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Functional morphological imaging of autism spectrum disorders: Current position and theories proposed

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Abstract Autism is a pervasive disorder of childhood development. Polymorphous clinical profiles combining various degrees of communication and social interaction with restricted and stereotyped behaviour are grouped under the heading of 'autism spectrum disorders' (ASD). Many teams are trying to pick out the underlying cerebral abnormalities in order to understand the neuronal networks involved in relationships with others. Here we review the morphological, spectroscopic and functional abnormalities in the amygdala-hippocampal circuit, the caudate nuclei, the cerebellum, and the frontotemporal regions, which have been described in subjects with ASD. White matter abnormalities have also been described in diffusion tensor imaging, leading to suspected damage to the subjacent neural networks, such as mirror neurones or the social brain.

Autism is a pervasive developmental disorder with an estimated prevalence of six children per 1000 [1].

Since Kanner's first description in 1943 [2], the view of autism has changed greatly, and the term 'autism spectrum disorders' (ASD) nowadays includes polymorphous clinical profiles combining early, lasting and extensive abnormality in the areas of communication (verbal and non-verbal) and reciprocal social interactions with restricted, stereotyped behaviour [3,4]. Autism is a condition which appears very early, but while certain signs (absence of visual contact, imitation behaviour, etc.) may alert those around the child

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before he or she is 2—3 years old, paradoxically it is diagnosed on average only at about 6 years of age [5]. Diagnosis is above all clinical and requires the coordinated involvement of a multidisciplinary team (psychologists, paedopsychiatrists, etc.) working with members of the profession able to provide genetic and neurological consultations [5]. Autistic traits are found in many pathological neurodevelopmental conditions, but when no specific aetiology can be shown, we speak of 'non-syndromic autism'.

While autism has primarily been related to psychiatric and relational disorders, the hypothesis of an at least partly organic aetiology has gradually been accepted over the last 30 years [6]. Characterisation of an organic substratum to autistic disorders has obviously exploited the incredibly rapid growth of neuroimaging techniques, so that since the first MRI papers appeared at the end of the 1980s [7], 780 studies have been published on the subject. Nevertheless, imaging results can suffer from at least two types of bias, which doubtless explains certain contradictory data: insufficient definition of the nosological context and selection bias concerning subjects included in the imaging studies. With the wide clinical polymorphism of ASD, precise clinical characterisation of the patients studied is a prerequisite for any study, in particular for imaging. Defining this nosological context depends on standardised diagnostic methods, such as the Autism Diagnostic Interview - Revised (ADI-R) [8] or the Childhood Autism Rating Scale (CARS). Selection bias is linked to the fact that not all autistic subjects can take part in MRI protocols requiring perfect immobility, or, in the case of functional MRI, requiring active participation without sedation.

The objective in producing this review is to bring together the aspects of current knowledge concerning the morphological and functional differences associated with abnormalities of cerebral function which hinder the relationship with others in ASD. We will also present the paths which have begun to be explored by current imaging techniques, in the hope of highlighting the points which are relevant for diagnosis as early as possible, as this is the key to appropriate management.

Autism and macrocephaly

Macrocephaly is a physical difference regularly observed in autistic subjects [9,10] and was part of Kanner's original observations [2]. Even if a large skull does not necessarily mean a large brain, many papers have assessed brain volume in subjects with ASD by measuring head circumference [11], by MRI [12], or at autopsy [13]. The 15 main studies on this subject were used in 2005 in a meta-analysis [10] that showed abnormal brain growth dynamics: head circumference being normal at birth — even slightly reduced during the first 2 months [14] — followed by an abnormally rapid phase of growth leading to macrocephaly at the end of the first year of life. After a plateau phase, head circumference becomes normal. The fact that macrocephaly can appear secondarily raises several questions. Is it an acquired abnormality, an increase in gliogenesis, etc., or is it the consequence of less effective elimination of pre-existing neuronal connections (*neuronal pruning*) [15]?

Target regions with morphological, spectroscopic and functional abnormalities

The choice to specifically study certain target regions was guided both by pre-existing neuropsychological theories and clinical observations or autopsy studies.

