The nature of brain dysfunction in autism: functional brain imaging studies

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Current Opinion in Neurology 2010, 23:124–130

Purpose of review

Functional magnetic resonance imaging studies have had a profound impact on the delineation of the neurobiologic basis for autism. Advances in fMRI technology for investigating functional connectivity, resting state connectivity, and a default mode network have provided further detail about disturbances in brain organization and brain–behavior relationships in autism to be reviewed in this article.

Recent findings

Recent fMRI studies have provided evidence of enhanced activation and connectivity of posterior, or parietal-occipital, networks and enhanced reliance on visuospatial abilities for visual and verbal reasoning in high functioning individuals with autism. Evidence also indicates altered activation in frontostriatal networks for cognitive control, particularly involving anterior cingulate cortex, and altered connectivity in the resting state and the default mode network. The findings suggest that the specialization of many cortical networks of the human brain has failed to develop fully in high functioning individuals with autism.

Summary

This research provides a growing specification of to the neurobiologic basis for this complex syndrome and for the co-occurrence of the signs and symptoms as a syndrome. With this knowledge has come new neurobiologically based opportunities for intervention.

Keywords

autism, connectivity, fMRI

Curr Opin Neurol 23:124–130

1350-7540

Introduction

Functional magnetic resonance imaging (fMRI) studies have had a profound impact on the understanding of the neurobiologic basis for autism and autism spectrum disorders (ASD). Initial studies led to the delineation of many neural systems for brain–behavior relationships in ASD. Some relationships were previously well established, but others were elucidated in response to distinctive impairments in autism. This body of research clearly established autism and its signs and symptoms as being of neurologic origin, decomposed the unusual complex behavior into recognizable neural components, and established autism as a distributed neural systems disorder that disproportionately impaired many higher order abilities. The second phase of fMRI research in autism focused largely on the development of functional connectivity fMRI (fc-fMRI) methods and evidence that established autism as a disorder of underconnectivity among the brain regions participating in cortical networks. Supporting evidence of network dysfunction was provided by increased cerebral white matter volume on structural MRIs in very young but not older children with autism, accompanied by a diffuse increase in cortical gray matter volume. This constellation, together with other evidence, identified the cortical neuron(s) as the unit of dysfunction in autism. The growth dysregulation, i.e. early brain overgrowth followed by growth plateau, was classic evidence of disturbances in developmental neurobiologic events, specifically neuronal organizational events. Notably though, all developmental trajectories for brain growth are seen in autism, suggesting considerable heterogeneity in the specific underlying genetic mechanisms affected. With the discovery of about 20 mostly rare genes or gene mutations that are each involved in a molecular aspect of the development of neuronal connections, the fMRI and genetic findings in autism closed a loop that validated a developmental neurobiological based model of autism. Recent fMRI studies in autism focus on further articulation of functional connectivity disturbances, further delineation of the neural bases of deficits and skills, and delineation of disturbances in higher levels of brain organization related to control and regulation of thinking, feeling, and behaving.

Task-related functional connectivity

Task-related fc-fMRI studies have provided the most direct and extensive evidence of alterations in cortical connectivity in autism and led to the reconceptualization of autism as a distributed cortical systems disorder resulting from underdevelopment of systems connectivity [1,2] This shift was supported by structural imaging data documenting accelerated brain growth beginning by 9–12 months of age coincident with the onset of symptoms and composed of increased total cerebral gray and white matter volumes [3] Underconnectivity of cortical systems is now a widely accepted characterization of the structural and functional brain abnormality in autism. The initial index of functional underconnectivity was reduced synchronization between fMRI-measured activation in co-activating cortical areas [1], which was subsequently demonstrated across a wide range of tasks to broadly involve cerebral-association cortex [2].

