect/total effect = 0.48), rendering the relation between conversational turns and verbal scores insignificant. This suggests that conversational turns may support children's verbal skills in part by influencing Broca's area activation during language processing. Further, this neural pattern explained 48% of the relation between children's conversational turns and their verbal scores.

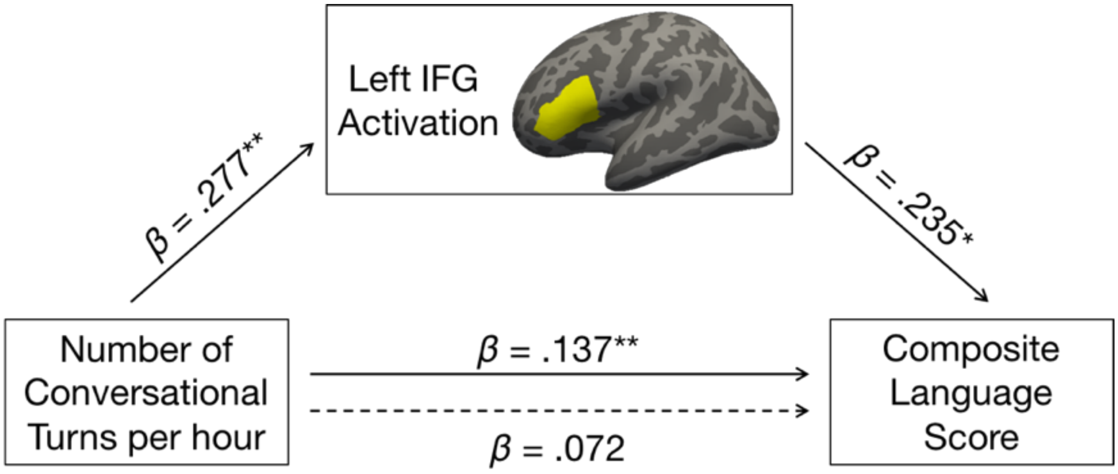


Figure 3.6. Mediation model showing the effect of conversational turns on language assessment scores as mediated by activation in the left inferior frontal gyrus, shaded in yellow. Activation significantly mediated the relation between the number of conversational turns children experience and their language scores. Solid arrows represent direct paths, whereas the dotted arrow represents the indirect (mediated) path. β coefficients represent unstandardized regression coefficients. $^*p<0.01$ and $^{**}p<0.001$

Finally, conversational turns and Broca's activation jointly mediated the relationship between parent education and children's language scores, (indirect effect = 1.69, 95% CI = [0.24, 3.75], indirect/total effect = 0.23), indicating that conversational turns and Broca's activation during language processing could account for 23% of the total relationship between SES and children's language skills.

Discussion

This study provides the first evidence of the neural activation patterns underlying the relation between children's early language exposure and verbal skills. Using at-home, real-world audio recorders, we replicated behavioral findings that higher SES is correlated with both greater language experience and verbal abilities in children ages 4-6 years. Specifically, it was the number of conversational turns between children and adults (and not the sheer number of adult words) that significantly mediated the SES-verbal ability relationship. Further, neuroimaging revealed a neural mechanism by which language experience may influence brain development; namely, children who experienced more conversational turns exhibited greater activation in left inferior frontal regions ("Broca's area") during language processing, which explained nearly half the relationship between children's language exposure and verbal abilities. Finally, conversational turns and Broca's activation jointly mediated the relationship between SES and children's language abilities, demonstrating both environmental and neural mechanisms underlying SES disparities in early language skills.

These findings are consistent with evidence that *qualitative* aspects of children's language experience (such as turn-taking) may have a greater impact on language development than sheer *quantitative* measures (Hirsh-Pasek et al., 2015; Zimmerman et al., 2009). While the conversational turn count likely includes more child-directed speech than the adult word count (which also includes any "overheard" speech), it is unlikely that the quantity of child-directed speech alone explains the significance of the conversational turn measure. Studies of child-directed speech suggest that contiguity (temporal connectedness) and contingency (contextual relevancy) with children's utterances are critical for word-learning (Roseberry, Hirsh-Pasek, & Golinkoff, 2014), and that the fluency, connectedness, and joint engagement of communication predict later language skills over and above the number of adult words (Hirsh-Pasek et al., 2015). In fact, conversational turns fully explain the effect of adult words on 2-to-48-month-old children's language skills (Zimmerman et al., 2009). The present results extend the importance of conversational turns to language skills at age 6, suggesting a continued role for this essentially social aspect of language development.

Conversational turns may be particularly important for language development because they provide increased opportunities for children to practice language and receive feedback from adults. Furthermore, this creates a feedback loop to help adults hone their own speech to the optimal complexity to best support children's language development (Zimmerman et al., 2009). While it is possible that children with better language abilities may better engage in these conversations, child utterances had the weakest relation to language scores and brain functions, suggesting that the strong effect of conversational turns is not simply a reflection of more talkative children. More broadly, the importance of conversational turns supports theories that language development crucially relies on social interaction and social neural circuitry (Kuhl, 2007) and that pre-linguistic communicative turn-taking was essential for the evolution of language (Levinson, 2016).

The present study is the first to provide evidence of a localized (left inferior frontal) neural mechanism that underlies the relation between children's direct language exposure and language processing. This is consistent with findings that language input is related to infants' ERP responses in left frontal regions during a phonological task (Garcia-Sierra et al., 2016). Thus, linguistic experience appears to have a particular influence on language processes in left prefrontal cortex, beginning in infancy and continuing through early childhood.

The finding that participants as a group yielded left-lateralized superior temporal activation is likely indicative of a relative invariance in activation related to the acoustic/sub-discourse aspects of language. However, *variation* in participants' language experience correlated exclusively with activation in Broca's area. The localization of this brain-behavior relationship may be related to the nature of conversational turns as a higher-level, supralexical language process. Although Broca's area is classically associated with speech production, research suggests it plays a much broader role in both receptive and expressive language processing, as well as a variety of non-linguistic functions. The specific role of Broca's area in passive language comprehension is still a matter of debate, although it may function as a convergence zone, in which small, independent elements of language (e.g., phonemes, words) are unified into a coherent overall representation (Hagoort, 2014). The present functional task—listening to meaningful, connected stories—requires integration across phonological, semantic, and syntactic units; thus, greater activation in Broca's area may represent a deeper engagement with the linguistic structure of the stories. Alternatively, regions of Broca's area also support several domain-general functions, including action perception, working memory, and executive functioning/cognitive control (Fedorenko, Duncan, & Kanwisher, 2012); by this view, greater activation could represent a neural representation of the speaker's/characters' movements, and/or relating current verbal information to recently heard sentences/stories. Conversational experience could plausibly contribute to either or both neural systems, and future studies are needed to delineate the precise cognitive process(es) associated with language exposure.

Several limitations of the present study are noted. To study typical development, children with language disorders/delays or language scores below the 16th percentile were excluded. Given the strong relation between SES and language scores, this may have disproportionately excluded lower-SES children, which some argue may itself be considered a “learning disability” (Ryan, 2013). As such, future studies should delineate the generalization of these findings to children with a greater variety of language abilities. Additionally, participants’ young age required minimization of in-scanner tasks; as such, the functional task was passive in nature. Although children were required to demonstrate listening comprehension before entering the scanner, monitored for alertness during scanning, and incentivized to listen closely, children could have varied in their level of task engagement. However, this is unlikely to wholly account for activation differences, because there were no temporal-lobe differences in relation to language experience and because this task has revealed robust perisylvian activation even in young, sleeping children (Redcay, Haist, & Courchesne, 2008). Nevertheless, any functional activation is constrained by the nature of the task and material used in an experiment, and further studies will be needed to characterize the scope and limits of the present findings. Finally, while LENA provides immense, naturalistic data on the quantity of speech experienced, it does not parse *what* is said, and thus provides little information about other qualitative aspects of language, such as lexical diversity and grammatical complexity. Future studies should determine the precise relation between conversational quantity and quality on brain and language development.

Although it has been theorized that the home language environment underlies the link between SES and the structure and function of canonical language-related brain regions (Noble et al., 2012; Perkins et al., 2013), this is the first study to reveal a direct relation between a specific aspect of language exposure, namely conversational turns, and brain function during language processing. While causation cannot be implied, results suggest that early language exposure, a proximal aspect of children's environment, may alter the way in which their brains process language. These findings also have clear practical implications. While many early intervention programs aim to increase the amount of language parents address *to* their children, these findings suggest programs should also encourage parents to talk *with* their children by engaging in more interactive, back-and-forth conversation (Leech, Wei, Harring, & Rowe, 2017; McGillion, Pine, Herbert, & Matthews, 2017; Suskind et al., 2016). Future longitudinal studies may determine if increasing the number of conversational turns affects the neural patterns supporting language processing, and if there is a critical/sensitive period for such neural changes. Nevertheless, the present study provides initial information on the neural mechanisms underlying the link between children's linguistic exposure and their language development.

