Beyond Symptoms: Integrating Neurobiological Insights into the Diagnosis of Autism Spectrum Disorder

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Abstract

Autism Spectrum Disorder (ASD) is characterized by persistent deficits in social communication and interaction, as well as restricted and repetitive behaviours (RRBs). ASD's heterogeneous nature often leads to overdiagnosis and hampers the development of treatments. This raises the question whether the current diagnostic approach, based on the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) criteria, is the most accurate and effective. Therefore, the aim is to explore a neurobiological perspective on diagnosing the core symptoms of ASD besides the currently used DSM-5.

The amygdala exhibits atypical activity that contributes to core social deficits, particularly through its impaired ability to enhance activity in the fusiform gyrus (FG). This dysfunction in amygdala-visual cortex connectivity leads to underactivation of the FG during social tasks. Two important neural circuits involved in social and emotional processing in ASD are the amygdala-medial prefrontal cortex (mPFC) circuit and the mirror neuron system (MNS). In addition to social deficits, RRBs in ASD are linked to abnormalities in the thalamus. Altered thalamocortical connectivity plays a critical role in sensorimotor processing abnormalities observed in ASD, contributing to RRBs. Further research shows that RRBs are also associated with disruptions in the connectivity between the striatum and the cerebral cortex, particularly within the limbic, frontostriatal, and motor circuits.

When diagnosing ASD, it is crucial to combine symptom-based criteria from the DSM-5 with neuroimaging techniques, rather than relying solely on either approach. This is of importance because it can enhance diagnostic accuracy, and provide a better understanding of ASD. While the DSM-5 provides a framework based on observable behaviours, neuroimaging techniques offers insights into brain activity and connectivity patterns, providing additional evidence for ASD's neurobiological basis. The diagnostic process for ASD should start with assessing core behavioural traits to distinguish it from other disorders. To enhance accuracy and minimize over- and misdiagnosis, neuroimaging can complement behavioural assessments by identifying atypical brain activity and connectivity patterns, aligning with the neurobiological underpinnings of ASD. By highlighting disrupted neurocircuits associated with ASD and shedding light on the diverse pathways contributing to its symptoms, neuroimaging helps capture ASD's heterogeneity. This dual-layered approach would offer a more personalized understanding of each individual's neurodevelopmental profile, thereby improving diagnosis, what can lead to more precise treatments and support for individuals with ASD.

Introduction

Autism Spectrum Disorder (ASD), commonly referred to as autism, is a complex neurodevelopmental condition that impacts brain development and function (Genovese & Butler, 2020). In 2022, the prevalence rates of ASD were estimated at 1 in 100 children globally (Zeidan et al., 2022). ASD is characterized by persistent deficits in social communication and interaction, accompanied by restricted and repetitive patterns of behaviour and interests (Ghamdi & AlMusailhi, 2024). Because of the neurodevelopmental origin of ASD, the hallmark symptoms often emerge within the first two years of life, although ASD can be diagnosed at any age (Zeidan et al., 2022). ASD is not a singular condition but a spectrum that includes several disorders such as autism, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS) (Ghamdi & AlMusailhi, 2024).

In addition to the core characteristics outlined in the Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5), ASD is frequently associated with additional features not included in its diagnostic criteria. These include atypical language development and motor abnormalities (Lai et al., 2014). Language development in individuals with ASD can be examined across two primary age groups: from birth to 6 years, and beyond 6 years of age. For children under 6 years, language development often demonstrates significant deviations, including delays in comprehension, as well as challenges with expressive phonology and grammar (Lai et al., 2014). In individuals older than 6 years, atypicalities persist, particularly in the areas of pragmatics, semantics, and morphology. However, syntax and articulation generally remain intact in this age group, indicating selective aspects of language function are preserved (Lai et al., 2014).

The two primarily tools currently used to diagnose ASD are the DSM-5 and the Modified Checklist for Autism in Toddlers (M-CHAT) (Grabrucker, 2021).

