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Pattern Recognition of Multimodal Magnetic Resonance Brain Imaging in Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorder (ASD) constitutes a group of highly complex neurodevelopmental disorders. Characterized by increasing prevalence, high heterogeneity, and lifelong impact, its neuropathological mechanisms remain elusive. Multimodal magnetic resonance brain imaging offers novel approaches for elucidating the imaging-based brain mechanisms of ASD. Research based on unimodal magnetic resonance brain imaging has revealed extensive abnormalities in ASD across brain structure, function, and brain networks, with affected regions including the amygdala, fusiform gyrus, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex, temporoparietal junction, and insula—most of which are implicated in the “social brain” network. Although multimodal brain imaging analysis frameworks employing image-level, feature-level, and decision-level fusion provide multidimensional and multilevel information for revealing neural mechanisms in subjects, ASD research based on multimodal magnetic resonance brain imaging fusion remains in its nascent stages. ASD auxiliary diagnosis and subtype classification based on magnetic resonance brain imaging hold promise for providing objective evidence for clinical diagnosis and treatment. Future studies may construct an integrated multimodal brain imaging analysis framework that incorporates multidimensional information regarding brain function, structure, and networks to comprehensively characterize the onset and progression patterns of ASD and uncover its atypical neurodevelopmental mechanisms. Moreover, future research should delve deeper into the aberrant mechanisms of the ASD “social brain” network, explore circuits underlying social impairment in ASD, identify potential precise neuromodulation targets, and facilitate the implementation of precision diagnosis and treatment for ASD in clinical settings.

Full Text

Multimodal Magnetic Resonance Imaging Pattern Recognition in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is a highly complex neurodevelopmental disorder characterized by increasing prevalence, strong heterogeneity, and lifelong impact, yet its neuropathological mechanisms remain unclear. Multimodal magnetic resonance imaging provides a novel approach to uncovering the neuroimaging mechanisms of ASD. Studies based on single-modal MRI have revealed widespread abnormalities in brain structure, function, and network connectivity in ASD, with affected regions including the amygdala, fusiform gyrus, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex, temporoparietal junction, and insula—most of which are involved in the “social brain” network. Although multimodal brain imaging analysis frameworks involving image-level, feature-level, and decision-level fusion provide multidimensional and multilevel information for revealing neural mechanisms in participants, research on ASD based on multimodal MRI fusion remains in its early stages. MRI-based assisted diagnosis and subtype classification of ASD hold promise for providing objective evidence for clinical diagnosis and treatment. Future research should construct an integrated analysis framework that fuses multimodal brain imaging, combining multidimensional information on brain function, structure, and networks to comprehensively characterize the developmental patterns of ASD and reveal its atypical neurodevelopmental mechanisms. Additionally, future studies need to deeply investigate the abnormal mechanisms of the ASD “social brain” network, explore social impairment circuits, and identify potential precision neural regulation targets, thereby assisting in achieving precision diagnosis and treatment for ASD.

Keywords: Autism spectrum disorder, multimodal magnetic resonance imaging, brain function and structure, assisted diagnosis, subtype classification

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with increasing prevalence, high heterogeneity, and severe impact on child health. The core symptoms of ASD include social communication deficits, restricted interests, and repetitive stereotyped behaviors, often accompanied by sensory abnormalities (Lai et al., 2014). The latest data from the U.S. Centers for Disease Control and Prevention indicate an ASD prevalence of approximately 1/36 (Maenner et al., 2023). Although nationwide ASD prevalence data are lacking in China, the “Report on the Development of Autism Education and Rehabilitation in China IV” published in 2022 indicates a prevalence of approximately 1% in China

(Wang, 2022). Based on this estimate, the ASD population in China exceeds 10 million. ASD has become an increasingly serious global public health concern.

Currently, the pathogenesis of ASD remains unclear. Existing research suggests that ASD results from multiple factors, including genetic influences, neurodevelopmental issues, environmental factors, immune system abnormalities, and neurotransmitter imbalances (Keil & Lein, 2016; Livingston & Happé, 2017; Quesnel-Vallieres et al., 2019; Won et al., 2013). With continuous advances in neuroscience and artificial intelligence, magnetic resonance brain imaging provides a new perspective for revealing the neuroimaging mechanisms of ASD and holds promise for offering objective evidence to achieve precision diagnosis and treatment (Duan & Chen, 2022). Over the past decade, researchers have utilized structural magnetic resonance imaging (sMRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS) to reveal abnormalities in gray matter, white matter, brain activation, functional connectivity, and large-scale brain functional networks in ASD from multiple perspectives (Duan et al., 2020; Guo et al., 2019; Guo, Duan, Suckling, et al., 2020; He et al., 2018; He et al., 2021; Yeh et al., 2022; Y. Zhao et al., 2022). Based on these findings, researchers have proposed hypotheses such as the amygdala theory, social motivation theory, and mirror neuron system theory to explain ASD abnormalities (Baron-Cohen et al., 2000; Chevallier et al., 2012; Hamilton, 2008). Additionally, with continuous advances in information fusion technology, researchers have attempted to integrate multimodal MRI data to characterize the disease at multiple levels, comprehensively and from various angles, aiming for clinical diagnosis and treatment evaluation (He et al., 2020; Hirjak et al., 2022; Maglanoc et al., 2020; Park et al., 2021; Weng et al., 2020; Zhang et al., 2020). For example, Park et al. integrated functional and structural connectivity to investigate the relationship between structure-function coupling in ASD using Riemannian optimization algorithms, finding that differences in structure-function coupling reflect individual symptom variations in ASD (Park et al., 2023). Kim et al. established an ASD-assisted diagnosis model based on features from T1-weighted imaging and DTI, achieving a classification accuracy of 88.8%.

