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General

Neuroimaging Insights into Autism Spectrum Disorder: Structural and Functional Brain

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Autism Spectrum Disorder (ASD) is a condition that affects social communication, behavior, and interests. This review analyzes recent brain imaging studies to understand the biological basis of ASD. Studies using structural magnetic resonance imaging (sMRI) show that people with ASD often have less gray matter in key brain areas like the amygdala and superior temporal sulcus. There are also concerns with white matter connections in the brain. Functional magnetic resonance imaging (fMRI)studies show reduced connectivity within critical brain networks and irregular activation patterns when processing social information. Intervention studies suggest that targeted training can improve brain function related to social skills. Postmortem research reveals cellular and synaptic changes, such as fewer Purkinje cells and altered neuron organization. These findings highlight the importance of studying the social brain network in ASD and suggest the need for more long-term, comprehensive studies. This review is intended to contribute to the development of advanced diagnostic tools and therapies that will ultimately enhance the quality of life for individuals with ASD.

INTRODUCTION

ASD, although a complex diagnosis, is most frequently and best defined, as a neurodevelopmental condition characterized by continuing challenges in social communication and interaction, alongside restricted and repetitive behaviors, and interests.[1] This definition presents a broad overview of the condition, and usually, in formal diagnosis, several criteria are used to narrow identification. These criteria include interpersonal communication difficulties, restrictive pattern of behavior, an early onset of symptoms, clinically significant impairment, and a lack of other possible diagnosis. These criteria, along with their descriptions are represented in Table 1.

Diagnosis of ASD is primarily observational and qualitative, focusing on behavior. Clinicians rely on detailed observations of a child's social interactions, communication skills, and behavior patterns to identify characteristics of ASD. Standardized diagnostic tools, such as the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised, are used to systematically assess these behaviors. These tools involve structured and semi-structured interactions that allow professionals to observe key behaviors that are indicative of ASD. The reliance on behavioral observation highlights the importance of qualitative assessments in the diagnostic process, as there are no definitive medical tests that can diagnose ASD, as of yet.[1-3]

Although inconclusive, magnetic resonance imaging (MRI) techniques can aid in diagnosing ASD in a patient-specific manner, despite inconsistent findings due to the broad spectrum of disorders encompassed by ASD. MRIs provide detailed images of brain structure and function, allowing researchers to identify potential biomarkers associated with ASD, such as abnormalities in brain volume, connectivity, and cortical thickness.[4,5] These neuroimaging biomarkers can help tailor diagnostic and therapeutic approaches to the individual's specific neural profile, offering a more personalized understanding of the disorder. However, the heterogeneity of ASD, with its wide range of symptoms and severities, poses challenges in identifying consistent MRI-based markers across all individuals.[6] This variability underscores the need for individualized assessments and highlights the potential of MRI to contribute to a nuanced, patient-specific diagnostic process.

The etiology and presentation of ASD are multifaceted, involving a combination of genetic, environmental, and neurobiological factors. The concept of the social brain, (a network of brain regions implicated in processing social information) provides a crucial aspect of understanding the characteristics and social divergence present in those with ASD. This "social brain" includes but is not limited to areas such as the amygdala, superior temporal sulcus (STS), fusiform gyrus, and prefrontal cortex, and is involved in facial recognition, interpreting emotional expressions, and understanding the actions and intentions of others.[7,8]

Advancements in neuroimaging techniques, namely sMRI and fMRI , have significantly amplified our understanding of the neural underpinnings of social atypicalities

Table 1. A table describing the five distinct criteria for the diagnosis of autism spectrum disorder as per the American Psychiatric Association, DSM-5, 2013.

Diagnosing ASD as per the DSM-5 Criteria[1]		
	Criteria	**Description**
A	**Persistent deficits in social communication and social interaction**	Deficits in social-emotional reciprocity, nonverbal communicative behaviors, and developing, maintaining, and understanding relationships. Examples: Abnormal social approach, reduced sharing of interests, failure to initiate/respond to social interactions, poorly integrated verbal/nonverbal communication, abnormalities in eye contact and body language, difficulties in making friends.
B	**Restricted, repetitive patterns of behavior, interests, or activities**	At least two of the following: stereotyped/repetitive motor movements, insistence on sameness, highly restricted interests, hyper-/hypo-reactivity to sensory input. Examples: Simple motor stereotypes, lining up toys, echolalia, extreme distress at small changes, rigid thinking patterns, strong attachment to unusual objects, adverse response to specific sounds/textures.
C	**Symptoms present in early developmental period**	Symptoms may not become fully manifest until social demands exceed capacities or may be masked by learned strategies.
D	**Clinically significant impairment**	Symptoms cause significant impairment in social, occupational, or other important areas of functioning.
E	**Not better explained by intellectual disability or global developmental delay**	Social communication should be below that expected for general developmental level in cases of comorbid diagnoses.

in ASD. In individuals with ASD,sMRI studies have revealed atypical brain morphometry;particularly, gray and white matter volume abnormalities, as well as atypicalities in white matter integrity within the social brain network.[9,10] fMRI studies (in which the patients are either at rest or completing task-based activities as a form of stimulation), have demonstrated altered functional connectivity and atypical regional brain activity associated with social processing in ASD. Patients with ASD present abnormalities in the default mode network (DMN) that hinder their ability to not only integrate and process information about themselves in relation to others, but also to adapt and attend to social stimuli.[11,12] In addition to MRI, postmortem studies provide critical insights into the neurobiological aspects of ASD, including the distinguishment of cellular anomalies, including: alterations in neuron count, glial cell numbers, dendritic morphology, and synaptic density.[13,14] Integrating findings from both structural and functional MRIs, postmortem research, and other neuroimaging techniques is essential to comprehensively understanding the neuropathology of those with ASD and may contribute to methods of treatment and recovery.