According to the DSM-5, a diagnosis of ASD requires a child to exhibit persistent difficulties in three key areas of social communication and interaction: (i) social-emotional reciprocity, (ii) the ability to form, comprehend, and sustain relationships, and (iii) nonverbal communication. Additionally, at least two of the following four behaviours must be observed: (i) resistance to changes in routine, (ii) restricted or intense interests that are unusual in focus or intensity, (iii) heightened or reduced sensitivity to sensory stimuli or an unusual preoccupation with sensory elements of the environment, and (iv) repetitive actions, speech patterns, or use of objects. These symptoms must result in significant functional impairment and cannot be better accounted for by other intellectual disabilities or developmental disorders.

The M-CHAT consists of 23 "yes/no" questions covering various developmental domains and is designed for children aged 16 to 30 months. This tool relies on parents' descriptions of their child's behaviours and abilities rather than direct observations by a professional. The M-CHAT includes a follow-up interview with parents to clarify responses and reduce the likelihood of false positives.

However, despite the utility of these diagnostic tools, challenges remain. ASD is a highly heterogeneous disorder as approximately 75% of individuals with ASD also experience comorbid psychiatric conditions such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, and bipolar disorder (Ghamdi & AlMusailhi, 2024). Diagnosing ASD for the first time in adulthood can be challenging for clinicians. One major difficulty arises from the overlap of ASD symptoms with those of other mental health conditions. Additionally, although ASD symptoms are present from childhood, they may not become evident until social expectations surpass the individual's abilities (Iversen & Kildahl, 2022). Consequently, individuals with milder symptoms or those with an average to high IQ may not meet diagnostic thresholds, especially if they have masked their difficulties or if symptoms only become apparent later in life.

Given that the heterogeneity of ASD is not adequately captured by the current diagnostic framework, thereby leading to difficulties facing the diagnosis of ASD, the question raises whether the current

diagnostic approach, based on DSM-5 criteria, is the most accurate and effective. Therefore, this essay explores a neurobiological perspective on diagnosing ASD besides the currently used DSM-5. In this essay, the neurobiology of the core symptoms of ASD, including social behaviour and the repetitive and/or restrictive behaviour, will be investigated. By examining the brain areas and neural circuits involved in ASD a more precise and comprehensive diagnostic framework may be achievable.

Brain areas involved in social behaviour

Amygdala and Fusiform Gyrus

Understanding the brain regions affected in ASD is crucial to determining whether these regions directly cause the symptoms observed. The amygdala, a key structure involved in emotional and social processing, shows atypical activity across multiple domains in individuals with ASD (Weston, 2019). However, it is essential to distinguish amygdala dysfunction specifically linked to ASD from that seen in other conditions. To make this distinction, researchers often focus on how amygdala activity relates to the core social deficits characteristic of ASD.

One notable feature of ASD is a diminished interest in other people, including close family members, a phenomenon called visuosocial atypicality (Weston, 2019). On a neural level, this reduced interest may be linked to a failure of the amygdala to effectively enhance activity in the visual cortex, including the fusiform gyrus (FG) region. The visual cortex, which receives strong excitatory projections from the amygdala, is thought to play a critical role in processing facial expressions and other socially significant stimuli (Weston, 2019). While the FG in individuals with ASD is often underactive compared to typically developing (TD) individuals during social tasks, it is capable of functioning at typical levels when stimulated by appropriate inputs. This suggests the FG itself is structurally intact but its activity is not adequately modulated by the amygdala, which is impaired and shows reduced connectivity with the FG in ASD. This dysfunction in amygdala-visual cortex interaction likely underlies the diminished interest in social stimuli observed in ASD (Weston, 2019).

Pierce et al. further demonstrated how amygdala dysfunction manifests differently depending on the familiarity of social stimuli (Pierce, 2004). In their study, individuals with ASD and TD individuals were shown familiar and unfamiliar faces. While unfamiliar faces elicited reduced amygdala activation in individuals with ASD compared to TD individuals, familiar faces evoked similar levels of activation in both groups (Pierce, 2004). This suggests a nuanced deficit in the amygdala's response to novel social stimuli.

