European Psychiatry 30 (2015) 214–220

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Volumetric alterations in the heteromodal association cortex in children with autism spectrum disorder

J. Richter [a,b], L. Poustka [c], K. Vomstein [a,c], J. Haffner [b], P. Parzer [b], B. Stieltjes [a], R. Henze [a,b,*]

[a] Section Quantitative Imaging-Based Disease Characterization, Department of Radiology, German Cancer Research Center, Heidelberg, Germany
[b] Section Disorders of Personality Development, 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

ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form 10 November 2014
Accepted 11 November 2014
Available online 2 January 2015

Keywords:
Heteromodal association cortex
Autism spectrum disorder
FreeSurfer
Gray matter volume
Hemispheric lateralization

ABSTRACT

Background: We investigated if alterations in higher-order association areas related to schizophrenia, namely the heteromodal association cortex (HASC), are also observable in subjects with autism spectrum disorder (ASD).
Methods: A group of 18 children with ASD and 18 healthy controls (HC) underwent magnetic resonance imaging (MRI). The examination comprised an analysis of group differences in gray matter (GM) volume, surface area (SA) and hemispheric lateralization.
Results: Differences in GM volumes in children with ASD and HC were detected in frontal and parietal areas related to the HASC. No HASC structure that showed changes in GM volume exhibited differences in SA. Alterations in hemispheric lateralization between ASD and HC are seen in a frontal area of the HASC.
Conclusions: Our results indicate that changes in HASC areas are not restricted to schizophrenia, but extend to other psychiatric disorders, namely ASD. The lacking group differences in SA indicate that changes in GM volume are possibly evoked by other variables than SA in children with ASD.

1. Introduction

Autism spectrum disorder (ASD) is a severe neurodevelopmental disorder. It is characterized by a triad of impairments, consisting of deficits in social interaction and communication as well as restrictive repetitive and stereotyped behavior. ASD has a strong genetic underlying [19], presuming structural and functional changes in the central nervous system being responsible for the symptomatology.

1.1. Structural neuroimaging findings in children and adolescents with ASD

With regard to gray matter (GM) volumes, structural differences between subjects with ASD and healthy controls (HC) vary at different developmental stages. The hypothesis of enlarged GM volumes in very young children and decreased GM volumes in older children and adolescents suffering from ASD in several neuroanatomical structures was frequently replicated and is widely accepted (enlarged GM volumes in early childhood: global cerebral cortical GM [16,17,30], temporal, frontal, and parietal GM volumes [52]; decreased GM volumes in later childhood and adolescence: fronto-striatal and parietal regions, ventral and superior temporal gyrus [41], ventromedial regions of the temporal cortex [36], reduced frontal and temporal GM [49], left-hemispheric angular and postcentral gyrus, putamen bilaterally [47]).

However, there is evidence that GM volumes might also be enlarged in older children and adolescents with ASD [29,35,60] when compared with HC, probably due to dysfunctional brain maturation in subjects with ASD in comparison to HC beyond childhood [49].

Two recent meta-analyses analyzing GM alterations in subjects with ASD revealed decreases of GM volume in the bilateral amygdala-hippocampus complex and the bilateral precuneus, and

* Corresponding author. Section Disorders of Personality Development, 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).

http://dx.doi.org/10.1016/j.eurpsy.2014.11.005
0924-9338/

a GM volume increase in the middle inferior frontal gyrus [59] as well as a GM reduction in the left putamen and the medial prefrontal gyrus, and a GM increase in the later prefrontal cortex [20]. Children with ASD exhibit increased GM volumes in the bilateral fusiform gyrus, the right cingulate and insula compared to adults with ASD [20].

Structural differences in subjects with ASD are not only restricted to GM volumes, but also include changes in structural connectivity. A recent meta-analysis concludes that GM abnormalities are always accompanied by white matter (WM) alterations in subjects with ASD, either in terms of concordances or discordances [9]. Differences in structural connectivity in subjects with ASD compared with HC were found by several studies, most of them indicating a similar developmental trajectory as already observed in GM abnormalities. In very young children, increased structural connectivity, especially in frontal areas, were detected [6]; in older children and adolescents, mainly decreased structural connectivity was observed [4,12,47,55]. However, two studies [11,12] show increased fractional anisotropy (FA) in several brain areas (right inferior frontal gyrus, left occipital lobe [11]; frontal lobe, right cingulate gyrus, bilateral insula, right superior temporal gyrus, bilateral middle temporal peduncle [12]). A meta-analysis described that in children with ASD WM decreases were mainly seen in fronto-striatal pathways [20].

Very recently, a graph-based large-scale network analysis study evaluated the betweenness centrality of putative important neuroanatomical structures in ASD compared with HC, namely Wernicke's and Broca's area [28] and detected a reduced betweenness centrality in Wernicke's, but not in Broca's area in children with ASD [28].

