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Diminished grey matter within the hypothalamus in autism disorder: a potential link to hormonal effects?

Florian Kurth¹, Katherine L Narr², Roger P. Woods², Joseph O'Neill¹, Jeffry R. Alger², Rochelle Caplan¹, James T. McCracken¹, Arthur W. Toga², and Jennifer G Levitt¹

¹Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California—Los Angeles, Los Angeles, CA, USA

²Department of Neurology, David Geffen School of Medicine, University of California—Los Angeles, Los Angeles, CA, USA

Abstract

Background—Subjects with autism suffer from impairments of social interaction, deviations in language usage, as well as restricted and stereotyped patterns of behavior. These characteristics are found irrespective of age, IQ and gender of affected subjects. However, brain changes due to age, IQ and gender may pose potential confounds in autism neuroimaging analyses.

Methods—To investigate grey matter differences in autism that are not related to these potential confounds, we performed a VBM analysis in 52 affected children and adolescents and 52 matched control subjects.

Results—We observed diminished grey matter in a region of the hypothalamus, which synthesizes the behaviorally relevant hormones oxytocin and arginine vasopressin.

Conclusions—This finding provides support for further investigations of the theory of abnormal functioning of this hormonal system in autism and potentially for experimental therapeutic approaches using oxytocin and related neuropeptides.

Keywords

ASD; VBM; children; adolescents; oxytocin; morphometry

Introduction

Autism disorder is highly heritable, has an onset in early childhood, and affects approximately 1 in 150 individuals (1, 2). As currently defined, it is comprised of abnormalities in three core domains: impairments in social interaction; language and communication; as well as restricted or stereotyped patterns of behavior, interests and activities (3). The clinical appearance of autism is markedly heterogeneous. Range of

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*Correspondence should be addressed to: Florian Kurth, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, 760 Westwood Plaza 47-417, Los Angeles, CA 90024-1759, Phone: (310)-206-9585, Fax: (310)-206-4446, fkurth@loni.ucla.edu.

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functioning varies widely, and intellectual capacity can range from severe deficits to near or above normal. But in spite of all heterogeneity, the defining manifestations like impaired social interaction or stereotyped patterns of behavior remain characteristic throughout life and appear impervious to IQ deficits or developmental stage (4).

A variety of biologic studies have associated autism with genetic and hormonal factors, as well as with morphometric and functional changes in the brain (1, 5, 6). However, the findings from brain imaging investigations vary considerably and lack consensus. This is particularly true for morphometric brain changes. In children and adolescents, contradictory results have been noted, e.g. in total brain size (7–10), and in local grey matter volume as identified by voxel-based morphometry (VBM) (7, 11–13). Some variation might partly be explained by age effects between subjects with autism and controls (1, 2), while other morphometric differences may be associated with IQ differences rather than specific for autism (6, 14). These potential confounds may exert greater impact in studies with small sample sizes. In general, a consistent difference in brain morphology between subjects with autism and controls cannot be identified from current literature. Thus, the question remains whether the defining features of this disorder as determined in the DSM IV (3) possess a common and defining brain morphological signature.

To address this question, we analyzed overall changes in brain tissue volume and regional changes in grey matter in high-resolution whole-brain MRIs of 104 children and adolescents. Of all subjects, 52 were diagnosed with autism and 52 were healthy controls (Table 1). Both groups were closely matched for age, IQ and gender to control for putative confounds. To further account for variability in age range, IQ, and gender across the sample these parameters were also included as covariates in statistical analyses. To identify global volumetric differences, the tissue volumes between the groups were compared using a MANCOVA. Potential between-group differences in local grey matter were assessed using optimized voxel-based morphometry (VBM) (15) with a high-dimensional warping algorithm and customized templates (16–18).

Methods and Materials

Subjects

Participants included 104 children (mean age 11.2 ± 3.7), consisting of 52 subjects meeting DSM-IV criteria for autism and 52 healthy controls. The groups were matched for age and gender and as closely as possible for IQ (Table 1). All 52 subjects with autism had a high familial incidence for this disorder, i.e. they had at least one sibling who was diagnosed with autism as well. Of the subjects in the autism study group, 44 were sibling pairs, while for eight subjects the sibling did not meet inclusion criteria. None of the control subjects were related. Of the 52 subjects in each group, 38 were male and 14 were female, which is consistent with the higher prevalence of autism in males. All subjects with autism were recruited from the “Cure Autism Now / Autism Genetic Resource Exchange” (CAN / AGRE) project, which aims at finding the genetic underpinnings of this disorder. For this project, families with at least two children meeting DSM-IV criteria for autism were recruited and the diagnosis confirmed by trained child psychiatrists using the standard autism diagnostic interview revised (ADI-R) (19) algorithm as well as the autism diagnostic observation schedule (ADOS) (20). Control subjects were recruited from local schools and from concurrent studies of normal development at the University of California – Los Angeles (UCLA).