In another task, individuals with ASD and a control group had to make judgements about the gender or expression of the person shown (Meisner et al., 2022). In line with the previous result, individuals with ASD performed the task less accurately and also showed a reduced activation of the amygdala compared to TD individuals. The reduced activation of the amygdala contributes to the deficits in social cognition in individuals with ASD, demonstrating that the amygdala plays an important role (Meisner et al., 2022). This is to be expected, as the amygdala is involved in various behavioural processes and shares connections to various cortical and subcortical regions.

Neuro-circuits involved in social behaviour

While much research has focused on individual brain areas, such as the amygdala, studying isolated regions alone provides only a partial view. Complex behaviours, especially those related to social interactions, are rarely the product of a single brain region. Instead, they emerge from the dynamic interplay of multiple interconnected regions functioning as neural circuits. Investigating the functionality of neuro-circuits in ASD provides insight into how disruptions in neural networks might underlie these challenges.

The following sections will delve into two key circuits implicated in social and emotional processing in ASD: the amygdala-medial prefrontal cortex (amygdala-mPFC) circuit, which is central to emotion recognition and regulation, and the Mirror Neuron System (MNS), which is critical for imitation.

The Amygdala-Medial Prefrontal Cortex (Amygdala-mPFC) Circuit

Emotional stimuli engage a wide network of brain regions, including the amygdala, dorsomedial prefrontal cortex (dmPFC), and ventromedial prefrontal cortex (vmPFC) (Sun et al., 2023). As previously noted, the amygdala plays a crucial role in identifying facial emotions. The dmPFC, which encompasses areas like the dorsal anterior cingulate cortex (dACC) and pre-supplementary motor area (pre-SMA), is involved in various cognitive control functions such as detecting errors, learning, and regulating emotions. The vmPFC, on the other hand, is integral to emotional processing and social cognition, playing roles in value assessment and emotion regulation (Sun et al., 2023).

There is increasing evidence highlighting the importance of the functional connectivity between the PFC and the amygdala in processing facial emotions in humans. This connectivity forms a crucial circuit for interpreting and resolving emotional ambiguity (Sun et al., 2023). The amygdala is responsible for encoding and representing emotional content, sending signals to the PFC. The dmPFC is mainly involved in cognitive processes, while the vmPFC plays a larger role in affective processing. Specifically, the vmPFC regulates autonomic and internal emotional responses, whereas the dmPFC is involved in selecting actions and motor behaviour (Sun et al., 2023).

In individuals with ASD, research has found abnormal functional and structural connectivity between the amygdala and PFC. In children with ASD, reduced habituation to repeated facial stimuli is associated with altered connectivity between these brain areas. Additionally, individuals with ASD show diminished amygdala-PFC connectivity during both emotional face processing and resting states, along with structural abnormalities in these connections (Sun et al., 2023). The amygdala typically organizes cognitive responses to social stimuli but relies on the PFC for contextual input. When this input is disrupted, the amygdala may misinterpret social cues, which could contribute to the social challenges seen in ASD. Deficits in amygdala-PFC connectivity may, therefore, affect not just the processing of facial emotions, but other important social cues as well (Sun et al., 2023).

Mirror Neuron System (MNS)

Another key neuro-circuit involved in social behaviour is the MNS, which plays a vital role in the ability to imitate. Imitation is the process by which individuals observe and replicate the actions of others, a skill that is crucial for early socialization and cognitive development (Chan & Han, 2020). The MNS is a network of interconnected brain regions responsible for processing both the perception and execution of biological movements. Key regions involved in the MNS include the premotor cortex, inferior frontal gyrus, and inferior parietal lobule (Chan & Han, 2020). Studies have demonstrated that the organization of the MNS is task-specific. For instance, during the imitation of facial expressions, regions associated with face processing, such as the fusiform face area, as well as areas related to visual attention (e.g., the inferior occipital gyrus), and subcortical structures involved in emotional processing, such as the amygdala, show coactivation with MNS regions (Chan & Han, 2020).

However, some fMRI studies on MNS yield mixed results. For instance, a study by Perkins et al., using non-social stimuli observed greater activation in the right dorsal premotor cortex in ASD compared to TD individuals (Perkins et al., 2015), while the study of Pokorny et al., found no significant differences in MNS activation (Pokorny et al., 2015). Additionally, research using social-emotional stimuli, such as happy and fearful faces, also reported varied findings: the study of Kim et al., noted reduced activation in the right inferior frontal gyrus and amygdala (Kim et al., 2015), while the study of Sato et al., observed bilateral reductions (Sato et al., 2012).

