Title

Neural correlates of Socioeconomic Status and Language Skills in Young Children with Autism Spectrum Disorders

Author

Olson, Lindsay

Publication Date

2021

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Neural correlates of Socioeconomic Status and Language Skills in Young Children with Autism Spectrum Disorders

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Lindsay Alexandra Olson

Committee in charge:

University of California San Diego

Professor Lauren Brookman-Frazee
Professor Shana Cohen

San Diego State University

Professor Inna Fishman, Chair
Professor Allyson Abel-Mills
Professor Ruth Carper

2022

The Dissertation of Lindsay Olson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California San Diego

San Diego State University

2022

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ACKNOWLEDGEMENTS

I am extremely grateful to the many people who have generously guided and supported me throughout my time in graduate school. I would first like to acknowledge Dr. Inna Fishman, my dissertation chair, for her encouragement to pursue a line of research that deviated somewhat from the lab's and her own previous areas of focus. I'm grateful to her for her patience with me, her cunning intellect, and her invaluable scientific insight over the years it took to produce this work. I also would like to thank my dissertation committee for their collaboration, mentorship, and support. To my partner, Phil, my family, my JDP/BDIL families, and my friends who have cheered me on year after year- thank you for your unwavering support.

VITA

2022 **Doctor of Philosophy** in Clinical Psychology
San Diego State University/ University of California San Diego Joint Doctoral Program in Clinical Psychology
Major Area of Study: Experimental Psychopathology
Emphasis: Child and Adolescent Psychopathology
Dissertation Chair: Inna fishman, Ph.D.
Dissertation Title: *Neural correlates of Socioeconomic Status and Language Skills in Young Children with Autism Spectrum Disorders*

2021-2022 **Pre-doctoral Internship**
University of Colorado School of Medicine
Major Area of Study: Clinical Health Psychology / Pediatric Neurodevelopmental Disabilities

2018 **Master of Science** in Clinical Psychology
San Diego State University
Thesis Chair: Inna Fishman, Ph.D.
Thesis Title: *Sex-Related Patterns of Intrinsic Functional Connectivity in Children and Adolescents with Autism Spectrum Disorder*

2012 **Bachelor of Arts** in Psychology with honors, Cum Laude
Whitman College

PEER-REVIEWED PUBLICATIONS

Chen, B., Linke, A., **Olson, L.,** Kohli, J., Kinnear, M., Sereno, M., Müller, R-A., Carper, R., Fishman, I. (2022). Cortical Myelination in Toddlers with Autism Spectrum Disorder. *Developmental Neurobiology.*

Linke, A., Chen, B., **Olson, L.,** Ibarra, C., Fong, C., Reynolds, S., Apostol, M., Kinnear, M., Müller, R-A., Fishman, I. (2021). Sleep Problems in Preschoolers with Autism Spectrum Disorder Are Associated with Sensory Sensitivities and Thalamocortical Overconnectivity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.*

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Olson, L., Chen, B., & Fishman, I. (2021). Neural correlates of socioeconomic status in early childhood: A systematic review. *Child Neuropsychology.*

Article selected for American Academy of Clinical Neuropsychology (AACN) Continuing Education (CE) credit

Olson, L., Kinnear, M., Linke, A., Chen, B., Ibarra, C., Wang, T., Reynolds, S., & Fishman, I. (2021). Socioeconomic factors account for variability in language skills in preschoolers with autism spectrum disorders. *Journal of Developmental and Behavioral Pediatrics.*

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ABSTRACT OF THE DISSERTATION

Neural correlates of Socioeconomic Status and Language Skills in Young Children with Autism Spectrum Disorders

by

Lindsay Alexandra Olson

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2022
San Diego State University, 2022

Professor Inna Fishman, Chair

Despite great strides in characterizing autism spectrum disorder (ASD) in early childhood, ASD research has largely overlooked the role socioeconomic status (SES) plays in early development. Broadly, SES captures the degree to which individuals are better or worse off in terms of their access to material and social resources (often measured via income and educational attainment). It remains unknown to what extent SES may be associated with the neural correlates

of emerging language skills, above and beyond the known developmental vulnerabilities associated with ASD alone.

This project was conducted using data collected through the SDSU Toddler MRI Project, which included behavioral and MRI data from 15- to 64-month-old children with autism and their typically developing (TD) peers ($N_{ASD} = 39$, $N_{TD} = 37$). SES predictor variables included family-level (parental education, income-to-needs ratio) and population-level SES factors (neighborhood advantage index). Neural outcome measures included anatomical features (cortical thickness, surface area, and local gyrification) of canonical language regions, and functional connectivity between these regions (bilateral superior temporal gyrus—STG, posterior superior temporal sulcus—pSTS, inferior frontal gyrus—IFG, and middle temporal gyrus—MTG). Multiple linear regression models were used to test for associations between socioeconomic variables and neural indices, as well as SES x diagnosis (ASD vs. TD) interaction effects, controlling for covariates. FDR correction was used to control Type I error rate.

Neighborhood advantage index (N-SES) was negatively associated with interhemispheric connectivity between several canonical language regions (partial r^2 values = [0.07-0.10], all ps < 0.02), and with cortical surface area in the left and right IFG (partial $r^2 = 0.08$ and 0.10, $p < 0.02$, respectively), in all children regardless of the diagnosis. Income-to-needs ratio (INR) was positively associated with local gyrification and cortical thickness in some of the same language regions (partial r^2 values = [0.07-0.09], all ps < 0.03), in all children regardless of the diagnosis.

This is the first study to report associations between SES variables and neural measures in young children with ASD, and serves as a starting point to better understand how SES becomes embedded in the brain early in life. Results from the present study demonstrate that SES variables account for variation in neural measures within the regions supporting language function in preschool children with and without ASD. These findings enhance our understanding of the effects of SES on brain development and are expected to contribute to developing improved prevention and intervention programs and policies aimed at reducing these effects.

Background

1. Neural Correlates of Language in Early Development and Autism

1.1 Language Abilities in ASD:

As disorders of development, autism spectrum disorders (ASD) can have profound, life-long consequences for affected individuals and their families. Although language delays are no longer required for a diagnosis of ASD (American Psychiatric Association, 2013), they are extremely common in children who develop the disorder, and are often the first indicator for parents or pediatricians that a child's development may not be progressing typically (Richards et al., 2016; Wetherby et al., 2004; Zwaigenbaum et al., 2013). It is estimated that up to one-quarter of individuals with ASD never acquire spoken language (Tager-Flusberg et al., 2013), and in those who do acquire functional language, age at first spoken word (as well as age of phrase speech onset) can be delayed by upward of two years (Howlin, 2003; Wodka et al., 2013). Yet, others can be highly verbal but may still display language abnormalities (Tager-Flusberg & Kasari, 2013), including problems with pragmatic aspects of language, such as prosody and turn-taking (Bonneh et al., 2011; McAlpine et al., 2014) and staying on topic (Adams et al., 2002; Lam & Yeung, 2012).

Given that pragmatic language includes the socially-oriented elements of language use, it is often impaired in children and adults with ASD (Klin et al., 2005; Landa & Goldberg, 2005). For instance, one quantifiable aspect of pragmatic language, the use of *uh* and *um* fillers, which reflect difficulties with speech planning or fluency but also carry communicative function, appears to discriminate young children with ASD from their typically developing peers, as well as from children with specific language impairments (Gorman et al., 2016). Overall, while language abilities vary across the spectrum (Wittke et al., 2017), most young children with ASD are at risk for some form of language delay or speech anomaly (Boucher, 2003; Luyster et al., 2008), which can impede later academic performance, social communication, relationships, and quality of life (Petersen et al., 2013). Further, early language abilities are among the best predictors of later functional outcomes in people with ASD (Anderson et al., 2014; Bacon et al., 2019; Pickles et al., 2014).

1.2 Language Development

In typical development, the bulk of language acquisition occurs during a sensitive period for language learning between birth and five years of age. Within this time period, there are several stages of language development, characterized by the onset of distinct skillsets. Even prenatally, the human fetus shows sensitivity to human voices (Voegtline et al., 2013) and can distinguish between different vowels in utero (Skeide & Friederici, 2016), highlighting the fundamental prominence of language early in human life. From birth, newborns show a bias for human speech compared to non-speech analogues (controlling for spectral and temporal aspects of speech) within the first days of life (Cheng et al., 2012; Vouloumanos & Werker, 2007). These biases set the foundation for early language and social development, and extend beyond speech to attention to the eyes and biological motion (Klin et al., 2014), and are shown to go awry or be absent in infants later diagnosed with ASD, who are increasingly studied prospectively (Jones, 2006; Jones & Klin, 2013; Klin et al., 2009). Typical language development is contingent on and constrained by early reciprocal social engagement (Klin et al., 2014). Extreme examples of this contingency come from studies of early deprivation of social stimuli and its association with severe language delays (van Ijzendoorn et al., 2011). Further evidence for the social environment shaping and constraining language development comes from studies of infants who show increased specialization for perceiving their native language, and reduced capacity for perceiving phonemes associated with their non-native language between 6- and 12-months of age (Kuhl, 2007; Kuhl et al., 2006).

Typical language development continues through infancy with the onset of canonical babbling during which infants produce syllables in sequences (e.g., “bababa”; Oller et al., 1999). Typically developing (TD) infants begin to understand words around the age of 9 months (evidenced by correctly directing their gaze to named pictures or objects), and often produce their first words at 12 months of age (Bergelson & Swingley, 2012; Fenson et al., 1994). In the toddler years, around age 1.5-2 years, neurotypical children experience a vocabulary “explosion” (McMurray, 2007), and after early childhood it becomes increasingly difficult to acquire language. Further, during this early sensitive period, brain structures and functional networks subserving language are particularly vulnerable to environmental risk factors, such as impoverished language exposure, early life stress, and poor nutrition (Kuhl, 2010, 2011). Indeed, some evidence suggests that language brain circuits may be affected by a child’s socio-demographic circumstances, as reviewed in detail in **2.3**.

1.3 Brain Organization for Language

Current understanding of the neural foundation of language comes both from traditional neuropsychology utilizing ‘natural experiments’ in adults who experienced neural injury (e.g., trauma, stroke) and displayed subsequent deficits in language comprehension or production, and from modern neuroimaging studies (e.g., with functional magnetic resonance imaging (fMRI) and positron-emission topography (PET) methods) allowing for the in-vivo observation of neural activity associated with language production and comprehension (Rodd et al., 2015). Language processing and production relies heavily on the activity in the perisylvian brain regions, including temporal and inferior frontal cortices, with left lateralization of function shown in most people (i.e., 95 percent of right-handed individuals). In particular, Broca’s area (left posterior inferior frontal gyrus) is linked to speech production (Rodd et al., 2015), while Wernicke’s area (located in the posterior section of the superior temporal gyrus [STG] in the language-dominant, usually left hemisphere) is associated with receptive language, and damage to this part of the brain is associated with deficits in word comprehension (as opposed to word production; Rodd et al., 2015).

Modern neuroscientific understanding of neural correlates of language production and comprehension has evolved significantly since the earliest neurological studies localizing language function to Broca's and Wernicke's areas. Neuroimaging studies in recent decades have revealed that language relies on a more expansive functional and structural network of regions distributed throughout the brain (with Broca's and Wernicke's areas playing key roles in language processing). In particular, the language functional network also involves parts of the middle temporal gyrus (MTG) and inferior parietal and angular gyri in the parietal lobe (Friederici, 2011). Imaging studies in neurotypical adults, using a variety of receptive and expressive language tasks, have revealed that that language neural function is predominately lateralized to the left frontal-temporal, or perisylvian network (Berl et al., 2014). However, language processing in children appears to also involve homologous regions in the right hemisphere, showing overall reduced lateralization, as well as activation of regions outside the canonical language network, including subcortical regions (e.g., caudate, cingulate; Berl et al., 2014). Thus, it is thought that increased hemispheric laterality of language processing corresponds to maturation of the brain network subserving language development.

1.4 Aberrant Development of Early Language Neural Processing in ASD

A growing body of evidence suggests that neural processes supporting language are atypical in ASD, although only limited evidence, with inconsistent pattern of results, is available on brain correlates of language in young children with ASD, in the first years of life, when delayed or aberrant language emergence in ASD is particularly salient, as reviewed above. Among the few fMRI studies conducted in young children with ASD, Dinstein and colleagues reported weaker interhemispheric synchronization of activation in putative language areas (i.e., the inferior frontal and superior temporal gyri) in toddlers with ASD (mean age: 29 months) exposed to speech stimuli delivered during natural sleep in the scanner, as compared to typically developing peers (Dinstein et al., 2011). The authors interpreted this finding as reflecting early "overlateralization" of the emerging language function, although their data did not allow for inferences regarding whether the directionality of this effect was driven by the left or right hemisphere. Other studies from the same group revealed decreased activation in the left superior temporal cortex in response to speech stimuli in toddlers with ASD with poor performance on language measures (Lombardo et al., 2015), and an atypical hemispheric lateralization, with disproportionate involvement of the right superior temporal gyrus in processing language stimuli in children with ASD between 12 and 48 months of age (Eyler et al., 2012).

The diminished activation in the left superior temporal gyrus (STG) observed in toddlers with ASD appears to persist through preschool years (between ages 3 and 5 years) when children with ASD are compared to TD peers (Yoshimura et al., 2017). Utilizing MEG to measure the cortical pre-attentive response to changes in speech tone (magnetic mismatch field—MMF), these authors demonstrated reduced MMF amplitude evoked by human voice stimuli in the left STG in preschoolers with ASD. Given that MMF serves as a measure of change detection used to study speech discrimination, the authors interpreted the reduction in MMF amplitude in the left, but not right STG as evidence of atypical lateralization of language processing in ASD, consistent with findings from fMRI studies reviewed above.

In addition to the abnormal functional lateralization and activation patterns of language processing, studies have also shown atypical cortical morphology of language regions in young children with ASD. For example, reduced pit depth of the ascending ramus of the lateral (or Sylvian) fissure, which forms Broca's area, was reported in male children with ASD between the ages of 1.5 and 10 years (Brun et al., 2016). Further, the sulcal depth of the lateral fissure adjacent to Broca's area was correlated with social communication impairments measured with the Vineland Adaptive Behavior Scales, a caregiver-report of adaptive skills (Brun et al., 2016). Others have found increased grey matter rightward asymmetry of the pars opercularis, a part of Broca's area, in 4-7 years old children with ASD (Joseph et al., 2014). In a longitudinal study of toddlers and preschoolers with ASD (1.5 years up to 5 years of age), Schumann and colleagues found both gray and white matter enlargements by 2.5 years of age in fronto-temporal regions along with cingulate cortices, regions related but not limited to language development (Schumann et al., 2010).