Chapter 4: Relationship between Language Exposure and Structural Neural Connectivity in Young, Typically-Developing Children

Submitted as

Romeo, R. R., Segaran, J., Leonard, J. A., Robinson, S., West, M. R., Mackey, A. P., Yendiki, A., Rowe, M. L., Gabrieli, J. D. E. Language exposure relates to structural neural connectivity in childhood. *Under review.*

Author Contributions

R. R. Romeo and J. D. E. Gabrieli developed the study concept. R. R. Romeo, J. A. Leonard, A. P. Mackey, M. L. Rowe, and J. D. E. Gabrieli designed the study. R. R. Romeo, J. A. Leonard, and S. T. Robinson collected the data. R. R. Romeo and J. Segaran performed the data analysis and interpretation under the supervision of J. D. E. Gabrieli, M. L. Rowe, and A. P. Yendiki. R. R. Romeo and J. D. E. Gabrieli wrote the manuscript. All authors approved the final version of the published manuscript.

Abstract

Neuroscience research has elucidated broad relationships between socioeconomic status (SES) and young children's brain structure, but there is little mechanistic knowledge about specific environmental factors that are associated with specific variation in brain structure. One environmental factor, early language exposure, predicts children's linguistic and cognitive skills and later academic achievement, but how language exposure relates to neuroanatomy is unknown. By measuring young children's real-world language exposure, we confirmed the preregistered hypothesis that greater adult-child conversational experience, independent of SES and the sheer amount of adult speech, is related to stronger, more coherent white matter connectivity in the left arcuate and superior longitudinal fasciculi on average, and specifically near their anterior termination at Broca's area in left inferior frontal cortex. Fractional anisotropy of significant tract sub-regions in turn related to children's language skills. Post-hoc whole-brain analyses revealed that language exposure was not related to any other white matter tracts, indicating the specificity of this relationship. Results suggest that the development of dorsal language tracts is environmentally influenced, specifically by early, dialogic interaction. Furthermore, these findings suggest that early intervention programs aiming to ameliorate disadvantages in development due to family SES may focus on increasing children's conversational exposure in order to capitalize on the early neural plasticity underlying cognitive development.

Introduction

Socioeconomic status (SES) is a multifaceted index of one's financial resources, educational capital, and relative social status. Neuroimaging studies have found relatively consistent evidence that SES is associated with brain development, including gray matter volume (Hanson et al., 2013; Jednorog et al., 2012; Luby et al., 2013; Noble et al., 2012; Raizada et al., 2008), thickness (Lawson, Duda, Avants, Wu, & Farah, 2013; Mackey et al., 2015; Romeo et al., 2017), and surface area (Noble, Houston, et al., 2015), in addition to white matter macrostructure (Luby et al., 2013; Raizada et al., 2008) and microstructure (Gianaros et al., 2013; Ursache et al., 2016). Presumably these neural disparities arise because of systematic differences in certain immediate environmental factors during early childhood. There is, however, a paucity of evidence as to which specific aspects of children's experiences are associated with individual variation in specific neuroanatomical developments.

Behaviorally, it is well known that the quantity and quality of the language young children are exposed to early in life predicts their later linguistic and cognitive skills (Hirsh-Pasek et al., 2015; Huttenlocher, Haight, Bryk, Seltzer, & Lyons, 1991; Rodriguez & Tamis-LeMonda, 2011; Rowe, 2012; Weisleder & Fernald, 2013). Furthermore, children from lower-SES backgrounds are exposed to, on average, fewer utterances of lower complexity than their higher-SES peers (Hoff et al., 2002; Huttenlocher et al., 2007; Rowe et al., 2005). A seminal study estimated that by the time children reach school age, children growing up in higher-SES families were, on average, exposed to 30 million more words than children growing up in lower-SES families (Hart & Risley, 1995).

Subsequent research has found that more important than the simple *quantity* of words heard is the *quality* of language exposure, including linguistic features such as vocabulary diversity and sophistication, grammatical complexity, and narrative use (Rowe, 2012), as well as interactional features such as contiguous (time-locked), contingent (topically similar), back-and-forth conversation (Hirsh-Pasek et al., 2015). Conversational turn-taking involves a rich experience of high quality linguistic, attentional, and social features. There is now some evidence that certain aspects of children's language environments relate to *functional* brain responses in prefrontal cortical regions (Garcia-Sierra et al., 2016; Romeo et al., 2018; Sheridan et al., 2012). However, there is no evidence as yet relating children's language exposure to their brain *structure*, including the white matter tracts that connect brain regions into networks.

The white matter tract most associated with language is the left arcuate fasciculus, a component of the superior longitudinal fasciculus (SLF) that connects two cortical regions critical for language: the left inferior frontal gyrus ("Broca's area") and the left posterior superior temporal gyrus ("Wernicke's area"; Figure 4.1a). Microstructure of this tract has been associated with scores on language and literacy measures in children (Saygin et al., 2013; Skeide, Brauer, & Friederici, 2016; Yeatman et al., 2011), and is often altered in both children and adults with disorders of speech, language, and/or literacy (Catani & Mesulam, 2008; Vandermosten, Boets, Wouters, & Ghesquiere, 2012). Given the importance of this tract for language development, we tested the pre-registered hypothesis that early language experience—independent of SES—might be related to the microstructure of the left arcuate/superior longitudinal fasciculi; if true, this would suggest that these dorsal language tracts may be a neuroanatomical mechanism by which children's language environments affect their linguistic and cognitive skills.

Methods

Experimental Design

A priori hypotheses and exploratory analyses were pre-registered at https://osf.io/fes4j/register/564d31db8c5e4a7c9694b2be. Specifically, the present study was designed to confirm or refute the hypothesis that young children's language exposure, and particularly the number of conversational turns with adults, would be positively correlated with the fractional anisotropy of the left arcuate/superior longitudinal fasciculi (and/or a portion thereof), independent of SES and the sheer quantity of adult and child speech alone. As such, this experiment aimed to recruit a socioeconomically diverse sample of young children and their parents to complete diffusion magnetic resonance imaging (dMRI), standardized cognitive assessments, and two full days of real-word auditory language recordings. All analyses were within-group correlations with specific covariates (nuisance and interest) as described below.

Participants

Forty children (27 male) aged 4 years, 2 months to 6 years, 10 months (M = 5.78 years, SD = 0.72 years) and their parents completed this study. Children were in either pre-Kindergarten or Kindergarten grades and were required to be native English speakers with no history of premature birth (< 37 weeks), neurological disorders, developmental delay, speech/language therapy, or grade repetition. Nineteen additional children were initially assessed and excluded for not meeting these inclusion criteria.

Twenty-three other children participated but did not have complete data sets, either because they did not complete the home recordings (n = 6), did not participate in the DTI scan (n = 7), or exhibited excessive movement during the DTI scan (n = 10, details below). Excluded participants did not differ from the included sample on age, SES, behavioral scores, or language exposure measures. However, the groups did differ on child gender; unintentionally, all home-recording non-completions occurred with female participants, so that girls were more likely to be excluded. Thus, all analyses control for gender. Additionally, half of the final sample additionally participated in a larger randomized controlled intervention study on parenting practices; only their baseline data (before learning of group assignment) was used here. Furthermore, task-based functional MRI results were previously reported for a partially overlapping subset of this sample (Romeo et al., 2018). Forty-four participants had either/both useable fMRI and DTI data; of these, 32 had both useable fMRI and DTI data, 4 had only useable fMRI data (for a final fMRI sample of 36), and 8 had only useable DTI data (for a final DTI sample of 40). All procedures were approved by the Institutional Review Board at the Massachusetts Institute of Technology, and written informed consent was obtained from parents.

Socioeconomic Measures

Participants were from a wide SES range. Parent(s) filled out a short questionnaire about total gross annual household income and the highest level of education obtained by each parent and/or primary caregiver (0 = less than high school, 1 = high school, 2 = some college/associate's degree, 3 = bachelor's degree, 4 = advanced degree). When a father was present in the home, maternal and paternal years of education were averaged to create a parental education metric. For the final sample, parental education ranged from 0.5 to 4 (*M* = 2.81, *Mdn* = 3.50, *SD* = 1.17), and gross household income ranged from \$6,000 to \$250,000 (*M* = \$108,728, *Mdn* = \$93,000, *SD* = \$69,064), which is equivalent to the median family income of the Metro region from which participants were sampled (American Community Survey, 2016).

Standardized Behavioral Assessments

Children completed standardized behavioral assessments to characterize verbal and nonverbal cognitive skills. A nonverbal composite score comprised the average of the age-normed standard scores from the Matrix Reasoning, Picture Memory, and Bug Search subtests of the Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV) (Wechsler, 2012). A verbal composite score comprised the average age-normed standard scores of the Peabody Picture Vocabulary Test (PPVT-4) (Dunn & Dunn, 2007) and the Core Language Score of the Clinical Evaluation of Language Fundamentals, 5th edition (CELF-5) (Wiig et al., 2013). To be included in the final sample, participants were required to score scores greater than or equal to one standard deviation below the mean (16th percentile) on both composite scores.

