Increased left parietal volumes relate to delayed language development in autism: a structural MRI study

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Summary

The neural basis of language and motor deficits in autism is still not completely clear. The aim of this study was to explore the involvement of the parietal lobe in language and motor development in autism, in view of the recognized role of this region in language and imitation functions. Twenty-eight autistic children underwent an extensive clinical assessment and an MRI examination. A significant direct correlation between age at first word and left parietal gray matter volumes was found (r=0.50, p=0.007). Conversely, age at reaching milestones of motor development, such as the ability to sit and to walk unaided, was not significantly associated with parietal size, after correcting for chronological age and for gender.

To the best of our knowledge, this is the first structural MRI report demonstrating a role of left parietal gray matter volumes in delayed language development in autistic children representative of the ‘real world’ autistic population.

KEY WORDS: Asperger’s syndrome, brain, magnetic resonance imaging, motor functions, neuroimaging, speech

Introduction

Autism is a neurodevelopmental disorder characterized, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (1), by the presence of abnormalities of social interaction, verbal/non-verbal communication and behavior (restricted and stereotyped interests and/or activities), evident before 3 years of age. Nowadays clinicians easily recognize classical autism and related clinical manifestations of the “autism spectrum disorders”, even though the pathophysiology of the disorder has still not been fully clarified (2-4). From this perspective, over the past few decades, researchers have endeavored to discover possible brain abnormalities in autism. Initially, post-mortem studies showed smaller and more densely packed neurons than usual in the hippocampus, corpus mammillary and amygdala, less density of Purkinje cells in the cerebellum, and neocortical mini-columnar abnormalities (5-7). Subsequently, in vivo magnetic resonance imaging (MRI) investigations showed increased head circumference or macrocephaly in the first 2-3 years of life (8-11). Increased total brain, tempo-parietal lobe, and cerebellar size were the most replicated abnormalities in autism (12-14), along with increased amygdala volumes (15,16) and an antero-posterior gradient of white and gray matter hyperplasia (13). An extensive neural network, involving the fronto-temporo-parietal cortex, limbic system and cerebellum, thus seems to play a role in the pathophysiology of autism, which may be due to abnormal brain growth during early life (13,17,18).

Interestingly, dysfunctional integration of the parietal with prefrontal (i.e. dorsolateral prefrontal cortex) and cingulate regions has also been shown in autism by functional MRI studies during working memory and motor sequence learning (19-24). Furthermore, decreased activity at the right temporo-parietal junction during the process of imitation has been reported (25). According to neuropsychological studies, parietal lobes are also involved in the spatial analysis of sensory afferents (26), in manipulation of objects in surrounding space, in visual attention tasks (27) and in the observation of object-related actions, performed by others, followed by imitation tasks (28). In addition, parietal lesions may be a cause of aphasia or agnosia as well as of difficulties in understanding non-syntactic elements, underlining the
key role of the parietal cortex in speech and language. In the healthy brain, language is subtended by a left neural circuitry involving the frontal, temporal and parietal lobes (29,30), whereas in autism speech deficits may be due to anomalies in the dentato-thalamo-prefrontal pathway and to reversed dominance in the right hemisphere (31). Therefore, there is evidence that the parietal cortex is involved in language and motor functions in humans, although its role in autism is not yet completely clear. The aim of this study was to explore the relationship between parietal lobe volumes and language and motor development in children with autism.

Materials and methods

Sample

A sample of 28 children with autism (mean age±SD=5.75±3.90 years; 25 males) (Table 1) was recruited at the Child Neuropsychiatry Section of the G.B. Rossi University Hospital in Verona, Italy. All the children had a diagnosis of autism spectrum disorder fulfilling the DSM-IV criteria, and these diagnoses were validated through a consensus meeting between a child psychiatrist and a child psychologist. The Childhood Autism Rating Scale (CARS) was administered to measure disease severity (mean±SD=36.46±4.32). The children's developmental quotients (DQ) and intelligence quotients (IQ) were established using the Leiter-R or Griffiths scales for children aged 5-11 years (32). The research was approved by the local ethics committee.