Both single-modal and multimodal fusion studies have deepened our understanding of the neuroimaging mechanisms of ASD, yet each approach has its own advantages and limitations. Single-modal brain imaging studies, while straightforward and focused on specific research questions, cannot capture complementary information across modalities or comprehensively explore abnormal functional and structural mechanisms in ASD at multiple levels. Although multimodal brain imaging fusion integrates multidimensional information, it faces challenges such as fusion difficulties, poor interpretability, and limited application of its analytical frameworks in ASD. Therefore, this review summarizes current findings from single-modal ASD brain imaging studies, systematically outlines multimodal brain imaging fusion methods and their preliminary applications in ASD research from three perspectives—image-level, feature-level, and decision-level fusion, summarizes the strengths and limitations of existing ASD

MRI studies, and concludes with reflections and future directions to provide important support for subsequent research on ASD brain imaging and other psychiatric or neurodevelopmental disorders.

2. ASD Single-Modal Brain Imaging Research

Magnetic resonance imaging technology has been widely applied in ASD research due to its advantages of being non-radiative, non-invasive, and high-resolution. Previous studies have not only investigated local feature abnormalities in structural and functional imaging but also explored abnormalities in structural or functional networks at the network level. Typically, these abnormalities demonstrate certain correlations with clinical features of ASD, which is significant for understanding the etiology and neural mechanisms of ASD, as well as for promoting early diagnosis and guiding rehabilitation therapy.

2.1.1 ASD Structural Imaging Local Feature Abnormalities

Structural imaging studies typically employ T1-weighted imaging and DTI, where T1-weighted imaging is commonly used to measure morphological indicators such as gray matter volume and cortical thickness, while DTI is used to assess the microstructure of white matter fiber tracts and conduction pathways. T1-weighted imaging studies have reported increased gray matter volume in children with ASD compared to typically developing (TD) individuals in the right angular gyrus, left middle frontal gyrus, left superior frontal gyrus, left precuneus, left inferior occipital gyrus, and right inferior temporal gyrus; decreased gray matter volume in the left cerebellum and left postcentral gyrus; and a significant correlation between increased gray matter volume in the right angular gyrus and repetitive stereotyped behaviors in ASD (Liu et al., 2017). Other studies have shown that adults with ASD exhibit decreased gray matter volume compared to TD individuals in the right inferior occipital gyrus, left fusiform gyrus, right middle temporal gyrus, bilateral amygdala, right inferior frontal gyrus, right orbitofrontal cortex, and left ventromedial prefrontal cortex (Sato et al., 2017). Meanwhile, Yang et al. found that adults with ASD showed significantly increased gray matter volume in the left middle temporal gyrus, left superior temporal gyrus, left parahippocampal gyrus, and right postcentral gyrus, along with significantly decreased gray matter volume in the right cerebellum and left anterior cingulate cortex compared to TD individuals (Yang et al., 2016).

Reviewing these abnormal regions reveals considerable overlap between gray matter volume abnormalities and the default mode network (DMN). The DMN is considered one of the primary networks involved in introspection and self-reflection, playing important roles in memory and emotional regulation processes (Raichle et al., 2001; Sheline et al., 2009). Abnormalities in DMN regions in ASD may lead to problems in self-awareness and other aspects, subsequently affecting their engagement in and perception of social interactions (Padmanabhan et al., 2017; Washington et al., 2014). Additionally, T1-weighted imaging

studies have reported widespread significantly increased cortical thickness in the left hemisphere of children and adolescents with ASD, while adults with ASD showed decreased cortical thickness in the frontal lobe (Khundrakpam et al., 2017; Premika S.W. Boedhoe et al., 2020).

The number of participants used in studies and the heterogeneity of ASD may contribute to inconsistencies in some research findings. Meanwhile, as ASD is a neurodevelopmental disorder, age is a primary factor influencing research outcomes. Reviewing previous studies reveals that ASD demonstrates patterns of deviating from TD developmental trajectories in both gray matter volume and cortical thickness across different age groups (Khundrakpam et al., 2017; Koolschijn & Geurts, 2016; van Rooij et al., 2018; Wang et al., 2017; Yamasaki et al., 2010; Zabihi et al., 2019; X. Zhao et al., 2022). Researchers have thus speculated that ASD exhibits overdevelopment in early stages, followed by slowed or even arrested growth in later childhood, and subsequently accelerated decline in gray matter volume and cortical thickness (Lange et al., 2015; Zielinski et al., 2014). Therefore, future studies need to establish a developmental framework to investigate morphological abnormalities in ASD.

Fractional anisotropy (FA) is commonly used in DTI studies to characterize the integrity of white matter fibers. Decreased FA values reflect impaired organizational integrity of white matter fiber tracts. For both children and adults with ASD, most studies have found decreased FA in ASD compared to TD, with reduced regions including the ventromedial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, temporoparietal junction, bilateral superior temporal sulcus, temporo-occipital fasciculus, and corpus callosum (Alexander et al., 2007; Barnea-Goraly et al., 2004; Haigh et al., 2020; Lee et al., 2007; Pardini et al., 2009; Sundaram et al., 2008; Temur et al., 2019). However, some studies have found increased FA in children with ASD in the left posterior limb of the internal capsule, genu of the corpus callosum, splenium of the corpus callosum, and left external capsule; and increased FA in adolescents with ASD in the frontal lobe, right cingulate gyrus, bilateral insula, right superior temporal gyrus, and bilateral middle cerebellar peduncles (Bashat et al., 2007).

