Brain and Language 175 (2017) 11–17

Contents lists available at ScienceDirect

Brain and Language

journal homepage: www.elsevier.com/locate/b&l

Changes in intrinsic local connectivity after reading intervention in children with autism

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ARTICLE INFO

Keywords:
ASD
Intervention
Local connectivity
Translational neuroscience
Reading

ABSTRACT

Most of the existing behavioral and cognitive intervention programs in autism spectrum disorders (ASD) have not been tested at the neurobiological level, thus falling short of finding quantifiable neurobiological changes underlying behavioral improvement. The current study takes a translational neuroimaging approach to test the impact of a structured visual imagery-based reading intervention on improving reading comprehension and assessing its underlying local neural circuitry. Behavioral and resting state functional MRI (rs-fMRI) data were collected from children with ASD who were randomly assigned to an Experimental group (ASD-EXP; n = 14) and a Wait-list control group (ASD-WLC; n = 14). Participants went through an established reading intervention training program (Visualizing and Verbalizing for language comprehension and thinking or V/V; 4-h per day, 10-weeks, 200 h of face-to-face instruction). Local functional connectivity was examined using a connection density approach from graph theory focusing on brain areas considered part of the Reading Network. The main results are as follows: (I) the ASD-EXP group showed significant improvement, compared to the ASD-WLC group, in their reading comprehension ability evidenced from change in comprehension scores; (II) the ASD-EXP group showed increased local brain connectivity in Reading Network regions compared to the ASD-WLC group post-intervention; (III) intervention-related changes in local brain connectivity were observed in the ASD-EXP from pre to post-intervention; and (IV) improvement in language comprehension significantly predicted changes in local connectivity. The findings of this study provide novel insights into brain plasticity in children with developmental disorders using targeted intervention programs.

1. Introduction

Language and communication deficits are a core feature of autism spectrum disorders (ASD) (American Psychiatric Association, 2013), which usually extend to impairments in reading comprehension (Nation, Clarke, Wright, & Williams, 2006). These deficits in reading comprehension need early identification and intervention in order to ameliorate the impact on academic achievement. There seems to exist a demonstrated discrepancy between expected achievement (based on intellectual functioning) and actual achievement in at least one of spelling and word reading skills in children ASD (Brown, Oram-Cardy, & Johnson, 2013; Estes, Rivera, Bryan, Cali, & Dawson, 2011). Behavioral studies have reported high-functioning children with ASD having problems with different aspects in higher order processing skills (reading comprehension) including pragmatics, semantics, and phonological processes (Groen et al., 2010; Williams, Botting, & Boucher, 2008), while more basic processing skills (decoding and word identification) remain relatively intact (Norbury & Nation, 2011).

Neuroimaging research has demonstrated alterations in the synchronization of brain activity underlying different aspects of language comprehension in individuals with ASD. These include areas such as semantics and integration of social information (Groen et al., 2010), lexical over thematic processing (Just, Cherkassky, Keller, & Minshew, 2004), and pragmatics and syntax (Groen, Zwiers, van der Gaag, & Buitelaar, 2008). In typically developing (TD) individuals, the brain regions that are primarily activated during reading comprehension show greater left hemisphere than right hemisphere activation. The left inferior frontal gyrus (LIFG) or Broca's area has generally been

Abbreviations: ASD, autism spectrum disorder; fMRI, functional magnetic resonance imaging; rs-fMRI, resting state functional MRI; ASD-EXP, Experimental group; ASD-WLC, Waitlist control group; LIOG, left inferior occipital gyrus; LFFG, left fusiform gyrus; LSTG, left superior temporal gyrus; LPCG, left precentral gyrus; LSPL, left superior parietal lobule; LSMA, left supplementary motor area; LIFG, left inferior frontal gyrus; LMFG, left middle frontal gyrus; LTHAL, left thalamus; ADOS, Autism Diagnostic Observation Schedule; ADI, Autism Diagnostic Interview-Revised; SORT-R, Slosson Oral Reading Test – Revised; GORT-4, Gray Oral Reading Test – Fourth Edition; WASI, Wechsler Abbreviated Scale of Intelligence; V/V, Visualizing and Verbalizing