Neuroimaging Data Acquisition

Neuroimaging sessions occurred at the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research, at the Massachusetts Institute of Technology. Children were acclimated to the MRI environment and practiced lying still in a mock MRI scanner before data acquisition on a 3 Tesla Siemens MAGNETOM Trio Tim scanner equipped for echo planar imaging (EPI; Siemens, Erlangen, Germany) with a 32-channel phased array head coil. First, an automated scout image was acquired, and shimming procedures were performed to optimize field homogeneity. Then a whole-head, high-resolution T1-weighted multi-echo MPRAGE structural image was acquired using a protocol optimized for movement-prone pediatric populations (TR = 2530 ms, TE = 1.64 ms/3.5 ms/5.36 ms/7.22 ms, TI = 1400 ms, flip angle = 7°, resolution = 1 mm isotropic). Whole brain diffusion-weighted images were acquired in 74 axial interleaved slices of thickness 2mm and axial in-plane isotropic resolution 2mm (128×128×74 image matrix, TR = 9.3 s, TE = 84 ms, and GRAPPA acceleration factor 2). The series included 10 non-diffusion weighted reference volumes ($b = 0$) and 30 diffusion-weighted volumes ($b = 700$ s/mm^2). Resting state and one task-based functional scans were also collected in the same session, but are not reported here.

Neuroimaging Processing and Analysis

First, all diffusion data underwent quality control via visual inspection of all volumes followed by the fully automated DTIPrep pipeline (Oguz et al., 2014), which corrects artifacts caused by Eddy currents, head motion, bed vibration/pulsation, and slice-wise, interlace-wise, and gradient-wise intensity inconsistencies. Participants with more than 5 unusable volumes (12.5%) were excluded (n = 10), leaving the final sample of 40 participants.

All preprocessing was implemented via a custom script in Nipype version 0.13.0 (Gorgolewski et al., 2011). All images in the diffusion series were aligned to the first non-diffusion-weighted image using affine registration, and corresponding diffusion-weighting gradient vectors were reoriented accordingly, in order to reduce misalignment. A per-subject total head motion index (TMI) was computed from volume-by-volume translation and rotation, percentage of slices with signal dropout, and signal drop-out severity (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). All analyses statistically control for the TMI.

Eighteen major white matter fascicles were automatically reconstructed using TRACULA implemented in FreeSurfer version 6.0 (Yendiki et al., 2011), which uses global probabilistic tractography and the ball-and-stick model of diffusion to estimate the posterior probability distribution of each pathway. This distribution includes the prior probabilities of the pathway given the cortical parcellation and subcortical segmentation of the anatomical image, which had been processed and manually edited as necessary in FreeSurfer (version 5.3.0)(Fischl, 2012) to ensure correct gray and white matter boundaries. Each pathway distribution was thresholded at 20% of the maximum value, and the values at each voxel in the pathway were weighted by the pathway probability at that voxel in order to obtain whole-tract average measures of microstructure.

Of interest were three measures of water diffusion within tracts: axial diffusivity (AD), which measures the rate of diffusion parallel to the tract; radial diffusivity (RD), which measures the rate of diffusion in perpendicular to the tract; and fractional anisotropy (FA), a summary measure of microstructural organization that indexes the overall strength and directionality of diffusion (Lebel et al., 2017). These measures were analyzed within two a priori components of the left SLF: the arcuate fasciculus, which runs between inferior frontal and superior posterior temporal regions (roughly corresponding to SLF II), and SLF III, which runs between inferior frontal and inferior parietal regions(Yendiki et al., 2011), henceforth referred to as SLF.

TRACULA was also used to calculate FA at successive cross-sections as a function of position along the trajectory of both tracts in an anterior-to-posterior direction. Correspondence of nodes across subjects was based on the Euclidean distance in MNI space. Because tracts are reconstructed in each subject's native space and not in a template space, individual participants' tracts are of varying length. For participants with shorter tracts, tail FA values were extrapolated by calculating moving averages of the previous 3 points in order to ensure uniform length (35 points along the superior longitudinal fasciculus and 48 points along the arcuate fasciculus). The presented results do not change if instead no extrapolations are made.

Finally, whole-brain voxel-wise statistical analysis was conducted with Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), as implemented in FSL version 5.0.9 (Jenkinson et al., 2012). Diffusion space FA images were aligned to each participant's anatomical image using boundary-based registration (BBR; Greve & Fischl, 2009), which was then affine aligned to MNI space. Each subject's MNI-space image was eroded to remove the highly variable lateral regions of the FA map. The images were averaged to generate an inter-subject FA skeleton, and each voxel from participants' FA volumes were projected onto the FA skeleton. Voxel-wise regression analyses were conducted with FSL's randomise tool with 5,000 permutations, and threshold free-cluster enhancement (TFCE) was used to correct for multiple comparisons with $p < 0.05$ (Smith & Nichols, 2009). Significant voxels were then back-projected from skeleton positions to the position at the center of the nearest tract in the subject's FA image in standard space. These points were then inversely warped to each subject's native diffusion space for localization within the probabilistic tractography.

Home Audio Recordings

Specific details of the home audio recordings have been previously reported (Romeo et al., 2018). Briefly, parents recorded two consecutive weekend days of audio from the child's perspective via the Language Environmental Analysis (LENA) Pro system (Gilkerson, Richards, Warren, et al., 2017). LENA software automatically processes the recordings and estimates the number of words spoken by an adult in the child's vicinity ("adult words), the number of utterances the key child made ("child utterances"), and the number of dyadic conversational turns, defined as a discrete pair of consecutive adult and child utterances in any order, with no more than 5 seconds of separation ("conversational turns"). As such, conversational turns measure the contiguous, linguistic interaction between children and adults. Running totals for each speech category were calculated for each consecutive 60 minutes across the two days in 5-minute increments (e.g., 7:00 AM – 8:00 AM, 7:05 AM – 8:05 AM, etc.), and the per-participant highest hourly total of adult words, child utterances, and conversational turns were separately extracted for statistical analysis. This metric helped minimize differences in language measures due solely to different recording lengths and/or loud activities that may have masked speech and misrepresented language input.

Statistical Analysis

Statistical analysis of behavioral and summary diffusion measures were executed in SPSS Statistics version 24 (IBM Corp., 2016). Given that all participants constituted a single group and all independent and dependent variables were continuous, all relational analyses are two-tailed regressions, reporting Pearson's *r* (if no covariates) or partial *r* (with covariates listed in results). For the node analysis within tracts, independent regressions with listed covariates were conducted with FA at each node as the dependent variable, and p-values were FDR corrected for the total number of nodes in both tracts (n = 83).

Results

Replicating prior studies, higher SES correlated significantly with higher composite verbal scores (education: $r(38) = 0.65$, $p = 5 \times 10^{-6}$; income: $r(38) = 0.46$, $p = 0.003$) and measures of language exposure, including adult words (education: $r(38) = 0.41$, $p = 0.008$; income: $r(38) = 0.28$, $p = 0.08$) and conversational turns (education: $r(38) = 0.38$, $p = 0.02$; income: $r(38) = 0.40$, $p = 0.01$), but not child utterances alone (both $r(38) < 0.27$, both $p > 0.10$). After controlling for SES (parental education and income), conversational turns was the only exposure measure that correlated with children's composite verbal scores (partial $r(36) = 0.51$, $p = 0.001$; adult words: partial $r(36) = 0.08$, $p = 0.65$; partial $r(36) = 0.10$, $p = 0.57$), indicating that differences in conversational exposure relate to variance in children's language skills over and above socioeconomic disparities.

Controlling for age, gender, and head motion, neither the number of adult words nor the number of child utterances were correlated with any diffusion measure in either the arcuate or SLF (all partial $r(35) < 0.17$, all $p > 0.32$). However, the number of conversational turns correlated positively with FA (arcuate: partial $r(35) = 0.46$, $p = 0.004$; SLF: partial $r(35) = 0.45$, $p = 0.005$; Figure 1b and 1c) and negatively with RD (arcuate: partial $r(35) = -0.34$, $p = 0.04$; SLF: partial $r(35) = -0.37$, $p = 0.02$), but did not correlate with AD (both partial $r(35) < \mathrm{abs}(0.07)$, both $p > 0.70$). Combined, these measures indicate that greater conversational turns correspond with greater coherence of diffusion parallel to the tract, which may be a marker of greater axonal myelination (Lebel et al., 2017). Importantly, these relationships remained significant when controlling for SES (arcuate FA partial $r(33) = 0.48$, $p = 0.003$; SLF FA partial $r(33) = 0.45$, $p = 0.007$; arcuate RD partial $r(33) = -0.37$ $p = 0.03$; SLF RD partial $r(33) = -0.36$, $p = 0.04$), the two other LENA measures (arcuate FA partial $r(33) = 0.46$, $p = 0.005$; SLF FA partial $r(33) = 0.42$, $p = 0.01$; arcuate RD partial $r(33) = -0.35$ $p = 0.04$; SLF RD partial $r(33) = -0.37$, $p = 0.03$), or all of these factors combined (arcuate FA partial $r(33) = 0.49$, $p = 0.003$; SLF FA partial $r(33) = 0.43$, $p = 0.01$; arcuate RD partial $r(33) = -0.38$ $p = 0.03$; SLF RD partial $r(33) = -0.36$, $p = 0.04$), indicating that the relations between conversational turns and SLF microstructure cannot be explained by these other child-level or environmental variables.

