The functional neuroanatomy of autism

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Summary

Autism is a neurodevelopmental syndrome characterized by impaired social and executive functions. Functional magnetic resonance imaging (fMRI) is a non-invasive technique that allows investigation of the neural networks underlying cognitive impairments in autism. In this article, brain imaging studies investigating the functional brain anatomy of autism are reviewed. Face recognition, theory of mind and executive functions have all been explored in functional neuroimaging studies involving autistic patients. The available literature suggests an involvement of abnormal functional mechanisms in face recognition, mentalization and executive functions in adults with high-functioning autism or Asperger's syndrome, possibly due to brain maturation abnormalities, and resulting in dysfunctional reciprocal cortico-subcortical connections. Future functional neuroimaging research should investigate subgroups of autistic children and adolescents longitudinally and attempt to integrate genetic, cognitive and empirical approaches. Such studies will be instrumental in furthering understanding of the pathophysiology of autism and in exploring the importance of dimensional measures of the broader phenotype currently defined as autism.

KEY WORDS: brain imaging, fMRI, MRS, neuroimaging, PET, SPECT.

Introduction

Autism is a pervasive neurodevelopmental syndrome mainly characterized by poor social communication, inadequate response to others' emotions, and stereotypic and obsessive behaviors (1). Individuals with classic autism also have delayed language development and, in most cases, mental retardation or learning disabilities; people with Asperger's syndrome, on the other hand, present no history of significant language delays or abnormalities and have normal or superior intellectual abilities, but still show impairments of social interaction. Structural magnetic resonance imaging (MRI) investigations have reported increased total brain, parieto-temporal lobe, and cerebellar hemisphere volumes in autism (2). Magnetic resonance spectroscopy (MRS) studies have found evidence for decreased synthesis and increased degradation of prefrontal cortical membranes (3) and reduced concentration of N-acetyl-aspartate (NAA) in the amygdala, hippocampus, cingulate, Wernicke's area and cerebellum (4-7) in subjects with autism. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have shown temporal and frontal lobe hypoperfusion (8-10) and abnormal temporal cortex activation during auditory tests (11,12). On the basis of these findings, it has been suggested that structural and biochemical abnormalities in neural networks involving the fronto-temporo-parietal cortex, limbic system, and cerebellum underlie the pathophysiology of autism (2). These changes could possibly result from abnormal neuronal development during early life, which may be a result of or triggered by genetic and environmental factors.

Functional MRI (fMRI) is an imaging tool that, allowing non-invasive examination of the functional brain architecture of individuals with autism during performance of experimental tasks, makes it possible to study the relationship between regional brain activation and psychopathological symptoms (12). Technically, fMRI explores oxygen consumption and distribution in biological tissues, exploiting the para-magnetic properties of the oxygenated and deoxygenated hemoglobin molecule (blood oxygen level dependent technique, BOLD). During the activation of a specific brain region there is increased blood flow in that region with relatively re-
duced oxygen extraction fraction, and consequently reduced deoxyhemoglobin levels (13). The BOLD effect is the basis of most fMRI investigations that attempt to elucidate the neural basis of higher cognitive functions. This review summarizes findings from functional neuroimaging studies performed in autism, divided into three categories of investigation: face recognition, theory of mind and executive functions. We discuss the limitations of the fMRI studies conducted to date and outline perspectives for future investigations in this field.

Searching and evaluating fMRI studies in autism

Through a comprehensive Medline search of the period 1966-October 2003, and manual search of bibliographic cross-references, we identified all original fMRI research papers, published in English, that have included autistic patients. We rated each paper for completeness on the basis of a 12-point check-list divided into 3 categories: subjects (items 1-4), methods used for image acquisition and analysis (items 5-10) and results and conclusions (items 11,12) (2). The 12 criteria in the check-list were:

1) Patients were evaluated prospectively, specific diagnostic criteria were applied, and demographic data are reported;
2) Healthy comparison subjects were evaluated prospectively, psychiatric and medical illnesses were excluded, and demographic data are reported;
3) Major confounding factors (e.g., age, gender, IQ, handedness, socioeconomic status, educational level, height, total brain measures) were controlled, either by stratification or statistically;
4) Sample size per group ≥ 10;
5) Tasks administered during the fMRI session were standardized and related to the hypothesis of the study;
6) Measures of brain activation are reported;
7) MRI tesla ≥ 1.5;
8) Task procedures and measurement of region of interest (ROI) activity are described clearly enough to be reproducible;
9) Measurements are described clearly enough to be reproducible;
10) ROIs were defined a priori or an exploratory approach is justified;
11) Statistical parameters for significant and important non significant differences are given;
12) Conclusions are consistent with results and limitations are discussed.