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http://dx.doi.org/10.1016/j.bandl.2017.08.008
Received 26 March 2017; Received in revised form 30 July 2017; Accepted 27 August 2017
0093-934X/ Published by Elsevier Inc.

implicated in semantic processing, and the left posterior superior temporal gyrus (LpSTG) or Wernicke's area in lexical access (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). Other regions such as the left posterior middle temporal gyrus (LMTG, accessing word meaning while reading), superior temporal sulcus (STS, differential activation for listening over reading), and middle frontal gyrus (MFG, single word reading) are also found to play a role in reading comprehension (Tomasi & Volkow, 2012). Adults with ASD, on the other hand, seem to recruit right hemisphere homologues of language regions (Eyler, Pierce, & Courchesne, 2012; Mason, Williams, Kana, Minshew, & Just, 2008; Redcay & Courchesne, 2008), in addition to brain regions primarily involved in visuospatial processing such as fusiform gyrus (BA19, 37), medial parietal cortex (BA7), and posterior MTG (BA21) (Samson, Mottron, Soulieres, & Zeffiro, 2012). It is worth mentioning that the some of these findings of recruitment of right hemisphere regions have also been reported in children with ASD (Eyler et al., 2012; Redcay & Courchesne, 2008), while decreased activation in language regions are mostly reported in adults with ASD (Harris et al., 2006; Just et al., 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2006) Thus, the neural response to language comprehension in ASD is different from TD individuals with additional recruitment of right hemisphere and relatively posterior cortical areas. This is also suggestive of a developmental trajectory of difficulties seen in children with ASD, including recruitment of right hemisphere regions in addition to decreased activation in core left-hemisphere language cortical areas (see Herringshaw, Ammons, DeRamus, & Kana, 2016 for a more in-depth review).

While task-based fMRI studies are important in addressing the recruitment of brain regions in relation to cognitive/linguistic demands, these are also constrained by factors such as subject compliance, response time, and variations in task performance in clinical populations such as ASD (Maximo, Cadena, & Kana, 2014). The advent of resting state functional MRI (rs-fMRI) has marked a paradigm shift in the field of neuroimaging (Raichle, 2009) and has opened new doors for understanding the neurobiology of complex disorders. More recently, studies have used rs-fMRI to assess brain functioning underlying reading comprehension in TD individuals (Koyama et al., 2010, 2011; Tomasi & Volkow, 2012). Previous fMRI studies have identified a set of brain regions that activate during reading comprehension (Lohmann et al., 2010; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Koyama and colleagues expanded upon this work to identify the extent of this activation across children and adults (Koyama et al., 2010, 2011). These regions were described as the "Reading Network", which encompasses inferior occipital gyrus, fusiform gyrus, superior temporal gyrus (STG), pre/postcentral gyrus, intraparietal sulcus (IPS), supplementary motor area (SMA), inferior frontal and middle frontal gyrus (IFG, MFG), and thalamus (THAL).

Early intervention studies targeting reading comprehension deficits in ASD have been sparse and have only examined behavioral performance with no accompanying neurobiological measures (El Zein, Solis, Vaughn, & McCulley, 2014). Research examining behavioral interventions in combination with neural level inferences are needed to better understand the observed language comprehension deficits in ASD and to address them at the neurobiological level (Calderoni et al., 2016). In ASD, two recent functional neuroimaging studies from our group (*the participants of which are the same as in the results reported here*) have shown increased brain activation and long-distance functional connectivity as a result of behavioral intervention in regions associated with language processing (Murdaugh, Deshpande, & Kana, 2016; Murdaugh, Maximo, & Kana, 2015). In addition, such changes in the neural indices were correlated with improvement in language comprehension. The findings from these studies underscore possible brain plasticity and the need for appropriate intervention to effect changes in brain functioning in order to facilitate better language comprehension. In addition, these findings provide promising avenues for future intervention-based neuroimaging studies in autism.