Theory of Mind (ToM) is the ability to attribute mental states (e.g. beliefs, intentions, and desires) to oneself and others. ToM is an extremely fundamental psychological aspect of social cognition, one that is often impaired in individuals with ASD.[15] Frequently, neurological studies of ASD involving social stimuli and task-based assessment of subjects will integrate ToM to assess the differences in brain processing and connectivity, considering the fact that ToM is a recognized distinction between patients with ASD and those without the condition. An individual's ToM is strongly correlated to their demonstration of pragmatic communication, involving the use of language in social contexts to convey meaning effectively in response to the presented social circumstances. Impaired social interaction and conversation, including pragmatic comprehension, is a well-known characteristic of ASD.[16] Functional MRI studies have highlighted key brain regions involved in ToM, including the medial prefrontal cortex (MPFC), temporoparietal junction (TPJ), and STS.[17] Similarly, regions such as the inferior frontal gyrus (IFG) and superior temporal gyrus (STG) have been implicated in pragmatic language processing.[18,19]

The trajectory of brain development in individuals with ASD is characterized by early overgrowth followed by a deceleration in growth in which the brain volume "normalizes" during later childhood and adolescence, particularly in regions such as the frontal and temporal lobes, the amygdala, and the cerebellum.[20,21] This atypical development is reflected in sMRI and fMRI studies. Investigations on ASD using fMRI have revealed atypical activation patterns and connectivity during tasks involving social cognition, communication, and executive functions in subjects with ASD as compared to the control.[22]

Early brain development studies have demonstrated that brain overgrowth is a common indication of ASD in children, with retrospective studies of head circumference and longitudinal brain volume indicating that increased brain volume emerges early in development and is linked to the severity of autistic social deficits.[5] Prospective neuroimaging studies of infants at high familial risk for ASD have shown that hyperexpansion of the cortical surface area between 6 and 12 months precedes brain volume overgrowth observed between 12 and 24 months, suggesting that early

brain changes occur during the period when autistic behaviors are first emerging.[5]

Understanding these neural mechanisms is essential for developing effective diagnostic tools and support strategies. The integration of neuroimaging and postmortem research findings can provide a clearer picture of the structural and functional brain abnormalities in ASD.

Neuroimaging techniques such as MRI, fMRI, and diffusion tensor imaging (DTI) provide insights into structural and functional anomalies in the brains of individuals with ASD, revealing volumetric differences, connectivity issues, and variations in brain activity. For instance, DTI studies have highlighted disruptions in white matter connectivity, suggesting that atypical neural connections may provide an underlying reason to the leading symptoms of ASD.[23]

By compiling and analyzing findings from multiple studies and by examining structural and functional brain abnormalities, this review seeks to highlight the relationship between these neural alterations and the behavioral characteristics of ASD, thus offering insights that can inform the development of targeted interventions and improve outcomes for individuals with ASD. Further exploring the developmental trajectory of brain abnormalities and their connections to the behavioral symptoms of ASD will highlight the neurobiological features of ASD and their implications in developing more targeted and effective interventions to assist patients with ASD.

METHODOLOGY FOR LITERATURE SEARCH

To gather relevant research articles for this review paper, a systematic and comprehensive literature search was conducted across multiple databases and sources. The primary goal was to identify key studies that provide significant insights into the neurobiological and diagnostic aspects of ASD, particularly focusing on structural and functional neuroimaging findings. The following steps outline the methodology employed:

Database Selection: The search was conducted using major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. These databases were chosen for their extensive coverage of biomedical, psychological, and neuroscientific research.

Search Terms and Keywords: A combination of keywords and medical subject headings terms were used to ensure a thorough search. The key terms included: Autism Spectrum Disorder, Neuroimaging of ASD, ASD-MRI/fMRI/structural MRI/functional MRI, ASD Brain structure or Brain function or Brain connectivity, Theory of Mind, pragmatic communication, and Autism Diagnostic Interview

Eligibility Criteria: Articles were selected for this review based on specific eligibility criteria to ensure the inclusion of high-quality and relevant research. Inclusion criteria mandated that articles be published in peer-reviewed journals and focus on neuroimaging findings in ASD. Additionally, included studies needed to detail diagnostic criteria and tools for ASD, and provide insights into structural and functional brain abnormalities associated with the disorder. Conversely, exclusion criteria eliminated non-peer-reviewed articles, studies unrelated to ASD, and papers that focused solely on clinical or behavioral interventions without incorporating neuroimaging data. This stringent selection process aimed to refine the scope of the review to the most pertinent and scientifically robust studies available.

