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Cohesion of Cortical Language Networks During Word Processing Is Predicted by a Common Polymorphism in the *SETBP1* Gene

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Abstract

The etiological mechanisms of the genetic underpinnings of developmental language disorder (DLD) are unknown, in part due to the behavioral heterogeneity of the disorder's manifestations. In this study, we explored an association between the *SETBP1* gene (18q21.1), revealed in a genome-wide association study of DLD in a geographically isolated population, and brain network-based endophenotypes of functional intracortical coherence between major language-related brain areas. We analyzed electroencephalogram (EEG) data from thirty-nine children (twenty-three with, sixteen without DLD) aged 7.17–15.83 years acquired during an auditory picture–word matching paradigm. Variation at a single nucleotide polymorphism in the intronic region of the *SETBP1* gene, rs8085464, explained 19% of the variance in intracortical network cohesion ($p = .00478$). This suggests that the development of these brain networks might be partially associated with the variation in *SETBP1*. © 2020 Wiley Periodicals, Inc.

Introduction

Developmental language disorder (DLD) is the diagnostic category¹ for neurodevelopmental disorders of language that affect children's ability to acquire and efficiently use their native language (American Psychiatric Association, 2013). These disorders manifest in multiple modalities (e.g., spoken, written, sign language) and in a multitude of linguistic domains, including lexical, morphosyntactic, and pragmatic development. Despite its high prevalence (5–10%; Law, Boyle, Harris, Harkness, & Nye, 2000; Tomblin et al., 1997), DLD remains one of the most understudied neurodevelopmental disorders with regard to its neurobiological (i.e., molecular-genetic, neuro-anatomical, and neuro-functional) etiology (Bishop, 2017). Recently, a number of whole-genome association studies of language-related traits and DLD have been published (e.g., Chen et al., 2017; Devanna et al., 2018; Eicher et al., 2013; Gialluisi et al., 2014; Harlaar et al., 2014; Kalnak et al., 2018; Kornilov et al., 2016; Laffin et al., 2012; Luciano et al., 2013; Nudel et al., 2014; Simpson et al., 2015; St. Pourcain et al., 2014). As reviewed in detail elsewhere (e.g., Deriziotis & Fisher, 2017; Reader, Covill, Nudel, & Newbury, 2014), these studies identified a number of tentative genetic associations with small effect sizes implicating a complex network of genes in the development of language and language-related traits and disorders; however, the majority of reported associations did not survive stringent statistical corrections for multiple comparisons. The complexity of the etiological mechanisms of DLD is underscored not only by the slow progress in discovering risk genes for common language-related disorders (Deriziotis & Fisher, 2017), but the discovery of a plethora of rare genetic conditions characterized with language difficulties combined with other impairments (e.g., Fedorenko et al., 2016; Lai, Fisher, Hurst, Vargha-Khadem, & Monaco, 2001; Peter et al., 2017; E. van den Heuvel, Manders, Swillen, & Zink, 2018). Thus, a search for the symptom “language abnormalities” on the *Online Mendelian Inheritance in Men* (OMIM), an international database that curates genetic and clinical data on rare Mendelian diseases (Amberger, Bocchini, Schiettecatte, Scott, & Hamosh, 2014) and the Genetic and Rare Diseases Information Center (GARD), a program funded by the NIH, yielded a list of over 200 DLD phenotypes, each with a distinct genetic mutation, for the former and 1268 entries for the latter. Such variable causality is not surprising given the immense richness and complexity of language, as a multifaceted system of symbolic knowledge involved in comprehension and expression, the acquisition and use of which engages multiple interfaces (motor, sensory, social, and cognitive) and is characterized by substantial individual variation.

Research Highlights.

- We investigated lagged intracortical coherence using eLORETA in a mixed sample of children with and without developmental language disorders.
- Cohesion of cortical networks in the beta EEG band was predicted by the variation at rs8085464, located in the *SETBP1* gene.
- Higher beta cohesion was associated with lower language performance.
- The *SETBP1* gene is a novel candidate developmental language disorders gene that regulates the development of functional cortical networks that support language.

The study of atypical language development in the absence of any obvious explanatory factors (i.e., a concomitant genomic, neurological, sensory, intellectual, or social-cognitive disturbances) is complicated by the all-inclusive nature of the DLD diagnostic category, which stems from having to rely on broad (rather than precise) inclusionary criteria in conjunction with exclusionary criteria for a diagnosis, resulting in a highly heterogeneous population. This has important consequences for genetic association studies, dramatically reducing statistical power and, correspondingly, increasing sample size requirements to efficiently address the etiology of DLD.

Our study attempted to overcome the problem of heterogeneity of DLD in two ways. First, we capitalized on the unique nature of the population we sampled from: a small geographically isolated Russian-speaking population with a significantly elevated prevalence of DLD, the AZ population, namely, 40% among pre-school and 23% among primary-school-aged children (Rakhlin et al., 2013). The genetically isolated character of the population, coupled with high environmental uniformity suggests that DLD in AZ might have potentially more circumscribed (compared to the general population) genetic bases, limiting the etiological heterogeneity of the disorder.

