Sultan *Egypt J Neurol Psychiatry Neurosurg (2022) 58:139*
https://doi.org/10.1186/s41983-022-00578-3

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

REVIEW

Open Access

Translating neuroimaging changes to neuro-endophenotypes of autistic spectrum disorder: a narrative review

Sadia Sultan*

Abstract

Background: Autism-spectrum disorder is a neurodevelopmental disorder with heterogeneity in etiopathogenesis and clinical presentation. Neuroanatomical and neurophysiological abnormalities may represent neural endophenotypes for autism spectrum disorders which may help identify subgroups of patients seemingly similar in clinical presentation yet different in their pathophysiological underpinnings. Furthermore, a thorough understanding of the pathophysiology of disease can pave the way to effective treatments, prevention, and prognostic predictions. The aim of this review is to identify the predominant neural endophenotypes in autism-spectrum disorder. The evidence was researched at the following electronic databases: Pubmed, PsycINFO, Scopus, Web of Science, and EMBASE.

Results: Enlarged brain, especially frontotemporal cortices have been consistently reported by structural neuroimaging, whereas functional neuroimaging has revealed frontotemporal dysconnectivity.

Conclusions: Regrettably, many of these findings have not been consistent. Therefore, translating these findings into neural endophenotype is by far an attempt in its budding stage. The structural and functional neuroimaging changes may represent neural endophenotypes unique to autism-spectrum disorder. Despite inconsistent results, a clinically meaningful finding may require combined efforts of autism-spectrum-disorder researchers focused on different aspects of basic, genetic, neuroimaging, and clinical research.

Keywords: Autism-spectrum disorder, Autism, Diffusion tensor, Endophenotypes, Neural endophenotype, Neuroimaging, Brain imaging, Structural neuroimaging, Magnetic resonance imaging, Functional neuroimaging

Background

This paper attempts to review the endophenotype concept and its application in understanding the etiopathogenesis of Autism spectrum disorders (ASD). Therefore, we first review the endophenotype concept and various endophenotypes in ASD. We then present a brief overview of the predominant neuroanatomical endophenotypes in ASD with evidence from neuroimaging and discuss the potential relevance of the neural endophenotypes to ASD.

*Correspondence: sssultan@fcms.edu.sa; drsaddy2003@yahoo.com

Clinical Science Department, Fakeeh College for Medical Sciences, Jeddah, Saudi Arabia

Measurable biological (physiological, biochemical, and anatomical features), behavioral (psychometric pattern), or cognitive markers are found more often in individuals with a disease than in the general population. Phenotype not visible from outside (internal phenotype) which is detectable using biochemical tests or microscopic examination is termed an endophenotype [1]. Endophenotype must fulfill the following criteria, (a) it should be associated with a disease of interest in the general population, (b) it should be heritable, and (c) trait dependent which means it should be detected in high-risk individuals irrespective of whether he or she is in an acute state of illness, (d) co-segregation of illness and endophenotypes in families and (e) Reported in both affected and nonaffected family members more than the general population

[2]. Autism endophenotype is grouped under seven categories: neuroanatomical, neurophysiological, biochemical, morphological, immunological, hormonal, and behavioral [3]. Most psychiatric disorders are polygenic and multifactorial in origin which limits, an in-depth understanding of the pathophysiology of the illness. Identification of endophenotypes may be a more compelling approach to understanding ASD, their intermediate position between genotype and behavior may help researchers in classifying autistic patients based on the underlying pathophysiology [4]. However, the endophenotypes are not specific to ASD and can be reported in other developmental disorders [5, 6].

ASD despite heterogeneity in clinical presentation, share two essential features: (a) deficit in social interaction and communication and (b) behavioral abnormalities in the form of stereotypies (repetitive movements), restricted interests, and inability to adapt to a change [7].

Various factors contribute to the heterogeneity in ASD, which include a high incidence of comorbid medical (sleep disorders, gastrointestinal dysfunction, autoimmune disorders), neurological (seizures), and psychiatric conditions (ADHD, anxiety disorders). Furthermore, intellectual ability is another contributor to the heterogeneity leading to the concept of high-functioning and low-functioning ASD. There is no evidence to suggest the common co-occurrences of specific disorders are an independent phenotype of ASD or true comorbidity [8].

The estimated heritability for ASD is 80–90% [9, 10]. Evidence from twin pair studies reported 60% concordance in monozygotic (MZ) twins and 0% in dizygotic (DZ) twins for autism and 92% of MZ twins were concordant for broad-spectrum autism-related cognitive and social abnormalities compared to 10% DZ twins [11]. The concordance rate in siblings varies between 3 and 14% [12–15]. Moreover, 10–20% of individuals with known genetic disorders (Fragile X syndrome, Rett's syndrome) may present with autistic features which further supports the genetic liability of ASD [16, 17]. Linkage analysis and candidate gene analysis found mutations in genes that are very important for brain development. These include genes important for synaptogenesis and pruning (such as SHANK, neurexin, and neuroligin families) others that regulate growth (RELIN, HOXA1, and PTEN), or are involved in other aspects of brain development such as signaling pathways. These genetic factors are likely to play an important role in the development of the brain in ASD [18].