Taken together, functional and structural neuroimaging studies examining the early development of language-related brain areas demonstrate aberrant function and organization of the cerebral regions responsible for language processing in the first years of life in ASD.

2. Socioeconomic Status and Disparities, and Their Links to Child Development

2.1 Factors Associated with Socioeconomic Status (SES)

In typical development, language development is associated with sociodemographic factors collectively referred to as Socioeconomic Status (SES). Importantly, variability along the SES spectrum is associated broadly with health, developmental, and cognitive indices across the lifespan (Adler & Newman, 2002; Farah, 2017). Although researchers do not necessarily agree on a single definition, socioeconomic status is a multidimensional construct meant to characterize the degree to which individuals are better or worse off in terms of their access to material and social resources (Adler & Newman, 2002). These resources include access to adequate nutrition, housing, safe and enriching neighborhoods, income, and education. While the measures that comprise SES may differ cross-culturally, variation in terms of access to resources exists across societies (and species, e.g., Rowell, 1974). The degree to which individuals differ in terms of access to resources corresponds with SES. In other words, SES is a measure of an individual or group's social and economic standing, usually classified by income and education level (and sometimes occupation). Generally, researchers measure SES using several distinct factors, which are usually highly (but not perfectly) correlated, e.g., income, education, occupational prestige, and neighborhood qualities (although there are drawbacks to each of these indices, as discussed below).

2.2 SES and Health Disparities

Health disparities related to SES have been well-documented in a wide array of health-related conditions across the life-span, including low birthweight, heart disease, diabetes, and cancer (Adler & Newman, 2002). Lower SES is associated with higher rates of mortality, especially in middle adulthood (Adler & Newman, 2002). In addition to associations with physical health, SES has also been associated with life-long mental health (Reiss, 2013). Socioeconomically disadvantaged children and adolescents are two to three times more likely to develop mental health conditions over the course of their lifetimes (Reiss, 2013). In particular, individuals from low-SES backgrounds are more likely to develop ADHD (Russell et al., 2016), externalizing behavior problems (Hosokawa & Katsura, 2018), depressive symptoms, substance use problems (Goodman & Huang, 2002), and schizophrenia (Werner et al., 2007), among others. The SES-related disparities associated with prevalence and ascertainment rates in ASD are discussed in section **3.2** below.

2.3 SES and Language Development

The factors associated with SES can have broad-reaching impacts on clinical and developmental outcomes, particularly in the domain of language. Specifically, findings on SES disparities in linguistic skills (and literacy) are some of the most robust in the developmental literature (e.g., upon high school entry, adolescents from lower-SES backgrounds perform, on average, 5 years behind their higher-SES peers on measures of literacy (Reardon et al., 2013)). Associations between SES and pre-linguistic cognitive skills can be observed in typical development as early as the first year of life, with lower pre-language skills reported in low vs. mid-high SES female infants at 7 months of age (Betancourt et al., 2015). By age 12 months, infants from lower-SES households already show poorer developmental indices on early language measures, compared to higher-SES peers, highlighting the importance of early interventions targeting literacy and language skills for low SES communities and families with young children (Wild et al., 2013).

By 18 months of age, toddler vocabulary and speed and accuracy of language understanding, or language processing efficiency, are associated with family SES (Fernald et al., 2013), and by 21 months of age large differences in language, as well as memory skills, are observed based on parental education (Noble, Engelhardt, et al., 2015). The relationship between SES and language outcomes has also been reported in children who were born prematurely, with those receiving Medicaid-based insurance (indicating lower financial resources, compared to families with private health insurance) showing lower scores on measures of both receptive and expressive language between ages 15 and 30 months (Wild et al., 2013). The authors attributed their findings to multiple factors associated with SES, including the quality of the child's home environment and language exposure in the home.

Several factors may account for the reported associations between SES and language development. Language exposure in the home, for example, has been shown to mediate the relationship between maternal education and language skills in young children, as children from lower SES backgrounds often hear less complex speech and fewer words spoken in the home (Hoff, 2003). Further, the interactional nature of early language exposure, including child-directed utterances, rather than mere exposure to words, appears to play a key role in language acquisition (Zimmerman et al., 2009). Both the number of conversational turns (back-and-forth) and the inclusion of questions has been associated with language skills in preschool children (Rowe et al., 2017). For example, Romeo and colleagues have demonstrated that SES correlates with verbal ability and the number of words children heard at home, with children from higher SES backgrounds hearing more words and showing greater verbal skills (Romeo et al., 2018). In addition to number of words heard, the authors also measured the number of conversational turns taken between children and their primary caregivers over approximately 16 hours (split across two consecutive days). The number of conversational turns over this time period was also correlated with children's verbal skills, and mediated the relationship between SES and language skills (Romeo et al., 2018).

Associations between the home language environment and language skills have also been observed in infants later diagnosed with ASD for whom the association between parental educational level and pre-linguistic development is mediated by hearing more words and experiencing more conversational turns in the home (Swanson et al., 2019). Further, the home literacy environment may also affect children's language development (Payne et al., 1994). Variables constituting the home literacy environment include frequency of book reading, age of onset of book reading, duration of book reading, number of books in the home, frequency of child's requests to engage in shared book reading, frequency of child's independent play with books, frequency of trips to the library, frequency of caregiver's individual reading, and caregiver's enjoyment of individual reading (Payne et al., 1994).

Although a growing literature suggests that SES is associated with children's language development, there are several limitations in the field of SES research as it relates to early language and brain development that need to be considered. Firstly, SES is confounded with cultural language variables (e.g., use of dialect, bilingualism), which could impact children's performance on measures of language skills (Ellwood-Lowe et al., 2016). Further, because SES is a multidimensional construct that correlates with a vast array of other variables, it remains unclear whether distinct aspects of SES correlate differentially with different language skills. Beyond the commonly measured aspects of SES often discussed (e.g., parental educational level, parental income), other potentially relevant variables that may account for SES associations with language skills include prenatal and early childhood nutrition, amount and quality of early child care, environmental enrichment, cognitive enrichment, exposure to environmental pollutants, and prolonged stress (Hackman et al., 2010; McEwen & McEwen, 2017).

2.4 Neuroscience of SES and Links Between Brain Development and SES

Given all that is known about how reduced access to social and educational resources can impact one's physical and mental health via different mechanisms (e.g., access to healthcare, education, exposure to environmental pollutants), some may reasonably question whether it makes sense for neuroscience to approach a problem as fundamentally societal and complex as SES disparities (Farah, 2017). While neuroscience research could not replace sociological and psychological approaches to understanding how SES impacts the lives of individuals, neuroscience research may offer unique insights into *how* SES-related health disparities manifest and persist

(Farah, 2017). Understanding SES-related differences in brain structure and function may increase our understanding of how SES-based health gradients emerge. Specifically, neuroscience approaches to understanding how SES-related differences in cognitive function emerge may indicate a physical locus underlying these differences. Measures of brain function can also reveal whether lower SES is associated with distinct neural processes, or whether it is characterized by reduced recruitment of the same processes as those employed by higher-SES individuals. Knowledge of these neural mechanisms may help inform interventions to ameliorate the disparity effects.

The extant literature on neuropsychological correlates of SES reveals somewhat consistent associations between SES and neurocognitive performance, although not all neurocognitive systems have been shown to equally relate to SES (Farah, 2017; Noble et al., 2005). In particular, findings from studies with children, adolescents, and adults suggest that language, executive function, and declarative memory are among the most strongly associated with SES (Fernald et al., 2013; Lawson et al., 2018). Further, studies in school-age children have revealed altered associations between brain activity and behavioral performance on arithmetic and literacy tasks as a function of SES (Demir et al., 2015; Raizada et al., 2008). Maternal education has also been shown to correlate with IQ, vocabulary, and phonological awareness (a skill highly correlated with reading ability) in 7- to 12-year-old children. (Conant et al., 2017)

Research with nonhuman animals demonstrates associations between social status, early life stress, and brain structure and function. In rodents, for example, pre-and peri-natal glucocorticoid administration (stress hormone) is associated with reduced birth weight and brain weight, and delays neuronal maturation, myelination, gliogenesis, and synapse formation (Hackman et al., 2010). In rhesus macaques, fetal exposure to elevated glucocorticoid levels is associated with reduced hippocampal volume (Sapolsky,' et al., 1990; Uno et al., 1989). Further, social status in primates (rhesus macaques) is associated with stress physiology and also relates to brain structure and function, including alterations observed in the amygdala and hypothalamus (Feng et al., 2016; Noonan et al., 2014).

Several studies have investigated whether brain structure (i.e., cortical volume, white matter integrity, cortical surface area or thickness) correlates with SES in humans. There is a growing evidence relating factors associated with SES to many aspects of brain structure in school-age children, adolescents, and adults (Gianaros et al., 2008, 2015; Mackey et al., 2015; Noble, Houston, et al., 2015). Low-SES has also been associated with alterations to language as well as socioemotional brain networks in early childhood, including reduced cortical surface area in regions involved in language production and emotion-regulation (Noble, Houston, et al., 2015).

SES and brain structure associations have been observed as early as 5 weeks of age in human infants (Betancourt et al., 2016), with family income-to-needs ratio correlated with neonatal cortical (cortex of both hemispheres and hippocampi) and deep (thalami and basal ganglia) gray matter volume (although there were no associations between SES and white matter volume; Betancourt et al., 2015). Others have reported that infants and toddlers (1.5 months to 4 years of age) from low SES backgrounds have lower total gray matter volumes than higher-SES children, and that these differences were also reflected in the gray matter growth trajectories measured longitudinally in a subset of the participants (Hanson et al., 2013). In a recent study, SES, operationalized using the four-factor Hollingshead index as a composite measure of marital togetherness vs. separation, occupational status, education, and income, was associated with brain growth trajectories in infants (Spann et al., 2020), and these differences were not accounted for by infant birthweight, early health, or head size at birth. The brain growth differences between the low and high SES infants were specifically observed in the frontal and parietal regions, with children from lower-income families having smaller volumes in these regions.

In addition to typical brain development trajectories, the relationship between SES and neurodevelopment is also of interest in children born pre-term, who are at greater risk for neurodevelopmental and psychological disorders. In a longitudinal investigation of 170 preterm neonates (with gestational age of 26 to 32 weeks at birth) studied with structural MRI, maternal education level, which was used to estimate SES, was associated with children's cognitive outcomes at 4.5 years of age as strongly as was brain injury at birth (Benavente-Fernández et al., 2019).

The links between brain structure and SES have also been described in a large cohort of children, adolescents, and young adults between ages 3 and 21 years (Ursache & Noble, 2016). Higher family income was associated with increased white matter integrity (i.e., higher fractional anisotropy—FA), specifically in the parahippocampal cingulum and right superior corticostriate tract, as well as in the left superior corticostriate tract, putatively involved in memory and executive functions, reward processing, and language, respectively.

Because SES is strongly associated with other demographic factors such as ethnicity and exposure to multiple languages in the home (Brito & Noble, 2018), some researchers have examined distinct contributions of SES and dual-language exposure to brain structural development in children and adolescents ages 3- to 21-years (Brito & Noble, 2018). They reported that income, but not dual-language, was associated with total cortical surface area, and this association was more pronounced in adolescence than early childhood. Increased cortical surface area is generally associated with improved performance on neural tasks, and in children, thought to reflect maturational processes (Brito & Noble, 2018). Notably, income and parental education (but not dual language use) were also associated with cognitive skills in this cohort.

In addition to studying brain structure, a burgeoning literature has focused on brain functional correlates of SES in early development (as reviewed in Olson et al., 2021). Gao et al. (2015) observed moderate correlations between SES measures (income and maternal education) and functional connectivity in the default mode and sensorimotor networks in a large cohort of 6-month-old infants. In adolescents and adults, default mode network connectivity is thought to relate to self-referential thinking (Tomasi & Volkow, 2012). Although its behavioral correlates are not characterized in infancy, default mode network connectivity in childhood increases with age; therefore, stronger network connectivity found in infants from higher SES backgrounds was thought to reflect within-network synchronization associated with maturation (Gao et al., 2015).

SES-related differences in brain function have also been reported in preschool children in Japan (Moriguchi & Shinohara, 2019). Using functional near infrared spectroscopy (fNIRS), a measure of hemodynamic responses associated with neuronal activity quantified as concentration of oxygenated hemoglobin, investigators used a card-sorting task (the Dimensional Change Card Sort, a putative measure of executive function) to measure brain activation in executive networks, and its links with SES (estimated with maternal education and household income variables). The authors reported that the percentage of correctly obtained switches in the card task (with higher percentage corresponding to better or more developed executive function) was not correlated with SES when used as a continuous variable. However, when they dichotomized SES (poverty vs. no poverty), children in the no-poverty or higher SES group exhibited expected changes in oxy-hemoglobin between the task-switch vs. consistent conditions, whereas the children experiencing poverty showed no such changes (Moriguchi & Shinohara, 2019), indicating hypoactivation of executive networks during an executive function task in low-SES children. Notably, SES did not affect performance on the card-sorting task on the behavioral level; therefore, the distinct neural profiles observed in low vs. high-SES children may reflect compensatory mechanisms adapted by these children in response to experiences associated with low SES conditions.

Despite the known associations between SES and language skills in childhood (reviewed in **2.3**), only few recently emerging studies have investigated the links between SES and *language network function* in young children. Measuring the difference in neural activation in language regions in response to forward vs. backward speech (as forward speech reliably elicits greater activation than backward speech in language-specific regions) in young children (~4-6 years of age), Romeo and colleagues reported that the activation difference (forward vs. backward) in Broca's area mediated the relationship between the number of conversational turns children heard in the home, and children's verbal skills (Romeo et al., 2018). A larger difference in activation to forward vs. backward speech is thought to reflect increased neural specialization for speech in language areas; as such, these results suggest that children's home language environment (characterized by amount, complexity, and reciprocity of speech and conversations) is related to their verbal skills, as well as to brain activation in language circuitry.