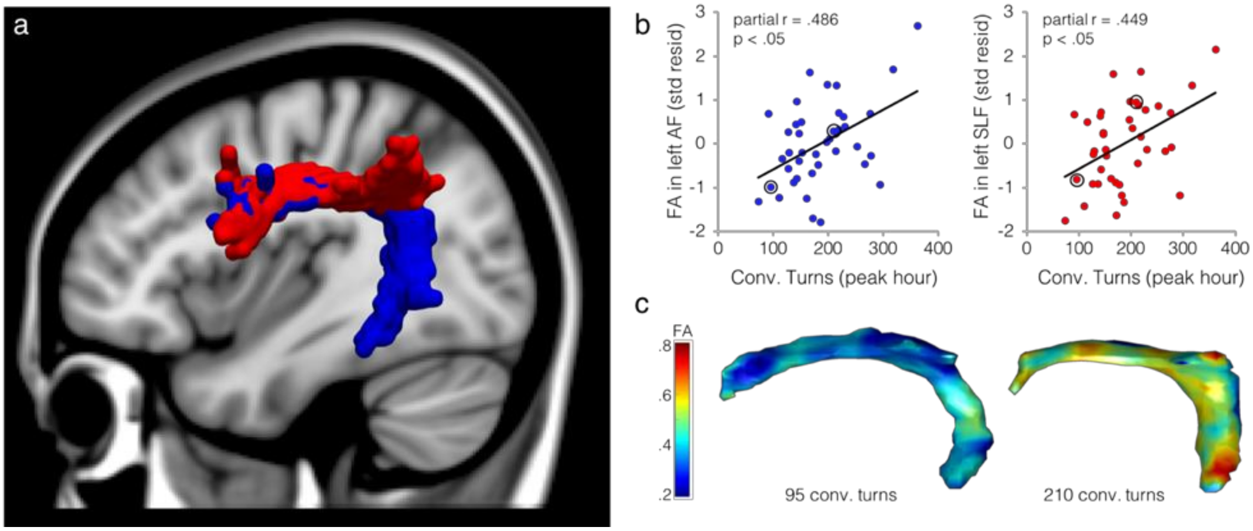


Figure 4.1 Conversational exposure relates to white matter microstructure. (a) Illustration of the four left-hemisphere white matter tracts known to be involved in receptive and expressive language. Tracts were reconstructed in each participant's native diffusion space, and the left hemisphere tracts were extracted from an example participant and registered to MNI template space for visualization. Red = Superior Longitudinal Fasciculus (SLF), Blue = Arcuate Fasciculus (AF). (b) Fractional anisotropy (FA) in the left AF and left SLF as a function of the peak number of conversational turns per hour experienced by each participant, controlling for age, gender, and head motion. P-values are FDR corrected for multiple comparisons across the 8 tracts of interest. (c) Reconstructed left AF and SLF tracts combined for two participants matched on age, gender, and SES, but differing in the number of conversational turns experienced (open black circles in Figure 4.1b). Warmer colors indicate voxels with higher FA, while cooler colors indicate voxels with lower FA.

A node analysis was conducted to explore whether a specific sub-location within these tracts was driving observed relationships. Controlling for age, gender, motion, and SES, 25 (of 83) nodes exhibited significant correlations (FDR-corrected $p < 0.05$) between conversational turns and local FA; these nodes occurred in four clusters located toward both the anterior and posterior ends of the left arcuate and SLF (Figure 4.2), suggesting that the strong correlations in these regions drive the relation between conversational turns and whole tract averages. Furthermore, when controlling for age, sex, motion, and SES, the average FA across all significant nodes combined was positively correlated with children's composite verbal scores (partial $r(33) = 0.35$, $p = 0.038$), such that higher FA in these regions corresponded with better language skills.

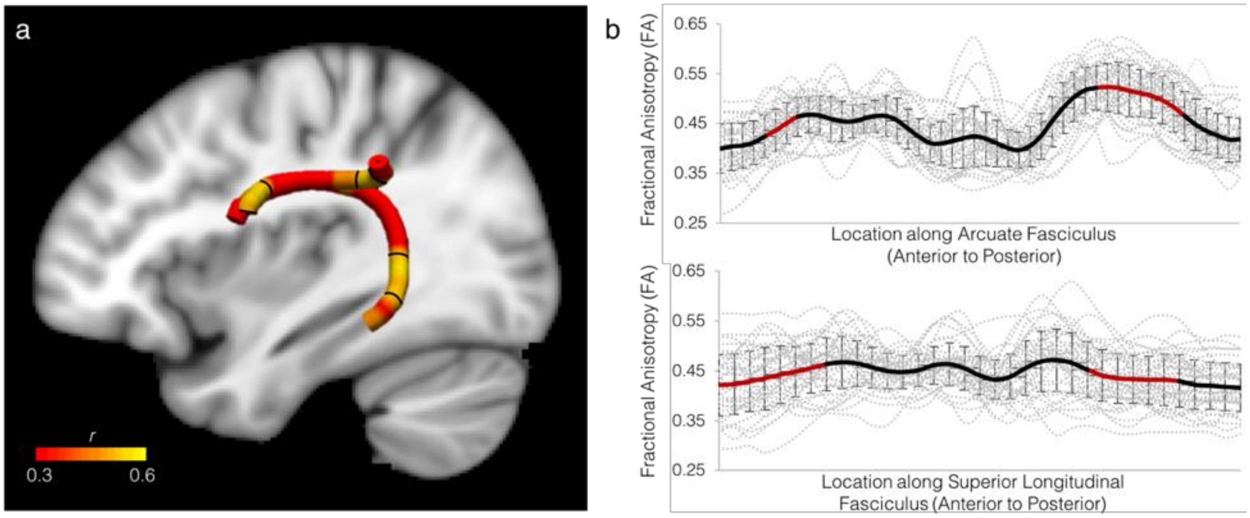


Figure 4.2 Within-tract localization of the relation between conversational turns and white matter integrity. (a) Partial correlations between the number of conversational turns and FA at 35 nodes along the left Superior Longitudinal Fasciculus (SLF) and 48 points along the left Arcuate Fasciculus (AF), controlling for age, gender, motion, and SES (both parental education and family income), projected onto group average tracts in MNI space. Clusters of significant nodes are marked with black lines. (b) FA as a function of position along the AF (top) and SLF (bottom) from anterior to posterior. Gray dotted lines represent individual participants; thick dark line represents the mean of all participants; error bars represent the standard error of the mean. Regions marked in red correspond to the clusters of significant nodes marked in Figure 4.2a.

Finally, a post-hoc, whole-brain, voxel-wise analysis was conducted to assess the anatomical specificity of these correlations across all white matter tracts. Convergent with the node analysis, the number of conversational turns was positively correlated (TFCE corrected $p < 0.05$) with FA in a cluster of 513 voxels at the anterior end of the left arcuate/SLF where these tracts terminate with Broca's area in the left inferior frontal gyrus (Figure 4.3). To confirm localization in each participant's native space, back-projection revealed that the maximally significant voxel of this cluster occurred within the TRACULA-defined bounds of the intertwining arcuate/SLF near the anterior termination.

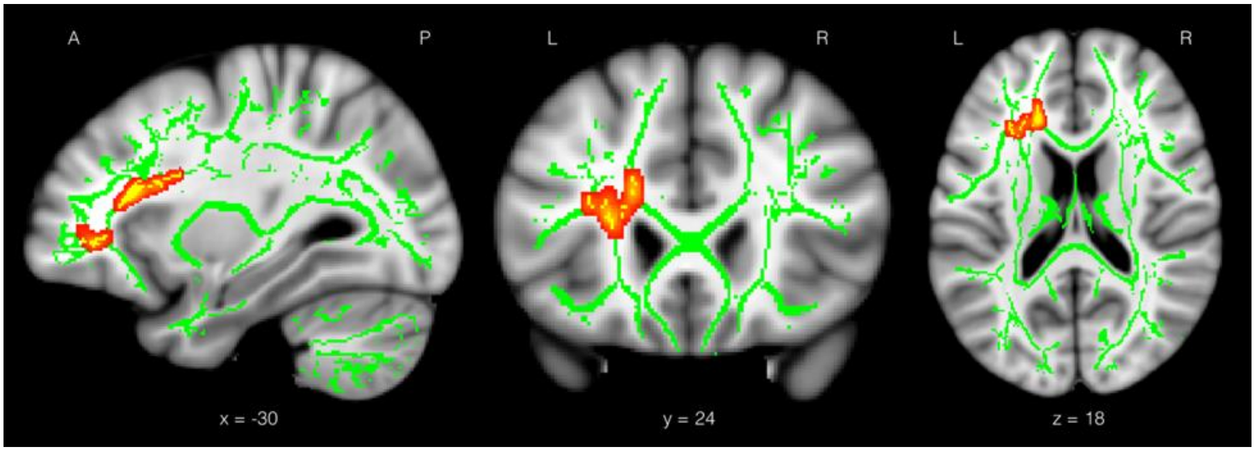


Figure 4.3 Whole-brain voxel-wise analysis of the relation between conversational turns and white matter integrity. The number of conversational turns was associated with FA in a cluster of voxels ($p < 0.05$ corrected) at the anterior end of the left SLF and left AF where these tracts terminate with Broca's area in the left inferior frontal gyrus. Analyses were computed on a skeleton (green), and thresholded values (red/yellow) were thickened and overlaid on the MNI template for visualization purposes. A = Anterior, P = Posterior, L = Left, R = Right.