The current theoretical approach to autism includes executive dysfunction, weak central coherence (difficulties integrating information into meaningful wholes), and impaired ability to understand mental states (theory of mind) [19]. The social impairment in ASD is related to misinterpretation of social signals. Proximity to others can trigger autonomic symptoms that helps maintains distance between themselves and others exhibiting the critical role of social signal interpretation in social interaction [20]. Abnormal social behavior in children with ASD is associated with a set of brain regions constituting the so-called "social brain". The social brain includes the superior temporal sulcus (STS) and fusiform gyrus that recognize facial expression and understands the eye gaze, amygdala and ventromedial prefrontal cortex (vmPFC) that are involved in processing the emotional significance of social stimuli, temporoparietal junction (TPJ) and mPFC that infers goals, intentions, and desires of other people. From a perspective of cognitive functions, abnormalities of the PFC (required for attentional control) may lead to deficits in both social and non-social behavior. This dysfunction in attentional control may lead to a lack of learning of social behaviors and interactions. Evidence showing structural and/or functional abnormalities in these regions in individuals with ASD may underlie behavioral and social problems in ASD [21]. See Table 1, correlating the symptoms of ASD with atypicality in specific brain areas).

Methods

Search strategy

The evidence was researched at the following electronic databases: Pubmed, PsycINFO, Scopus, Web of Science, and EMBASE. The following descriptors registered in Mesh were considered Autism spectrum disorders[MeSH]OR Autism AND neuroimaging OR "Brain Mapping" [MeSH Terms]OR "Magnetic Resonance Imaging" [MeSH] OR Diffusion tensor imaging.

Result

To understand the neuroimaging changes in ASD, it is imperative to recognize the normal brain development and brain development in children with ASD.

Normal brain development

Brain development is a dynamic interplay between genes and environmental factors. Although brain development starts in utero synaptogenesis and myelination peak in toddlerhood forming early neural circuits and genetically programmed pruning continues in childhood and adolescence [22, 23]. The brain attains 80% of its size at 2 years and adult size at 5 years, followed by a reduction in grey matter GM after 12 years and an increase in white matter (WM) during childhood and adolescence. There is variation in the maturation of cortical area with primary cortices maturing earlier than the association cortex. The cortical centers for higher cognitive functions such as the prefrontal cortex mature at a later time [24, 25].

Table 1 Evidence of structural brain alterations (MRI) in children with ASD along with associated symptoms

Author	Brain structure	MRI structural finding	MRI functional changes
Hazlett et al. [44], Courchesne et al. [37]	Total brain volume	Increased brain volumes. Both GMV and WMV in autism compared to TD	Social interaction and communication deficits
Carper et al. [45] Hazlett et al. [46]	Frontal lobe Temporal lobe	Increased Volume	Language delay and impaired social cognition
Courchesne et al. [47]	dmPFC, Medial frontal region	Increased volume	Impaired social cognition
Sato et al. [49]	IOG, fusiform gyrus, STS, amygdala, vmPFC, IFG, and dmPFC	GMV and cortical thickness reduced	Impaired capacity to understand mental states
Pereira et al. [50], Pappaiann et al. [51]	STS, Fusiform gyrus Amygdala and IFG	GMV and cortical thickness reduced	Impaired facial recognition
Schumann et al. [56]	Amygdala	Enlarged in children	Social interaction and communication deficits
Schumann et al. [57]		Enlarged in children and not in adolescents	
Aylward et al. [55] and Xu et al. [60]		Smaller	
Haznedar et al. [58]		No change in volumes	
Aylward et al. [55] and Xu et al. [60]	Hippocampus	Decreased volume	Disruptive activity during repetitive behavior
Spark [61]		Increased volume	
Piven et al. [62]		No change in volumes	
Hollander et al. [65], Estes et al. [66], Thabault et al. [67], Voelbel et al. [68] and Langenet al [69]	Caudate	Increased Volume	Repetitive or restricted behavior
Murakami et al. [74], Courchesne [75] and Stoodley et al. [83]	Cerebellum	Reduced size	Motor deficits and impairment in cognitive functions such as associative learning, verbal ability, planning, and working memory
Hardan et al. [73], Sparks et al. [61], Carper et al. [77]		Enlarged	
Kilian et al. [84]	Corpus callosum	Increased volume in children with ASD	Deficit in executive functioning
Anderson et al. [85] and Frazier et al. [86]		Decreased volume in youth with ASD	
Lo et al. [52]	SLF, which connects the STS and IFG	Reduced white matter connectivity	Inability to infer intentions of others
d'Albis et al. [53]	Frontal, parietal, and temporal regions, including STS and vmPFC,	Reduced white matter connectivity	Social interaction and communication deficits
Gibbard et al. [54]	Between amygdala and neocortex	Reduced white matter connectivity	Impaired emotional regulation

SLF Superior longitudinal fasciculus, *STS* Superior temporal sulcus, *IOG* inferior orbital gyrus, *vm PFC* Ventromedial prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex, *ILF* inferior frontal gyrus, *GMV* grey matter volume, *WMV* white matter volume, *TBV* total brain volume