The amygdaloid bodies and the medial temporal structures

The amygdaloid bodies (Fig. 1) are deep structures forming part of the limbic system [16] close to the Papez circuit (amygdala-hippocampus-thalamus) (Fig. 2). They have been attributed a role in perception and showing emotions (fear, anger, sexual pleasure, distaste, etc.) and in interfacing with the system developing memory. Since Brothers' work [17] they are considered to be one of the pillars of the social brain and damage to them [18] may induce social adaptation disorders recalling those of autism. On the other hand, certain autistic disorders are associated with the presence of a hamartoma in the amygdaloid body in individuals with Bourneville's disease (tuberous sclerosis) [19]. Consequently, the amygdaloid bodies were one of the first targets studied in autism.

Histopathological abnormality has been reported in the amygdaloid bodies [14,20], in which the neurones are smaller and more numerous and described as 'tightly packed'.

Using SPECT, Onishi et al. [21] showed a positive correlation between reduction in perfusion of the right amygdalo-hippocampal regions and the severity of autistic symptoms, particularly resistance to change.

Spectroscopy has also found abnormalities: a reduced NAA/Cr ratio has been reported in the medial part of the right temporal lobe related to a fall in NAA in this region [22]. This reduction in the NAA/Cr ratio, interpreted as an alteration to the neural integrity of the amygdalo-hippocampal structures, is positively correlated [23] with the severity of social behaviour abnormalities assessed by the CARS.

Temporal lobe

Many studies have referred to the structural and functional differences in the temporal lobes in autistic subjects [24—27]. The main abnormalities concern the superior temporal sulcus and the ventral-basal temporal region, involved in decoding social stimuli: voices, faces, changes in the direction of gaze. Alteration in these regions may produce an inability to pick out features relevant for defining the mental state of another individual and, because of this, may account for the difficulties encountered by autistic subjects in entering into a relationship with others.

Superior temporal sulcus (STS)

Brodman area 21 (BA 21) [28] is mainly situated on the inferior edge of the STS, while BA 22 (the auditory association area) is found on the superior edge, contiguous with BA 42 (the primary auditory cortex). Owing to the proximity of the areas involved in hearing and language, the STS

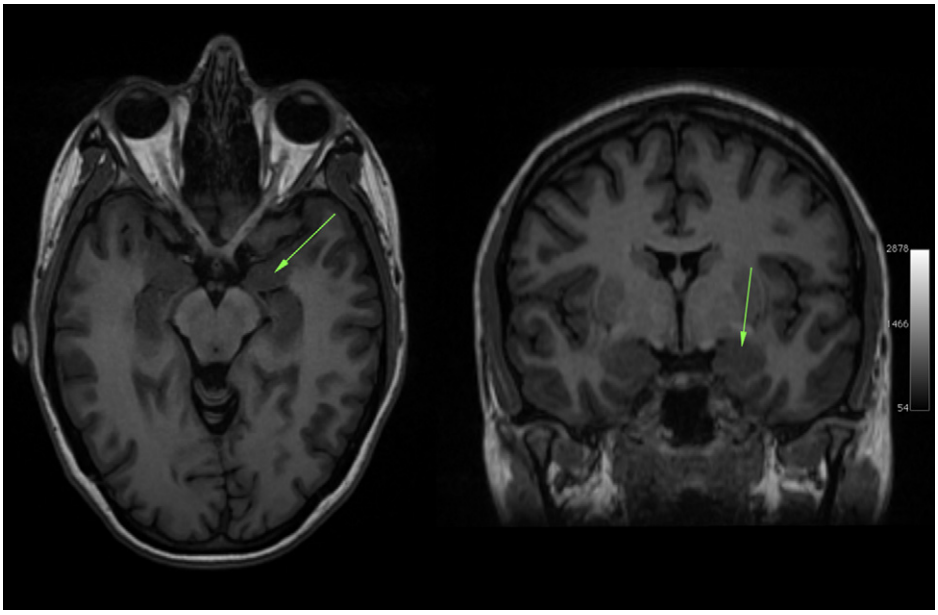

Figure 1. T1 3D FSPGR axial and coronary slices passing through the amygdaloid bodies (arrow). These oval nuclear complexes are located in front of the hippocampi and opposite the rostromedial and rostrodorsal walls of the temporal horns of the lateral ventricles [16].