MRI procedure

MRI scans were acquired using a 1.5T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B. A standard head coil was used for RF transmission and reception of the MR signal and foam pads were utilized to minimize head motion. The procedure consisted of: i) scout view; ii) spin-echo (SE), T1-weighted (sagittal plane) images obtained to verify subject's head position and image quality (TR=450 ms, TE=14 ms, FOV=230x230, 18 slices, slice thickness=5 mm, matrix size=384x512); iii) turbo spin-echo (TSE), PD/T2-weighted (axial plane) images, acquired in the axial plane parallel to the anterior-posterior commissure (AC-PC), for clinical neurodiagnostic evaluations (exclusion of focal lesions) (TR=2500 ms, TE=24/121 ms, FOV=230x230, 20 slices, slice thickness=5 mm, matrix size=410x512); iv) 3D MPR sequence (sagittal plane), acquired to obtain 120 images covering the entire brain (TR=1750 ms, TE=3.93 ms, flip angle=15°, FOV=238x238, slice thickness=1.25 mm, matrix size=410x512, TI=1100).

Imaging post-processing

All imaging data were transferred to a PC workstation and analyzed using the BRAINS2 software, developed at the University of Iowa (http://www.psychiatry.uiowa.edu/mhcrcl/pplpages/BRAINS2.htm). The parietal lobes were manually traced in all sagittal slices, according to the protocol of the Laboratory of Neuroimaging (LONI) at the University of California, Los Angeles (http://www.loni.ucla.edu). The landmarks for delineating the parietal lobe included the central sulcus, parieto-occipital sulcus, lateral ventricle, Sylvian fissure, superior temporal sulcus (horizontal and ascending), and anterior calcine sulcus (Fig. 1). The parahippocampal gyrus and the fusiform gyrus were not considered. Using these landmarks, the parietal lobe was defined as the portion of the brain superior and anterior to the parieto-occipital sulcus, posterior to the cen-
The parietal cortex in autism

The parietal lobe was defined as the portion of the brain superior and anterior to the parieto-occipital sulcus, posterior to the central sulcus, and superior to the corpus callosum. To locate the central sulcus on the axial plane, identification of the superior frontal sulcus, which runs directly perpendicular to the pre-central sulcus, was essential. Indeed, the sulcus immediately posterior to the pre-central sulcus is the central sulcus. Delineation began slightly off-center from midline and proceeded laterally in the sagittal plane. Moving from the middle to the side of the brain, after the disappearance of the corpus callosum, the parietal lobe was traced above the lateral ventricle down to the tip of the hippocampus. The inferior boundary was drawn from the hippocampus to the parieto-occipital sulcus. Once the parieto-occipital sulcus had disappeared, the lateral ventricle replaced the hippocampus as the lobe’s inferior boundary, which was then determined, following the disappearance of the lateral ventricle, by the horizontal ramus of the superior temporal sulcus. Drawing continued laterally until it was no longer possible to distinguish cerebral matter.

Intracranial volume, traced in the coronal plane along the border of the brain, included the cerebrospinal fluid, dura mater, sinus, optic chiasm, brainstem, and cerebral and cerebellar matter. The inferior border did not extend below the base of the cerebellum. Tracings were performed by single raters blind to the subjects’ identity and sociodemographic and clinical variables. Two raters achieved high reliability, as shown by intra-class correlation coefficients (ICCs) of 0.99 for the left parietal lobe, 0.96 for the right parietal lobe and 0.97 for the intracranial volume. The ICCs were obtained from tracings of 10 randomly selected scans, performed blindly.

**Statistical analysis**

All statistical analyses were conducted using the SPSS for Windows software, version 11.0 (SPSS Inc., Chicago). Spearman’s correlation analyses were used to examine the associations of age and clinical variables with parietal and intracranial volumes.