Estimates of the individual intelligence quotients (IQ) were obtained for all children to match autism and control subjects as closely as possible. For 8 subjects the IQ was estimated using the Block Design and Vocabulary subtests of the Wechsler Intelligence Scale for

Children, 3rd edition (WISC-III), 25 completed the whole WISC-III and 71 did the Wechsler Abbreviated Scale of Intelligence (WASI). From these tests the estimates for Full IQ were calculated and used to match the subjects pair-wise as closely as possible. Inclusion criteria for all subjects were the absence of any contraindications for MRI, and completion of the intelligence test. In addition, control subjects were required to be free from any current or lifetime history of Axis I mental disorder as assessed by DISC interview or any other neurological or serious medical conditions. Accordingly, subjects with autism were required to be free from any accompanying current or lifetime history of Axis I mental disorders, or other neurological or serious medical conditions. The Institutional Review Board of UCLA approved the experimental protocols for this study and after a complete description of the study procedures all subjects and their guardians provided written informed consent and/or assent.

Image acquisition

For each subject, two consecutive high-resolution T1-weighted spoiled gradient (SPGR) scans (repetition-time = 24ms, echo-time = 12.6ms, flip angle = 22°, field-of-view = 256 × 256 mm², slice thickness = 1.2 mm, 128 slices, voxel size = 0.94 × 0.94 × 1.20mm³) were acquired on a 1.5T Siemens Sonata scanner at the Ahmanson-Lovelace Brain Mapping Center at UCLA. The two scans per subject were realigned and averaged prior to further analysis to improve the signal to noise ratio.

Image Preprocessing

Structural MRI processing was directed towards comparing the two subject groups for potential global differences in brain size and whole-brain tissue volumes as well as highly localized regional differences in grey matter volume. All Images were processed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) and the VBM8 Toolbox toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>). Since the investigated population consisted of children with a mean age of 11.2 years rather than adults, we calculated customized Tissue Probability Maps in MNI space for use with the VBM8 Toolbox. This was accomplished using the average Template approach of the TOM8 Toolbox with average age and gender as defining variables (18). As a first step the T1-weighted images were bias field corrected and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The volumes for whole-brain GM, WM, CSF and total intracranial volume (TIV) were then calculated in native space for each subject and used for the corresponding global between-group comparisons. The individual native-space GM and WM segments were then normalized to the customized Tissue Probability Maps using an affine registration. This procedure accounts for global inter-individual differences in whole-brain volume, leaving local volumetric differences for further analysis (21). From these affine-registered GM and WM segments an average DARTEL template of all subjects in MNI space was created (16). Subsequently, the affine-registered GM segments were warped to this average template using the high-dimensional DARTEL approach (16) and modulated (15), which is consistent with the modulation for the non-linear component of normalization only (21). The resulting GM maps code the relative local volume of GM in MNI space (15). To identify possible artifacts and failed segmentation or normalization we performed a quality check using the respective tools of the VBM8 Toolbox, SPM's "check reg" function and MRIcron. As the quality check indicated none of the possible problems existed within this analysis, the GM maps were then smoothed with an 8 × 8 × 8mm³ FWHM kernel.

Statistical analysis

Global differences in tissue and whole-brain volumes were assessed using a MANCOVA in SPSS. GM, WM, CSF volumes and TIV were included as dependent variables, diagnosis (two levels: autism or control) was the between-subjects factor and age, IQ and gender were

covariates. Differences in local GM volume (i.e., the VBM analysis) between children with autism and controls were assessed using a two-sample T-test in SPM8. To account for volumetric variability associated with age, IQ, and gender of the subjects (22, 23), these parameters were again included as covariates. The results were thresholded at $p \leq 0.05$ (corrected for multiple comparisons using the family-wise error estimation (24)).

Results

Comparisons of total intracranial volume, and whole-brain grey matter, white matter, and cerebro-spinal fluid volumes between subjects with autism and controls showed slightly higher global volumes for all brain tissue compartments in autism. However, these differences did not reach significance (Table 2).

