



Review Article

Predictors of functional ability in autism spectrum disorder: A scoping review

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INTRODUCTION

Autism spectrum disorder (ASD) encompasses a group of diverse neurodevelopmental conditions characterized by deficits in social communication and interaction, as well as restricted and repetitive patterns of behaviors, interests, or activities. ASD remains a significant national and global health concern [1,2]. In 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5), updated the diagnostic criteria for ASD from its previous edition (DSM-4). The DSM-5 introduced the concept of a “spectrum” for ASD diagnosis, consolidating the separate pervasive developmental disorder (PDD) diagnoses from DSM-4 (autistic disorder, Asperger’s disorder, childhood disintegrative disorder, and PDD not otherwise specified) into a single diagnosis category [3]. In clinical practice, physicians employ rating tools such as the childhood autism rating scale (CARS) and the autism diagnostic observation schedule (ADOS) to assist in diagnosis. A study involving 78 children (2–10 years old)

ABSTRACT

Autism spectrum disorder (ASD) is a group of diverse neurodevelopmental conditions characterized by deficits in social communication and interaction, as well as confined and repetitive patterns of behaviors, interests, or activities. Currently, there are no standardized techniques for predicting functional ability in children with ASD, which can lead to undetected clinical impairments and delayed targeted treatments. To address this issue, a scoping review was conducted following the preferred reporting items for systematic reviews and meta-analyses criteria. Twelve articles met the inclusion criteria for this review. This study summarized the potential tools and parameters that may benefit in predicting abilities used in the daily lives of children with ASD. The collected tools varied widely, including clinical questionnaires, physical symptoms, laboratory tests, and imaging studies. These tools provided descriptions of various functional abilities that are altered in ASD, offering insights into the diverse manifestations of the disorder and potential approaches for assessment and intervention.

KEYWORDS: *Autism spectrum disorder, Functional ability, High-functioning autism, Low-functioning autism, Predictors*

demonstrated high agreement between CARS and ADOS in diagnosing autism [4]. These findings were further corroborated by a larger study of 237 children with autism using an updated version, the CARS-2 and ADOS-2 [5].

While all individuals with ASD meet the core diagnostic criteria, their functional estimates remain highly variable [6,7]. The term “High-functioning autism” (HFA) is often used to describe individuals diagnosed with ASD who have an intelligence quotient (IQ) of 70 or above. This term first appeared in the 1980s, specifically referring to individuals without moderate-to-severe intellectual disability (ID) or with IQ above 70. Conversely, “low-functioning autism” (LFA)

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typically refers to individuals with an IQ below 70) [8]. Individuals with high-functioning ASD have been observed to be more aware of their communication difficulties and often have low self-perceived social competence. This self-awareness may contribute to the development of depressive and anxious symptoms [9]. On the other hand, LFA represents the more severe end of the autism spectrum. Children diagnosed with this type of autism often require substantial assistance to perform daily tasks due to significant challenges in communication and behavior management [10,11].

Cognitive skills are closely linked to adaptive functioning, which is a critical area of assessment for individuals with ASD [6]. Research underscores the importance of cognitive abilities in predicting adaptive outcomes, as demonstrated by a study of 77 preschool-aged children with ASD using the Vineland Adaptive Behavior Scales (VABS), second edition (Vineland-II), which found that age and nonverbal ability were more significant predictors of adaptive functioning than ASD symptom severity in young children [12]. Similarly, another study involving 99 preschool-aged children with ASD (mean age 50.5 months) identified cognitive ability and socioeconomic status (SES) as significant contributors to both domain-specific and global adaptive functioning, with cognitive ability emerging as the strongest predictor [13]. This highlights the value of early cognitive assessments and targeted interventions to enhance adaptive outcomes in children with ASD. Furthermore, higher SES was associated with better adaptive functioning, emphasizing the need for support strategies tailored to families across diverse socioeconomic backgrounds [6].

Building on these findings, neuroimaging research has provided further insight into the neural mechanisms underlying cognitive and adaptive challenges in ASD. A meta-analysis of 33 functional magnetic resonance imaging (fMRI) studies focusing on inhibition, updating, and switching in individuals with HFA revealed that the executive function (EF) construct in ASD may be unitary (common EF) in children and adolescents, while in adults with ASD, EF structure appears both integrated and heterogeneous, encompassing common EF and specific inhibition processes [14]. Abnormalities in EF were found across development in individuals with ASD compared to typically developing (TD) individuals. Extensive structural and functional imaging investigations have linked ASD to brain abnormalities, particularly in the prefrontal cortex (PFC), with fMRI studies showing abnormal activation in the PFC and parietal regions during various EF tasks [14]. To further assess these cognitive processes, a novel test called the linguistic evaluation of prefrontal synthesis (LEPS) was developed to assess prefrontal synthesis, which, combining mental objects in novel ways, is indeed essential for complex language comprehension and imagination. It enables humans to understand and generate complex linguistic structures and to imagine novel scenarios, which are crucial abilities for advanced cognition and communication. The study found LEPS was 90% accurate in predicting high-functioning versus low-functioning class assignments in individuals with impairments, underscoring its potential utility for advanced cognitive and communication assessment [15].

Despite these advances, research on predicting HFA versus LFA has yielded inconsistent results, highlighting the complexity of this classification. Consequently, assessing adaptive functioning is a crucial component of the diagnostic process for individuals suspected of having ASD, as it provides essential information about the level of functional and familial support required. This study aims to investigate and elucidate the factors influencing adaptive functioning and broader functional abilities in ASD. Furthermore, it includes studies that compare individuals with ASD to TD groups when such comparisons provide relevant insights into functional outcomes. Ultimately, the goal is to inform the development of more effective strategies for early detection and intervention.