In addition to FA, mean diffusivity (MD) has been used to investigate the microstructure of white matter. MD reflects the overall level of mean diffusion and diffusion resistance. Compared to TD, ASD shows increased MD in regions such as the corpus callosum and cingulum (Cai et al., 2022; Valenti et al., 2020). Abnormalities in FA and MD in ASD participants suggest that white matter structural abnormalities may play an important role in its pathological mechanisms. In recent years, some researchers have begun investigating white matter function in addition to its structure; however, abnormalities in white matter function in ASD remain unclear, and future studies need to explore white matter functional abnormalities in ASD and their relationship with behavior (Li et al., 2019; Peer et al., 2017).

2.1.2 ASD Functional Imaging Local Feature Abnormalities

fMRI reflects the activity level of neuronal populations in various brain regions by detecting changes in blood oxygen saturation, serving as an important tool for probing human brain functional activity. In neuroimaging research, functional imaging studies primarily include two major directions: task-based studies and resting-state studies.

Task-based fMRI studies in ASD have primarily investigated abnormalities in face processing, motion perception, language processing, and reward processing (Hernandez et al., 2015). During face processing, most studies have found reduced activation in the fusiform gyrus and amygdala in ASD (Corbett et al., 2009; Kleinhans et al., 2011; Nickl-Jockschat et al., 2015; Nomi & Uddin, 2015), with activation levels in the fusiform gyrus showing a significant negative correlation with social anxiety (Kleinhans et al., 2010). However, one study found that activation in the fusiform gyrus in ASD during processing of their mother's face was comparable to that in TD, while showing reduced activation when processing stranger faces (Pierce & Redcay, 2008). These results suggest that anxiety generated during processing of stranger faces in ASD may lead to social avoidance.

During motion perception, ASD shows reduced activation in the superior temporal sulcus, ventrolateral prefrontal cortex, and temporoparietal junction (Davies et al., 2011; Koldewyn et al., 2011; von dem Hagen et al., 2013). Rapid perception of biological motion can guide attention to emerging social stimuli, and abnormalities in biological motion perception in ASD may impair the ability to capture social cues effectively in social scenes. During language processing, compared to TD, ASD shows stronger activation in Broca's area and anterior temporal lobe (Graves et al., 2022; Knaus et al., 2008), and reduced activation in the left ventral central sulcus and superior temporal sulcus (Tanigawa et al., 2018). Additionally, studies have found reduced functional lateralization between hemispheres during language processing in ASD (Deemyad, 2022; Knaus et al., 2010). During reward information processing, under both monetary and social reward conditions, ASD shows reduced activation in the nucleus accumbens, amygdala, anterior cingulate cortex, and ventral striatum (Baumeister et al., 2023; Kohls et al., 2018; Kohls et al., 2013). Therefore, abnormalities in brain reward circuits may lead to reduced sensitivity to social stimuli in ASD and contribute to symptoms such as restricted interests.

Resting-state fMRI studies in ASD primarily include two major directions: static functional connectivity research and dynamic functional connectivity research. Over the past two decades, numerous studies have identified abnormalities in static functional connectivity in ASD. However, some studies have found hyperconnectivity in ASD, others have found hypoconnectivity, and some have found both hyperconnectivity and hypoconnectivity (Di Martino et al., 2011; Hull et al., 2016; Oldehinkel et al., 2019; Reiter et al., 2019; Uddin et al., 2013; Xiao et al., 2023). To explain this phenomenon, Uddin et al. reviewed

previous literature and proposed a “hyperconnectivity-hypoconnectivity” model from a developmental perspective, suggesting that ASD typically exhibits hypoconnectivity during adolescence and adulthood, while showing hyperconnectivity during childhood (Uddin et al., 2013). However, the specific time point at which static functional connectivity transitions from hyperconnectivity to hypoconnectivity in ASD remains unclear.

Additionally, increasing evidence indicates that functional connectivity patterns in the human brain change over time (Chang & Glover, 2010). Dynamic functional connectivity analysis can capture the time-varying characteristics of brain functional connectivity, which helps understand the organizational architecture of brain function and the basis of information processing, and may reconcile inconsistencies found in previous static functional connectivity studies (Gonzalez-Castillo & Bandettini, 2018; Preti et al., 2017; Shine & Poldrack, 2018). Using sliding window analysis, one study found increased variability in dynamic functional connectivity in ASD in the posterior cingulate and middle temporal pole, and inferior frontal gyrus, while decreased variability was observed between the posterior cingulate and precentral gyrus, with abnormalities in posterior cingulate dynamic functional connectivity significantly correlating with the severity of social symptoms in ASD (He et al., 2018; Y. Li et al., 2020). Another study found that both within and between hemispheres, compared to TD, ASD showed increased variability in dynamic functional connectivity density in the anterior cingulate cortex and medial prefrontal cortex, while showing decreased variability in the fusiform gyrus and inferior temporal gyrus. Additionally, the sensorimotor region in ASD showed decreased variability in dynamic functional connectivity density within hemispheres (Guo, Duan, Chen, et al., 2020). Dynamic functional connectivity analysis provides a new perspective for investigating brain function in ASD; however, future research needs to combine dynamic and static analyses to clarify the relationship between abnormal brain functional activity and symptoms, as well as gene expression in ASD.