Our previous genome-wide association study of DLD in AZ revealed several novel candidate genes (Kornilov et al., 2016), including *SETBP1*, which demonstrated a statistically significant gene-level association with the quantitative trait “syntactic complexity” (a phenotype derived from a combination of syntactic indices we obtained from language samples of the participants) after corrections for multiple comparisons. *SETBP1* provides instructions for making the protein called SET binding protein 1, which functions as a regulator of gene activity. It binds to the promoter regions of the DNA to increase gene expression in cells throughout the body, including the brain. Although the full set of functions of the *SETBP1* protein is not fully known, it is highly expressed in the brain during prenatal development and thought to control the genes involved in neuronal growth, division, and migration (Amberger et al., 2014). Mutations in *SETBP1* are associated

with Schinzel–Giedion syndrome (OMIM#269150), characterized by severe developmental delays. *SETBP1* has also recently been implicated in several other developmental disorders, including childhood apraxia of speech (Eising et al., 2019) and intellectual disabilities with impaired language (R. Wang et al., 2019). *SETBP1* haploinsufficiency, that is, a condition in which a heterozygous combination of a single copy of the standard allele with a variant allele is insufficient to produce the standard phenotype, has been documented in cases of severe expressive DLD (Bouquillon et al., 2011; Filges et al., 2011; Marseglia et al., 2012) and intellectual disability (Coe et al., 2014). Moreover, common variation in *SETBP1* was reported to be associated with individual differences in reading and reading-associated behavior and brain phenotypes (Perdue et al., 2019). In light of the previous findings, the current study focused on genetic variation in *SETBP1* as a potential contributor to the etiology of DLD in AZ.

Our second strategy in tackling the challenge of unraveling genetic basis of DLD involved simultaneously pursuing and linking three levels of analysis: genetic, neurophysiological, and behavioral. Research has previously established atypical cortical connectivity patterns in a number of developmental disorders that are often comorbid with language impairment, such as autism spectrum disorders (ASD; Kleinhans et al., 2008; Rudie et al., 2013), attention deficit and hyperactivity disorder (ADHD; Hoekzema et al., 2014; Uddin et al., 2008), and specific reading disability (SRD; Schurz et al., 2014). Furthermore, the risk allele of the gene *CNTNAP2*, implicated in genetic studies of autism and specific language impairment (SLI; an alternative term often used in the literature on DLD), was found to be associated with altered brain connectivity in risk allele carriers compared to non-carriers (Scott-Van Zeeland et al., 2010; cf. also von Hohenberg et al., 2013). The relationship between altered brain connectivity and language impairment was demonstrated in a number of studies of children born preterm, many of whom experience language problems (Barnes-Davis, Merhar, Holland, & Kadis, 2018; Degnan et al., 2015; Gozdas et al., 2018; Kwon et al., 2016; Rowlands et al., 2016). The altered patterns of connectivity found in school-aged children and adolescents born preterm involved increased connectivity between language areas and other areas, such as sensory motor areas, right inferior frontal gyrus (Broca's homologue), and bilateral supramarginal gyri (a region involved in tasks requiring visual attention, working memory, and semantic processing (Gozzo et al., 2009; Schafer et al., 2009).

Recent studies applied graph theory to brain connectivity (i.e., temporal dependency between separate brain regions) data obtained with functional magnetic resonance imaging (fMRI), magnetic resonance imaging (MRI), electroencephalogram (EEG), and magnetoencephalography (MEG). This approach allows one to study the properties of neural networks applying mathematical methods to representations of networks reduced to their core elements: nodes and edges (i.e., connections), and

characterize their efficiency based on various parameters, for example, clustering (“small-worldness,” or high degree of clustering combined with short path length) and internal cohesion, that is, the degree to which all voxels within a network display similar activity and are resistant to “being pulled apart” (Lee & Frangou, 2017).

Alterations in network behavior have substantial consequences for the topological properties of the brain as an organized information processing network, and, correspondingly, for its processing efficiency (Bullmore & Sporns, 2009). Therefore, alterations in network-based parameters may be a promising biomarker of DLD.

Several recent behavioral genetic studies point to the substantial heritability (23–89%, median at 40–50%) of cortical connectivity estimates obtained using fMRI/MRI and electroencephalography (EEG), including network measures of connectivity patterns (Schutte et al., 2013; Smit, Stam, Posthuma, Boomsma, & De Geus, 2008; M. P. van den Heuvel et al., 2013). These findings suggest that brain network organization parameters (a) are substantially influenced by genetic factors (along with and/or in an interaction with environmental influences), and (b) can serve as endophenotypes in genetic association studies. Studying endophenotypes serves the goal of reducing the complexity and heterogeneity of end-point behavioral phenotypes, thus providing an intermediate level linking the biological and behavioral-syndromic levels of analysis (Cannon & Keller, 2006). Correspondingly, although the initial AZ genetic study utilized behavioral phenotypes, the current study takes a network connectomics approach by focusing on neurobiological endophenotypes of DLD in AZ. This approach has the potential to provide new insights into the functional roles of *SETBP1*, by examining its association with the organization of functional cortical language processing networks in DLD compared to typical development, which, if successful, would constitute an advancement in the study of neurodevelopmental disorders that affect language.