METHODS

Eligibility criteria

This scoping review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [16], with the research protocol registered in the international platform of registered systematic review and meta-analysis protocols (INPLASY) (No. INPLASY2024120045). This review synthesizes studies investigating factors influencing functional ability in both high-functioning and low-functioning ASD. The review integrated findings from research employing a variety of assessment methods, including symptomatology evaluations, standardized questionnaires, laboratory tests, and imaging studies. The scope of implementation spanned all healthcare settings, including in-home care, hospitals, and community care, across diverse geographical locations.

In defining the study population, pediatrics generally refers to the prenatal, neonatal, child, and adolescent populations (0–18 years of age), but in some cases, it may also encompass young adults, as the age range distinguishing young adults from pediatric populations can vary across countries. To accommodate these cultural and healthcare system differences, this review included studies with mixed samples of pediatric and young adult participants, as well as those focused solely on young adults, provided the findings were relevant to the functional abilities of individuals with ASD.

A key aspect of the inclusion criteria was the population focus, ensuring that studies comparing individuals with ASD to TD controls were included only if they offered insights into predictors or correlates of functional ability within the ASD group; comparative studies that did not contribute to understanding functional outcomes in ASD were excluded to maintain the review's focus and coherence.

The scoping review encompassed a broad range of research methodologies, including quantitative, qualitative, and mixed-methods designs, but, due to resource constraints, was limited to studies published in English, as translation of non-English literature was not feasible. In addition, to ensure comprehensive and detailed findings, publications lacking full reports, such as conference abstracts, were excluded from the analysis.

Data sources and search strategy

A preliminary search was conducted in PubMed, Scopus, and Google Scholar to identify relevant articles on the topic. The text words contained in the titles and abstracts of pertinent articles, along with the index terms used to describe these articles, were utilized to develop a comprehensive search strategy. The search was conducted from June 24, 2024, to June 29, 2024, and was restricted to English-language publications from the past 10 years. To identify relevant gray literature, Google Scholar searches were performed in addition to manually searching pertinent articles. The keywords for this study were the following: (“Autism Spectrum Disorder” OR “ASD” OR “Autism” OR “Autistic” AND “High” OR “HFA”, AND “Low,” “LFA” AND “Functional Ability” OR “Function” OR “Prediction”, OR “Indicator”).

Study literature

After the search, all identified records were compiled and uploaded to Rayyan. ai, with duplicates removed. Following a pilot test, two independent reviewers screened titles and abstracts against the inclusion criteria. The full texts of selected citations were then thoroughly examined by two independent reviewers to ensure compliance with the inclusion criteria. Reasons for excluding full-text papers that did not meet the criteria were documented and reported in the scoping review. Any disagreements between reviewers at each stage of the selection process were resolved through consultation with a third reviewer.

Data extraction

Data were extracted from the selected papers by two independent reviewers using a custom-designed data extraction tool. The extracted information included, at minimum, the number of participants, age range, demographic of study, research design, and ASD characteristics. The data extraction tool was iteratively refined as needed during the review process to ensure comprehensive data capture from each included paper.

RESULTS

Study selection

Following the PRISMA guidelines, the article inclusion process is depicted in Figure 1. Initially, 3895 articles were identified across five databases, including 3052 from PubMed, 808 from Scopus, and 35 from Google Scholar. After removing duplicates, 3565 articles underwent screening, resulting in the exclusion of 3476 records based on titles and abstracts. This left 89 articles for full-text retrieval; however, three articles were unavailable, reducing the number to 86. On full-text review, 74 articles were excluded due to reasons such as inappropriate study design, irrelevant outcomes, or failure to meet target population criteria. Ultimately, 12 articles met all inclusion criteria and were included in the study, encompassing a total of 4087 children and adolescents aged 1–30 years, of whom 3349 had ASD and 838 were TD.

Risk of bias

In this systematic review, the quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort and case–control studies, with a modified version of

the NOS applied to evaluate the cross-sectional studies [17]. The assessment was tailored to the design of each study. The review included 7 cross-sectional studies, 3 case–control studies, and 1 prospective cohort study. Overall, 60% of the studies were classified as very good quality [Tables 1 and 2].

DISCUSSION

This scoping review integrates a broad spectrum of multidimensional data (ranging from behavioral and cognitive profiles to neuroimaging and biochemical markers) to deepen our understanding of functional connectivity (FC) differences across the autism spectrum, particularly distinguishing HFA, LFA, and TD individuals. The findings underscore the complexity and heterogeneity inherent in ASD and highlight the importance of comprehensive, multidimensional assessment approaches.

The ability of functional capacity to differentiate ASD subtypes is substantiated by diverse data sources, including:

- Nominal data: Behavioral patterns, cognitive profiles, and severity complexity [6,18,19]
- Observational data: Gait patterns, EF, and prosodic skills [20,21]
- Laboratory data: Salivary and urinary cortisol, glutathione S-transferase (GST) gene polymorphisms, and serum zonulin [22-24]
- Neuroimaging data: Resting-state fMRI (Rs-fMRI) revealing FC and regional homogeneity (ReHo) differences [25-28].