2.2 ASD Brain Network Research

The human brain is a complex network. Researchers typically construct brain networks from both structural and functional perspectives. Brain network analysis provides a means to investigate brain functional organization, information interaction, and even pathological mechanisms of diseases at the systems level (Bullmore & Sporns, 2009). Numerous studies have demonstrated abnormalities in both functional and structural brain networks in ASD (Duan et al., 2020; He et al., 2018; He et al., 2021; Rudie et al., 2013; Yang et al., 2023).

Functional brain networks are typically constructed based on functional connectivity. Graph theory-based studies have found that at the global level, the clustering coefficient and shortest path length of functional networks in ASD are significantly reduced, indicating that ASD functional networks are more randomized; at the local level, regions such as the bilateral superior temporal sulcus, right dorsolateral prefrontal cortex, and precuneus lose their hub proper-

ties (Itahashi et al., 2014). Additionally, some studies have found increased degree centrality in bilateral temporolimbic regions in ASD (Di Martino et al., 2013). Furthermore, Menon proposed a triple-network model to help understand cognitive and affective dysregulation in psychiatric and neurological disorders (Menon, 2011). This model posits that abnormalities in the function and dynamic interaction of the DMN, salience network (SN), and frontoparietal network (FPN) are among the causes of psychiatric disorders and neurodevelopmental disorders, including ASD. Studies have reported static and dynamic interaction abnormalities among these three networks in ASD, which significantly correlate with core ASD symptoms (Guo et al., 2023; Hogeveen et al., 2018; Qing Wang et al., 2021). Analysis of large-scale functional networks provides a novel approach for characterizing psychiatric or neurodevelopmental disorders. However, future research needs to analyze the potential relationship between interaction abnormalities in large-scale functional networks and abnormalities in structural networks.

Structural networks exert certain constraints on brain functional activity. Abnormalities in structural connectivity may lead to cognitive and affective dysfunctions, which clinically manifest as symptoms of certain disorders. Structural brain networks are typically constructed based on white matter fiber connectivity. Studies have found that for structural networks constructed from FA values, ASD shows reduced small-world properties, increased global efficiency, and increased nodal efficiency in the inferior frontal gyrus, postcentral gyrus, left precuneus, thalamus, and bilateral superior parietal cortex (Cai et al., 2022; Qin et al., 2018). Currently, some studies have also utilized gray matter volume or cortical thickness to construct structural covariance networks to investigate the relationship between morphological covariation across brain regions and brain development, cognition, and disease pathological mechanisms (DuPre & Spreng, 2017; Montembeault et al., 2016; Prasad et al., 2022; Sha et al., 2022; Zielinski et al., 2010). Compared to TD, studies have found decreased covariation in interhemispheric subcortical regions and increased covariation in intrahemispheric subcortical regions in ASD (Duan et al., 2020), along with reduced nodal centrality in the medial frontal lobe, parietal lobe, and temporo-occipital cortex in ASD structural covariance networks (Balardin et al., 2015). Structural network research quantitatively characterizes brain structure in ASD at the network level, helping to understand brain information transmission and processing mechanisms, elucidate developmental patterns of the ASD brain, and potentially provide key clues for understanding the pathological mechanisms of ASD.

3. ASD Multimodal Brain Imaging Fusion

An important goal of neuroimaging research in neurodevelopmental disorders and psychiatric diseases such as ASD is to comprehensively characterize them and reveal their neuropathological mechanisms. While a few brain disorders can be precisely characterized using single-modal imaging, for most early-stage

non-organic psychiatric diseases, single-modal brain imaging provides limited information, necessitating the fusion of multimodal brain imaging for multilevel, comprehensive, and multi-angle characterization to guide clinical diagnosis and treatment evaluation (Calhoun & Sui, 2016). Although researchers have long proposed the concept of multimodal brain imaging fusion, how to truly achieve it remains a persistent challenge in the field. Therefore, this section systematically reviews multimodal brain imaging methods and their applications in ASD research from three levels: image-level fusion, feature-level fusion, and decision-level fusion.

3.1 Image-Level Fusion

Image-level fusion is the most fundamental and straightforward approach to multimodal brain imaging fusion. For example, T1-weighted imaging is commonly used for brain anatomical imaging, effectively reflecting gray and white matter; T2-weighted imaging is often used to observe brain lesions, being sensitive to hemorrhage with relatively few artifacts; and T1/T2 ratio maps can be used to reflect the degree of myelination in the human cerebral cortex. Myelination maps obtained from this T1 and T2 imaging fusion have been shown to significantly correlate with human cortical evolutionary expansion and neuronal density maps in non-human primates (Glasser & Van Essen, 2011). Molecular genetics studies have also identified abnormal expression of myelination-related genes in ASD (Richetto et al., 2017; Zhao et al., 2018). T1 and T2 image-level fusion studies provide neuroimaging evidence for this finding. Daeki et al. found that infants at high risk for ASD showed widespread reductions in T1/T2 values in both gray and white matter, with T1/T2 values showing a significant positive correlation with behavioral developmental levels (Darki et al., 2021). These findings indicate that T1/T2 values are a developmentally sensitive metric, and subsequent studies should use this metric to explore the role of myelination abnormalities in ASD pathological mechanisms.