Without any intent to criticize either the investigators or the studies themselves, the completeness of these published studies was thus rated with a numeric score. Half points were assigned when criteria were partially met.

Face and emotion recognition

Recognition of individual facial expressions facilitates the understanding of emotional information that is necessary for adequate interpersonal and social relationships. Individuals with autism and Asperger’s syndrome make little eye contact and seem to treat people as if they were objects, tendencies that could be related to their aberrant social and affective functions (14). Neuro-psychological studies have shown specific impairments in face recognition in patients with autism, such as decreased ability to identify faces, and lack of ability to process faces as whole images, these subjects instead concentrating on parts of the face (e.g., the lower face and mouth area) (15-19).

Abnormal brain activation during face discrimination has been found, in functional neuroimaging studies, in adults with high-functioning autism or Asperger’s syndrome (Table I). Specifically, increased activity in the bilateral inferior temporal gyrus (ITG), right thalamus, left superior temporal gyrus (STG), and left peristriate visual cortex has been found in subjects with autism, but not in healthy controls, when they process facial features (identity) and facial expressions (emotion) (20-22). In controls, on the other hand, the ITG has been found to be the area most strongly associated with object processing (21). Furthermore, control subjects showed activation in the right fusiform gyrus (FG) (21-23), left cerebellum, left amygdalohippocampal complex, left middle temporal gyrus (MTG) (24), and left inferior and middle frontal gyrus (MTG) (22,25) during face discrimination, while the autistic patients did not.

Physiologically, face recognition (perceived holistically) and object recognition (processed analytically) are subtended by separate neural systems employing different strategies or algorithms (26-28). The fusiform, lateral occipital, parahippocampal and posterior inferior temporal gyri are involved in common object perception (29,30). On the other hand, the neural system involved in recognition of faces includes the ITG (early perception of facial features), lateral FG (invariant aspects of faces, i.e., identity), superior temporal sulcus (STS) (changeable aspects of faces, e.g., eye gaze) and amygdala (emotional significance of facial expressions) (31-35). None of the brain regions subtending face processing in individuals without social disability was found to be significantly active in autistic populations (20-23).

Specifically, abnormal activity within the medial temporal lobe (i.e., amygdalohippocampal junction, ITG, STG, and MTG), peristriatal visual cortex, and thalamus has been described in autism, possibly explaining some of the social deficits observed in these patients. It is thus possible that individuals with autism do not have a cortical specialization for face recognition, and that they employ, instead, the same neurocircuitry that is used for object processing. A critical test would be to explore, using fMRI, face recognition performance before and after interventions intended to motivate young subjects with autism to look at, and to take an interest in, faces (‘Look at me’ followed by a reward for doing so) (18). Eye tracking movement investigations during fMRI would also be crucial to further explore the correlation of configural/segmental strategies with activation of face processing brain systems.

Theory of Mind

‘Theory of Mind’ (ToM) or ‘mentalization’ is the cognitive capacity to infer others’ mental states (thoughts, desires and beliefs) in order to explain their behavior (36). This function is usually acquired in normal children in the first 3-4 years of life. ToM can be seen as a mea-
sure of social intelligence, that is, of the ability to interact in complex social groups and in close relationships, to mediate self-reference and to predict how others will feel, think and behave (18,37). People with autism have deficits in their ability to think of other people in terms of mental states (36,38).

