The relationship between brain abnormalities and autistic psychopathology in pervasive developmental disorders

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Abstract
The aim of the present research has been to determine whether there is a relationship between brain abnormalities found on magnetic resonance imaging (MRI) and autistic psychopathology.

A retrospective analysis covering a period between 1998 and 2015 included 489 children with autism (404 boys, 85 girls; average age 8.0 ± 4.2 years) who underwent an MRI of the brain. For clinical diagnosis of autism, the International Classification of Diseases, 10th revision (ICD-10), was used. Autistic psychopathology was evaluated by means of the Autism Diagnostic Interview – Revised. The Spearman nonparametric correlation analysis and chi-square test were used to examine the possible relationships between variables.

The group of autistic children did not manifest a statistically significant correlation between the parameters examined on MRI and autistic psychopathology. A correlation between other cysts and repetitive behavior was significant only at trend level (P = 0.054). Gliosis of the brain was significantly more frequent in autistic children with mental retardation than in children without mental retardation (14.1% vs. 7.4%; P = 0.028). Nonmyelinated areas in the brain were significantly more frequent in autistic children with autistic regression than in children without autistic regression (29.9% vs. 15.7%; P = 0.008). Mental retardation was significantly more frequent in autistic children with autistic regression than in children without regression (73.2% vs. 52.5%; P = 0.002).

Our research study did not reveal a statistically significant correlation of brain abnormalities on MRI with autistic psychopathology.

Keywords: Autism; Brain; MRI; Psychopathology

Highlights:
• Magnetic resonance imaging is a powerful tool for researching the autistic brain.
• The connection between brain abnormalities and autism in children is already proven.
• Autism is linked to atypicalities in corpus callosum, caudate nucleus, and cerebellum.
• Psychopathological manifestations can be correlated with specific brain structures.
• Clinical endophenotypes of ASD may be associated with gliosis or nonmyelinated areas.

Introduction
With the advent of modern magnetic resonance imaging (MRI), in recent decades the opportunity has arisen to study brain morphology and pathology with high accuracy. The MRI technology has gained its place in the clinical and scientific fields due to its absence of ionizing radiation, excellent soft tissue imaging, and better contrast sensitivity and spatial resolution compared with computed tomography (CT). To research the autistic brain, structural MRI (sMRI), functional MRI (fMRI), and tractography based on diffuse tensor imaging (DTI) are used. The aim of this retrospective study is to determine whether there is a relationship between MRI findings and autistic symptomatology.

Based on the current state of knowledge about the autistic brain, we can start establishing the first consistent correlates between psychopathological manifestations and individual brain structures, areas, and connections, in the following way.
(1) Disruption of socio-emotional interactions is associated with frontotemporal regions and the amygdala (Allison et al., 2000; Boddart et al., 2004; Juranek et al., 2006; Nacewicz et al., 2006; Rojas et al., 2006). (2) Disruption of social communication and speech is associated with the Broca’s and Wernicke’s areas (Redcay, 2008). (3) Repetitive and stereotyped behaviors are associated with the caudate nucleus (Hollander...
Materials and methods

Our retrospective analysis involved a sample of children who had attended a diagnostic examination focused on autism at the Department of Child Psychiatry of the Second Faculty of Medicine at Charles University and University Hospital Motol between the years 1998 and 2015. The parents of our patients provided an informed consent to a routine brain MRI as part of the examination, and most of the examinations were performed under general anesthesia. The study was approved by the Ethics Committee of University Hospital Motol under reference number EK-124/17.