Reduced frontal-posterior cortical connectivity

Over the course of many studies, frontal-posterior underconnectivity emerged as a common finding [4••]. It was found to be related to white matter properties [5], and was proposed to represent a constraint on the capacity of cortical networks to coordinate information processing, akin to a limitation in bandwidth in computational modeling [2]. These fMRI studies also established functional underconnectivity in these cortical systems and disturbances in integrative information processing as the basis for the clinical deficits that define autism. As regards potential implications for remediation of underconnectivity in autism, it is noteworthy that 10 weeks of reading intervention in poor readers resulted in improved reading and measureable changes in cortical connectivity and white matter [6•].

Enhanced dependence on visuospatial abilities and parietal-occipital circuitry

The second characteristic of the altered task-related cortical connectivity in autism has been enhanced activation of occipitoparietal areas. This activation pattern was hypothesized to result from increased local connectivity posteriorly and to account for the unusual strengths also typical of autism. The dissociation between impaired higher order skills and intact basic skills was commonly characterized in the past in terms of a distinction between verbal and visuospatial abilities, rather than in terms of reduced frontal and enhanced posterior neural connectivity. A recent fMRI study of the neural networks underlying visuospatial and linguistic reasoning has provided direct evidence that verbal individuals with average intelligence quotient (IQ) scores and autism (HFA) have increased activation and intact connectivity of occipito-parietal and ventral temporal circuits, greater reliance on visuospatial skills for solving both visual and verbal problems, and reduced activation and connectivity of frontotemporal language areas [7••]. The study concluded that the HFA group's engagement of posterior regions along with its weak connections to frontal language areas resulted in reliance on visual mediation even for higher order cognitive tasks. This study recapitulates the findings of the connectivity studies and adds the clearest evidence yet to support the neural basis of the visuospatial processing strengths. This framework provides a reminder that it is easy to overestimate and exceed the language skills of a verbal person with autism. If what is said cannot be said in pictures, a person with autism may not understand it in the way it is said. Not surprisingly, strategies to improve communication in autism have been to promote visual imagery of verbalization and use written instructions or picture cues.

Broad involvement of cortical systems and higher order abilities

The third feature of the fMRI and fc-fMRI studies in autism has been the demonstration of broad involvement of cortical systems and higher order abilities. These findings are consistent with the recent report of the results of the longitudinal study of infants with older siblings diagnosed with autism (about 20% of whom develop autism) describing the first signs of autism as unusual motor movements, unusual response to sensory stimuli and unusual visual preoccupations emerging between 9 and 12 months of age [8]. Between 12 and 24 months, disturbances in temperament and regulation of activity, mood, and sleep emerged along with intellectual disability, and social and communication disturbances. This description of the natural history of autism defines all manifestations as integral aspects of this syndrome as proposed previously [9]. Consistent with this broader view, an fMRI study of motor function reported that children with and without HFA activated the same cortical and subcortical regions during repeated sequential finger opposition [10•]. However, the control group also activated cerebellar regions, whereas the HFA group activated SMA. The HFA group exhibited diffusely decreased functional connectivity across the motor execution network. These findings were hypothesized to reflect difficulty shifting motor execution from cortical regions and effortful control to regions associated with habitual control. Similar findings were reported in a study of visually guided saccades, with increased activation of pre-SMA, DLPFC, and dorsomedial thalamus in HFA individuals [11•]. However, these results were attributed to an atypical way of utilizing frontal cortex to initiate simple motor acts resulting from atypical brain

development, as procedural learning, an implicit process, was found to be intact in HFA [12]. These findings raise several interesting points with the most obvious being that the motor system is involved by the same neurobiologic mechanisms as other cortical systems in autism.

Whole-brain activation disturbances under real-life viewing conditions

Although fMRI studies typically employ narrowly designed tasks, one recent fMRI study investigated the whole-brain activation profile in adults with and without HFA during natural viewing of a movie segment selected to activate large regions of the brain [13••]. In contrast to the well defined and predictable response time course in the controls, the cortical response profile in autism was marked by idiosyncratic alterations in areas ranging from primary sensory cortices to high-level association cortex. This finding suggests that autism is associated with broad neuronal dysfunction affecting multiple disparate cortical areas. Second, within each subject with autism, there was higher intrasubject correlation than intersubject correlation of voxel-wise activation across repeated viewing of the movie. Hence, at least part of the variability in the idiosyncratic response was consistent; the brain in a person with autism perceived a different movie from other people with and without autism, but a somewhat similar movie each time. Lastly, it was possible to uncover a weak typical response profile underneath the idiosyncratic profile; even though the idiosyncractic fluctuations interfered with the neuronal processing of the movie, they did not entirely abolish it, suggesting an avenue for cognitive intervention.