Beyond T1/T2 fusion, researchers have proposed multivariate methods such as joint independent component analysis (j-ICA), multimodal canonical correlation analysis (mCCA), and partial least squares to achieve data-level fusion by identifying components (or patterns) that are independent yet covary across multiple modalities, show maximal covariation between subjects, or are most correlated across different modalities (Qi et al., 2018; Qi et al., 2019; Sui, Adali, et al., 2012; Sui, Yu, et al., 2012). Qi et al. used mCCA+jICA to fuse gray matter and functional activity, identifying brain regions with shared structure-function covariation across ASD subtypes as well as regions with subtype-specific changes (Qi et al., 2020). Using the mCCA+jICA method, researchers fused task-based data with gray matter data to identify brain regions associated with novelty-seeking traits, enabling prediction and classification of risk factors for alcoholism, smoking, attention-deficit/hyperactivity disorder, depression, and schizophrenia (Qi et al., 2021). However, such data-driven multimodal imaging fusion analysis methods are not widely applied in ASD, and future research needs to explore

covariation relationships between different modalities of brain imaging in ASD and investigate imaging markers specific to ASD.

3.2 Feature-Level Fusion

Feature-level fusion is the most common approach to multimodal brain imaging fusion. Different imaging modalities provide various features; for example, gray matter volume, gray matter density, cortical thickness, gray-white matter contrast, and gyrification index can be obtained from T1-weighted images; functional connectivity, functional connectivity density, amplitude of low-frequency fluctuations, regional homogeneity, dynamic functional connectivity, and dynamic functional connectivity variability can be derived from functional images; and FA, MD, radial diffusivity, axial diffusivity, fiber bundle count, and fiber bundle density can be obtained from diffusion tensor images. Based on these metrics, feature-level fusion can be broadly categorized into four types: feature coupling models, feature joint selection models, similarity network models, and large-scale neural circuit models.

The most common feature coupling model investigates the coupling between structure and function. Typically, coupling is defined as the correlation coefficient between two metrics (Baum et al., 2020; Zhang et al., 2011). Previous research has shown that coupling, which combines structural and functional metrics, is more sensitive than any single modality in detecting physiological abnormalities in brain diseases. For example, Zhang et al. defined the Pearson correlation coefficient between structural and functional connectivity as structure-function coupling, finding that in patients with generalized epilepsy, structure-function coupling was significantly reduced and negatively correlated with disease duration (Zhang et al., 2011). In ASD research, Ma et al. found reduced coupling between white matter volume in the left superior corona radiata and left posterior limb of the internal capsule and regional homogeneity in ASD (Ma et al., 2022). Recently, another study found that in TD individuals, structure-function coupling in the lateral prefrontal cortex is significantly correlated with executive function and partially mediates the relationship between age and executive function (Baum et al., 2020). Researchers have also proposed using predictive models to characterize structure-function coupling relationships, with results showing a gradient pattern of decoupling from unimodal to transmodal regions between structure and function (Vázquez-Rodríguez et al., 2019). He et al. used this predictive model to find that structure-function coupling abnormalities in the right supplementary motor area, right insula, and left inferior frontal gyrus were higher in ASD than in TD, and that structure-function coupling values in abnormal regions could be used to predict clinical symptoms in ASD (He, 2021). These previous studies suggest that structure-function coupling relationships may provide new insights for understanding the pathological mechanisms and clinical diagnosis and treatment of ASD. However, current research on structure-function coupling relationships in ASD remains limited and requires further exploration in future studies.

Feature joint selection models are commonly used to fuse multimodal imaging features for classifying subjects or predicting their clinical symptoms. Typically, fusing features from multiple modalities yields higher classification accuracy or better predictive performance (Liem et al., 2017; Meng et al., 2017; Qi Wang et al., 2021). For example, He et al. used cross-validation recursive feature elimination to select structural network features and functional network connectivity features, then predicted brain age using support vector regression, finding that brain age in ASD was significantly higher than chronological age during childhood but significantly lower during adolescence, indicating accelerated brain development in childhood and delayed development in late adolescence in ASD (He et al., 2020).

Similarity network models represent a novel approach for fusing multimodal imaging to reveal macroscopic organizational structures of the cerebral cortex (Seidlitz et al., 2018; Yang et al., 2021). Typically, similarity networks are constructed using correlations between multiple different modality metrics across regions within individual subjects, including morphological similarity and functional similarity networks (J. Li et al., 2021; Meng et al., 2022). Similarity network analysis has been widely applied in diseases such as depression and schizophrenia (J. Li et al., 2021; Martins et al., 2022; Xue et al., 2023; Zong et al., 2023). For example, Li et al. fused metrics including cortical surface area, gray matter volume, cortical thickness, Gaussian curvature, mean curvature, FA, and mean diffusivity to construct a morphological similarity network, identified abnormalities in the morphological similarity network in patients with depression, and identified genes associated with these abnormalities, finding that these genes were mainly enriched in microglia and neuronal cells (J. Li et al., 2021). Similarity network models provide a novel, stable, and neuroscientifically interpretable means to understand human brain network structure. However, abnormalities in morphological and functional similarity networks in ASD and their underlying molecular mechanisms remain unclear. Future research needs to construct similarity networks separately from structural and functional perspectives to investigate the relationship between abnormalities in ASD similarity networks and microscale indicators such as gene expression and cellular laminar differentiation.