While changes in brain activation and "long-distance" functional connectivity were observed in our previous studies, it remains unknown whether these changes will also be reflected at a smaller scale. Despite significant progress in examining brain network connectivity in ASD over the past few years (Kana, Uddin, Kenet, Chugani, & Muller, 2014), the majority of findings of atypical brain connectivity in ASD have focused on "long-distance" connectivity (Nair et al., 2014). While these findings are important, local connectivity (examining the BOLD signal between parts of cortex that are spatially near each other) also provides valuable information about the specialization and integration of brain function. While there has been limited literature on local connectivity in ASD using fMRI, these have elucidated rather interesting findings on children (Keown et al., 2013; Shukla, Keehn, & Muller, 2010), adolescents (Paakki et al., 2010), individuals from all ages (Di Martino et al., 2014), developmental trajectories (Dajani & Uddin, 2016), and methodological approaches (Maximo, Keown, Nair, & Muller, 2013; Nair et al., 2017). Local connectivity is a relatively ill-defined concept, which can encompass a spatial scale from a few microns to millimeters and even to centimeters. For the proposed study, local connectivity will be defined as the BOLD correlations between a reference voxel and its nearest neighbors within a 14 mm radius (see Section 2.4). Functional differences in local connectivity in individuals with ASD may underlie anatomical and microstructural differences. Evidence from postmortem studies suggests that cytoarchitectonic abnormalities exist in cerebral cortex in ASD (Amaral, Schumann, & Nordahl, 2008). In particular, tighter packing of cortical minicolumns with reduced lateral inhibition (Casanova & Trippe, 2009) could likely affect local connectivity, and may result in a "hyper-specific brain" in individuals with ASD (Casanova, Buxhoeveden, Switala, & Roy, 2002; Casanova et al., 2006).

In the present study, we examined intrinsic rs-fMRI data before and after a reading intervention program to assess changes in intrinsic local functional connectivity of the Reading Network in a group of high-functioning children with ASD. The intervention used in this study (Visualizing and Verbalizing for Language Comprehension and Thinking; V/V) has been found to be successful in children with reading disorders, and our group has recently shown that improvement in reading comprehension skills due to this intervention correlated with changes in functional brain activation and functional connectivity (Murdaugh et al., 2015, 2016). This intervention is a practical application of the principles of dual coding theory, which posits that cognition involves the activity of two distinct subsystems, a verbal system specialized for dealing directly with language, and a non-verbal (imagery) system specialized for dealing with non-linguistic objects and events (Pavio, 2007; Sadoski & Paivio, 2001). The intervention relies primarily on visual imagery, which has important implications considering that visual processing is an area that is relatively spared in relation to general intelligence in individuals with ASD (Joseph, Keehn, Connolly, Wolfe, & Horowitz, 2009). In addition, visual imagery can aid in developing both oral and reading comprehension (Bell, 1991a, 1991b).

We hypothesized that children with ASD who participated in the reading intervention would show stronger intrinsic local functional connectivity in relatively posterior regions of the Reading Network. This study is novel in its focus on translational neuroimaging and the findings will have a significant impact on understanding and in applying targeted behavioral interventions to children with ASD.

2. Methods

2.1. Participants

Twenty-eight children with ASD (mean age = 10.5 years, SD = 1.5), who underwent two fMRI sessions, 10 weeks apart, were randomly assigned to participate in the V/V intervention either between their first and second imaging sessions (ASD-EXP; n = 14) or after completing both imaging sessions (ASD-WLC; n = 14). Children were determined to have an ASD diagnosis by a licensed clinical