1.2. Overlap of ASD with other psychiatric disorders with regard to anatomical alterations

Subjects with ASD often exhibit differences in neuroanatomical structures or networks in comparison to HC that have been already observed in other psychiatric disorders. Frequently reported in terms of neuroanatomical abnormalities is an overlap of ASD with attention-deficit/hyperactivity disorder (ADHD) [7,27], and, more recently, an overlap of ASD with schizophrenia [3].

ASD and schizophrenia share similar clinical features such as problems with social interaction and emotion, verbal and nonverbal communication, and odd or inflexible behavior [57]. Mana et al. [40] indicate that alterations in ASD and schizophrenia are mainly observed in regions involving cortical areas, especially frontal, temporal and parietal cortices, with schizophrenia additionally showing abnormalities in the hippocampus. A meta-analysis revealed lower GM volumes within limbic-striato-thalamic circuitry in subjects with ASD and schizophrenia in comparison to HC. However, both psychiatric disorders additionally exhibited distinct neuroanatomical differences [13]. Investigating the brain anatomy of ASD subjects with and without a psychosis revealed that all ASD subjects exhibit less GM in the temporal lobes and in the cerebellum bilaterally, but those ASD subjects with psychosis additionally show significantly reduced GM volumes in the right insular cortex and in the cerebellum bilaterally [58].

1.3. Aims and hypotheses

In an earlier voxel-based morphometry (VBM) study using statistical parametric mapping (SPM5) [1,2], we found reduced left-hemispheric volumes in the angular and postcentral gyrus and in the putamen bilaterally in children suffering from ASD in comparison with HC without correcting for multiple comparisons [47]. However, analyzing structural connectivity and betweenness centrality in the same data set, differences in neuroanatomical areas spread over the whole brain (uncinate fasciculus, superior longitudinal fasciculus, Wernicke's area) were revealed [28,47]. Many of these affected areas belong to the heteromodal association cortex (HASC), such as altered connectivity in frontal and parietal areas by the uncinate and the superior longitudinal fasciculus and altered betweenness centrality in Wernicke's area. To date, the HASC has mainly been investigated with regard to schizophrenia [8,44,51]. As described above, an overlap in neuroanatomical alterations between the two psychiatric disorders in comparison to HC is suspected [13,40,58].

To the authors' knowledge, only one study including ASD subjects dealt with differences in a cortical higher association area, namely the language association cortex between ASD and HC, comprising neuroanatomical areas also considered as regions of the HASC [31]. However, the study focused rather on asymmetry than on volume changes of the aforementioned areas and centered more on the language-related aspect of the observed differences [31]. No other study dealt with differences in association cortices between subjects with ASD and HC.

According to the current state of the art in neuroimaging, different imaging analyzing methods that are supposed to measure the same variable (i.e., GM volumes) differ in their results due to varying analytic approaches. Two common methods to analyze neuroimaging data are SPM5 [1,2] and FreeSurfer (available under http://surfer.nmr.mgh.harvard.edu/). When neuroimaging data is analyzed using SPM5, neuroanatomical structures are compared on a voxel-by-voxel basis [22]. On the contrary, FreeSurfer analyzes GM volumes as structures as a whole without voxel-wise comparisons between individual magnetic resonance (MR) images, using surface geometry to do inter-subject comparisons of cortical brain areas [22]. As FreeSurfer does not work on a voxel-by-voxel basis, it exhibits higher sub-voxel accuracy than voxel-based methods and is more robust to mis-segmentation [14].

Other potential contributors to varying results between FreeSurfer and SPM are different processing pipelines and a varying atlas composition [18]. In the present study, we decided to re-analyze our data set with FreeSurfer, expecting varying results from our former VBM study using SPM5 [47].

Re-analyzing the data set with FreeSurfer, we expect significantly reduced GM volumes in neuroanatomical structures belonging to the HASC (dorsolateral prefrontal cortex [DLPFC], Broca's area, planum temporale, angular and supramarginal gyrus) in subjects with ASD compared with HC, due to the aforementioned overlap between ASD and schizophrenia.

Recent studies showed that differences in GM volumes in subjects with ASD are mainly caused by differences in surface area (SA), rather than provoked by changes in cortical thickness (CT) [21,30]. Due to these results, we hypothesized to find differences in SA between subjects with ASD and HC in neuroanatomical structures related to the HASC.

The analysis of SA is implemented in FreeSurfer, but not in SPM5. Using the same analyzing method to examine GM volume and SA minimizes systematic errors, which might occur when using different analyzing methods. This constitutes another advantage in re-analyzing the dataset with FreeSurfer.

Subjects with ASD show a shift in lateralization towards the right hemisphere in comparison with HC in WM tracks related to language functions [33,62] and in brain structures belonging to higher association areas [31,32]. We hypothesize that we observe a shift towards the right hemisphere in neuroanatomical structures belonging to the HASC in subjects with ASD in comparison to HC.