While many studies focus on the relationship between key parameters and symptom severity rather than directly measuring functional adaptation and ability, it is important to recognize that symptom severity is often positively correlated with and predictive of poorer functional outcomes. Nevertheless, these indirect associations highlight the need for further research that explicitly connects symptom measures with adaptive functioning to strengthen the evidence base. Together, these multidimensional data streams provide a robust framework for differentiating ASD subtypes and tailoring individualized diagnostic and intervention strategies.

Behavioral and cognitive profiles: complexity beyond intelligence quotient

The nominal data encompassing behavioral patterns, cognitive profiles, and severity complexity reinforce the inherently heterogeneous and spectrum nature of ASD [6,18,19]. Consistent with prior research, cognitive ability emerges as a pivotal predictor of adaptive functioning; however, IQ alone proves to be a weak predictor when controlling for sex and other factors [19,21]. This is evidenced by the persistent and substantial discrepancy observed between IQ and adaptive behavior scores across all age groups at diagnosis [29]. Such findings emphasize the necessity of comprehensive assessments that integrate adaptive functioning alongside cognitive evaluations to better capture real-world capabilities and support needs. This multidimensional approach reflects the nuanced interplay between intellectual ability and daily living skills, moving beyond the limitations of IQ as a sole indicator.

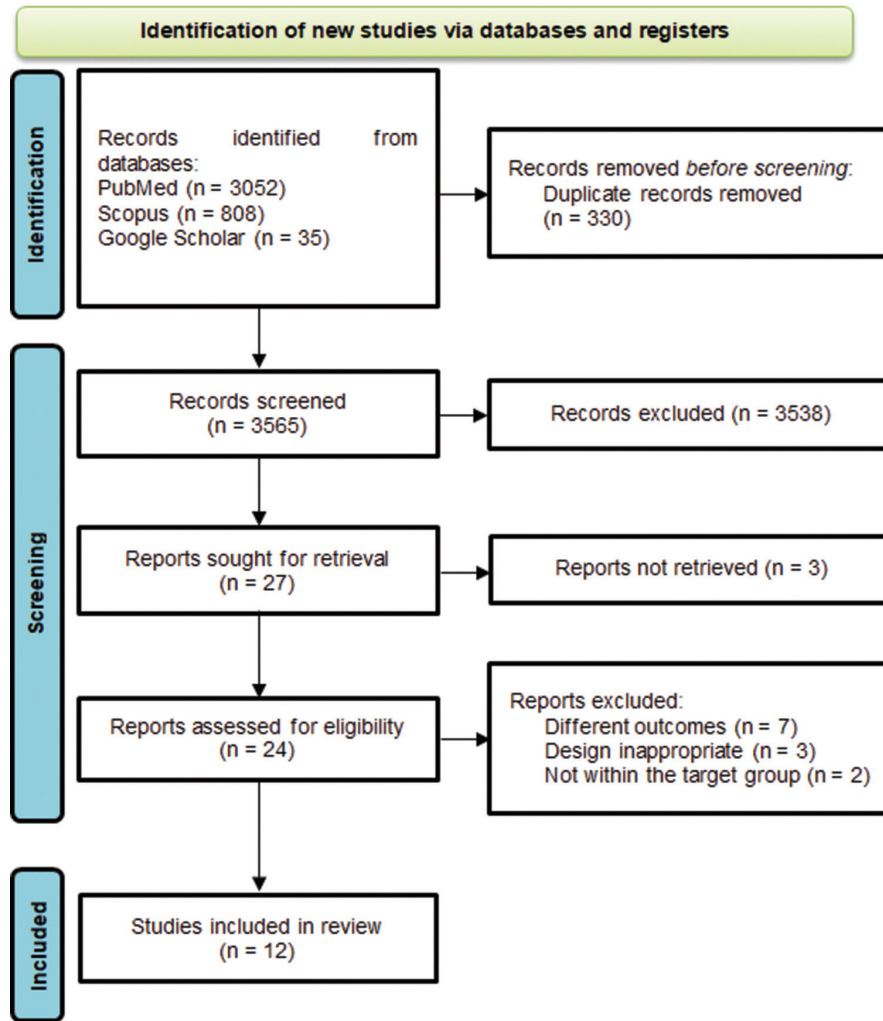


Figure 1: The preferred reporting items for systematic reviews and meta-analyses flow diagram describing selecting study process

Table 1: Critical appraisal summary based on Newcastle-Ottawa Scale

Author	Study design	NOS			Total	Quality
		Selection	Comparability	Outcome		
Hill (2015) [18]	Cross-sectional	****	**	**	8/9	Very good
Alvares (2020) [19]	Cross-sectional	***	**	**	7/9	Good
Casula (2024) [6]	Prospective cohort	***	**	***	8/9	Very good
Gong (2020) [20]	Cross-sectional	****	**	***	9/9	Very good
Filipe (2018) [21]	Case-control	***	**	**	7/9	Good
Tordjaman (2014) [22]	Case-control	***	**	***	8/9	Very good
Mandic-Maravic (2021) [23]	Cross-sectional	****	*	***	8/9	Very good
Kara (2021) [24]	Case-control	****	**	**	8/9	Very good
Reiter (2019) [25]	Cross-sectional	**	**	***	7/9	Good
Li (2020) [26]	Cross-sectional	**	**	***	7/9	Good
Chen (2021) [27]	Cross-sectional	****	**	**	8/9	Very good
Zhao (2022) [28]	Cross-sectional	***	**	**	7/9	Good

*Newcastle-Ottawa scale, item adequacy of monitoring does not score; Zero star the item is not registered in the article; Very good studies: 8–9 points; Good studies: 6–7 points; Satisfactory Studies: 4–5 points; Unsatisfactory Studies: 0–3 points [17]. NOS: Newcastle-Ottawa Scale

Supporting this complexity, epidemiological data reveal that among children with ASD, approximately 44% possess average intellectual ability, 24% have borderline IQ, and 32% meet criteria for ID [30]. This distribution underscores the spectrum’s diversity and the inadequacy of relying solely on IQ to predict

functional outcomes. Many individuals with ASD demonstrate significant discrepancies between intellectual ability and adaptive functioning, highlighting the importance of evaluating executive functioning, socio-environmental factors, and adaptive skills to guide personalized interventions effectively.