From 1998 to 2015, a total of 489 children were diagnosed with pervasive developmental disorder (404 boys, 85 girls). The mean age in the group was 8.0 ± 4.2 years (range 1.7–26.0 years). The upper age limit was 26 years because in a few exceptional cases, adult patients were examined within the observed period of time as well, using the same diagnostic tools as those used for child patients. Rather than excluding the several adult patients from the study sample, we decided to utilize the valuable data obtained from their examination and include them in the study despite their age. The diagnoses, based on ICD-10, included 314 patients with childhood autism, 68 patients with atypical autism, 82 patients with Asperger syndrome, and 4 patients with other childhood disintegrative disorders. Two patients were diagnosed with Rett syndrome, 6 patients with other pervasive developmental disorders, and 7 patients with a pervasive developmental disorder not otherwise specified. Data on intellectual functioning were available in 322 out of 489 autistic patients (65.8% of the autistic group). Out of 322 children, 189 were diagnosed with mental retardation (58.7%).

The International Classification of Diseases, 10th revision (1996), was used for the clinical diagnosis of ASD. Each patient was examined by an experienced child psychiatrist. Between 1998 and 1999, the assessment of the patient’s condition was supported by the Childhood Autism Rating Scale (Schopler et al., 1980). Starting in 2000, the third version of the Autism Diagnostic Interview – Revised (ADI-R) was used for assessments (Lord et al., 1994); and from 2012 onwards, the Autism Diagnostic Observation Schedule – Generic (Lord et al., 2000) was added to diagnostic procedures. Both methods continue to be used at our department to this day. The assessment and categorization of the findings were performed by an experienced neuroradiologist (JL). Between 1998 and 2002, the scans were assessed using hard copies; and after 2003, digital images were used. The radiologic assessments of pathologies were divided into three categories: (1) normal, (2) benign pathology (e.g., mega cisterna magna, gliosis, arachnoid cysts), and (3) severe pathology (e.g., septo-optic dysplasia, pilocytic astrocytoma, cavernoma, mesial temporal sclerosis). All digital MRI images were assessed again within this study. Hard copy MRI scans were no longer available for reassessment, therefore, only some parameters (severe pathologies, gliosis, arachnoid cysts, and other cysts), once assessed by the same radiologist (JL), could be transferred to the current study.

The data collection matrix devised for the purpose of this research included: (1) assessment and categorization of MRI scans, (2) ADI-R assessment (Autism Diagnostic Interview – Revised), (3) presence of autistic regression, and (4) presence of mental retardation.

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS, version 22.0). Descriptive statistics was used. Spearman nonparametric correlation analysis was used to evaluate the relationship between brain abnormalities on MRI and autistic psychopathology. A chi-square test was used to compare the incidence of mental retardation and autistic regression with the incidence of pathology on MRI. Only MRI findings with a total number >10 were included in the assessment.

Theory

The above-described connections of specific psychopathological manifestations with individual areas of the brain are based on the results of research studies. However, the situation is different in the field of routine MRI. Major organizations such as the American Academy of Child and Adolescent Psychiatry (Volkmar et al., 2014) or the National Institute for Health and Care Excellence (NICE, 2011) do not recommend routine brain MRI as part of diagnostic procedures for autism.

Not much is known about the utility of routine brain MRI in either. There are only a few research studies that address the benefits of routine brain MRI. We identified only six studies, with 33, 55, 70, 70, 85, and 782 children, respectively. Two of the six studies were methodologically compromised by having examined some of the children by CT and others by MRI; nevertheless, both studies reported negative results (Kosinovsky et al., 2005; Shevell et al., 2001). Challman et al. (2003) reported central nervous system (CNS) abnormalities in 17 out of 70 children (24%). None of the abnormalities required intervention, and only one MRI scan (in a patient with multiple cortical tubers) led to a specific diagnosis. Battaglia and Carey (2006) found abnormalities in 2 out of 85 children (2.4%). In one case, it was a relative macrocrania with right lateral ventricular heterotopia, with no manifestation of neurological symptoms. The other case involved partial agenesis of the corpus callosum (CC) with right cerebellar hemisphere hypoplasia. Zeglam et al. (2015) found abnormalities in 26 out of 782 autistic children (3.3%). These abnormalities included 8 subjects with leukodystrophy, 4 with periventricular leukomalacia, 3 with brain atrophies, 3 with CC agenesis, 2 with tuberous sclerosis, 2 with vascular changes, and one each with a pineoblastoma, a cerebellar angioma, a cerebellar hypoplasia, and a neuroepithelial cyst. Minor findings or variants of the norm (ventricular dilatation, enlarged Virchow–Robin space, arachnoid cysts) were not classified as abnormalities. However, the study of this team raises some concerns about methodology, e.g., the age of the youngest subject in the autistic
children sample is given as one month (sic) and the diagnostic procedures are not further specified. Ming et al. (2016) reported parenchymal abnormalities in 8 out of 55 children (14.6%). These abnormalities included 2 children with type 1 Chiari malformation; 1 child with hamartoma and 6 café-au-lait spots, not classified as neurofibromatosis; 1 child with enlarged Virchow–Robin space; 1 child with venous angioma in the right frontal lobe; and 3 children with abnormal white matter signals (classified as non-specific changes).