These inconsistencies raise questions about whether the MNS is genuinely impaired in ASD. Chan et al., performed a meta-analysis to investigate this. The meta-analysis revealed that ASD individuals exhibit significant hyperactivation in the right inferior frontal gyrus when observing emotional stimuli compared to TD individuals. The right inferior frontal gyrus plays a critical role in social-emotional perception, with its connectivity to the limbic system influencing emotional regulation. Its dysfunction may be linked to impaired social-emotional processing, as seen in individuals with ASD.

Brain areas involved in repetitive behaviour

Thalamus

Another prominent characteristic of ASD is the presence of repetitive and/or restrictive behaviours (RRBs). To better understand the brain regions involved in these behavioural symptoms, researchers have employed magnetic resonance imaging (MRI) to investigate the neural mechanisms underlying RRBs in ASD. One brain region that has been identified as playing a significant role in these behaviours is the thalamus. Traditionally recognized as a central hub for relaying sensory information to the cortex, the thalamus also modulates motor signals (Ayub et al., 2021). It achieves this by exerting fine-tuned inhibitory control over both cortico-cortical and subcortical-cortical signalling pathways. This inhibitory function of the thalamus in motor processing, along with evidence of cortical disinhibition in individuals with ASD, suggests that thalamic connectivity may differ in those with the condition (Ayub et al., 2021).

Research conducted by Green et al., highlighted that in individuals with ASD, there is a disruption in the connectivity between the thalamus and certain cortical regions, including the bilateral pre- and post-central gyrus and the left superior parietal lobule (Green et al., 2017). This finding has been further corroborated by Ayub et al., who discovered atypical thalamocortical connectivity to sensorimotor regions in ASD (Ayub et al., 2021). These findings support the idea that altered thalamocortical connectivity plays a crucial role in the sensorimotor processing abnormalities seen in ASD, which are thought to contribute to the manifestation of RRBs.

This evidence reinforces the concept that disruptions in the thalamus' ability to modulate motor and sensory signals may underlie some of the core features of ASD, particularly in the context of repetitive and restrictive behaviours.

Neuro-circuits involved in repetitive/restrictive behaviour

To better understand the neural mechanisms underlying RRBs in individuals with ASD, it is important to examine the neural circuits involved. These behaviours have been strongly associated with dysfunctions in several interconnected brain regions, particularly those within the basal ganglia and cortical areas. A key neural pathway involved in RRBs is the cortico-striato-thalamo-cortical (CSTS) circuit, which connects the striatum, thalamus, and various cortical regions. Disruptions within this circuit, along with other associated neural pathways, are thought to play a significant role in the manifestation of these behaviours in ASD.

Cortico-striato-thalamo-cortical (CSTS) Circuit

RRBs have been strongly linked to the basal ganglia, particularly the striatum, as well as cortical regions spanning the frontal, temporal, and parietal lobes. The basal ganglia interacts with cortical areas through parallel circuits, which are organized to support limbic, cognitive, and motor functions. These circuits follow specific cortico-striato-thalamo-cortical pathways and involve additional structures such as the subthalamic nucleus and substantia nigra (Abbott et al., 2018).

The substantia nigra, critical for learned behaviours, has varying levels of connectivity with corticostriatal circuits. For example, the ventral striatum exhibits strong output (efferent) connectivity but weaker input (afferent) connectivity from the substantia nigra. In contrast, the dorsal striatum has strong input connections but weaker output, while the central striatum has moderate connectivity in both directions (Abbott et al., 2018). This feedforward path within the striato-nigro-striatal pathways suggests a hierarchy where limbic processing influences cognitive functions in the frontoparietal regions, which subsequently guide motor actions. This hierarchy is particularly important for learning and habit formation. The RRBs seen in ASD may arise from dysfunctions within specific subcortical-cortical circuits or from inefficient communication between striatal circuits (Abbott et al., 2018).

