NEUROIMAGING IN AUTISM
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Summary

Childhood autism is now widely viewed as being of developmental neurobiological origin. Yet, localized structural and functional brain correlates of autism have yet to be established. Functional brain imaging, such as positron emission tomography (PET), single positron emission tomography (SPECT) and functional MRI (fMRI) have opened a new perspective to study normal and pathological brain functions. Three independent studies have found anatomical and at-rest functional temporal abnormalities. These anomalies are localized in the superior temporal sulcus bilaterally, a region critical for perception of key social stimuli. In addition, functional studies have shown hypervigilation 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. The understanding of such crucial abnormal mechanisms may drive the elaboration of novel and more adequate social re-educative strategies in autism.

Key Words: Autism – PET – SPECT – MRI – Brain Imaging – Developmental Disorders

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Introduction

Childhood autism is a severe developmental disorder that impairs the acquisition of some of the most important skills in human life. Core clinical features include impaired social interactions, verbal and non-verbal communication deficiencies, limited activities and interest, and stereotypic patterns of behavior (APA 1994, Kanner 1943).

Autism is now considered as an organic cerebral dysfunction based on several sources of evidence. First, mental retardation is associated with 70% of cases (IQ < 70) and seizures with 33% of cases (Gillberg and Coleman 2000, Gillberg and Coleman 1996). Second, recurrence risk for siblings is approximately 3-5%, corresponding 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 a genetic predisposition (Fombonne 1999, Fombonne 2002, Fombonne 2003, Frith 2003, Rapin and Katzman 1998).

Despite this evidence for a cerebral dysfunction, first-generation studies using brain imaging have failed to report consistently localized neocortical brain dysfunction. Structural neuroimaging investigations, including CT-scan and MRI, have indicated various sites of anatomic abnormalities that include the cerebral cortex, the ventricular system and the cerebellum of autistic adults and relatively old autistic children (for review see Cody et al. 2002). The advent of functional brain imaging techniques, such as positron emission tomography (PET), single photon emission tomography (SPECT) and functional MRI (fMRI), has opened a new and promising way to study brain dysfunction in childhood autism. Both emission tomography 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 tasks.

This review addresses the main anatomical and functional brain imaging investigations performed in autistic subjects during the last 20 years. An overview of published data suggests classification 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 could underlie several neurodevelopmental disorders, contributing to better understanding of brain and behavior relationships during normal and abnormal child development.

The first MRI studies concerning autism were published at the end of the 1980’s. Since these pioneering studies about 200 more have been published. A review of this extensive literature in autism reveals a 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 studies concern the limbic system and the cerebellum, there were few MRI data on neocortical involvement in autism. However, a recent convergence of studies reported increased total brain volume in autism (Courchesne et al. 2001, Piven et al. 1995, Piven et al. 1992, Piven et al. 1996, Sparks et al. 2002). Post-mortem studies and documentation of increased head size associated with autism support these MRI findings.

The cerebellum is one of the most studied structures in autism. In 1988 a quantitative MRI study showed evidence of hypoplasia of the vermician lobules VI and VII in a group of patients with autism (Courchesne et al. 1988). This vermician hypoplasia was not replicated by others researchers, and seems not specifically linked to autism and more related to mental retardation (Piven et al. 1992, Piven et al. 1997).

Concerning the amygdala, some studies show increased volume (Howard et al. 2000, Sparks et al. 2002), some describe decreased volume (Aylward et al. 1999) and others reveal no significant abnormalities (Haznedar et al., 2000). Likewise, to date no consistent hippocampal findings in individuals with autism have been reported. Some studies revealed no hippocampus size anomalies in autism (Haznedar et al. 2000, Howard et al. 2000, Piven et al. 1998, Saitho et al. 1995), others reported both decreased volume (Aylward et al. 1999) or increased volume of the hippocampus (Sparks et al. 2002). Concerning the cingulate, Haznedar et al. have reported that individuals with autism displayed a decreased volume (Haznedar et al. 2000). 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 (Egaas et al. 1995). This result was confirmed by subsequent studies (Manes et al. 1999, Piven et al. 1997) measured the size of the corpus callosum in a sample of autistic individuals and compared them to mentally retarded non-autistic controls. Corpus callosum decreased size was also described by subsequent studies (Cody et al. 2002, Egaas et al. 1995, Pierce et al. 2004).