Discussion

These results provide the first evidence of direct association between a specific aspect of children's language experience, namely adult-child conversational turns, and particular neuroanatomical structural properties, specifically the connectivity of the left arcuate and the left superior longitudinal fasciculi. The number of adult-child conversational turns young children experience, independent of SES, was positively correlated with the strength of coherence of two dorsal white matter tracts: the left arcuate fasciculus and the left superior longitudinal fasciculus. This relationship appeared to be driven by the FA in a sub-region of the tracts near where these tracts terminate in the left inferior frontal lobe, which is a hub for expressive and receptive language processing.

This localization is consistent with functional findings that children's language exposure is related to activation specifically in left prefrontal cortical regions (Garcia-Sierra et al., 2016; Romeo et al., 2018; Sheridan et al., 2012). Together this suggests that "Broca's area" and adjacent pathways may be components of the perisylvian language network that are particularly sensitive to early linguistic input, especially dialogic conversation. Because the arcuate fasciculus bidirectionally connects Broca's area to primary receptive language regions in superior posterior temporal cortex, this uniquely human tract may be evolutionarily specialized for language (Rilling et al., 2008), as evidenced by correlations between language skill and structural properties of the left arcuate. Classically, damage to the arcuate fasciculus is associated with conduction aphasia (Catani & Mesulam, 2008). Further, individual microstructural variation in the absence of overt damage is related to a number of linguistic skills in childhood, including phonological knowledge and literacy skills (Saygin et al., 2013; Yeatman et al., 2011), presence or risk for developmental dyslexia (Langer et al., 2017; Vandermosten, Boets, Wouters, et al., 2012; Wang et al., 2017), rate of vocabulary growth (Su et al., 2018), as well as word learning (Lopez-Barroso et al., 2013), verbal memory (Catani et al., 2007), and speech perception (Vandermosten, Boets, Poelmans, et al., 2012) in adulthood. In all cases, greater coherence in the left arcuate fasciculus reflected better linguistic skills, suggesting that that fast, efficient connectivity between frontal and temporal areas facilitates verbal skills throughout the lifespan. The present results further suggest that variation in early childhood language experience may underlie individual differences in neuroanatomy and behavior.

The apparent environmental influence of conversational turn-taking on left arcuate and superior longitudinal microstructure is congruent with findings that dorsal language tracts (superior longitudinal and arcuate fasciculi) develop more slowly than their ventral counterparts (inferior longitudinal, inferior-frontal-occipital, and uncinate fasciculi) (Brauer, Anwander, Perani, & Friederici, 2013; Perani et al., 2011). Specifically, the terminal projection of the arcuate fasciculus at the furthest anterior point near Broca's area is the latest developing component of the dorsal pathway, which is still not fully mature at age seven years (Brauer et al., 2013). As such, this period of protracted development in early and middle childhood may correspond to a sensitive period of neurodevelopment in which children's anterior dorsal language circuitry is highly susceptible to their environments.

The present finding that conversational exposure correlated positively with FA and negatively with RD in the left arcuate and superior longitudinal fasciculi indicates greater coherence of diffusion parallel to the tracts, which is often considered a marker of greater axonal myelination

(Lebel et al., 2017). Considering that myelination increases throughout childhood and early adulthood (Miller et al., 2012), these findings suggests that increased conversational exposure in early childhood might advance maturation of the anterior terminations of the dorsal language pathways important for language processing. However, longitudinal studies of children are necessary to determine precise developmental trajectories in relation to language exposure.

With regard to language exposure, dorsal pathway microstructure was related only to the quantity of dialogic adult-child conversational turns, and not to the sheer volume of speech spoken in the child's presence. Conversational turns incorporate social interactional features, such as contiguity (temporal connectedness), contingency (contextual relevancy), and joint attention, beyond simple linguistic features of the spoken content. The specificity of the relation between conversational turns and white-matter microstructure further supports the idea that qualitative aspects of children's early language experience, as opposed to sheer quantitative aspects, may be the largest influence on children's language development (Hirsh-Pasek et al., 2015; Roseberry et al., 2014; Rowe, 2012; Zimmerman et al., 2009). The present findings suggest that neuroanatomical maturation may critically rely on social exchanges of linguistic information (Kuhl, 2007), rather than purely passive speech exposure.

The present results may also have practical implications. Community-based intervention programs designed to close the SES "word gap" (Cartmill, 2016) have often focused on closing this gap by increasing the quantity of speech that low-SES parents direct toward children. However, the present results build on previous behavioral findings that the *quality* of language—specifically conversational interaction—is more strongly linked to children's behavioral outcomes by revealing that this same quality is associated with white-matter development in children's language brain circuitry. This suggests that early intervention programs should not only encourage parents to talk *to* their children, but to talk *with* their children to promote optimal brain development. Further research is needed to determine if enrichment of the language environment in at-risk children could reduce the measurable socioeconomic disparities in academic achievement and brain development (Johnson et al., 2016; Mackey et al., 2015; Noble, Houston, et al., 2015). More generally, the finding that more conversational turns are associated with more coherent white-matter connectivity *independent of SES* indicates that promoting such conversational turns may enhance structural brain development and the language abilities supported by that brain development in children from all backgrounds.

Chapter 5: Summary and General Discussion

This thesis explored relationships between socioeconomic status (SES) and neural measures underlying language and literacy development in both typically developing children and children with reading and language impairment. It further explored whether certain aspects of children's early language environments drive this neural development independent of SES.

The first study (chapter 2) investigated how SES relates to neuroanatomy and neuroplasticity in 6-9 year-old children with developmental reading disabilities. Findings revealed that SES is related to cortical thickness in broad bilateral perisylvian and occipito-temporal regions over and above individual reading scores, and that the volume of left pars opercularis, part of Broca's area in the inferior frontal gyrus, significantly mediated the SES vocabulary gap. Furthermore, after an intensive summertime reading intervention, SES uniquely predicted treatment response, such that lower-SES children exhibited significantly greater improvements in reading scores and cortical thickening in similar bilateral occipito-temporal regions that had been initially depressed. This study extended the literature of SES disparities in developmental cortical structure to a linguistically atypical sample and additionally demonstrated demographically constrained neuroplasticity.

Describing and quantifying these SES disparities is a crucial first step toward identifying causal pathways. However, SES is a *distal* factor that presumably affects children's neurocognitive outcomes via more immediate, *proximal* environmental influences (Bronfenbrenner & Morris, 1998). Thus, the second study (chapters 3 and 4) investigated how the more proximal influence of children's early language experience related to 4-6 year-old children's brain structure and function, independent of SES. By measuring children's real-world, first person auditory language exposure, we found that while the amount of adult speech does not relate to children's language skills after controlling for SES, the amount of interactive, adult-child conversational turns predicts unique variance in children's language scores over and above SES. Moreover, individual differences in conversational turns related to activation in Broca's area during language processing as well as the directional strength of dorsal white matter tracts, indicating both a structural and functional mechanism by which children's language experience contributes to their language skills. These relationships were independent of SES and the sheer amount of adult or child speech, suggesting that there is socioeconomically independent value of conversational exchanges in childhood. Finally, conversational turns, combined with neural measures, jointly mediated the SES gap in children's language skills. This study is the first to find a neural mechanism by which children's language exposure relates to their language skill, and points to a specific aspect of language experience, namely conversational turn-taking, that may be actionable for interventions aiming to close the neurocognitive achievement gap.

In combination, the studies presented here contribute essential pieces to the puzzle of how children's environments contribute to their language development. These findings demonstrate that SES has strong and unique associations with neural and cognitive development in a variety of pediatric populations, and that these relationships may be due to individual differences in specific aspects of their language experiences early in life. However, several questions remain:

Are parent language practices malleable? If so, can parental interventions cause lasting pediatric neuroplasticity & behavioral outcomes?