Method

Participants. The participants came from a small, geographically isolated Russian population (AZ; Rakhlin et al., 2013) characterized by an unusually high prevalence of DLD. Thirty-nine AZ children 7.17–15.83 years of age ($M = 10.54$, $SD = 2.34$; twenty-three boys) participated in the study. Of these, twenty-three met criteria for DLD (age ranged from 7.33 to 15.25, $M = 10.12$, $SD = 2.40$; sixteen boys) and sixteen were classified as typically developing (TD; age ranged from 7.17 to 15.83, $M = 11.14$, $SD = 2.18$; seven boys). The language status classification was based on a set of expressive and receptive language measures obtained using a comprehensive standardized language development test in conjunction with a language sample analysis (see Kornilov et al., 2014, 2015, 2016; Rakhlin et al., 2013, for detailed descriptions). All children demonstrated normal hearing acuity

by passing a bilateral hearing screening at 25 dB (500, 1000, 2000, and 4000 Hz). All children had intellectual functioning within normal limits (scored above the cut-off for intellectual disability and received a non-verbal IQ score of >70). Groups did not differ on non-verbal IQ ($F(1, 37) = .7, p = .408$).

Language and Cognitive Development Measures. Children's language development was assessed using two diagnostic tools. The first was an elicited story generation task developed to assess language development in Russian. The narratives were analyzed and assigned scores or ratings (depending on the measure) for articulation quality, syntactic complexity, grammatical well-formedness, semantic quality, and narrative structure (Rakhlin et al., 2013). The second was a standardized test developed to assess language development in Russian, which was previously shown to have psychometric properties (ORRIA; Kornilov et al., 2016), comparable to such established instruments as the clinical evaluation of language fundamentals (CELF) (Semel, Wiig, & Secord, 1995), test of language development (TOLD) (Newcomer & Hammill, 1982), and comprehensive assessment of spoken language (CASL) (Carrow-Woolfolk, 1999). ORRIA is aimed at assessing a child's language development in the areas of morphology, syntax, compositional semantics, and lexicon in both receptive and expressive domains. Scores were standardized to have a mean standard score of 100 (SD of 15). We used five ORRIA subtests (Expressive Vocabulary, Receptive Vocabulary, Linguistic Operators, Sentence Structure, and Word Structure) to obtain a standardized age-adjusted score for overall language development. Children were classified as affected if they scored eighty-five or below on the ORRIA and received at least two narratives scores that were at least 1 SD below the mean established on a normative comparison population.

To rule out global developmental delay and intellectual disability, the children were assessed with a test of non-verbal cognitive functioning, using Scale 2 of the Culture-Fair Intelligence Test (CFIT; Cattell & Cattell, 1973), a standardized measure of linguistically and culturally diverse individuals.

Experimental Stimuli and Procedure. To characterize neurophysiological signatures of language processing, we collected evoked EEG potentials, while participants performed a picture–word matching experimental task (Kornilov, Magnuson, Rakhlin, Landi, & Grigorenko, 2015; Malins et al., 2013). Event-related potential (ERP) studies of lexical processing have uncovered the N400 component, that is, increased negativity in response to semantically incongruent utterances (e.g., “I like drinking milk with boots”) at approximately 400 ms after the anomalous stimulus, thought to index lexical processing or semantic integration or the retrieval of word meaning from semantic memory (Kutas & Federmeier, 2011; Lau, Phillips, & Poeppel, 2008; Schafer et al., 2009). The absence of N400 response was shown to be longitudinally associated with subsequent language deficits in infants, and a weaker or delayed N400 was found in

children with DLD compared to typically developing controls (Friedrich & Friederici, 2006; Popescu, Fey, Lewine, Finestack, & Popescu, 2009).

In our study, children were presented with a series of pictures on a laptop PC, each paired with a set of spoken words matched on frequency and imageability. They had to judge whether each word matched the pictures. The experiment had block design and consisted of forty blocks of eight trials each. On each trial, a fixation cross appeared for 250 ms, following which a picture was presented, which remained on the screen until the end of the block. After 1500 ms, a spoken word was played, and the participants had to indicate whether the picture and word matched by pressing a mouse button for “yes” and by giving no response for “no.” After 1500 ms a new word was presented, without changing the picture (which remained on the screen until the end of the block). The eight trials in each block contained the following conditions: (a) match condition (a picture-matching word, e.g., a picture of a cake in conjunction with the word /tort/ “cake”); (b) mismatch with an initial phonological overlap (IOP; e.g.; a picture of a cake (/tort/ in Russian) in conjunction of the word /tors/ “trunk”); (c) mismatch with a final phonological overlap (e.g., a picture of a cake (/tort/ in Russian) with the word /bort/ “side”); (d) a mismatch without phonological overlap but with a semantic association with the depicted item (e.g., a picture of a cake (/tort/ in Russian) with the word /chai/ “tea”); (e) a mismatch without either a phonological or semantic overlap (e.g., a picture of a cake (/tort/ in Russian) with the word /sad/ “garden”). Each block contained four trials in the match condition and one trial from each of the mismatch conditions (eight trials in total) (presented in a random order). See the Appendix for the schematic representation of the experimental setup. The words were presented binaurally at 70 dB (SPL) via Etymotic insert headphones (Etymotic Research, Inc.).

Our previous study (Kornilov et al., 2015) demonstrated that children with DLD showed a significantly reduced N400 amplitude in the IPO condition and, to a lesser extent, in the *no overlap* condition. In the IPO condition, the bottom-up, phonetic information, is consistent with the target word (depicted by picture) for about 324 ms, after which the expectation is violated and an N400 is elicited in typically developing children, but is significantly attenuated in children with DLD.

Because of the robustness of this finding, for the purposes of the present study, we focused on the electrophysiological data from the IPO condition, which we re-analyzed using graph theory, creating measures of topological properties of estimated intracortical networks as phenotypes for the genetic association study, described in detail below.

