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Experimental Neurobiology

Review Article: Autism Spectrum Disorders

Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan

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Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder characterized by impaired social communication and restricted and repetitive behaviors (RRBs). Over the past decade, neuroimaging studies have provided considerable insights underlying neurobiological mechanisms of ASD. In this review, we introduce recent findings from brain imaging studies to characterize the brains of ASD across the human lifespan. Results of structural Magnetic Resonance Imaging (MRI) studies dealing with total brain volume, regional brain structure and cortical area are summarized. Using task-based functional MRI (fMRI), many studies have shown dysfunctional activation in critical areas of social communication and RRBs. We also describe several data to show abnormal connectivity in the ASD brains. Finally, we suggest the possible strategies to study ASD brains in the future.

Key words: Autism spectrum disorder (ASD), Neuroimaging, Magnetic resonance image (MRI), Functional MRI (fMRI), Diffusion tensor image (DTI)

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and restricted repetitive behaviors (RRBs). Recently, there have been some changes in diagnostic criteria of ASD in The Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (American Psychiatric Association, 2013). Several diagnoses have been integrated into one dimensional diagnosis, or ASD. As well, three criteria of ASD; (1) qualitative impairment in social interaction (2) in communication and (3) restricted repetitive and stereotyped patterns of behavior, interests, and activities have been reconstructed two domains; (1) persistent deficits in social communication and social interaction (2) restricted, repetitive patterns of behavior, interests, or activities [1].

According to the Centers for Disease Control and Prevention (CDC) report, ASD affected nearly 1 in 68 children in the United States in 2014. In Korea, the prevalence of ASD was estimated to be 2.64% in school-age children [2]. The global prevalence of ASD has rapidly increased over time, however, the etiology for ASD has been poorly understood [3]. It is believed that ASD is a highly heritable disorder and that genetic susceptibility interacts with

environmental factors in ASD etiology [4].

Neuroimaging is a powerful tool for *in vivo* study to investigate the brain structure and function. Since Horwitz et al. reported linkage of ASD to abnormal brain activity using Positron Emission Tomography (PET) [5], many brain imaging studies have been conducted and provided understanding the underlying neurobiological mechanisms of ASD [6]. As Lange et al. described ASD as a dynamic disorder with complex changes over time from childhood into adulthood [7], developmental perspective may help to understand some contradictory findings in ASD studies [8]. Therefore, it is meaningful to review about the ASD brain features depending on age. The objective of this review is to summarize recent findings from brain imaging researches and to show characteristics of ASD brains in terms of structure, function, and connectivity across the lifespan. By overviewing the previous researches, we will discuss abnormalities of ASD brains and will suggest the future directions of ASD research.

BRAIN STRUCTURES IN ASD

Since neuroimaging approach is one of the few methods that enable to make direct observation of the brain *in vivo*, Magnetic Resonance Image (MRI) studies have provided many implications of neurodevelopmental characteristics underlying ASD [9]. Although various results were shown from structural MRI (sMRI) studies over the past decade, there are abnormalities in gray and white matter with some regional brain differences between ASD and typically developing (TD) control [7, 10, 11]. Many sMRI studies have investigated volumetric and morphometric brain in order to examine atypical brain anatomy and neurodevelopment in ASD. Reviewing these findings provides insights into the neural substrates and autistic symptoms across the human lifespan.

Total Brain Volume

The most coherent finding is an accelerated total brain volume growth in early children with ASD around 2~4 years of age [10]. Many age-related studies have examined group differences in the total brain volume between ASD and TD. Fig. 1 is a plot of whole brain volume by age and group, ASD and TD control (TDC) [7]. As shown in Fig. 1, findings generally have evidence of its atypical developmental trajectory with enlarged brain volume in younger individuals with ASD [12], but decreased volume or no difference in older individuals with ASD compared to TDC [13]. Although it has not been identified abnormal brain maturation during adolescence and adulthood in ASD, brain development during early childhood in ASD seems to be predominated by an enlarged brain volume of the frontal and temporal lobes [14] followed by
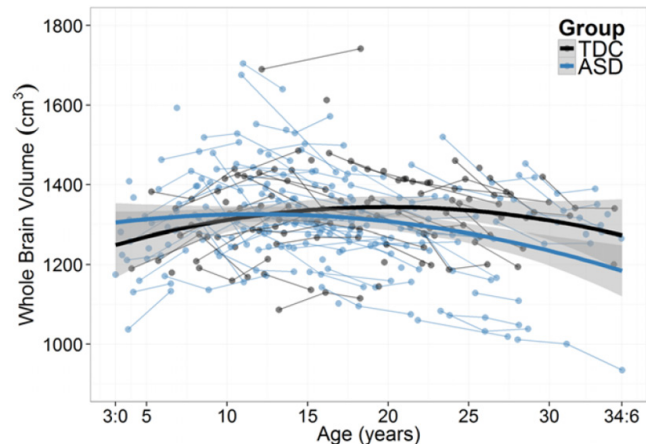