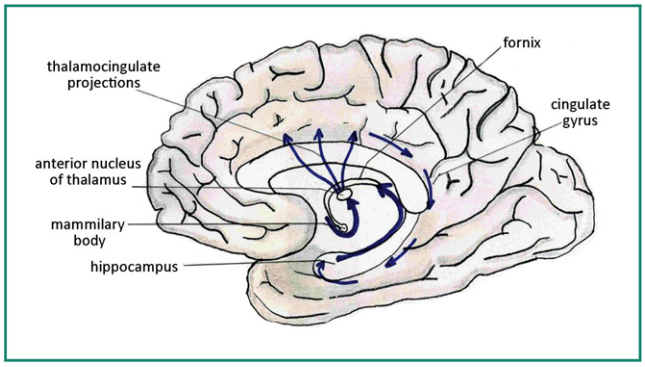

Figure 2. Diagram representing Papez' hippocampo-mamillo-thalamic circuit, described between the hippocampus, the posterior commissure of the fornix, the mammillary body, the anterior nucleus of the thalamus, then the cingulate gyrus via thalamocingulate projections.

has been targeted by studies concerning autism. Observation of a lack of preference for the mother's voice in an infant is one of the first warning signs for suspecting an ASD [29]. Using fMRI, Gervais et al. [26] observed cortical activation of these regions while listening to vocal and non-vocal sounds, in autistic and control subjects. Hearing a human voice caused significant activation of the two STS in control subjects, but it was observed that the subjects with ASD did not activate them. They however presented a normal cortical response for non-vocal sounds.

Several MRI morphometric studies using voxel-based morphometry (VBM) have found a reduction in concentration of the grey matter of the STS. This abnormality was found bilaterally by Boddaert et al. [24], but solely on the left side (in BA 22 and BA 42) by McAlonan et al. [30], with a reduction in the concentration of grey matter of 25% relative to the control group.

Two independent studies performed on sedated sleeping subjects have revealed temporal perfusion abnormalities. Using PET, Zilbovicius et al. [31] showed hypoperfusion of the superior temporal gyri (BA 22 and BA 42) extending to the STS on the right side. Ohnishi and his team [21] identified a bilateral reduction in regional blood flow in the insulae and the superior temporal gyri (BA 22), using SPECT with technetium-99m. The reduction in blood flow in the left superior temporal gyrus has even been positively correlated with the severity of autistic disorders [25].

The STS and the superior temporal areas — areas of cognitive processing of sounds and the human voice — have a less concentrated cortex and appear to be less well perfused, therefore, in autistic subjects.

Face fusiform area (FFA)

One of the diagnostic criteria for autism is the lack interest in faces [3]. The right fusiform or lateral occipitotemporal gyrus (Brodman area 37) includes an area (the FFA, Face Fusiform Area) specifically activated by control subjects during facial recognition, and particularly by the triangular eyes-nose-mouth area. A recent VBM study noted abnormally concentrated grey matter in the right fusiform gyrus of autistic subjects [32].

Cognitive processing of faces by autistic subjects does not occur in the same way as by control subjects. It was first suggested that they do not use the FFA when they visualise faces but rather activate the inferior temporal gyri, allocated, in control subjects, to processing common objects [33,34]. Moreover, functional MRI has shown hypoactivation in the FFA during facial observation tasks [35]. We cannot, nevertheless, reduce the difficulties that autistic subjects encounter to simple prosopagnosia, and we know, through eye-tracking techniques, that they do not fix on the eyes-nose-mouth area [36] when they are shown a face, unlike a control group which is capable of what is known as a

'holistic' facial recognition [37]. To date it has been established that autistic subjects are quite capable of activating their FFA [38] if their attention is forced onto faces, the classically described hypoactivation being in fact probably related to avoiding the stimulus presented. Having said that, the activation that can be observed in the FFA of autistic subjects for faces expressing an emotion remains less intense than in the control group [39] (Fig. 3).

