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Topological properties of large-scale structural brain networks in children with familial risk for reading difficulties

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ABSTRACT

Developmental dyslexia is a neurobiological deficit characterized by persistent difficulty in learning to read in children and adults who otherwise possess normal intelligence. Functional and structural connectivity data suggest that developmental dyslexia could be a disconnection syndrome. However, whether abnormalities in connectivity exist in beginning readers at-risk for reading difficulties is unknown. Using graph-theoretical analysis, we investigated differences in global and regional topological properties of structural brain networks in 42 beginning readers with (FH+) and without (FH−) familial risk for reading difficulties. We constructed separate structural correlation networks based on measures of surface area and cortical thickness. Results revealed changes in topological properties in brain regions known to be abnormal in dyslexia (left supramarginal gyrus, left inferior frontal gyrus) in the FH+ group mainly in the network constructed from measures of cortical surface area. We also found alterations in topological properties in regions that are not often advertised as dyslexia but nonetheless play important role in reading (left posterior cingulate, hippocampus, and left precentral gyrus). To our knowledge, this is the first report of altered topological properties of structural correlation networks in children at risk for reading difficulty, and motivates future studies that examine the mechanisms underlying how these brain networks may mediate the influences of family history on reading outcome.

Introduction

Developmental dyslexia, the most common form of all learning disabilities, is a neurobiological deficit characterized by persistent difficulty in learning to read (Shaywitz, 1998; Shaywitz et al., 2003). While the neurobiological etiology of developmental dyslexia is a matter of debate, the most accepted model, derived from both functional and structural neuroimaging studies reporting impairment in the left temporo-parietal (including the inferior parietal lobule) and occipito-temporal regions, suggests a dysfunction in neural circuits associated with phonological and orthographic processing (Eckert et al., 2005; Hoeft et al., 2006, 2007; van der Mark et al., 2009) [see (Maisog et al., 2008; Richlan et al., 2009) for a review]. These regions are also abnormal in beginning readers at familial risk for reading difficulties (Brem et al., 2010; Maurer et al., 2007; Raschle et al., 2011, 2012; Specht et al., 2009).

Recent data suggest that developmental dyslexia could be a disconnection syndrome. Specifically, individuals with developmental dyslexia have shown disrupted functional connectivity in the language-dominant left-hemisphere (Horwitz et al., 1998; Pugh et al., 2000; van der Mark et al., 2011), altered effective connectivity between the left-hemisphere language regions and bilateral frontal regions (Cao et al., 2008), and decreased fractional anisotropy in the left-hemisphere white matter tracts, fronto-temporal and temporo-parietal white matter (Frye et al., 2010a, 2010c; Odegard et al., 2009; Steinbrink et al., 2008). This body of evidence suggests that developmental dyslexia is associated with alterations in connectivity of diffuse regions that might affect the topological properties of brain networks.

An abundance of research has shown that dyslexia is highly familial [see (Petryshen and Pauls, 2009) for a review]. Children with family history of reading difficulties have a 34–65% chance of developing dyslexia (Pennington and Lefly, 2001). Therefore, alterations in brain networks might be evident in beginning readers at familial risk for reading difficulties. In the present study, we applied graph theoretical analysis to investigate differences in global and regional topological properties of structural brain networks in children with and without familial risk for reading difficulties as they were beginning formal

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reading instruction in kindergarten. The unique feature of graph-theoretical analysis, compared with traditional connectivity analysis, is that it provides a unique framework to directly test the differences in topological properties of brain networks. Coordinated variations in brain morphology have been proposed as a valid measure to infer large-scale structural brain networks (He et al., 2007). The structural networks constructed from morphometric correlations of cortical volume, thickness, and surface data are consistent with those constructed from tract-tracing data (Bernhardt et al., 2008; He et al., 2007; Lerch et al., 2006; Sanabria-Diaz et al., 2010), and have been shown to follow small-world characteristics in healthy individuals (Bassett et al., 2008; Chen et al., 2008; Fan et al., 2011; He and Evans, 2010). A small-world architecture reflects a network that is simultaneously highly segregated and integrated and allows more efficient rates of information processing and learning (Simard and Nadeau, 2005). Since quantitative description of small-worldness has been presented for brain networks (Watts and Strogatz, 1998), a large number of studies have shown alterations in topological properties of brain structural networks associated with Alzheimer's disease, schizophrenia, and multiple sclerosis (Bassett et al., 2008; He et al., 2008, 2009).

While still under debate, recent evidence suggests that the two independent measures of cortical volume, i.e. cortical surface area and thickness, may be driven by distinct cellular mechanisms that are genetic in their origins (Eyler et al., 2011; Kapellou et al., 2006; Rimol et al., 2010; Sanabria-Diaz et al., 2010). Perhaps driven by these effects, previous neuroimaging studies found more pronounced association between alterations in surface-area measures, rather than thickness measures, and history of dyslexia (Frye et al., 2010b) as well as severity of family history of reading difficulties (Black et al., 2012). Thus, we constructed separate structural networks based on surface area and cortical thickness data to further account for these mechanistic/genetic differences. We predicted alterations in topological properties in the left-hemisphere reading network that would be more pronounced in the surface area network.