Given that language neural function is generally strongly lateralized to the left hemisphere, Raizada and colleagues used the difference between activation in left vs. right inferior frontal gyrus (iFG, a canonical language region) in response to aurally-delivered words, and correlated those scores with socioeconomic variables in 14 young children (Raizada et al., 2008). The authors reported that the degree of interhemispheric difference (i.e., language lateralization) was correlated with socioeconomic status, reflecting increased specialization for language processing in higher-SES children, compared to lower-SES peers. They also found that SES was associated with grey and white matter volumes in the left iFG (in Broca's area, specifically), consistent with their findings on increased lateralization associated with SES.

3. Early Childhood

3.1 Early Childhood and Brain Development

Early childhood, which refers to the first years of life prior to entry into kindergarten (i.e., infancy, toddlerhood and preschool age), is a critical period for the development of brain structure and functions that set the stage for later cognitive and psychological activity and behavior throughout life, including language development (Gilmore et al., 2018). Despite the increasing focus on early childhood development, relatively few studies have focused on *brain development* measures in this time period (in comparison to neuroimaging studies in adults), in large part because of the practical difficulties associated with acquiring these measures in young children (i.e., adherence to behavioral protocols requiring children to remain still for long periods of time in an MRI scanner, etc.). Brain growth occurs rapidly during the first years of life, doubling in overall size in the first post-natal year (Gilmore et al., 2018). Although the bulk of neurons in the human brain are generated prior to birth, some neurogenesis continues postnatally. Further, the complexity of cortical neurons increases rapidly over the first years of life, giving rise to imaging findings demonstrating increases in gray matter volume, associated with cortical thickness growth and surface area expansion, over the first years of development (Gilmore et al., 2018). White matter myelination also begins prenatally (especially in primary sensory and motor pathways), with the majority of major white matter pathways present at birth, but maturing (becoming increasingly myelinated and, hence, more efficient) over a protracted developmental period from birth into adulthood (Gilmore et al., 2018). From the limited extant evidence on functional network development to date, findings suggest the presence of functional brain networks similar to those observed in adults very early in development (i.e., in the first years of life; Fransson et al., 2007). For example, primary sensory networks strengthen over the first years of life and strongly resemble adult sensory networks by the time children turn two (Gao et al., 2015). However, distinct functional networks develop on different timescales, with higher-order, multimodal or associative functional networks maturing and developing over a much longer period of time, well into and beyond adolescence (Dosenbach et al., 2010; Fair et al., 2008).

3.2 SES and ASD in Early Childhood

Although there is a growing literature providing compelling evidence for relationships between socioeconomic context and brain development in early childhood, prior to entry into kindergarten and as early as shortly after birth, as reviewed in **2.4** above (cf., Benavente-Fernández et al., 2019; Betancourt et al., 2015; Brito, Fifer, Myers, Elliott, & Noble, 2016), much less is known regarding how SES relates to neurodevelopment in young children with neurodevelopmental disorders such as ASD. The dearth of research focusing on children and adults with ASD from under-resourced communities is partly related to societal challenges and barriers associated with participating in research studies experienced by lower-SES families (e.g., limited access to transportation or ability to take time off work, inadequate parenting supports, etc.). There is, however, some limited evidence suggesting that SES is associated with clinical and diagnostic outcomes in autism (Fountain et al., 2012), such as symptom trajectories and developmental gains over time. In particular, children with autism are more likely to experience improvements in social and communication skills when they come from higher SES households (characterized by higher levels of maternal education (Delobel-Ayoub et al., 2015; Levaot et al., 2018). Children with ASD from lower-SES families are also more likely to receive a co-occurring intellectual disability diagnosis than their mid-to-high-SES peers (Dickerson et al., 2016; Mandell et al., 2009; Thomas et al., 2012). Our own work has revealed positive associations between SES, as indexed by parental education level and family income-to-needs ratio, and language skills in young children with ASD (see Figure 1; Olson et al., 2020). Possibly accounting for these links is the fact that lower SES is associated with later age of autism diagnosis and reduced access to intervention services (Oakes & Rossi, 2003), highlighting the significant socioeconomic disparities in ascertainment of autism.

As reviewed above, in **1.4**, the limited neuroimaging evidence available to date on language brain function and connectivity in autism *early in life* indicates reduced neural response to speech (Curtin & Vouloumanos, 2013), recruitment of atypical brain regions during speech (Dinstein et al., 2011; Eyler et al., 2012; Redcay & Courchesne, 2008), as well as altered language network connectivity in toddlers with ASD (Verly et al., 2014). Notably, as highlighted in **2.4**, low-SES has also been associated with alterations to language as well as socioemotional brain networks in early childhood (in typical development), including reduced cortical surface area in regions involved in language production and emotion-regulation (Noble, Houston, et al., 2015). However, little to no data exist linking early atypical brain organization and function to factors associated with low SES *in autism spectrum disorders*. To address this gap in knowledge, this project aimed at examining brain functional (Aim 1) and structural (Aim 2) connectivity of language networks and their relation to SES factors in early childhood in autism.

4.0 Current Project and Its Aims

This project aimed to *characterize the neural correlates of language abnormalities associated with both low-SES and ASD,* to enhance our understanding of how the early experiences associated with ASD and SES are *embedded in brain organization and connectivity*, setting the stage for functioning across multiple domains (e.g., literacy, school achievement, social communication). The overarching objective was to fill a gap in our basic knowledge on SES and early brain development in ASD, and to understand whether children with ASD and lower SES may have additive developmental vulnerabilities. Understanding the links between family and neighborhood resources and children's developmental outcomes is needed to inform interventions that may be targeted specifically to children with ASD from low-resource communities (e.g., Carr et al., 2016; Kasari et al., 2014), given the evidence on the positive impact of *early interventions* on both behavior and the developing brain (Bor et al., 2002; Dawson et al., 2012; Hampton & Kaiser, 2016).

The current project thus focuses on functional connectivity and brain anatomy of the neural circuits and regions supporting language, as they relate to socioeconomic variability in a diverse group of young children with ASD and typically developing (TD) peers, enrolled in a larger study examining early brain markers of autism. Based on findings demonstrating positive associations between SES and language skills in toddlers with ASD (Olson et al., 2021), the specific aims and hypotheses are as follows:

Aim 1: SES and Functional Connectivity of Language Regions: Hypothesis 1: Functional connectivity between the canonical language regions is expected to differ between ASD and TD toddlers, controlling for SES factors. Hypothesis 2: SES factors are expected to predict functional connectivity, controlling for diagnosis, with higher SES corresponding to increased functional connectivity within language networks. Hypothesis 3: A diagnosis by SES interaction effect is predicted, with children with ASD and lower SES expected to show more atypical functional connectivity between the language regions.

AIM 2: SES and Anatomical Features of Language Regions: Hypothesis 1: Neuroanatomical features (cortical thickness—CT, surface area—SA, and local gyrification—lGI) are expected to differ between ASD and TD young children, controlling for SES factors.

Hypothesis 2: Neuroanatomical features (CT, SA, and lGI) are expected to be associated with SES factors, controlling for diagnosis (ASD vs. TD). Hypothesis 3: A diagnosis by SES interaction effect is predicted, with children with ASD and lower SES expected to show more atypical cortical morphology of the language regions.

METHODS

Participants

Data were drawn from the San Diego State University (SDSU) Toddler MRI Project, an ongoing longitudinal study of early brain markers of ASD. Children between the ages of 15 and 64 months with a diagnosis of ASD (or behavioral concerns consistent with ASD symptoms) were referred to the Toddler MRI Project from specialty autism clinics, state-funded early education and developmental evaluation programs, local pediatricians, service providers, and community clinics, and followed up through age 5 years. Typically developing (TD) children were recruited from the community, including early head start programs, and via print and social media advertisements. Participants in either group were screened and excluded for any co-occurring neurological disorders (e.g., cerebral palsy), history of perinatal CNS infection or gross CNS injury, non-febrile seizures, contraindications for MRI. Participants with known syndromic forms of ASD (e.g., fragile X or Rett syndrome), as ascertained from parent report, were also excluded. To limit known risk factors for developmental delays among children enrolled in the TD group, TD participants were also screened and excluded for prematurity (<36 weeks of gestation), family history (in first-degree relatives) of ASD, intellectual disability, or other heritable psychiatric or neurological disorders. Informed written consent was obtained from caregivers under protocols approved by the SDSU and UCSD Institutional Review Boards.

Given the cross-sectional design and objectives, only cross-sectional data (i.e., datasets from one data collection for each participant) were included, with some participants contributing data from later datasets (contingent on availability of all required MRI datasets). In light of the known practical and methodological challenges associated with obtaining quality MRI data from young children (Turesky et al., 2021), the cohorts with fully useable functional and anatomical

MRI data (required for Aim 1 and Aim 2 analyses, respectively) are largely, but not completely overlapping. This is due to (a) some children waking up during the scan, prior to the completion of all MRI sequences (acquired during natural sleep), resulting in acquisition of some but not all sequences (e.g., functional MRI but not anatomical MRI data, given the order in which they are acquired), and (b) exclusion of some acquired datasets following stringent quality control protocols resulting in exclusion of data from one MRI modality, but not another. In total, seventy-three children (ASD: n = 36, TD: n = 37) were included in the functional MRI sample (from here on, *fMRI Cohort*), and 70 children (ASD: n = 39, TD: n = 31) were included in the anatomical MRI sample (from here on, *aMRI Cohort*).

Diagnostic classification. Upon enrollment, all participants with ASD or suspected to have ASD underwent full diagnostic evaluation, using standardized measures in combination with clinical judgment (in accordance with the current recommendations by the American Academy of Pediatrics and Society for Developmental and Behavioral Pediatrics; Duby et al., 2006; Weitzman et al., 2015). Only participants who met diagnostic criteria for ASD (or Clinical Best Estimate [CBE] in children younger than age three; Ozonoff et al., 2015) on the DSM-5 (American Psychiatric Association, 2013) were included in the ASD group. The diagnosis was supported by the Autism Diagnostic Observation Schedule, 2^{nd} Edition (ADOS-2; Lord, C., Rutter, M., Dilavore, P., Risi, S. Gotham, K., Bishop, 2012), administered by research-reliable clinicians, and the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), a standardized diagnostic interview with a caregiver assessing early developmental history, administered to caregivers of children older than 36 months. Diagnostic evaluation was repeated at follow-up visits (between 1.5 and 2 years following 1^{st} study visit), and only children with confirmed diagnosis were included in the current dataset. For inclusion and retention in the TD group, children had below-clinical cutoff scores on ASD screeners (e.g., Social Communication Questionnaire) and demonstrated (upon testing) developmental skills falling no more than 1.5 SD below the normative mean for their age on measures of early learning (as described in the Measures section below).

Measures

Developmental assessment and explanatory variables. In addition to the diagnostic measures administered to children with ASD, as described above, developmental skills were assessed in all TD and ASD participants with the Mullen Scales of Early Learning (MSEL; Mullen, 1995), a clinician-administered assessment of language, cognitive, and motor development, which yields age-corrected standardized scores. The Vineland Adaptive Behavior Scales, 2nd Edition, Survey Interview (Sparrow et al., 2005), a semi-structured caregiver interview yielding age-normed standard scores, was administered to assess the adaptive communication, daily living, social, and motor skills the child demonstrates at home and other settings, outside of the testing context. The Vineland scores were utilized to support the diagnostic and developmental classification, and did not serve as explanatory variables. Caregivers also completed the Social Communication Questionnaire (SCQ, Current form; Rutter, M., Bailey, A., Lord, 2003), a screener for autism spectrum disorders, used to screen participants in the TD group for any previously-unrecognized signs of atypical development (using the recommended cut-off score of 15) and to support ASD diagnosis in young children with ASD. While these evaluations were performed at study enrollment and repeated at follow-up appointments scheduled at approximately 1.5-year intervals, only cross-sectional data from one time point for each participant (determined by the fully available MRI data) were included in this project, as detailed above.

The following developmental and clinical variables derived from the available measures were used as covariates in subsequent analyses: the ADOS-2 calibrated severity scores serving as a measure of autism symptomatology, and the MSEL Receptive and Expressive Language subscales and the overall Early Learning Composite score serving as measures of language skills and overall developmental level, respectively.

Socioeconomic and sociodemographic variables. Because there is no consensus in public health research regarding measurement of SES (Center for Education Statistics, 2012), we used several individual- and neighborhood-level SES indicators (including household income taking into account household size, parental education, and a neighborhood advantage index; Ramphal et al., 2020; Tooley et al., 2020) to examine the relationships between factors associated with SES and receptive and expressive language skills. *Household-level SES* was assessed based on the demographic information provided by participants' caregivers, including household income, number of individuals in the household, and highest level of education attained by either parent. Gross annual income was reported on the following scale: <$10,000, $10,001-20,000, $20,001-30,000, $30,001-40,000, $40,001-50,000, $50,001-60,000, $60,001-80,000, $80,001-100,000, $100,001-150,000, $150,001-200,000, $200,001-250,000 and >$251,000. Income measurements were converted to income-to-needs ratio (INR) to account for family size. INR is derived by dividing the household income by the federal poverty threshold defined by family size; an INR of one indicates living at the federal poverty line, which, according to the 2019 US government poverty definition, is $25,750 per year for a family of four. Maternal educational level was rated on a six-point scale (less than high school, completed high school, vocational or technical school, some college, completed college, professional or doctoral training beyond college).

Neighborhood-level SES was estimated from Census tract-level data which capture macroeconomic neighborhood characteristics (proportion of individuals living under the federal poverty threshold, housing/rental costs, etc.) using the American Community Survey (2018), based on the US Census data. US Census tracts are small, relatively stable statistical subdivisions of a county, with an average of 4,000 inhabitants (minimum = 1,200 and maximum = 8,000; once a tract exceeds the maximum of 8,000, it is split into two or more tracts). The following variables were extracted for each child based on their household's tract (determined by their street address): average income, percentage of individuals living below the federal poverty line, median rental values, median home values, proportion of individuals receiving public assistance, proportion of individuals who report being unemployed, and proportion of adults with a bachelor's degree. The tract-level variables were submitted to Principal Component Analysis (PCA) in order to reduce the dimensionality of the data. Individual PC scores were then used as an explanatory variable in multiple regression models. Specifically, the first principal component constituted a Neighborhood Advantage Index, with higher values representing greater access to material and social resources (i.e., higher neighborhood SES; Berl et al., 2014), and served as a neighborhood SES outcome variable (see Results section for additional details).