Frontal lobe

Perfusion abnormalities, as in the temporal lobe, have been detected by Ohnishi's team with SPECT [21] in the left medial prefrontal cortex (BA 9 and BA 10) and in the anterior cingulate gyrus (Brodman area 32). Positive correlation has been shown between hypoperfusion in these regions and the severity of autistic disorders, particularly concerning social components. In addition to these perfusion abnormalities, VBM measurements in subjects with ASD have indicated reduced cortical thickness in the middle frontal and bilateral orbital regions [30] and in the inferior frontal gyrus (where neurones with 'mirror' properties have been described) [38].

Cerebellum

We now know that the functions of the cerebellum by far exceed just motor coordination, to which they were thought to be limited until recently, and that cerebellar lesions can produce what has been described as a 'cerebellar cognitive affective syndrome' (combining a lack of visual/spatial and executive functioning, language and behavioural disorders, and dulling of affects) [40]. The hypothesis that the cerebellum plays a role in modulating social and cognitive functions has been borne out by a study reporting a series of cases of behavioural disorders close to those observed in autism in children surgically treated for tumours of the vermis [41]. Cerebellar function has therefore been studied in autistic subjects, and it seems that the activation pattern of the different cerebellar areas during motor tasks is not the same as it is in control subjects. For example, it has been observed in autistic subjects that during a simple motor task (pressing on a button when the instruction ''Go'' appears), there is an increase in motor activation in the anterior cerebellar hemisphere and the homolateral vermal lobule VI compared with the control group [42,43].

In autoptic studies [14,44] a reduction has been reported in autistic subjects in neurone size (particularly of the Purkinje cells) in the cerebellar hemispheres and the vermis of the neocerebellum after reaching 12 years of age (from 5 to 12 years old these neurones are numerous and enlarged). Several morphometric MRI studies on the vermis [45,46] have also shown hypoplasia (lobules VI and VII) in subjects with ASD when compared with a control group. This was confirmed by a meta-analysis published in 2008 by Stanfield et al. [27,47].

Another argument for cerebellar neurone abnormality has furthermore been provided by spectroscopic studies,