Study Selection and Data Abstraction: The review process consisted of several rigorous steps to ensure the inclusion of the most relevant and high-quality articles. Initially, the titles and abstracts of the retrieved articles were screened to determine their relevance to the review topic, with non-relevant articles and those not meeting the inclusion criteria being excluded. This was followed by a detailed full-text review of the selected articles, during which key information such as study design, sample size, neuroimaging techniques used, primary findings, and conclusions was extracted. Additionally, the reference lists of these articles were checked to identify any further relevant studies that may have been missed in the initial search. Finally, the selected articles were organized based on specific themes pertinent to the review, including structural abnormalities, functional connectivity, diagnostic tools, and intervention studies. This structured approach ensured a comprehensive and focused synthesis of the existing literature. Following this series of criteria the total number of articles reviewed narrowed from 150 to 53, which represented the final number of studies referenced and included in this review.

RESULTS

The key takeaways of the 53 studies reviewed are highlighted and divided into relevant subsections. These subsections include findings related to sMRI studies, resting-state fMRI studies, task-based f-MRI studies, neural correlates of ToM in autism, neural correlates of pragmatic communication in autism, overlap and distinctions in neural activity, MRI findings in autism, postmortem findings in autism, connectivity and network analysis, and developmental trajectory.

STRUCTURAL MRI STUDIES

- **Gray Matter Abnormalities:** Structural MRI studies have provided compelling evidence for abnormalities in gray matter within the social brain network in individuals with ASD. Notably, a significant finding is the decreased gray matter volume in the amygdala, a region crucial for emotional processing and social behavior. A large multisite study involving over 1500 participants reported reduced volumes of the amygdala of individuals with ASD across different age groups, from toddlers to older adults.[10] This reduction in gray matter volume has been associated with the severity of social impairments observed in ASD. Research by Sato et al. highlighted that the gray matter volume in the STS, a region involved in interpreting social cues, was positively correlated with the ability to understand mental states based on others' eyes in typically developing individuals but not in those with ASD.[24] This suggests a disruption in the

typical development of social brain regions in ASD. Pereira et al. found that individuals with ASD exhibited reduced cortical thickness in distributed brain regions, including the fusiform gyrus and STS, which correlated with the severity of social deficits.[25]

- **White Matter Abnormalities:** In addition to gray matter abnormalities, studies have identified network-level atypicalities in white matter structure surrounding social brain regions. For example, Lo et al. reported reduced tract integrity in the superior longitudinal fasciculus, which connects the STS and IFG, in individuals with ASD.[26] This reduction was associated with impairments in social interaction. Similarly, d'Albis et al. found that individuals with ASD showed reduced connectivity in short-ranged white matter regions, which was linked to difficulties in social awareness and empathy.[27]

FUNCTIONAL MRI STUDIES: RESTING-STATE

- **Intrinsic Activity and Connectivity:** Resting-state fMRI studies have revealed abnormalities in intrinsic activity and connectivity within the social brain network in ASD. Several studies have consistently shown reduced functional connectivity between the dorsomedial prefrontal cortex (dmPFC) and posterior cingulate cortex (PCC)/precuneus, key components of the default mode network.[12] This reduced connectivity has been implicated in the social cognitive deficits observed in individuals with ASD.[28] Odriozola et al. reported weaker functional connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC) in individuals with ASD during resting state. This finding was further associated with the severity of social affective impairment.[29] Fishman et al. found reduced functional connectivity between the amygdala and inferior occipital gyrus in ASD, suggesting disrupted communication between regions critical for emotional and visual processing.[30] These resting-state abnormalities indicate that intrinsic neural activity and connectivity in the social brain network are altered in ASD, contributing to the social difficulties characteristic of the disorder.

FUNCTIONAL MRI STUDIES: TASK-BASED

- **Social Stimuli Processing:** Task-based functional MRI studies have provided insights into how individuals with ASD process social stimuli differently. These studies have generally reported reduced activity in social brain regions during tasks involving social perception and cognition. Ciaramidaro et al. found that individuals with ASD exhibited reduced activity in the amygdala, fusiform gyrus, and STS during the implicit processing of emotional facial expressions compared to typically developing individuals.[31] Sato et al. demonstrated that subliminally presented averted eye gaze stimuli elicited reduced activation in the amygdala in individuals with ASD, indicating that atypical activation can occur at automatic and unconscious stages of social processing.[32] These findings suggest that the neural mechanisms underlying social perception and attention are disrupted in ASD.
- **Intervention and Improvement:** Recent studies have explored the potential for improvement through targeted interventions. Yang et al. conducted a study where individuals with ASD participated in a social skills training course using virtual reality.[33] Functional MRI measurements taken before and after training showed increased activity in the STS, correlating with improved mentalizing scores. This suggests that targeted training can enhance social brain function in individuals with ASD.