Individual differences in parenting practices are rooted in deep cultural traditions (for review, see Hoff, 2006). Early sociological research suggested that language exposure was linked to class differences, cultural transmission, and an "intergenerational transfer of competence" (Bernstein, 1961, 1970; Heath, 1983; Hess & Shipman, 1965; Hymes, 1972; Olim, 1970). They found that the purpose of child-directed speech differed by SES, such that in higher in SES families, parents aimed to elicit conversation with the child, while speech directed to children in lower-SES homes was often meant to direct children's behavior (Bee, Van Egeren, Pytkowicz Streissguth, Nyman, & Leckie, 1969; Hart & Risley, 1992; Hart & Risley, 1995; Heath, 1983; Hoff-Ginsberg, 1991; Hoff-Ginsberg, 1998; Lareau, 2003).

Later research delved further into differences in the purposes of child-directed speech, and found that socioeconomic differences in the quantity and quality of child-directed language were linked to parents' knowledge and beliefs about child development, including knowledge of cognitive and linguistic developmental milestones, developmental processes, and health and safety practices (Luster, Rhoades, & Haas, 1989; Rowe, 2008; Rowe & Casillas, 2011; Rowe et al., 2005). Combined with findings of a somewhat universal benefit of certain qualitative aspects of children's language experiences regardless of SES, ethnicity, or cultural norms (Song, Spier, & Tamis-Lemonda, 2014; Tamis-LeMonda, Song, Leavell, Kahana-Kalman, & Yoshikawa, 2012), this suggests that *cultural* practices should not be the target of word-gap interventions, per se. Rather, modification of caregivers' *knowledge* of child development and the importance of interactive, early language exposure is simultaneously a more ethical, culturally-sensitive target, in addition to being a more efficacious target that is potentially more amenable to modification (Rowe, 2017).

Several researchers have specifically investigated the malleability of children's early language exposure via parent education programs (Cates, Weisleder, & Mendelsohn, 2016; for review, see Kaiser et al., 2017; Roberts & Kaiser, 2011; Te Kaat-van den Os, Jongmans, Volman, & Lauteslager, 2017; Topping, Dekhinet, & Zeedyk, 2013). In general, these studies have found that parent-coaching programs, especially those focused on contingent communication, increase parents' responsiveness to their children, their use of language modeling, and the amount of overall child-directed communication, with reciprocal improvements in children's receptive and expressive language skills. However, intervention effects do not typically persist in the long term after the intervention ends. Several more recent studies have found similar results when specifically educating parents about contingent conversation and turn taking (e.g., Gilkerson, Richards, & Topping, 2017; McGillion et al., 2017; Suskind et al., 2016; Suskind et al., 2013), with the greatest improvements seen for children in lower-SES homes; however, these too exhibit washout after treatment ceases.

As such, it remains to be seen if parent-coaching interventions—of any intensity or duration—can instill long-term behavioral change in parents and concomitant child outcomes. Similarly, there is no evidence, in either the short or long term, whether parent interventions specifically focused on language skills can cause lasting pediatric (and/or parental) neuroplasticity. Several early intervention studies have found short-term fade out on operationalized outcome measures (e.g., standardized tests) followed by longer-term benefits in less tangible life outcomes; this suggests the existence of intervention-induced neural changes measurable in the short term that predict behavioral outcomes in the longer term (Raizada & Kishiyama, 2010). Future cognitive neuroscience research must focus on effective, scalable, and long-lasting programs that ensure optimal neurocognitive development for children at risk of impoverished language environments.

Are certain populations of children more sensitive to their language environments than others?

Twin studies on the heritability of cognitive abilities often find evidence of gene × environment interactions, in which the genetic contribution to children's cognitive skills is modified by the environment (Plomin & von Stumm, 2018). This means that the effects of children's environments on the development of their cognitive ability can be nonlinear, such that the environment "matters more" for certain populations of children.

One such finding specifically involves SES. Many studies have found that the majority of variance in IQ (verbal and non-verbal combined) for children growing up in lower-SES homes was due to aspects of their environment, with very little genetic contribution, while higher-SES children exhibited the opposite pattern of higher heritability and lower environmental contribution (Harden, Turkheimer, & Loehlin, 2007; Kirkpatrick, McGue, & Iacono, 2015; Tucker-Drob, Briley, & Harden, 2013; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). This is in line with the "environmental disadvantage hypothesis," also known as the "Scarr-Rowe hypothesis of Gene × Socioeconomic Status (SES) interaction" whereby the disadvantages conferred by poverty prevent individuals from achieving their optimum development, as would have otherwise been genetically determined (Lewontin, 1970; Rowe, Jacobson, & Van den Oord, 1999; Scarr-Salapatek, 1971).

These findings suggest that children growing up in lower-SES homes are disproportionately sensitive to their childhood experiences. This interaction emerges before age two (Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask, 2011), has lasting effects on children's cognition throughout adulthood (Bates, Lewis, & Weiss, 2013), and may be particularly strong in the realm of *verbal* ability (Rowe et al., 1999). Interestingly, gene x SES effects seem largely restricted to the United States; other western societies, where there is more universal access to high-quality early education programs, do not exhibit these effects (Tucker-Drob & Bates, 2016). In sum, this genetic research suggests that children's language exposure may be disproportionately influential in lower-SES environments.

The data from study 2 partially support this hypothesis. Lower-SES children exhibited a slight trend toward a stronger relationship between conversational turns and verbal scores (lower-SES $r(29) = 0.37$; higher-SES $r(29) = 0.10$; Fisher $z = 1.03$, one-tailed $p = 0.15$). Largely, it appears that conversational turns strongly predict verbal scores across all portions of the SES spectrum sampled here. However, study 2 did not sample many very low-SES families; only 4 of 58 (7%) families with language exposure data had parents with less than a high school degree, so it is possible that the sampled SES range was not wide enough to fully reveal potential socioeconomic interactions. Additionally, it is possible that other aspects of children's language environments not measured here are more important in lower-SES populations. A more detailed analysis of the qualitative aspects of children's language environments would be necessary to answer this question (see section below).

Furthermore, other populations of at-risk children, such as those at an increased genetic/biological risk of language disorders and/or learning disabilities, may exhibit increased sensitivity to their language environments. In a study reviewed in the introduction, children with poor phonological awareness differed in their reading skills depending on their socioeconomic background (Noble, Farah, et al., 2006). Children from higher-SES families exhibited reading skills within the average range, no matter their phonological skills; however, children from lower-SES families did not exhibit this buffering effect, and those with low phonological skills were poorer readers. Similar findings have emerged with neural predictors, such that structural characteristics of gray and white matter predict reading outcomes in lower-SES children, but not higher-SES children (Noble, Wolmetz, et al., 2006; Ozernov-Palchik et al., under review), and twin studies have revealed the expected finding that there is a relatively stronger influence of the environment on the manifestation of reading disability in children from low-SES families (Friend et al., 2008). This may indicate that some aspect of low-SES environments multiplies a hereditary risk for reading disability, suggesting that early literacy exposure may be especially important for buffering this risk. The same relationship may be true for early oral language exposure and children at risk for genetically-determined language impairments, such as Specific Language Impairment, and other neurodevelopmental disorders that affect communication, such as Autism Spectrum Disorder and Intellectual Disability. Further research is needed from a variety of populations to determine if children at risk for language, reading, and communication disorders are more susceptible to reduced language exposure in childhood.

Do other qualitative aspects of language exposure specifically, or cognitive stimulation/social responsiveness in general, predict neural and cognitive development better than conversational turns?

One of the primary findings of this thesis was that a strong predictor of children's linguistic skills and neural structure and function is the number of conversational turns exchanged between a child and surrounding adults. However, conversational turns may not necessarily be the *best* predictor of developmental outcomes. The measure used exists at an intermediate level of specificity; in other words, there are more specific factors, such as the exact timing of turns or the exact words used, as well as less specific factors, such as any kind of verbal or nonverbal parent-child interaction, that could be better predictors of linguistic and cognitive development.

For example, in the introduction, I reviewed many qualitative aspects of child-directed speech that predict children's language development, such as the variety, complexity, and sophistication of vocabulary and grammatical constructions; the use of questions, narrative, and decontextualized language; and the temporal and topical contingency of dialogic exchanges (for review, see Schwab & Lew-Williams, 2016). Although conversational turns were more strongly related to children's brain and language than the sheer quantity of adult speech, any one or more of these other qualitative factors could predict children's language development better than conversational turns alone. Such in-depth investigations were not possible with the current methods; while LENA provides an incredibly comprehensive account of the quantity and timing of speech in children's environments over an extended period of time, it does not provide information on the content of speech. These analyses would require time-intensive transcriptions of the recorded audio, and such efforts are currently ongoing. Future investigation, preferably with longitudinal measures, will be critical in determining exactly which aspect(s) of the language environment, if any, are most strongly related to children's neural and behavioral language development.

Importantly, though, the measure of conversational turns is not an exclusively linguistic measure. Turns imply the existence of broader categories of early experience such as cognitive stimulation and social interaction. Therefore, it is plausible that the frequency of one of these more general experiences may actually drive language and brain development.