Materials and Methods

Participants

A total of 42 (22 males, 38 right-handed) healthy, native English-speaking children (aged 5.59 ± 0.39) participated in this study. Children (with and without family history of reading difficulties based originally on parental self-report) were recruited from local newspapers, school mailings (including both schools for children with learning disabilities and conventional schools), flyers, and mother's clubs. The participants' data used in this study is a subset of data used in our recent study (Black et al., 2012).

Family history of reading difficulty was operationally defined as parental report of reading disability in a first-degree relative (either biological parent or sibling). The children did not have any neurological or psychiatric disorders, were not on medication, and had no contraindications to MRI. The Stanford University Panel on Human Subjects in Medical Research approved the study and written informed consent was obtained from the parent/legal guardian of participants. Children were between 5 and 6 years of age and hence did not complete an assent form.

Assessment of family history and behavioral, cognitive and environmental measures

Once recruited, as in previous literature, family risk was assessed using the Adult Reading History Questionnaire (ARHQ) (Lefly and Pennington, 2000). An ARHQ cut-off score of 0.39 was used to determine the existence of family history based on previous literature (Black et al., 2012; Maurer et al., 2003, 2007, 2009) and in our prior paper where we established reliability and performed receiver operating characteristic (ROC) analysis using Test of Word Reading Efficiency Phonemic Decoding Efficiency (TOWRE PDE), a timed measure of reading non-words (Black et al., 2012). There were no significant correlations identified between ARHQ scores (maternal and paternal) and demographic information such as socio-economic status (SES) (or any of the individual factors such as education and occupation) or percentage of time spent with child generally and related to educational activities specifically (all p's > 0.05) [refer to (Black et al., 2012) for the details].

SES was measured based on the procedure and questionnaire of Noble et al. (2006). Parents completed a brief questionnaire with items related to parental education, occupation and income. Parental education was defined as the average education of any parents (and step-parents/guardians) in the home. We used the 9-point Hollingshead Index Occupational Status Scale (Bornstein and Bradley, 2003) to score parental occupation, and used only the highest score of any parent, stepparent or guardian in the home. The income score was defined as the total family income divided by the official federal poverty threshold for a family of that size. Thus, for each family, an income-to-needs ratio was computed whereby the total family income was divided by official poverty threshold. Finally, a composite SES score was calculated for each child by factor analyzing the three scores (parental education, occupation, and income) using principal component analysis. A single principal component emerged, accounting for 57.1% of the variance. SES in our study refers to the factor loading score (mean 0; SD 1) that was computed for each child and entered into our subsequent analyses (Table 1).

In addition, the Home Observation for Measurement of the Environment (HOME) Inventory (Caldwell and Bradley, 1984) was used to measure the quality and quantity of stimulation and support available to the child in the home environment. The focus of HOME is on the child in the environment, child as a recipient of inputs from objects, events, and transactions occurring in connection with the family surroundings. We did not find any significant difference between groups in learning materials, language stimulation and academic stimulation in the home (all p's > 0.05) (Table 1).

Among those with a family history (FH+ group, N = 22, age: mean, 5.65; SD, ± 0.46, 3 left-handed), 13 children had paternal history, 9 had maternal history. In those without a family history (FH− group, N = 20, age: mean, 5.51; SD, ± 0.30, 1 left-handed), there was no reported history of reading impairment in any family member and both parents' ARHQ were less than 0.39. The demographics of the two family history groups (FH+ vs. FH−) (e.g., child age, parent age, SES, maternal and paternal education level, percentage of time spent with mother and father overall and related to education) were not significantly different (Table 1).

For parents without reading disabilities (as based on ARHQ less than 0.39) there were no significant differences between ARHQ scores and between the TOWRE PDE scores of the two groups (those labeled as FH+ and FH− but all without indication of reading disabilities as based on ARHQ less than 0.39) (Table 1).

It is noteworthy that the FH+ group showed significantly lower scores in phonological awareness, letter knowledge and verbal IQ compared with FH− group. These measures are known as predictors of reading outcome (Lyytinen et al., 2006, 2008; Puolakanaho et al., 2007), and hence it is no surprise that these measures were significantly lower in the FH+ group.

MRI data acquisition

Imaging data were acquired at the Richard M. Lucas Center for Imaging at Stanford University. Imaging data was acquired using GE Healthcare 3.0 Tesla 750 scanner 20.x software revision and an 8-channel phased array head coil (GE Healthcare, Waukesha, WI). Images acquired included an axial-oblique 3D T1-weighted sequence with the following parameters: fast spoiled gradient recalled echo