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ORIGINAL CONTRIBUTION

Subtypes of autism by cluster analysis based on structural MRI data

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Abstract The aim of our study was to subcategorize Autistic Spectrum Disorders (ASD) using a multidisciplinary approach. Sixty four autistic patients (mean age 9.4 ± 5.6 years) were entered into a cluster analysis. The clustering analysis was based on MRI data. The clusters obtained did not differ significantly in the overall severity of autistic symptomatology as measured by the total score on the Childhood Autism Rating Scale (CARS). The clusters could be characterized as showing significant differences: Cluster 1: showed the largest sizes of the genu and splenium of the corpus callosum (CC), the lowest pregnancy order and the lowest frequency of facial dysmorphic features. Cluster 2: showed the largest sizes of the amygdala and hippocampus (HPC), the least abnormal visual response on the CARS, the lowest frequency of epilepsy and the least frequent abnormal psychomotor development during the first year of life. Cluster 3: showed the largest sizes of the caput of the nucleus caudatus (NC), the smallest sizes of the HPC and facial dysmorphic features were always present. Cluster 4: showed the smallest sizes of the genu and splenium of the CC, as well as the amygdala, and caput of the NC, the most abnormal visual response on the CARS, the highest frequency of epilepsy, the highest pregnancy order, abnormal psychomotor development during the first year of life was always present and facial dysmorphic features were always present. This multidisciplinary approach seems to be a promising method for subtyping autism.

Key words childhood autism – pervasive developmental disorders – subtyping – cluster analysis – magnetic resonance imaging

Introduction

It is well known that Autistic Spectrum Disorders are a very heterogenous group showing a wide range in type, number and severity of social deficits, behavior and communication problems [7]. Many past and recent studies have attempted to describe subtypes within the spectrum of Pervasive Developmental Disorders (PDD). Identification of autistic subtypes within the spectrum is needed to clarify the etiology, pathophysiology, course, treatment, and outcomes for children with PDD [20].

ECAP 453

The majority of published reports have attempted to subcategorize children based on the presence of specific psychopathological symptom clusters. The most famous attempt was by Wing and Gould [31]. They identified three subtypes of autism characterized by particular patterns of social behavior: (1) aloof, (2) passive, or (3) active-but-odd. These subtypes have received extensive research [5, 6, 7, 16, 29]. Generally, the data support the existence of the three Wing social subtypes: along with the characteristic features they proposed [4]. With one exception [16], these investigators have replicated the original findings – that the "most autistic" children were found in the aloof group and the least autistic were found in the active-but-odd group.

Other studies seeking to categorize the psychopathological symptoms did not find such a simple and comprehensible solution as did Wing and Gould. Cluster analytic studies based on two cluster solutions [18, 28], three cluster solutions [21], four cluster solutions [7, 14, 26, 27], or on multiple solutions [19] were performed. The majority of these attempts sorted cases either with respect to the severity of autistic symptoms [18, 19, 26], or with respect to the severity of co-morbid mental retardation [7, 27, 28]. A detailed overview of the studies was presented by Beglinger and Smith [4].

Only a few studies have dealt with subtyping autism based on both psychopathological and neurobiological variables. Balottin et al. [3] studied 45 autistic children who were divided into two groups: one with serious language impairment and the other with less-serious language impairment. The study failed to demonstrate any significant differences between the two groups based on neuroradiological parameters as measured by computerized tomography. Hameury et al. [10] studied 202 subjects with developmental disorders (Autistic Spectrum Disorder, PDD not otherwise specified and mental retardation). For each child, a quantification of autistic behavior, intellectual impairment, neurological signs and language and communication disorders was performed. A cluster analysis of these quantified data generated four subgroups based on the scores obtained in these four areas. Group I was characterized by subjects with severe autistic behavior, profound intellectual impairment, and severe neurological signs. Group II was characterized by autistic behavior and language and communication disorders, with slight or moderate intellectual impairment and mild neurological signs. Group III was characterized by severe intellectual impairment and neurological signs with little or no autistic behavior. Group IV was characterized by multiple, but mild, disorders.

Finally, Roux et al. [22] reported the results of a multivariate statistical approach (correspondence analysis followed by cluster analysis) applied to clinical and electrophysiological data (i. e., averaged evoked potentials in response to auditory stimulation). The analysis was performed on a group of 145 developmentally disordered children (autistic disorder, PDD not otherwise specified and mental retardation). The authors identified two main bioclinical dimensions. These dimensions reflected the association of intellectual impairment and centroparietal electrophysiological activity on the one hand, with autistic behavior and temporal electrophysiological activity on the other.

