Autism: neuroimaging
Autismo: neuroimagem

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Abstract
Autism is a neurodevelopmental disorder with a range of clinical presentations. These presentations vary from mild to severe and are referred to as autism spectrum disorders. The most common clinical sign of autism spectrum disorders is social interaction impairment, which is associated with verbal and non-verbal communication deficits and stereotyped and repetitive behaviors. Thanks to recent brain imaging studies, scientists are getting a better idea of the neural circuits involved in autism spectrum disorders. Indeed, functional brain imaging, such as positron emission tomography, single photon emission tomography and functional MRI have opened a new perspective to study normal and pathological brain functioning. Three independent studies have found anatomical and rest functional temporal lobe abnormalities in autistic patients. These alterations are localized in the superior temporal sulcus bilaterally, an area which is critical for perception of key social stimuli. In addition, functional studies have shown hypoactivation of most areas implicated in social perception (face and voice perception) and social cognition (theory of mind). These data suggest an abnormal functioning of the social brain network in autism. The understanding of the functional alterations of this important mechanism may drive the elaboration of new and more adequate social re-educative strategies for autistic patients.

Keywords: Autistic syndrome; Magnetic resonance imaging; Tomography, emission-computed; Acoustic stimulation; Auditive perception

Resumo
O autismo é um transtorno de neurodesenvolvimento com diversas apresentações clínicas. Essas apresentações variam em gravidade (leves a graves) e são denominadas transtornos do espectro do autismo. O sinal mais comum aos transtornos desse espectro é o déficit de interação social, que está associado a déficits de comunicação verbal e não-verbal e a comportamentos estereotipados e repetitivos. Graças a estudos recentes que utilizam métodos de imagem cerebral, os cientistas obtiveram uma idéia melhor dos circuitos neurais envolvidos nos transtornos do espectro do autismo. De fato, os exames de imagem cerebral funcionais, como tomografia por emissão de pósitrons, tomografia por emissão de fóton único e ressonância magnética funcional abririam uma nova perspectiva para o estudo do funcionamento cerebral normal e patológico. Três estudos independentes encontraram anormalidades da anatomia e do funcionamento em repouso do lobo temporal em pacientes autistas. Essas alterações estão localizadas bilateralmente nos sulcos temporais superiores. Essa região anatômica é de grande importância para a percepção de estímulos sociais essenciais. Além disso, estudos funcionais demonstraram hipoativação da maior parte das áreas envolvidas na percepção social (percepção de faces e voz) e cognição social (teoria da mente). Esses dados sugerem um funcionamento anormal da rede de pensamentos do cérebro social no autismo. A compreensão das alterações nesse importante mecanismo pode estimular a elaboração de novas e mais adequadas estratégias sociais de reeducação para pacientes autistas.

Descritores: Síndrome autística; Imagem por ressonância magnética; Tomografia computadorizada por emissão; Estimulação acústica; Percepção auditiva

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Introduction

Childhood autism is a severe developmental disorder that impairs the acquisition of some of the most important skills for human life. Core clinical features of this disorder include impairment of social interactions, verbal and nonverbal communication deficiencies, limitation of activities and interest, and stereotyped patterns of behavior.1-2

Autism is now considered as an organic cerebral dysfunction thanks to several evidences. These evidences include the fact that mental retardation is associated to autism in 70% of cases (IQ < 70) and seizures in 33% of cases.3,4 In addition, recurrence risk for siblings is approximately 3-5% what corresponds to an incidence 75 times greater than in the general population. This, as well as the high rate of male subjects (3 males to 1 female), suggests that there is a genetic predisposition for this disorder.5-9

Despite these evidences for a cerebral dysfunction underlying autism, the first-generation studies using brain imaging have failed to report consistently localized neocortical brain alterations in this disorder. Structural neuroimaging investigations, including CT-scan and MRI, had indicated various sites of abnormalities in individuals with autism. Structural neuroimaging techniques allow noninvasive and accurate measurements of cerebral glucose metabolism and/or cerebral blood flow (CBF). A large number of strategies can be used in the study of a specific brain disorder using functional brain imaging. Measurements can be performed at rest or during the performance of specific sensory, motor or cognitive task.