Table 2: Literature matrix of accepted articles

References	Sample size and age	Demographic characteristics	ASD characteristics	Parameters	Description (methodological)	Clinical result
Nominal data						
Hill <i>et al.</i> [18]	220 children and adolescents aged 4–16 years	193 males, 27 females (21.8% African American, 69.1% Caucasian, 3.6% Hispanic, 4.1% Biracial, and 1.4% other)	DSM-4-TR (96 autistic disorder, 86 PDD-NOS, 31 Asperger's Disorder), DSM-5 (7 ASD)	IQ (Leiter-R, WNV, WPPSI-III, WISC-IV, WASI), ADI-R, ADOS-2, ABAS-II	This study used hierarchical regression analyses to examine how age, IQ, and the severity of autism symptoms affect daily living skills in ASD. It focused on whether age and IQ together change how autism symptoms impact these daily skills	The three-way interaction between age, intellectual functioning, and ASD symptom severity was a significant predictor of adaptive functioning, highlighting the need for individualized interventions to enhance outcomes in children and adolescents with ASD
Alvares <i>et al.</i> [19]	2225 children aged 1–18 years	1818 males, 403 females (85.0% Caucasian, 10.9% Asian, 1.6% Aboriginal, 2.5% other)	DSM-4 (1662 Autistic disorder, 299 PDD-NOS), DSM-5 (216 ASD)	IQ or DQ (BSID, SBIS, MSEL, WPPSI, WISC-IV, GMDS, Leiter-3), VABS	This study evaluated whether IQ scores at ASD diagnosis reliably predict adaptive functioning, focusing on differentiating children with and without ID. Standardized diagnostic data were analyzed using ANOVA, regression, and discrepancy comparisons across age and ID groups	IQ alone does not adequately reflect adaptive functioning in individuals with HFA, especially those without ID. The study recommends comprehensive assessments that include adaptive skills, as relying solely on IQ may misrepresent the functional abilities of children with ASD
Casula <i>et al.</i> [6]	95 preschool children aged 3–4 years	79 males, 16 females (100% Italian Caucasian)	DSM-5 (95 ASD)	ADOS-2, GDQ from GMDS-ER, ABAS-II	This study employed a longitudinal design at two time points one year apart. Its primary objective was to identify predictors of adaptive functioning by examining ASD core symptoms, cognitive abilities, and sociodemographic factors	Higher initial severity of repetitive and restricted behaviors and lower cognitive abilities predicted poorer adaptive functioning after 1 year in preschoolers with ASD, emphasizing the need for early, targeted interventions to improve adaptive skills and quality of life
Observational data						
Gong <i>et al.</i> [20]	86 children aged 4–6 years	58 ASD (52 males, 6 females), 28 TD (26 males, 2 females)	DSM-5 + AQ-C + SRS (12 LFA, 46 HFA, with FIQ cut-off 80), RCPM + GMDS + PPVT	Gait patterns	This study quantitatively assessed foot-ground interaction during straight walking in children with ASD using plantar pressure analysis and investigated its association with ASD symptom severity. Barefoot walking trials over a 6-m pressure mat were analyzed for various gait variables using ANOVA and partial correlations controlling for IQ	Most gait abnormalities in children with ASD are closely related to the severity of their autistic symptoms, especially social impairments. Plantar pressure measurements show that children with ASD have a flatter-footed gait, more asymmetry, and greater step variability than controls, emphasizing the importance of motor assessment in clinical evaluation and intervention planning for ASD
Filipe <i>et al.</i> [21]	30 children aged 6–9 years	15 ASD (12 males, 3 females; 100% Portuguese), 15 TD	DSM-5 + ADI-R + ADOS + WISC-III (15 HFA, IQ >80)	PEPS-C, CCTT (CCTT-1, CCTT-2, and CCTT Interference Index)	The study investigated the association and potential bidirectional mediation between prosodic skills and executive function abilities in children with HFA and TD peers by comparing group performance, analyzing correlations between PEPS-C and CCTT scores, and conducting mediation analyses	HFA children demonstrated significantly lower prosodic skills and greater EF challenges compared to TD peers, with moderate correlations found between prosodic abilities and complex EF measures. The study highlights a bidirectional relationship between prosodic and EF deficits in HFA, emphasizing the need for integrated assessment and intervention targeting both domains

Contd...

Table 2: Contd...