Thus, the following household- and neighborhood-level SES variables were used: Maternal Education Level and Income-to-Needs Ratio (INR; both household-level), and Neighborhood Advantage Index (neighborhood-level); see Figure 2 for distribution of these variables in the present sample. Additional variables derived from the demographic information provided by parents include the child's exposure to more than one language (i.e., regularly hearing and/or speaking languages other than English at home). The present cohort of participants from the SDSU Toddler MRI project shows a great deal of variability in household- and neighborhood-level SES, with household income ranging from <\$10,000 to >\$250,000 annually (see Figure 2). Further, families come from diverse communities throughout and beyond San Diego County, including neighborhoods that have a high density of low-income families. Additionally, a large proportion of the participants are exposed to more than one language in the home (see Tables 1 and 2).

MRI data. MRI data were acquired during natural, nocturnal sleep on a GE Discovery

MR750 3T scanner at the UCSD Center for Functional MRI (CFMRI), using a Nova Medical 32 channel head coil. *Anatomical MRI:* Whole-brain high-resolution anatomical images were acquired with an Inversion Recovery Fast Spoiled Gradient Recalled (IR-SPGR) T1-weighted sequence (isotropic voxel size = $0.8mm^3$, FOV = 25.6cm, TE/TI=min full/1060ms, flip angle = 8°; scan time ~6min). Motion during anatomical scans was corrected in real-time using three navigator scans and real-time prospective motion correction (PROMO; White et al., 2010), and images were bias corrected using the GE PURE option. *Functional MRI:* A multiband EPI sequence allowing simultaneous acquisition of multiple slices was used to acquire two fMRI runs (400 volumes per each 6-minute run), with high spatial resolution and fast acquisition (isotropic resolution = $2mm^3$ with 72 contiguous slices [AC-PC orientation], TR=800ms, TE=35ms, flip angle=52°, 104x104 matrix, multiband acceleration factor=8). Two 6-min fMRI runs are acquired (scan time ~13min, including two 20sec spin-echo EPI scans with opposite phase encoding directions acquired using the same matrix size, FOV and prescription to correct for susceptibility-induced distortions). The total duration of the scanning session (post-preparation) was ~45min (up to ~60min if needed to repeat sequences due to motion), including initial head alignment, localizer scans, prescription of individual sequences, and other inter-scan delays.

Sleep MRI protocol. In preparation for the scan night, and to optimize MRI data acquisition, a comprehensive habituation protocol was implemented. An individualized scan night sleep strategy (e.g., time of arrival, approximating home-like sleeping arrangements, including access to a double MRI bed for co-sleeping families, rocking chair, modular playpen mounted on the MRI bed, lighting in the MRI suite, etc.) was developed for each child, based on the typical bedtime routines and habits assessed in advance with an in-house Sleep Habits Questionnaire. To habituate the child to the scanning environment, the parents were instructed to practice nightly inserting soft foam child-size earplugs after the child had fallen asleep, and to play an mp3 file containing the MRI sounds of the scan sequences employed in the study at progressively louder volumes for a week. On the night of the scan, noise protection was provided with MRI compatible sound reducing headphones and earplugs. In an attempt to standardize sleep stage during scans, scanning commenced after approximately 15-30min of sleep.

Data Analysis and Analytic Strategy

MRI data were preprocessed with FMRIB's Software Libraries (FSL v5.0.10; Smith et al., 2004), Matlab 2015b (Mathworks Inc., Natick, MA, USA) using SPM12 (Wellcome Trust Centre for Neuroimaging, University College London, UK), the CONN toolbox v17f (Whitfield-Gabrieli & Nieto-Castanon, 2012; http://www.nitrc.org/projects/conn), and FreeSurfer v.5.3.0-HCP (Dale et al., 1999).

Functional MRI preprocessing. Standard preprocessing procedures were implemented, including correction for susceptibility-induced distortions using the two spin-echo EPI acquisitions with opposite phase encoding directions and FSL's TOPUP tools; motion correction using rigid-body realignment as implemented in SPM12; spatial smoothing using a 6mm Gaussian kernel at full-width half maximum; outlier detection using the Artifact Detection Toolbox as installed with CONN v17f (ART; https://www.nitrc.org/projects/artifact_detect) to identify outlier volumes with frame-wise displacement (FD) >0.5mm and/or changes in signal intensity >3 standard deviations; nuisance regression including censoring of outliers detected by the ART toolbox, regression of the 6 motion parameters and their derivatives, and the first five PCA components derived from the CSF and white matter compartments (obtained from segmentation of the structural image for each subject, thresholded at 0.95 and eroded by 1 voxel) using aCompCor (Behzadi et al., 2007); and band-pass temporal filtering (0.008-0.08 Hz). Functional images were directly normalized to MNI space non-linear registration and the default tissue probability maps included with SPM12.

In order to ensure that the findings were not affected by group differences in motion, ASD and TD groups were matched, at the group level, on mean head motion indexed by root mean square of displacement (RMSD) across two fMRI runs, calculated from rigid-body realignment of the raw data prior to TOPUP correction, and on the percentage of censored volumes across two fMRI runs. Mean RMSD was also included as a covariate for all analyses including fMRI data.

Anatomical MRI preprocessing. Structural images were bias corrected, skull stripped, normalized to the Montreal Neurological Institute (MNI) atlas space using non-linear registration and the default tissue probability maps included with SPM12, and transformed to surface space. Reconstructed data were examined visually to identify potential inaccuracies in surface placement (and these inaccuracies were be corrected as needed). Scans showing major artifacts (e.g., ghosting, ringing) were excluded. Segmentation of gray matter, white matter, and the CSF was carried out, with the following morphometric parameters of the cerebral cortex calculated in FreeSurfer v.5.3.0-HCP and HCP workbench tools: cortical thickness (CT; estimated as the average distance, in mm, between the white and pial surfaces), surface area (SA; the area of the pial surface, in mm^2), cortical volume (the volume contained between the white and pial surfaces, in mm^3), and local gyrification index (lGI; a measure of gyral complexity calculated as the ratio cortical surface area within the sulcal folds relative to the amount of cortex on the outer cortex). In order to ensure that the findings were not affected by group differences in image quality, ASD and TD groups were matched, at the group level, on contrast-to-noise ratio (CNR). CNR was also included as a covariate for all aMRI analyses.

Functional Connectivity (FC) outcome variables and analyses (Aim 1). Spherical 10mm regions of interest (ROI) were generated for the following canonical regions implicated in language processing: bilateral superior temporal gyrus (STG), posterior superior temporal sulcus (pSTS), inferior frontal gyrus (IFG), and middle temporal gyrus (MTG). The ROI selection was based on the functional mapping studies localizing various language subdomains to these regions and reviews of language substrates in the brain (e.g., Branco et al., 2016; McCormick et al., 2018). Preprocessed fMRI data (from two runs) were used to extract and average the residual BOLD time series across voxels contained in each language-related ROI. FC was estimated with Fisher's z-transformed Pearson correlations calculated between the time courses from each ROI (all pairwise comparisons between bilateral ROIs: 8x7/2 = 28 ROI-ROI pairs), resulting in a language functional connectivity matrix. Mean z scores for each ROI pair served as FC dependent variables in multiple regression models, with SES and diagnosis serving as predictor variables. SES by diagnosis interaction terms were tested during the model specification phase to rule out (or in) distinct SES effects by diagnostic group. Relevant covariates were included as described below. Family-wise FDR correction was applied to correct for multiple comparisons.

Neuroanatomical outcome variables and analyses (Aim 2). The specified morphometric measures (CT, SA, lGI) were extracted from language-related surface-based (bilateral) ROIs from the Desikan-Killiany Atlas implemented in FreeSurfer (Desikan et al., 2006); middle temporal gyrus (MTG), superior temporal gyrus (STG), and 3 subdivisions of the inferior frontal gyrus (IFG): pars opercularis, pars orbitalis, and pars triangularis. Separate models were used for CT, SA, and lGI as outcome measures (3 x 12 ROIs = 36 regression models in total), with SES and diagnosis as predictor variables, including relevant covariates (see below). Family-wise corrections for multiple comparisons were applied using FDR correction with a threshold of $p <$

0.05. SES by diagnosis interaction terms were tested in the model specification phase to test for the possibility of distinct SES effects in the ASD vs. TD groups.

Covariates. Potentially relevant covariates were included in all models during model specification. Covariates were retained in models only when shown to be significantly associated with neural outcome measures. Covariates included chronological age, gestational age at birth, gender, total brain volume (TBV), contrast-to-noise ratio (CNR), language skills (MSEL Receptive and Expressive Language skills), current ASD symptoms (ADOS-2 CSS), overall developmental level (MSEL Early Learning Composite), ethnicity, and exposure to multiple languages in the home.

RESULTS

Participant characteristics: In both fMRI and aMRI cohorts, the TD and ASD groups did not differ on proportion of males:females, proportion of children exposed to more than one language in the home, and age. In both cohorts, participants with ASD had lower levels of maternal education and lower neighborhood advantage, and in the fMRI cohort, lower income-to-needs ratio, compared to their TD peers (all ts > 2.0, all ps < 0.05; see Tables 1 and 2). However, distributions of these variables did not differ between diagnostic groups (Kolmogorov-Smirnov tests: all Ds < 0.36, all ps > 0.06). As expected, participants with ASD also showed significantly lower scores on the MSEL measures of expressive and receptive language, as well as the MSEL Early Learning Composite (all ps < 0.001; see Tables 1 and 2).

Neighborhood Advantage Index: To reduce the dimensionality of the set of 7 tract-level neighborhood variables, PCA was conducted on the correlation matrix, using varimax rotation, retaining only factors with eigenvalues greater than 1. The first component (PC1; eigenvalue: 3.76) accounted for 53.7% of the variance in the neighborhood-level data, with factor loadings ranging from |0.02| to |0.87|. It was positively associated with median income (r = 0.87), median rent (r = 0.86), and proportion of individuals with a bachelor's degree (r = 0.80), and negatively associated with percentage of individuals living below the poverty line (r = -0.84), percentage of individuals receiving public assistance (r = -0.73), and percentage of adults who were unemployed (r = -0.61). PC2 accounted for an additional 16% of the variance (eigenvalue: 1.13) and was positively correlated with median home values (r = 0.97). PC1, corresponding to neighborhood advantage, was used as an explanatory variable in multiple regression models (termed here Neighborhood Advantage Index, or N-SES, for neighborhood-SES).

Aim 1: Associations between Functional Connectivity in Language Regions and SES

Effects of diagnosis on language functional connectivity: The results of multiple regression models revealed no significant diagnosis-FC relationships after applying FDR correction for multiple comparisons (total comparison n = 28). There were also no significant main effects of diagnosis on functional connectivity z-values for any ROI-ROI pairs, when using a per comparison alpha of 0.05, uncorrected (all z < 1.43; see Figure 3). There was, however, a significant (at an uncorrected alpha of 0.05) diagnosis by age interaction on functional connectivity between the left inferior frontal gyrus (l-IFG) and the left middle temporal gyrus (l-MTG), controlling for exposure to multiple languages (t =2.64, $r^2 = 0.09$, $p = 0.01$; see Table 3), such that TD children showed a positive association between age and FC, whereas no such relationship was found among participants with ASD (see Figure 4a).

Relationships between SES and language functional connectivity: Neighborhood SES (Neighborhood Advantage Index) was negatively associated with functional connectivity z-scores between the right superior temporal gyrus (r-STG) and the left posterior superior temporal sulcus (l-pSTS; $t = -2.68$, partial $r^2 = 0.10$, $p = 0.009$) and r-STG and left inferior frontal gyrus (l-IFG; $t = -2.17$, partial $r^2 = 0.08$, $p = 0.03$), controlling for RMSD and regardless of the diagnosis (see Figure 5a,b). N-SES was also negatively associated with FC between the left and right pSTS ($t = -2.3$, $r^2 = 0.07$, $p = 0.03$) and the left and right IFG ($t = -2.3$, $r^2 = 0.08$, $p = 0.02$), regardless of the diagnosis, with no covariates emerging as significant predictors in these two models (see Figure 5c,d). These effects revealing diagnosis-independent associations between N-SES and functional connectivity are summarized in Table 4. Although there were no significant diagnosis by N-SES interaction effects on FC, when examined separately within diagnostic group, the ASD group showed significant negative associations between N-SES and FC for the ROI-ROI pairs listed above and shown in Figure 5 (r-STG – l-pSTS, r-STG – l-IFG; l-IFG – r-IFG, l-pSTS – r-MTG;

all rs > |0.35|, all *p*s < 0.05), whereas no significant associations between neighborhood advantage and FC were found in the TD group for any of these ROI pairs.

Finally, no significant associations were detected between maternal education or income-to-needs ratio and FC z-scores for any ROI-ROI pairs.

Aim 2: Associations between Structural Features in Language Regions and SES

Effects of diagnosis on neuroanatomical features of language regions: There were no significant associations between any explanatory variables of interest and local gyrification in language regions after applying an FDR correction for multiple comparisons. As such, we are reporting results that were significant using a per comparison alpha of 0.05, accompanied by effect size estimates (partial r^2) for each of these results. Participants with ASD showed higher LGI in the left IFG, pars opercularis compared to TD participants ($t = 2.20$, partial $r^2 = 0.07$, $p = 0.03$; see Figure 4b; Table 5), controlling for TBV and sex, and lower cortical thickness in the left hemisphere pars orbitalis ($t = 2.52$, partial $r^2 = 0.09$, $p = 0.01$; see Figure 4c; Table 5), controlling for age.

Relationships between SES variables and local gyrification in language regions: Income-to-needs ratio was significantly positively associated with local gyrification index (LGI) in the following regions: left transverse temporal gyrus, controlling for TBV ($t = 2.15$, partial $r^2 = 0.08$, $p = 0.04$); left superior temporal gyrus, controlling for TBV ($t = 2.26$, partial $r^2 = 0.09$, $p = 0.03$); and right IFG, pars opercularis, controlling for TBV and exposure to more than one language in the home ($t = 2.10$, partial $r^2 = 0.07$, $p = 0.04$). Neither neighborhood advantage nor maternal educational level were associated with LGI in any language regions. See Table 6 for results summary and Figure 6 for scatterplots depicting significant associations.