Fig. 1. Whole brain volume by age and group. ASD: autism spectrum disorder, TDC: typically developing control, For more information, see [7] (From Nicholas Lange et al., *Autism Research* (2015) by permission of John Wiley & Sons).

arrested growth and a possible declined volumetric capacity of the brain after around 10~15 years of age [7].

Regional Brain Structure

The pathological mechanism that represents an ongoing enlargement of the brain is unclear. Recent progress has evidence that early overgrowth of ASD brain is caused by an accelerated expansion of cortical surface area but not cortical thickness before the age of 2 years [15]. It was a meaningful finding because it showed potential for clarification of the neurobiological mechanisms that might be deficient in ASD. An early white matter differences in ASD brains might explain the brain being connected atypically [16]. Thus, accelerated expansion of cortical surface area of the gray matter in ASD seems to be associated with impaired maturation of the cortical white matter.

The constituent parts of the neural systems associated with clinical symptoms in ASD were examined by many studies. Specific core regions have been suggested to mediate clinical phenotypes of ASD such as the frontotemporal lobe, frontoparietal cortex, amygdala, hippocampus, basal ganglia, and anterior cingulate cortex (ACC) [17]. For example, abnormalities in (1) the inferior frontal gyrus (IFG, Broca's area), superior temporal sulcus (STS), and Wernicke's area might be related to defects in social language processing and social attention [18], (2) the frontal lobe, superior temporal cortex, parietal cortex, and amygdala might mediate impairments of social behaviors [19, 20] and (3) the orbitofrontal cortex (OFC) and caudate nucleus have been associated with RRBs of ASD [21]. Although deficits in these regions seem to be general in ASD, some findings proposed that abnormalities in these brain regions are not peculiar to ASD

and seem to be common in other disorders such as obsessive-compulsive disorder, general anxiety disorders, and schizophrenia [22-24].

Zielinski et al. measured cortical thickness in various regions of ASD brains and reported accelerated cortical thinning in individuals with ASD aged 3~39 years in a longitudinal study [25]. Findings from a vertex-based measurements study suggested that individuals with ASD tend to have thinner cortices and reduced surface area by age-related effects [26]. These findings point that a plot of cortical development is curvilinear across the human lifespan and there are evidences of abnormal cortical expansion during early childhood followed by rapid cortical thinning during adolescence and adulthood.

Cortical Area

Brain overgrowth in childhood of ASD mediates a significant difference in geometry of the brain. Several neuroimaging studies have examined other aspects of the cerebral cortex, such as cortical shape and sulcal patterns. Abnormalities in cortical folding might be caused by mechanical tension of axonal white matter fibers pulling force on the neocortex [27]. Since cortical gyrification seems to be associated with an expansion of the outer cortical layers relative to the microstructural deeper layers of the gray matter, atypical cortical folding in the brains of children with ASD have been observed in several studies [28, 29]. These findings suggest that there is remarkably enlarged gyrification of the frontal lobe in children and adolescents with ASD [28]. Regional cortical folding is increased in bilateral posterior brain regions in individuals with ASD during early adolescence and adulthood [30]. Whereas, reduced local gyrification has been reported in the right inferior frontal and medial parieto-occipital cortices in children with ASD [31] and in the left supramarginal gyrus in individuals with ASD aged 8~40 years [32]. These various findings imply that the specific pattern of cortical gyrification has been altered across the lifespan and that genetic and environmental factors contribute to aspects of cortical geometry.