This review addresses the main anatomical and functional brain imaging investigations performed in autistic subjects during the last 20 years. Published data can be classified into three different groups: 1) anatomical brain imaging studies 2) rest measurements of regional cerebral glucose metabolism or cerebral blood flow (CBF), mostly performed in primary autistic subjects; 3) studies performed during brain activation paradigms.

1. Anatomical brain imaging in autism

Structural MRI is now currently applied in order to elucidate brain anomalies that can underlie several neurodevelopmental disorders, contributing to the better understanding of brain and behavior relationships during normal and abnormal child development.

The first MRI studies concerning autism were published in the end of the 80’s. Since then about 200 studies have been published. A review of this extensive literature in autism reveals series of non-replicated findings. The main brain structures that were implicated in autism include the cerebellum, the amygdala, the hippocampus, the corpus callosum and the cingulate. While these findings concern the limbic system and the cerebellum, few MRI data helped to explain the neocortical involvement in autism.

A recent convergence of studies that used MRI reported increased total brain volume in autism.10-15 These findings are corroborated by post-mortem studies and documentation of increased head size associated with autism.

The cerebellum was one of the most studied structures in autism. In 1988 a quantitative MRI study showed evidence of hypoplasia of the vermis lobules VI and VII in a group of patients with autism.16 This vermian hypoplasia was not replicated by others researchers, and seems not specifically linked to autism and more related to mental retardation.13,17 Concerning the amygdala, some studies show increased volume,15,18 some described decreased volume19 and others reveal no significant abnormalities related to autism.20 Likewise, to date no consistent hippocampal findings in individuals with autism have been reported. Some studies revealed no hippocampus size anomalies in autism,18,20-22 others reported both decreased volume19 or increased volume of the hippocampus.18 Concerning the cingulate, Haznedar et al., has reported that individuals with autism displayed a decreased volume.20

Several MRI studies of the corpus callosum were performed in individuals with autism. Egaas et al., found that the area of the caudal third of the corpus callosum was reduced in subjects with autism compared to healthy controls.23 This result was confirmed by subsequent studies.17,24 In one of these studies the authors measured the size of the corpus callosum of a sample of autistic individuals and compared these measures to the ones of mentally retarded non-autistic subjects.10,23,25

The lack of replication of localized brain anomalies in autism using quantitative MRI may be attributed to some design methodological limitations. These limitations concern, for example, the inclusion of individuals with various IQ levels, older age range and comorbid epileptic syndromes. Moreover, classical MRI morphometric techniques are based upon region of interest type metrics, what makes these techniques inherently subjective and operator-dependent.

Recently, quantitative structural imaging studies have greatly benefited from both new technologies for data acquisition and new approaches to image analysis. These upgraded methods are also more adequate to the study of complex neocortical abnormalities that may underlie autism. Some very recent results are very promising. Using parametric mesh-based analytic techniques in order to create a three-dimensional model of the cerebral cortex and detailed maps of 22 major sulci in stereotaxic space, Levit et al.26 showed significant differences of cortical sulcal patterns in children with autism. These differences were mainly situated in the frontal and temporal sulci.

New whole brain analysis methods have also intensely improved during the last years. Voxel based morphometry (VBM), which is a fully automated technique, provides a voxel-wise assessment of regional grey and white matter abnormalities in the whole brain without a priori hypothesis about their localization.27 This whole-brain imaging technique enables detection of subtle changes in grey and white matter on a voxel-wise basis between two groups and can provide helpful insights about grey and white matter distribution in autism. Since its publication VBM has generated substantial methodological improvements. A pioneer study in high-functioning adults with autism using VBM was published in 1999 by Abell et al. showing fronto-temporal gray matter...
abnormalities. We performed an anatomical MRI study using optimized whole-brain VBM. In this study, high-resolution 3-D T1-weighted MRI datasets were acquired from 21 children with primary autism (mean age 9.3 ± 2.2 years) and 12 healthy control children (mean age 10.8 ± 2.7 years). By comparing data from autistic children to data from normal children, we found significant decreases of grey matter concentration located bilaterally in the superior temporal sulcus (STS) (p < 0.05 corrected, small volume correction) (Figure 1). It is remarkable that bilateral temporal abnormalities found in autistic children have been replicated in three independent MRI, PET and SPECT studies.