The VBM analysis of between-group differences in local grey matter revealed significantly lower volume in the hypothalamus of the subjects with autism ($T = 5.24$, $p = 0.017$ (*FWE corr.*), $Z = 4.91$, $k_E = 13$). This decrease of grey matter was found directly adjacent to the optic chiasm with a maximum at MNI -3, 1, 22 (Figure 1), an area in which the supraoptic and paraventricular nuclei of the hypothalamus are located. Significant between-group differences in regional grey matter surviving the corrected significance threshold ($p \leq 0.05$, *FWE corr.*) were not observed in any other brain region.

Discussion

In the present analysis we observed diminished grey matter in the hypothalamus in children with autism compared to healthy controls. Given the tight matching for age, IQ, and gender, as well as the additional inclusion of these parameters as covariates, this difference seems to be independent of these possible confounds. We therefore interpret this finding to be associated with the defining criteria of autism, which according to the DSM IV (3) include impaired social interaction and stereotyped behaviors. The locally diminished grey matter was observed in a region of the hypothalamus, which synthesizes the behaviorally relevant hormones oxytocin and arginine vasopressin. This reduction may therefore reflect the mounting evidence that the oxytocin/vasopressin system is affected in individuals with autism (5, 25–28). The analysis of total brain volume, however, did not reveal significant differences between the two groups. This is well in line with the theory, that a difference in total brain or tissue volumes might only be observed within discrete developmental epochs, reflecting specific disruptions in brain development, which may not remain apparent at later stages of brain maturation (1, 9).

Empathy, eye contact and face memory have been described as altered in autism (1, 4, 5, 25). Reinforced by the two hormones oxytocin and arginine vasopressin, these adaptive traits allow us to create and maintain successful social interaction (25, 28). Oxytocin, which is sometimes described as the “cuddling hormone”, is responsible for milk let down and uterus contractions after birth. It also increases trust, empathy, eye contact, face memory, and strengthens the bonds between individuals (5, 25, 28–35). Arginine vasopressin, which is well known for its anti-diuretic effect, influences social behavior as well, although its effects are more diverse. For example, in males arginine vasopressin was described to enhance aggression against other males, while females tended to perceive other females as more friendly (33, 36, 37). Also effects on altruism, stronger bonding and enhanced encoding of emotional faces have been described, which may be relayed by specific receptors (33, 38–40). Interestingly, arginine vasopressin also binds to oxytocin receptors, where it might elicit similar effects as oxytocin (5). Both substances are synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, with arginine vasopressin synthesized in the suprachiasmatic nucleus as well (5, 25). From here, they are transported

to the posterior part of the hypophysis, the location where both hormones are released into the blood. Also an additional direct release within the brain was described for both hormones, which facilitates them to work directly as neuromodulators (5, 25, 41).

The observed diminished grey matter volume in this study might be due to a diminished number and/or a smaller size of neurons. Another possible explanation may be a compacting of the neuropil, which consists in particular of glia, axons and dendrites, synapses, and blood vessels. This compacting may be caused for example by an accelerated synaptic pruning as described by Giorgio et al. (42), fewer connections to other brain regions, or an alteration of the glia. In the following, we will briefly discuss the potential relations between these possible morphological changes and deviations in the oxytocin/vasopressin system.

Deviations in the oxytocin/vasopressin system in autism may comprise globally diminished hormonal levels due to diminished synthesis, a dysregulation of hormonal release, or a relative local deficit of these hormones as neuromodulators in the brain. Of these possibilities, a dysregulation of hormonal release may present most variable, ranging from globally diminished hormonal levels to an inadequate hormonal release with a seemingly unaffected hormonal concentration in the blood. A relative deficit of the hormones as neuromodulators, however, might present with otherwise normal hormonal levels, normal capacity for synthesis, and normal regulation of hormonal release.

A diminished capacity to synthesize oxytocin and arginine vasopressin may be due to fewer or smaller neurons that synthesize these hormones. Mechanisms for a dysregulation of hormonal release may be an accelerated synaptic pruning, an alteration of the glia, which was reported to modulate directly the neuronal activity in the hypothalamus of the rat (43–45), or a change in the sensitivity of the hormonal receptors, which was previously observed in autism (38, 39, 46, 47). Finally, a relative deficit of these hormones as neuromodulators may be caused by a reduced connectivity to other brain areas (5, 25, 41). However, as the present data cannot directly address the link between volumetric changes and possible deviations in the oxytocin/vasopressin system, further studies will be needed to illuminate the exact pathophysiology of the oxytocin/vasopressin system in autism.