EEG Recording and Processing. The EEG signal was recorded using a BioSemi ActiveTwo system (BioSemi, Inc.) with sixty-four sintered Ag/AgCl electrodes mounted using electrolyte gel (SignaGel, Parker Laboratories, Inc.) in an elastic cap, approximating the standard 10–20 system. We also recorded electrical activity at the two mastoids: the vertical

electrooculogram (VEOG; electrodes placed above and below the left eye), and the horizontal electrooculogram (HEOG; electrodes positioned lateral to the outer canthi of both eyes). All impedances were kept below 25 k Ω . We excluded the Iz electrode from all analyses due to technical problems with this electrode that could not be resolved on-site. The EEG signal was sampled at 1024 samples/second, average-referenced offline, and downsampled to 500 samples/second for the purpose of analysis. The pre-processing of the data was carried out using Brain Vision Analyzer 2.1 (BrainProducts, Inc). In rare cases, when necessary, we reconstructed EEG channels containing artifacts (e.g., due to loss of contact) using spline interpolation. Then, a digital zero phase-shift two-stage IIR bandpass filter of .10 to 35 Hz (12 dB/oct) and a notch filter of 50 Hz were applied to the signal, followed by epoch segmentation (0–1000 ms relative to word onset), DC detrending, and independent component analysis (ICA) for the correction of ocular artifacts. We only analyzed trials where the correct response was provided and in which the EEG activity did not exceed $\pm 150 \mu\text{V}$ in any of the EEG channels. This threshold was set to minimize artifacts (Luck, 2014). All participants provided at least ten trials (and corresponding EEG epochs) for analysis, with an average of twenty-seven trials. The two language groups (TD and DLD) did not differ in the average number of epochs included in the analysis, $t(37) = -.71, p = .480$, or the signal to noise ratio for EEG data estimated for the Cz electrode, $t(37) = .84, p = .405$.

Connectivity Analysis. For the connectivity analyses, we used *exact low-resolution electromagnetic tomography* (eLORETA; Jatoi, Kamel, Malik, & Faye, 2014; Pascual-Marqui et al., 2011), an EEG source localization algorithm for modeling 3D distribution of electric neuronal activity with maximum synchronization between neighboring neuronal populations (represented by adjacent voxels, i.e., volume elements), in terms of orientation and strength. We used the LORETA software package (<http://www.uzh.ch/keyinst/loreta>) to estimate intracortical current density at 6239 voxels in specific regions of interest (ROI) within the Montreal Neurological Institute (MNI) coordinate space (specifically, the MNI152 template), a three-dimensional atlas of brain structures used as a standard reference for brain localization without having to rely on MRI data (Singh, Okamoto, Dan, Jurcak, & Dan, 2005). This technique produces results with high accuracy and exact localization (Jatoi et al., 2014). It corresponds to modelling connectivity using “virtual” intracortical electrodes for each participant and for each of the four EEG frequency bands (delta, 0–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; and beta, 12–30 Hz). Connectivity was estimated for the set of 18 bilateral ROI (i.e., a total of 36 ROI, see Supporting Information, Table S1) or 630 unique pairwise connectivities per band per child. These ROIs were chosen based on the published reviews of lesion and neuroimaging studies of the neural systems that support language and working memory (Friederici, 2012; Liemburg et al., 2012; the full list and description of ROIs is available in the Supporting Information), including

temporal, inferior frontal, parietal, extrastriate, and cingulate cortices. The analysis was based on the average intracortical current density for all voxels within each ROI.

Connectomics: Analytic Approach. The network connectomics approach taken in this study required multi-step analytic procedures, described in detail below for each step and summarized graphically in the Supporting Information (Figure S1). Broadly, our analysis focused on the association between multiple common single nucleotide polymorphisms (SNPs) in the *SETBP1* gene and three connectivity measures derived using a graph-theoretic approach. The connectivity networks themselves were constructed separately for each child using estimates of the pairwise functional lagged coherence between the eighteen major brain areas that support language and EEG frequency band. Instead of focusing on coherence in the electrode space (i.e., head-surface recorded time series), our analysis was based on the evaluation of the functional connectivity in the intracortical source space to circumvent problems specific to the analysis of multichannel EEG coherence (Nolte et al., 2004). Standard connectivity measures of linear interdependence among brain regions (i.e., coherence) are contaminated with instantaneous, non-physiological contributions due to volume conduction, low resolution, as well as by common-source synchronization, for example, zero-phase thalamic synchronization. Therefore, we relied on a recently developed measure of lagged linear coherence (LCoh; Pascual-Marqui, 2007) that partials out the zero-phase contributions to coherence estimates. Pairwise LCoh values were averaged across EEG epochs for each child and EEG band; they served as the building blocks of networks, whose topological properties defined the phenotypes for the genetic association analysis.