NEURAL CORRELATES OF THEORY OF MIND IN AUTISM

- **Activation Patterns:** The neural basis of Theory of Mind (ToM) has been extensively studied using fMRI, revealing a network of brain regions involved in mental state attribution. Key areas consistently implicated include the MPFC, TPJ, STS, and the PCC.[34] In individuals with ASD, these regions often show atypical activation patterns during ToM tasks. For instance, studies have reported reduced activation in the MPFC and TPJ in autistic individuals compared to typically developing individuals.[35] These findings suggest that impairments in ToM may be related to dysfunctional neural processing within this network. An ALE meta-analysis found significant hypoactivation in the MPFC, anterior cingulate cortex, and TPJ in individuals with ASD during ToM tasks.[36] This hypoactivation was associated with difficulties in understanding and predicting others' mental states, a core component of ToM. Additionally, the amygdala has shown both hypo- and hyperactivation in response to ToM tasks, depending on the complexity of the task.[37]

NEURAL CORRELATES OF PRAGMATIC COMMUNICATION IN AUTISM

- **Brain Regions and Activation:** Pragmatic communication involves understanding and using language in context, and several brain regions are implicated in this process. The IFG, particularly in the left hemisphere, is crucial for integrating semantic and contextual information, essential for pragmatic language processing.[19] Studies have shown that individuals with ASD often exhibit reduced activation in the left IFG and STG during pragmatic language tasks.
- **Atypical Lateralization**: Some studies have found increased activation in the right hemisphere, particularly in the right IFG, during pragmatic tasks in ASD. This atypical lateralization suggests that autistic individuals may rely more on low-level semantic processing rather than higher-level integrative processing required for pragmatic comprehension. The right IFG's involvement may indicate a more effortful and

less efficient strategy for processing pragmatic information.

OVERLAP AND DISTINCTIONS IN NEURAL ACTIVATION

- **Shared and Distinct Networks:** There is considerable overlap in the neural networks involved in ToM and pragmatic communication. Both processes engage regions such as the IFG, STG, and MPFC, reflecting the shared cognitive demands of understanding others' mental states and using language effectively in social contexts.[38] However, there are also distinct activation patterns that differentiate the two processes. For ToM, regions like the TPJ and PCC are more prominently involved, highlighting their role in attributing mental states and understanding others' perspectives.[17] Pragmatic communication, on the other hand, relies more heavily on the IFG and STG for integrating contextual and linguistic information.[19] Pereira et al. revealed that those with ASD possess weaker cortical thickness in multiple regions of the brain, notably the IFG and STS, suggesting an intrinsic weakness in integrative processing and cognitive control in ASD.[25]

MRI FINDINGS IN AUTISM

- **Brain Volume and Growth Trajectory:** MRI studies have consistently shown that individuals with ASD exhibit an abnormal trajectory of brain growth. This trajectory involves an initial period of overgrowth during infancy and early childhood, followed by a slowing in growth during later childhood and adolescence.[20,21] For example, Schumann et al. reported significant enlargement of the frontal and temporal lobes in children with ASD compared to typically developing peers.[21] These findings suggest that early brain overgrowth may contribute to subsequent developmental abnormalities in ASD.
- **Amygdala and Cerebellum:** The amygdala, a region involved in social and emotional processing, also shows an aberrant growth pattern in individuals with ASD. Studies have found that the amygdala is enlarged in young children with ASD but tends to normalize in size by adolescence.[39,40] This pattern of early enlargement followed by normalization suggests a complex developmental trajectory that may be related to the social and emotional difficulties which often characterize individuals with ASD. Similarly, the cerebellum, which plays a role in motor control and cognitive functions, has been a focus of MRI studies in ASD. While some studies have reported an enlargement of the cerebellum gray matter,[41] others have found specific alterations in the cerebellar vermis, a region involved in coordinating voluntary movements.[42,43] These findings indicate that both global and regional cerebellar abnormalities may contribute to the motor and cognitive symptoms observed in ASD.
- **Cortical Thickness and Surface Area:** Research on cortical thickness and surface area has yielded mixed results, reflecting the heterogeneity of ASD. Some studies have reported increased cortical thickness in the temporal lobes,[44] while others have found cortical thinning in portions of the temporal cortex.[45] These discrepancies may be due to differences in study populations, imaging techniques, and analytic methods. However, they collectively highlight that cortical abnormalities are a significant feature of the ASD brain and may underlie the cognitive and behavioral symptoms of the disorder.

POSTMORTEM FINDINGS IN AUTISM

- **Neuronal and Glial Abnormalities:** Postmortem studies have provided detailed insights into the cellular abnormalities associated with ASD. One of the most consistent findings is a reduction in the number of Purkinje cells in the cerebellum, particularly in the lateral regions.[13] Purkinje cells play a crucial role in motor coordination, and their loss may contribute to the motor difficulties observed in ASD. Studies have reported increased microglial activation and volume, suggesting a neuroinflammatory response.[46] Additionally, abnormalities in the organization and density of cortical neurons have been observed, including reduced minicolumnar width and increased cell density.[47,48] These findings indicate that both neurodevelopmental and neuroinflammatory processes may contribute to the neuropathology of ASD.
- **Synaptic and Dendritic Changes:** Synaptic abnormalities have also been a focus of postmortem research in ASD. Studies have reported a reduction in synaptic density and alterations in dendritic morphology, or more specifically, a lack of mature morphology of the dendritic spines in autistic brains.[49] These changes may reflect disruptions in synaptic pruning and dendritic growth, which are critical processes during early brain development. The observed synaptic deficits are likely to contribute to the cognitive and social impairments characteristic of ASD.