Three functional brain imaging studies have investigated the role of ToM in adults with high-functioning autism or Asperger's syndrome, showing impaired task performances and abnormal brain activation (Table II, see over). These tests investigated the ability to attribute mental states to others, using the story comprehension paradigm (39), photographs of other people's eyes (40), and animated sequences (41). In general, high-functioning autistic or Asperger's syndrome subjects were found to show reduced activation of the STG, STS, and basal temporal areas, and no activation of the amygdala (40) and left medial prefrontal cortex (Brodmann's area 9/10) (39,41). In contrast, hyperactivation of an unusual prefrontal area was noted (Brodmann's area 9/10) (39). Also, fewer and less accurate interpretations during mentalizing tasks were revealed in subjects with autism compared to normal controls. However, it should be noted that individuals with Asperger's syndrome have also been shown to be capable of conversing with others about mental states (42). This finding could reflect possession of a second-order ToM, which may help performance on experimental tasks, but still does not facilitate social adaptation in real life (43). Additionally, the relationship between the deficits in ToM and the degree of social dysfunction in autistic patients remains unclear.

In normal individuals, mentalization has been shown to be associated with a complex brain network including the cingulate, medial prefrontal/orbitofrontal cortex, amygdala, STS and STG (44-49), in which the prefrontal regions may be the execution component and the posterior regions (temporal and parietal) the representational component (50). In particular, the cingulate is active during error monitoring and selection between competing responses, the orbitofrontal cortex mediates decision making, the dorsomedial prefrontal cortex is involved in the regulation of the amygdala (51), and the hippocampus and parahippocampal cortex mediate the storage of episodic and semantic memory (52).

### Table I - Functional brain imaging studies investigating face processing in autism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Autistic patients</th>
<th>Controls</th>
<th>Methods</th>
<th>Findings in autism</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schultz et al. (21)</td>
<td>14 male ADI, ADOS &amp; ICD-10 AU (8) or AS (6), right-handed</td>
<td>28 normal males right-handed</td>
<td>fMRI 1.5T</td>
<td>– abnormal face performance</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>23.8±12.4 y-o; IQ=109.5±19.5</td>
<td>21.6±8.9 y-o; IQ=109.6±16.8</td>
<td>Tasks: object and face discrimination</td>
<td>– active in patients during face task: right and left ITG</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>– active in controls during face and object task: right FG and ITG, respectively</td>
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</tr>
<tr>
<td>Critchley et al. (20)</td>
<td>9 male ADI &amp; ICD-10 AU (2) or AS (7), right-handed</td>
<td>9 normal males right-handed</td>
<td>fMRI 1.5T</td>
<td>– normal task performance</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>37±7 y-o; IQ=102±15</td>
<td>25.5±2.8 y-o; IQ=116±10</td>
<td>Task: face emotion recognition</td>
<td>– active in patients: left STG and left perisylvian visual cortex</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>– active in controls: right FG and left cerebellum, amygdalohippocampal region and MTG</td>
<td></td>
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<tr>
<td>Pierce et al. (23)</td>
<td>7 male ADI &amp; ADOS DSM IV AU</td>
<td>8 healthy subjects</td>
<td>fMRI 1.5T</td>
<td>– normal task performances</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>4 right-handed</td>
<td>4 right-handed</td>
<td>Task: face and shape perception</td>
<td>– reduced bilateral FG and left amygdala activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.5±8.0 y-o (21-41); IQ=83.7±10.9 (72-102)</td>
<td>28.3±0.9 (20-42); IQ=supposed normal</td>
<td>– normal activation of ITG and MTG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hall et al. (22)</td>
<td>8 male DSM IV AU (6) or AS (2), right-handed</td>
<td>8 healthy males</td>
<td>H$_{15}$O PET</td>
<td>– increased number of errors during task</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>20-33 y-o; IQ=105±18 (80-130)</td>
<td>right-handed</td>
<td>Task: face and voice emotion recognition</td>
<td>– increased activation in right thalamus, right anterior temporal lobe and left AC during emotion recognition</td>
<td></td>
</tr>
<tr>
<td>Ogai et al. (25)</td>
<td>5 DSM IV AU</td>
<td>9 normal controls</td>
<td>fMRI 1.5T</td>
<td>– normal task performances</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>right-handed</td>
<td>right-handed</td>
<td>Task: face emotion recognition</td>
<td>– reduced activation in left MFG during fear recognition and in left insula, left IFG and left putamen during disgust test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.8±5.9 y-o; IQ=112.4±10.5</td>
<td>23.0±5.2; IQ=113.3±5.2</td>
<td>– normal activation during happy face recognition</td>
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</tr>
</tbody>
</table>