Reward processing and the social impairment in autism

The discovery of deficits in theory of mind (the mind's capacity to make inferences about what other people know, feel and think) and 'mind blindness' (the inability to read meaning in eye gaze, face expression, gesture, body language, and prosody) in individuals with autism provided the critical beginnings of a neurologic basis for the disturbances in social behavior in autism, but were far from a complete account. Recent research focuses on the role of disturbances in rewarded learning and frontostriatal limbic circuitry. Schmitz *et al.* [14•] focused on the neural substrates of reward feedback during a continuous performance task (sustained attention) with monetary reward in adults with and without ASD. Compared with controls, the ASD group showed significantly greater activation of the left rostral anterior cingulate cortex to reward, which correlated positively with social impairment on the autism diagnostic interview (ADI). There were no between-group differences in behavioral performance on the task. The rostral part of the anterior cingulate is thought to be responsible for the cognitive aspects of error detection and risk assessment during reward tasks, whereas the caudal anterior cingulate is involved in emotional functions. The hyperactivation may reflect compensatory activity of rostral anterior cingulate, increased arousal or attention to rewarded stimuli, or that the small monetary reward was a greater incentive for those with ASD. The finding also suggests that if the reward system is dysfunctional in HFA it is not general to all rewards or all circumstances. Some individuals with autism may be able to earn rewards of value to them when given specific instructions about what to do. Questions yet to be answered are how is it that typical individuals learn things automatically and individuals with autism do not? And how is it that typical individuals apply what they learn (from experience or are taught) to real life (generalize), and individuals with autism often do not?

Neural mechanisms of face and emotion processing

Underactivation of the fusiform gyrus during face processing has been one of the most frequently reported imaging findings in autism, though not universal. About 1/3 of individuals with autism have clinical impairments in face recognition and most of the remainder exhibit slow processing speeds on experimental tests of face processing. Several studies have added some specification to this mechanism. A study of working memory for faces found lower activation in a left inferior prefrontal area (verbal processing and working memory maintenance) and a right posterior temporal area (theory of mind processing) in HFA relative to controls, as well as a somewhat different location of the activation in the fusiform area [15•]. These findings suggest that the neural circuitry in autism may be analyzing faces more in terms of objects and less in the context of their human significance. Functional connectivity analyses showed that the fusiform face activation occurred in the context of smaller and less synchronized frontal connections but preserved posterior cortical connections, recurring themes. Similar findings with regard to fusiform activation have been reported in two other recent studies, which also reported variable activation of the amygdala to faces [16,17]. It is certain that the amygdala is involved in the affective disturbances in autism given its overgrowth early in life and histologic abnormalities, but it has been more difficult capturing the nature of the dysfunction, as activation results have been highly variable.

Pierce and Redcay [18••] investigated face processing in children with and without HFA using familiar and unfamiliar child and adult faces and found normal fusiform activation in the HFA children to child faces and their mother's faces but only 25% of the activation to unfamiliar adult faces compared with controls. Whole

brain analyses also revealed a reduction in anterior and posterior cingulate activity, and region of interest (ROI) analyses revealed reduction in posterior cingulate activity when children with HFA looked at familiar children. A third finding was the failure of the HFA children to show strong patterns of bilateral fusiform activity suggesting abnormal interhemispheric connectivity in early development.