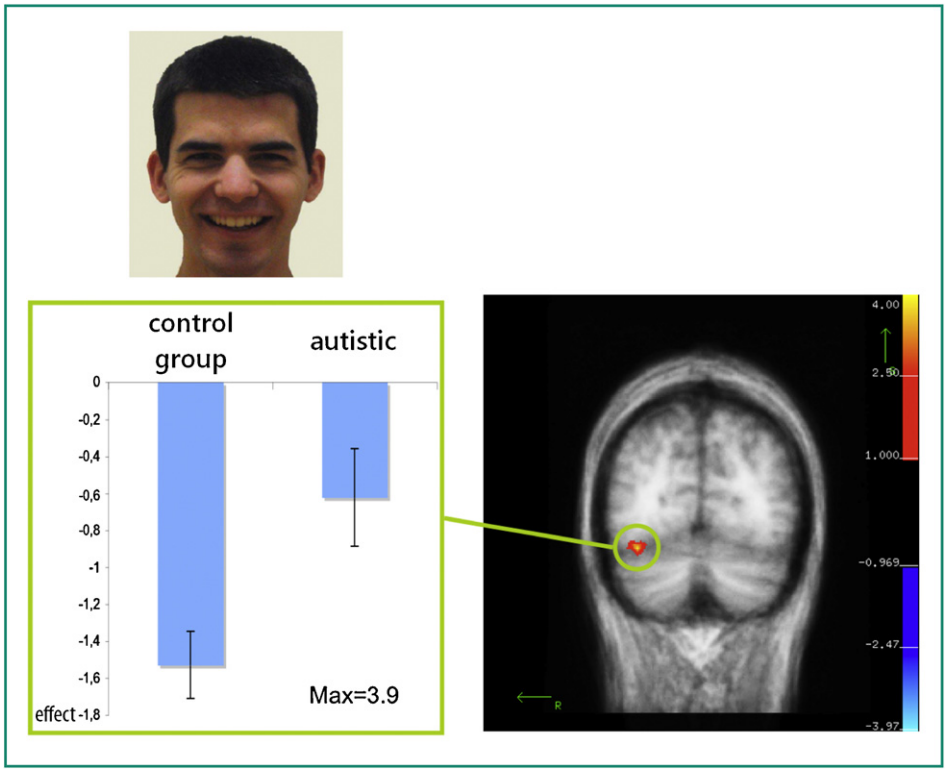

Figure 3. fMRI study made during passive observation of neutral and expressive faces (see example above) in autistic subjects and in a control group: in the autistic subjects, less activity is seen in the right fusiform gyrus (Talairach coordinates: 38-74-14; $P < 0.01$ not corrected) when observing the expressive face than observing the neutral face, compared with the control group. Graph showing the mean effect size for control and autistic subjects, for neutral face/expressive face contrast [38].

which have demonstrated a reduction in NAA (a neurone integrity marker) in the left cerebellar hemisphere [22], or even throughout the whole cerebellum [43,48].

Caudate nuclei

One of the diagnostic criteria for ASD depends on observation of ritualistic, repetitive behaviour and some resistance to change. These stereotypic, repetitive behaviour patterns have been compared to those seen in obsessive-compulsive disorders, which are known to be associated with structural and functional abnormalities of the basal ganglia [49].

This has encouraged several teams to study them in autistic subjects, in whom manual contouring [50,51] then VBM [32,47,49] found the caudate nuclei to be of greater volume. Langen et al. [49] showed an increase in volume of the heads of the caudate nuclei with age (while their volume decreased with age in the control group), and a positive correlation between the volume of the caudate nuclei and repetitive behaviour.

In a spectroscopic study, Levitt et al. [52] found an approximately 20% increase in choline and creatinine levels in the head of the right caudate nucleus, associated with a reduction in NAA and creatinine levels in the body of the left caudate nucleus. These abnormalities have been interpreted as reflecting an alteration in energy metabolism there.

Mirror neurones and the social brain: neuronal network theories

Autism and a defective mirror neurone mechanism

The mirror neurone mechanism generates internal representations of actions, whether they are performed or just simply observed by a subject. It was initially described in a group of neurones of the F5 area (the frontal premotor cortex) of a macaque monkey, which were activated both when it brought something to its own mouth and when it saw a man bring something to his mouth [53]. It is now agreed that a mirror neurone mechanism also exists in humans [54], associating the inferior parietal lobule (IPL, BA40) and the inferior frontal gyrus, (pars opercularis —BA44— and triangularis —BA45— of the inferior frontal gyrus), and the insula and anterior cingulate gyrus [55]. Somatotopic organisation of neurones with mirror properties has been described for various types of action [56]. When we observe others taking action, therefore, we can make sense of their actions and automatically understand their behaviour (even their intentions), because we observe them via the internal representation of our own actions. This mirror neurone mechanism, together with the limbic system, is thought to be a structure for learning by imitation or even for being able to empathise [57].

Hadjikhani et al. [38] showed that in people with ASD, there is thinning of the cortex of the frontal opercular and inferior parietal regions belonging to the mirror neurone system, with a positive correlation between the degree of cortical thinning and the severity of the autistic disorders.

Moreover, several functional MRI studies have provided evidence of mirror neurone system dysfunction. During imitation tasks, hypoactivation has been shown in the opercular regions of subjects with ASD [43,58], even though the imitations performed by the people in this group were correct. Martineau et al. [43] found hyperactivation in these same opercular regions, when compared with a control group, during simple observation of hand movements. It would seem that the mirror neurone system is activated in a different way in autistic subjects when observing movement, and that the strategies used by these subjects to imitate use different neuronal networks.