References	Sample size and age	Demographic characteristics	ASD characteristics	Parameters	Description (methodological)	Clinical result
Laboratory data						
Tordjman <i>et al.</i> [22]	87 children and adolescents (mean age ASD 11.3±4.1 years)	55 ASD (36 males, 19 males; 100% Caucasian) and 32 TD (22 males and 10 females; 100% Caucasian)	DSM-4-TR, ICD 10, and CFTMEA (55 Autistic disorder-LFA), ADI-R + ADOS	Salivary and urinary cortisol levels	The study evaluated circadian cortisol patterns and basal HPA axis activity in LFA through salivary measurements (five times daily) and overnight urinary analysis, aiming to identify cortisol secretion abnormalities and their potential links to autism severity in social and language domains	Children with LFA exhibit elevated and more variable salivary cortisol levels with flattened circadian rhythms linked to severe social interaction impairments and presence of verbal language, suggesting heightened stress responses in those with greater social engagement
Mandic-Maravic <i>et al.</i> [23]	113 children and adolescents (mean age 9.36±5.88 years)	92 males, 21 females	ICD-10 + ADI-R (113 Atypical ASD), VABS-II, WASI	GSTs (GSTA1, GSTM1, GSTT1, and GSTP1)	This study investigated whether specific GST gene polymorphisms are associated with the severity of symptoms, cognitive and adaptive abilities in children with ASD. Employing PCR-based genotyping and regression models, it further investigated how prenatal environmental exposures might modify genetic effects on these clinical outcomes	The study found that GST gene polymorphisms, moderated by prenatal factors (like maternal smoking or medication), influence ASD symptom severity, cognitive function, and adaptive skills, underscoring the need for personalized interventions integrating genetic and environmental risks
Kara <i>et al.</i> [24]	44 children (mean age ASD 72.12±33.68 months)	25 ASD (18 males, 7 females), 19 TD (10 males, 9 females)	DSM-5 + K-SADS PL-DSM-5 (25 ASD), CARS + CPRS-CTRS	Serum zonulin levels	This study investigated the gastrointestinal permeability of individuals with ASD by determining serum zonulin levels and assessed its correlation with symptom severity	Elevated serum zonulin levels in ASD are significantly associated with heightened symptom severity, especially in social functioning, indicating intestinal barrier dysfunction may influence clinical manifestations and warranting further research to establish causality and diagnostic utility
Imaging data						
Reiter <i>et al.</i> [25]	88 children and adolescents (aged 6–15 years)	44 ASD (37 males, 7 females), 44 TD (32 males, 12 females; 22 average FIQ, 22 higher FIQ)	ADOS and ADI-R (22 LFA (FIQ ≤ 85), 22 HFA (FIQ ≥ 115))	rs-fMRI (from ABIDE database)	This study compared functional connectivity patterns in ASD across different cognitive functioning levels, analyzing key brain networks and regions associated with ASD	The study found distinct brain connectivity patterns in ASD, with LFA showing reduced integration in default mode and visual networks, while HFA exhibited diminished segregation between key networks, highlighting the necessity of stratifying by functional level in ASD research and interventions

Contd...

Table 2: Contd...

References	Sample size and age	Demographic characteristics	ASD characteristics	Parameters	Description (methodological)	Clinical result
Imaging data						
Li <i>et al.</i> [26]	125 children (aged 7–18 years)	62 ASD (58 males, 4 females), 63 TD (59 males, 4 females)	ADOS, SCQ, SRS, FIQ >75 (62 ASD)	rs-fMRI (from ABIDE II database) – both static and DFC	This study analyzed DFC patterns in ASD versus TD peers, employing preprocessing (motion correction, normalization), sliding-window/k-means clustering across 90 brain regions, and comparing static/DFC metrics (temporal variability via DFC, recurring states) with statistical controls for age, sex, IQ, and motion	Higher ASD severity is associated with increased variability over time in connectivity between brain regions involved in social cognition. The study demonstrated that DFC patterns, particularly hyper-connected brain states occurring more frequently in ASD children, are linked to symptom severity, highlighting their potential as neural markers for diagnostic or therapeutic applications
Chen <i>et al.</i> [27]	863 individuals (aged 6–30 years)	260 ASD (237 males, 23 females), 574 TD (405 males, 169 females) + 29 independent ASD validation (27 males, 2 females)	DSM-5 + ADOS (169 mild HFA, 91 severe HFA, FIQ ≥70)	rs-fMRI (from ABIDE I and II) - FC	The study employed rs-fMRI and advanced statistical methods to identify neural biomarkers that differentiate severe from mild ASD among HFA individuals by stratifying participants based on whole-brain FC	rs-fMRI FC differentiated severe from mild ASD subgroups and, through a support vector machine model, moderately predicted ADOS scores, thereby supporting brain-based biomarkers for objective ASD severity stratification and personalized interventions
Zhao <i>et al.</i> [28]	111 adolescents (aged 10–18 years)	48 ASD (39 males, 9 females; 100% Han Chinese), 63 TD (43 males, 20 females; 100% Han Chinese)	DSM-5 + ABC + WISC-IV or WAIS-IV (48 HFA, FIQ >80)	rs-fMRI - ReHo	The study assessed local brain FC in individuals with ASD using ReHo, applied data preprocessing and group-level voxel-wise comparisons, and examined associations between ReHo alterations and ABC symptom scores in regions with group differences	The study found increased synchronization in brainstem, limbic, and cerebellar regions and decreased synchronization in sensorimotor areas, with brainstem ReHo negatively correlating with social symptom severity, thereby advancing understanding of ASD neuropathology and suggesting ReHo as a potential biomarker for diagnosing and targeting brainstem dysfunction in future interventions

