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Connectivity in Autism: A review of MRI connectivity studies

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Abstract

Autism Spectrum Disorder (ASD) affects 1 in 50 children between the ages of 6–17 years as per a 2012 CDC survey of parents. The etiology of ASD is not precisely known. ASD is an umbrella term, which includes low (IQ<70) to high functioning (IQ>70) individuals. A better understanding of the disorder, and how it manifests in an individual subject can lead to more effective intervention plans to fulfill the individual's treatment needs.

Magnetic resonance imaging (MRI) is a non-invasive investigational tool that can help study the ways in which the brain develops and/or deviates from the typical developmental trajectory. MRI offers insights into the structure, function, and metabolism of the brain. In this article, we review published studies on brain connectivity changes in ASD using either resting state functional MRI or diffusion tensor imaging.

The general findings of decreases in white matter integrity and long-range neural coherence are prevalent in ASD literature. However, there is somewhat less of a consensus in the detailed localization of these findings. There are even fewer studies linking these connectivity alterations with the behavioral phenotype of the disorder. Nevertheless, with the help of data sharing and large-scale analytic efforts, the field is advancing towards several convergent themes. These include reduced functional coherence of long-range intra-hemispheric cortico-cortical default mode circuitry, impaired inter-hemispheric regulation, and an associated, perhaps compensatory, increase in local and short-range cortico-subcortical coherence.

Keywords

autism; diffusion tensor imaging; resting state MRI; connectivity; behavioral correlation

INTRODUCTION

A 2012 survey published by the Centers for Disease Control and Prevention found that autism spectrum disorder (ASD) affects 1 in 50 children between the ages of 6 and 17 years.[1] This estimate is significantly higher than the 2007 estimate of 1 in 88.[2] The prevalence seems to be increasing with time, whether as a result of broader diagnostic criteria, increased awareness of the disorder, or additional unknown factors.

In the most recent, fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), ASD is characterized by deficits in social communication and social interaction,

and by restricted, repetitive patterns of behavior, interests, or activities.[3] *ASD* is an umbrella term that includes low-functioning (IQ < 70) to high-functioning individuals (IQ > 70), and that ranges over the broad DSM-IV categories of autistic disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified.[2,4] It is more prevalent in males than females; 1 in 54 boys and 1 in 252 girls were identified as having ASD in a 2008 study.[2] Females with ASD typically present higher cognitive impairments—such as a lower reported IQs—than males with ASD. Males with ASD are reported to have more stereotypical mannerisms and restricted/repetitive behaviors than females.[5]

In most cases, the initial behavioral signs of ASD present as early as 12 to 24 months of age.[6,7] The differences between ASD infants and normal infants in the first year of development, however, are not very apparent. Additionally, ASD is associated with a high comorbidity rate and also with diverse symptoms, making reliable clinical diagnoses possible only around the age of 2–3 years.[4,7] Children with ASD often develop maladaptive behaviors such as irritability, hyperactivity, aggression, depression, and anxiety, which seem to worsen during puberty.[8] Social symptoms such as withdrawal can worsen over time,[8] and about 46% of adults with ASD have poor to very poor outcomes in terms of independence, social life, and employment.[9]

The etiology of ASD is not precisely known. Additionally, neurobiologic findings reported in ASD change with age. For example, head circumference, which has been noted to be smaller in ASD individuals at birth, grows rapidly to be larger than those in typically developing children around toddler age, and then normalizes to near normal by adulthood.[4] Magnetic resonance imaging (MRI), a noninvasive investigational tool, can help describe the various ways in which the brain develops, identify aspects of brain development that deviate from the typical developmental trajectory, and capture features of structure, function, and metabolism in the brain. As a noninvasive tool, it is the only high-resolution, complete-brain-coverage technique suitable for use in children in the clinical research setting.

A more precise understanding of an individual's condition can lead to a better-targeted and customized intervention plan to fulfill the individual's treatment needs. Each individual's brain functions involve many different sets of interconnected regions, or circuits. These circuits are made up of distributed gray matter (processing) regions interconnected by specific white matter tracts and pathways. For circuits to function properly, all aspects of the circuit need to be intact. Improper circuit function has numerous potential causes: improper "structure" of the processing units in the gray matter, improper connectivity of the distributed aspects of the circuit, improper inputs to the circuit, and so on.

In order to better understand the functioning of neural circuitry of ASD subjects, we focus our review on the newly amassed literature concerning brain connectivity. From that particular perspective, two types of connectivity have been studied in this population in depth. We refer to these dimensions *structural connectivity*, reflecting the brain's neuron-to-neuron connections, and *functional connectivity*, reflecting the correlated neural activity of the disparate parts of a circuit. Structural connectivity at the neuron level is, to date, actually measured directly only postmortem, and is principally achieved with antero- or retrograde tracers in experimental animals.[10,11] The advent of water-diffusion sensitivity in MRI (most

commonly practiced as diffusion tensor imaging [DTI]) provides a macroscopic view of the ultrastructural organization of the tissue within the imaged voxel. Within the white matter of the brain, where axon trajectories are the principal cellular organizational construct, water diffusion tends to reflect the average magnitude of diffusion, or mean diffusivity (which is related to the presence of impediments to diffusion such as density of cellular components or fluidity of the intracellular medium), and the average orientation of the cellular components, as water tends to diffuse in parallel to, as opposed to against, the impediments within the cell. The degree of orientation specificity within a voxel is referred to as the *anisotropy*, ranging from low anisotropy in nondirectional tissue (such as in the cerebrospinal fluid) to high anisotropy in highly directionally oriented tissues (such as in the main trunk of a white matter fiber pathway or within muscle tissue). Fractional anisotropy, ranging from 0 to 1.0, is the most commonly expressed metric in use to quantify this orientation anisotropy in brain diffusion imaging.[12] In oriented tissues, diffusion magnitude along the main direction of the tissue orientation is referred to as *axial diffusivity*, and diffusion perpendicular to this principle direction is referred to as *radial diffusivity*. While often used as a proxy for true structural connectivity, diffusion MRI is an approximation of this connectivity in that it reflects spatially averaged properties over the imaged voxel that is very large with respect to the axons themselves. In addition, as a spatial average of potentially many discrete directional components that may be present within a voxel, the average direction of the tissue in a voxel may not match any of the specific orientations that reside within. Higher-order techniques for diffusion acquisition and analysis—ones that can resolve multiple directional components within the imaged voxel—are becoming available for use but have yet to become practical for widespread application in studies on autism.

A brain circuit and its components can also be identified by their common pattern of neuronal firing. Functional MRI (fMRI), while not designed to observe neuronal firing per se, is able to detect the changes in hemodynamics necessary to support neural activity. Bulk changes in cerebral hemodynamics associated with changes in neural activity associated with specific tasks can be localized by using well-designed behavioral tasks that tease apart the component functions associated with the specific tasks (task-based fMRI). More recently, it has been observed that, even in the absence of a specific task, the brain “at rest” exhibits a rich set of networks of correlated and anti-correlated fMRI signals. These distributed resting-state (RS) fMRI correlations mimic many of the same circuits that respond to specific tasks and, as nodes of a circuit, imply an “effective” connectivity (which may, or may not, reflect a direct anatomic structural connectivity).

Various other reviews on particular aspects of MRI and ASD have been published.[13,14] Unfortunately, reports from imaging studies have been inconsistent. It has been suggested that both variations in MRI data collection and differences in methodologies for data processing and analysis could be responsible for the vastly varying results in the literature.[15,16] For example, a survey of functional connectivity studies in ASD by Muller and colleagues[16] suggested that the inconsistent findings may partially result from different methodological approaches—such as the type of filtering of time courses (low pass or band pass; frequency range of filtering), statistical removal of task-related activation, and choice of whole-brain analysis versus analysis of regions of interest (ROIs) chosen a priori. Another explanation for the inconsistencies is the inherent heterogeneity of ASD itself, which is

further complicated by comorbidities. In this article, we reviewed studies that report connectivity changes in ASD either in the form of RS blood-oxygenation-level dependent (BOLD) network or as DTI parameters.