"Cognitive stimulation" is a term that encompasses materials and experiences that support cognitive development, such as the availability of learning materials and toys, access to enriching experiences (i.e., museums, libraries, etc.), conscious efforts to teach children various concepts, language exposure, and parental responsivity. The most common measure of cognitive stimulation is the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley, 1984), an experimenter-administered home-based evaluation with items relevant to children's specific ages, although survey-based instruments (e.g., the StimQ; Dreyer, Mendelsohn, & Tamis-LeMonda, 1996) and experimental lab-based rating scales (Brady-Smith, O'Brien, Berlin, Ware, & Brooks-Gunn, 1999) are becoming more common.

Indeed, these global measures of cognitive stimulation specifically predict the development of children's language skills (Camp, Cunningham, & Berman, 2010; Cates et al., 2012; Chapin & Altenhofen, 2010; Chazan-Cohen et al., 2009; Farah et al., 2008; Fuligni, Han, & Brooks-Gunn, 2004; Tamis-LeMonda, Shannon, Cabrera, & Lamb, 2004; Tucker-Drob & Harden, 2012; Vallotton, Mastergeorge, Foster, Decker, & Ayoub, 2017), as well as measures of cortical thickness (Avants, Epstein, Grossman, & Gee, 2008; Rosen et al., 2018). Furthermore, there is significantly less cognitive stimulation in lower-SES homes (Bradley & Corwyn, 2002; Bradley, Corwyn, McAdoo, & Coll, 2001); in extreme forms, this may constitute cognitive "deprivation," which can constrain learning and result in severely disadvantageous cognitive and neural outcomes (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014).

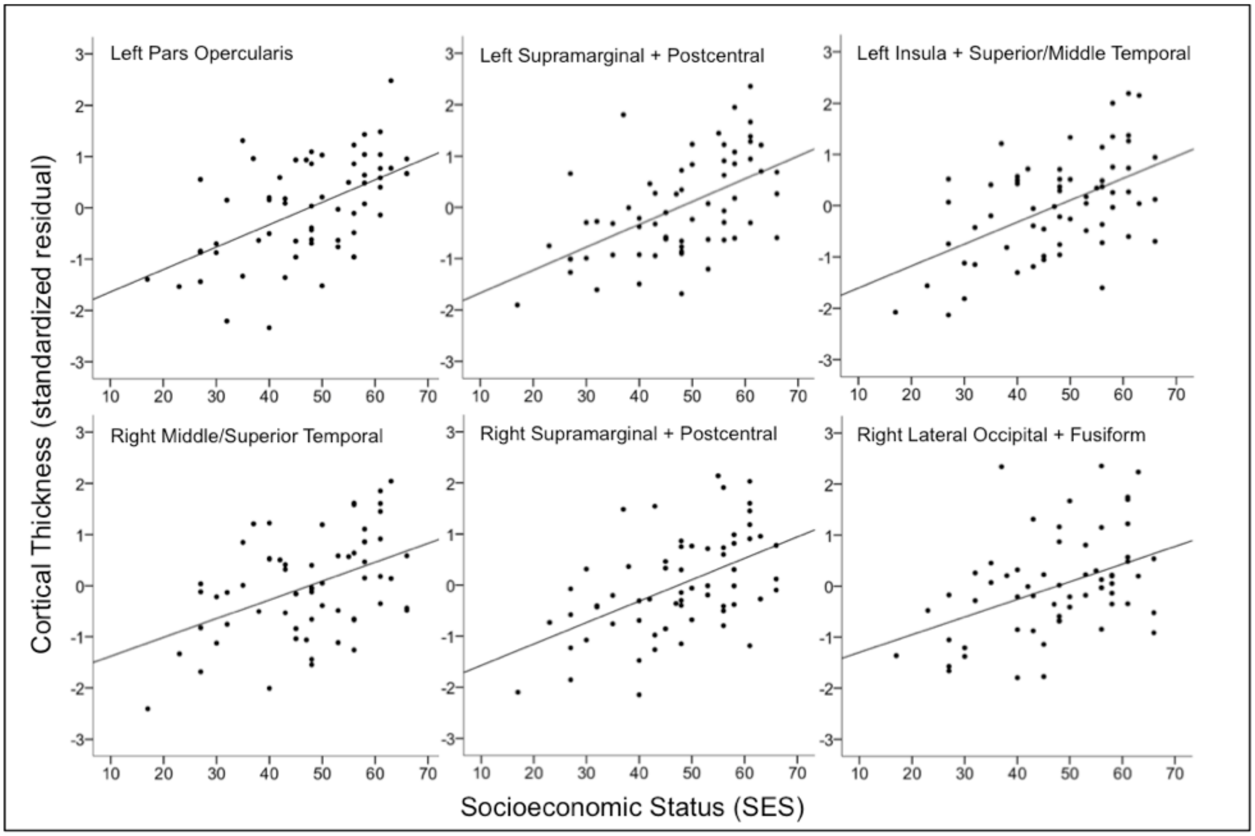
Similarly, children's cognitive outcomes may also be predicted by socioemotional aspects of caregiving that are related, but not identical, to cognitive stimulation, such as parental warmth, sensitivity, nurturance, reciprocity, and authoritative/authoritarian parenting styles. While these aspects are typically more strongly linked to children's socioemotional development (for review, see Morris, Silk, Steinberg, Myers, & Robinson, 2007), they may be either directly or indirectly related to cognitive development as well. Thus, future research must explore a variety of in-depth measures of linguistic and cognitive stimulation at multiple levels, as well as socioemotional parenting, to disentangle which specific environmental factors are most influential on children's neural and linguistic development.

Conclusion

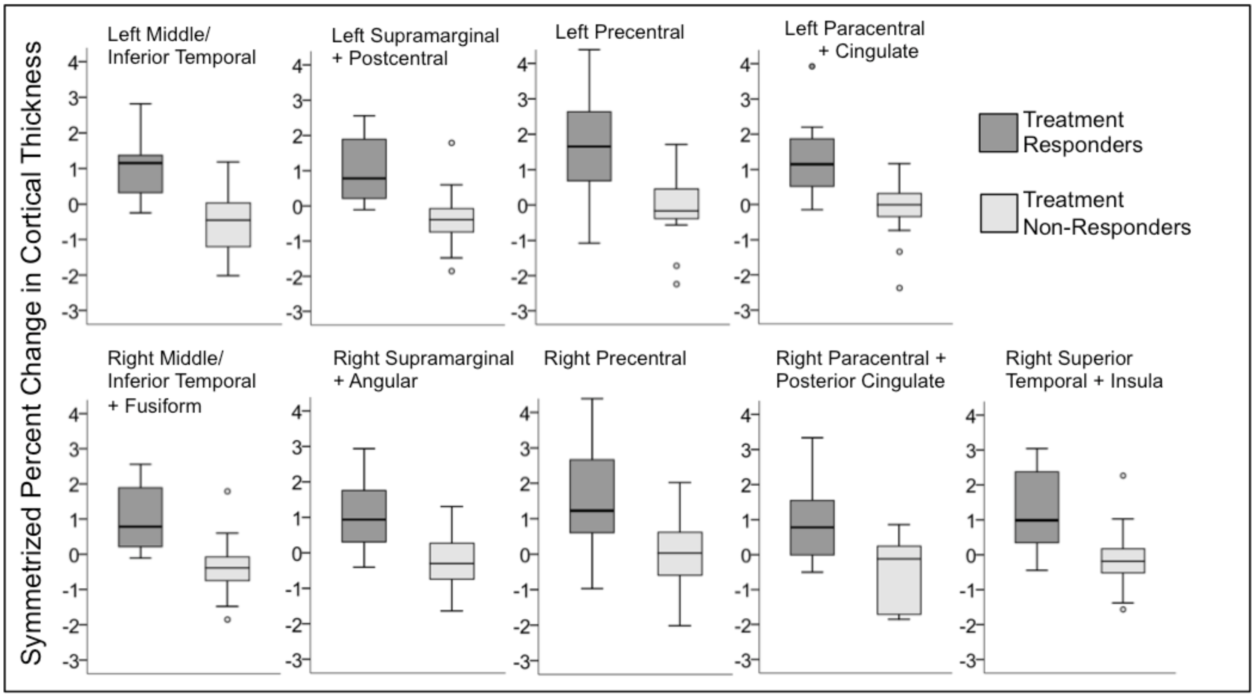
In summary, this thesis demonstrated that socioeconomic status is strongly linked to neuroanatomy, neurophysiology, and neuroplasticity in young children, and that the influence of SES on these systems seems to be driven by children's interactive language experiences early in life. While future research is necessary to elucidate the precise nature of these relationships and long-term intervention effects, the present results may be used to inform social, educational, and clinical policies and practices.