ABAS-II: Adaptive Behavior Assessment System, Second Edition, ABC: Autism Behavior Checklist, ABIDE: Autism Brain Imaging Data Exchange, ADOS/ADOS-2: Autism Diagnostic Observation Schedule, Second Edition, ANOVA: Analysis of variance, ASD: Autism spectrum disorder, AQ-C: Autism Spectrum Quotient-Children's Version, BSID: Bayley Scales of Infant Development, CCTT: Children's Color Trails Test, CFTMEA: French Classification of Child and Adolescent Mental Disorders, CPRS-CTRS: Conner's Parents and Teacher; s Rating Scales-Revised/Long Forms, DFC: Dynamic Functional Connectivity, DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-4-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, DQ: Developmental quotient, EF: Executive function, FC: Functional connectivity, FIQ: Full Intelligence Quotient, GDQ: Global Developmental Quotient, GMDS/GMDS-ER: Griffiths Mental Developmental Scale - Extended Revision, GSTs: Glutathione S-transferases, HFA: High-functioning autism, IQ: Intelligence quotient, K-SADS PL-DSM-5: Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version-DSM-5, LFA: Low-Functioning Autism, Leiter-3: Leiter International Performance Scale, Third Edition, MSEL: Mullen Scales of Early Learning, PCR: Polymerase chain reaction, PEPS-C: Profiling elements of prosody in speech communication, PPVT: Peabody picture vocabulary test, RCPM: Raven's Colored Progressive Matrices, ReHo: Regional homogeneity, rs-fMRI: Resting-state functional magnetic resonance imaging, SBIS: Stanford-Binet Intelligence Scale, SCQ: Social Communication Questionnaire, SRS: Social Responsiveness Scale, TD: Typically developing, VABS: Vineland Adaptive Behavior Scale, WAIS: Wechsler Adult Intelligence Scale, WASI: Wechsler Abbreviated Scale of Intelligence, WISC: Wechsler Intelligence Scale for Children, WPPSI: Wechsler Preschool and Primary Scale of Intelligence, PDD: Pervasive developmental disorder

Adaptive functioning has been rigorously assessed using standardized tools such as the VABS, which measures everyday functioning across communication, daily living, sociability, and motor skills domains based on caregiver reports. Alvares *et al.* demonstrated that while there is

a relationship between adaptive functioning and IQ, age at diagnosis explained a greater portion of the variance in adaptive scores than IQ alone. Specifically, IQ was a weak predictor for all domains except communication, and incorporating age at diagnosis significantly enhanced

predictive models [19]. This suggests that adaptive functioning is dynamic and influenced by developmental timing, challenging assumptions that functioning levels remain stable over time or circumstances.

Further reinforcing these findings, Casula *et al.* reported that children with ASD exhibited lower VABS composite scores, particularly in the communication domain, alongside higher ADOS scores, indicating worsening symptoms and deteriorating adaptive behaviors. Their study highlighted maternal education as a critical factor influencing how children receive advice for everyday skills, which in turn affects their adaptive functioning, underscoring the important role of familial and environmental support in shaping developmental outcomes. Interestingly, unlike some previous research, maternal SES did not predict adaptive functioning in their Italian sample, a phenomenon possibly explained by the traditional caregiving role of mothers who are often unemployed despite higher educational levels, thus creating a complex dynamic that diminishes the direct impact of SES. Nevertheless, the data revealed a significant interaction between maternal education and the child's general and practical adaptive skills, suggesting that higher maternal education positively influences how children with ASD acquire guidance for everyday life skills. This influence enhances adaptive abilities in areas such as home living, community use, and health and safety, effectively acting as a protective factor in the development of adaptive behaviors [6].

The adaptive behavior assessment system – second edition, another comprehensive tool assessing adaptive functioning, evaluates ten skill categories and generates composite scores in conceptual, social, practical, and general adaptive domains. Hill *et al.* identified a significant three-way interaction among age, intellectual functioning, and ASD symptom severity in predicting adaptive functioning. Notably, older children with higher intellectual functioning showed a positive association between adaptive functioning and ASD symptom severity [18]. This counterintuitive finding may be explained by the development of compensatory strategies over time, enabling these individuals to mitigate some negative impacts of symptom severity on their adaptive skills.

Collectively, these studies illustrate that ASD is not a dichotomous condition but a spectrum characterized by diverse cognitive and adaptive profiles. They emphasize the critical need for multidimensional assessments that incorporate cognitive ability, adaptive functioning, environmental context, and developmental timing. Such comprehensive evaluations are essential to inform personalized interventions aimed at enhancing functional outcomes and quality of life for individuals with ASD and their families.

Observational insights: Gait patterns, executive function, and prosodic skills

Children with ASD often exhibit a range of motor impairments, including abnormalities in gross and fine motor control, decreased postural stability, altered motor planning, and abnormal motor coordination. Among these, gait abnormalities have emerged as a significant indicator of

motor dysfunction in ASD. Walking involves the coordination of multiple brain regions, including both cortical and subcortical areas [31], and impairments in gait can reflect underlying neural abnormalities. Notably, studies suggest that dysfunctions in the basal ganglia and cerebellum contribute substantially to gait impairments observed in children with ASD [20,32].

Research examining gait characteristics in relation to autism symptom severity has identified significant correlations between aberrant gait variables and social responsiveness scores. Specifically, measures related to foot contact timing and forefoot force showed strong associations with autism quotient and social responsiveness scale (SRS) scores, even after controlling for IQ. These findings indicate that the more pronounced the gait abnormalities, the more severe the autistic symptoms, highlighting the potential of motor assessments as valuable components of comprehensive ASD evaluations. Furthermore, these insights underscore the promise of motor-based interventions as complementary therapies alongside traditional approaches [30].