Transformation of Multi-ROI Connectivity Into Graph Theory Networks. For each participant and frequency band, we used pairwise LCoh values for 36 ROIs to build a 36×36 adjacency matrix with each ROI representing an individual “vertex” (or “node”) of a graph network, and each LCoh value representing an “edge” of the network. In order to transform construct undirected non-weighted graph networks, we thresholded each adjacency matrix (see Figure S2) using a pre-defined cut-off, retaining 54% of the most robust connections for each matrix. The use of the proportional or sparsity threshold was motivated by (a) recent evidence suggesting that proportional thresholds produce more replicable results compared to absolute thresholds (Garrison, Scheinost, Finn, Shen, & Constable, 2015); and (b) our focus on the topological properties of the studied intracortical networks. Correspondingly, as the latter measures are affected by network sparsity, we chose to evaluate network properties at the constant level of sparsity/wiring cost. Prior to analysis, we estimated network connectedness in the range from 10% to 90% and retained the strongest connections; the specific threshold value of 54% was chosen because it was the minimal network sparsity at

which all of the nodes were connected to at least one other node in the network for each child and EEG band (Rudie et al., 2013).²

Graph Theory Analysis of Estimated Intracortical Networks. We analyzed the resulting networks using the *igraph* and *qgraph* R packages (Csardi & Nepusz, 2006; Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012). Various graph-theoretic measures of network properties have been proposed (El Gamal & Kim, 2011). We chose a set of three parameters (applied to each individual and frequency band) that capture various network properties: *cohesion* (CO; the number of times a node moves together with other nodes from one community to another), *small-worldness* (SW; the extent to which the network is characterized by dense high clustering of local connectivity with a relatively short path lengths between any two nodes), and *transitivity* (TR; the extent to which nodes in the network tend to cluster together). The measure of cohesion, which indicates robustness of a network to disruptions of connectivity, was shown as particularly appropriate for determining collective changes in a coordinated activity of brain regions reflecting the dynamics of cognitive processes (Telesford et al., 2017). Small-worldness provides a measure of network efficiency, thought to support both segregated and distributed information processing, confer resilience against pathological attack, and minimize wiring costs (Achard & Bullmore, 2007). Small-world organization was shown to be altered in various clinical populations (Liang Wang et al., 2009; Zhao et al., 2012). Transitivity reflects connectivity of a region to its neighbors and is a measure of functional segregation reflecting network communication (Goñi et al., 2014).

DNA Genotyping. Genomic DNA was extracted from peripheral blood or saliva samples and quality controlled for purity and degradation following standard recommended collection, storage, and extraction procedures (Qiagen, N.V., Hilden, Germany; DNA Genotek, Inc., Ottawa, Canada). Samples were genotyped using the HumanCoreExome v.1 or HumanCNV 370k-Duo (Illumina, Inc.); the data of the two BeadChips were used to increase the validity of the candidate gene variants detection. Allele calling for both platforms was performed using the GenCall algorithm in Illumina's GenomeStudio software (version 2011.1). Samples and markers were quality controlled with GenomeStudio and SNP & Variation Suite (SVS version 7.7.8; GoldenHelix, Inc., Bozeman, MT).

The main focus for the association analysis was on rs8085464 (chr18:42358137; hg19; G > A, with G being the ancestral/major allele; the derived/minor A allele frequency in the sample was 29%). This SNP (the most common type of genetic variation between individuals) was chosen because it was the only SNP from the set of variants in the gene of interest (*SETBP1*) that had previously demonstrated a statistically significant ($p = .0357$) association with a quantitative phenotype of syntactic complexity, a major facet of DLD in the population of interest (Kornilov et al., 2016). The two genotype groups (the two groups of participants based on the presence

of ancestral vs. derived, or G vs. A, rs8085464 allele) did not differ in either number of analyzed epochs $t(37) = .28, p = .783$, or signal to noise ratio for EEG data estimated for the Cz electrode, $t(37) = -1.72, p = .101$.

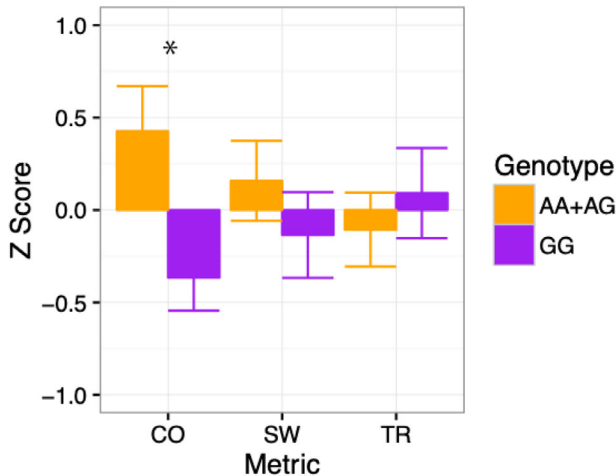
In addition to the SNP of interest, the genotyping platforms used in this study contained four other markers located within the *SETBP1* gene, which had a significant frequency of a derived allele of >10% in the studied population: rs10853522, rs1223278, rs10502849, and rs4890506. Given that *SETBP1* is a relatively large gene (388,338 base pairs), we chose to retain these four SNPs to capture any additional variation in this gene that could be linked to the network phenotypes in the study.

Analysis of Genetic Associations Between Selected SNPs and Topological Properties of Intracortical Language Processing Networks. We performed a genetic association analysis using the graph theory network measures as phenotypes in a mixed linear modeling framework using the Efficient Mixed-Model Association eXpedited algorithm (EMMAX; Kang et al., 2010) method as implemented in SVS under the additive model. Briefly, mixed linear modeling as applied to genetic association involves (a) estimating a genetic relationship matrix that models the genome-wide structure of the sample (i.e., empirically evaluating the extent to which each pair of individuals is similar genetically); (b) evaluating the contribution of this structure to phenotypic variance as random effects; and (c) testing for association between individual markers and phenotypes as fixed effects, while controlling for relatedness. The pairwise identity-by-state (IBS) relatedness matrix was estimated for our sample using a larger set of 16,197 SNPs. Phenotypes were regressed on children's age and gender, and quantile-normalized prior to the analysis using the *rntransform* function as implemented in GenABEL (Aulchenko, Ripke, Isaacs, & van Duijn, 2007). Analyses were carried out separately for each SNP, EEG band, and network measure, and the resulting *p*-values were corrected for multiple comparisons band-wise using the FDR procedure.

