Research in Autism Spectrum Disorders 7 (2013) 221–234

Contents lists available at SciVerse ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

Corpus callosum area in children and adults with autism

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ARTICLE INFO

Article history:
Received 3 May 2012
Received in revised form 17 September 2012
Accepted 21 September 2012

Keywords:
Autism
Corpus callosum area
Development
MRI

ABSTRACT

Despite repeated findings of abnormal corpus callosum structure in autism, the developmental trajectories of corpus callosum growth in the disorder have not yet been reported. In this study, we examined corpus callosum size from a developmental perspective across a 30-year age range in a large cross-sectional sample of individuals with autism compared to a typically developing sample. Midsagittal corpus callosum area and the 7 Witelson subregions were examined in 68 males with autism (mean age 14.1 years; range 3–36 years) and 47 males with typical development (mean age 15.3 years; range 4–29 years). Controlling for total brain volume, increased variability in total corpus callosum area was found in autism. In autism, increased midsagittal areas were associated with reduced severity of autism behaviors, higher intelligence, and faster speed of processing ($p = 0.003$, $p = 0.011$, $p = 0.013$, respectively). A trend toward group differences in isthmus development was found ($p = 0.029$, uncorrected). These results suggest that individuals with autism benefit functionally from increased corpus callosum area. Our cross-sectional examination also shows potential maturational abnormalities in autism, a finding that should be examined further with longitudinal datasets.

1. Introduction

A central long-range goal of in vivo magnetic resonance brain imaging research in autism is to help identify and describe neuropathological changes during development that are linked to the disorder, further understand inter-individual

Abbreviations: CC, corpus callosum; TBV, total brain volume.

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http://dx.doi.org/10.1016/j.rasd.2012.09.007

differences in severity, course, and outcome, and discover biological targets for the development of specific treatments (Lainhart & Lange, 2010). Multiple lines of evidence suggest that one of the brain structures most commonly affected in autism is the corpus callosum (CC), the major white matter fiber system connecting the cerebral hemispheres. It remains unclear if CC pathology in autism is primary or secondary, or how risk genes, environmental factors and daily life experience may affect CC development. For autism imaging research to move closer to its goal, several basic uncertainties about pathological development of CC size in autism need to be addressed.

Many studies have suggested that structural pathology contributes to cortical underconnectivity in autism and that there is reduced CC area, volume, and white matter (WM) density in autism compared to typical development (Alexander et al., 2007; Casanova et al., 2011, 2009; Chung, Dalton, Alexander, & Davidson, 2004; Frazier & Hardan, 2009; Freitag et al., 2009; Hardan et al., 2009; He, Karsch, & Duan, 2008; Hong et al., 2011; Keary et al., 2009; Kilian et al., 2008; Waiter et al., 2005) with a few exceptions (Elia et al., 2000; Kilian et al., 2008; McAlonan et al., 2002; Rice et al., 2005; Tepest et al., 2010). Genetic research aimed to benefit individuals with autism depends more strongly on individual phenotypes than it does on clinical group means. Although decreased mean CC size is one of the most replicated findings in autism neuroimaging research, the CC size distribution has not been examined in detail and the proportion of affected individuals with abnormally small CC not yet reported. Previous reports show that not all individuals with autism present with larger head circumferences, increased numbers of prefrontal neurons (Courchesne et al., 2011; Lainhart & Lange, 2011), and abnormalities in CC microstructure (Alexander et al., 2007); such is likely the case for small CC size. Decreased CC size appears most evident when it is considered relative to total brain volume (TBV; Boger-Megiddo et al., 2006; Just, Cherkassky, Keller, Kana, & Minshew, 2007), though an exception has been found in a high-functioning adult sample (Tepest et al., 2010). However, scaling CC size to TBV in autism and the age-invariance of such scaling have not yet been examined. Similarly, although studies report atypically decreased mean CC size in individual samples of young children, older children, adolescents, and adults with autism, information about age-related changes in CC area is limited (Chung et al., 2004). Other investigators have shown the danger of assuming a typical relationship between age and changes in WM tracts in individuals with developmental neuropsychiatric disorders (Jones et al., 2006).

Clinico-pathological studies using structural MRI have suggested a relationship between CC size and clinical features of autism (Hardan et al., 2009; Keary et al., 2009). Functional magnetic resonance imaging (fMRI) studies have shown correlations between the size of CC subregions and functional connectivity measured during tasks that tap cognitive skills frequently impaired or relatively preserved in autism (Damarla et al., 2010; Just et al., 2007; Just, Cherkassky, Keller, & Minshew, 2004; Kana, Keller, Cherkassky, Minshew, & Just, 2009, 2006; Keary et al., 2009; Mason, Williams, Kana, Minshew, & Just, 2008; Schipul, Williams, Keller, Minshew, & Just, 2011). Nonetheless, the relation between severity of core diagnostic features of autism, intelligence quotient and CC size from childhood into adulthood is not yet known.

In this study we examined CC size from a developmental perspective across a 30-year age range in a large cross-sectional sample of individuals with autism. Consistent with the underconnectivity theory of CC involvement in autism, we hypothesized (1) smaller mean CC size in autism, especially when considered relative to TBV, and (2) association of small CC size with more severe core features of autism, lower IQ, and slower processing speed. In addition, we predicted that there are (3) atypical age-related changes in CC size, and (4) differences in the distribution of CC area in the autism group.

2. Materials and methods

2.1. Participants

Sixty-eight (68) individuals with autism spectrum disorder (lifetime diagnosis autistic disorder in 62, PDD-NOS in 6) and 47 typically developing controls were selected from a large, ongoing neuroimaging study. Participants were selected if they met the following inclusion criteria: male; age between 3 and 36 years; performance IQ $\geq$ 70; quantitative handedness score, which ranges from completely left-handed ($-$100) to completely right-handed (+100), $\geq$0; and very good quality of scan at the 1st wave of data collection. The inclusion criteria were chosen to decrease heterogeneity other than age in the autism sample and potential associated neuroanatomic heterogeneity, and, as a result, increase statistical power. Handedness in particular may be associated with CC morphology in both typical and atypical development (Gilliam et al., 2011; Witelson, 1985).

Diagnoses of autism were based on the Autism Diagnostic Interview-Revised [ADI-R; (Lord, Rutter, & Le Couteur, 1994)], Autism Diagnostic Observation Schedule-Generic [ADOS-G; (Lord et al., 2000)], and DSM-IV (American Psychiatric Association, 1994). Participants were excluded if history, Fragile-X gene testing, karyotype, or examination identified medical causes of autism or other medical conditions that could affect brain morphometry, such as history of severe head injury, hypoxia-ischemia, seizures, and other neurologic disorders. Forty-one percent of the autism participants were taking psychotropic medication (28% serotonin reuptake inhibitor, 13% stimulant, 9% neuroleptics, 1.5% atypical agents, 16% multiple medications). Possible effect of psychotropic use on CC size was explored in the data analysis.

Control participants underwent neuropsychological testing, standardized psychiatric assessments (Leyfer et al., 2006), and were assessed with the ADOS-G (Lord et al., 2000) to confirm typical development. Controls with any history of developmental, learning, cognitive, neurological, or neuropsychiatric conditions were excluded. All autism and control participants were recruited, assessed, and scanned at the University of Utah.