In parallel, cognitive and language domains such as EF and prosodic skills also demonstrate interconnected developmental trajectories in HFA children. EFs (particularly response inhibition and working memory) are moderately correlated with prosodic impairments, which are critical for effective communication. This relationship suggests that deficits in cognitive control and language processing evolve together, influencing one another throughout development [21].

The prosody in speech-communication test, which assesses prosodic abilities through twelve subtests (half addressing receptive skills and half expressive skills), revealed that children with HFA scored significantly lower than TD peers. These prosodic deficits were moderately correlated with performance on the Children's Color Trail Test-2 and its Interference Index, which measures divided attention, working memory/sequencing, set-switching, and inhibition (key components of EF). This evidence supports the notion that prosody and EF are closely linked cognitive domains [21].

Further mediation analyses demonstrated a bidirectional influence: prosodic skills had a stronger effect on EFs, but EFs also impacted prosodic abilities. This reciprocal relationship aligns with neurodevelopmental theories suggesting that delayed maturation of frontal lobe regions may affect brain areas critical for both EF and language processing [8,33]. Since both EF and prosodic abilities emerge early in childhood and continue to develop into adolescence, interventions targeting these domains may yield synergistic benefits for improving communication skills in children with ASD.

Laboratory biomarkers: Stress response, genetic polymorphisms, and gut-brain axis

Laboratory data provide compelling evidence of biological underpinnings influencing functional outcomes in ASD. One key area of investigation is the dysregulation of the hypothalamic-pituitary-adrenal axis and stress response systems. Elevated salivary and urinary cortisol levels, along

with disrupted circadian rhythms, have been consistently observed in individuals with ASD. Tordjman *et al.* revealed a strong link between cortisol levels and the severity of autistic deficits in social interaction. Compared to TD controls, LFA children and adolescents exhibited altered circadian cortisol patterns, characterized by higher salivary cortisol at multiple time points (notably at 16:00 h, 24:00 h, and 08:00 h on Day 2) and significantly flatter daytime and nighttime slopes [22]. This group also showed increased within-group variability, and cortisol levels correlated significantly with impairments in social interaction and verbal language [22,34]. These hormonal alterations suggest that physiological stress mechanisms may exacerbate core ASD symptoms, highlighting the importance of considering stress biomarkers in ASD assessment and management.

Genetic factors also play a crucial role in ASD pathophysiology, particularly polymorphisms in GST genes such as GSTA1, GSTM1, GSTT1, and GSTP1. These genetic variations have been linked to differences in ASD symptomatology and adaptive functioning. Mandic-Maravic *et al.* found that the GSTA1 genotype was associated with lower ADI-R nonverbal scores, indicating less impairment in nonverbal communication skills such as pointing, nodding, and social imitative play. Beyond polymorphisms, studies examining GST enzymatic activity revealed that children with ASD have significantly reduced GST activity alongside elevated blood levels of heavy metals such as lead and mercury. These biochemical alterations correlated with greater social responsiveness impairment and higher clinical severity scores measured by CARS [23,35,36]. These findings underscore the role of oxidative stress and detoxification pathways in ASD and suggest gene-environment interactions moderated by prenatal exposures such as maternal smoking and medication use.

Another emerging area of interest is the gut-brain axis, particularly the role of intestinal permeability in ASD. Zonulin, a precursor of haptoglobin, regulates tight junction integrity in the intestinal epithelium and is released in response to enteric bacteria and gliadin through CXCR3 chemokine receptor activation [37]. Elevated serum zonulin levels have been associated with increased ASD symptom severity and social dysfunction. Kara *et al.* examined specific functional domains of ASD using CARS parameters and found that higher zonulin levels correlated with impairments in verbal and nonverbal communication, emotional reactions, adaptability, and social relationships. Their findings suggest that increased intestinal permeability may exacerbate ASD severity rather than its origin [24]. Similarly, Özyurt *et al.* reported elevated zonulin levels in children with ADHD, who also exhibited greater social dysfunction compared to healthy controls. Regression analyses identified serum zonulin as an independent predictor of hyperactivity and social impairment scores, further supporting the link between gut permeability and neurobehavioral symptoms [37]. These results advocate for integrative approaches addressing both neurological and systemic health in ASD management.

Taken together, these biochemical and genetic findings open promising avenues for targeted biomedical interventions

in ASD. The interplay between stress response dysregulation, genetic polymorphisms affecting detoxification pathways, and gut-brain axis dysfunction highlights the complexity of ASD pathophysiology. Future research and clinical practice should consider these systemic physiological factors alongside traditional neurobehavioral assessments to improve personalized treatment strategies and functional outcomes for individuals with ASD.

Neuroimaging evidence: Functional connectivity and brain network organization

Rs-fMRI studies have significantly advanced our understanding of the neural underpinnings of ASD, revealing distinct patterns of FC that correlate with symptom severity and functional levels. One key finding across multiple investigations is the presence of altered ReHo in brain areas critical for cognitive and social functioning. Zhao *et al.* demonstrated that adolescents with high-functioning ASD exhibit increased ReHo in the bilateral anterior cingulate cortex, left caudate, right posterior cerebellum (cerebellar tonsil), and bilateral brainstem, alongside decreased ReHo in the left precentral gyrus, left inferior parietal lobule (IPL), bilateral postcentral gyrus, and right anterior cerebellum (culmen). The reduced ReHo in the IPL and postcentral gyrus—regions implicated in visuospatial processing—provides a neural basis for some of the visuospatial and sensorimotor difficulties observed behaviorally in ASD [28,38]. These ReHo abnormalities align with symptom severity, supporting the notion that local brain synchrony disruptions contribute to the heterogeneity of ASD manifestations.