Results

Associations Between Genotype and Topological Properties of Intracortical Language Processing Networks. Genetic association analyses revealed two nominally significant associations (see Supporting Information for the full set of association results, Table S2). None of the signals survived corrections for multiple comparisons. Note, however, that the primary focus of this study was on rs8085464. In our data, rs8085464 was nominally significantly associated with the cohesion of language networks in the beta EEG band ($p = .00478$), which suggested that carrying a copy of the derived A allele increased the cohesion of the cortical language networks in the beta frequency band by 2/3 of a standard deviation ($B = .604, SE = .201$), explaining 19.59% of the variance in this phenotype (Figure 9.1). The second nominally significant association ($p = .02761$) was obtained for beta

Figure 9.1. Average scores for main graph theory network metrics for beta frequency bands in the GG and GA + AA rs8085464 genotype groups.



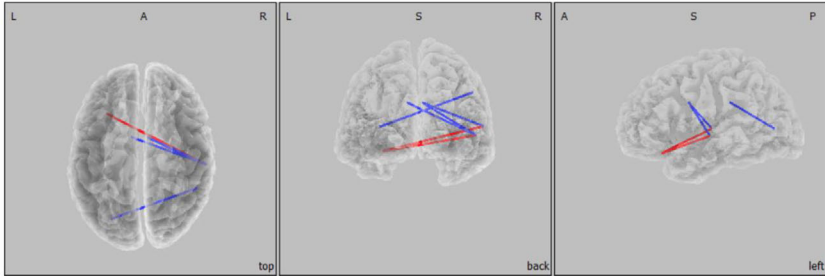
Note: CO, cohesion; SW, small-worldness; TR, transitivity

cohesion and rs12232728, located 1,701 bp downstream of rs8085464. Carrying a copy of the derived allele at rs12232728 increased the cohesion of cortical language networks in the beta frequency band by half of a standard deviation ($B = .497$, $SE = .217$), explaining 12.45% of the variance in this phenotype.

An analysis of the source activity across epochs in the intracortical space did not reveal significant differences between the rs8085464 and rs12232728 genotype groups with respect to average estimated current source density in any voxel (all p 's $> .05$; data not shown).

Correlation Between Intracortical Network Cohesion and Children's Language Development. We further investigated the established association signal by examining the relationship between obtained graph theory network parameters, including network cohesion, and children's overall language development as measured by children's performance on the subtests of the ORRIA, while controlling for age and gender. This analysis revealed a significant negative correlation between network cohesion in the beta band and the scores in the subtest Linguistic Operators (Pearson's $r = -.34$, $p = .035$), as well as a marginally significant negative correlation between beta cohesion and Receptive Vocabulary ($r = -.30$, $p = .063$). These results suggest that increased network cohesion in the beta band is associated with depressed scores on the indicators that tap into the comprehension of complex sentences, verbal working memory, and lexical development.

Figure 9.2. Differential functional lagged coherence in the GG versus GA + AA rs8085464 genotype groups. Blue lines represent coherences that were statistically significantly more strongly pronounced in the GA + AA, compared to the GG group.



Note: Red lines represent coherences that were statistically significantly more strongly pronounced in the GG compared to the GA + AA group

Investigating the Source of Altered Network Cohesion in the Carriers of the Derived Allele of rs8085464. Alterations in network cohesion could stem from differential connectivity between any of the ROI pairs. To investigate sources of altered network connectivity, we compared specific patterns of connectivity in two groups of children—homozygous for the ancestral allele (i.e., GG genotype) and carriers of at least one copy of the derived allele (i.e., GA or AA genotypes). The analysis was performed on log-transformed LCoh values using *t*-tests in LORETA. Table 9.1 and Figure 9.2 present the corresponding results. We identified six pairwise coherences that were differentially pronounced in the alpha band in the GG versus GA/AA groups. Of these six, four represented higher coherences observed for the GA/AA group. Carriers of the derived rs8085464 allele showed enhanced functional connectivity between (a) the ventral anterior cingulate (vACC) as well as superior temporal gyrus (STG) and the auditory cortex in the right hemisphere; (b) the left vACC and right STG; and (c) the left extrastriate cortex and right supramarginal gyrus. This enhanced connectivity between several ROIs in the carriers of the derived rs8085464 allele might be the source of the increased network cohesion associated with this *SETBP1* polymorphism we found.