**Abbreviations:** AU=autism, AS=Asperger; ADI=Autism Diagnostic Interview-Reviewed; ADOS=Autism Diagnostic Observation Schedule; ITG=inferior temporal gyrus; FG=fusiform gyrus; STG=superior temporal gyrus; MTG=middle temporal gyrus; AC=anterior cingulate; MFG=middle frontal gyrus; IFG=inferior frontal gyrus; y-o=years old; PET=positron emission tomography.
critical for self reference, the amygdala modulates social emotional stimuli, the STG is crucial in processing signals of intention coming from motion of other agents (e.g., human body movements) and the STG is involved in phonological and auditory processing. Thus, on the basis of the neurophysiology of ToM and functional neuroimaging studies exploring ToM in autism, it is conceivable that the brain system subserving ToM in humans is abnormally hypoactive in autistic subjects, and does not involve the amygdala and left medial prefrontal cortex.

**Executive functions**

Generally, the term executive functions refers to a group of higher-level neuropsychological capacities that allow the maintenance of a problem-solving mindset appropriate to the attainment of a goal (18), like planning of behavior, inhibiting automatic actions and retaining information in the working memory (51). Neuropsychological studies have shown impairments in executive and language abilities in autism (52,53), which may underlie inflexibility and difficulty adapting to novel situations, while functional neuroimaging studies have been employed in adults with high-functioning autism to elucidate the brain regions that subserve abnormal executive functions. These studies are described below.

**Working memory**

In an fMRI study, Ring et al. (54) found that people with autism or Asperger’s syndrome show a trend to slightly better performance than normal controls on the Embedded Figures Task (EFT), a test – to find simple shapes hidden within complex forms – that investigates information processing relating to object feature analysis. The group with autism showed a right-sided activation of an area near the junction of the middle occipital and middle temporal regions (Brodmann’s area 17/18/19), whereas in normal controls the right dorsolateral prefrontal cortex (DLPFC) and bilateral parietal and occipital cortex were activated (Table III). Also, the subjects with autism employed an approach characterized by fewer demands on working memory during the EFT task, but greater activity in some of the regions involved in object perception. In another fMRI report, Luna et al. (55) found that patients with autism were significantly less able than healthy individuals to shift their eyes accurately to remembered target locations in the oculomotor delayed response (ODR) task (assessing spatial working memory). On the other hand, their performance in the visually guided saccade (VGS) task (assessing basic sensorimotor and attention processes) was unimpaired (Table III). Furthermore, the autistic patients presented no deficits in saccade velocity, duration or latency in either the ODR or the VGS tasks, indicating normal sensorimotor processes and preserved cerebellar and subcortical mechanisms. Furthermore, in the ODR versus VGS comparison, individuals with autism were found to show significantly less activation bilaterally in the DLPFC and posterior cingulate cortex compared to healthy subjects. In normal individuals, parietal regions are involved in visual attention and in spatial processing, whereas the ventrolateral prefrontal cortex (Brodmann’s area 46), inferior parietal lobe (Brodmann’s 40) and MFG (Brodmann’s 6) have been reported to be implicated in working memory (56-58). In particular, during visuospatial working memory processing, the DLPFC integrates sensory information and response plans over time, while the posterior cingulate monitors sensory events related to spatial orientation and memory (59,60). The findings of Ring et al. (54)