Results

In the Czech Republic, some hospitals (including ours) perform routine brain MRI as part of diagnostic procedures for autism. In the first, already published analysis of our data, we showed that CC hypoplasia was significantly more common in autistic children compared with the control group (13.7% vs. 0%) (Lisy et al., 2019).

In the autistic group, no statistically significant correlation was found between the monitored parameters on MRI and autistic psychopathology as measured by the ADI-R (Table 1). The correlation between other cysts and repetitive behavior was significant only at the trend level ($P = 0.054$). Gliosis was significantly more common in autistic children with mental retardation compared to children without mental retardation ($P = 0.028$). Nonmyelinated areas of the brain were significantly more common in autistic children with autistic regression compared to children without regression ($P = 0.008$). For details, see Table 2. It is worth noting that mental retardation was significantly more common in autistic children with autistic regression compared to children without regression (73.2% vs. 52.5%; $\chi^2 = 9.893; df = 1; P = 0.002$).

Table 1. Correlation between MRI pathologies and scores of the Autism Diagnostic Interview – Revised

<table>
<thead>
<tr>
<th>Finding</th>
<th>Score ADI-R SI</th>
<th>Score ADI-R VC</th>
<th>Score ADI-R NVC</th>
<th>Score ADI-R RB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliosis</td>
<td>$R$</td>
<td>0.030</td>
<td>0.019</td>
<td>0.114</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>335</td>
<td>233</td>
<td>208</td>
</tr>
<tr>
<td>Arachnoid cysts</td>
<td>$R$</td>
<td>0.036</td>
<td>0.099</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>335</td>
<td>233</td>
<td>208</td>
</tr>
<tr>
<td>Other cysts</td>
<td>$R$</td>
<td>0.006</td>
<td>0.005</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>335</td>
<td>233</td>
<td>208</td>
</tr>
<tr>
<td>Nonmyelinated areas</td>
<td>$R$</td>
<td>0.092</td>
<td>0.053</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>285</td>
<td>198</td>
<td>159</td>
</tr>
<tr>
<td>CC hypoplasia</td>
<td>$R$</td>
<td>0.011</td>
<td>0.018</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>285</td>
<td>198</td>
<td>159</td>
</tr>
<tr>
<td>Mega cisterna magna</td>
<td>$R$</td>
<td>0.061</td>
<td>0.024</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>$N$</td>
<td>285</td>
<td>198</td>
<td>159</td>
</tr>
</tbody>
</table>

$R$ – Spearman correlation coefficient; $N$ – number of patients; * $p < 0.05$; ** $p < 0.01$. ADI-R – Autism Diagnostic Interview – Revised; SI – social interaction; VC – verbal communication; NVC – nonverbal communication; RB – repetitive behavior and interests.

Table 2. Relationships of MRI findings to other psychopathologies

<table>
<thead>
<tr>
<th>MRI finding</th>
<th>Presence of the MRI finding</th>
<th>Mental retardation absent</th>
<th>Mental retardation present</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliosis</td>
<td>NO</td>
<td>174 (92.6%)</td>
<td>219 (85.9%)</td>
<td>$\chi^2 = 4.810; df = 1; P = 0.028$</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>14 (7.4%)</td>
<td>36 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Nonmyelinated areas of the brain</td>
<td>NO</td>
<td>214 (84.3%)</td>
<td>47 (70.1%)</td>
<td>$\chi^2 = 6.938; df = 1; P = 0.008$</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>40 (15.7%)</td>
<td>20 (29.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Column percentages are given.