Discussion

In this study, we examined the relationships between topological properties of cortical language processing networks and common variation in the *SETBP1* gene. Our main findings concern rs8085464, an SNP located in the intron region of *SETBP1*. Intron is a non-coding DNA sequence within a gene, which is eliminated by RNA splicing during the final gene product

Table 9.1. Pairwise LCoh Coherences That Were Differentially Strong (at $p < .05$) in the GG versus GA + AA rs8085464 Genotype Groups

ROI	BA	Hem	Anatomical Region	ROI	BA	Hem	Anatomical Region	t^*
31	BA40	Right	Supramarginal gyrus	2	BA6	Left	Extrastriate	-2.095
22	BA22	Right	Superior temporal gyrus	6	BA24	Left	Ventral anterior cingulate cortex	-2.077
22	BA22	Right	Superior temporal gyrus	18	BA47	Left	Inferior prefrontal gyrus	2.434
33	BA44	Right	Auditory cortex	18	BA47	Left	Inferior prefrontal gyrus	2.825
24	BA24	Right	Ventral anterior cingulate cortex	22	BA22	Right	Superior temporal gyrus	-2.495
33	BA44	Right	Auditory cortex	24	BA24	Right	Ventral anterior cingulate cortex	-2.140

*Negative coefficients indicate higher connectivity in the minor allele carrier group (GA + AA) compared to the homozygous for major allele group (GG). Positive coefficients indicate higher connectivity in the GG compared to the GA + AA group.

maturation but is integral to gene expression regulation mechanism. Introns may generate RNA molecules essential for the transcription regulation, such as long non-coding RNA (lncRNA) and microRNA (miRNA), and/or may contain regulatory elements, such as enhancers, alternative transcription start sites (TSSs), and transcription factor binding sites (TFBSs). Consequently, the rs8085464 likely does not exert direct effects on protein function but might have regulatory functions, being localized within a TFBS for the *HOXB2* and *NHLH1* transcription factors creating cascades of gene expression essential for the development, and/or be in linkage disequilibrium (non-random association of alleles at different loci influenced by many factors, such as the rate of genetic recombination and mutation, population structure, selection, and genetic drift) with another, “true” causal variant. It is known that rs8085464 is evolutionarily conserved (Genome Evolutionary Rate Profiling Rejected Substitutions [GERP RS] score = 340), with 0 indicating no selective/conservation constraints; Cooper et al., 2005), consistent with the observation that disease-associated SNPs are enriched for conserved regions (Lindblad-Toh et al., 2011).

As mentioned in the Introduction, relatively little is known about the function of the protein encoded by *SETBP1* and its role in neural development, yet several independent case studies report *SETBP1* haploinsufficiency causing expressive DLD (Filges et al., 2011; Marseglia et al., 2012), and the GWAS findings (Kornilov et al., 2016) suggest that it might be a key player in the regulation of the development of cortical language networks. This suggestion is supported by the present finding that rs8085464 predicted the extent to which these networks were cohesive in the beta band in a mixed sample of AZ children with and without DLD. Event-related network cohesion was negatively related to children’s language development, in particular on the task that involved comprehension of syntactically and semantically complex sentences, which imposes heavy demands on working memory resources.

The negative association between network cohesion and language comprehension is in concert with the studies that showed alterations of interhemispheric connectivity to be important predictors of language impairment in preterm children (Northam et al., 2012). In that study, increased cortical language network cohesion during word processing was associated with depressed language development scores, suggesting that increased cohesion within the cortical language network may be a neural marker of language impairment. Studies also demonstrated global functional overconnectivity in individuals with ASD (Keown et al., 2013; Supekar et al., 2013). However, for ASD, patterns of anomalous brain connectivity are rather complex, with underconnectivity having also been observed, and overconnectivity possibly limited to local connections (Courchesne & Pierce, 2005) or be age dependent (see review in Rudie & Dapretto, 2013).

Dynamic network cohesion quantifies the extent to which a group of interacting nodes displays similar behavior and is resistant to disruptions of connectivity by removal of the connections between them. An increase in network cohesion may be due to an increase in the number of independent and frequently indirect redundant information flow pathways in the network (White & Harary, 2001). The increased cohesion associated with a decline in language processing skills we found may indicate such redundant information flow pathways in children with DLD.

For example, we found the carriers of the derived rs8085464 allele to have enhanced functional cohesion between the right STG, an area, the left homologue of which contains the classic Wernicke area and which is known to be involved in word comprehension (Liu & Liu, 2019), and the right auditory cortex. This group also had increased connectivity between the left extrastriate cortex (an area involved in visual attention) and right supramarginal gyrus, the left homologue of which is involved in visual word recognition, particularly when the focus is on the sound form rather than meaning (Stoekel, Gough, Watkins, & Devlin, 2009). These findings might be indicative of weaker functional hemispheric lateralization for language (e.g., as has been demonstrated for adults with a history of DLD; Whitehouse & Bishop, 2008).

Finally, the carriers of the derived rs8085464 allele also had increased cohesion between the right auditory cortex and the vACC, as well as the left vACC and the right STG. ACC is functionally complex and is involved in both emotional and cognitive control (Tang et al., 2019). Increased connectivity between vACC and the areas involved in word processing is suggestive of a less localized (more diffuse) pattern of functional connectivity and/or greater engagement of effortful control during the processing of linguistic information associated with the derived rs8085464 allele.

This is in accord with the proposal that greater effort involved in coping with environmental challenges is the basis for the association between increased within-network coherence and a decrement in performance (Scult, 2017). This effect was previously demonstrated in research on emotional processing (Young et al., 2019), where the primary indicator of arousal was correlated with network cohesion within the “salience network” (the network associated with orienting attention to relevant stimuli). Our results seem to indicate that being a carrier of the derived rs8085464 allele predisposes one to weaker language processing skills requiring a greater allocation of resources and greater engagement of systems outside of the typical language network during language processing. This conclusion is strengthened by the observation that the patterns of heightened functional connectivity discussed above was found in the alpha band (~8–12 Hz). Oscillatory activity in this band during cognitive processing is thought to mark inhibition of sensory stimuli, inward direction of attention, and integration between brain areas (Boudewyn & Carter, 2018).