### Table II - Functional brain imaging studies investigating theory of mind in autism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Autistic patients</th>
<th>Controls</th>
<th>Methods</th>
<th>Findings in autism</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happe et al. (40)</td>
<td>5 male right-handed AS 24 y-o (20-27) IQ=100 (87-112)</td>
<td>6 retrospective male controls, right-handed 38 y-o (24-65)</td>
<td>H215O PET Task: story comprehension</td>
<td>– worse scores on ToM stories, but not on physical stories or unconnected sentences</td>
<td>7.5</td>
</tr>
<tr>
<td>Baron-Cohen et al. (39)</td>
<td>6 DSM IV &amp; ICD-10 AU or AS 4 M, right-handed 26.3±2.1 y-o IQ=108.5±10.5</td>
<td>12 normal controls 6 M, right-handed 25.5±2.8 y-o IQ=110±8.5</td>
<td>fMRI 1.5T Task; photographs of other person’s eyes</td>
<td>– impaired task performances</td>
<td>8</td>
</tr>
<tr>
<td>Castelli et al. (41)</td>
<td>10 DSM IV AU or AS 33±7.6 y-o IQ=not reported (high-functioning)</td>
<td>10 normal controls 25±4.8 y-o IQ=supposed normal</td>
<td>H215O PET Task; silent animation sequences</td>
<td>– ↓ mental state attribution during task</td>
<td>9</td>
</tr>
</tbody>
</table>

**Abbreviations**: AU=autism, AS=Asperger; ADI=Autism Diagnostic Interview-Reviewed; ADOS=Autism Diagnostic Observation Schedule; M=males, ToM=theory of mind; STG=superior temporal gyrus; IFG=inferior frontal gyrus; FG=fusiform gyrus; TmP/Am=temporal pole adjacent to amygdala; STS=superior temporal sulcus; SFG=superior frontal gyrus; y-o=years old; PET=positron emission tomography; ↑ or ↓=ab normal enhanced or reduced activation.

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### Table III - Functional brain imaging studies investigating executive functions in autism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Autistic patients</th>
<th>Controls</th>
<th>Methods</th>
<th>Findings in autism</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ring et al. (54)</td>
<td>6 AU or AS DSM IV &amp; ICD-10, 4 M, all right-handed</td>
<td>12 normal controls, 6 M, all right-handed</td>
<td>fMRI</td>
<td>– normal task performance</td>
<td>10.5</td>
</tr>
<tr>
<td>Lona et al. (55)</td>
<td>11 ADI &amp; ADOS, 9 M, 9 right-handed</td>
<td>6 healthy males, right-handed</td>
<td>fMRI</td>
<td>– active in patients: right cuneus, right middle and inferior occipital gyrus</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>Motor control, language and attention</strong></td>
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<tr>
<td>Muller et al. (65)</td>
<td>4 DSM IV AU men, 3 right-handed</td>
<td>5 healthy males, right-handed</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O PET</td>
<td>– reduced accuracy in shifting eyes to remembered target locations in the ODR task; normal VGS task</td>
<td>9.5</td>
</tr>
<tr>
<td>Muller et al. (62)</td>
<td>7 male DSM IV &amp; ADI, 4 right-handed</td>
<td>7 healthy males, right-handed</td>
<td>fMRI</td>
<td>– increased bilateral parieto-occipital &amp; controlateral prefrontal activation</td>
<td>9.5</td>
</tr>
<tr>
<td>Allen &amp; Courchesne (64)</td>
<td>8 ADI, ADOS &amp; DSM IV AU, 7 M</td>
<td>8 healthy controls, 7 M</td>
<td>fMRI</td>
<td>– normal attention and motor task performance accuracy</td>
<td>10</td>
</tr>
<tr>
<td>Muller et al. (63)</td>
<td>8 male ADI &amp; DSM IV AU, 5 right-handed</td>
<td>8 healthy males, 5 right-handed</td>
<td>fMRI</td>
<td>– increased number of errors during task</td>
<td>10.5</td>
</tr>
<tr>
<td>Belmonte &amp; Yurgelun-Todd (66)</td>
<td>6 ADI &amp; DSM IV AU (5) or AS (1) right-handed</td>
<td>6 right-handed normal controls</td>
<td>fMRI</td>
<td>– normal task performance</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**Abbreviations:** AU=autism, AS=Asperger; ADI=Autism Diagnostic Interview-Reviewed; ADOS=Autism Diagnostic Observation Schedule; EFT=Embedded Figures Task; ODR=oculomotor delayed response; VGS=visually guided saccade; DLPPC= dorsolateral prefrontal cortex; VOC=ventral occipital cortex; MFG=middle frontal gyrus; SFG=superior frontal gyrus; y-o=years old; PET=positron emission tomography.
and Luna et al. (55) suggest that dysfunctional integration among neocortical regions (DLPFC, posterior cingular, and parietal cortex) underlies the visual search and spatial components of working memory in autism. On the contrary, no abnormalities were found in the circuitry participating in basic sensorimotor control of saccadic eye movements (55). This could be consistent with Frith’s theory of ‘weak central coherence’ (61) according to which the distinctive cognitive style of autism is characterized by predominance of piecemeal analysis over configural processing. Thus, people with autism would seem to employ a more local approach to the processing of complex stimuli, involving an incremental process rather than a ‘normal’ use of working memory and a global approach.