BRAIN FUNCTIONS IN ASD

At a neuroimaging level, functional MRI (fMRI) and magnetoencephalography (MEG) enable the exploration of atypical brain functions of ASD. Many studies have shown that structural differences between ASD and TD are different depend on age. As structural differences are related to different functions of brain domain, it is necessary to observe the brain functions across the human lifespan. According to the DSM-5 diagnostic criteria, social communication impairments and restricted,

repetitive patterns of behaviors, we will review recent studies about the atypical brain functions of ASD based on two core features in age-dependent manner.

Infants, Toddlers and Children

Social communication and social interaction

Language development is a critical neurobiological process to communicate each other. Delayed language development is one of the early warning signs of ASD [33]. Children with ASD commonly show impaired language development that leads to social communication deficits. Some fMRI studies have examined the neurobiological differences of impaired language development between children with ASD and TD children [34, 35]. Wang et al. used fMRI to examine the neurobiological deficits in understanding irony in high-functioning children with ASD. In contrast to previous studies showing hypo-activation of regions involved in understanding the mental states of others, children with ASD showed hyper-activation than TD children in the right IFG as well as in bilateral temporal regions. Greater activity children with ASD fell within the network recruited in the TD children and this may reflect more efforts needed to interpret the intention of a word. They concluded that children with ASD have impairments interpreting the communicative intention of others'. These results also indicated that children with ASD can recruit regions activated as part of the normative brain circuitry when task requires some degree of explicit attention to socially relevant cues [34].

Deficits in working memory are important aspects of ASD, as there are some studies suggesting relations between deficits in working memory and social communication impairments [36]. Using MEG, Urbain et al. revealed significant correlation between hypo-activation in the ACC and increased social communication impairments in children with ASD. They suggested that ACC has a critical role in the regulation of both cognitive and emotional processing [37].

The ability to perceive emotional facial expressions and to represent co-speech gestures are critical to social interactions and deficits of these abilities have been reported in previous fMRI studies in children with ASD [38, 39]. ASD children are known to be less reinforced by positive social reward such as smiling. Some studies reported that impairments in social reward learning could result in social communication impairments in children with ASD [40]. As shown in Fig. 2, Kim et al. found that children with ASD showed lower activation of the right amygdala, right STS, and right IFG than TD children when they stimulated with fearful face. For the happy face stimuli, children with ASD showed hypo-activation
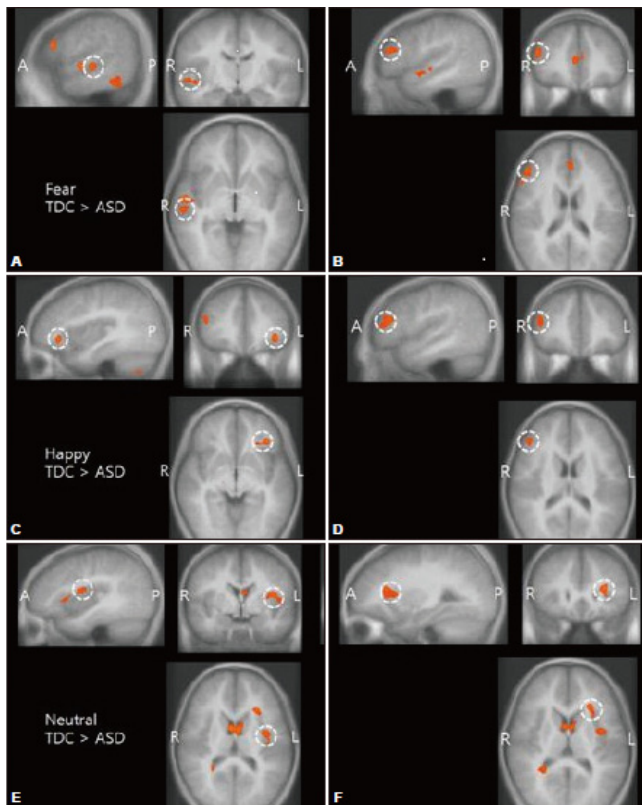
Fig. 2. Main effect of emotional face perception (A and B: fearful stimuli, C and D: happy stimuli, E and F: neutral stimuli). Reduced activities were observed in several parts of the social brain network in the ASD group compared with the TDC group while pictures of emotional faces were shown (uncorrected, p<0.01). Brain regions indicated are right superior temporal sulcus (STS) (A), right inferior frontal gyrus (IFG) (B); left insular cortex (C); right IFG (D); left superior insular sulcus (E); left superior insular sulcus (F). ASD: autism spectrum disorder, TDC: typically developing children, A: anterior, P: posterior, R: right, L: left. For more information, see [39] (From Kim et al., *Psychiatry Investig* (2015), open access article).

of the left insular cortex. They concluded that the deficits in social cognition of ASD children could be explained by the impairment of the capacity for visual analysis of emotional facial expressions, the subsequent inner imitation through mirror neuron system (MNS), and the ability of transmitting it to the limbic system and processing the transmitted emotion [39].