The overall purpose of this review is to identify consistencies in the DTI and RS connectivity literature in relation to subjects with ASD. From this emerging consensus we then seek to draw conclusions about biological significance and functional/behavioral implications of these changes in connectivity in order to help us understand the pathophysiology of the disorder.

METHODS

PubMed was used to identify peer-reviewed publications within the last ten years that explored DTI or RS connectivity in autism using MRI. The search terms used were the following: autism AND DTI AND MRI; autism AND connectivity AND MRI; autism AND resting state AND MRI; and autism AND default mode AND MRI. The cutoff date for latest publication was 15 January 2014. PubMed produced 57, 199, 49, and 26 results for each of the searches, respectively. These lists of publications were narrowed down to research studies, eliminating any review articles. Studies of autism with other severe comorbidities or with other disorders exhibiting autism-like symptomologies were also eliminated, as were single case studies and ones that used *default mode network* only as an anatomic reference term. Since studies of task-based connectivity vary significantly in the tasks used, each focuses on only a specific aspect of ASD connectivity; they are not of general application in this context. By contrast, much research has already been done on RS connectivity, and a basic understanding of the default mode network has been established. For that reason, only studies that focused on RS, rather than task-based, connectivity, have been included here. The final list includes 33 RS connectivity studies and 36 DTI studies.

All studies were read and tabulated for population characteristics, such as number of subjects in the autism and control groups, IQs, and age ranges of each group. Each was also tabulated for methodological details such as imaging methods used for DTI or RS acquisitions, details of the MRI system used, and software methods used to analyze DTI or RS data. For the DTI studies, results were tabulated to include any change of the white matter properties of fractional anisotropy, mean diffusivity, radial diffusivity, or axial diffusivity as well as the white matter brain regions where these changes were reported as occurring. For the RS studies, results were tabulated for seed-based analyses to include seed and target anatomic regions and the direction of the functional connectivity change observed between patient and control populations.

From these primary tabulations of the literature, we sought to express the observed major findings in a more directly comparable manner. The resulting RS connectivity literature was summarized by tabulating inter-regional increases or decreases in observed connectivity in a common neuroanatomic framework.[17] This summary can be visualized as a connectivity matrix where we can indicate concordance or discordance in the literature of RS connectivity changes in ASD.

Similarly, the DTI literature was also narrowed down into tabular format indicating changes in fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity as a function of standardized brain regions.[18] These results were further broken down into association fiber components, corpus callosum components and projection fiber components for fractional anisotropy and mean diffusivity.

Articles that had explored correlations between changes in RS parameters or DTI parameters and any of the behavioral measures or age were tabulated separately.

RESULTS

RS fMRI

Our literature search for RS fMRI in autism generated 33 studies (Supplemental Table A). Nineteen of those studies reported between-diagnostic-group comparisons in RS connectivity/correlation patterns using seed-based analysis; seven used an approach involving either principle component analysis or independent component analysis; one used both independent component analysis and anatomic ROI-based analysis; three used regional homogeneity analysis; and three looked at the efficiency of the voxel-wise network. The study populations varied widely, with the ages ranging from very young children between the ages of 12 and 46 months[19] to adults up to 40 years of age.[20] Autism severity also varied from high-functioning ASD, Asperger's disorder, autism with and without language deficiency, pervasive developmental disorder not otherwise specified, and ASD with and without the MET receptor tyrosine kinase gene (MET) allele. Though some studies limited their study populations to males, 24 studies also included females.

Methodologically, most of the studies (27 out of 33) used a 3-Tesla (3T) scanner, and 4 used a 1.5T scanner. Two studies were based on the multisite Autism Brain Image Data Exchange (ABIDE; http://fcon_1000.projects.nitrc.org/indi/abide/) data set, in which the magnet strengths varied. General Electric and Siemens were the scanner manufacturers, with an almost equal number of studies using one or the other. For these RS studies, the repetition time and echo time values varied between 1 and 3 seconds and between 25 and 45 milliseconds, respectively. About half of the scans (15 studies) were performed while the subjects were keeping their eyes open and staring at a fixation marker, and 2 were performed on between-task fixation blocks.[21,22] Five studies instructed their participants to keep their eyes closed; 1 instructed them to relax and stay awake but without any particular direction concerning the eyes; and 1 was performed while the participants were in their natural sleep cycles. The 2 ABIDE studies contained data with mixed subject instructions. Six studies failed to mention their instructions in the published article. One study had subjects participate in both conditions (open vs. closed eyes) and did not report any effect on the results.[23] However, a number of studies have looked explicitly at this effect.[24–28] While the effect size of the eyes-condition (open versus closed versus fixation) is only modest, it has been shown to have a detectable, anatomically variable effect. Thus, it is important to have the eyes-condition information reported distinctly and clearly in order to control for this (and other) known sources of variance in future meta-analyses of pooled study results. The analysis packages in these studies varied widely, and included the following: Analysis of Functional NeuroImages (AFNI), Functional Magnetic Resonance Imaging of the Brain

groups Software Library (FSL), Statistical Parametric Mapping (SPM), Brain Voyager, Group ICA of fMRI Toolbox (GIFT), and home-grown software.

For studies using principle component/independent component analyses, a direct comparison between studies is not attempted in this review due to variability in component matching across these data sets. Similar to a review by Muller and colleagues,[16] 26 of the 33 the studies report some amount of either reduction or loss of local or long-distance connectivity in subjects on the autism spectrum compared to control subjects without autism, as can be seen in Table 1.

Also, as described previously, the current publications utilize a broad variety of acquisition and analysis techniques, and vary widely in terms of the specific neuroanatomic localization techniques used to report summary results.. Since the anatomic bases for the description of altered RS functional connectivity is so variable, assessment of the concordance (or lack thereof) of the descriptions as provided in the original publications is extremely limited. Supplemental Table B highlights the paucity of corroborated observations.

Most studies dealt with long-distance connectivity. Among the regions studied, prefrontal cortex (PFC) was most often reported (in ten studies) to have reduced connectivity to other regions.[20,22,29,33,39,40,47,49,50,55] Posterior cingulate cortex (PCC) was reported in eight studies to have reduced,[21,29–31,40,41,47,50] and in three reports to have increased, long-range connectivity to other ROIs.[30,41,43] The precuneus,[29,33,41,43,47,50] anterior cingulate cortex (ACC),[21,22,33,43,50] superior temporal gyrus,[34,39,43,50,54] posterior superior temporal sulcus,[20,49,53] anterior insula,[20,37,49] and parietal lobule[35,50,53,55] each had four to five reports of reduced, with either one or two reports of increased, long-range connectivities. Verly and colleagues[54] reported a widespread reduction in inter-hemispheric connectivity among the ROIs studied, with the exception of the arcuate fasciculus part of the superior longitudinal fasciculus). In their research-based study, the DiMartino group, reported an increased degree of centrality (i.e., number of direct connections) for posterior parahippocampal gyrus and amygdala, and decreased degree of centrality for precuneus,[23] and in their article based on the ABIDE data set, the same group reported a decreased degree of centrality and regional homogeneity for striatum[48] (Supplemental Table B).

Among the groups that studied local/regional connectivity, Starck and colleagues[47] reported a lack of difference between study groups in local connectivity for any of the brain regions studied. Among other reports, PFC and inferior and superior frontal gyrus each had one report of increased, and one report of decreased, local connectivity. PCC, superior temporal sulcus, and precuneous had only one report of decreased local connectivity or regional coherence. The inferior temporal gyrus,[56] temporal pole,[56] posterior insular cortex,[48] thalamus,[32] and supramarginal gyrus[46] had one report of increase in either of local connectivity, regional coherence, or regional homogeneity. The medial cingulate cortex had two reports of decreased local connectivity[46,56] and one report of increased regional coherence. The medial frontal gyrus had one report of decreased regional coherence[32] and two reports of increased local connectivity.[46,56] The medial temporal gyrus had two reports of increased local connectivity[46,56] and one report of increased regional coherence.[32] And

finally, the posterior parahippocampal gyrus had only two reports of increased local connectivity.[46,56] See Supplemental Table B.