The aim of our study was to subcategorize Autistic Spectrum Disorders using a multidisciplinary approach, involving psychopathological, psychological, structural imaging, genetic, neurological as well as electrophysiological data.

Methods

Patient recruitment was based on consecutive referrals to the Department of Child Psychiatry and to the Department of Child Neurology in the years 1998–2002. Referrals of autistic patients were facilitated by advertisements directed to child psychiatrists, psychologists, neurologists, and pediatricians. Inclusion criteria for the study involved meeting the ICD-10 criteria [32] for Pervasive Developmental Disorders, and the diagnosis had to be confirmed by the Autism Diagnostic Interview – Revised, ADI-R [13]. We excluded patients with Rett syndrome, children with other diagnosable causes of autism, with structural brain lesions, or with severe sensomotor abnormalities. Sixty four autistic patients (52 boys, mean age 9.4 ± 5.6 years) met the inclusion criteria, completed the entire data collection, and entered the cluster analysis.

A clinical psychiatric and genetic interview, a neurological examination (focused on the evaluation of epilepsy), an assessment using the Childhood Autism Rating Scale (CARS [23]) and IQ testing were all performed. The Gesell Developmental Scales were used for the youngest children and the Stanford-Binet Intelligence Scale, 4th Edition, was used for the older children. Based on intelligence testing, the patients were divided into 5 categories: 1) profound mental retardation, 2) severe mental retardation, 3) moderate mental retardation, 4) mild mental retardation and 5) non-retarded individuals.

The patients underwent structural magnetic resonance imaging (MRI) of the brain as part of a complex clinical examination. MRI scans were carried out by using a 1.5 Tesla Philips Gyroscan ACS 15NT Scanner. A four pulse sequence was used in the imaging protocol: T2-weighted/TSE axial plane, FLAIR axial plane, T1-weighted/IR-TSE coronal plane, and T1-weighted/SE sagittal plane. The quantitative planimetric measurements focused on cortex thickness (measured on frontal lobes), size of corpus callosum (genu, corpus and splenium), hippocampus (feet – head size), caput of caudate

nucleus (transversal size), and amygdala (feet – head size). For a more detailed description see Table 1. The measurements were done by an experienced neuroradiologist using calipers, on hard copies of the MRI scans. The examiner was unaware of the psychopathology of the patients.

A twenty-one channel EEG (including night sleep EEG) recording was performed using a Schwarzer EPAS 32 Portable, a Schwarzer EPAS 32 Video/Audio, or a Walther Graphtek EEG. The electrodes were placed in accordance with the 10/20 international system. The EEG assessment was performed by an experienced neurologist, specialized in the field of EEG: as before, the examiner was unaware of the psychopathology of the patients. The EEG records were divided into three groups: 0) normal EEG, 1) EEG with non-epileptiform abnormality of background activity and 2) abnormal EEG with epileptiform discharges.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 10.0). Data analysis consisted of a hierarchical cluster analysis using squared Euclidean distance measures and Ward's [30] minimum variance method to establish homogenous subgroups of PDD. Clustering was based on the MRI data. From the analysis the four cluster solution was selected. Decisions concerning the number of clusters were based on distances between the two clusters joined at each stage of the hierarchical clustering process. The last four distances were considerably higher than the previous ones. Thus the four cluster solution seemed to be optimal from a statistical point of view. It also seemed to be a meaningful solution from a clinical point of view. Descriptive statistics were performed to provide a clearer picture of the clusters. In order to study the differences among the clusters, the following were performed: a one-way ANOVA for continuous data (age, MRI and CARS data), a median test for ordinal data (intellectual functioning) and a chi-square test for categorical data (EEG, frequency of epilepsy and genetic data).

Results

Table 2 shows descriptive characteristics for the clusters obtained. There were no significant age differences among the clusters ($F = 1.197$; $df = 3$; $p = 0.319$). The

Table 1 Description of brain measurements on MRI scans

Brain structure/parameter	Diameter/location	Description
Cortex thickness	frontal lobe/medial frontal gyrus	on coronal image
Genu of corpus callosum	antero-posterior diameter in most rostral part of the genu	on midline sagittal image
Corpus of corpus callosum	craniocaudal diameter in the middle part of the corpus	on midline sagittal image
Splenium of corpus callosum	diameter perpendicular to the long axis of the splenium	on midline sagittal image
Hippocampus	feet-head diameter of the anterior part of the hippocampus	on coronal image
Caput of caudate nucleus	transversal diameter of the caput of caudate nucleus	on axial image
Amygdala	feet-head diameter of the amygdala	on coronal image