Restricted and repetitive patterns of behavior, interests, or activities

Restricted, repetitive patterns of behaviors, interest, or activities indicate heterogeneous features of ASD. They include a wide range from stereotypies, echolalia, rituals, restricted interest, cognitive inflexibility, to excessive sensitivity to change [41]. Presence of RRBs is an important diagnostic criterion for ASD and it has been linked to differences in the striatum. Such RRBs in ASD are

evident in infants with ASD [42], and persist in children with ASD [43]. Sharer et al. used fMRI to examine the functional differences about RRBs in children with ASD. In this study, children with ASD demonstrated hypo-activity in the brain regions such as STS and posterior cingulate cortex related to visuomotor sequence learning. They suggested that differences in the brain mechanisms may support initial sequence learning in ASD and can help explain behavioral observations of ASD associated impairments in skill development [44]. Response monitoring is an important process that involves abilities to evaluate, monitor, and adjust one's own behavior if it does not match an intended goal. Impairments in adjusting behavioral strategies may be critical in ASD because failure to adjust that may contribute to the RRBs [45].

Goldberg et al. examined the neural basis of error monitoring using fMRI in children with ASD. Compared to TD children, ASD children showed increased activities in the anterior medial prefrontal cortex (mPFC) and the left superior temporal gyrus (STG) during commission error (versus correct inhibition) trials. These results suggest a greater attention towards the internal emotional state associated with making an error in children with ASD [46].

Adolescents and Adults

Social communication and social interaction

Several models have been proposed to explain impairments in social communication and interaction of ASD. For example, deficits in theory of mind (ToM), facial expression processing, language processing, and many other models have been suggested [47]. Although several studies have suggested various brain regions and hypo- or hyper-activity associated with impairments in social communication and interaction of ASD, neural correlates have been thought to underlie the deficits with basis of evidence through diverse functional imaging studies for several decades [47, 48]. The brain areas that have been associated with social communication and interaction are referred to as "social brain area". The social brain area includes the STS and its adjoining areas, such as the middle temporal gyrus, fusiform gyrus (FG), amygdala, mPFC, and IFG [39, 48]. It is thought that the social brain areas play a pivotal role in social cognition and interaction, and abnormal activities in these areas are associated with clinical manifestation in ASD.

ToM, an ability to understand others' intention, predict others action and, if needed, imitate that, is important in social communication and interaction. Association of ToM and MNS has been demonstrated by previous studies [49, 50]. Some differences between ASD and TD children in performing imitation task

have been reported through several studies [51]. Moreover, some investigators have proposed impaired MNS has a critical role in ASD [52]. Williams et al. showed aberrant activity in adolescent with ASD during observing others' behavior and imitating in the right temporo-parietal junction which has been known to be associated with ToM [53].

Face recognition is a primary step and has an important role for social communication and interaction. Impaired facial processing is an early-emerging feature of ASD. Therefore several imaging studies have been interested in facial processing [48]. In the study performed to high-functioning adults with autism, Humphrey et al. showed hypo-activation in bilateral fusiform face area and occipital face area [54]. There have been other reports about the FG and occipital area. In the meta-analysis of social process in ASD, relative hypo-activities have been exhibited in the left FG and bilateral occipital lobe [48, 55]. Dalton et al. also reported hypo-activation in FG in facial processing task in adolescent with ASD [56].

Language processing impairments in ASD have heterogeneous range from absence of communication to high-order communication such as pragmatic language deficits. Several neuroimaging studies have proposed that aberrant activations in the Broca's area (left IFG) and Wernicke's area (left STG) may play a critical role in impaired language processing in ASD [47]. In the functional imaging study performed by Kana et al., the left inferior and middle frontal gyrus, and left angular gyrus have been showed hypo-activation in adolescent with ASD compared with healthy control [57].