Discussion

None of the studies on the etiological utility of MRI discussed in the theoretical section (Battaglia and Carey, 2006; Challman et al., 2003; Kosinovsky et al., 2005; Ming et al., 2016; Shevell et al., 2001; Zeglam et al., 2015) attempted to correlate MRI findings with psychopathology, which makes discussion difficult. The fact that CC hypoplasia did not correlate with psychopathology in our study means that it is a trait marker rather than a state marker. At present, diagnostic procedures rely on a clinical description of ASD using diagnostic manuals for clinical interview (ADI-R) and clinical observation (ADOS). While these diagnostic manuals (ADI-R, ADOS) are very useful and reliable examination tools, they do not address the neurobiological nature of the disease. Validated biomarkers are urgently needed to detect ASD at the earliest possible stage, establish a prognosis, and start timely intervention. Accordingly, the role of neuroimaging methods in the study of the autistic brain appears to be shifting from the scientific setting to the clinical...
one. In our previous study (Lisy et al., 2019), we reported that CC hypoplasia could be one of the possible biomarkers in suspected ASD. However, the clinical application of neuroimaging approaches remains dependent on their validation in the clinical setting, which requires large independent research samples obtained both in the clinical setting and in the real world. If the validation is successful, these new approaches can one day become invaluable in the diagnostic procedures, treatment, and description of ASD.

In our present study, we identified an association of mental retardation with autistic regression. Several studies have reported that autistic children with a history of developmental regression show more severe autistic symptoms, especially in relation to the level of intellectual functioning, verbal abilities, and adaptation skills, compared to autistic children without developmental regression (Bernabei et al., 2007; Rogers and DiLalla, 1990; Tuchman and Rapin, 1997). Other studies either reported differences in only a few functional areas (Brown and Prelock, 1995; Kobayashi and Murata, 1998), or found no differences between the groups at all (Davidovitch et al., 2000; Tolbert et al., 2001; Werner et al., 2005), or even reported higher performance in children with developmental regression (Harper, 1975). The presence of autistic regression is assessed retrospectively from a clinical interview with the child’s parents and/or from provided home videos, where regression is determined based on obvious major signs of skill loss. Some authors (Jones et al., 2014; Ozonoff et al., 2018; Pearson et al., 2018) regard autistic regression diagnosed in this way as the “tip of the iceberg” and consider the presence of autistic regression in ASD as the rule rather than the exception. Current research focuses on the prospective study of autistic regression, which allows for the mapping of an even subtler loss of previously acquired skills. In their article, Ozonoff and LoSif (2019) discuss the validity of previous autistic regression research studies that do not include the influence of etiological and environmental factors involved in the development of ASD. Subtypes of autism must be identified first and only then is it possible to subsume under them the individual genetic variations (Geschwind, 2011) that lead to the manifestation of differences in neurobiological brain development in early childhood (Konopka et al., 2012).

Current studies report a significant association of mental retardation with epilepsy in ASD. The severity of mental retardation, female sex, and older age are risk factors for comorbid epilepsy in ASD (Amiet et al., 2008; Hrdlicka et al., 2004; Viscidi et al., 2013). The relationship between autistic regression and epilepsy is still unclear, but some results suggest that the higher the incidence of epilepsy in the research sample, the greater the probability of a significant link between them (Hrdlicka, 2008).