CONNECTIVITY AND NETWORK ANALYSIS

- **Functional Connectivity:** Beyond individual brain regions, recent studies have focused on the connectivity and network organization of the social brain in ASD. Functional connectivity analyses have shown that the coordination between critical social brain regions is often disrupted in individuals with ASD. For instance, in a positron emission tomography (PET) study by Castelli et al. examining brain activation during a social attribution test, functional connectivity between the anterior and posterior brain was different in autism.[50] To elaborate, the ASD group exhibited significantly decreased connectivity between the extrastriate region (V3) and the STS as compared to the control. It was then hypothesized that the

weakened brain connectivity could be correlated to an impaired top-down modulation for the anterior brain responsible for attending to visual stimuli from V3. In light of the absence of top-down regulation, it is more challenging to understand the social significance of other's actions in people with ASD.

- **Task-Based and Resting-State Connectivity:** Moreover, task-based functional MRI studies have demonstrated that the atypical activity in the social brain regions during social cognition tasks is associated with the severity of ASD symptoms.[51] For example, weaker functional coupling between the PCC and the superior frontal gyri, the PCC and the temporal lobes, as well as the PCC and the parahippocampal gyri correlates with more severe social impairments. These findings underscore the importance of examining both the activity and connectivity within social brain networks to understand the neural basis of social deficits in ASD. Resting-state fMRI studies have provided further insights into the functional connectivity disruptions in ASD. These studies have shown that individuals with ASD often exhibit reduced connectivity within key brain networks, such as the default mode network, which is involved in self-referential thought and social cognition.[51] Additionally, increased activation of the amygdala and other brain regions in response to seeing other's faces, may underlie the social and emotional difficulties characteristic of ASD.[52] Moreover, rs-fMRI studies have identified both hypo- and hyperconnectivity in various brain regions in individuals with ASD. For example, increased connectivity in sensory networks and primary sensory cortices has been associated with heightened sensitivity to sensory stimuli in ASD.[53] These findings highlight the complex and heterogeneous nature of functional connectivity disruptions in ASD. Furthermore, overstimulation within crowds is seen in many patients with autism, an observation that can potentially be explained because of the elevated sensory connectivity.

DEVELOPMENTAL TRAJECTORY

- **Early Brain Development:** The neurodevelopmental trajectory of brain abnormalities in ASD is another critical area of research. Studies have shown that while early brain overgrowth is a common feature in young children with ASD, this growth pattern often normalizes or even reverses by adolescence. This dynamic trajectory suggests that the neurobiological mechanisms underlying ASD are complex and may involve different processes at different stages of development. Hazlett et al. conducted a longitudinal MRI study that demonstrated early brain overgrowth in infants who later developed ASD.[5] The study found significant increases in total brain volume, particularly in the frontal and temporal lobes, during the first two years of life.[5] This early overgrowth is linked to the severity of autistic social deficits at 24 months. Lainhart et al. using longitudinal MRI data found that while children with ASD had larger brain volumes at an early age, their brain growth rates slowed down over time, resulting in comparable brain sizes to typically developing peers by adolescence.[23] This finding highlights the importance of considering developmental changes when studying the neurobiology of ASD.

DISCUSSION

The neuroimaging studies of ASD reveal significant structural and functional abnormalities in the brain, providing a deeper understanding of the disorder's neurobiological underpinnings. These abnormalities are evident in both gray and white matter, encompassing various brain regions involved in social communication, cognitive processing, and sensory integration. One of the most consistent findings is the reduced gray matter volume in the amygdala and other social brain regions. The amygdala's critical role in emotional processing and social behavior is well-established, and its reduced volume across different age groups suggests a fundamental disruption in the neural circuits that govern social interaction.[10] Additionally, the correlation between gray matter volume in the STS and social cognitive abilities in typically developing individuals, but not in those with ASD, illustrates specific neural deficits that contribute to the social challenges observed in ASD.[24] The reduction in cortical thickness in distributed brain regions, such as the fusiform gyrus and STS, aligns with the severity of social deficits, emphasizing the importance of these regions in social cognition.[25]

White matter abnormalities add another layer of complexity to our understanding of ASD. Reduced tract integrity in the superior longitudinal fasciculus, which connects the STS and IFG, highlights connectivity issues that may underlie impairments in social interaction.[26] Similarly, reduced connectivity in short-ranged white matter regions correlates with difficulties in social awareness and empathy, suggesting that local connectivity disruptions are critical for understanding the social deficits in ASD.[27] These findings underscore the necessity of examining both gray and white matter to gain a comprehensive understanding of the neurobiological basis of ASD.

fMRI studies, both resting-state and task-based, provide valuable insights into the intrinsic activity and connectivity within the social brain network in ASD. Resting-state studies consistently show reduced functional connectivity between key components of the DMN, such as the dmPFC and PCC/precuneus, which are implicated in social cognitive deficits.[12] The weaker functional connectivity between the amygdala and vmPFC during resting state is associated with the severity of social affective impairment, highlighting disrupted communication between regions critical for emotional and social processing.[29] Task-based fMRI studies reveal reduced activity in social brain regions during tasks involving social perception and cognition, indicating that individuals with ASD process social stimuli differently. For instance, reduced activity in the amygdala, fusiform gyrus, and STS during implicit processing of emotional facial ex-

pressions points to atypical neural mechanisms underlying social perception.[31]

The findings regarding intervention and improvement are particularly promising, as they suggest that targeted interventions can enhance social brain function in individuals with ASD. For example, functional MRI measurements taken before and after a social skills training course using virtual reality showed increased activity in the STS, correlating with improved mentalizing scores.[33] These results indicate the potential for neural plasticity in the social brain network and highlight the importance of developing targeted interventions to improve social cognitive abilities in ASD.