Restricted and repetitive patterns of behavior, interests, or activities

The neural correlates underlying RRBs have been investigated less than social communication and interaction even though RRBs contain diverse manifestation in ASD and has clinical significance [47]. RRBs symptoms are not usually manifested in the same way and they are changed variously over time. Some studies have reported that the RRBs are manifested differently depending on age. Watts et al. showed ASD children (the age of 18 months ~24 months) had more frequency and longer duration in RRBs than TD children [58]. However, the same results have not been showed in older subjects [59]. Younger ASD children showed more motor and sensory repetitive behaviors, while older ASD children had more complex behaviors [60]. Considering the nature and severity of RRBs that are not stable over time, putative neural circuitry underlying RRBs can be exhibited differently depending on developmental stage.

Deficits in executive cognitive function may be related to RRBs

of ASD, especially impairments in control of inhibition and cognitive flexibility [47]. A few studies have suggested associations of RRBs with functional and structural alterations in cortical-basal ganglia circuitry [59]. Mosconi et al. reported neurocognitive disturbances in voluntary behavioral control and suggested alterations in the front striatal systems contribute to higher-order repetitive behaviors in adolescents with ASD compared to normal control group [61]. Thakkar et al. demonstrated response monitoring, which involves evaluating the outcome of action and adapting to the contexts, is important in RRBs of ASD. According to several studies, response monitoring has been considered to depend on the ACC. Thakkar et al. performed eye movement task consisted of pro-saccade and anti-saccade. ASD subjects significantly made more errors than HCs and showed functional abnormalities of the ACC that may contribute to RRBs. Compared with HCs, ASD subjects showed increased rostral ACC activation in both correct and error responses [45].

Abnormal sensory processing also has been proposed to relate to RRBs in ASD [62]. Clery et al. examined brain activity during performing the task consisted of continuous visual changing stimuli. Adults with ASD exhibited greater activity in the bilateral occipital cortex and in the ACC associated with smaller activation in the superior and middle frontal gyri than control groups. Atypical connectivity between frontal and occipital regions was also found in ASD brains [63].

BRAIN CONNECTIVITY IN ASD

The brain is a structural and functional system that has features of complex networks [64]. Early brain imaging studies have focused on region specific differences in activity however, accumulated data implicate an important role of brain network activity in the brain function [65]. Brain connectivity can be divided into functional and structural connectivity: temporal similarities of brain activity in multiple regions and physical connections between the brain regions. A number of studies using the brain imaging techniques such as fMRI and diffusion tensor image (DTI) identified abnormal brain connectivity in individuals with ASD. Long-range cortical hypo-connectivity theory has been largely supported by many investigators [66, 67], even there are some opposite reports to show hyper-connectivity in ASD [68, 69]. Other investigators also demonstrated that local-range hyper-connectivity [70, 71], however, these results are controversial and the agreement on terminology, local- and long-range, is still lacking.

Thus, below we mainly focused on the global connectivity depending on the developmental stage.

Toddlers and Children

Since Biswal et al. detected low frequency fluctuations which means manifestation of functional connectivity (FC) of the brain in the absence of task [72], resting-state fMRI (rsfMRI) is widely used in neuroimaging field. Few studies have examined FC in children with ASD. Using rsfMRI, Di Martino et al. measured striatal FC in ASD children and revealed widespread excessive pattern of FC in striatal-cortical circuitry, relative to TD children. Increased FCs were shown in nearly all striatal regions, limbic cortex, insula and pons. It is likely that these ectopic circuits reflect developmental derangement rather than immaturity [73]. Uddin et al. observed hyper-connectivity within several large-scale brain networks such as salience, default mode, frontotemporal, motor, and visual networks in children with ASD compared with TD children. Using maps of each individual's salience network, they could discriminate ASD from TD with 78% accuracy. They also suggested that salience network may be a distinguishing feature in ASD children [74]. The default mode network (DMN) which includes the posterior cingulate gyrus, retrosplenial cortex, lateral parietal cortex, mPFC, superior frontal gyrus, and temporal lobe consistently has shown greater activity during resting-state than during cognitive tasks [75]. While the DMN has been identified as hypo-connected in adult ASD, the DMN-related circuits in ASD children were hyper-connected [76].