Relationships between SES variables and cortical thickness in language regions: Independent of diagnosis, income-to-needs ratio was positively associated with cortical thickness in the left middle temporal gyrus (t = 2.14, partial r^2 = 0.07, p = 0.04), controlling for age, sex, and exposure to more than one language in the home (see Table 6 and Figure 7). Neither neighborhood advantage nor maternal educational level were associated with cortical thickness in any region.

Relationships between SES variables and surface area in language regions: Independent of diagnosis, neighborhood advantage was negatively associated with surface area in the left IFG, pars orbitalis (t = -2.31, partial r^2 = 0.08, p = 0.02; see Table 7 and Figure 8a), and right IFG, pars triangularis (t = -2.35, partial r^2 = 0.10, p = 0.02; see Table 7 and Figure 8b), controlling for TBV and age. No significant associations were detected between household-level SES (maternal education or income-to-needs ratio) with surface area in language regions.

DISCUSSION

The present study set out to investigate neural correlates of language in young children with ASD and age-matched TD peers. To understand whether children with ASD *and* lower SES may have additive developmental vulnerabilities related to language, the study aimed to examine whether functional connectivity and neuroanatomy of the brain regions supporting language relate to socioeconomic variability measured both at the household- and neighborhood-level. The study used functional and anatomical MRI data acquired during natural sleep to examine these links in a cross-sectional cohort of toddlers and preschoolers enrolled in a larger study of early brain markers of autism.

The main finding emerging from the present study was a consistent pattern of associations between SES variables and neural measures in language regions observed in all children, with and without ASD. Specifically, neighborhood advantage was negatively associated with inter-hemispheric functional connectivity between several canonical language regions (including superior temporal gyrus, posterior superior temporal sulcus, and inferior frontal gyrus), and with surface area in the inferior frontal gyrus (left pars orbitalis and right pars triangularis). Income-to-needs ratio was positively associated with local gyrification and cortical thickness in a few of the same language regions.

Effects of diagnosis on language functional connectivity: While there was no significant main effect of diagnosis on functional connectivity between language regions, in contrast to our prediction (Hypothesis 1), we observed a significant diagnosis by age interaction on functional connectivity between the left inferior frontal gyrus (l-IFG) and the left middle temporal gyrus (l-MTG), with positive association with age present in TD participants but not in children with ASD. This finding of greater within-hemisphere language connectivity with age observed (crosssectionally) in TD preschoolers is in line with prior studies in this age range (Berl et al., 2014; Dinstein et al., 2011).

An absence of such relationship between age and FC in language regions in the ASD group suggests an altered developmental trajectory of language functional connectivity, as compared to a neurotypical maturation. This finding aligns with previous work indicating atypical language functional connectivity in young children with ASD (Eyler et al., 2012; Lombardo et al., 2015), possibly reflecting distinct brain organization and function supporting language. Dinstein and colleagues (2011) also reported altered patterns of language functional connectivity in toddlers with ASD (mean age = 29 months) exposed to speech stimuli delivered during natural sleep in the scanner, including reduced inter-hemispheric synchronization interpreted as evidence of early "overlateralization" of language function in young children with ASD.

Overall, outside of the aforementioned age by diagnosis interaction effect on functional connectivity, the patterns of connectivity between canonical language regions examined in this study were largely comparable in the two groups (as illustrated in Figure 3). While the lack of detected differences could be interpreted as reflecting broadly 'typical' neurodevelopment of language circuits in young children with ASD, a more plausible explanation involves a number of other neurobiological mechanisms not captured by BOLD signal but likely at play contributing to atypical language function in autism (such as cortical morphology, as discussed below). Additionally, fundamental group differences in functional connectivity in language circuits may have been masked by differential maturational trajectories across the sampled age range characterizing TD children and those with ASD (as evidenced by at least one functional connectivity effect with divergent age-related trajectories in ASD and TD children). Other, alternative explanations implicating methodological limitations are discussed in the *Limitations* section.

Effects of SES on language functional connectivity: In addition to the unsupported hypothesis regarding diagnostic effects on language FC, we also hypothesized that SES variables would be associated with functional connectivity, controlling for diagnosis and other relevant covariates, such that higher SES would correspond to increased functional connectivity within language networks. We did not observe such *positive* associations between FC in language regions and SES. There were, however, *negative* associations between SES indices (neighborhood SES in particular) and FC between *inter-hemispheric* language regions. Because increased hemispheric laterality of language function corresponds with neurocognitive maturation (as it increases with age across early childhood), negative associations between SES and inter-hemispheric FC in language regions are consistent with the growing evidence that children from higher SES backgrounds show more mature neural phenotypes of language (Raizada et al., 2008; Ramphal et al., 2020). For instance, Raizada and colleagues reported a link between lower SES, measured with the Hollingshead Index, and reduced hemispheric specialization in the left inferior frontal gyrus (measured by reduced left-right asymmetry of the IFG functional activation on a rhyming-judgement task) in typically developing 5-year-old children.

More broadly, these results are in line with a growing body of evidence demonstrating SES associations with brain maturation in early childhood, outside of language regions (as reviewed in Olson et al., 2021). For example, Gao and colleagues (2015) observed moderate, positive associations between SES variables (family income, maternal education) and functional network maturation indices in the default mode network (DMN) and sensorimotor network among typically developing infants, with multiple indicators of network maturation including similarity/matching score with adult templates, greater within-network connectivity, and lower outside-network connectivity (with the latter two indicating increasing network differentiation). Similar patterns have been reported in late childhood and adolescence cohorts (Tooley et al., 2020). Thus, taken together with the previous findings, our finding of negative associations between SES and inter-hemispheric FC in language regions suggests that brain network maturation – in language circuits and beyond – is sensitive to the variability along the SES spectrum.

Notably, the majority of previous studies on associations between SES and neural function in language regions in early childhood have utilized measures assessing SES at the household-level, such as maternal educational level and family income (Olson et al., 2021; Ramphal et al., 2020). To our knowledge, this is the first report showing associations between population-level SES, *neighborhood advantage*, and neural function in young children with ASD. Our reported findings align with those from a recent study of typically developing infants showing links between a comparable neighborhood adversity index and fronto-striatal connectivity, which were also predictive of externalizing behavioral challenges at 2 years of age (Ramphal et al., 2020). Similarly, links between neighborhood SES and functional network connectivity were reported in a large, cross-sectional sample of youth between ages 8 and 22 years (n = 1012; Tooley et al., 2020). In particular, Tooley and colleagues have shown that neighborhood SES moderated the relationship between age and network differentiation, such that children and teens from lower SES neighborhoods had an attenuated (i.e., less positive) relationship between network differentiation and age, compared to their peers from higher SES neighborhoods. Thus, the results from the present study indicate that the effects of neighborhood advantage on functional brain connectivity can be detected from very early in life, in both typical and atypical development, and suggest that higher neighborhood SES is associated with a more mature functional organization of the language network.

Intriguingly, neighborhood advantage was the only SES variable significantly associated with language FC, as neither of household-level SES measures examined (income-to-needs ratio, maternal educational level) was associated with FC indices. It is possible that neighborhood advantage relates differently to brain development and maturation than household measures of SES (Leventhal & Brooks-Gunn, 2000; Tooley et al., 2020). This may be due, in part, to aspects of the neighborhood environment (e.g., air quality, environmental noise, etc.) that could affect development broadly in distinct ways from aspects of the home or family environment. Further, distinct aspects of SES (environmental conditions associated with household vs. neighborhood indices of SES) may differentially relate to neural function at varying times throughout child development. For example, household income may more strongly relate to neurodevelopment and brain function at birth, whereas neighborhood SES may show stronger associations in the early childhood years, as neighborhood-level factors and characteristics may become more salient as children age (Gao et al., 2015). A longitudinal design would be required to test this hypothesis (as discussed in more detail in the *Limitations* section). It is also possible that brain functions supporting other neurocognitive aspects of development (e.g., executive function, visual or motor skills) relate to other aspects of SES, including family income and/or maternal educational level (Moriguchi & Shinohara, 2019; Raizada et al., 2008). Indeed, many others have shown associations between functional connectivity and more traditional SES metrics at different ages along the child development (e.g., Mcewen & Gianaros, 2010).

Although not directly measured or tested in the present study (see *Limitations*), there are several potential causative mechanisms underlying observed associations between neighborhood advantage and inter-hemispheric functional connectivity between language regions. As reviewed in *Introduction*, socioeconomic disadvantage is correlated with higher stress, which relates with higher levels of maternal stress hormones during pregnancy (Graham et al., 2019). Indeed, maternal prenatal levels of cortisol have been linked with functional connectivity of the default mode network in neonates (Marshall et al., 2018). Beyond potential prenatal causative mechanisms, neighborhood environment accounts for additional variance in the types of early life experiences children have, above and beyond the simultaneous (and partially overlapping) effects of household-level SES factors (Hackman et al., 2010). For example, neighborhood affluence relates to opportunities for enrichment and cognitive stimulation early in life, through expanded access to parks, museums, libraries, etc. (Christensen et al., 2014).

The lack of any observed diagnosis by SES interaction effects on FC between any language ROI pairs indicates that, early in life, language network connectivity is sensitive to socioeconomic environmental context in both young children with ASD and TD children alike. To our knowledge, this is the first study examining associations between SES and neural measures in young children with ASD, controlling for the effects of diagnosis and associated developmental variables (including exposure to more than one language in the home). Overall, these findings extend previously reported links between SES variables and language skills in preschool children with and without ASD (Olson et al., 2020; Swanson et al., 2019) to the neural circuits supporting the emerging language skills in early childhood.

Effects of diagnosis on cortical morphology and neuroanatomy of language regions: We hypothesized that neuroanatomical features, including cortical thickness, surface area, and local gyrification, would differ between ASD and TD young children, controlling for SES factors. As hypothesized, we found that ASD diagnosis was associated with higher local gyrification (or increased cortical folding) in the left inferior frontal gyrus, pars opercularis, and lower cortical thickness in the left inferior frontal gyrus, pars orbitalis. Neuroanatomically, the IFG is bound by the sylvian fissure which is one of the earliest sulci of the human brain to develop, first appearing as early as the sixteenth week of gestation (Garel et al., 2001). As such, increased local gyrification of the IFG subdivisions (carved by the horizontal ramus of the lateral or sylvian fissure) in preschoolers with ASD may reflect very early perturbations to neurodevelopment of these regions in utero. Findings indicating increased local gyrification in toddlers with ASD align with previous reports of greater gyrification in perisylvian regions in older children with ASD (Kohli et al., 2019; Libero et al., 2014). Additionally, increased local gyrification in ASD may be consistent with the early brain overgrowth documented in ASD (Courchesne et al., 2003; Ecker et al., 2016; Yang et al., 2016). Interestingly, in the only other published study examining local gyrification in preschool children with ASD (Libero et al., 2019), right inferior frontal gyrus was one of the few regions showing increasing gyrification between ages 3 and 5 years, longitudinally, in boys with ASD, as compared with TD boys. Taken together with these findings, our results suggest that both the pattern and trajectory of cortical folding development in one of the canonical language regions may be altered in young children with ASD.

Next, our finding of lower cortical thickness in the left inferior frontal gyrus, pars orbitalis in preschool children with ASD needs to be interpreted in the face of mixed evidence on cortical thickness in ASD (Ecker et al., 2014; Hardan et al., 2006; Kohli et al., 2019; Nunes et al., 2020; Zielinski et al., 2014). For example, Kohli et al. (2019) reported reduced cortical thickness in the insula in a cross-sectional cohort of children and adolescents with ASD, while Smith and colleagues identified a lack of typical age-related cortical thinning, including in regions involved in language, in children with ASD between the ages of 4 and 6 years (Smith et al., 2016).

Generally, cortical thinning across development is related to 3 fundamental aspects of brain maturation: pruning of inefficient synapses, dendrites, and neurons (resulting in cortical tissue loss and thinner cortex), increasing myelination, and changing morphology, including cortical folding and surface area expansion (Brown & Jernigan, 2012; Stiles & Jernigan, 2010). As such, reduced cortical thickness of the inferior frontal gyrus known to support language function detected in preschoolers with ASD may reflect atypicalities in any or all of these neurodevelopmental processes.

Effects of SES on cortical morphology and neuroanatomy of language regions: In testing the hypothesis that neuroanatomical features would be associated with SES factors, controlling for diagnosis and other relevant covariates, we identified positive associations between income-to-needs ratio and local gyrification in the left hemisphere transverse temporal gyrus, left superior temporal gyrus, and right inferior frontal gyrus, pars opercularis. These findings are in line with previous reports on school age children (ages 8-10 years) indicating associations between SES and gyrification in the left hemisphere (Blanton et al., 2001; Jednoróg et al., 2012). To our knowledge, this is the first study reporting SES associations with local gyrification in preschoolers with ASD, and in early childhood (prior to age 5 years) more broadly. The complexity of gyral/sulcal folds has been shown to increase with age, and in this context, the current set of results suggests that lower SES corresponds with a less mature neural phenotype of language regions (Kelly et al., 2013) and that slower developmental trajectories, at least within language circuits, may characterize children from lower SES backgrounds (as recently reviewed by Olson et al., 2021).

Notably, reduced local gyrification in the inferior frontal gyrus, pars opercularis has also been shown in children who have experienced maltreatment (Sheridan & McLaughlin, 2014). Although low SES and early adversity represent distinct dimensions of environmental experience

(Lawson et al., 2017), both have been shown to be associated with altered patterns of brain development in early life, perhaps via parallel mechanisms involving stress (Lawson et al., 2013). As such, the observed SES associations with local gyrification in early childhood reported in the present study align with those reported in children who have experienced early adversity.

We also observed a positive association between left middle temporal gyrus cortical thickness and income-to-needs ratio. To our knowledge, this is the first report of significant effects of SES on cortical thickness in early childhood, and they are well aligned with results from a large sample of school-age children (n = 238, mean age = 11 years), showing positive associations between parental educational level and cortical thickness in the prefrontal cortex (Lawson et al., 2013). However, the finding of positive association between SES and cortical thickness in one of the language regions may be difficult to interpret in the face of the age-related thinning observed (as expected in this age range; Brown & Jernigan, 2012) in our cohort.