2. Functional brain imaging and autism
1) Functional imaging at rest
Changes in glucose metabolism and CBF reflect changes in the synaptic functional activity. It has been shown that neurons increase their utilization of glucose in direct proportion to their activity. In addition, in normal conditions, the rate of glucose utilization is coupled to CBF.

The first functional studies concerned mainly “primary” or “non syndromic” autism, i.e., excluded patients with identifiable neurological syndromes, seizures or focal signs. In the end of the 80’, due to technical difficulties, the studies have evaluated adult subjects. In these studies, the authors reported rest cerebral glucose utilization (CMRglu) rates measured with PET and 18F-fluorodeoxyglucose (FDG). Normal or near normal regional brain metabolism was observed in adult autistic patients. The first PET study performed in autistic children was described by DeVolder et al. in 1987, but results were compared to adult controls. They found also normal rates and regional distribution of brain glucose metabolism.

In our laboratory we have measured regional CBF (rCBF) with SPECT in primary autistic children and found no evidence of localized brain cortical dysfunction. The lack of focal rCBF abnormalities in autistic children was also confirmed by Chiron et al. These negative results may be explained by some methodological limitations. All studies were performed with low spatial resolution cameras (20 mm). In addition, images were analyzed with the region-of-interest method, which only allowed analysis of large cerebral regions. Thus, well-situated brain abnormalities in autism may have been overlooked with first-generation functional brain imaging techniques.

Some studies were performed in secondary autism (autism associated with a neurological disease). In these studies, functional abnormalities were detected. In autistic subjects with epilepsy, for example, SPECT studies detected fronto-temporal and temporo-parietal hypoperfusion.

Recently, in PET and SPECT studies localized bilateral temporal hypoperfusion in children with autism has been described. Specifically, hypoperfusion was found at rest and centered in the STS and superior temporal gyrus. High-resolution functional imaging and whole brain VBM analysis (Statistical Parametric Mapping software) were used in these studies. Autistic and control groups were matched for age and developmental quotients. Children with idiopathic mental retardation constituted control groups so the findings could not be attributed to the mental retardation. These results are represented in the Figure 1.

Zilbovicius et al. performed an individual analysis of their data comparing each autistic child to the control group. They detected individually a significant temporal hypoperfusion in 16 of the 21 autistic children (77%). In addition, a replication study was performed in an additional group composed of 12 autistic children. This study confirmed both group and individual results. Thus, the bitemporal hypoperfusion has been confirmed in 3 independent groups of autistic children and represents the first robust evidence for temporal lobe dysfunction in school-aged children with autism.

We have also recently performed a correlation analysis in order to investigate a putative relationship between regional rest CBF and the clinical profile of 45 autistic children. Autistic behavior was evaluated with the Autism Diagnosis Interview (ADI-R). Significant negative correlation was observed between rest CBF in the left superior temporal gyrus and the ADI-R score. The higher the ADI-R score, the more severe the autistic syndrome and the lower the rest CBF in the left temporal region.

The temporal regions dysfunction may be implicated in almost every clinical symptoms (perceptive, emotional and cognitive deficit) observed in autism. In addition, temporal associative regions are highly connected with the frontal, parietal and limbic associative sensory systems. Consequently, the dysfunction of the STS may also explain the emotional and cognitive components of autism.

Temporal lobe is thought to be central to the processing of numerous environmental signals that enter the nervous system through visual and auditory sense organs. The temporal lobe is also critical in order to process these signals into structured patterns of neural activity forming the experiences that bring meaning to the world around us.