Another interesting aspect of our findings was an association between the rs8085464 genotype and network cohesion in the beta (13–30 Hz) EEG band. Previous studies linked oscillations in the beta frequency band with language processing (Lewis, Lemhöfer, Schoffelen, & Schriefers, 2016; Lewis, Schoffelen, Hoffmann, Bastiaansen, & Schriefers, 2017; Weiss & Mueller, 2012). Beta oscillations play a key role in the generation of the N400 component (Lin Wang et al., 2012) and were robustly elicited in the paradigm we used in our study (Kornilov et al., 2015). Importantly, left-lateralized beta activity has been proposed to serve as a biomarker of language hemispheric dominance in children as well as adults (Spironelli & Angrilli, 2010).

Although we did not observe significant differences between the two rs8085464 genotype groups with respect to the localization of the source of neural oscillations, these differences might be diffuse and possibly better captured by alterations in the connectivity patterns observed in our study. The pattern of associations between beta cohesion and language processing observed in our study, namely, the observation that atypically high beta cohesion was associated with poorer receptive vocabulary and lower ability to comprehend complex sentences, converge with previous research suggesting that beta oscillations and beta desynchronization are key players in higher-order cognitive and linguistic processing, including attentional processing and semantic memory access (Bastiaansen & Hagoort, 2006). These findings are in concert with recent findings of atypical neural responses in attentional/working memory as well as lexical/semantic processing tasks in children with DLD (Malins et al., 2013; Stevens, Sanders, & Neville, 2006), including the present sample of AZ school-aged children (Kornilov et al., 2014; Kornilov et al., 2015).

In sum, our results suggest that *SETBP1* might be an important regulator of the development of functional cortical networks involved in spoken language processing, and that alterations of the organization of functional connectivity in the beta band might modulate its effects on language development. This conclusion is tentative given the limited sample size of this study; the reported effects should be treated cautiously, pending future replication. Furthermore, because of the unique nature of our study population, our conclusions should be tested in other populations to ensure its generalizability.

Future studies should also examine the differences between event-related and resting-state coherence in terms of their relationship to language development and associations with polymorphisms in the *SETBP1* and other DLD candidate genes. Nevertheless, the current study demonstrates the utility of using a network connectomics approach to studying the neurobiological bases of DLD and highlights the utility of topological network measures as endophenotypes that capture the specifics of neural processing of language in DLD and other neurodevelopmental disorders.

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Notes

1. The term most commonly used in the literature to refer to a developmental (rather than acquired) disorder of language development in the absence of obvious explanatory factors is specific language impairment (SLI). However, SLI is not a clinical diagnostic category, and the “specific” nature of this disorder is hotly debated. We would like to note that all children classified as DLD in this study would satisfy the conventionally used inclusion and exclusion criteria for both SLI and DSM-V DLD (American Psychiatric Association, 2013).

2. As was pointed out by an anonymous reviewer, the range of density provides additional information regarding the topological change in the network (see Hosseini et al., 2012). Hence, in further studies it would be interesting to test the association in other network densities other than only those above the threshold of 54% presented in the study.

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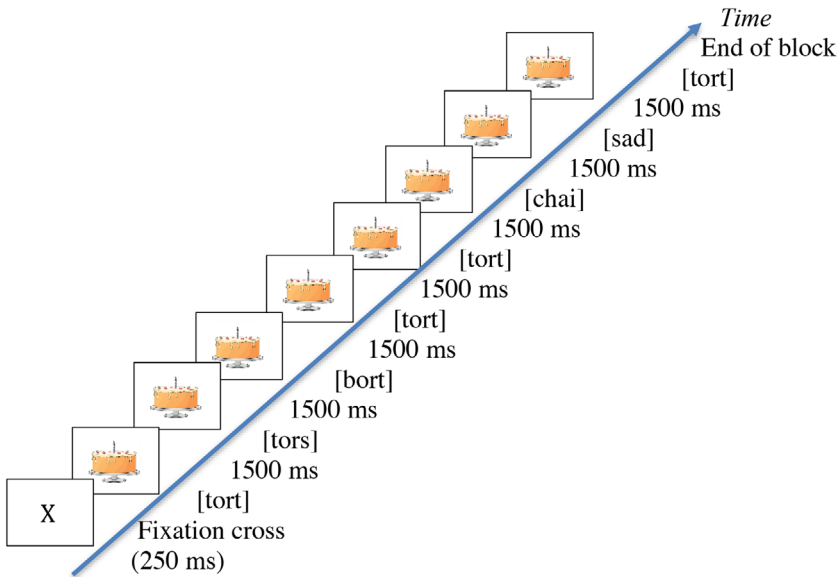
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Appendix

Figure A1. Experimental design.



NATALIA RAKHLIN is an Associate Professor of Linguistics at Wayne State University, who specializes in child language acquisition and developmental language disorders. Her work bridges traditional disciplinary boundaries in search of the processes and systems underlying difficulties with language acquisition in children with language disorders, as well as genetic and environmental factors that influence differential outcomes in language development.