Structural connectivity (SC) can be measured using MRI-based DTI that provides information about white matter connection and the communication integrity. The study conducted with ASD toddlers using DTI demonstrated that frontal tracts displayed abnormal age-related changes with greater fractional anisotropy (FA) and volume than TD control. These deviant early development and age-related changes in frontal fiber tracts may underlie impaired social and communication behaviors in ASD [77]. Disturbances in the thalamo-frontal connections also reported in Korean boys with high-functioning ASD by our group. In this study, we firstly suggested involvement of the right anterior thalamic radiation (ATR) in ASD. As shown in Fig. 3, FA was significantly decreased and mean diffusivity was significantly increased in the right ATR in subjects with ASD. These reduced FA was negatively correlated with total Social Responsiveness Scale (SRS), rating scale that quantifies the presence and severity of ASD symptoms [78].

Adolescents and Adults

Using the fMRI, most studies suggested that hypo-connectivity in ASD during the task performance examining language [79], face processing [80] including emotional face [81], visuomotor coordination [82], working memory [83] and executive function [84]. Otherwise, there are some reports to show hyper-connectivity
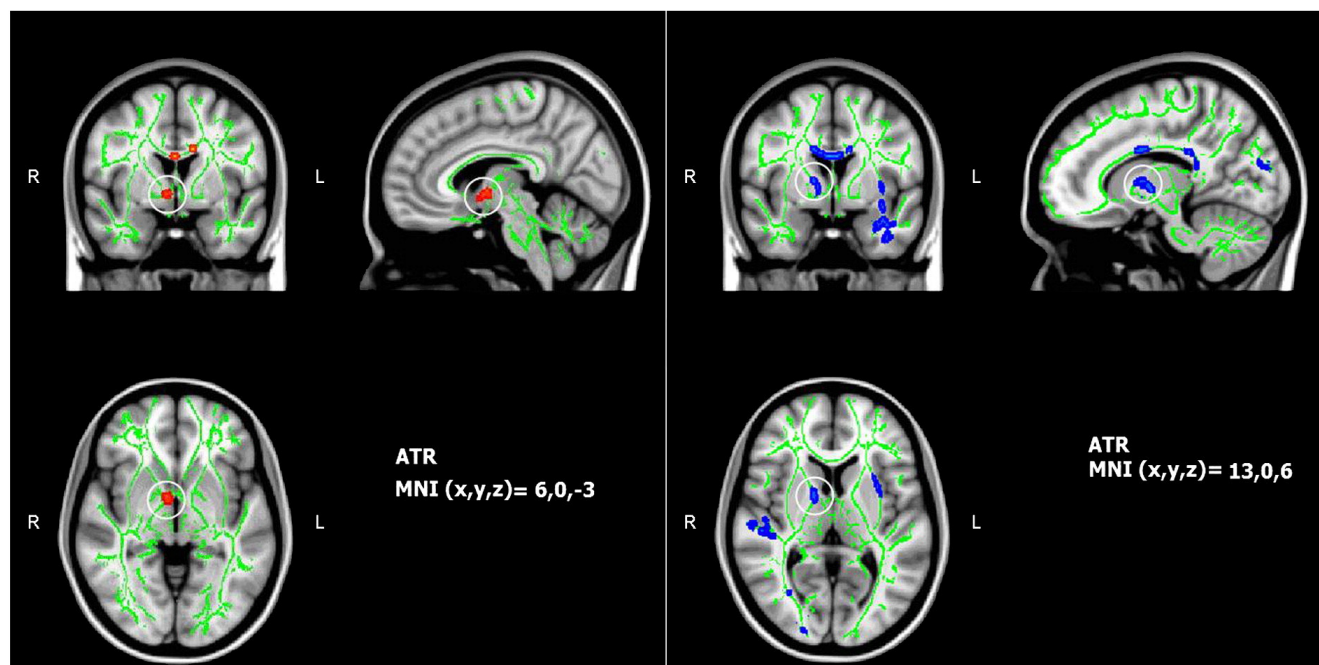

Fig. 3. Anterior thalamic radiation (ATR) showing reduced fractional anisotropy (FA, red) and increased mean diffusivity (MD, blue) in ASD group compared to control boys. Between-group analysis using FMRIB Software Library (FSL, Oxford, United Kingdom) after correction for multiple comparisons at p<.05. R: right, L: left, MNI: Montreal Neurologic Institute coordinates. Right ATR cluster size: 477 1 mm^3 voxels. For more information, see [78] (From Cheon K-A et al., *Brain Research* (2011) by permission of Elsevier).

http://dx.doi.org/10.5607/en.2015.24.4.273

in ASD brains in language [68], visuomotor processing [85], selective attention [69]. Although the task-based fMRI studies have showed mixed results in both hypo- and hyper- connectivity, these results suggested that the functional connectivity in ASD brains differed from TD brains.