The STS is increasingly recognized as a key component of the “social brain”. Neuroimaging studies in normal subjects
and single-cell recordings in monkeys have emphasized the role of this structure in the processing of biological movements (movements of the eyes, mouth, hands and body) and in social perception. Such processing may be a prerequisite for higher-level appreciation of the minds of others and is part of a larger cognitive domain referred to as ‘theory of mind’ or social cognition, which is severely impaired in autism. Children with autism also have deficits in the perception of eye gaze, poor eye contact during communication and difficulties accessing information to infer the mental state of others.

Furthermore, there is evidence that the STS is implicated in successful imitation and in human voice perception. These are essential skills for interpersonal communication and are critically impaired in very young autistic children.

The finding of bilateral temporal hypoperfusion extended to primary autism previous results suggesting a link between temporal lobe dysfunction and autistic behavior in children with neurological disorders. Autistic behavior has been reported in clinical temporal lobe pathology, such as epilepsy and herpes simplex encephalitis. In addition, recent neuroimaging studies have shown an association between temporal lobe abnormalities and the occurrence of syndromic autism. In children with infantile spasms, an early bilateral temporal hypometabolism is strongly associated with later emergence of an autistic-like disorder. In children with tuber sclerosis, there is a strong association between temporal lobe tubers detected by MRI and autistic syndrome. In summary, behavioral, lesional, and up to date functional brain imaging studies at rest suggest a link between temporal lobe dysfunction and autistic behavior.

2) Functional brain imaging during cortical activation

The activation studies measure local changes of CBF or blood oxygenation. These factors reflect the variation of synaptic activity during sensorial, cognitive or motor paradigms. The PET, SPECT or fMRI studies realized in autism suggest that autistic subjects activated different brain regions than controls indicating a singular configuration of their cerebral circuits.

Auditory stimulation studies

The first SPECT activation study performed in autistic children was realized in our laboratory. Since autistic children have inadequate reaction to sensorial stimuli, especially in the auditory domain, we looked for an abnormal cortical activation during auditory stimuli (simple non verbal sounds). As predicted, the cortical response was abnormal in the autistic group compared to the non-autistic group. The autistic children activated the right posterior associative cortex unlike the control group who activated the left side.

Similarly, Muller et al have studied 5 high-functioning autistic males and 5 normal adults using PET during verbal and non-verbal sounds listening. The autistic group compared to the control group showed a right hemispheric dominance during verbal auditory stimulation.

More recently, auditory activation PET studies were performed in adults and children with autism during passive listening to speech-like stimuli. Sounds were composed by spectral motion (SM), i.e.: a change in time of acoustic energy maxima frequencies. SM is a crucial component of speech. Both children and adults with autism showed less activation of left temporal word processing network compared to age-matched controls.

These findings suggest that autism is associated with an abnormal pattern of auditory activation of the left temporal cortex. Because the left temporal region is involved in brain organization for language, this abnormal left hemisphere activation could be implicated in autism language impairments and inadequate behavioral response to sounds.

Social perception and mentalizing studies

1. Face perception

Functional neuroimaging studies performed in normal volunteers have showed the presence of a area in the fusiform gyrus (FG) that is more strongly activated during face perception than during perception of any other class of visual stimuli. This area is known as the fusiform face area (FFA). Schultz et al. were the first to use fMRI to study face perception in autistic persons. They found in 14 high functioning individuals with autism or Asperger syndrome a significantly less activation of the middle aspect of the right FG compared to controls.

Hypoactivation of the FFA in autism was replicated in a series of functional studies. Critchley et al. investigated whether or not high functioning people with autistic disorder showed a different pattern of cortical activation when processing facial expressions. Nine autistic adults and 9 age-matched controls were asked to perform explicit (conscious) and implicit (unconscious) identification of emotional facial expressions. Autistics differed significantly from controls in the activation of the cerebellum, the mesolimbic and temporal lobe cortical regions when observing facial expressions (consciously as well as unconsciously). Notably, they didn’t activate the FFA when explicitly appraising expressions. Pierce et al. also used an active perceptual task involving gender discrimination of neutral faces in a sample of six adults with autism and found reduced FFA activation. Hubl et al. showed also FFA hypoactivation in seven adult males with autism using both a gender discrimination and a neutral versus expressive discrimination task. Hall et al used PET in a group of eight high functioning males with autism as compared to eight healthy male controls during an emotion recognition task and also showed hypoactivation of the FFA.