Large-scale neural circuit models represent a powerful approach for establishing associations between brain microcircuits and macroscopic organization (Breakspear, 2017; Kong et al., 2021; P. Wang et al., 2019). Simply put, this model integrates structural and functional connectivity based on spiking neural network models and hemodynamic models to simulate the dynamic characteristics of brain microcircuits, including recurrent (or periodic) inputs within brain regions, external inputs, and neural noise. Researchers have conducted multiple studies based on large-scale neural circuit models; for example, Weng et al. identified abnormalities in recurrent and external stimulus inputs in patients with temporal lobe epilepsy and generalized epilepsy, finding that different epilepsy subtypes result from disruptions in different microcircuit characteristics (Weng et al., 2020); Park et al. found that changes in recurrent and external inputs

in ASD correlate with distortions in structural connectivity prevalence (Park et al., 2021); and Kong et al. discovered that the sensorimotor cortex is a driver of brain functional connectivity dynamics. Transcranial magnetic stimulation and transcranial direct current stimulation have played important roles in neural regulation, but currently lack reliable, stable, and efficient personalized intervention targets (Cash et al., 2021; Cocchi & Zalesky, 2018). Constructing accurate large-scale neural circuit models provides us with a digital twin brain, and if personalized precision neural regulation targets for ASD can be simulated through this digital twin brain, more significant therapeutic effects may be achieved.

3.3 Decision-Level Fusion

Decision-level fusion refers to extracting features from different imaging modalities according to certain rules to construct classifiers, then fusing the discriminant results from multiple classifiers to make a globally optimal decision (Huang & Li, 2023). Dimitriadis et al. applied decision fusion concepts using multiple morphological metrics and ensemble learning algorithms to achieve multiclass classification of healthy controls, early mild cognitive impairment, late mild cognitive impairment, and Alzheimer's disease (Dimitriadis et al., 2018). Similar studies have emerged in ASD. For example, one study trained ensemble classifiers based on structural and functional connectivity to achieve precise classification of ASD within a single center; while ElNakieb et al. fused three-channel primary classifiers for comprehensive decision-making, ultimately achieving an ASD classification accuracy of 80.5% (Dekhil et al., 2019; ElNakieb et al., 2018). Currently, decision-level fusion research primarily focuses on structural and functional imaging; future studies could consider incorporating magnetic resonance spectroscopy features, electrophysiological features, and biochemical features to synthesize multi-angle information for comprehensive decision-making.

4. ASD-Assisted Diagnosis

ASD is characterized by increasing prevalence, strong heterogeneity, diagnostic difficulty, and heavy burden (Lai et al., 2014; Maenner et al., 2023), and early detection, diagnosis, and intervention can significantly improve prognosis. How to achieve precise diagnosis of ASD is a current research hotspot (Kaur & Kaur, 2023). Most previous studies have used single-modal brain imaging for classification. Anderson et al. classified ASD and TD based on functional connectivity in a small sample, achieving 79% accuracy (Anderson et al., 2011). Models trained on small sample data may lack robustness and generalizability due to limited data volume and ASD heterogeneity. Therefore, researchers have gradually shifted toward analyzing large multi-center samples to enhance model robustness and generalization ability. For example, Nielsen et al. achieved over 60% classification accuracy based on functional connectivity in a large sample from a multi-center public database (Nielsen et al., 2013). In addition to functional connectivity, some structural metrics are also frequently used for ASD classification (Ali et al., 2022; Uddin et al., 2011). For example, Gori et al. achieved ASD

classification based on morphological metrics such as gray matter volume, cortical thickness, and surface area (Gori et al., 2015); and ElNakieb et al. achieved ASD classification based on features such as FA and mean diffusivity from DTI data (ElNakieb et al., 2021).

Single-modal identification often fails to achieve excellent classification accuracy and remains far from clinical application. Therefore, researchers have attempted to improve classification accuracy based on more comprehensive multimodal imaging (Kim et al., 2022; Libero et al., 2015; Liu et al., 2015). For example, one study fused structural and functional connectivity data using autoencoder models and multilayer perceptrons, achieving 85.06% classification accuracy for ASD (Rakić et al., 2020); while Kim et al. fused features from T1 and DTI images to obtain 88.8% classification accuracy (Kim et al., 2022).

In addition to applying traditional machine learning methods such as support vector machines, random forests, and multilayer perceptrons for ASD classification and identification, deep learning technology, as an important branch of machine learning, has gradually been widely applied in assisted diagnosis research due to its powerful learning capabilities. Building associations between multimodal brain images, establishing efficient task models with parameter sharing, achieving precise diagnostic classification with small samples, and interpreting the deep learning process are all research hotspots in deep learning-based multimodal brain imaging pattern recognition. Currently, deep learning-based ASD classification research mainly includes two types: deep neural networks and graph neural networks (Cackowski et al., 2023; Guo et al., 2017; Khodatars et al., 2021; Li et al., 2018).

Deep neural networks are the foundation of many artificial intelligence applications, using multiple layers of unsupervised hidden layers to map samples from the current space layer by layer to another space, fitting highly complex functions to achieve better representation of input features. Numerous studies have used deep neural networks and their derivatives to classify ASD based on functional or structural imaging data (Eslami & Saeed, 2019; Ismail et al., 2017; Leming et al., 2020; C. Wang et al., 2019; Xiao et al., 2018). For example, Kong et al. used functional connectivity as input and achieved 90.39% classification accuracy for ASD using a deep neural network model (Kong et al., 2019); Pinaya et al. established a normative model based on structural imaging using deep autoencoder models, using deviations from the normative range in ASD as features for classification (Pinaya et al., 2019); and Mostafa et al. fused structural and functional imaging features, achieving 79.2% classification accuracy for ASD based on autoencoder models and deep neural networks (Mostafa et al., 2020). Here we observe that classification accuracy fusing multimodal information does not always outperform single-modal imaging features, which may be related to sample size, model selection, and feature choice. How to train deep neural networks with stability, generalizability, and high classification accuracy on limited samples will be a key problem to address in the next step.