The social brain

The social brain is a concept developed by Brothers from the 1990s [17]. It functionally associates the amygdaloid bodies, the temporal areas decoding social stimuli (the fusiform area for the face, and the superior temporal sulcus for gazing and changes in its direction), the inferior frontal cortex (including the operculum, where 'mirror' properties are described), and a region associating the precuneus and posterior cingulum. VBM measurements in the McAlonan study found that the cortex was less concentrated in each of these regions [30]. In addition, using MRI, Kleinhans' team studied functional connectivity in autistic subjects [59] during cognitive processing of faces. They reported less functional connection between the right FFA on the one hand and the amygdaloid body, the precuneus and posterior cingulum on the other, than in a control group. The more severe the social components of the autistic syndromes, the more the connections between the FFA and the other structures of the social brain were altered.

On publication of a review of the literature concerning abnormalities of facial perception in autistic subjects, Schultz proposed a heuristic model of the physiopathology of autism [60]. The hypothesis is that an abnormality in the development of the amygdaloid bodies has distal consequences on social brain structures downstream (e.g. the STS and FFA, where morphological and functional abnormalities have been reported) (Fig. 4). By not receiving the stimulation provided by the amygdaloid efferents from the social brain 'in time', these structures seem to permanently lose a large part of their functional capacity (as in people who are blind from birth who remain so even if they recover a functional visual effector).

Autism and white matter (WM): the challenges for neuroimaging research

A retrospective study performed on a cohort of 77 children with ASD [61] reported a 48% level of white matter (WM) abnormality visible in conventional sequences, which corresponded to two endophenotypes: the first had dilated Virshow-Robin spaces, and the second had WM abnormalities associated with dedifferentiated appearance of the temporal pole (Fig. 5). These WM abnormalities corresponded to punctiform or plaque T2 hypersignals opposite the posterior horns of the lateral ventricles. Although non-specific, these

abnormalities could have indicated damage to the subjacent neuronal connections.

In diffusion studies, the WM of autistic subjects has many abnormal foci of fractional anisotropy (FA) —sometimes increased, sometimes decreased— indicating just as many areas of abnormality of the WM microstructure. Such abnormalities have been reported in the temporal region [62—64] (particularly adjacent to the right fusiform gyrus [64]), the bilateral frontal gyri [63,64] and the right cingulate gyrus [63]. Sundaram et al. reported that within the frontal lobe, FA abnormalities concern the short association fibres, while the long fibres seemed to have normal fractional anisotropy [65].

The corpus callosum also appears to be abnormal in autistic subjects. In a meta-analysis which appeared in 2009 [66], Frazier and Hardan concluded that the volume of the corpus callosum decreases overall in subjects with ASD, and that this reduction in volume is predominantly in the anterior part of the corpus callosum. It is also in the anterior region of the corpus callosum [67] that there is the greatest reduction in FA.

'Weak central coherence', the theory developed by Frith [68], goes hand in hand with the retained ability to process data (an ability which is sometimes hypertrophied in so-called 'high level' autistics), without being able to connect them to each other. This abnormality is illustrated by the persistent preoccupation of autistic subjects with parts of an object, a face or a scene, rather than with the object, face or scene as a whole [29].

The abnormalities of the microstructure of the WM revealed by diffusion imaging lend weight to the hypothesis of dysconnectivity between the parts of the different neuronal networks involved in relational life.

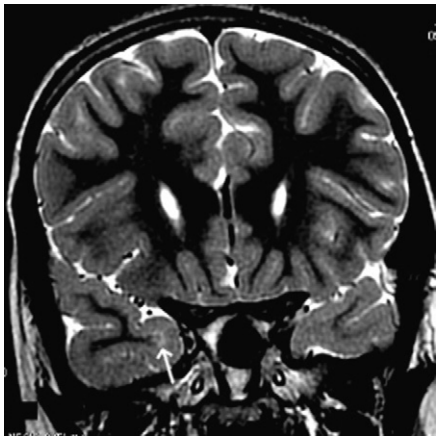

Figure 5. T2 coronary slice showing a subcortical temporopolar hypersignal indicating a maturation defect in this 10-year-old autistic child.

Conclusion

A growing number of teams are keenly working to characterise the encephalic abnormalities that can be detected in subjects with ASD. While the first imaging studies initially reported abnormalities in several isolated sites, the most recent hypotheses have moved towards a network deficiency involving several regions of the brain.