DTI

DTI studies were primarily performed on a 3T scanner (26/36), with 8 studies using a 1.5T scanner (Supplemental Table C). Two studies did not specify the strength of the magnet. Though General Electric and Siemens were the primary manufacturers, eight studies used Phillips scanners. The imaging parameters varied widely. The repetition time values varied from 4.1 to 21 seconds, and echo time values from 67 to 107 ms. The diffusion gradients b-value varied from 700 to 2000 s/mm^2, and the number of diffusion encoding directions ranged from 6 to 64. Similar to RS studies, the DTI studies also varied widely in their study populations, with ages ranging from 2[57] to 54 years.[58,59] Autism severity in the ASD groups varied from high-functioning autism, to Asperger's only, to combined groups of Asperger's syndrome, autism, and pervasive developmental disorder not otherwise specified. The gender ratio also varied widely, from all-male groups to mixed-gender groups. The data-processing tools utilized included the following: FMRIB's Diffusion Toolbox, DTI Studio, DTI task card software, B-spline fitting, Tract-Based Spatial Statistics (with whole-brain voxel-wise analysis and with tactography), BioImage Suite, SPM5 Diffusion Toolbox, tensor-based fast-marching method, Explore DTI, and home-grown software.

Thirty out of the 36 DTI studies reviewed examined fractional anisotropy differences, and 20 studies examined mean diffusivity differences, between the study groups. Four publications reported their results in terms of network statistics (i.e. clustering coefficients) and tractographic parameters (i.e. number of fibers) leaving 32 studies that can be directly compared (Table 2).

Most studies reported a lower fractional anisotropy and higher mean diffusivity in the ASD groups compared to the typically developing group. Exceptions include reports by the Ameis,[74] Billeci,[76] Nagae,[75] Nair,[55] Sivaswamy,[63] and Verly[54] groups. The Billeci group[76] has reported increased fractional anisotropy and mean diffusivity in multiple regions, including the corpus callosum, whereas the Sivaswamy group[63] has reported increased fractional anisotropy and mean diffusivity in the cerebellar peduncle area. Five of the 30 fractional anisotropy studies found no effect of group in fractional anisotropy,[65,85–87] (74, 75, 54, 55, 84) whereas one reported a hemispheric effect in the superior longitudinal fasciculus.[75] Another study looking at the effect of a particular allele of the *MET* gene—a gene variant thought to be a risk factor for more severe social and communication phenotypes in individuals with ASD—reported a significant effect of the gene allele on fractional anisotropy, irrespective of the diagnostic group.[40]

Most commonly reported areas for decreased fractional anisotropy were the association fibers (the most common being the superior longitudinal fasciculus, occipitofrontal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, and cingulum) and corpus callosum, as reported by 8 to 12 studies each. The internal capsule was also reported by 7 studies to have reduced fractional anisotropy in ASD. The superior longitudinal fasciculus, corpus callosum, and corticospinal track had the highest number of mentions among the reports of increased mean diffusivity in ASD (see Supplemental Tables D and E).

It is important to note that the Beacher group[77] found lower fractional anisotropy only in their Asperger's male participants compared to typically developing male. No similar difference was found in their female participants. Also, the Beacher group was the only group that reported lower mean diffusivity in the thalamus in the Asperger's group (no gender effect) compared to the typically developing group.

Combined Studies

Four studies performed both DTI and RS fMRI experiments.[40,50,54,55] Rudie and colleagues[40] found that the presence of the *MET* risk allele resulted in reduced connectivity from the PCC to medial PFC and reduced fractional anisotropy in the splenium of the corpus callosum (the fiber pathway originating from PCC/precuneus), irrespective of the study group. The presence of the *MET* risk allele in the ASD group, however, resulted in more severely compromised brain circuitry and greater impairment in social behaviors. Hence, it might be important to further separate the ASD subjects with respect to such risk factors, and to compare them to typically developing subjects without such gene alterations, in order to increase our understanding of the brain alterations in ASD.

The Verly group[54] focused on the language network (superior longitudinal fasciculus) in adolescents and found no difference between groups in their DTI study, but did report a significant leftward asymmetry in fractional anisotropy and apparent diffusion coefficient. The presence or absence of bilateral arcuate fasciculus had a significant effect on performance on a language test and on intra-hemispheric functional connectivity between cortical language centers (the inferior frontal gyrus and the superior temporal gyrus) in the ASD group. These effects were not observed in the control group, though in 29% of that group, only the left unilateral arcuate fasciculus was present. It is important to note that both ASD groups—those with and without bilateral arcuate fasciculus—had significantly lower verbal IQ and exhibited social behavior impairment.

The Mueller group[50] compared adults with high-functioning autism to healthy adult controls. For the high-functioning group it reported decreased fractional anisotropy values in the right temporo-parietal junction and decreased functional connectivity between right hemisphere clusters, including the cluster including the precentral gyrus and PCC, and the cluster including the precentral gyrus, postcentral gyrus, PCC, precuneus, and superior parietal lobule—the two clusters being a part of the dorsal attention network. The group reported decreased fractional anisotropy in the left frontal lobe and loss of functional connectivity between the left hemisphere medial PFC and ACC (part of left fronto-parietal network) in the high-functioning group compared to the healthy controls. The group also reported a trend toward decreased gray matter volume in the temporal lobe accompanied by decreased functional connectivity of the dorsal motor nucleus. Thus, the high-functioning group exhibited deficits in the higher-order association cortex (regarding both functional and structural connectivity), while exhibiting no differences in the primary sensory and motor cortices. According to the Mueller group,[50] these findings imply a probable impairment of higher-order multisensory integration in the adults with high-functioning autism.

The Nair group[55] worked with adolescents with high-functioning autism. They reported several clusters of underconnectivity in their RS analysis in the ASD group, and

hyperconnectivity between temporal seed and the right thalamus. In the DTI study, the group reported significantly increased mean diffusivity for bilateral tracts connecting the thalamus to the motor and somatosensory cortices, and for the connection between the right hemisphere of the thalamus and the PFC. They also reported increased radial diffusivity in the thalamic tracts for the bilateral motor cortex, left hemisphere somatosensory cortex, and right hemisphere PFC.

Behavioral Findings

Only seven (~21%) of the RS studies and ten (~28%) of the DTI studies looked at correlations between observed imaging parameters and specific behavioral measures in ASD (see Supplemental Table F).

These studies vary widely regarding the behaviors reported and whether RS activity or diffusion properties are correlated with those behaviors. When resting state correlations are observed between two regions that share connectivity with a major white matter fiber bundle (such as precuneus and superior frontal gyrus sharing the cingulum bundle as its principle white matter pathway), it is possible that the behavioral performance can be associated with that major fiber bundle. Overall, for the RS – behavioral correlations, of note is the preponderance of cortical-region pairs associated with the cingulum bundle.

Autism severity

Four RS studies found a correlation between reduced connectivity and ASD severity, irrespective of the measures used (Social Responsiveness Scale, Autism Diagnostic Observation Schedule (ADOS), Autism Spectrum Quotient), with the medial PFC being implicated in all, and the ACC, precuneus, and temporal and parietal lobes implicated in some.[20,33,39,44]

Among the DTI studies, four reported negative correlations between autism severity and fractional anisotropy;[55,61,64,69] the brain regions involved were the left superior longitudinal fasciculus,[64] right anterior thalamic radiation and right uncinate fasciculus,[69] and fronto-thalamic and temporo-thalamic tracts (anterior and posterior limbs of internal capsule, respectively).[55] One study reported no correlation between autism severity and fractional anisotropy.[70] Additionally, one study reported that the number of fibers numbers in the genu of the corpus callosum was negatively correlated with the Childhood Autism Rating Score.[85]

Social impairment

Six studies have reported negative correlations between RS connectivity and social impairment in ASD subjects (reported as negative correlations with the Autism Diagnostic Interview–Reciprocal Social Interaction score or ADOS–Social Scale score).[19,22,30,31,33,55] The connections involved in four of these studies were between the following: PCC and temporal lobe, posterior parahippocampal gyrus, and superior frontal gyrus;[31] PCC and right superior frontal gyrus;[30] PCC and right medial temporal gyrus;[22] and right hemisphere motor cortex and thalamus.[55] The other two studies reported negative correlations between ADOS–Social Scale scores and the synchronization between left and right hemisphere inferior frontal gyri,[19] and between ADOS–Social Scale scores and the total precuneus

connectivity z-scores.[33] Kewon and colleagues[56] reported a negative correlation between average local degrees of connectivity, the number of other regions to which the ROI connected, and social impairment (reported as a negative correlation with ADOS–Social Scale scores). The one outlier was a study by the Alaerts group,[53] which reported a positive correlation between RS connectivity involving posterior superior temporal sulcus seed and performance on the emotion-recognition task. The regions involved were the supplementary motor area, supramarginal gyrus, inferior frontal gyrus, and precentral gyrus.