Beyond local homogeneity, FC analyses have further refined our understanding of ASD subtypes. Chen *et al.* applied rs-fMRI FC-based stratification to distinguish mild from severe ASD cases within a high-functioning cohort, achieving high concordance with traditional behavior-based diagnostic tools such as ADOS. Intriguingly, three specific functional connections—between prefrontal areas, posterior cingulate cortex (PCC), and thalamus—exhibited a unique pattern: These connections were strongest in the mild ASD subgroup, weaker in the severe subgroup, and weakest in TD controls. This suggests that these FC patterns, particularly the connection between the left superior frontal gyrus and the left middle frontal gyrus, may serve as candidate neural biomarkers specific to milder forms of ASD [27,39]. Such findings highlight the complexity of neural network alterations in ASD, where increased connectivity in certain circuits may reflect compensatory mechanisms or distinct pathophysiological processes.

Dynamic FC (DFC) analyses add another layer by capturing the temporal variability of brain network interactions. Li *et al.* and Jung *et al.* focused on the DFC between the PCC and the pars opercularis of the inferior frontal gyrus (IFGoper), regions implicated in social cognition and executive control. Their studies revealed that increased instability or variability in this connection correlates positively with social symptom severity, as measured by parent-report instruments such as the social communication questionnaire (SCQ) and the SRS. Specifically, higher SCQ and SRS scores – indicating

more severe social communication deficits – were associated with greater DFC standard deviation between the PCC and IFGoper. Moreover, subscales of the SRS related to social awareness and social cognition showed stronger associations with this dynamic connectivity measure [26,40]. These results suggest that fluctuations in brain connectivity dynamics may underlie the social impairments characteristic of ASD and hold promise as sensitive neurobiological markers for diagnosis and phenotyping.

Importantly, neuroimaging comparisons between LFA and HFA groups reveal distinct patterns of brain network organization rather than a simple gradient of severity. Reiter *et al.* and Jack and Pelphrey found that LFA individuals exhibit significantly reduced intrinsic FC (iFC) between the medial PFC seed and the precuneus/posterior cingulate gyrus compared to HFA individuals. Furthermore, LFA participants showed widespread differences in iFC across multiple seed regions relative to HFA, while HFA individuals demonstrated over connectivity in the PCC and right insula compared to IQ-matched TD controls. These findings indicate that LFA is characterized by qualitatively different network disruptions, particularly reduced integration within the default mode network (DMN) and ventral visual stream, whereas HFA shows altered network segregation among the DMN, salience network, and task-positive frontal regions [25,41]. This distinction underscores the importance of considering functional level when interpreting neuroimaging data and tailoring interventions.

Collectively, these neuroimaging studies underscore the multifaceted nature of brain network alterations in ASD. The combination of static ReHo abnormalities, stratified FC patterns, and dynamic connectivity variability offers a comprehensive framework for understanding the neural correlates of symptom heterogeneity and functional capacity across the autism spectrum. These findings not only enhance our mechanistic insight into ASD but also pave the way for developing neural biomarkers that can improve diagnosis, phenotyping, and personalized treatment strategies.

Limitations and future directions

Despite these advances, the current body of research faces several limitations. Many studies focus predominantly on comparisons between HFA and TD controls, often neglecting the LFA subgroup, which limits the generalizability of findings across the full spectrum. In addition, there is considerable variability in the assessment tools and outcome measures used across studies, hindering direct comparability and synthesis of results. Some literature analyzed in this study primarily examines the relationship between key parameters and symptom severity rather than directly measuring how these factors relate to adaptive functioning and ability. While symptom severity is generally positively correlated with and predictive of poorer functional ability, such findings do not provide direct evidence of this relationship. Furthermore, the scope and depth of available data are also limited, particularly in capturing the complex interactions among cognitive, behavioral, biochemical, and neurobiological factors. These gaps highlight the need for more comprehensive, standardized,

and longitudinal studies that include diverse ASD populations, especially those with low-functioning profiles.

Moving forward, future research should prioritize multidimensional and integrative methodologies that combine behavioral assessments, EF measures, motor coordination evaluations, biochemical markers, and advanced neuroimaging techniques. Such approaches will deepen understanding of ASD heterogeneity and facilitate the identification of reliable biomarkers and functional indicators. Moreover, expanding research to include underrepresented groups within the spectrum and employing longitudinal designs will clarify developmental trajectories and intervention effects. Ultimately, emphasizing functional assessments over rigid diagnostic categories and fostering personalized intervention frameworks will be essential to improving support and outcomes for individuals with ASD and their families.

CONCLUSION

This scoping review reinforces the multifaceted nature of ASD and the critical role of adaptive functioning as both a diagnostic and prognostic indicator. By integrating multidimensional data – including cognitive, behavioral, motor, biochemical, and neuroimaging measures – researchers and clinicians can better capture the complexity of ASD heterogeneity. Future research should continue to explore the dynamic interplay between cognitive abilities, environmental influences, and neural mechanisms to refine early detection methods and develop personalized, equitable intervention strategies. Emphasizing functional assessments and individualized care will be essential to improving outcomes and quality of life for individuals with ASD and their families.

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Data availability statement

All data generated or analyzed in this study are available in this published article.

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Conflicts of interest

There are no conflicts of interest.

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