Graph neural networks are a type of artificial neural network for processing

graph-structured data that can model nodes and edges and capture interactions between nodes and global features during learning. The brain is a complex yet efficient system composed of trillions of synaptic connections among billions of neurons (Bullmore & Sporns, 2009). Traditional convolutional neural networks do not consider interactions between different nodes, ignoring the “deep relationship” between brain function and structure, whereas graph neural networks demonstrate their advantages in modeling complex networks. Therefore, for brain imaging research, brain regions can be abstracted as nodes in a graph, and relationships between regions as edges, leveraging the advantage of graph neural networks in having stronger expressive power for non-Euclidean spaces to achieve precise prediction or classification of subject features (Bessadok et al., 2022; X. Li et al., 2021; X. Li et al., 2020; Yang et al., 2019). Currently, studies have attempted to identify ASD using graph neural networks. For example, Chen et al. used gray matter density of regions of interest and low-frequency amplitude in slow-4 and slow-5 bands as node features, and functional connectivity between regions of interest as edges to construct multimodal individual-level graph networks, achieving 74.7% classification accuracy for ASD on a large-sample dataset using graph neural network models (Chen et al., 2022); while Yin et al. used graph-theoretic local properties of different brain regions (e.g., degree centrality) as node features and functional connectivity as edges to construct graphs, achieving 82.3% classification accuracy for ASD using graph neural networks (Yin et al., 2021). For future graph neural network models, constructing graph structures with physiological significance by referencing the brain’s efficient processing networks may be key to achieving excellent performance. The combination of graph neural networks and brain networks can not only make our constructed systems more flexible but also help us understand brain information processing mechanisms and identify specific neural circuits for neurodevelopmental disorders or psychiatric diseases such as ASD, providing scientific evidence for clinical precision medicine.

Whether based on single-modal brain imaging or multimodal brain imaging fusion technology, and whether using traditional machine learning frameworks or the latest deep learning techniques, establishing an ASD-assisted diagnosis system with high specificity and sensitivity has been a persistent goal for researchers. Developing an ASD-assisted diagnosis platform centered on multimodal brain imaging that suits China’s national conditions, possesses high stability and generalizability, and can be promoted in areas lacking ASD diagnostic professionals is a direction that requires focused development in the future.

5. ASD Subtype Identification

ASD is not a single clinical entity but a group of highly heterogeneous neurodevelopmental disorders (Masi et al., 2017). Heterogeneity is one of the greatest obstacles to understanding the neuropathological mechanisms of ASD and achieving precision diagnosis and treatment (Georgiades et al., 2013). Subtype

classification is the most commonly employed approach in ASD heterogeneity research. Previous ASD subtype classifications have mostly been based on behavioral manifestations. For example, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III and DSM-IV classified ASD into Asperger's syndrome, pervasive developmental disorder not otherwise specified, and autistic disorder (Kim, 2020). Over the past decade, clinically based behavioral subtype classification has divided ASD into subgroups with differences in verbal level, cognitive ability, social communication level, and repetitive behavior level, which has helped reveal heterogeneity in symptom developmental trajectories in ASD (Kim et al., 2018). However, behavioral subtypes appear to have limited utility in revealing the neural mechanisms of ASD and guiding clinical precision diagnosis and treatment.

In recent years, with continuous advances in brain imaging analysis methods, classifying imaging-based subtypes of ASD has shown certain advantages for understanding its neural mechanisms. Despite varying data and analytical methods, existing studies indicate that ASD can be divided into 2-4 subtypes based on brain imaging (Chen et al., 2019; Easson et al., 2019; Hong et al., 2018; Hong et al., 2020; Stefanik et al., 2018; Wang, 2022). For example, Easson et al. divided ASD into two subtypes with different connectivity patterns based on functional connectivity (Easson et al., 2019); Chen et al. used differences in ASD brain gray matter compared to TD as features to identify three ASD subtypes with different clinical symptoms and functional connectivity patterns (Chen et al., 2019); and Hrdlicka et al. clustered features including frontal lobe cortical thickness and sizes of the striatum, hippocampus, caudate nucleus, and amygdala to identify four ASD subtypes with different region-of-interest characteristics (Hrdlicka et al., 2005). Summarizing previous studies, some ASD subtypes show increased values on specific brain imaging features compared to TD, while others show decreased values, indicating that heterogeneity is a non-negligible factor in imaging research. Additionally, subtype studies based on functional connectivity have found that abnormalities in the DMN and frontoparietal network are consistently present across different subtypes, suggesting that abnormalities in these higher-order cognitive networks may underlie impaired social communication function in ASD.

DSM-5 classifies ASD diagnosis as a spectrum disorder, hoping that researchers and clinicians will adopt more dimensional approaches to study this continuously varying spectrum disorder rather than dividing ASD into independent subtypes (Kim, 2020). Based on this perspective, Tang et al. proposed a novel analytical framework that decomposes abnormal functional connectivity patterns in ASD into three factors, with different ASD subjects showing varying expression levels of these factors, and the expression levels of different factors correlating with clinical symptoms (Tang et al., 2020). The analytical framework proposed by Tang et al. represents a step forward in revealing ASD heterogeneity, and future studies need to explore the molecular mechanisms underlying these functional connectivity-based dimensional features of ASD and their role in achieving precision diagnosis and treatment.

ASD brain imaging research based on subtype and dimensional classification aims to explore the neural mechanisms underlying the high heterogeneity of ASD. However, most studies are based on single-modal brain imaging. How to fuse multimodal magnetic resonance brain imaging, establish relationships between subtypes/dimensions and clinical indicators such as ASD clinical symptoms and neural intervention efficacy, and explore personalized diagnosis and treatment strategies suitable for different subtypes/dimensions is an important direction for future ASD research.