Similarly, the observed negative associations between neighborhood advantage and surface area in the left inferior front gyrus, pars orbitalis and right inferior frontal gyrus, pars triangularis stand in contrast to previous reports indicating positive associations between SES measures and surface area in typically developing school-age children and adolescents (Noble, Houston, et al., 2015) and to the expected cortical surface expansion across development. However, there are few if any reports on the relationship between SES and surface area in early childhood, making the interpretation of these results more challenging.

Finally, there were no diagnosis by SES interaction effects on measures of cortical morphology in the language regions. Because this is the first study of neural correlates of SES in young children with ASD, we are unable to compare these findings to those from other neuroimaging studies. However, the main effects of SES on functional connectivity and neuroanatomical features in language regions are consistent with, and add to the behavioral results from a larger sample drawn from same cohort demonstrating SES effects on the emerging language skills in young children with and without ASD (Olson et al., 2020). These findings support the hypothesis that low SES contributes additive (but not multiplicative) vulnerability to atypical neurodevelopment when present in young children with ASD. However, in light of previously reported SES associations with functional outcomes in ASD (Fountain et al., 2012), it is possible that unique associations between SES and neural characteristics in language regions may become more prominent in children with ASD throughout development. Many of the participants with ASD enrolled in this study were very recently diagnosed with ASD and had yet to begin early intervention, or had just recently begun receiving services. Although intervention service receipt was not associated with any SES variables in the present sample (Olson et al., 2020), there have been widely documented disparities in access to evidence-based treatment services for youth with ASD, and it is possible that unique SES-neural patterns emerge later in childhood in ASD (Nguyen et al., 2016). Further, participating families have self-selected into a study of autism and brain development, likely indicative of the selection bias. Thus, it is possible that the results obtained from this cohort may not completely generalize to the broader population of lower SES families with a child with ASD (e.g., families who are hesitant to seek an ASD diagnosis).

Summary. Overall, findings indicate that associations between both household- and neighborhood-level socioeconomic variables and brain structure and function can be detected in early childhood in both ASD and typical development. These results provide compelling evidence for relationships between socioeconomic context and brain development in early childhood, prior to entry into kindergarten. The pattern of findings suggests that, broadly, socioeconomic context has implications for children’s neurodevelopment in language regions during a sensitive period that sets the stage for their later ability to learn in school and beyond. More specifically, in ASD, SES variables have an impact on neural function and structure in regions that may subserve responsivity to early intervention, particularly for language and socio-communicative delay. These findings provide neurobiological context for the well-established links between SES and language skills reported in typical and atypical development (Olson et al., 2020; Reardon et al., 2013; Swanson et al., 2019).

The general pattern of findings revealed delayed or lagging cortical maturation in the first years of life (evidenced by lower local gyrification in language regions, and reduced functional differentiation between interhemispheric language regions) associated with lower SES, regardless of the child's diagnosis. Delayed brain maturation associated with lower SES could be interpreted as compensatory or adaptive in response to stress. Broadly defined, such processes are thought to alter the duration of sensitive periods for certain aspects of structural and functional brain development in response to adverse or suboptimal conditions (e.g., lengthening sensitive periods for development to allow the brain more time to respond to learning opportunities; Tooley et al., 2021). In combination with previous work (Leonard et al., 2019), results from the present study reflecting lags in brain maturation indices (including local gyrification and functional differentiation) may reflect an adaptive response to stress associated with socioeconomic disadvantage. More importantly, a pattern of delayed maturation may also point to an optimal window for early intervention to leverage the plasticity of the developing brain when it is primed for language development.

Limitations: The results from the present study need to be interpreted in the context of several limitations. Firstly, as discussed in *Introduction*, SES is a difficult construct to measure and operationalize, as SES variables often serve as a proxy for many social and biological factors that represent putatively causal mechanisms underlying the observed effects on human development and cognition (Duncan & Magnuson, 2012; Romeo et al., 2018; Shavers, 2007). We attempted to capture the complexity associated with SES by using multiple variables, in line with best practices for SES measurement (Diemer et al., 2013). However, there are still many environmental or contextual factors that were not measured in the present study, which may serve more proximal, causal roles accounting for associations between SES and measures of brain development. For example, we lacked measures characterizing the home language environment, which has been shown to mediate associations between SES and neural function in language regions (Romeo et al., 2018; Swanson et al., 2019).

Further, in part due to associated challenges with neuroimaging research involving preschool children (i.e., achieving natural, continuous sleep during an MRI scan), our sample size was relatively modest, thereby limiting our power to detect some significant effects where they may exist. In addition, using a longitudinal design would have allowed us to make causal inferences regarding SES associations with neural function, which we are unable to do with the cross-sectional study design.

We must also consider that TD participants in the current sample showed significantly higher levels of maternal educational level, income-to-needs ratio, and neighborhood advantage than participants with ASD, perhaps as a result of differences in recruitment avenues and distinct motivations for research participation among families of young children with ASD vs. those with TD children. Although both TD and ASD participants were recruited from early head start programs serving low-income families, and community-oriented events such as wellness fairs or neighborhood fairs targeting all local families, children with ASD were also referred to the study from specialty clinics and service providers who do not serve TD children. Given the SES differences between the diagnostic groups, diagnosis and SES were correlated in our sample, thereby introducing increased susceptibility for error in the regression models including both diagnosis and SES variables.

Conclusions and future directions: Despite these limitations, to our knowledge, this is the first study to report associations between SES variables and neural measures in young children with ASD, and serves as a starting point to better understand how SES can become embedded in the brain early in life. Overall, results from the present study demonstrate that SES variables account for variation in neural measures supporting language function in preschool children with and without ASD. Findings add to and extend upon previous work demonstrating SES-neural associations in early childhood, indicating that SES-related alterations in brain regions and circuits supporting language can be observed prior to entry into kindergarten, building upon previous findings showing SES associations with language skills in this cohort (Olson et al., 2020). Although SES associations with brain structure and function have been documented in the first years of life (see Olson et al., 2021 for a review), it is important to consider that these associations are in no way innate or irreversible (Ramphal et al., 2020; Tooley et al., 2020). Indeed, both brain structure and function can change in response to environmental experience (c.f., Landa, 2018), and many aspects of SES are modifiable. Thus, the knowledge generated by this study may contribute to developing improved prevention and intervention programs and policies aimed at reducing these effects.

To further understand these SES-brain associations, future work must address questions regarding SES and neurodevelopment using longitudinal studies, ideally with multiple causal measures putatively correlated with SES (e.g., home literacy environment, access to nutrition, exposure to environmental pollutants, allostatic load, stress). Most importantly, studies and policy aimed at addressing and eliminating systemic causes of poverty and societal inequity are necessary. Ultimately, policy changes are required to reduce the inequities that contribute to developmental disadvantages from very early in life. The results of this study also show that the field of autism research and practice stands to benefit from increased attention to sociodemographic variables as they relate to language, cognitive outcomes, and neural measures in ASD. Individuals and families with limited access to financial and social resources are traditionally underrepresented in research, and their inclusion in autism research adds unique aspects to our understanding of development in autism. It will also render scientific findings of the field more equitable and applicable to a broader swath of society, especially those who may benefit most from the knowledge generated by these studies.

Table 1 Participant Characteristics: fMRI Cohort

		ASD (n=36) mean ± SD	range	TD (n=37) mean ± SD	range	*p*-value
Sex (%)[a]	Female	8 (22%)		16 (43%)		0.096
	Male	28 (78%)		21 (57%)		
Exposure to > 1 Language (%)[a]	No	15 (44%)		23 (62%)		0.199
	Yes	19 (56%)		14 (38%)		
Ethnicity (%)	Hispanic	19 (52%)		9 (24%)		0.012
	Not Hispanic	17 (48%)		28 (76%)		
Age (months)		36.5 (11.6)	17 - 62	35.5 (16.1)	15 - 64	0.765
Maternal Educational Level		3.4 (1.5)	2 - 6	4.4 (1.0)	2 - 6	0.002
Income:Needs Ratio		3.1 (2.5)	0.2 - 9.4	4.5 (2.3)	0.3 - 9.4	0.020
Neighborhood Advantage Index		-0.18 (1.00)	-2.6 - 1.5	0.26 (0.82)	-1.3 - 2.5	0.046
ADOS-2 Total		15.1 (5.5)	6 - 26	--	--	--
MSEL Exp. Lang. T-Score		30.9 (13.0)	20 - 62	49.0 (11.0)	30 - 75	<0.001
MSEL Rec. Lang. T-Score		32.3 (12.6)	20 - 61	53.7 (11.5)	26 - 76	<0.001
MSEL ELC		70.9 (20.5)	49 - 111	105.1 (16.4)	80 - 143	<0.001
In-scanner motion (RMSD)		0.12 (0.04)	0.05 - 0.22	0.11 (0.04)	0.05 - 0.22	0.097

Note. MSEL = Mullen Scales of Early Learning; Exp. Lang. = Expressive Language; Rec. Lang. = Receptive Language; ELC = Early Learning Composite, Standard Score; ADOS-2 = Autism Diagnostic Observation Schedule, 2nd Edition; RMSD = root mean square of displacement. Income-to-Needs Ratio (INR) was derived by dividing the household income by the federal poverty threshold defined by family size; an INR of one indicates living at the federal poverty level, which according to the 2019 US government official poverty definition was $25,750/year for a family of four. Neighborhood Advantage Index values are PCA-derived factor scores summarizing various neighborhood macroeconomic variables obtained from the Census tract-level data.

Table 2 Participant Characteristics: aMRI Cohort

		ASD (n = 39) mean ± SD	range	TD (n = 31) mean ± SD	range	*p*-value
sex (%)[a]	Female	11 (28%)		14 (45%)		0.223
	Male	28 (72%)		17 (55%)		
Exposure to > 1 Language (%)[a]	No	14 (39%)		18 (58%)		0.186
	Yes	22 (61%)		13 (42%)		
Ethnicity (%)	Hispanic	16 (41%)		9 (29%)		0.300
	Non-Hispanic	23 (59%)		22 (71%)		
Age (months)		38.7 (13.5)	17 - 62	37.6 (14.2)	15 - 64	0.746
Maternal Educational Level		3.6 (1.4)	2 - 6	4.4 (1.0)	2 - 6	0.007
Income:Needs Ratio		3.4 (2.5)	0.2 - 9.4	4.2 (2.1)	0.3 - 9.4	0.136
Neighborhood Advantage Index		-0.21 (1.03)	-2.6 - 1.2	0.28 (0.85)	-1.3 - 2.2	0.038
ADOS-2 Total		14.9 (5.9)	5 - 26	--	--	--
MSEL Exp. Lang. T-Score		33.0 (11.6)	20 - 62	48.8 (11.5)	40 - 75	<0.001
MSEL Rec. Lang. T-Score		33.6 (12.7)	20 - 61	53.3 (11.1)	40 - 76	<0.001
MSEL ELC		73.5 (19.7)	49 - 111	104.9 (16.6)	76 - 143	<0.001
CNR		2.10 (0.2)	1.7 - 2.4	2.06 (0.1)	1.7 - 2.3	0.42

Note. MSEL = Mullen Scales of Early Learning; Exp. Lang. = Expressive Language; Rec. Lang. = Receptive Language; ELC = Early Learning Composite, Standard Score; ADOS-2 = Autism Diagnostic Observation Schedule, 2nd Edition; CNR = Contrast-to-noise ratio. Income-to-Needs Ratio (INR) was derived by dividing the household income by the federal poverty threshold defined by family size; an INR of one indicates living at the federal poverty level, which according to the 2019 US government official poverty definition was $25,750/year for a family of four. Neighborhood Advantage Index values are PCA-derived factor scores summarizing various neighborhood macroeconomic variables obtained from the Census tract-level data.

[a] Values denote counts and corresponding χ^2 *p* values. Remaining comparisons reflect two-sample *t*-tests and corresponding *p* values

Table 3 Effects of diagnosis, age by diagnosis, and exposure to more than one language at home on functional connectivity between left inferior frontal gyrus (l-IFG) and left middle temporal gyrus (l-MTG)

	l-IFG – l-MTG FC			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	0.57	0.17 – 0.97	2.82	**0.006**
Exposure to >1 language	-0.09	-0.16 – -0.01	-2.21	**0.030**
Age	-0.01	-0.02 – 0.00	-1.88	0.064
Dx	-0.28	-0.51 – -0.06	-2.49	**0.015**
Age by Dx	0.01	0.00 – 0.01	2.64	**0.010**
Observations	71			
R^2 / R^2 adjusted	0.211 / 0.163			
F-statistic: 4.402, *p*-value: 0.003				

Note. *p*-values in **bold** denote significant effects at <.05.

Table 4 Effects of neighborhood SES (Neighborhood Advantage Index) on functional connectivity between several language ROIs

	r-STG – l-pSTS FC			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	0.12	-0.04 – 0.28	1.45	0.153
N-SES	-0.08	-0.13 – -0.02	-2.68	**0.009**
RMSD	1.36	-0.01 – 2.74	1.98	0.051
Observations	71			
R^2 / R^2 adjusted	0.155 / 0.130			
F-statistic: 6.2, *p*-value: 0.003				

	r-STG – l-IFG FC			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	-0.07	-0.19 – 0.05	-1.18	0.244
N-SES	-0.05	-0.09 – -0.00	-2.17	**0.034**
RMSD	1.61	0.62 – 2.60	3.24	**0.002**
Observations	71			
R^2 / R^2 adjusted	0.200 / 0.176			
F-statistic: 8.42, *p*-value: 0.0005				

	l-pSTS – r-pSTS FC			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	0.58	0.51 – 0.64	18.05	**<0.001**
N-SES	-0.08	-0.15 – -0.01	-2.29	**0.025**
Observations	71			
R^2 / R^2 adjusted	0.071 / 0.057			
F-statistic: 5.26, *p*-value: 0.025				

Table 4 Effects of neighborhood SES (Neighborhood Advantage Index) on functional connectivity between several language ROIs

	l-IFG – r-IFG FC			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	0.32	0.28 – 0.37	13.83	**<0.001**
N-SES	-0.06	-0.11 – -0.01	-2.35	**0.022**
Observations	71			
R^2 / R^2 adjusted	0.074 / 0.061			
F-statistic: 5.53, *p*-value: 0.0215				

Note. *p*-values in **bold** denote significant effects at <.05. STG: superior temporal gyrus; IFG: inferior frontal gyrus; pSTS: posterior superior temporal gyrus; r/l: right/left; FC: functional connectivity.