Table 2 Descriptive characteristics of the clusters

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Number of patients	18	33	9	4
Sex (boys/girls)	14/4	26/7	9/0	3/1
Age (years)	10.9±7.6	9.2±4.9	6.7±2.5	9.9±3.8
Diagnoses				
Childhood autism	13	22	4	3
Atypical autism	3	6	4	1
Other ch. disintegrative disorder	1	2	0	0
Asperger's syndrome	1	2	0	0
Other PDD	0	1	1	0
Mental functioning				
Profound MR	0	0	0	0
Severe MR	2	6	2	4
Moderate MR	5	6	2	0
Mild MR	3	9	5	0
Non-retarded individuals	4	10	0	0
Missing data	4	2	0	0

Ch. childhood; *PDD* pervasive developmental disorder; *MR* mental retardation
Cluster differences for age: $F = 1.197$; $df = 3$; $p = 0.319$
Cluster differences for mental functioning: $chi^2 = 5.403$; $df = 3$; $p = 0.145$

groups did not differ significantly in intellectual functioning ($chi^2 = 5.403$; df = 3; p = 0.145) although there was an obvious observation that the non-retarded individuals were represented only in clusters 1 and 2.

Table 3 demonstrates differences among the groups in selected brain structure sizes as measured by MRI. Table 4 demonstrates the differences among the groups in psychopathology as measured on the CARS total score and the CARS items. The differences in the CARS total score among the clusters were non-significant (F = 0.512; df = 3; p = 0.676). In the analysis of individual CARS items, the groups differed significantly only on item 7 ("Visual response"). The most abnormal visual response was found in cluster 4, whereas the least abnormal response was noted in cluster 2 (F = 3.161; df = 3; p = 0.032).

There were no significant differences among the groups relative to the EEG findings ($chi^2 = 8.157$; df = 6; p = 0.227). The frequency of epilepsy differed significantly between the clusters with the highest rate in cluster 4 (three from the four patients, 75 %) and the lowest rate in cluster 2 (9 % of the patients; $chi^2 = 11.076$; df = 3; p = 0.011).

The genetic history revealed three variables that

Table 3 Differences in selected brain structures sizes as measured by magnetic resonance imaging

Size	Cluster 1 Mean ± SD	Cluster 2 Mean ± SD	Cluster 3 Mean ± SD	Cluster 4 Mean ± SD	F*	p
Cortex thickness right	3.83 ± 0.86	3.65 ± 0.64	3.56 ± 0.73	3.25 ± 0.50	0.855	0.469
Cortex thickness left	3.61 ± 0.65	3.66 ± 0.59	3.22 ± 0.67	3.00 ± 0.00	2.388	0.078
Corpus callosum, genu	10.17 ± 1.08	9.03 ± 1.12	7.22 ± 1.56	7.00 ± 1.15	16.403	< 0.001
Corpus callosum, corpus	5.75 ± 1.74	5.55 ± 1.14	5.89 ± 0.60	4.50 ± 1.29	1.745	0.167
Corpus callosum, splenium	10.36 ± 1.24	8.55 ± 1.72	7.33 ± 1.32	5.75 ± 2.06	13.808	< 0.001
Amygdala right	13.97 ± 1.16	16.55 ± 1.45	15.22 ± 0.83	13.25 ± 0.96	19.896	< 0.001
Amygdala left	14.00 ± 1.57	16.06 ± 1.17	15.33 ± 1.50	12.00 ± 1.41	16.586	< 0.001
Hippocampus right	8.08 ± 0.88	8.23 ± 1.17	6.11 ± 0.78	7.75 ± 1.50	9.640	< 0.001
Hippocampus left	7.83 ± 1.00	8.17 ± 1.06	5.78 ± 1.09	6.50 ± 1.29	13.620	< 0.001
Caudate nucleus right	10.81 ± 0.97	9.65 ± 0.98	11.00 ± 1.22	7.75 ± 0.50	15.042	< 0.001
Caudate nucleus left	10.58 ± 1.35	9.77 ± 1.04	11.44 ± 2.12	8.50 ± 0.58	6.586	< 0.001

SD standard deviation. All measurements are expressed in mm (millimeters)
* df = 3

Table 4 Differences in psychopathology as measured by the Childhood Autism Rating Scale