Among the DTI studies, only two reported correlations between fractional anisotropy and either the Social Interaction subscale of the Gilliam Autism Rating Scale or the ADOS Social Scale score.[55,61] One of these studies—by the Nair group[55]—reported the negative correlation as specifically involving fractional anisotropy in the frontothalamic and temporothalamic tracts. The Sundaram group[61] did not report any specific brain region, and their results were not significant after Bonferroni correction.

Severity of restricted and repetitive behaviors

Three out of the seven RS studies reporting correlations with repetitive and restricted behavior describe a negative correlation between connectivity scores and the severity of that behavior {22, 31,33}. PCC connectivity, predominantly with the medial PFC, is reported in one study to have this negative correlation.[31] ACC seed connectivity also demonstrates a negative correlation with the severity of this behavior.[22,33] Other studies, however, indicate increasing severity with increasing connectivity strength between the PCC and right posterior parahippocampal gyrus[30], between voxels within the salience network (ACC, superior frontal gyrus, thalamus, and bilateral insular cortex),[43] and between the right temporal lobe and thalamus,[55] as well as with the density of cerebral cortex local connectivity and average local degrees of connectivity.[56]

One study using DTI to investigate the correlation with repetitive/restricted behavior in ASD, found a negative correlation between the white matter connectivity (as measured by number of streamlines and voxels) in the forceps minor of the corpus callosum and the severity of that behavior.[87]

Language and communication skills

Nine RS studies and five DTI studies have reported correlations between measured parameters and communication capabilities (Supplemental Table F). In an RS study by Weng and colleagues,[31] verbal and nonverbal communication skills decline with increased connectivity between the PCC and temporal lobe and also between the PCC right posterior parahippocampal gyrus. Likewise, in the same study, nonverbal communication skills were negatively correlated PCC–superior frontal gyrus connectivity.

But most RS studies reached contrary results. Dinstein and colleagues[19] reported lower ADOS communication scores and increased expressive language ability (measured by the Mullen scale for early learning) with increasing inter-hemispheric correlations bilaterally in the inferior frontal gyrus. Similarly ADOS communication scores were reported to be negatively correlated with anterior medial PFC to right lateral parietal connectivity by Redcay and colleagues[44] and with right motor cortex to thalamus connectivity by Nair and

colleagues.[55] Verly and colleagues[54] also reported a positive correlation between verbal skills and superior temporal gyrus–inferior frontal gyrus connectivity. A study by Assaf and colleagues[33] also points toward lower ADOS communication scores with increasing precuneus connectivity z-scores, and Maximo and colleagues[46] reported the ADI-R communicative score to be positively correlated with local connectivity within multiple cortical regions.

Among the DTI studies, a study by the Nagae group[75] reported a negative correlation between mean diffusivity in the left superior longitudinal fasciculus and Clinical Evaluation for Language Fundamentals–4 scores, whereas a study by the Billeci group[76] found a similar negative correlation between left arcuate fasciculus mean diffusivity and expressive language ability only in the typically developing group. A study by the Li group[86] did not report the anisotropy or diffusivity findings, but instead performed network analysis on the DTI data and found that as short-range connectivities increased in typically developing subjects, group Gray Oral Reading Test–4 scores go down, whereas in the ASD group, they improved. Hence, they suggested that the increase in short-range connectivity observed in the ASD group compared to the typically developing group might be a compensatory mechanism, which might be leading to the language/communication disabilities observed in ASD. One study reported a lack of correlation between the language scores and any of the DTI parameters.[59] A study by Joseph and colleagues,[83] which looked only at hemispheric asymmetry, reported that rightward asymmetry quotient of pars opercularis, a part of the inferior frontal gyrus important in speech and language production, was positively correlated with language scores.

Other behaviors

Lagen and colleagues[78] reported a positive correlation between inhibitory control in the autistic group as measured by the go/no-go task and fractional anisotropy in insular cortex.

DISCUSSION

Connectivity, represented either as axonal inter-nuron connectivity of the white matter or as the effective coordinated temporal activity of distributed nodes of a complex circuit, has become an area of increasing importance in the ongoing research into the etiology of ASDs. As altered circuit functions become elucidated, it is important to resolve the relative contribution of structural connectivity as a causative factor for these changes versus numerous other factors that can also alter these functions.

Resting State Connectivity

The majority of the reviewed RS functional connectivity studies report a loss or reduction in cortico-cortical functional connectivity in individuals with autism compared to the normative control population. Most reports for hypo-connectivity involved the PFC (ten independent reports). Previous structural imaging studies have reported enlarged gray and white matter in young children with ASD compared to their normative counterparts, with most of the overgrowth being noted in the frontal lobes, particular dorsal and medial prefrontal cortex.[14,54] The overgrowth observed in childhood, however, seems to slow down by the

pre-teenage years, and by adulthood, the brain volumes of individuals with ASD are comparable to those of normative adults.[14] It is well known that the human brain goes through extensive pruning from childhood to adulthood. Hence, it is suggested that the brains of children with ASD must go through more pruning than those of typical children in order to reach similar volumes by adolescence. It is suggested, in turn, that this greater amount of pruning accounts for the differences in the structural brain networks of individuals with ASD.[54] Hence, it is understandable that the most potential abnormal pruning would occur in the locations with the most original overgrowth, the medial prefrontal cortex. It is plausible that excessive pruning would lead to resultant fiber systems that are of lower packing density than typically expected, and would result in reduced fractional anisotropy and increased mean diffusivity.

Mounting evidence in the RS literature suggests that other regions also have reduced long-range connectivity—such as the PCC, ACC, superior temporal gyrus, insula, and precuneus (in the reverse order of number of reports per ROI). Given that the ACC and PCC support major connections to the cingulum bundle (and to the adjacent corpus callosum) and have projections into the PFC, superior temporal gyrus, and insula, one can see how these decreases can be interdependent.

It has been suggested that increased local connectivity and regional coherence in some brain regions observed in ASD is possibly a result of overcompensation for the reduced long-range connectivity. The studies reviewed here, however, do not consistently report heightened regional connectivity.

In terms of interpreting the presented results, only 17 of the 33 RS studies looked at any correlation of the changes identified with one or more behavioral measures of ASD. Five studies looked at correlations with overall autism score; nine studies looked at correlations with social impairment and with language and communication skills; and seven studies looked at correlations with repetitive/restrictive behavior. Nevertheless, many of the commonly reported regions with reduced functional connectivity are known to be involved in the relevant behavioral capacities. The degree to which these altered connectivities are predictive and specific for the altered behaviors is unknown.

Diffusion Connectivity

The DTI studies have more consistent results than the RS studies, and point toward an overall reduction of fractional anisotropy and increase of mean diffusivity in many white matter areas. The most reported ROIs were the corpus callosum, superior longitudinal fasciculus, and occipitofrontal fasciculus, with decreased fractional anisotropy (12, 11, and 10 reports, respectively) and increased mean diffusivity (7, 9, and 4 reports, respectively). The cingulum and internal capsule were not far behind in the number of reports. When it came to interpreting these results, though 14 of the 36 studies attempted to correlate the observed DTI changes with ASD behavioral markers, the DTI measures studied varied from fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity, to number of fibers,[85] number of lines depicting fibers in a tract and voxels,[87] local connectivity within ROIs,[86] and hemispheric asymmetry quotient of the ROIs.[83] Additionally, the behavioral measures themselves varied from autism severity, to restricted/repetitive behaviors, to

communication impairments, with only a limited number of studies per behavior. For example, only two studies reported correlations with social impairment,[55,61] and only one study reported any correlation with severity of restricted/repetitive behaviors.[87] Even though five studies looked at correlations with language/communication skills, one of these studies looked only at the correlation with local connectivity within different ROIs,[86] another at the correlation with the length of streamlines within the superior longitudinal fasciculus,[76] and yet another at the correlation with the hemispheric asymmetry quotient.[83] Again, while it is possible that structural connectivity changes are predictive and specific for the behavioral profiles in these subjects, the literature has yet to reach a consensus on these matters.