The neural correlates of ToM and pragmatic communication provide further insights into the specific cognitive processes disrupted in ASD. Atypical activation patterns in key ToM regions, such as the MPFC and TPJ, during ToM tasks suggest that impairments in understanding others' mental states are related to dysfunctional neural processing within this network.[35] Similarly, reduced activation in the IFG and STG during pragmatic language tasks indicates that individuals with ASD may struggle with integrating contextual and linguistic information essential for effective communication.[19] The overlap and distinctions in neural activation for ToM and pragmatic communication highlight the shared cognitive demands of these processes and suggest that targeted interventions could address both ToM and pragmatic communication deficits in ASD.[38]

The abnormal trajectory of brain growth in individuals with ASD, characterized by early overgrowth followed by deceleration, further complicates our understanding of the disorder. Early brain overgrowth, particularly in the frontal and temporal lobes, is linked to the severity of autistic social deficits and suggests that early neural changes may contribute to later developmental abnormalities.[5] The finding that brain growth rates in children with ASD slow down over time, resulting in comparable brain sizes to typically developing peers by adolescence, highlights the dynamic nature of brain development in ASD and underscores the need for longitudinal studies to capture these changes.[23]

Postmortem studies provide additional insights into the cellular and synaptic abnormalities associated with ASD. The reduction in the number of Purkinje cells in the cerebellum, increased microglial activation, and abnormalities in cortical neuron organization and density suggest that both neurodevelopmental and neuroinflammatory processes contribute to the neuropathology of ASD.[13,46,47] Synaptic abnormalities, such as reduced synaptic density and alterations in dendritic morphology, indicate disruptions in synaptic pruning and dendritic growth, which are critical processes during early brain development.[49] These cellular and synaptic changes likely underlie the cognitive and social impairments characteristic of ASD and highlight the importance of integrating postmortem findings with neuroimaging studies to gain a comprehensive understanding of the disorder.

Many of the major findings regarding specific neural regions regarding their regulation in ASD patients are summarized in Table 2. Collectively, the findings from structural and functional MRI studies, along with postmortem research, provide a detailed picture of the neurobiological underpinnings of ASD. The consistent abnormalities in gray and white matter, atypical functional connectivity, and altered activation patterns during social cognition tasks underscore the importance of the social brain network in ASD. The dynamic trajectory of brain growth and the cellular and synaptic abnormalities further highlight the complexity of the disorder and the need for longitudinal and multimodal studies to capture these changes. By synthesizing these findings, we can develop targeted interventions and support strategies that address the specific neural and cognitive deficits in ASD, ultimately improving outcomes for individuals with the disorder. Understanding the neural mechanisms underlying ASD is essential for developing effective diagnostic tools and interventions, and this review provides a comprehensive overview that can inform future research directions and potential clinical applications.

CONCLUSION

The comprehensive review of neuroimaging studies on ASD highlights significant structural and functional abnormalities in the brains of affected individuals. sMRI studies have consistently shown reduced gray matter volume in key social brain regions such as the amygdala and STS, which are crucial for emotional processing and social behavior. White matter abnormalities, including reduced tract integrity in the superior longitudinal fasciculus, further underscore the network-level disruptions that underlie impairments in social interaction and empathy.

fMRI studies, both resting-state and task-based, reveal reduced functional connectivity within critical components of the default mode network and altered activity in social brain regions during social cognition tasks. These findings highlight the disrupted communication between regions essential for emotional and social processing in individuals with ASD. The promising results from intervention studies, such as increased activity in the STS following social skills training using virtual reality, indicate the potential for neural plasticity and the importance of targeted interventions to improve social cognitive abilities.

The review also underscores the importance of ToM and pragmatic communication in understanding the cognitive processes disrupted in ASD. Atypical activation patterns in key ToM regions and reduced activation in regions involved in pragmatic language tasks suggest specific neural deficits that contribute to the social and communication challenges characteristic of ASD. The abnormal trajectory of brain growth, characterized by early overgrowth followed by deceleration, further complicates our understanding of ASD and highlights the need for longitudinal studies to capture these changes.

Postmortem studies provide additional insights into the cellular and synaptic abnormalities associated with ASD, including reduced Purkinje cell numbers, increased microglial activation, and altered cortical neuron organization and density. These findings indicate that both neurodevel-

Table 2. This table provides a summary view of various brain regions with their functions and reports the activity status of the region in ASD patients.