Motor control, language and attention

One functional brain imaging study reported the presence, during visually paced finger movement, of significant hyperactivation in parieto-occipital lobes and controlateral prefrontal cortices in the autistic group, as opposed to significantly increased activation in the controlateral sensorimotor cortex (i.e., peri-rolandic and supplementary motor areas) in the controls (62). Moreover, the strongest activations were located along the controlateral central sulcus in the primary motor and somatosensory cortices in control subjects, while their location varied from patient to patient in the autistic group, being observed particularly in the prefrontal and controlateral regions. Subsequently, the same group of researchers (63) showed that, during visuo-motor learning tasks, i.e., visually driven motor sequence learning (finger press movements), subjects with autism showed greater activation of prefrontal and posterior/inferior parietal cortices and less activation of superior parietal and occipital foci than normal individuals. Furthermore, increased spatial variability of activation foci was found in autism. Exploring cerebellar functions, Allen and Courchesne (64) showed diffuse hypopreactivation during motor task and hyperactivation during attention condition in autism. Specifically, abnormal patterns of activation were seen in the right superior hemisphere VIIa (superior semi-lunar lobe) and in lobule VI. On the contrary, only minimal cerebellar activation during a sensory test (i.e., only visual stimuli without the request to pay attention or respond) was observed both in the autistic and in the control subjects (Table III).

In a study investigating language functions (i.e., listening, repeating, and generating sentences), high-functioning adult autistic men showed abnormally low activation in the left DLPFC, left thalamus and right dentate nucleus during the receptive and expressive conditions and abnormally high activation in the left DLPFC and right dentate nucleus during motor speech functions (65). Moreover, the normal left-sided lateralization of language activation in the DLPFC during verbal auditory task, and in the thalamus during expressive language condition, were reversed in the autistic group. Interestingly, a recent fMRI study (66) found that, during a visual spatial attention task, high-functioning adult individuals with autism activated ventral occipital and striatal cortices instead of the normal network (i.e., the DLPFC, superior parietal cortex, MTG, MFG, and premotor cortices). Furthermore, in the autistic group, the normal tendency to activate the left ventral occipital cortex during right attention was reversed (Table III). In normal individuals, basic motor functions are subtended by the supplementary and pre-supplementary motor areas, primary sensorimotor cortices and paleo-cerebellum (67). Also, cortical activation associated with language functions is strongly lateralized to the left hemisphere and involves a network of regions in the frontal, temporal and parietal lobes (i.e., Broca’s area, located in the inferior frontal gyrus; Wernicke’s area, encompassing the superior temporal, supramarginal and middle temporal gyri; and the posterior superior temporal gyrus) (68-70). The altered neurofunctional organization reported in autism in relation to motor control and language functions (62,64,65) may potentially represent the functional substrate compensating the complex stereotyped behavior and delayed language acquisition associated with this condition. In particular, impaired development of the primary motor and somatosensory cortices (located along the central sulcus) and cerebellum may underlie motor anomalies, whereas maldevelopment of the dentato-thalamo-prefrontal pathway and reversed dominance in right hemisphere may underlie language deficits (Table III).