Resting-state studies have identified reduced connectivity in DMN that contains the brain regions relevant to social processing [36] and in right posterior STS that mediates deficits in emotional recognition in ASD [86]. Recently, Autism Brain Imaging Data Exchange (ABIDE), a consortium openly sharing existing rsfMRI data sets, was introduced. As shown in Fig. 4, whole-brain analyses based on ABIDE reconciled disparate results of both hypo- and hyper-connectivity in the ASD literatures; both were detected, although hypo-connectivity dominated, particularly for cortico-cortical and interhemispheric functional connectivity [87].

To measure SC, Peeva et al. collected DTI scan results from ASD adults and found that weaker connection between the left ventral premotor cortex, a region involved in speech motor planning, and the supplementary motor area in ASD group. These results indicated that an important pathway in the speech production network is impaired in ASD, and this impairment can occur even in individuals with normal language abilities [88]. Recent study

examined alterations in the neuroanatomy of adults with ASD using two different modalities: sMRI and DTI. In ASD brains, gray matter (GM) volumes were decreased in multiple regions, including the bilateral fusiform gyri, bilateral orbitofrontal cortices, and bilateral pre- and post-central gyri. These changes in GM were linked with a decreased FA patterns in several white matter tracts, such as the bilateral inferior longitudinal fasciculi, bilateral inferior fronto-occipital fasciculi, and bilateral corticospinal tracts [89].

CONCLUSION

Recent findings from neuroimaging studies have led to the understanding of structural and functional abnormalities of the brain development in individuals with ASD, and the genetic bases of the brain development [90]. Synaptic deficits mediated by genetic factors in ASD not only affect their anatomical structure, but also affect the aspects of local neuronal circuitry and the functions of brain regions [91]. These are also related to the neuronal development and microstructural makeup of cortical folding. Differences in brain anatomy examined in ASD are relevant to specific clinical symptoms and features of ASD. ASD is likely a 'neural systems' condition that is mediated by abnormalities
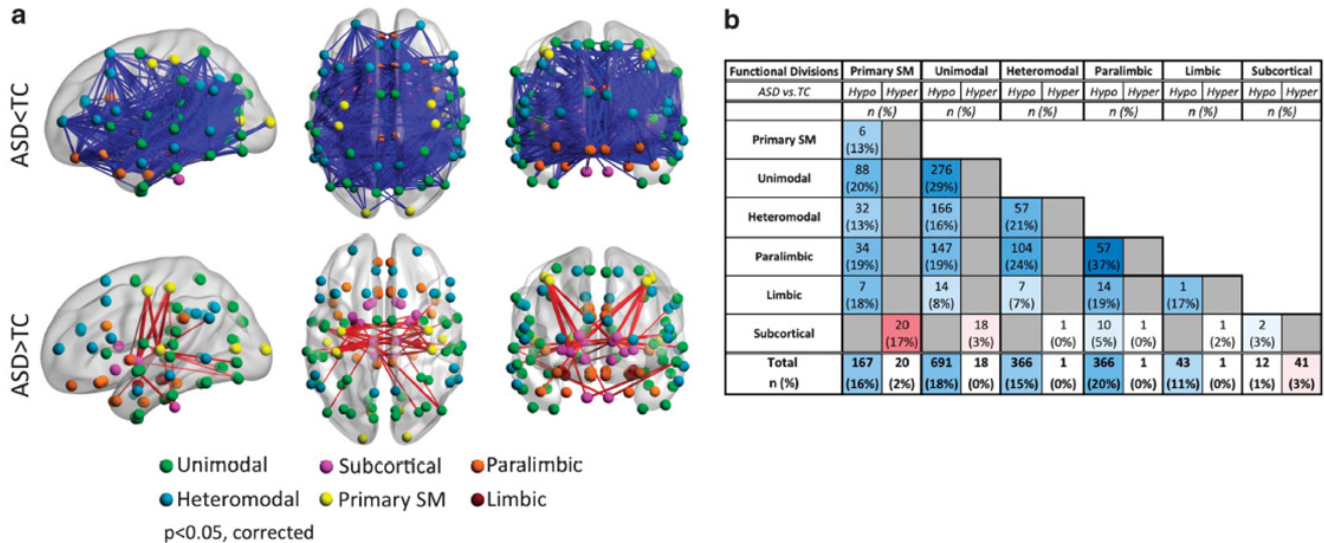