It is difficult in general to find a correlation between autistic symptoms and/or degree of their severity with objective neurophysiological parameters. Several studies found a positive relationship between EEG abnormalities and the severity of autism (Ekinci et al., 2010; Mulligan and Trauner, 2014), while other studies found no relationship (Hartley-McAndrew and Weinstock, 2010; Hrdlicka et al., 2004). Some studies reported a significant correlation of EEG abnormalities with lower IQ (Tuchman, 2017; Yasuhara, 2010), but other studies did not confirm this finding (Baird et al., 2006; Hrdlicka et al., 2004). EEG abnormalities are a sign of brain dysfunction, but it is not clear whether they are responsible for autistic traits (Mulligan and Trauner, 2014). Furthermore, some studies found abnormal skin conductance responses in autism (Joseph et al., 2008; Kylila and Hietanen, 2006), while others did not (Ben Shalom et al., 2006). Similarly, our present study does not find a significant correlation of CC hypoplasia with psychopathology.

According to the results of our study, gliosis of the brain is more common in autistic children with mental retardation than in children without mental retardation. In other research studies, gliosis of the brain is associated with autism (Fezer et al., 2017; Steiner et al., 2003; Wiegell et al., 2010) but also with mental retardation alone (da Rocha et al., 2006). Gliosis does not constitute a disease of its own, rather, it is the result of a repair mechanism which is triggered by early brain damage. Premature birth, perinatal asphyxia, and low birth weight are generally risk factors for early brain damage (Fezer et al., 2017). Severe hypoxic-ischemic brain damage in premature infants is manifested primarily as damage to gray matter and brainstem structures. Mild to moderate cases are usually manifested as either intraventricular hemorrhage or periventricular leukomalacia (Barkovich and Sargent, 1995; Barkovich et al., 1995). The location and severity of the damage then determine the resulting physical and mental condition of the individual.

Based on the results of our study, we identified a correlation between other cysts and repetitive behavior which was significant only at the trend level. The term “other cysts” covers the following: pineal cysts, subependymal cysts in the lateral ventricles and foramen Monroi, septum pellucidum cysts, choroidal cysts, and cystic encephalomalacia. Studies of pineal cysts show that the prevalence of pineal cysts is significantly higher in autistic children compared with non-autistic children (Coelho et al., 2020). One of the proposed biological causes of autism is dysfunction of the pineal gland, involving a deficiency of its principal hormone, melatonin. The resulting clinical sign of sleep disorder is often associated with ASD. Dysfunction of the pineal gland is also related to abnormal metabolism of N-dimethyltryptamine, which could explain the abnormal neuroplasticity and neuronal distribution that are present in some cases of autism (Bedford et al., 2016). Subependymal cysts were found to be closely associated with developmental delay and developmental disability, ADHD and ASD in particular, while the higher the extent of subependymal cysts, the higher the risk of neurodevelopmental delay (Chang et al., 2018). The pathogenesis of subependymal cysts in the lateral ventricles is unclear, but histological studies identified macrophages lining the cysts, which indicates preexisting malacia caused by old hemorrhage, hypoxia, metabolic disease, and viral infection insults of the germinal matrix (Maling et al., 2002; Shaw and Alvord, 1974). On the other hand, it is interesting that studies of the choroid plexus do not indicate any developmental delay (DiPietro, 2011). Generally, the discrepancy between various cysts may suggest the importance of anatomical location and the extent of the cysts because of their effect on neurodevelopment.

The modern MRI neuroimaging method is an excellent diagnostic tool that enabled us to identify brain abnormalities often associated with autism. However, the correlation of MRI findings with autistic symptomatology did not deliver a strong yield, and the interpretation of our negative results is problematic owing to the huge phenotypic heterogeneity of ASD. Most of the abnormalities found are regarded as signs of brain dysgenesis, but their role in the psychopathology of autism requires further research.
Conclusions

Our research study did not reveal a statistically significant correlation of brain abnormalities on MRI with autistic psychopathology.

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Author contributions

AE: drafted the manuscript and collected data; JL: assessed the MRI scans, commented on the manuscript, and contributed to the design of the study; MH: conceived the study, performed the design of the study; and in the writing of the report. All authors have approved the final article.

Conflict of interests

The authors state that there are no conflicts of interests regarding the publication of this article.

References