CARS item	Description	Cluster 1 Mean ± SD	Cluster 2 Mean ± SD	Cluster 3 Mean ± SD	Cluster 4 Mean ± SD	F*	p
1	Relating to people	2.34 ± 0.75	2.58 ± 0.90	2.72 ± 0.67	3.25 ± 0.87	1.384	0.257
2	Imitation	2.59 ± 0.95	2.43 ± 0.75	2.61 ± 1.08	3.25 ± 0.96	1.063	0.372
3	Emotional response	2.75 ± 1.08	2.68 ± 0.58	2.72 ± 1.09	2.50 ± 1.00	0.100	0.960
4	Body use	2.66 ± 0.57	2.52 ± 0.61	2.39 ± 0.89	3.12 ± 0.63	1.368	0.262
5	Object use	2.69 ± 0.79	2.45 ± 0.54	2.61 ± 0.92	2.88 ± 0.25	0.772	0.514
6	Adaptation to change	2.25 ± 0.97	2.19 ± 0.74	2.11 ± 0.89	1.62 ± 0.75	0.647	0.588
7	Visual response	2.28 ± 0.84	2.00 ± 0.50	2.33 ± 0.83	3.00 ± 0.40	3.161	0.032
8	Listening response	2.25 ± 0.58	2.23 ± 0.63	2.44 ± 0.85	2.12 ± 0.85	0.313	0.816
9	Taste, smell, and touch response	2.31 ± 0.96	2.10 ± 0.71	2.28 ± 0.71	2.25 ± 0.5	0.326	0.806
10	Fear or nervousness	2.31 ± 0.57	2.61 ± 0.90	2.44 ± 1.01	2.25 ± 0.96	0.565	0.640
11	Verbal communication	3.06 ± 0.81	2.95 ± 0.80	3.11 ± 1.02	3.88 ± 0.25	1.507	0.223
12	Nonverbal communication	2.44 ± 0.54	2.36 ± 0.64	2.44 ± 0.98	3.00 ± 0.41	1.114	0.351
13	Activity level	2.78 ± 0.95	2.53 ± 0.68	2.78 ± 0.83	2.75 ± 0.96	0.466	0.707
14	Intellectual response	2.59 ± 0.80	2.44 ± 0.66	2.56 ± 0.73	2.25 ± 0.50	0.361	0.781
15	General impressions	2.88 ± 0.62	2.55 ± 0.52	2.67 ± 0.75	3.00 ± 0.82	1.422	0.246
$\sum$	Total score	37.66 ± 7.47	36.83 ± 5.27	38.17 ± 9.39	41.00 ± 6.18	0.512	0.676

CARS Childhood Autism Rating Scale; *SD* standard deviation
* df = 3

turned out to be significant. Pregnancy order increased with the number of the cluster: the average values were 1.67 ± 0.90 for cluster 1, 2.00 ± 1.05 for cluster 2, 2.83 ± 1.47 for cluster 3, and 3.50 ± 1.73 for cluster 4 ($F = 3.780$; $df = 3$; $p = 0.016$). Abnormal psychomotor development during the first year of life was most frequent in cluster 4 (100% of the cases) and least frequent in cluster 2 (37.9% of the cases; $chi^2 = 9.068$; $df = 3$; $p = 0.028$). Facial dysmorphic features were always present in clusters 3 and 4 and were least frequent (53%) in cluster 1 ($chi^2 = 13.992$; $df = 6$; $p = 0.030$). In the values/frequencies of the other variables, the clusters did not differ significantly from each other. These other variables included: the age of the mother at conception, the age of the father at conception, medication taken during pregnancy, infections during pregnancy, gynecological complications during pregnancy, abnormal delivery, speech retardation as the first autistic symptom, psychomotor delay as the first autistic symptom, behavioral abnormality as the first autistic symptom, autistic regression, abnormally shaped ears and dermatoglyphic patterns.

In summary the clusters obtained could be characterized by significant differences:

Cluster 1 Largest size of the genu of the corpus callosum ($p < 0.001$) and splenium of the corpus callosum ($p < 0.001$), lowest pregnancy order ($p = 0.016$) and lowest frequency of facial dysmorphic features ($p = 0.030$).

Cluster 2 Largest size of right and left amygdala ($p < 0.001$), largest size of right and left hippocampus ($p < 0.001$), the least abnormal visual response on the CARS ($p = 0.032$), lowest frequency of epilepsy ($p = 0.011$) and least frequent abnormal psychomotor development during the first year of life ($p = 0.028$).

Cluster 3 Largest size of the caput of the nucleus caudatus (right and left) ($p < 0.001$), smallest size of right and left hippocampus ($p < 0.001$) and facial dysmorphic features were always present ($p = 0.030$).