The possible lack of replication of localized brain anomalies in autism using quantitative MRI may be attributed to some design methodological limitations (IQ heterogeneity, age range of autistic subjects, inclusion of epileptic autistic subjects). Moreover, these classical MRI morphometric techniques are based upon region of interest type metrics, which are inherently subjective and operator-dependent. In addition, such inconsistent results could be due to the well-known heterogeneity of autistic children. Autism does not necessarily represent a unitary disease state and could exhibit some heterogeneity in etiology and pathogenic mechanisms.

Recently, quantitative structural imaging studies have benefited greatly from both new technologies for data acquisition and new approaches to image analysis.

In addition, these upgraded methods are more adequate to the study of complex neocortical abnormalities that could underlie autism, and some very recent results are very promising.

Using a parametric mesh-based analytic technique 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. (2003) showed significant differences in cortical sulcal patterns in children with autism localized mainly in the frontal and temporal sulci.

New whole brain analysis methods have also intensely improved in 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 hypotheses about their localization (Ashburner and Friston 2000). This whole-brain imaging technique enables detection of subtle changes in grey and white matter on a voxel-wise basis between two groups and could provide helpful insights about grey and white matter distribution in autism. A pioneer study in high-functioning adults with autism using VBM was published in 1999 by Abell et al. showing frontal-temporal gray matter abnormalities (Abell et al. 1999). Since this publication VBM has enjoyed substantial methodological improvements. We performed an anatomical MRI study using optimized whole-brain voxel-based morphometry. High-resolution 3-D T1-weighted MRI datasets were acquired in twenty one children with non-syndromic autism (mean age 9.3 ± 2.2 years) and 12 healthy control children (mean age 10.8 ± 2.7 years).

By comparing autistic children to normal children, we found bilaterally significant decreases of grey matter concentration located in superior temporal sulcus (STS) (P < 0.05 corrected, after small volume correction) (Boddaert et al. 2004b) (Figure 1). The major finding of this study is the remarkable consistency between the bilateral temporal abnormalities found in autistic children by three independent MRI, PET (Zilbovicius et al. 2000) and SPECT (Ohnishi et al. 2000) studies (see below).

2. Functional brain imaging and autism

2.1 Functional imaging at rest

Changes in glucose metabolism and CBF reflect changes in synaptic functional activity. It has been shown that neurons increase their utilization of glucose in direct proportion to their activity. In addition, in nor-
mal conditions, the rate of glucose utilization is coupled to CBF.

The first functional studies concern mainly “non-syndromic” autism, i.e., excluding patients with identifiable neurological syndromes, seizures or focal signs. At the end of the 80’s, due to technical difficulties, the studies had focused on adult subjects. They 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 (Herold et al. 1988, Horwitz et al. 1988, Rumsey et al. 1985). The first PET study performed in autistic children was reported 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 (De et al. 1987).

In our laboratory we have measured rCBF with SPECT in primary autistic children and found no evidence of localized brain cortical dysfunction (Zilbovicius et al. 1992). The lack of focal rCBF abnormalities in autistic children was also confirmed by Chiron et al. (1995).

These negative results may be explained by some methodological limitations. They all were performed with low spatial resolution camera (20 mm). In addition, images were analyzed with the region-of-interest method, which only allowed analysis of large cerebral regions. Thus, well-localized brain abnormalities in autism may have been overlooked with first generation functional brain imaging techniques.

Some studies were realized in syndromic autism, which is associated with a neurological disease, and detected functional abnormalities. In autistic subjects with epilepsy, SPECT studies detected fronto-temporal (Gillberg et al. 1993) and temporo-parietal hypoperfusion (Mountz et al. 1995).

Recently, two independent groups have reported a marked bilateral hypoperfusion located in the temporal lobes in autistic children (Ohnishi et al. 2000, Zilbovicius et al. 2000). These results are represented in the Figure 1. They concerned high-resolution functional imaging and voxel-based whole brain analysis (Statistical Parametric Mapping software) (Friston 1995). In both 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.

Ohnishi et al. performed a SPECT study in 23 autistic children and 26 control children. They detected a significant bitemporal hypoperfusion located bilaterally in the superior temporal gyrus (STG) and in the left frontal region.

Zilbovicius et al. performed a PET study in 21 autistic children and 10 control children. They detected a high significant bitemporal hypoperfusion in autistic children located bilaterally in the superior temporal gyrus (STG) and in right superior temporal sulcus (STS).