Research showed that the RRBs are associated with the disrupted connectivity between the striatum and cerebral cortex. Notably, the connections can be identified to three particular neural circuits; the limbic circuit, the frontostriatal circuit and the motor circuit. In the study of Abbott et al., an overconnectivity was found in the limbic corticostriatal circuit in younger children. This overconnectivity indicates a delay in typical developmental processes. Thereby adding, individuals who exhibited more pronounced RRBs showed a reduced connectivity ratio between frontal and motor circuits, relative to limbic circuits (Abbott et al., 2018). This finding suggests that an imbalance among these circuits, rather than the isolated functioning of any single circuit, plays a role in the neural mechanisms underlying RRBs and restricted interests.

Taking everything together, by focusing on the neuro-circuits involved (such as the amygdala-mPFC, MNS, and CSTS) rather than just isolated brain areas (like the amygdala, fusiform gyrus, and thalamus), researchers can gain a deeper understanding of how disruptions in connectivity, communication, and integration within these circuits contribute to the symptoms of ASD. Adopting this systems-level approach allows for a more comprehensive diagnosis of ASD, incorporating both behavioural symptoms and the underlying neurobiological factors.

Discussion

The aim of this essay focused on a neurobiological perspective on diagnosing the core symptoms of ASD besides the currently used DSM-5. ASD is characterized by persistent deficits in social communication and interaction, accompanied by restricted and repetitive patterns of behaviour and interests (Ghamdi & AlMusailhi, 2024). ASD is an umbrella-term for several disorders such as autism, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS) (Ghamdi & AlMusailhi, 2024). Due to the heterogeneity of ASD, over- and misdiagnosis is common. Therefore, not only the symptoms should be taken into account when diagnosing, but also the neurobiology of ASD.

In individuals with ASD, the amygdala shows atypical activity that is closely tied to core social deficits. Specifically, the amygdala's impaired ability to enhance activity in the visual cortex, including the fusiform gyrus (FG), contributes to reduced interest in social stimuli (Weston, 2019). While the FG is structurally intact and capable of normal functioning, its underactivation during social tasks suggests inadequate modulation by the amygdala. This dysfunction in amygdala-visual cortex connectivity is thought to underlie diminished interest in others, a hallmark of ASD (Weston, 2019).

The two key circuits in social and emotional processing in ASD included the amygdala-medial prefrontal cortex (mPFC) circuit and the mirror neuron system (MNS). The amygdala-mPFC circuit integrates emotional and cognitive processes, involving the amygdala, dorsomedial prefrontal cortex (dmPFC), and ventromedial prefrontal cortex (vmPFC)(Sun et al., 2023). Reduced functional and structural connectivity is observed during emotional face processing and even at rest. These disruptions likely impair the amygdala's ability to organize social responses based on contextual cues provided by the PFC, contributing to difficulties in interpreting facial emotions and other social signals. Altered connectivity could extend to other social deficits, as seen in reduced habituation to facial stimuli and diminished sensitivity to emotional intensity in ASD individuals(Sun et al., 2023).

In ASD, the MNS plays a key role in imitation, involving regions such as the premotor cortex, inferior frontal gyrus, and inferior parietal lobule (Chan & Han, 2020). Meta-analyses have shown that individuals with ASD exhibit significant hyperactivation in the right inferior frontal gyrus during emotional tasks, suggesting dysfunction in this core MNS component, which may contribute to impairments in social-emotional processing. Altered MNS connectivity in ASD could disrupt its links to the limbic system, affecting emotional perception and regulation (Chan & Han, 2020).

The brain areas involved in repetitive and/or restrictive behaviours (RRBs) included the thalamus which is traditionally considered a hub for relaying sensory information to cortical circuits (Ayub et al., 2021). Research highlighted that in individuals with ASD, there is a disruption in the connectivity between the thalamus and certain cortical regions, including the bilateral pre- and post-central gyrus and the left superior parietal lobule. These findings support the idea that altered thalamocortical connectivity plays a crucial role in the sensorimotor processing abnormalities seen in ASD, which are thought to contribute to the manifestation of RRBs (Ayub et al., 2021; Green et al., 2017).