Combined Studies

The studies that begin to integrate analyses of RS and diffusion connectivity hold promise to better elucidate the causes of altered brain functioning in young individuals with ASD. Though the number of published studies currently remains small,[40,50,54,55] each adds a new dimension to understanding the complexities of structural-functional connections in this population. For example, specific behaviors and specific pathways, combined with genetic variations, are all so intertwined that they are nearly impossible to differentiate through studies that look as these factors separately.

The addition of behavioral correlates to the structural or functional connectivity studies would be immensely valuable but exceedingly complex. Because of all the potential confounds and covariates, the numbers of subjects necessary to extract meaningful, specific, and significant behavioral correlations would be large. Different diagnostic groups also overlap to some degree on most behavioral measures. Despite our search for autism-specific findings, such clarity may be precluded by the blurred diagnostic lines. Finally, behavioral measures may or may not be distributed in a continuum between typically developing subjects and their autistic subject counterparts—without which continuum, the behavioral measures would fail to yield to s simple correlation analysis, but rather require a more complex analysis of the interaction between diagnosis and connectivity measure. Although addressing these multidimensional problems is critical to understanding autism, the challenge adds complexity to study design and requires a substantial numbers of subjects to achieve statistical power.

Synthesis

Despite the many studies that point toward decreased RS connectivity in ASD, the field is still at an early stage regarding the reproducibility and replication of specific findings. To date, the replication across various studies requires a liberal interpretation of similarity or equivalence. RS studies have been documented as having good poolability despite minor variations in acquisition protocols.[89] While analysis methods are variable, the major barrier to integrating these findings is the heterogeneity of anatomic localization systems employed and the subsequent lack of reporting of observations from similar pairs of seed and target regions. Variability in positioning and size of seed regions inescapably introduces substantial variation in the resultant pattern of connectivity. It is interesting to see the emergence of dynamically defined networks taking the place of anatomic localization. When one reports the connectivity of the posterior cingulate cortex as that of “most of the default mode

network nodes," the pattern of connectivity remains uncertain; the default mode network remains a variable concept in the literature because it is defined functionally rather than anatomically. While the reader can make assumptions as to what this pattern of connectivity via the default node network might look like (as we have in our summary), there is ambiguity in regions reported in this manner that reduces both clarity and precision.

Another shortfall in the current literature is that the changes in connectivity patterns have yet to be clearly correlated with behavioral findings. Such correlated studies are critical in order to understand how findings of decreased functional connectivity are useful in understanding the particular behavioral manifestations of ASD. Because these manifestations fall along a spectrum, variations in subject sampling will dramatically affect the findings and the patterns identified; variations among individuals in the same sample may actually undercut the capacity to identify distinct patterns.

Notwithstanding the above, the preponderance of decreased diffusion connectivity in long-range association fiber systems is consistent with decreased RS connectivity in the networks subserved by those pathways. Furthermore, for the most part, the greater the reduction in efficiency of a network, as observed either by reduced diffusion or RS connectivity, the greater the behavioral deficits that are seen. These general trends all seem to point to a consistent pattern. Whereas inter- and intra-hemispheric cortico-cortical connectivity has been found to be decreased in ASD, cortico-subcortical (thalamic and striatal) connectivity has been reported to be increased (as in the study by DiMartino and colleagues[48]). Deep white matter pathways may have been relatively spared in the initial white matter structural overgrowth,[90] with the consequence that they may not have been subjected to the same overpruning that is potentially affecting cortico-cortical connections, particularly of the prefrontal cortex. This process may result in the relative upregulation of this subcortical connectivity, thereby serving a compensatory role.[34]

Autism Neuroimaging and "Big Data"

Given the existing variation in methodological approaches to data analysis in the ASD literature, it is reasonable to assume that the differences among studies may need to be resolved through some sort of combined analysis. Pooling data has benefits in both increasing the number of subjects in an experiment and decreasing methodological variability applied to those subjects. One way to promote additional common analysis is through the promotion of data sharing. A number of general resources for data sharing such as Neuroimaging Informatics Tools and Resources Clearinghouse (http://www.nitrc.org/)[91] and XNAT Central (http://central.xnat.org) exist. In addition, numerous child-specific data-sharing/data-access sites such as the Child and Adolescent Neurodevelopment Initiative (CANDIShare),[92] National Institutes of Health Pediatric Database,[93] and Pediatric Imaging, Neurocognition and Genetics[94] are available. Specific to the autism research community, both grass-roots (such as ABIDE) and federally sponsored facilities (such as the National Database for Autism Research) are becoming commonplace.

Numerous studies in this review have used data that were later contributed to the ABIDE collection,[49,50] and three of the studies utilized the combined data of the ABIDE collection.[45,48,53] The studies that utilize ABIDE data stand out for their large number of

patients (278–447 autism subjects) compared to the other studies (7–57 autism subjects). Nielsen and colleagues[45] used the data for classification purposes and had modest success in using the combined RS data to distinguish between controls and patients. As in the individual studies, regions with altered connectivity are implicated in the default mode network, parahippocampal and fusiform gyri, insula, Wernike's area, and intraparietal sulcus.[45] Di Martino and colleagues,[48] with their seed-based analysis of the ABIDE data set, have indicated both a massive predominance of hypo-connectivity within many of the cortico-cortical pairs of regions and a hyper-connectivity of the subcortical regions. In a study by Alaerts and colleagues,[53] a seed-based analysis in the posterior superior temporal sulcus confirmed their observation of underconnectivity with the inferior parietal lobule. In summary, while some of the findings of the smaller individual studies have been confirmed through studies based on the combined ABIDE collection, work is ongoing to disentangle the site-specific sources of variance that may be discovered as the data are pooled.

CONCLUSION

The general finding in the literature reviewed here is that decreases in diffusion and resting state connectivity are present in ASDs. While the literature is still largely characterized by methodological variability and studies with relatively small numbers of subjects, some common interpretational themes are emerging, and larger studies with pooled data and more homogeneous analytic approaches are now being conducted. Given the general findings for connectivity in autism, the next challenge is to generate more precise results and to determine whether those results can be correlated with the diverse symptomatologies and behavioral profiles of patients with autism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Resting state connectivity changes observed in ASD.

