Psychiatry Research: Neuroimaging 234 (2015) 15–24

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Reduced cortical thickness and its association with social reactivity in children with autism spectrum disorder

Julia Richter [a,b,1], Romy Henze [a,b,*,1], Kilian Vomstein [a,c], Bram Stieltjes [a], Peter Parzer [b], Johann Haffner [b], Daniel Brandeis [c], Luise Poustka [c,d]

[a] Department of Radiology, German Cancer Research Center, Heidelberg, Germany
[b] Department of Child and Adolescent Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Heidelberg, Germany
[c] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
[d] Department of Child and Adolescent Psychiatry, Medical University of Vienna, Austria

ARTICLE INFO

Article history:
Received 11 November 2014
Received in revised form
19 May 2015
Accepted 25 June 2015
Available online 22 August 2015

Keywords:
Autism spectrum disorder
Magnetic resonance imaging (MRI)
Brain
Neuroanatomy
Social impairment
Theory of mind
Surface analysis

ABSTRACT

Symptomatology and behavioral characteristics in autism spectrum disorders (ASD) have increasingly been linked to abnormalities in early brain growth patterns of affected children. Studies investigating specific components of gray matter structure, such as cortical thickness (CT), have produced conflicting results, and have rarely included additional measures of social impairment. In the present study, we applied a surface-based whole brain analysis to investigate CT in a sample of 36 pre-adolescent children [18 subjects with ASD (IQ mean: 111) and 18 healthy controls (IQ mean: 112.8), age range 6–12 years]. The CT analysis revealed widespread, but mostly left-hemispheric thinning in frontal, temporal, parietal and occipital brain areas related to the theory-of-mind network and the heteromodal association cortex. In an exploratory analysis, CT was observed to be differently associated with social impairment in children with ASD compared with typically developing children. The affected neuroanatomical regions are related to characteristic deficits in language, cognition and behavior that are often observed in the disorder. The relationship between social impairment and CT in children with ASD and controls seems to indicate aberrant developmental trajectories in ASD emerging early in life.

1. Introduction

Autism spectrum disorder (ASD) is a persisting neurodevelopmental condition with early onset, characterized by a triad of impairments in reciprocal interaction and communication as well as repetitive and restricted interests and activities. ASD has a strong genetic underpinning (DiCicco-Bloom et al., 2006) and is a highly heterogeneous disorder, with multiple causes and pathways leading to a broad range of characteristic symptoms. Findings from neurobiological research strongly suggest structural and functional changes in the central nervous system to be responsible for the characteristic symptomatology in ASD. There is now strong evidence that neuroanatomical alterations in ASD are not confined to single brain regions, but rather reflect disturbances of wider neural systems and networks (Kana et al., 2011; Schipul et al., 2011; Just et al., 2012). The well-replicated finding of early brain overgrowth (Courchesne et al., 2001, 2007; Hazlett et al., 2011) has led to a strong interest in studies on brain growth trajectories in ASD from birth. In the first longitudinal magnetic resonance imaging (MRI) study on early cortical development in ASD, Schumann et al. (2010) detected abnormal growth rates of both regional gray matter (GM) and white matter (WM) in toddlers with ASD, especially in frontal, temporal and cingulate areas. All investigated brain areas in this study, except for occipital GM, demonstrated significantly altered growth trajectories in ASD until the age of 5. Based on these and other findings, it was suggested that abnormal brain development in ASD reflects early overgrowth of WM, but also GM, followed by prematurely arrested growth during middle childhood (Courchesne et al., 2007).

Over the last decade, neuroimaging studies in ASD have increasingly been complemented by more sensitive methods, providing detailed insight into the nature of volumetric differences as well as the structure of GM and WM. A variety of studies demonstrated not only volumetric differences between individuals

* Corresponding author at: Department of Child and Adolescent Psychiatry, Center for Psychosocial Medicine, University of Heidelberg, Blumenstrasse 8, 69115 Heidelberg, Germany.
E-mail address: romy.henze@med.uni-heidelberg.de (R. Henze).
[1] Both authors contributed equally to this work.

http://dx.doi.org/10.1016/j.pscychresns.2015.06.011
0925-4927/

with ASD and healthy controls (HC), mainly in the frontal and temporal lobes (Herbert et al., 2004; Kwon et al., 2004; Rojas et al., 2005), but also alterations of structural integrity and organization of WM tracts in children, adolescents and adults with ASD (Barnea-Goraly et al., 2004; Ke et al., 2008; Cheung et al., 2009; Pugliese et al., 2009; Shukla et al., 2010; Poustka et al., 2012; Goch et al., 2014).

Nevertheless, these well-studied WM abnormalities can hardly exist without complementary abnormalities in GM. Spatially localized information on GM abnormalities can be obtained by measuring cortical thickness (CT), which reflects changes of myelination at the boundary of GM and WM (Sowell et al., 2007). Focusing on this more specific measure of brain morphology might further elucidate aberrant developmental trajectories in ASD. In the normal brain, CT decreases with age, beginning during childhood and adolescence (Gogtay et al., 2004). The reasons for these cortical processes are not yet understood, but they may be attributable to the increase of WM during development, changes in sulcal and gyral folding patterns, or synaptic pruning together with changes in cell state (Gogtay et al., 2004). The progress of reduction in CT has been reported not to stop during childhood and adolescence, but to continue in adulthood and to be widespread across the whole cortex (Salat et al., 2004), but most prominent in the prefrontal area (Sowell et al., 2003). Thus, CT can serve as a further indicator of growth trajectories and brain maturation, and is currently being increasingly investigated in ASD.