There is indeed a range of morphometric, spectroscopic, scintigraphic and functional evidence for the concomitant involvement of several cerebral regions — the cerebellum, the caudate nuclei, the amygdaloid bodies, the ventrobasal and superior temporal regions (decoding centres for social stimuli such as voices, gaze, and faces), and the frontal

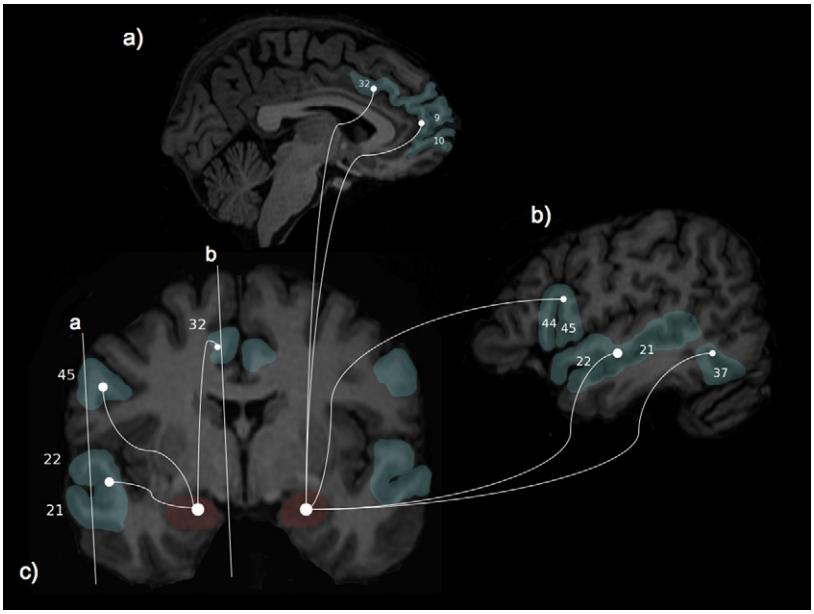

Figure 4. Diagram representing (in blue) the cortical areas (according to Brodman) efferent from the amygdaloid bodies (in red) in which spectroscopic, morphometric and/or functional abnormalities have been found [16]. On slice (c), the lines indicate the planes of the oblique sagittal slices (a) and (b). According to Brodman [28]: dorsolateral (BA9) and anterior (BA10) prefrontal cortex, middle (BA 21) and superior (BA 22) temporal gyrus, dorsal anterior cingulate cortex (BA 32), fusiform gyrus (BA37), pars opercularis (BA 44) and pars triangularis (BA 45) of the inferior frontal gyrus.

Box 1 Diagnosis of autism: current practices.

- a request for an MRI makes complete sense when it is made in the context of specialist multidisciplinary management;
- even if there is no specific iconographic marker for autism, a morphological MRI at the time of the initial diagnosis helps detect associated abnormalities (e.g. signs suggesting tuberous sclerosis [Bourneville's disease] or neurofibromatosis). Spectroscopy is also recommended to detect possible creatinine deficiency (which presents clinically as a picture of mental retardation and relational difficulties and which could be treated);
- professional practice recommendations for diagnosing autism advise the following sequences [5]:
  - 3D T1 acquisition (or failing this, sagittal T1),
  - coronal T2 slices perpendicular to the hippocampi,
  - coronal FLAIR slices perpendicular to the hippocampi,
  - spectroscopy (TE: 144 or TE 35),
  - T2 axial slices,
  - (injection of contrast agent not necessary).

and inferior parietal regions involved in the mirror neurone system.

However, no data has yet provided sufficiently strong evidence to act as a real iconographic marker for autism, diagnosis of which remains clinical (Boxed text 1). One of the aims of imaging research is nevertheless to be able to use diagnostic tools as early as possible so as to be able to stimulate the brain regions for social cognition as soon as possible, before they lose their potential to develop.

Expansion of the techniques for exploring the WM, particularly the techniques for studying morphological and functional connectivity statistically (by diffusion and fMRI, respectively) [69,70], may in the future allow exploration of the paths suggested concerning dysconnectivity between the various parts of the neuronal networks which underpin relationships to others.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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