Adding to this, research has linked RRBs in ASD to disruptions in the connectivity between the striatum and cerebral cortex, particularly within three neural circuits: the limbic, frontostriatal, and motor circuits (Abbott et al., 2018). In ASD, overconnectivity in the limbic corticostriatal circuit, especially in younger children, may reflect a delay in typical development. Additionally, individuals with more pronounced RRBs show an imbalance between the frontal/motor circuits and the limbic circuit, suggesting that dysfunctions in the communication and integration of these circuits contribute to the symptoms (Abbott et al., 2018).

By integrating the neurobiology into the diagnosis of ASD, clinicians need to make use of functional imaging as it has the potential to connect genetic, environmental, and behavioural factors in ASD. While functional imaging methods like functional magnetic resonance imaging (fMRI) have significantly advanced our understanding of mental health disorders, they also come with several

limitations. One key limitation is that fMRI measures brain activity indirectly through changes in blood oxygen levels, rather than directly measuring neuronal activity (Hashem et al., 2020). This can result in false-positive or false-negative signals, especially in individuals with rapidly changing behaviours, such as those seen in ASD. Another limitation with fMRI is that it can show which brain regions are involved in specific cognitive functions, but it cannot determine whether these regions are causing the functions or are simply a consequence of them (Hashem et al., 2020). However, integrating data and increasing the number of subjects can enhance the feasibility of fMRI in ASD research.

When integrating neurobiology into the diagnostic process for ASD, it is essential to recognize that relying solely on functional neuroimaging techniques, such as fMRI, may not provide a complete or definitive diagnosis. While neuroimaging offers valuable insights into brain activity and connectivity patterns associated with ASD, it should not be the sole determinant in diagnosing the disorder. The DSM-5 provides a clinically validated framework based on observable symptoms, which remains crucial in identifying ASD. The DSM-5 serves as the standardized framework used by clinicians, researchers, and public health professionals (Regier et al., 2013). The DSM-5 is considered clinically validated because it has been developed and refined through extensive research, expert consensus, and clinical studies to reliably identify and classify mental health and neurodevelopmental disorders. Its framework is based on decades of data from clinical observations, epidemiological studies, and diagnostic reliability trials, which ensure that the criteria are consistent, measurable, and applicable across diverse populations (Regier et al., 2013). Due to these reasons, it is premature to propose discarding the DSM-5 criteria entirely. A more effective and comprehensive approach to diagnosis would involve a dual-layered methodology that combines the symptom-based criteria from the DSM-5 with the insights gained from neuroimaging techniques. The first step in this approach is to evaluate the individual based on the core behavioural characteristics of ASD, such as deficits in social communication and interaction, and the presence of restricted and repetitive behaviours (RRBs). These symptoms form the foundation for distinguishing ASD from other developmental or psychiatric disorders.

However, to ensure diagnostic accuracy and reduce the risk of over- and misdiagnosis, it is important to complement the behavioural assessment with neuroimaging. Advanced neuroimaging techniques can provide further evidence supporting the diagnosis by highlighting atypical brain activity and connectivity patterns that are characteristic of ASD. By analysing the functional connectivity and structural anomalies in specific neural circuits, such as the amygdala-mPFC circuit or the MNS, neuroimaging may offer additional confirmation that the observed symptoms align with the neurobiological underpinnings of ASD.

In conclusion, integrating behavioural criteria with neuroimaging data offers the potential to enhance diagnostic precision while addressing the challenges posed by the heterogeneity of ASD. Neuroimaging provides insights into the disrupted neurocircuits that underlie core ASD symptoms. By identifying specific neural connectivity patterns associated with social deficits and repetitive behaviours, this approach addresses gaps in the DSM-5, which does not account for the neurobiological diversity within ASD. Understanding these circuits helps differentiate ASD from other psychiatric or developmental disorders, reducing overdiagnosis and misdiagnosis, particularly in cases with overlapping symptoms. Furthermore, neuroimaging sheds light on the diverse pathways contributing to ASD symptomatology, offering a framework to capture its heterogeneity more effectively. Ultimately, combining behavioural assessments with neurobiological data fosters a more accurate and individualized diagnostic process and provides a foundation for future research into tailored interventions.

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