Brain Part	Function of the Part	Status in ASD	Additional Information
Cerebrum-Frontal Lobe	Involved in decision making, problem-solving, and planning	Reduced gray matter	Shifting of major sulci, suggesting delayed or incomplete maturation.[54]
Cerebrum-Frontal Lobe - Inferior Frontal Gyrus (IFG)	Language production and comprehension	Hypoactivation	Abnormal activation patterns noted, contributing to difficulties in language tasks in ASD individuals.[55,56]
Cerebrum - Frontal Lobe - Dorsolateral and medial frontal cortices	Planning, decision-making, and social behavior	Hyperactivation	Increased volume in young children, localized enlargement.[23]
Cerebrum - Frontal Lobe - Frontal Cortex	Higher-order cognitive functions, decision-making, and social behavior	Hypoactivation	Abnormalities in individuals with autism include reduced minicolumn width, increased cell density, and glial activation, suggesting neuroinflammation. These changes, along with early overgrowth in the frontal cortex followed by reduced activation, are linked to impairments in social interaction, emotion regulation, and executive function.[23, 57-60]
Cerebrum - Frontal Lobe - Prefrontal Cortex	Executive functions, decision making	Hyperactivation	Reduced activation associated with difficulties in social cognition and executive function.[61]
Cerebrum - Parietal Lobe	Processes sensory information (touch, temperature, pain, and spatial orientation)	Reduced gray matter / mixed activation	Voxel-based analysis shows significant gray matter reductions and Volume changes are less documented.[23,54]
Cerebrum - Parietal Lobe - Angular Gyrus	Language, number processing	Hyperactivation	Reduced activation linked to deficits in language and cognitive functions.[61]
Cerebrum-Temporal Lobe - Superior Temporal Gyrus (STG)	Language processing and social communication	Hyperactivation	Reduced activation and abnormal right-lateralization observed in ASD, linked to delayed language acquisition and social communication deficits.[55,56]
Cerebrum - Temporal Lobe - Superior Temporal Sulcus (STS)	Processing of social stimuli and orientation to social cues	Hypoactivation	STS defects are early-emerging in ASD. Abnormalities in sulcal anatomy, with decreased volume in some areas.[23,55, 56]
Cerebrum - Temporal Lobe	Language processing, social cognition	Reduced gray matter	Anatomical abnormalities in key language regions; asymmetry reversal in inferior lateral frontal cortex.[54]
Cerebrum - Occipital Lobe	Visual processing	Reduced gray matter	Voxel-based analysis shows significant gray matter reductions.[54]
Cerebrum - Occipital Lobe - Visual Cortex	Visual processing	Hypoactivation	Underactivation related to impairments in visual processing.[61]
Cerebellum	Coordination of voluntary movements, motor control, and cognitive functions	Hypoactivation	MRI studies show cerebellar enlargement in individuals with autism, while postmortem studies report lower Purkinje cell density. These anomalies are linked to motor deficits and impairments in cognitive functions such as learning, planning, and verbal abilities.[57-60]
Cerebellum – Vermis	Motor control, balance, and coordination	Hypoactivation	Reduced activation affecting motor coordination and balance. Reduced areas for neocerebellar vermis lobules VI and VII in children and adults with autism. Two subtypes identified: hypoplasia and hyperplasia.[61,62]
Cerebellum -	Plays a role in fine	Hypoactivation	Hypoplasia in some studies; meta-analysis confirms

Brain Part	Function of the Part	Status in ASD	Additional Information
Posterior Lobe - Vermian Lobules VI and VII	motor control and voluntary movements		reduction in size.[54]
Cerebellum - Hemispheres	Motor control and cognitive functions	Hyperactivation	Enlarged cerebellar gray and white matter volumes in children and young adults with autism.[62]
Limbic System - Amygdala	Involved in emotion processing, fear response, social behavior and memory; located in the temporal lobe	Hyperactivation	MRI studies show that the amygdala is enlarged in children with autism, particularly during early childhood, and is associated with social interaction and communication deficits. Postmortem studies indicate neuron loss over time, linking structural abnormalities to the severity of social and communicative impairments. Also more involved in facial perception networks in ASD, associated with anxiety. Increased activation linked to heightened anxiety and emotional responses. Enlarged amygdala volumes in adolescent and adult patients with autism, linked to emotional processing and social behavior deficits.[23,54,59-62]
Limbic System - Hippocampus	Critical for the formation of new memories and spatial navigation; located in the temporal lobe	Hyperactivation	The hippocampus is enlarged in autistic patients across all age groups, with significant increases in early childhood. This enlargement is associated with memory and learning difficulties, disruptive activity during repetitive behaviors, and challenges in processing and integrating new information.[58,59,61]
Temporal Cortex	Auditory processing, language comprehension, and social communication	Hypoactivation	Enlargement in early development observed via MRI. Postmortem studies show lower neuronal densities and smaller neuron sizes in specific layers of the fusiform gyrus, a region involved in face processing.[57]
Anterior Cingulate Cortex (ACC)	Error detection, emotional regulation, and cognitive control	Hypoactivation	Abnormalities include decreased cell size and density of GABAergic receptors. Functional imaging studies suggest abnormal activation and connectivity in the ACC in individuals with autism.[57]
Posterior Cranial Fossa	Balance, motor control, and coordination	Hypoactivation	Significant changes in GM volume in the cerebellum are observed from an early age in ASD patients, linked to motor deficits and cognitive impairments. These modifications are associated with developmental challenges in motor and cognitive functions.[58,59]
Anterior Cingulate Cortex (ACC)	Error detection, emotional regulation, and cognitive control	Hypoactivation	Functional and structural abnormalities in the ACC can lead to repeated abnormal behaviors in ASD. Hypoactivation of the ACC is associated with enhanced lack of social contact.[58]
Superior Temporal Sulcus (STS)	Processing of social stimuli and orientation to social cues	Hypoactivation	Deficits in the STS are linked to abnormalities in social and language processing, impacting social focus and communication in individuals with ASD.[58]
Salience Network	Detecting and filtering salient stimuli, switching between default mode and executive networks	Hyperactivation	Hyperactivation in the salience network is linked to difficulties in filtering relevant social cues and maintaining appropriate social responses, contributing to the characteristic social challenges in ASD.[60]
Default Mode Network (DMN)	Resting state network, self-referential thought processes	Hypoactivation	Reduced functional connectivity within the DMN is associated with impaired resting state neural activity and cognitive functions, affecting self-referential and social cognitive processes.[60]
Posterior Cranial Fossa	Balance, motor control, and coordination	Hypoactivation	Structural changes in the posterior cranial fossa are linked to motor and cognitive impairments from an early age. MRI studies indicate significant volume changes that affect overall brain function.[60]
Cingulate Gyrus - Right Anterior	Emotion regulation, executive function	Hypoactivation	Metabolically less active in autistic subjects.[54]
Corpus Callosum	Interhemispheric	Reduced size	Diminished interhemispheric connectivity linked to