Table 5 Effects of diagnosis on local gyrification and cortical thickness

	Left IFG, pars opercularis LGI			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-Value*
Intercept	3.15	2.47 – 3.82	9.32	**<0.001**
Dx	-0.14	-0.27 – -0.01	-2.20	**0.031**
TBV	0.00	0.00 – 0.00	6.22	**<0.001**
Sex	-0.19	-0.33 – -0.05	-2.68	**0.009**
Observations	67			
R^2 / R^2 adjusted	0.423 / 0.395			

	Left IFG, pars orbitalis CT			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-Value*
Intercept	3.42	3.17 – 3.67	27.54	**<0.001**
Dx	0.15	0.03 – 0.27	2.52	**0.014**
Age	-0.01	-0.01 – -0.01	-4.45	**<0.001**
Observations	70			
R^2 / R^2 adjusted	0.288 / 0.267			

Note. lGI: local gyrification index; IFG: inferior frontal gyrus; TBV: Total Brain Volume.

Table 6 Effects of income-to-needs ratio (INR) and total brain volume on local gyrification

	Left transverse temporal lGI			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	2.77	2.14 – 3.39	8.86	**<0.001**
INR	0.03	0.00 – 0.06	2.15	**0.035**
TBV	0.00	0.00 – 0.00	7.66	**<0.001**
Observations	65			
R^2 / R^2 adjusted	0.505 / 0.489			

F-statistic: 31.6, *p*-value: 0.0000000003

	Left STG lGI			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	2.72	2.22 – 3.22	10.91	**<0.001**
INR	0.02	0.00 – 0.05	2.26	**0.027**
TBV	0.00	0.00 – 0.00	7.22	**<0.001**
Observations	65			
R^2 / R^2 adjusted	0.480 / 0.463			

F-statistic: 28.6, *p*-value: 0.000000002

	Right IFG, pars opercularis lGI			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	3.42	2.74 – 4.11	10.03	**<0.001**
INR	0.03	0.00 – 0.06	2.10	**0.040**
TBV	0.00	0.00 – 0.00	3.42	**0.001**
Exposure to >1 language	0.25	0.11 – 0.39	3.60	**0.001**
Observations	64			
R^2 / R^2 adjusted	0.328 / 0.294			

F-statistic: 9.76, *p*-value: 0.00002

Note. lGI: local gyrification index; INR: Income to Needs Ratio; TBV: Total Brain Volume; STG: superior temporal gyrus; IFG: inferior frontal gyrus.

Table 7 Effects of income-to-needs ratio (INR), age, and exposure to more than one language on cortical thickness

	Left MTG CT			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-Value*
Intercept	3.34	3.18 – 3.51	39.50	**<0.001**
Income:Needs	0.02	0.00 – 0.03	2.14	**0.036**
Age	-0.00	-0.01 – -0.00	-3.01	**0.004**
Sex	0.05	-0.02 – 0.13	1.39	0.169
Exposure to >1 language	-0.11	-0.18 – -0.04	-3.00	**0.004**
Observations	66			
R^2 / R^2 adjusted	0.275 / 0.227			
F-statistic: 5.78, *p*-value: 0.0005				

Note. MTG: middle temporal gyrus; CT: cortical thickness.

Table 8 Effects of neighborhood SES (Neighborhood Advantage Index) on surface area in left and right IFG

	Left IFG, pars orbitalis SA			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	-62.88	-231.16 – 105.40	-0.75	0.458
N-SES	-19.68	-36.72 – -2.64	-2.31	**0.024**
Total Brain Volume	0.00	0.00 – 0.00	5.83	**<0.001**
Age	2.34	0.92 – 3.77	3.29	**0.002**
Observations	69			
R^2 / R^2 adjusted	0.595 / 0.576			
F-statistic: 31.82 on 3 and 65 DF, *p*-value < 0.0000001				

	Right IFG, pars triangularis SA			
Coefficient	*Estimates*	*CI (95%)*	*Statistic*	*p-value*
Intercept	-479.54	-1071.94 – 112.85	-1.62	0.111
N-SES	-70.72	-130.69 – -10.74	-2.35	**0.022**
Total Brain Volume	0.00	0.00 – 0.00	5.40	**<0.001**
Age	4.02	-1.00 – 9.03	1.60	0.114
Observations	69			
R^2 / R^2 adjusted	0.481 / 0.457			
F-statistic: 20.1, *p*-value: 0.000000002				

Note. IFG: inferior frontal gyrus; SA: surface area; N-SES: neighborhood SES.

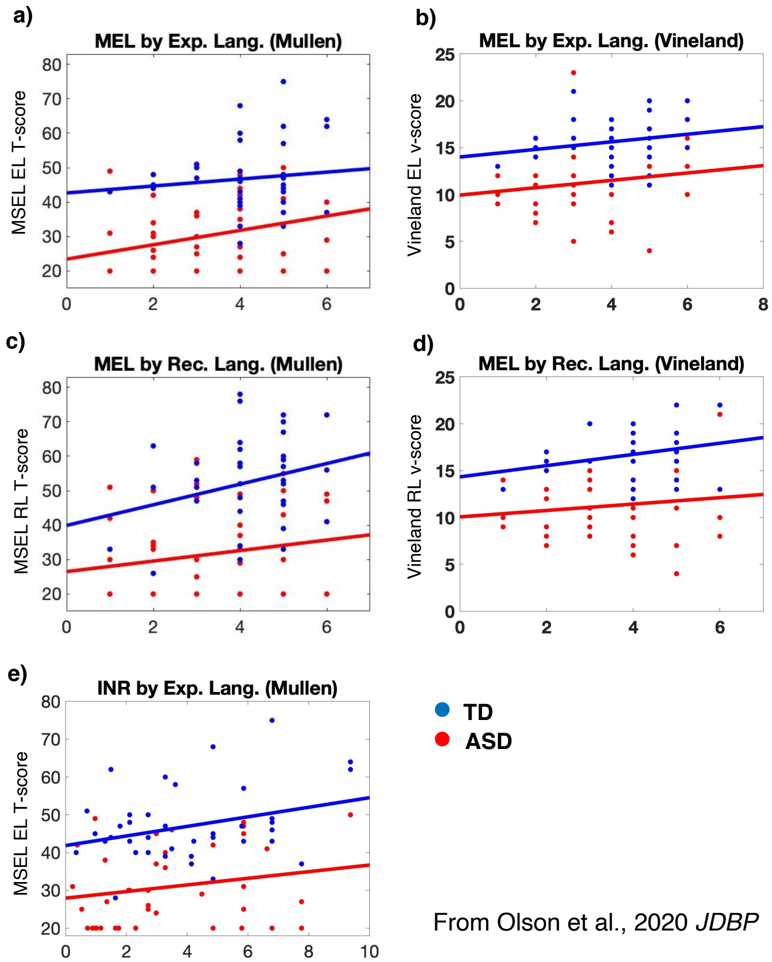

Figure 1 Associations between socioeconomic variables and receptive and expressive language in young children with and without ASD (ages 15-64 months). Panels **a-d**: Association between maternal education level (MEL) and **(a)** expressive language skills as measured with MSEL EL, **(b)** parent-rated expressive language skills as reported on the Vineland Adaptive Behavior Scales, **(c)** receptive language as measured with MSEL RL, and **(d)** parent-rated receptive language as reported on the Vineland Adaptive Behavior Scales. **(e)** Association between Income:Needs Ratio (INR) and expressive language skills as measured with MSEL EL. Individual dots represent individual participants; participants with ASD are depicted in red and TD participants are shown in blue.

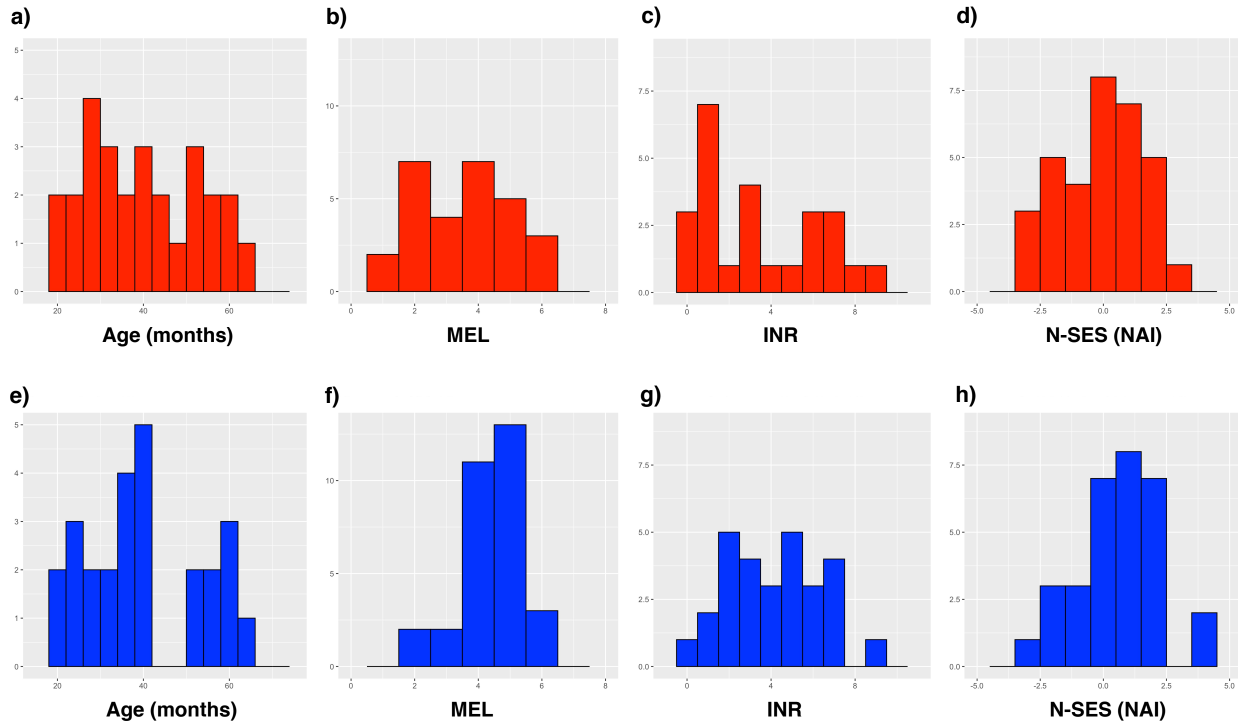

Figure 2 Histograms depicting distributions of **a,e**, age, **b,f,** maternal educational level, **c,g,** income-to-needs ratio (INR), **d,h,** neighborhood advantage index (NAI, or N-SES) for participants with ASD (**a-d,** depicted in red), and TD participants (**e-h,** shown in blue). There were no significant diagnostic group differences in the distribution of these variables (Kolmogorov Smirnov tests: all D < 0.36, all $p > 0.06$).

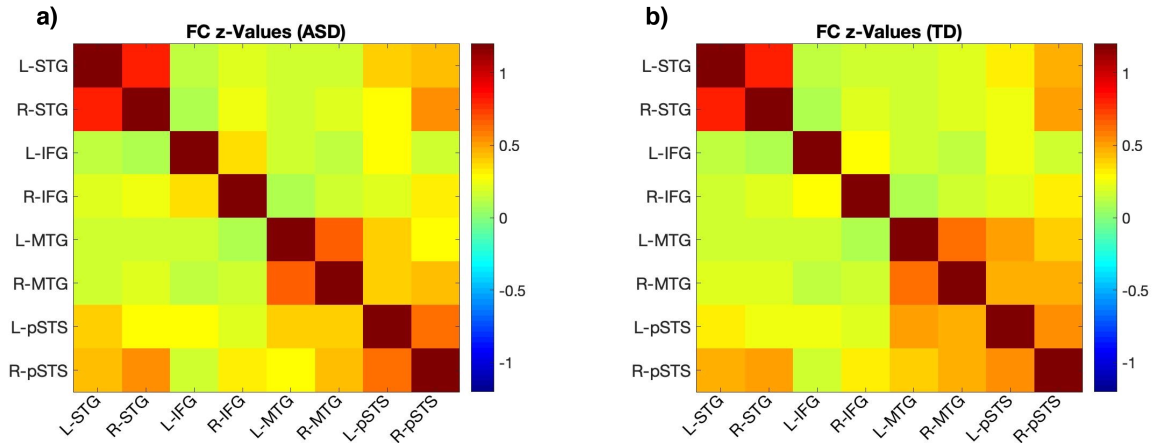

Figure 3 Connectivity Matrices for ROI-ROI functional connectivity for **a)** participants with ASD and **b)** TD participants. Values represent normalized pairwise (ROI-ROI) correlation coefficients (z-values). Both axes represent 8 language ROIs. Pixel color of each cell represents the magnitude of correlation for each ROI pair, with warmer colors indicating greater correlation coefficient values. Direct group comparison revealed no significant differences between groups in FC for any ROI-ROI pairs at $p < .05$, after controlling for RMSD (in-scanner motion).