While we were able to detect significantly diminished grey matter in the hypothalamus, no other region throughout the brain showed significant morphometric differences after correction for multiple comparisons. Previous VBM studies in children reported varying effects of autism on grey matter throughout the brain. For example, Bonilha et al. reported widespread augmented grey matter in autism, which comprised frontal, parietal and temporal lobes (12). Similarly, another study also reported augmented grey matter in these regions (13), with an additional isolated reduction in the right parahippocampal gyrus. In contrast to this, McAlonan et al. found widespread grey matter reductions in frontal, parietal and temporal lobes (7) and another study reported localized grey matter reductions in the superior temporal sulcus only (11). While in all studies the mean age difference between the autism and control groups was within 1.5 years, no study reported including age as a covariate in the model. Furthermore, only Boddaert et al. included IQ as a covariate (11), since the group with autism in their study had a mean IQ of 55.8 and thus differed substantially from their control group. Seeing that age and IQ effects on brain morphometry between subjects with autism and healthy controls are assumed (1, 2), these factors may well have influenced the findings of prior investigations. Since, in previous studies, group size varied between 12 and 21 subjects with autism and between 12 and 17 controls, this might be a confounding factor for previous analyses.

Recent research provides suggestive evidence that the administration of oxytocin to individuals with autism is associated with improvements in measures of social information

processing, and possibly reductions in impairments in social interaction (25, 27, 48). Furthermore, although data are limited, some data suggest that plasma levels of oxytocin might be lower in children with autism than in age-matched controls (49, 50). The reduction of grey matter observed here might therefore constitute a link between neuroanatomy and models of hormonal dysregulation in autism. Although this hypothesis may not explain all neurobiological aspects of the disorder, the convergence of findings of hypothalamic dysmorphology and dysfunction could provide more support for research focused on therapeutic interventions based on these systems, and for better understanding the neurobiological mechanisms associated with autism.

Summary

In a relatively large sample, we identified significantly lower grey matter volume in the hypothalamus of children with autism relative to control children, independent of age, IQ, or gender. This observation suggests that morphological change in the hypothalamus may serve as an anatomical correlate for the defining features of autism that include impairment in social interaction and restricted or stereotyped patterns of behavior, interests and activities (3). Since the hypothalamus synthesizes behaviorally relevant hormones (oxytocin and arginine vasopressin) our findings also support a direct link between neuroanatomy, endocrine function, and diagnosis. Future studies are required to further explore the links between hypothalamic hormonal dysregulation and autism. Optimally, replication studies would measure hormonal blood levels and characterize genetic alterations in the hormone specific receptors. This would be particularly salient, as the present results are concordant with a candidate pharmacologic intervention in autism, which has rendered early promising results (25, 27, 48). Subsequent studies, which investigate longitudinal hormonal effects on brain development and behavior, as well as similarities and differences across subtypes of autism, are also considered of fundamental importance.

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Figure 1.

Localization of significantly reduced grey matter in autism shown on the mean template generated from the entire study population in axial section (a) and basal view of 3D rendering (b). The depicted hypothalamic grey matter difference between the study groups is located adjacent to the optic chiasm. The color bar shows the value of the T-statistic (family-wise error corrected for multiple comparisons).

Table 1

Means, standard deviations (SD) and ranges of subject demographics.

	autism	control	Significance (p)
n	52	52	
gender	38 M / 14 F	38 M / 14 F	
Age	11.2±3.95 (5.91– 20.33)	11.14±3.58 (6.11– 19.75)	0.931
IQ	102.21±16.14 (65 – 142)	105.96±13.34 (76 – 131)	0.199

Potentially significant between-group differences in age and IQ were tested using a two sample T-test.

Table 2

Global brain tissue volume differences between subjects with autism and controls

	autism	control	Significance (p)
TIV	1437.1 ± 138.1	1411.1 ± 123.6	0.121
GM	680.5 ± 59.5	665.7 ± 74.1	0.479
WM	601.9 ± 95.2	593.9 ± 70.6	0.415
CSF	154.6 ± 26.6	151.3 ± 25.3	0.178

Group-means ± SD are in ml for brain size and whole-brain tissue volumes. TIV = total intracranial volume, GM = grey matter, WM = white matter, CSF = cerebrospinal fluid