Study	Connectivity results	Seed brain regions	Observations in ASD groups compared to the control groups
Cherkassky et al. (2006)[21]	↓	Numerous	General underconnectivity
	↓	Anterior cingulate cortex	Reduced connectivity to posterior cingulate cortex
	↓	L parahippocampal gyrus	Reduced connectivity with multiple ROIs
Kennedy & Courchesne (2008)[29]	↓		Connectivity within the task negative network comprising of dorsal and ventromedial prefrontal cortex, posterior cingulate cortex/precuneus, left and right angular gyrus, right temporal pole, and right superior temporal gyrus/superior temporal sulcus
Monk et al. (2009)[30]	↓	Posterior cingulate cortex	Reduced connectivity to right superior frontal gyrus
	↑	Posterior cingulate cortex	Increased connectivity to right temporal lobe and right parahippocampal gyrus
Weng et al. (2010)[31]	↓	Posterior cingulate cortex	Reduced connectivity to most of the default mode network nodes
Paakki et al. (2010)[32]	↓		Reduced regional activity coherence in right superior temporal sulcus, right inferior frontal and middle frontal gyrus, bilateral cerebellar crus I, right insula, and right postcentral gyrus
	↑		Increased regional activity coherence in right thalamus, left inferior frontal gyrus, left inferior, medial, and superior occipital gyri and fusiform gyrus with optic radiation, left middle cingulate cortex with corpus callosum, right middle temporal gyrus
Assaf et al. (2010)[33]	↓		Reduced connectivity strength in precuneus
	↓		Reduced connectivity strength in medial prefrontal cortex/anterior cingulate cortex
Dinstein et al. (2011)[19]	↓	Superior temporal gyrus and Inferior frontal gyrus	Reduced strength and spread of inter-hemispheric correlations
Di Martino et al. (2011)[34]	↑		Increased connectivity in striatal-cortical circuitry, including the right superior temporal gyrus and insular cortex
	↑		Striatal functional hyperconnectivity with the pons
	↑		Broad patterns of hyperconnectivity of brainstem area, with bilateral insular cortices
Anderson et al. (2011)[35]	↓		Reduced interhemispheric functional connectivity between homologous gray matter voxels (sensorimotor cortex, frontal insular cortex, and superior parietal lobule extending from the parieto-occipital junction to the intraparietal sulcus)
Anderson et al. (2011)[36]	↓		General underconnectivity
Ebisch et al. (2011)[37]	↓ (lost connectivity)	R anterior insular cortex	Lost connectivity to amygdala and thalamus
	↓ (lost connectivity)	L posterior insular cortex	Lost connectivity to dorsal postcentral gyrus
	↓ (lost connectivity)	R posterior insular cortex	Lost connectivity to dorsal postcentral gyrus
	↓ (lost connectivity)	L anterior insular cortex	Lost connectivity to orbitofrontal cortex and posterior insular cortex
	↓ Autism < typically developing, Autism < Aspergers	R anterior insular cortex	Reduced connectivity to right dorsal anterior cingulate cortex

Study	Connectivity results	Seed brain regions	Observations in ASD groups compared to the control groups
	↓ Autism, Asperger's < typically developing	R anterior insular cortex	Reduced connectivity to amygdala
	Asperger's = typically developing	R anterior insular cortex	No significant difference in connectivity to dorsal anterior cingulate cortex
Wiggins et al. (2011)[38]	↓	R superior frontal gyrus	Reduced connectivity to posterior superior frontal gyrus
Gotts et al. (2012)[39]	↓		Lower connectedness to other ROIs for social brain network regions such as ventromedial prefrontal cortex, left amygdala, left hippocampus, bilateral ventromedial anterior temporal lobes, left temporoparietal junction, bilateral postcentral gyrus, right lateral occipital cortex
	↓		Lower connectedness to other ROIs for right anterior middle temporal gyrus/superior temporal gyrus, left inferior and right posterior temporal gyrus, and left cerebellum
	No significant change	Posterior parahippocampal gyrus	No change in connectivity to the rest of the brain
Rudie et al. (2012)[40]	↓		Reduced overall default mode network connectivity
	↓	Posterior cingulate cortex	Reduced connectivity to medial prefrontal cortex in combined genotyped groups
	↓	Posterior cingulate cortex	Reduced connectivity to medial prefrontal cortex in the MET-homozygous (risk) group, irrespective of ASD
	↓	Posterior cingulate cortex	Reduced connectivity to medial prefrontal cortex within ASD group (MET-homozygous < MET-heteromozygous < nonrisk)
	↓	Posterior cingulate cortex	Reduced connectivity to medial prefrontal cortex (MET CC ASD < MET CC typically developing, and MET CG ASD< MET CG typically developing)
von dem Hagen et al. (2013)[20]	↓		Reduced correlation between the salience network and the medial temporal lobe network
	↓	Medial prefrontal cortex	Reduced connectivity to temporoparietal junction/posterior superior temporal sulcus
	↓	Amygdala	Reduced connectivity to left anterior insular cortex
Lynch et al. (2013)[41]	↑	Posterior cingulate cortex	Increased connectivity to medial and anterolateral temporal cortex, lingual gyrus, posterior parahippocampal gyrus, temporal pole, and both the entorhinal cortex and perirhinal cortex within the anterior aspect of the medial temporal lobe
	↑	Retrosplenial cortex	Increased connectivity to inferior frontal and middle frontal gyrus, dorsal medial prefrontal cortex, posterior insular cortex, lingual gyrus, posterior parahippocampal gyrus, temporal pole, posterior superior temporal sulcus, and anterior supramarginal gyrus
	↓	Precuneus	Reduced connectivity to cuneus, caudate, and dorsal and medial thalamic nuclei
Washington et al. (2013)[22]	↓	Various regions	Reduced connectivity within default mode network nodes and other functional networks
	↓	Dorsal anterior cingulate cortex/Medial prefrontal cortex	Reduced connectivity to ventral anterior cingulate cortex and medial prefrontal cortex
Tyszka et al. (2014)[42]	–		No significant between group differences for networks identified by independent component analysis
	–		No significant between group differences for ROI-based analysis
			Residual effect of subject motion was larger than the effect of diagnosis

Study	Connectivity results	Seed brain regions	Observations in ASD groups compared to the control groups
Uddin et al. (2013)[43]	↑	Anterior cingulate cortex	Increased connectivity to superior frontal gyrus, thalamus, and bilateral insular cortex
	↑	Precuneus	Increased connectivity to posterior cingulate cortex and left angular gyrus
	↑	Superior temporal gyrus	Increased connectivity to middle temporal gyrus
	↑	Postcentral gyrus	Increased connectivity to precentral gyrus, left posterior insular cortex, and thalamus
	↑	L lateral occipital cortex	Increased connectivity to intracalcarine cortex, and occipital pole
Redcay et al. (2013)[44]	↑ local connectivity	Medial prefrontal cortex	Increased local connectivity within ROI
	↑	Anterior medial prefrontal cortex	Increased long distance connectivity to right lateral parietal region
	↓	R lateral parietal region	Reduced connectivity to cerebellar tonsils
Neilsen et al. (2013)[45]			Classification accuracy analysis; No connectivity changes reported/ studied
Maximo et al. (2013)[46]	↑ local connectivity		Increased local connectivity in right middle frontal gyrus, bilateral striate and extrastriate cortices, parahippocampal gyrus, middle temporal gyrus, and supramarginal gyri
	↓ local connectivity		Reduced local connectivity in left superior frontal gyrus and bilateral middle cingulate cortex/posterior cingulate cortex, right paracentral cortex, left perisylvian and frontopolar regions (anterior prefrontal cortex), left insular cortex, bilateral precuneus
Starck et al. (2013)[47]	–		No significant between group differences for local connectivity
	↓	Medial prefrontal cortex	Reduced connectivity to posterior subnetworks of default mode network, dorsal (the central-posterior precuneus and the posterior cingulate cortex) subnetworks of default mode network, and to ventral (retrosplenial cortex) subnetworks of default mode network
DiMartino et al. (2013)[23]	↓ DC	Precuneus	Decreased DC (i.e., number of direct connections to precuneus)
	↑ DC		Increased DC for bilateral limbic areas including the superficial and latero-basal amygdala, the adjacent parahippocampus (posterior parahippocampal gyrus and fusiform gyrus), planum temporale, and temporal cortex
DiMartino et al. (2013)[48]	↓		Corticocortical intrinsic functional connectivity across all functional domains with paralimbic and unimodal association regions having the highest proportions of affected connections
	↑		Intrinsic functional connectivity for subcortical regions, particularly between subcortical (thalamus and globus pallidus) and primary parietal sensorimotor regions
	↓ VMHC, ReHo, and DC	L posterior insular cortex	Reduced VMHC, ReHo and DC in cluster extending from the left posterior insula to the central and parietal operculum
	↑ fALFF, ReHo, and DC	R superior frontal cortex	Increased fALFF, ReHo and DC in cluster located in right dorsal superior frontal cortex
	↓ at least 2 of ReHo, VMHC, fALFF, or DC		Reduced in at least 2 of ReHo, VMHC, fALFF, or DC in clusters in thalamus, posterior cingulate, bilateral middle-insula, and left middle occipital gyrus
Abrams et al. (2013)[49]	↓	Posterior superior temporal sulcus	Reduced connectivity to components of reward pathways such as bilateral ventral tegmental area, nucleus accumbens and putamen of the basal ganglia, ventromedial prefrontal cortex, as well as the left caudate, anterior insular cortex, and orbitofrontal cortex
Mueller et al. (2013)[50]	↓		Lower connectivity for dorsal attention network to a cluster including the right precentral gyrus, which reached into the right parietal lobe, and right parietal and precuneal cortex