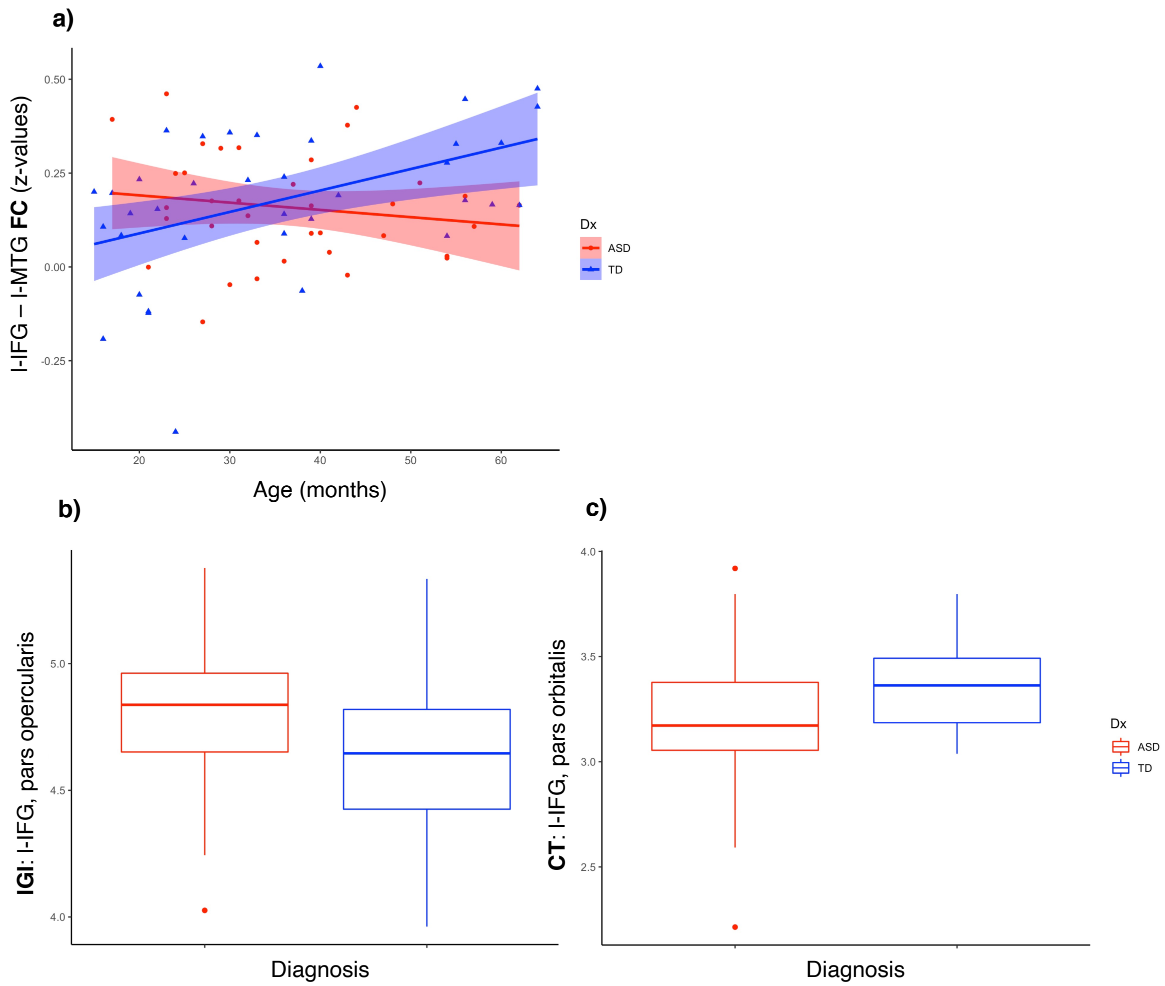

Figure 4 Effects of diagnosis on neural measures. **(a)** Scatterplot depicting **significant age by diagnosis interaction on FC between left IFG and left MTG** (t =2.64, r^2 = 0.09, p = 0.01), such that TD participants showed a positive association between age and FC, whereas participants with ASD showed no relationship. Dots represent individual participants. Shading indicates the 95% confidence interval on the partial correlations. **(b,c) Main effects of ASD diagnosis** on **b) local gyrification (lGI)** in the left IFG, pars opercularis (t = 2.20, partial r^2 = 0.07, p = 0.03), and **c) cortical thickness (CT)** in the left IFG, pars orbitalis (t = 2.52, partial r^2 = 0.09, p = 0.01).

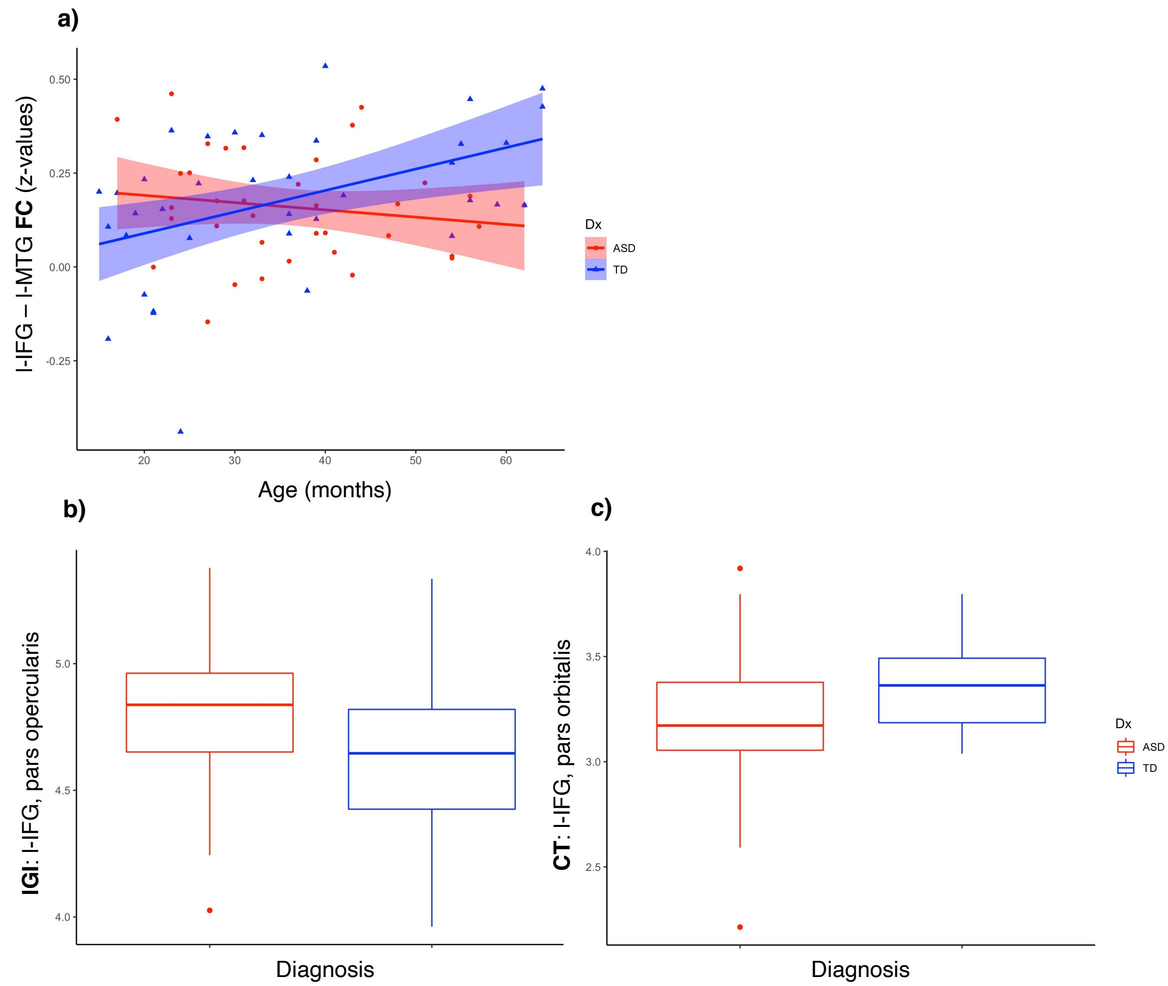

Figure 5 Associations between neighborhood SES (neighborhood advantage) and functional connectivity between **a)** right STG and left pSTS (partial $r^2 = 0.10$, $p = 0.009$), **b)** right STG and left IFG (partial $r^2 = 0.08$, $p = 0.03$), **c)** left and right pSTS ($r^2 = 0.07$, $p = 0.03$), and **d)** the left and right IFG ($r^2 = 0.08$, $p = 0.02$).

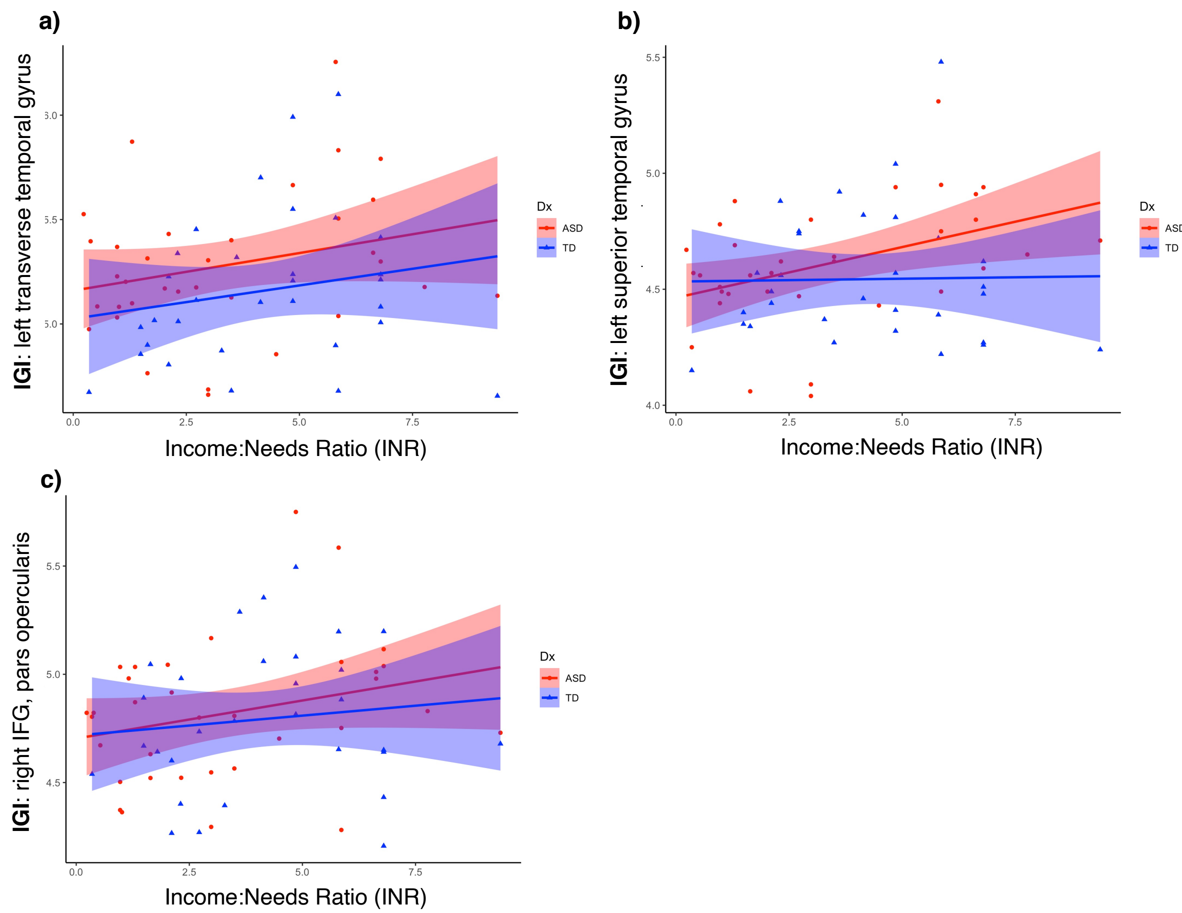

Figure 6 Associations between income-to-needs ratio and local gyrification in **a)** left transverse temporal gyrus (partial $r^2 = 0.08$, $p = 0.04$), **b)** left STG (partial $r^2 = 0.09$, $p = 0.03$), and **c)** right IFG, pars opercularis LGI (partial $r^2 = 0.07$, $p = 0.04$).

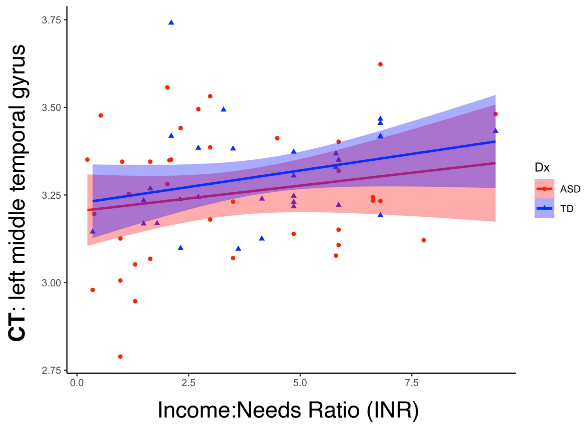

Figure 7 Associations between income-to-needs ratio (INR) and cortical thickness (CT) in left middle temporal gyrus (partial $r^2 = 0.07$, $p = 0.04$).

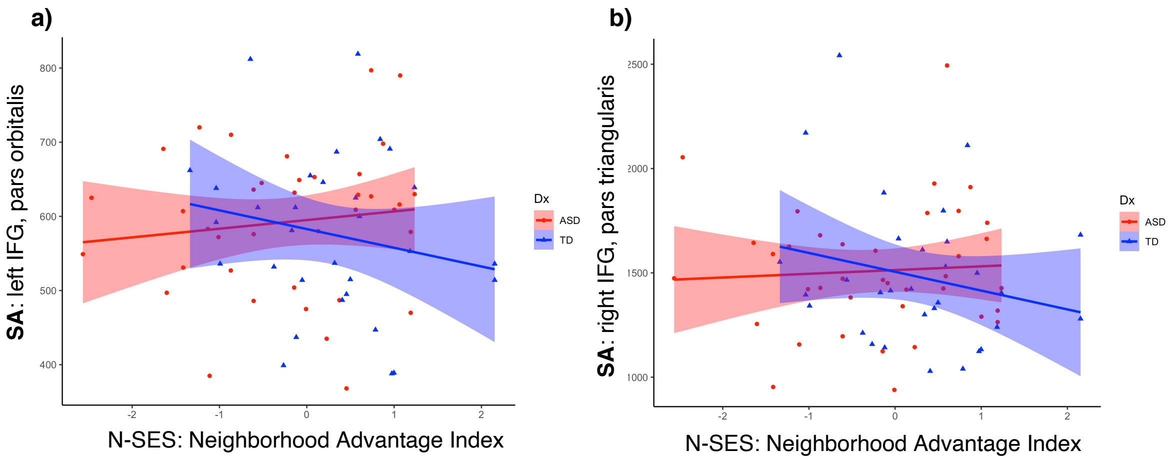

Figure 8 Associations between neighborhood SES (neighborhood advantage) and surface area (SA) in **a)** left IFG, pars orbitalis (partial $r^2 = 0.08$, $p = 0.03$), and **b)** right IFG, pars triangularis (partial $r^2 = 0.10$, $p = 0.02$).

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