6. Summary and Outlook

This review summarizes existing research findings from several aspects: ASD single-modal brain imaging studies, multimodal brain imaging fusion research, assisted diagnosis, and subtype identification. Reviewing previous studies, multimodal magnetic resonance brain imaging research has enriched our understanding of ASD neuropathological mechanisms, provided powerful tools for revealing the neural mechanisms of ASD, and is expected to promote the transformation of autism clinical diagnosis and treatment from subjective judgment to objective indicators. However, there remains a long way from neuroimaging findings to clinical precision diagnosis and treatment, and future research needs to continue focusing on the following issues:

6.1 Fusion of Multimodal Brain Imaging for Comprehensive Characterization

Currently, most ASD imaging studies are single-modal and small-sample, often yielding inconsistent results and failing to comprehensively characterize subtle changes in brain structure and function in ASD. Multimodal brain imaging fusion technology based on large samples and multi-centers provides new means for multiscale and multilevel characterization of ASD. However, ASD research utilizing image-level, feature-level, or decision-level fusion is still in its early stages. Future research can develop low-dimensional, individualized, and parameterized analytical frameworks based on multimodal brain imaging fusion technology to comprehensively reveal abnormal neural mechanisms in ASD, identify imaging markers with classification capability, and provide objective evidence for ASD-assisted diagnosis and subtype classification.

Furthermore, EEG-based studies have found abnormalities in spectral power, coherence, and hemispheric asymmetry in ASD (Wang et al., 2013); eye-tracking studies have found that ASD shows abnormal gaze patterns toward face images and social images compared to TD (Kou et al., 2019; Wang et al., 2020); and gut microbiome research has found that ASD gut dysbiosis may affect the relationship between brain and behavior through pathways such as immune responses and gastrointestinal systems (McElhanon et al., 2014; Noriega & Savelkoul, 2014; Vuong & Hsiao, 2017). Multi-source data including EEG, eye-tracking, and gut microbiome also hold promise for supporting the revelation of ASD pathological mechanisms. In future research, in addition to multimodal

brain imaging data, multi-source information such as electrophysiological, eye-tracking, and biochemical data can be incorporated to construct multi-center, large-sample, multi-source heterogeneous databases, effectively leveraging the advantages of each modality, strengthening information complementarity, and exploring the developmental patterns of ASD in a multidimensional and comprehensive manner.

6.2 Revealing “Social Brain” Network Abnormalities

Reviewing ASD brain imaging research reveals that most abnormal regions are concentrated in the “social brain” network, which is the most affected brain area in ASD across different levels. Previous results partially support the social motivation theory hypothesis of ASD. The “social brain” network mainly includes regions such as the medial prefrontal cortex, ventromedial prefrontal cortex, posterior superior temporal sulcus, precuneus, fusiform gyrus, inferior frontal gyrus, frontal-insular cortex, and amygdala (L. Li et al., 2021; Misra, 2014; Sato & Uono, 2019). These brain regions are primarily responsible for processing social stimuli, such as face recognition, emotional processing, eye gaze, and theory of mind (Sato & Uono, 2019), which aligns with the impairments in higher-order cognitive functions like social communication in ASD. Therefore, abnormalities in the “social brain” network may lead to brain information processing and integration deficits, subsequently affecting social, communication, and behavioral manifestations in ASD. Future studies can fuse multimodal brain imaging to focus on revealing the neuroimaging mechanisms of the ASD “social brain” network.

Over the past decade, transcranial magnetic stimulation, as a non-invasive neural regulation technique, has been widely applied in clinical research and has become a new treatment option for neurodevelopmental disorders and psychiatric diseases including ASD (Iglesias, 2020; Kang et al., 2019; Memon, 2021). Selecting appropriate stimulation targets is key to achieving expected regulatory effects. For example, the primary motor cortex is used to enhance motor control, conduct rehabilitation training, and treat movement disorders; the prefrontal cortex is used to improve executive function, working memory, decision-making ability, and emotional regulation; and temporal lobe regions are used to treat speech and mood disorders. However, existing neural regulation research has shown limited improvement in core social symptoms of ASD. Based on existing ASD brain imaging research results, we recommend that future studies consider key nodes in the “social brain” network (e.g., dorsolateral prefrontal cortex) as stimulation regions to improve social deficits in ASD. However, extensive clinical empirical evidence will be needed in the future to verify this hypothesis.

6.3 Assisting Clinical Precision Diagnosis and Treatment

Early precise diagnosis can provide earlier intervention and treatment for children with ASD, helping to formulate personalized education and rehabilitation plans. However, children with ASD exhibit strong heterogeneity, and tradi-

tional diagnostic methods require evaluation by experienced professionals, making early diagnosis more complex. Multimodal magnetic resonance brain imaging provides new means for assisted diagnosis and treatment of ASD, but still faces numerous challenges including small sample sizes, high model parameter dimensions, poor interpretability, weak generalization ability, difficulties in multimodal data fusion, lack of 完善的 strategies for multi-center data harmonization, challenges in early warning, and strong heterogeneity. Therefore, future research needs to deeply explore imaging markers with early diagnostic capability based on multi-center, large-sample data, and establish generalizable and stable ASD early warning and diagnostic models to achieve early diagnosis and intervention. On this basis, establishing treatment efficacy evaluation models based on multimodal brain imaging, developing different intervention strategies for different ASD subtypes/dimensions, optimizing traditional single treatment protocols, and providing objective evidence for clinical precision diagnosis and treatment.

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