Neural basis of cognitive dyscontrol: anterior cingulate cortex and frontostriatal circuitry

'Cognitive control' is a term used by cognitive neuroscientists to encompass a range of abilities previously considered executive functions. Using a target detection task to distinguish between shifts in behavioral response and cognitive set, Shafritz *et al.* [19] reported reduced activation of frontal, striatal, and parietal areas to both shifts in the HFA group. Within the autism group, the repetitive behavior scores from the ADI were negatively correlated with activation in anterior cingulate and posterior parietal areas. A second such study [20] also demonstrated anomalous activation using a nonsocial cognitive control task. In a study that utilized both nonsocial (geometric shapes) and social (faces) stimuli, the autism group demonstrated increased activation compared with controls to both stimuli [21]. The social or face targets evoked hyperactivation in dorsal medial prefrontal cortex/dorsal anterior cindulate cortex, thought to reflect 'impaired cognitive control processes responsible for flexible responding to social stimuli and inhibition of prepotent response sets.'

Using a more complex paradigm requiring individuals to hold information on line to overcome a prepotent response tendency, the brain in typical individuals recruited more anterior frontal (BA 10), parietal (BA 7 BA 40), and occipital (BA 18) areas during challenging cue phases than the ASD individuals; both groups exhibited the same amount of activation for low-challenge tasks [22••]. The HFA group also exhibited less functional connectivity and less network integration between frontal, parietal, and occipital regions. In the typical group, frontoparietal connectivity was associated with lower error rates on challenging trials in the autism group, the reduced fronto-parietal connectivity was associated with attention deficit disorder hyperactivity symptoms. The latter finding provides an example of how these signs are derived from a common neural substrate, i.e., autism and attention-deficit disorder. It is important to keep in mind that task-related fMRI studies involve high functioning individuals with autism with IQ scores in the normal range and who also speak in nonechoed complex sentences.

High functioning individuals with autism excel at some kinds of thinking but have great difficulty with others. This phenomenon has been partially characterized as a dissociation between concept identification and concept formation on tests of abstract reasoning [23]. A similar dissociation exists within executive function tests. In an effort to identify the neural bases for the varied performance on executive function tests, Gilbert *et al.* [24] compared performance on a classical embedded figures test and a novel embedded figures test, which were found to tap different areas of the brain. There was no between group differences in frontal lobe activation for the classical embedded figures test. For the novel test, which required multitasking and coordinated planning, the autism group exhibited increased activation of medial rostral prefrontal cortex (especially Brodmann area 10). In addition, the activation peak in medial rostral prefrontal cortex in the autism group was shifted posteriorly suggesting recruitment of areas usually devoted to mentalizing to perform this task. This subtle 'mislocation' is also seen in fusiform cortex and face processing.

The default-mode network

Analyses of fMRI data during periods of rest between performances of a task have identified a 'default-mode' network in normal individuals based on increased BOLD signal in the resting state relative to an active task state [25,26]. This network includes medial frontal regions (the medial prefrontal cortex and anterior cingulate), medial parietal areas (the precuneus and posterior cingulate), lateral parietal areas (left and right angular gyri), and medial temporal areas (parahippocampal gyrus). The default-mode network has particular relevance to autism because many of the same areas are activated by tasks requiring complex emotional and social processes, theory of mind, and self-referential thought.

Kennedy, Redcay, and Courchesne [27] found that individuals with autism failed to show the greater activation in the default network during rest relative to a difficult Stroop task and proposed the lack of activation reflected a lack of introspective and self-reflective thinking. However, Cherkassky *et al.* [28] found robust activation in the default-mode network during rest in both autism and control groups when the rest periods were contrasted with a variety of other cognitive tasks, and found no group differences despite a large sample size. Kennedy and Courchesne [29] have recently reported reduced activation in autism relative to controls when rest was contrasted with an arithmetic judgment task, but only in anterior regions of the default network. Clearly, further work is needed to elucidate the conditions under which individuals with autism do or do not show default-mode activity during rest.