**Results**

The age at first word showed a significant direct correlation with left gray matter parietal volumes ($r=0.50$, $p=0.007$), even after correcting for gender and for chronological age ($p<0.05$) (Fig. 2). No significant correlations were found between left white matter ($r=0.26$, $p=0.18$), right gray or white matter volumes ($r=0.23$, $p=0.25$; $r=0.30$, $p=0.13$, respectively), and gray or white matter intracranial volume ($r=0.18$, $p=0.38$; $r=0.15$, $p=0.46$, respectively).

The age at achievement of the ability to sit unaided, a sign of motor development, significantly correlated with left and right parietal white matter volumes ($r=0.45$, $p=0.03$; $r=0.43$, $p=0.04$, respectively), but these associations disappeared when gender or chronological age were taken into consideration ($p<0.05$).

Chronological age was significantly positively associated with intracranial volume (gray matter: $r=0.77$, $p<0.001$; white matter: $r=0.47$, $p=0.013$, respectively) and left (gray matter: $r=0.59$, $p=0.001$; white matter: $r=0.56$, $p=0.002$, respectively) and right parietal volumes (gray matter: $r=0.46$, $p=0.015$; white matter: $r=0.55$, $p=0.002$, respectively).

**Discussion**

This study showed a significant correlation between left parietal gray matter volumes and age at first word in autistic children, i.e. the greater the size of the left parietal lobe the more delayed language development was. This finding suggests that the parietal cortex plays a crucial role in language development in autism. The association of the parietal cortex with human language functioning has been demonstrated extensively.
ic literature indeed reports many cases of aphasias and other language disorders involving the non-syntactic elements of language function (such as lack of tone modulating and lack of understanding of sonority, volume and tone of speech), caused by damage to the left or right parietal lobe (36-38).

More recently, some authors have been speculating on the discovery of a new population of neurons called mirror neurons and have demonstrated that these specific neurons are involved in imitation of actions (28,39,40) and can be activated not only by visual stimuli, but also by auditory and tactile stimuli. In addition to the frontal cortex, mirror neurons have now also been discovered in the inferior parietal lobule, which, together with part of the temporal cortex, constitutes the Wernicke area. Some researchers have demonstrated that mirror neurons of the inferior parietal lobule are activated not only during the observation of an action, but also during the phases that precede that action, which could explain why the human brain is able to predict other people’s intentions. The assumption at the basis of this theory is that intentions are linked to the language domain which, like the imitation domain, is usually impaired in autistic patients (41). Therefore, as argued by many authors (14,42), a genetically determined disruption of neuronal growth, occurring early in life, might also affect the parietal lobe and consequently speech and language abilities in autism. This hypothesis seems to be supported by our finding of increased volumes of the left parietal gray matter in the autistic children who presented delayed language development.

Interestingly, our sample is representative of the general population of autistic children, their clinical presentation matching that of the majority of autistic children (43). On the contrary, most scientific studies in this field include young male adults diagnosed with high-functioning autism or Asperger’s syndrome whose functioning is usually better than that of most of patients with autism. Therefore, we believe that our findings can be generalized to most of the clinical population of children with a diagnosis of autism.

In conclusion, to the best of our knowledge, this is the first structural MRI study showing a significant correlation between left parietal gray matter volumes and language abilities in autism. However, further research, which should also include control children, seems essential to confirm our data. In particular, longitudinal studies should explore the relationship between the parietal cortex and language development by applying innovative techniques such as diffusion tensor imaging to allow a better investigation of parietal microstructure organization.

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References

33. Ania G. Test del Primo Linguaggio. Florence; Giunti O.S. 1995
37. Ibayashi K. [A case of conduction aphasia due to small infarction in the left parietal lobe]. Rinsho Shinkeigaku 2002;42:731-735