However, two recent studies using different strategies for faces presentation failed to find hypoactivation of FFA in autism.

2. Voice perception

Recent results with fMRI point out the absence of activation of the voice selective area (VSA) in autism similarly to previous functional data that highlighted the absence of normal face processing in autism. In the auditory domain, voice is, as face, at the epicenter of human social interactions. Voice can be thought of as an “auditory face”. Like face, each voice contains in its acoustic structure a lot of information about the speaker’s identity and his emotional state, which we perceive easily. A recent fMRI study identified in normal adults that the VSA is located bilaterally along the upper bank of the STS, confirming previous data showing that the human brain contains regions that are strongly selective to human voice. As proposed by Belin et al., this cortical area can be considered as the equivalent to the FFA in the visual cortex.
Gervais et al., found significant differences in the pattern of brain activation during voice perception among individuals with autism compared to normal controls. In normal controls, listening to voice compared to non-voice sounds significantly activated the VSA (Figure 2). Such VSA activation has been observed in both group and individual analysis. In one study of our group, in accord with our hypothesis, voice perception in autistic group did not yield activation of any specific brain region compared to non-voice sound perception. In the autistic group listening to voice and to non-voice sounds activated the same brain regions. In addition, conversely to individual data obtained in controls, all but one autistic subject did not activate the VSA. The absence of activation of the VSA in autistic was also confirmed by a direct comparison of the two groups’ activation maps. These studies allow us to highlight an abnormal cortical processing during voice perception in autistic patients.

Combining the results of abnormal voice perception with previous results in autism which showed no FFA activation during face perception, we may explain why autistic subjects are known to have difficulties to perceive socially meaningful stimuli. Well then, those data provide new outlook in autism’s understanding, stating a deficit in socially relevant stimuli’s perception, called “Social perception”. And thus, it could allow us to develop new physiotherapy approach, focusing on face and voice perception, in order to lead to a specific and normally innate processing of these stimuli.

Mentalizing tasks

Happé et al. performed a water-labeled PET study to test the ability to recognize mental states of others (theory of mind) that is severely impaired in autistic individuals. They compared normal volunteers and 5 patients with Asperger syndrome, a mild variant of autism with normal intellectual functioning. While listening a story that implicated a theory of mind reasoning, normal subjects activated the left medial prefrontal cortex area 8 of Brodmann. The Asperger patients didn’t activate this left medial prefrontal cortex but an adjacent region area 9/10 of Brodmann. These results suggest that the autistic subjects have an abnormal activation pattern during a cognitive task. This study corroborates with the cognitivist theory and suggests a dysfunction of the brain system that underlies the normal understanding of others’ minds in autism.

Baron-Cohen et al. have tested the social intelligence (theory of mind) of autistic adults. The cerebral activation of 6 autistic men and 12 healthy volunteers was compared during 2 tasks: 1) visual presentations of photographs of eyes and subjects were asked to indicate whether each stimulus was a man or a woman; 2) identical visual presentations but subjects were asked to describe the mental state of the photographed person (test the theory of mind). In normal subjects, the theory of mind test activated two main brain systems: 1) fronto-temporal neocortical regions, comprising left dorsolateral prefrontal cortex, the left medial frontal cortex, supplementary area and bilateral temporo-parietal regions including middle and superior temporal gyri 2) non neocortical areas, including the left amygdala, the left hippocampus gyrus, the bilateral insula, and the left striatum. The autism group activated less extensively the frontal components than the control group and did not activate the amygdala. This study’s results suggest that mental state concepts are also processed in the amygdala when the task involves inferring mental states from eyes and that there is an amygdala dysfunction in autism.