Appendices

A. Supplementary Material for Chapter 2



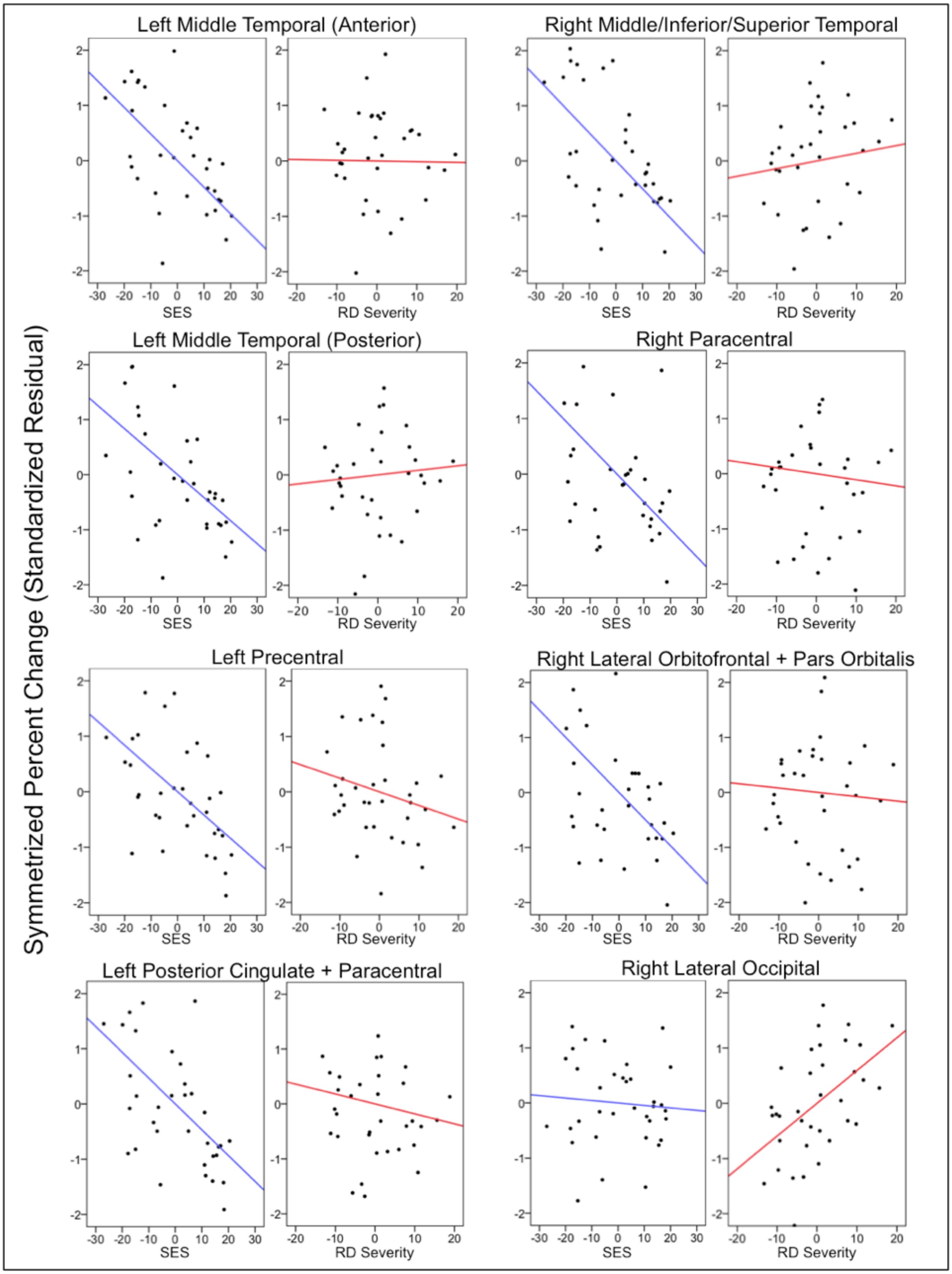
Supplementary Figure S2.1 Correlations between SES and cortical thickness at pre-test. Cortical thickness is controlled for gender and age in months, and then averaged over the area of each significant cluster. Each scatter plot contains the best-fitting linear regression line. Cluster heat maps are shown in Figure 2.1, and cluster statistics are shown in Table 2.2.



Supplementary Figure S2.2 Change in cortical thickness between pre-test and post-test in regions that exhibit significant differences between treatment responders (*n* = 18) and treatment non-responders (*n* = 18). Symmetrized percent change (SPC) is the rate of change at each vertex with respect to the average thickness across both time points, and is averaged over the area of each significant cluster. Cluster heat maps are shown in Figure 2.6, and cluster statistics are shown in Table 2.4.

Supplementary Figure S2.3. Partial regression plots showing the change in cortical thickness between pre-test and post-test as a function of SES and reading disability (RD) severity (*n* = 36 children who received intervention), including gender as a nuisance variable. Each scatter plot contains the best-fitting linear regression line. Symmetrized percent change (SPC) is the rate of change at each vertex with respect to the average thickness across both time points, and is averaged over the area of each significant cluster. SES was significantly correlated, and RD severity uncorrelated, with SPC in each region presented with exception of the right lateral occipital cluster, in which the reverse was true. Cluster heat maps are shown in Figure 2.7, and cluster statistics are shown in Table 2.5.

Supplementary Figure S2.3 (Continued)



B. Supplementary Material for Chapter 3

Method

Sample size justification

Because this is the first study to examine individual relationships between children's language exposure and fMRI measures of language-related brain activation, effect size estimates were not available to inform sample size. However, the behavioral correlations between language input quantity/quality and children's language scores are typically moderate to strong ($0.4 < r < 0.6$) (Hirsh-Pasek et al., 2015; Hoff, 2003; Rowe, 2012; Weisleder & Fernald, 2013). For 80% power to detect such an effect in the expected direction at $\alpha = 0.05$, one would need to recruit 15-36 participants. Similarly, a majority of studies investigating correlations between behavioral measures and fMRI activation using appropriate *independent analyses* report correlations in the 0.5 to 0.7 range, with a median of 0.6 (Figure 5 of Vul, Harris, Winkielman, & Pashler, 2009). Given that individual differences analyses (i.e., correlational analyses) have lower power than within-subjects analyses (i.e., condition differences), common sample-size planning tools for fMRI studies are not appropriate for the present power analysis. Instead, power curves specific to Pearson's correlations in the context of fMRI were consulted (Yarkoni & Braver, 2010). By these estimates, one would need to recruit 15-30 participants for the same parameters stated above. Combined, a sample size of 15-36 is recommended to find expected behavioral and neural effects. However, because of the likelihood of publication bias in previously reported effects (Anderson, Kelley, & Maxwell, 2017), we aimed for the highest end of this range ($n = 36$).

Statistical Analysis

All statistical analyses (with exception of whole-brain fMRI analyses) were performed in IBM SPSS Statistics version 24 (IBM Corp., 2016). The first approach was to conduct zero-order Pearson's correlations between children's assessment scores, SES demographics, and LENA measures of language exposure. Because all three variables were intercorrelated, we conducted linear regressions to determine which independent variables predicted unique variance in children's language scores, while controlling for the other independent variables. Finally, we conducted bootstrapped mediation with 10,000 iterations using the PROCESS macro for SPSS (Hayes, 2013) to determine whether language exposure mediated the relationship between SES and children's language scores. The same bootstrapping approach was applied to neural activation measures extracted from a region of interest (see main text).

Executive Functioning measure

In addition to the standardized assessments described in the main text, children also completed a non-standardized executive functioning (EF) task. Because EF relies on prefrontal regions adjacent to/overlapping with frontal language regions, EF was included to serve as a covariate/nuisance variable. The Hearts and Flowers version of the dots task (Davidson, Amso, Anderson, & Diamond, 2006) is commonly used to assess EF in both children and adults, because it requires all three EF dimensions (working memory, inhibition, and cognitive flexibility/switching) with simple instructions. Children rested their hands on a handlebar adjusted to finger-distance away from a touch screen computer and completed a practice run of quickly pressing on-screen buttons in this way. Then, a red heart or flower would appear on the right or left side of the screen, and children were instructed to press the button on the *same* side as a heart (congruent condition) and the button on the *opposite* side of a flower (incongruent condition). The task consisted of three consecutive blocks: a congruent block of 12 trials, an incongruent block of 12 trials, and a randomly mixed block (congruent and incongruent) of 49 trials. For all conditions, stimuli were displayed for 500 milliseconds (ms) with 1500 ms to respond and an interstimulus interval of 500 ms. Any response faster than 200 ms were considered to be anticipatory (Davidson et al., 2006) and excluded from analyses. Children received up to 12 practice trials before the congruent and incongruent blocks to ensure understanding of the rule. No practice was included before the mixed block, and thus the first trial was additionally excluded from analyses. The main outcome measures were the average accuracy across all trials in the mixed block and average reaction time (RT) in milliseconds across all correctly answered trials in the mixed block. Although rare, accuracy scores below 50% were not discarded because they could have been obtained by rule reversal, indicating an error in cognitive flexibility/switching.

Results

Mean accuracy on the EF task was 72%, (*SD* = 22%) with a mean reaction time on correctly answered trials of 1140 ms (*SD* = 207). None of the fMRI analyses – including group mean task activation and whole brain correlates with LENA measures – changed with the inclusion of EF scores as a nuisance variable. This suggests that correlations between conversational turns and activation in Broca's area are not driven by differences in executive functioning.

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