Study	Connectivity results	Seed brain regions	Observations in ASD groups compared to the control groups
	↓	Superior temporal gyrus	Reduced connectivity to default mode network
	↓	Medial prefrontal cortex	Reduced connectivity to left anterior cingulate cortex
Cardinale et al. (2013)[51]	↑ rightward asymmetry		Significant rightward asymmetry in ASD for all components.
You et al. (2013)[52]	↑ modularity		Increased modularity of network
	-		No between group difference in global efficiency of networks
Alaerts et al. (2013)[53]	↓	Posterior superior temporal sulcus	Reduced connectivity with inferior parietal lobule, precentral gyrus, supramarginal gyrus, inferior frontal gyrus (pars triangularis)
	↑	Posterior superior temporal sulcus	Increased connectivity with lingual gyrus, calcarine gyrus, fusiform gyrus
	↓ in ABIDE group	Posterior superior temporal sulcus	Reduced connectivity with right inferior parietal lobule, left premotor area, fusiform gyrus and bilateral superior occipital gyrus
	↑ in ABIDE group	Posterior superior temporal sulcus	Increased connectivity with left thalamus and right inferior frontal gyrus
Verly et al. (2014)[54]	–	Arcuate fasciculus	No between group difference for connectivities observed for bilateral arcuate fasciculus seed
	↓	L Broca's area (part of inferior frontal gyrus)	Reduced connectivity to bilateral Wernicke's area (superior temporal gyrus) in ASD group with only unilateral arcuate fasciculus
	↓		Reduced interhemispeheric connectivity (besides arcuate fasciculus)
Nair et al. (2013)[55]	↓		Several clusters of underconnectivity in ASD, especially for right prefrontal cortex, right parietal-occipital, and bilateral motor and bilateral somatosensory seeds
	↑	R thalamus	Increased connectivity to temporal seed
	↓	Thalamus	Reduced connectivity to prefrontal, parietal-occipital, and somatosensory cortical seeds
Keown et al. (2013)[56]	↑ local connectivity		Increased local connectivity in temporo-occipital regions (including inferior temporal gyrus and middle temporal gyrus, temporal pole, middle and superior occipital gyri, calcarine cortex, right parahippocampal gyrus, right fusiform gyrus, and left cuneus) and right middle frontal and superior frontal gyrus
	↓ local connectivity	Middle cingulate	Small clusters of local underconnectivity
	↓ local connectivity	R inferior parietal sites	Small clusters of local underconnectivity
	↓	L lateral and bilateral polar and medial frontal cortices	Low-severity ASD subgroup < typically developing
	↑	Posterior brain regions	Higher-severity ASD subgroup > typically developing (predominantly)

↑, increased (connectivity unless otherwise stated) in disorder groups; ↓, reduced (connectivity unless otherwise stated) in disorder groups; –, no significant change; ABIDE, Autism Brain Imaging Data Exchange; ASD, autism spectrum disorder; DC, degree of centrality; fALFF, fractional amplitude of low-frequency fluctuations; L, left hemisphere side of an ROI; MET CC/CG,MET rs1858830 CC/CG genotype; R, right hemisphere side of an ROI; ReHo, regional homogeneity; ROI, region of interest; VMHC, voxel-matched homotopic connectivity.

Table 2

Diffusion parameter changes reported

Study	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity [λ(1)]	Brain regions
Lee et al. (2007)[60]	↓				Bilateral superior longitudinal fasciculus and right temporal stem[a]
		↑			Bilateral superior longitudinal fasciculus and right temporal stem[a]
			↑		All regions (bilateral superior temporal gyrus white matter and bilateral temporal stem[a])
				↓	Right superior longitudinal fasciculus
Sundaram et al. (2008)[61]	↓				Bilateral frontal short-range fibers
Brito et al. (2009)[62]	↓				Anterior body of corpus callosum, right corticospinal tract, posterior limbs of internal capsule, and left superior and bilateral middle cerebellar peduncle
	↑				Left putamen
		–			No significant difference observed in any white matter region
Pugliese et al. (2009)[59]	↓				Bilateral inferior fronto-occipital fasciculus and right uncinate fasciculus
		↑			Bilateral inferior longitudinal fasciculus and right cingulum
Bloemen et al. (2010)[58]	↓				Inferior fronto-occipital fasciculus, forceps major and minor, anterior, posterior, and superior corona radiata, bilateral anterior thalamic radiation, bilateral uncinate fasciculus, genu of corpus callosum, posterior limbs of internal capsule, splenium and dorsal body of corpus callosum, corticospinal tract, sagittal stratum (inferior longitudinal fasciculus and occipito-frontal fasciculus), retrolenticular parts of internal capsule, inferior longitudinal fasciculus, and superior longitudinal fasciculus and cingulum
		↓			Brain stem
			↑		Clusters in right inferior frontal gyrus, bilateral temporal lobe, right corpus callosum, right cuneus, left insula, left parietal lobe, bilateral corpus callosum, right inferior parietal lobule, bilateral frontal lobe, and left precuneus
			↓		Clusters in left cerebellum and left corpus callosum
Sivaswamy et al. (2010)[63]	↑				Right middle cerebellar peduncle
		↑			Superior cerebellar peduncle
Noriuchi et al. (2010)[64]	↓				White matter surrounding anterior cingulate cortex, dorsolateral prefrontal cortex, posterior superior temporal sulcus/ temporoparietal junction, right temporal pole, amygdala, superior longitudinal fasciculus, occipito-frontal fasciculus, and mid and left anterior corpus callosum

Study	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity [λ(1)]	Brain regions
				↓	Dorsolateral prefrontal cortex, posterior superior temporal sulcus/temporoparietal junction, right temporal pole, amygdala, superior longitudinal and occipito-frontal fasciculus, mid and left anterior corpus callosum, and mid and right anterior cingulate cortex
				↑	Cerebellar vermis lobules
Fletcher et al. (2010)[65]		↑			Left arcuate fasciculus
			↑		Left arcuate fasciculus
Sahyoun et al. (2010)[66]	↓				Pathways between left frontal gyrus and left inferior frontal (Inferior frontal area, corona radiata), right frontal gyrus and right inferior frontal (corona radiata), and right inferior frontal and right medial temporal gyrus (right uncinate fasciculus)
	–				Pathways between frontal gyrus and inferior parietal sulcus I (superior longitudinal fasciculus), and frontal gyrus and superior temporal sulcus/medial temporal gyrus (superior longitudinal fasciculus)
		↓			Brain stem
Shukla et al. (2010)[67]	↓				Whole brain white matter; genu, body, and splenium of corpus callosum; anterior limbs, posterior limbs, and genu of internal capsule; and middle cerebellar peduncle
		↑			Splenium of corpus callosum, and anterior and posterior limbs of internal capsule
			↑		Whole brain white matter; genu, body, and splenium of corpus callosum; and anterior limbs, posterior limbs, and genu of internal capsule
Shukla et al. (2011)[68]	↓				Bilateral frontal lobes
		↑			Bilateral frontal, temporal, and parietal lobes
			↑		Bilateral frontal, temporal, and parietal lobes
Cheon et al. (2011)[69]	↓				Anterior thalamic radiation, corpus callosum, and left uncinate fasciculus in both ROI-based and voxel-based analysis
		↑			Corpus callosum in ROI-based analysis, and anterior thalamic radiation, corpus callosum, and left uncinate fasciculus in voxel-based analysis
				↓	Bilateral inferior longitudinal fasciculus
			↑		Left anterior thalamic radiation, corpus callosum, left uncinate fasciculus, and left inferior longitudinal fasciculus
Jou et al. (2011)[70]	↓				Inferior fronto-occipital fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, cingulum, forceps major and minor of corpus callosum, thalamic radiation, and corticospinal tract
Jou et al. (2011)[71]	↓				Bilateral anterior radiation of the corpus callosum/cingulum, left anterior and posterior body of corpus callosum/cingulum, right body of corpus callosum/cingulum, left superior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus/inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus/fusiform face areas on ipsilateral sides