Abnormalities in resting state connectivity

Along with studies of task-related functional connectivity, research in autism has also searched for

abnormalities in resting state functional connectivity. By measuring intrinsic, or spontaneous, fluctuations in BOLD signal in the absence of an externally imposed task it is possible to characterize anatomical connectivity and spontaneous communication across large-scale networks in the brain [30]. The above study by Cherkassky *et al.* [28] also assessed functional connectivity between pairs of regions defined by the default-mode activation and found that most (94%) of the pairs of regions examined showed reduced connectivity in the group with autism, with the largest reduction between frontal and posterior areas. Kennedy and Courchesne [31] acquired continuous resting-state data from individuals with and without autism and examined voxel-wise connectivity between three 'seed' regions of the default-mode network (posterior cingulate, medial prefrontal cortex, and left angular gyrus) and all voxels in the brain. Reduced functional connectivity was found in autism in the default network only, and only for connectivities involving medial prefrontal cortex and left angular gyrus ROIs.

More recently, Monk *et al.* [32•] have replicated the finding of reduced frontal-posterior functional connectivity in autism in continuous resting data, but they also found evidence of increased connectivity among posterior areas. Using a single seed region in the posterior cingulate they found decreased functional connectivity in autism between posterior cingulate and right superior frontal gyrus, but increased functional connectivity between posterior cingulate and right temporal gyrus and right parahippocampal gyrus.

Studying intrinsic connectivity by statistically removing task effects

Another approach to investigating intrinsic functional connectivity is to partial out task-related effects from the time series of BOLD signal and then examine correlations of the residual signal between regions. Early studies using this method found evidence of frontal-posterior underconnectivity in autism [33] but also found higher connectivity with subcortical structures in autism [34,35] Recently Jones *et al.* [36] used this approach in a ROI-based analysis and found that pairs of regions showing a group difference in functional connectivity were always characterized by lower connectivity in autism and that the pairs showing the greatest underconnectivity in autism involved frontal-lobe regions, consistent with the studies discussed earlier that have used actual resting data and also with the studies of task-related functional connectivity. Noonan *et al.* [37•], however, used this approach in a voxel-based analysis and found that areas showing a partial correlation with three cortical-seed regions were more extensive in the autism group, suggesting a more diffuse pattern of intrinsic connectivity. As these authors note, either overconnectivity or underconnectivity could result in inefficiency of complex integrative information processing, as either could alter the signal to noise ratio of the system, with overconnectivity introducing more noise and underconnectivity providing less signal.

Although many unanswered questions remain, resting-state designs have obvious advantages for clinical and pediatric populations in that they do not require participant compliance and they simplify comparison across groups and ages with very different cognitive abilities. They also offer the potential for easily sharing and combining of data across sites. New techniques for analyzing these data focus on characterizing intrinsic connectivity across the entire network using measures derived from graph theory, and such work has already shown promise in providing general developmental principles for understanding the maturation of the cognitive system [38••–40••].

Conclusion

Functional MRI studies in the past 12–15 months have provided further specification of the alterations in task-related connectivity in autism, including direct evidence of enhanced activation and connectivity in posterior areas and enhanced reliance on visuospatial abilities for verbal and visual reasoning and reduced frontal systems connectivity. Across studies, it was not uncommon for the cortical location of areas to be shifted slightly, perhaps reflecting recruitment of adjacent cortical areas and lack of the usual cortical specialization for task performance. It is also notable that fronto-parietal connectivity was related to attention deficit manifestations in autism. FMRI studies of resting state connectivity and the default mode network also suggest abnormalities in intrinsic mechanisms of thinking, feeling, and behaving, and for regulation of these. However, there is a long way to go to understand these critical complex processes. Imaging studies have small sample sizes and it will take some time for the research to address the large number of relevant issues. The implications of hyperactivation versus hypoactivation are less clear when there is not a range of task challenges to probe system capacity. Many unanswered questions will be resolved in the next 5 years to produce even more detailed understanding of the brain–behavior relationships in autism. With this knowledge will come new neurobiologically based interventions and the capacity for using genetic advances to account for heterogeneity in syndrome expression.

Acknowledgement

This work is funded by NIH HD055748.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 196–197).

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