In addition, 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%). This hypoperfusion was unilateral in 4 autistic children and bilateral in 12. Moreover, a replication group study was performed in an additional group constituted by 12 autistic children and confirmed both group and individual results.

Thus, the bitemporal hypoperfusion was confirmed in 3 independent groups of autistic children and provided the first robust evidence for a localized dysfunction of cerebral cortex in school aged children with primary autism (Figure 1).

The temporal region dysfunction may be implicated in most of the clinical symptoms (perceptive, emotional and cognitive deficit) observed in autism. These association regions are highly connected with the frontal, parietal, limbic and sensory association systems (Pandya and Yeterian 1985). For example, a dysfunction of the auditory cortex may explain why young autistic children are so often misdiagnosed as deaf and why they always have severe communication impairments. Dysfunction of the superior temporal sulcus may explain the emotional and cognitive components of autism, since this multimodal association region is strongly connected with the frontal-parietal and limbic regions. In summary, the 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 to processing these signals into structured patterns of neural activity forming the experiences that bring meaning to the world around us (Gloor 1997).

The STS is increasingly recognized as a key component of the “social brain” (Allison et al. 2000). Neuroimaging studies in normal subjects and single-cell recordings in monkeys have emphasized the role of this structure in the processing of biological movements, including movements of the eyes, mouth, hands and body and in social perception (Allison et al. 2000, Blakemore and Decety 2001). Such a capacity 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 (Baron-Cohen et al. 1985, Frith 2003). Furthermore, children with autism have deficits in the perception of eye gaze, poor eye contact during communication and difficulties accessing information to infer the mental state of others (Klin et al. 2003). There is also evidence that the STS is implicated in successful imitation (Rizzolatti et al. 2001) and in human voice perception (Belin et al. 2000) essential skills for interpersonal communication, which are two critical deficits observed in very young autistic children (Rapin 1997).

The finding of a bilateral temporal hypoperfusion extends to primary autism recent 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 (Chugani et al. 1996). In children with tuber sclerosis, there is a strong association between temporal lobe tubers detected by MRI and autistic syndrome (Bolton and Griffiths 1997).
Temporal Abnormalities in Autism

All of these behavioral, lesion, and recent functional brain imaging studies at rest suggest a link between temporal lobe dysfunction and autistic behavior.

2.2 Functional brain imaging during cortical activation

The activation studies measure local changes of cerebral blood flow (CBF) or blood oxygenation, reflecting the variation of synaptic activity during sensorial, cognitive or motor paradigms. The PET, SPECT or fMRI studies realized in autism suggest that autistic subjects activate various brain regions 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 nonverbal 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 (Garreau et al. 1994).

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 predominant hemispheric dominance during verbal auditory stimulation (Muller et al. 1999).

More recently, auditory activation PET studies were performed in adults and children with autism during passive listening to speech-like stimuli. Sounds were decomposed by spectral motion (SM), i.e., 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 networks compared to age-matched controls (Boddaert et al. 2003, Boddaert et al. 2004a).

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

Social Perception and Mentalizing Studies

Face Perception

Functional neuroimaging studies performed in normal volunteers have showed the presence of an area in the fusiform gyrus (FG) that is more strongly acti-
vated during face perception than any other class of visual stimuli (Haxby et al. 2000, Kanwisher et al. 1997). This area is known as the fusiform face area (FFA) (Kanwisher et al. 1997). 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’s syndrome significantly less activation of the middle aspect of the right fusiform gyrus compared to controls (Schultz et al. 2000). Hypoactivation of the FFA was replicated in a series of functional studies (Crick et al. 2000, Piercy et al. 2001, Hall et al. 2003, Hubl et al. 2003). Critchley et al. investigated whether or not high functioning people with autistic disorder showed a different pattern of cortical activation when processing facial expressions (Critchley et al. 2000). Nine autistic adults and 9 age-matched controls were asked to perform an explicit (conscious) and an 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 a cortical face fusiform area (fusiform gyrus) when explicitly appraising expressions. Piercy 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 (Piercy et al. 2001). Hubl et al. also showed FFA hypoactivation in seven adult males with autism using both a gender discrimination and a neutral versus expressive discrimination task (Hubl et al. 2003). 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 showed hypoactivation of the FFA (Hall et al. 2003). However, two recent studies using different strategies for face presentation failed to find hypoactivation of FFA in autism (Hadjikhani et al. 2004, Pierce et al. 2004).