Cluster 4 Smallest size of the genu of the corpus callosum ($p < 0.001$) and splenium of the corpus callosum ($p < 0.001$), smallest size of right and left amygdala ($p < 0.001$), smallest size of the caput of the nucleus caudatus (right and left) ($p < 0.001$), most abnormal visual response on the CARS ($p = 0.032$), highest frequency of epilepsy ($p = 0.011$), highest pregnancy order ($p = 0.016$), abnormal psychomotor development during the first year of life was always present ($p = 0.028$) and facial dysmorphic features were always present ($p = 0.030$).

Discussion

More than 40 studies have dealt with structural MRIs of autistic patients. Findings of significant differences between participants with autism and controls have been inconsistent, however, and the research has suggested abnormal development in several brain structures [9]. The majority of studies have found autism to be associated with a larger total brain size, increased ventricle volume and a smaller cerebellum and brainstem [12]. Several studies also supported the involvement of the corpus callosum [11, 15, 17], hippocampus [2], amygdala [1, 2] as well as the caudate nucleus [25] in the pathogenesis of Autistic Spectrum Disorders. Because of methodological limitations associated with planimetric measurements on MRI pictures, we selected only certain specific structures (corpus callosum, hippocampus, amygdala, and caudate nucleus) and parameters (cortex thickness) as variables suitable for clustering analysis.

We are not aware of any other studies of cluster analysis based on MRI findings. The only similar study, Balottin et al. [3], used computerized tomography and failed to demonstrate significant differences between autistic subjects with serious and those with less-serious language impairment. This finding is in accordance with our findings, although the two studies were designed differently. Balottin et al. used other diagnostic criteria for childhood autism (DSM-III), and their sample group was slightly younger (7.42 ± 3.40 years) and had an unusually high frequency of females (44.4% of the sample); in addition the authors did not use a standardized assessment for autistic symptoms (including language impairment). Computerized tomography is also considered to be somewhat less precise in brain imaging than the MRI [33].

The limitation of our sample was the wide age range of the sample as expressed by a standard deviation of 5.6 years. However, the age differences between the clusters were non-significant. Thus, we were able to assume that age factors did not interfere directly or indirectly with the clustering process.

The clusters obtained in our study did not differ significantly in overall severity of autistic symptomatology as measured by the CARS total score, or in intellectual functioning. This was in marked contrast to the cluster analytic studies based primarily on psychopathologic measures [7, 10, 18, 19, 21, 26].

The clusters differed in the early psychomotor development, with the most frequent normal development found in cluster 2, while there was always abnormal development noted in clusters 3 and 4. The distinction between clusters in early psychomotor development corresponds partially with the Prior et al. findings [18] that differentiated subjects with early onset and late onset of autistic symptomatology. Furthermore, the clusters differed significantly in the frequency of comorbid epilepsy, with the lowest rate found in cluster 2. This may reflect the neurobiological diversity of identified clusters. From the psychopathological point of view we can briefly characterize patients in cluster 2 as having the

most normal visual response to external stimuli according to the CARS (Item 7), whereas the subjects described in cluster 4 were the most impaired. The remaining two clusters could not be separated by means of psychopathological description.

All these findings show that the patients in cluster 2 were the least impaired. This cluster was the cluster with the largest sized amygdala and hippocampus. We can only speculate that the larger amygdala and hippocampus could have been factors associated with the "least impaired" findings for cluster 2, or could possibly be protective factors in Autistic Spectrum Disorder. This hypothesis awaits proof from future longitudinal studies.

The 7th item of the CARS ("Visual response") was also found to be a significant factor in other types of neurobiological studies. Elia et al. [8] reported that visual response (and non-verbal communication) on CARS showed a significant correlation with some tonic sleep parameters, such as sleep period time, wakefulness after sleep onset, and total sleep time. The abnormal processing of visual stimuli (especially face-recognition skills) has already been recognized as an important part of the mechanisms involved in the pathobiology of autism [24].

Although there have only been a few studies that tried to identify psychopathological symptoms correlated with neurobiological variables, the abnormal visual response seems to be an interesting finding identified in these types of studies. Whether such findings imply that the visual response might be an important link between the psychopathology and the neurobiology of autism remains to be demonstrated in future studies.

Conclusion

Our study was one of the first attempts to subcategorize Autistic Spectrum Disorders using a multidisciplinary approach, as well as the first attempt at subtyping using, primarily, MRI data for cluster analysis. This approach seems to be a promising method for subtyping autism. The only methodological limitations of this study were associated with the planimetric measurements of brain structures, and the wide range of ages of the subjects. Further validation of our findings using volumetric measurements on a larger sample with a more narrowly defined age structure is needed. Longitudinal observation would also be helpful in assessing the prognostic value of the identified clusters.

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