Studies on CT in ASD have produced convergent results. In early childhood, no difference between CT in ASD and HC was reported (Hazlett et al., 2011), while in samples of adolescents and young adults, predominantly decreased CT in temporal and parietal regions (Hadjikhani et al., 2006; Wallace et al., 2010) and frontal, temporal and occipital regions (Chung et al., 2005) was found. Investigating CT in adults with high-functioning autism (HFA) and HC, Scheel et al. (2011) found decreased CT in brain regions associated with social cognition as well as a steady decline in CT in HC; no alterations of CT were found in the group of HFA subjects (Scheel et al., 2011). In contrast, Hyde et al. (2010) found both increased (anterior and medial frontal regions, anterior cingulate, superior temporal sulcus, Herschl´s gyrus and inferior parietal lobule) and decreased CT (parts of pre-, para- and post-central gyri) in a sample of adolescents and young adults in ASD. A very recent study investigating longitudinal changes in subjects with ASD and HC (age range 3–36 years) using a mixed cross-sectional and longitudinal design affirmed an expansion of CT in early childhood, an accelerating thinning in later childhood and adolescence, and a decelerated thinning in early adulthood (Zielinski et al., 2014). These results reflect a similar pattern of aberrant trajectories in GM and CT.

Very few studies have provided results on CT in pre-adolescent children. In a sample of 6-15-year-old boys with ASD, Jiao et al. (2010) found both cortical thickening (left caudal anterior cingulate gyrus and in the left precuneus) and thinning (left and right pars triangularis, left medial orbitofrontal gyrus, left parahippocampal gyrus and left frontal pole). In this study, four different machine-learning approaches were applied, and the authors concluded that thickness-based classifications were more accurate for predicting a correct diagnosis than volume-based classifications. Hardan et al. (2006) conducted the first longitudinal study on CT in children aged 8-12 years (Hardan et al., 2006). At baseline, the authors reported exclusively thicker cortices in the ASD group, which was most obvious in temporal brain regions. The follow-up of the sample after a 30-month time interval (on average 2.1 years later) revealed significantly greater thinning of the temporal and occipital lobes in the ASD group. Findings suggest substantial alteration on the GM/WM boundaries in ASD, which may be related to altered myelination processes. This corroborates the reported pattern of early brain overgrowth and subsequent plateau of brain growth in ASD (Hardan et al., 2009) as well as the notion that developmental pathways of the brain in ASD might be more disturbed than previously assumed on the basis of mere cross-sectional analysis. Moreover, a recent study by Mak-Fan et al. (2012) found significant age-by-group effects in children and adolescents with ASD and HC aged 6–15 years. While in the younger age range, increased CT was observed in the ASD group, greater cortical thinning emerged in the older age range of the sample.

To date, only a small number of studies have explored the associations between neuroanatomical parameters including CT and symptom severity in ASD. The aforementioned study by Hardan et al. (2006, 2009) included correlations of the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview Revised (ADI-R) with CT in both the cross-sectional and longitudinal analyses; while no associations were found between CT and symptom scores at baseline, elevated scores on several subscales of the ADI-R were related to a greater decrease in CT in the ASD group, suggesting that alterations of CT serve as an indicator of illness severity (Hardan et al., 2009). In a recent study by Ecker et al. (2013), these findings could not be confirmed, possibly reflecting the examination of different age groups in the two studies. In the left frontal brain regions, positive associations were observed between increased CT and the ADI-R domains communication and repetitive behavior. Moreover, clusters in the left temporal brain were positively correlated with repetitive behavior symptom scores (Ecker et al., 2013). Both of these studies integrated the ADI-R, which provides retrospective information on categorical autistic symptoms reported by the parents or caregivers at the participants' age of 4–5 years. No study to date has provided information on the associations of current symptom severity via direct observation by trained raters (ADOS) or via information from parents on general social impairment (SRS).

In the present study, we aimed to analyze CT in a sample of young, pre-adolescent children that had been previously examined in a diffusion tensor imaging (DTI) study by Poustka et al. (2012), in order to supplement the results on WM microstructure with a specific component of GM volume. As decreased fractional anisotropy (FA, a measure of fiber integrity and an index of the preferential diffusion of water parallel to the main fiber direction that is related to myelination and disturbed axonal coherence) was found in fiber tracts connecting the frontal and temporal lobes, it was hypothesized that children with ASD would show decreases in CT in predominantly fronto-temporal brain regions. Additionally, we explored the relationship between autistic symptoms in ASD, as measured with the ADOS, the ADI-R and the SRS, with CT.

2. Methods

2.1. Participants and diagnostic procedures

The ASD group comprised 18 right-handed children (age: mean 9.7; SD 2.1, range: 6.1–12.8 years; IQ: mean 110, SD: 14.4, range 91–145). Participants were recruited through local outpatient clinics. The diagnosis of ASD (Asperger syndrome or HFA) was assessed using the ADI-R (Lord et al., 1994) and the ADOS (Lord et al., 2000). Three subjects missed the clinical cut-off on the ADI-R (Interaction cut-off=10; Communication cut-off=8; Repetitive Behavior cut-off=3) or on the ADOS, module 3 (Interaction cut-off=2; Communication cut-off=4) by 1 point, but were nevertheless included as diagnosis was confirmed by two expert clinicians according to ICD-10 criteria.

The SRS (Constantino et al., 2003) was administered to assess the severity of social impairment and to screen for social difficulties in HC. All subjects had an intelligence quotient (IQ) higher