Castelli et al. have studied with PET the cortical activation enhanced by animation of geometric figures. The animations depicted two triangles moving about on a screen in three different conditions: moving randomly, moving in a goal-directed fashion (chasing, fighting), and moving interactively with implied intentions (coaxing, tricking). The last condition frequently elicits descriptions in terms of mental states that viewers attribute to the triangles (mentalizing). Ten able adults with autism or Asperger syndrome and 10 normal volunteers were PET-scanned while watching animated sequences. The autism group gave fewer and less accurate descriptions of mentalizing animations, but equally accurate descriptions of the other animations compared with controls. While viewing animations that elicited mentalizing, in contrast to randomly moving shapes, the normal group showed increased activation in a previously identified mentalizing network (medial prefrontal cortex, STS at the tempo-parietal junction and temporal poles). The autism group showed less activation than the normal group in all these regions. However, one additional region, extrastriate cortex, which was highly active when watching animations that elicited mentalizing, showed the same amount of increased activation in both groups. In the autism group this extrastriate region showed reduced functional connectivity with the STS, which is associated with the processing of biological motion as well as with mentalizing.

More recently, Pelphrey et al. also found in autistic adults an abnormal STS activation in an eye gaze perception task. On congruent trials, subjects watched as a virtual actor looked towards empty space, violating the actor ‘ought to do’ in this context. On incongruent trials, the virtual actor looked towards empty space, violating the...
subject's expectation. In normal subjects incongruent trials evoked more activity in the STS and other brain regions linked to social cognition, indicating a strong effect of intention. The same brain regions were activated during observation of gaze shifts in subjects with autism, but did not differentiate congruent and incongruent trials, indicating that the activity in these regions was not modulated by the context of the perceived gaze shift. These results indicate a difference in the response of brain regions underlying eye gaze processing in autism. The authors suggest that lack of modulation of the STS region by gaze shifts that convey different intentions contributes to the eye gaze processing deficits associated with autism.

Functional brain imaging has been used for the study of some extraordinary autistic cases (autistic savant). For example, a PET activation study was performed in one autistic adult who has an extraordinary capacity to associate a date to the corresponding day of the week. During the activation task the subject was asked to perform these associations (when asking which day of the week was 29 march 1996, he answered Wednesday). This task activated regions that are usually implicated in verbal memory – left hippocampus and left fronto-temporal regions.\(^6\)

In a different strategy, using paradigms that autistics normally perform well or better than normal, Ring and Baron-Cohen tested for a visual search (embedded figure test).\(^7\) Normal controls activated prefrontal cortical areas that were not recruited in the group with autism. However, subjects with autism demonstrated greater activation of ventral occipito-temporal regions. This study suggests that autistic subjects activate different brain regions and that differences in the patterns of regional activation could support distinct models of cerebral processing, underlying embedded figure task performance in the two groups. These differences in functional anatomy suggested that the cognitive strategy adopted by the two groups is different: the normal strategy invoked a greater contribution from working memory systems, while the autistic group strategy depends on an abnormally large extension of visual systems for object feature analysis.

**Conclusion**

Three independent studies have found anatomical and rest functional abnormalities in the temporal lobes of autistic subjects. These anomalies are localized in the STS bilaterally. STS regions are critical for perception of key social stimuli such as biological motion, gaze direction, gesture and facial displays of emotion and are highly connected with other parts of the “social brain” such as the FG and amygdala. All these areas are hypoactive in autism during tasks requiring social cognition suggesting an abnormal functioning of the entire social brain network. This abnormal activation of the social brain involves areas implied in face and voice perception as well as in higher-order social tasks such as making judgments or inferences about social information. Failure to perceive social material could underline the difficulties in extracting mental states from social material (i.e. impairment in theory of mind tasks), which suggests that social communication impairment in autism could be based on abnormal perceptual processing of socially relevant information.

Finally, recent brain imaging studies revealed that abnormal brain perception and processing of social stimuli underlie social impairment in autism. The understanding of such crucial abnormal mechanism may drive the elaboration of new and more adequate social re-educative strategies in autism.

**References**

19. Aylward EH, Minshew NJ, Goldstein G, Honeycutt NA, Augustine AM, Yates KO, Barta PE, Pearlson GD. MRI volumes of amygdala and...