Brain Part	Function of the Part	Status in ASD	Additional Information
	connectivity		cognitive impairments.[54]
Caudate Nucleus	Behavioral inhibition	Enlarged	Correlation with ritualistic and repetitive behaviors.[54]
Default Mode Network (DMN)	Resting state network, self-referential thought processes	Hypoactivation	Reduced functional connectivity in DMN, affecting resting state neural activity and cognitive functions.[55,56]
Auditory Network - Auditory Cortex	Auditory processing and perception	Hypoactivation	Decreased within-network connectivity observed in children with low verbal and cognitive performance.[56]
Frontoparietal Network	Executive functions, working memory, and attention control	Hypoactivation	Reduced within-network connectivity, impacting cognitive functions and attention in ASD patients.[56]
Cerebral cortex - Gray matter	Higher-order functions including perception, cognition, and motor control	Mixed	Increased volume in young children, decreased volume in some regions in older children and adults.[23]
Occipital lobe	Visual processing	Mixed	Volume changes are less documented.[23]
Subcortical regions - Caudate	Motor and cognitive functions	Mixed	Mixed volume changes, some areas show increase, others decrease.[23]
Fusiform gyrus	Face perception	Hypoactivation	Abnormal activation to faces, involved in social perception deficits.[23]
White matter - Radiate white matter, U-fibers	Connectivity and communication between brain regions	Mixed	Increased volume in young children, abnormalities in connectivity.[23]
Frontal Lobe	Higher-order cognitive functions and social behavior	Mixed	Abnormal growth patterns with early overgrowth in childhood followed by reduced activation, linked to social interaction and executive function deficits.[62]
Brainstem - Midbrain	Basic bodily functions	Mixed	Smaller midbrain areas reported in some studies, but findings are inconsistent.[62]
Basal Ganglia - Caudate	Motor control and cognitive functions	Hyperactivation	Enlarged caudate volumes linked to repetitive behaviors in autism.[62]
Corpus Callosum - Anterior sub-regions	Inter-hemispheric communication	Hypoactivation	Reduced anterior, middle, and posterior sub-regions, suggesting diminished inter-hemispheric connectivity.[62]
Parieto-Temporal - Lobes	Sensory processing and integration	Hyperactivation	Increased volumes of parieto-temporal lobes, linked to sensory processing abnormalities in autism.[62]
Frontal Lobe	Higher-order cognitive functions and social behavior	Mixed	Abnormal growth patterns with early overgrowth in childhood followed by reduced activation, linked to social interaction and executive function deficits.[62]
Superior Temporal Sulcus (STS) - Adjacent middle and superior temporal sulci	Processing invariant and changeable aspects of faces	Hypoactivation	Gray matter volume reduction is linked to social impairment severity.[32]
Fusiform Gyrus	Processing invariant aspects of faces	Hypoactivation	Decreased cortical thickness associated with social impairment severity.[25]
Inferior Frontal Gyrus (IFG)	Understanding and resonating with actions of others	Hypoactivation	Reduced cortical thickness correlated with social impairment severity.[25]
Ventromedial Prefrontal Cortex (vmPFC)	Processing emotional significance of social stimuli	Hypoactivation	Reduced connectivity with amygdala linked to social affective impairment.[29]

Brain Part	Function of the Part	Status in ASD	Additional Information
Dorsomedial Prefrontal Cortex (dmPFC)	Social cognition such as mentalizing	Hypoactivation	Reduced connectivity within default mode network.[63]
Inferior Occipital Gyrus (IOG)	Processing basic components of faces	Hypoactivation	Reduced functional connectivity with amygdala associated with symptom severity.[30]
Posterior Cingulate Cortex (PCC)/Precuneus	Social cognition such as mentalizing	Hypoactivation	Reduced connectivity within default mode network.[63]

opmental and neuroinflammatory processes contribute to the neuropathology of ASD.

In summary, the integration of findings from structural and functional MRI studies, postmortem research, and intervention studies provide a comprehensive understanding of the neurobiological underpinnings of ASD. These insights are crucial for developing effective diagnostic tools and targeted interventions to improve outcomes for individuals with ASD. By addressing the specific neural and cognitive deficits identified in this review, future research can inform clinical applications and support strategies that enhance the quality of life for those affected by ASD.

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