Functional Divisions	Primary SM		Unimodal		Heteromodal		Paralimbic		Limbic		Subcortical	
ASD vs.TC	Hypo	Hyper	Hypo	Hyper	Hypo	Hyper	Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
	n (%)		n (%)		n (%)		n (%)		n (%)		n (%)	
Primary SM	6 (13%)											
Unimodal	88 (20%)		276 (29%)									
Heteromodal	32 (13%)		166 (16%)		57 (21%)							
Paralimbic	34 (19%)		147 (19%)		104 (24%)		57 (37%)					
Limbic	7 (18%)		14 (8%)		7 (7%)		14 (19%)		1 (17%)			
Subcortical		20 (17%)	18 (3%)			1 (0%)	10 (5%)	1 (0%)		1 (2%)	2 (3%)	
Total n (%)	167 (16%)	20 (2%)	691 (18%)	18 (0%)	366 (15%)	1 (0%)	366 (20%)	1 (0%)	43 (11%)	1 (0%)	12 (1%)	41 (3%)

● Unimodal　● Subcortical　● Paralimbic
● Heteromodal　● Primary SM　● Limbic
p<0.05, corrected

Fig. 4. Whole-brain intrinsic functional connectivity analyses. (a) Significant group differences (that is, autism spectrum disorder [ASD] vs typical control [TC]) for intrinsic functional connectivity between each of the 112 parcellation units (56 per hemisphere) included in the structural Harvard–Oxford Atlas. Parcellations are represented with their center of mass overlaid as spheres on glass brains. The upper panel shows the intrinsic functional connections (blue lines) that were significantly weaker in ASD vs TC. The lower panel shows the intrinsic functional connections that were significantly stronger in ASD relative to TC (red lines). Each Harvard–Oxford Atlas unit is colored based on its membership in the six functional divisions. (yellow: primary sensorimotor (SM); green: unimodal association; Blue: heteromodal association; orange: paralimbic; red: limbic; pink: subcortical). Displayed results are corrected for multiple comparisons using false discovery rate at p<0.05. (b) The table summarizes the absolute number and percentage of node-to-node intrinsic functional connectivity surviving statistical threshold for group comparisons within and between functional divisions. Gray cells represent the absence of significant intrinsic functional connectivity, blue cells represent ASD-related hypoconnectivity (Hypo: ASD<TC), while red cells represent hyperconnectivity (Hyper: ASD>TC). Blue and red shadings decrease proportionally from the highest percentage (37%) to the lowest (~0%). For more information, see [87] (From Di Martino et al., *Molecular Psychiatry* (2014) by permission of Nature Publishing Group).

in regionally distributed cortical networks rather than separated brain regions. Therefore, ASD has also been referred to as a 'developmental disconnection syndrome' [92].

The clinical diversity of ASD phenotype might be also reflected on the level of brain structure and function. In this regard, it is important to know about the relationship among the structure, function and connectivity in the ASD brains. To elucidate associations between different aspects of the brain, multimodal imaging technique, the combination of multiple functional and structural measures can be a promising approach for investigating ASD brains.

Despite considerable evidence for abnormalities in ASD brain, there are inconsistent results from different groups. One of the reasons for these contradictory results is that researchers overlooked developmental changes in the brains [8]. In this regard, we introduce age-related changes of structure, function, and connectivity in ASD brains in this review. Brain is a complex organ that has been occurred dynamic changes over time as a normal developmental process [7]. Longitudinal studies will provide reliable information about atypical developmental patterns of the ASD brains. For this, national support on research and collaboration among the ASD family, researchers and clinician are necessary. The movement for open data sharing like ABIDE is a good example for worldwide collaboration.

Alternatively, the possible strategy is to define more homogenous subgroups of ASD. Individuals with ASD show enormous heterogeneity depending on age, gender, intellectual ability, genetic factor, and environmental risk factor [93]. Studies regarding these affective factors will bring more consistent data and improve understanding of neurobiological mechanisms of ASD.

ACKNOWLEDGEMENT

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