Limitations of and future perspectives for fMRI studies in autism

Although our check-list ratings, presented in the last column of the tables, show that the quality of fMRI investigations in this field has improved over recent years, available fMRI studies nevertheless present several methodological limitations. The majority of the studies enrolled small groups of adult high-functioning patients, often mixed with individuals with Asperger’s syndrome, without comorbidity epilepsy or other neurological disorders. Thus, the sample is not completely representative of the general autistic population and the results cannot be generalized to low-functioning individuals with autism or to autistic children/adolescents. Regarding fMRI studies in general, it should be noted that the experimental tasks implemented in these investigations were not always specifically related to the hypotheses the studies set out to test (71). Additionally, the exact spatial specificity of fMRI, the accuracy of the functional maps when compared with the actual sites of neuronal activity, and the nature of the fMRI signals when correlated with processes that define neuronal signaling are all aspects that remain to be determined (72,73).

Future functional neuroimaging studies should attempt to overcome the sample and design limitations of earlier investigations. First, fMRI investigations should investigate longitudinally larger samples of young individuals with autism, using individuals very closely matched for age, gender, socioeconomic status and IQ. However, as fMRI is very difficult to perform in children with autism, one possible strategy could be to use appropriate neuropsychological tasks outside the scanner for children and to utilize similar tasks inside the scanner for older children, adolescents and adults. Use of this strategy may not solve the problem, but it would help in
the generalization of the results to all subgroups. Considering homogeneous subgroups of individuals affected by autism would facilitate understanding of the time frame of development of specialized brain functions underlying cognitive abilities in autism, allowing better understanding of the links between neurofunctional anatomy and behavioral features in this condition. Also, areas of activation should be considered individually by manually tracing the relevant anatomy, in order to increase the spatial localization of functional brain maps. Improvements to task design and imaging sequences could include shorter spin-echo times, the averaging of a greater number of signals to boost the signal-to-noise ratio, and gradient-coil shimming tailored to individual subjects.

Concluding remarks

The available functional brain imaging literature points to the existence of aberrant neural networks subverting facial recognition, mentalization and executive functions in autism. Specifically, abnormal activity within the medial temporal lobe and peristriatal visual cortex may underlie deficits in face recognition, while abnormally low activation in a brain system that includes the orbitofrontal cortex, STS and STG may subvert mentalization. With regard to executive functions, dysfunction in integration of the DLPFC, posterior cingulate cortex, and parietal cortex may underlie working memory impairments, while disturbances of the primary motor and somatosensory cortices and cerebellum may underlie motor anomalies. Finally, language deficits may be subtended by abnormalities in the dentato-thalamo-prefrontal pathway and reversed dominance in the right hemisphere, while selective attention may activate an aberrant network including the ventral occipital cortex and striatum. Thus, information is not processed normally by multimodal brain systems, even though the visual system is intact. According to the ‘experience-expectant’ model of neural plasticity, cortical regions are genetically pre-programmed to become specialized for a particular function, but exposure to appropriate stimuli is necessary for that specialization to occur (74). Synaptic connections are produced in these brain areas during the period of cortical specialization and are rapidly and selectively strengthened or eliminated, depending on the stimuli received. The perceptual neural system thus adapts to input received from the environment (e.g., exposure to faces). Also crucial to the correct development of this brain system are visuo-spatial abilities and the natural inclination for social communication and interaction. It can be hypothesized that an aberrant ‘expectant’ neural system involved in face recognition, mentalization and executive functions would not be able to process correctly environmental stimuli, and that this would ultimately lead to the activation of alternative (and aberrant) brain circuitry. Early impairment of brain maturation, gene mutations, inappropriate expression of neurotrophins, and environmental factors could all play a major role in this process (2,75). Moreover, the innate failure to respond to external stimuli would mean failure to stimulate synaptic plasticity and pruning during sensitive periods for the development of neural cognitive networks.

In summary, future functional neuroimaging research should investigate longitudinally subgroups of autistic children and adolescents with homogeneous demographic and behavioral features. Also, brain imaging techniques should be integrated with genetic, cognitive and empirical approaches. This will be instrumental in furthering understanding of the pathophysiology of autism and in exploring dimensional measures of the broader autistic phenotype, such as face recognition or social brain.

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