Voice Perception

Recent results with fMRI point out the absence of activation of the voice selective area in autism and are in agreement with previous functional data in autism highlighting abnormal face processing (Gervais et al. 2004). In the auditory domain, voice is, as face, at the epicenter of human social interactions. Voices can be thought of as “auditory faces”. Like a 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 voice-selective areas in normal adults located bilaterally along the upper bank of the superior temporal sulcus (STS) (Belin et al. 2000). 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 significantly activated a “voice-selective area” located bilaterally along the upper bank of the STS. This result confirms 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 could be considered as the counterpart of the “Face Fusiform Area” in the visual cortex, an area specialized in face perception. Such “voice-selective area” activation was observed in both group and individual analysis. In accord with our hypothesis, voice perception in the autistic group did not yield activation of any brain region compared to non-voice 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 “voice-selective area”. The absence of activation of the “voice-selective area” in autistics was also confirmed by a direct comparison of the two groups’ activation maps. These results can be combined with previous results in autism using fMRI, which showed no Face Fusiform Area activation during face perception. Autistic subjects were, in fact, already known to have difficulties in perceiving socially meaningful stimuli in the visual world. That study now allows us to highlight an abnormal cortical processing during voice perception. Moreover since voice contains in its acoustic structure a lot of socially relevant information, such as identity and emotional state, we thus have evidence for difficulty in social perception in the auditory world. Those data therefore provide a new outlook in the understanding of autism, arguing for a deficit in the perception of socially relevant stimuli, “social perception”. This could thus enable us to develop a new physiotherapy approach, focusing on face and voice perception, aiming to instill a specific and normally innate processing of these stimuli.

Mentalizing Tasks

Happe et al performed a water-labeled TEP study to test the ability to recognize the mental states of others (theory of mind) that is severely impaired in autistic individuals (Happe et al. 1996). They compare normal volunteers and 5 patients with Asperger’s syndrome, a mild variant of autism with normal intellectual functioning. During listening to a story that required 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 rather 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 cognitivist theory and suggests a dysfunction of the brain system that underlies the normal understanding of others’ minds in autism (Happe et al. 1996).

Baron-Cohen et al. have tested the social intelligence (theory of mind) of autistic adults (Baron-Cohen et al. 1999). The cerebral activation of 6 autistic men and 12 healthy volunteers was compared during 2 tasks: 1) visual presentations of photographs of eyes for which subjects were asked to indicate whether each stimulus was a man or a woman; 2) identical visual presentations, but for which subjects were asked to describe the mental state of the person photographed (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, left medial frontal cortex, supplementary cortex and bilateral temporoparietal regions including middle and superior temporal gyri and 2) non-
neocortical areas, including the left amygdala, the left hippocampal gyrus, the bilateral insula, and the left striatum. The autism group activated the frontal components less extensively than the control group and did not activate the amygdala. This study suggested that mental state concepts are also processed in the amygdala when the task involves inferring mental states from eyes and that there is an amygdalar dysfunction in autism.

Castelli et al. have studied the cortical activation enhanced by animation of geometric figures with PET (Castelli et al. 2002). 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 (coaching, tricking). The last condition frequently elicited descriptions in terms of mental states that viewers attributed to the triangles (mentalizing). Ten task-capable adults with autism or Asperger’s 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, superior temporal sulcus at the temporoparietal 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 superior temporal sulcus, an area associated with the processing of biological motion as well as with mentalizing.

More recently, Pelphrey et al. also found in autistic adults an abnormal superior temporal sulcus (STS) activation in an eye gaze perception task (Pelphrey et al. 2005). On congruent trials, subjects watched as a virtual actor looked towards a checkerboard that appeared in her visual field, confirming the subject’s expectation regarding what 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 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 suggests 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 allows 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 asked 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 frontotemporal regions (Boddaert et al. 2005).

In a different strategy, using paradigms that autistics normally perform well or better than normals, Ring and Baron-Cohen tested visual search (embedded figure test) (Ring et al. 1999). Normal controls activated prefrontal cortical areas that were not recruited in the group with autism. However, subjects with autism demonstrated greater activation of ventral occipitotemporal 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 at-rest functional temporal abnormalities. These anomalies are localized in the superior temporal sulcus 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 fusiform gyrus and amygdala. All these areas are hypoactive in autism in 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 underlie 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 social impairment in autism are underlied by abnormal brain perception and processing of social stimuli. The understanding of such crucial abnormal mechanisms may drive the elaboration of new and more adequate social re-educative strategies in autism.

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