Study	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity [λ(1)]	Brain regions
Shukla et al. (2011)[72]	↓				Bilateral anterior limbs of internal capsule and posterior limbs of internal capsule, and of retrolenticular part of the internal capsule, body of corpus callosum, genu of corpus callosum, splenium of corpus callosum, bilateral inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, corticospinal tract, cingulum, anterior corona radiata, right superior corona radiate, and forceps major
		↑			Splenium of corpus callosum, bilateral inferior longitudinal fasciculus, inferior fronto-occipital and superior longitudinal fasciculus, corticospinal tract, cingulum, anterior thalamic radiation, anterior and right superior corona radiata, forceps major, uncinate fasciculus, anterior and posterior limbs of internal capsule, and external capsule.
			↑		Genu of corpus callosum, and anterior body of corpus callosum
Groen et al. (2011)[73]	↓				Bilateral superior longitudinal fasciculus and inferior longitudinal fasciculus on the border of the temporal and occipital lobe, and bilateral corona radiata (left side was significant)
		↑			Most of the brain (including frontal, temporal, parietal and occipital regions, and cerebellum)
		↑			Bilateral corona radiata, anterior limbs of internal capsule, posterior limbs of internal capsule, middle cerebellar peduncle, thalamus and thalamic radiations, inferior and superior longitudinal fasciculus, and genu, body, and splenium of corpus callosum
Ameis et al. (2011)[74]	–				No difference between groups
		↑			Observed in children only: Frontal regions, uncinate fasciculus, inferior fronto-occipital and superior longitudinal fasciculus, forceps minor of corpus callosum, bilateral medial frontal gyrus and inferior frontal gyrus, and, within the superior corona radiata, white matter connecting superior frontal and parietal regions.
			↑		Observed in children only: Frontal regions, uncinate fasciculus, inferior fronto-occipital fasciculus, forceps minor of corpus callosum, bilateral medial frontal gyrus and inferior frontal gyrus, superior longitudinal fasciculus, white matter connecting superior frontal and parietal regions (within the superior corona radiata), and inferior longitudinal fasciculus and forceps major of corpus callosum.
Walker et al. (2012)[57]	↓				Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, cingulum, and genu, body, and splenium of corpus callosum; anterior and posterior limbs of internal capsule; corticospinal tract; and anterior thalamic radiation
		↑			Inferior longitudinal, superior longitudinal, and inferior fronto-occipital fasciculus; cingulum; splenium of corpus callosum, anterior and posterior limbs of internal capsule; external capsule; corticospinal tract; uncinate fasciculus; and anterior thalamic radiation
			↑		Inferior longitudinal, inferior fronto-occipital, and superior longitudinal fasciculus; cingulum;, genu body, and splenium of corpus callosum;

Study	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity [λ(1)]	Brain regions
					anterior and posterior limbs of internal capsule; external capsule; corticospinal tract, uncinate fasciculus, and anterior thalamic radiation
Nagae et al. (2012)[75]	–				No effect of group, but left superior longitudinal fasciculus FA > right superior longitudinal fasciculus FA
		↑			Superior longitudinal fasciculus for both ASD groups, with ASD with language impairment significantly more than typically developing in left superior longitudinal fasciculus and left temporal lobe superior longitudinal fasciculus
				↑	ASD with language impairment significantly more than typically developing in superior longitudinal fasciculus
Billeci et al. (2012)[76]	↑				Corpus callosum, cingulum, external and internal capsule, and arcuate fasciculus
		↑			Right indirect posterior and the right indirect anterior segments of the fasciculus arcuate and left cingulum
Rudie et al. (2012)[40]	–				No significant difference when genotype groups were combined
	↓				Splenium of corpus callosum, superior longitudinal fasciculus/inferior longitudinal fasciculus, and cingulum; the MET corpus callosum and MET CG groups < MET GG nonrisk group, irrespective of diagnosis[b]
	↓				Within ASD group, MET corpus callosum & MET CG < MET GG[b]
Beacher et al. (2012)[77]	↑				Observed in control males compared to control females (not observed in Asperger's groups): Corpus callosum, bilateral cingulum, corona radiata.
	↓				Observed in Asperger's males compared to control males: Corpus callosum, bilateral cingulum, corona radiata
		↓			Thalamus
Langen et al. (2012)[78]	↓				White matter tracts connecting putamen to frontal cortical areas
		↑			White matter tracts connecting accumbens to frontal cortex
Kleinhans et al. (2012)[79]	↓				Association fibers (cingulum, fornix, stria terminalis, sagittal stratum, superior fronto-occipital and superior longitudinal fasciculus, uncinate fasciculus), projection fibers (anterior and superior corona radiata, anterior and posterior limbs and retrolenticular part of internal capsule, external capsule, cerebral peduncle, corticospinal tract, posterior thalamic radiation), brain stem fibers (Inferior, middle, and superior cerebellar peduncle, medial lemniscus, and pontine crossing tract), corpus callosum, tapetum
		↑			Cingulum, SS, superior longitudinal fasciculus, body of corpus callosum, splenium of corpus callosum, tapetum, and projection fibers (external capsule, posterior corona radiata, posterior limb and retrolenticular part of internal capsule, posterior thalamic radiation, and superior corona radiata).
			↑		Association fibers (cingulum, fornix, stria terminalis, sagittal stratum, superior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus), corpus callosum and tapetum, and projection fibers (anterior and posterior corona radiata, cerebral peduncle, corticospinal tract, external capsule, posterior limb and retrolenticular part of internal capsule, posterior thalamic radiation, and middle

Study	Fractional anisotropy	Mean diffusivity	Radial diffusivity	Axial diffusivity [λ(1)]	Brain regions
					cerebellar peduncle)
Mueller et al. (2013)[50]	↓				Right cluster reaching from the splenium of corpus callosum into the superior longitudinal fasciculus within the parietal and temporal lobe and into the lateral occipital cortex
	↓				Cluster in anterior portion of the corpus callosum, reaching into the left anterior cingulate cortex and the left medial frontal cortex
	↓				Bilateral corticospinal tracts
Verly et al. (2013)[54]	–				No between-group difference was found in FA (or in apparent diffusion coefficient); leftward asymmetry in both groups
Lewis et al. (2013)[80]			–		No significant between-group difference was found in radial diffusivity
Nair et al. (2013)[55]	–				No between-group difference was found in FA
		↑			Tracts connecting thalamus with motor (anterior limbs of internal capsule) and somatosensory cortices (posterior limbs of internal capsule) bilaterally, and with the right prefrontal ROI
			↑		Bilateral thalamus tracts for the motor ROI, left somatosensory ROI, right prefrontal ROI, and (marginal increase) right somatosensory ROI
McGrath et al. (2013)[81]	↓				White matter directly connecting left Brodmann area 19 and left thalamus regions (thalamic radiation), and white matter tracts directly connecting the regions in left Brodmann area 19 and left caudate head
McGrath et al. (2013)[82]	↓				Right inferior fronto-occipital fasciculus (implying increase in microstructural organization of the right inferior fronto-occipital fasciculus in the ASD group)
Joseph et al. (2014)[84]	–				No between-group difference was found in FA, but rightward asymmetry of FA in arcuate fasciculus in both groups
			↓*		Decreased rightward asymmetry of radial diffusivity in arcuate fasciculus in ASD group
Kana et al. (2014)[85]	↓				White matter underlying the right middle/superior temporal lobe in ASD participants

↑, increased; ↓, decreased; ↓*, decreased rightward asymmetry; –, no significant change; FA, fractional anisotropy; MET CC/GG, MET rs1858830 CC/GG; ROI, region of interest.

[a] 'temporal stem' is comprised of the uncinate fasciculus and occipito-frontal fasciculus.

[b] MET is one of multiple genes encoding proteins in the ERK/ PI3K signaling pathway.