Brain development in Autistic spectrum disorders

Evidence from the last three and a half decades has proved that the typical course of brain development is altered in children with ASD, which starts prenatally [26, 27] and extends into adulthood [28, 29]. Even though the brain size is normal or smaller at birth compared to typically developing (TD) children [30], there is accelerated growth starting at 6 months and extending into toddlerhood [31–34] followed by a slowing in brain growth by school-age and stabilization. The early abnormalities include abnormal brain growth patterns and aberrant neural architecture and connectivity [28]. Sometimes, there may be a normalization of brain size during the late teenage called pseudo-normalization [35]. Disturbances in the development of neural circuitry were typically noted in frontal, temporal, and cerebellar regions contributing to the early clinical features of ASD [29, 35, 36]. Given the fact that there is accelerated brain growth in infants and toddlers with ASD [37, 38], macrocephaly is one of the most replicated findings reported in both children with ASD and their family members [32, 39–42].

Neuroimaging in autism

Remarkable advances in neuroimaging techniques have revealed typical and atypical neurodevelopmental abnormalities. Since ASD has a strong genetic underpinning, neuroimaging may help identify neuro-endophenotypes. Any consistent structural or functional neuroimaging findings may presumably represent neuro-endophenotype. Structural neuroimaging addresses the neuroanatomical changes such as the size of cerebral structures, whereas functional imaging

detects the abnormalities in the functioning of the brain. MRI has proven its ubiquity in identifying both neuroanatomical and neurophysiological endophenotypes. Both structural and functional imaging using MRI has proven to be safe in children owing to their non-invasive nature. Nevertheless, neuroimaging in children has inherent limitations such as (a) difficulty in training children to stay still during the procedure, (b) reliability of the findings depending on image resolution, and (c) findings may not be generalizable as most subjects involved are high functioning children as it is not easy to train low functioning autistic children. However, functional near-infrared spectroscopy (fNIRS) is a relatively new technique that allows the measurement to be taken in any body position while retaining good temporal resolution making it an easier technique to be used for children [43]. The following is a brief overview of some consistent neuroimaging changes which may fit the criteria for neuro-endophenotype.

Structural neuroimaging–structural MRI

Structural MRI (sMRI) studies have been instrumental in finding the neuroanatomical changes and their progression concerning brain development.

Total brain volumes The estimation of total brain volume (TBV) and volumes of specific brain areas have been done using structural MRI (sMRI). Voxel (volumetric pixel)-based morphometry (VBM) has been instrumental in measuring cortical thickness, surface area, grey matter volume (GMV), and white matter volume (WMV). Evidence suggests an increase in TBV including both GMV and WMV in children with ASD when compared to TD subjects [37, 44]. Mean cortical volumes (both GM and WM) of frontal and temporal lobes were found to be increased with no effect on parietal and occipital lobes [45, 46]. Other regional variations include enlarged dorsolateral prefrontal cortex and medial frontal regions with limited change in the precentral cortex [47]. Dissociation between volumes of the cerebrum and the subcortical structures was noted in some studies. For example, a study of 15-year-old autistic children compared to TD subjects reported a relatively smaller cerebral cortex, the hippocampus–amygdala when compared to larger cerebral white matter volumes [48]. Lower GMV was noted especially in right inferior occipital gyrus, left fusiform gyrus, right middle temporal gyrus, bilateral amygdala, right inferior frontal gyrus, right orbitofrontal cortex, and left dorsomedial prefrontal. Reduced GMV and white matter connectivity in these areas of social cognition represents the neural underpinnings of behavioral and social malfunctioning in ASD [49–54] (see Table 1).

Amygdala The amygdala plays an important role in attachments, social behavior, and understanding the recognizing emotions making it an important area of research in ASD. Inconsistency in amygdala volume has been reported across studies. Some studies have found decreased volumes [55–60], while others have found increased volumes [56, 57] in children and not adolescents [57], and some studies did not find differences [58] (see Table 1).

Hippocampus The hippocampus plays an important role in learning and memory. This could be a key area of research about the difficulty in learning encountered in ASD. Although postmortem studies have found the abnormal size of neurons in the hippocampus [59], MRI studies have shown inconsistent results. Few studies have reported a decrease in the volume of the hippocampus [55–60], while others have reported an increase in volume [61] or no significant difference [62]. However, the smaller volumes of the amygdala and hippocampus are normalized by adolescents and adulthood [60] (see Table 1).

Basal ganglia Basal ganglia play a major role in cognition and modulation of movements via the cortico-striatal–thalamic loops and limbic circuits [63]. It is a key area of research about the repetitive behavior encountered in ASD [63, 64]. Increased volume of caudate has been the most consistent finding which was proportionately related to an increase in TBV [65–69]. However, changes in other basal ganglia structures such as globus palladium and putamen have not been reported [70]. Abnormal shapes of basal ganglia have been reported in boys which correlated with motor and social and communicative defects in ASD [71] (see Table 1).

Cerebellum Cerebellum has dense interconnections with cortical regions important for cognition, language, executive and socioemotional functions [72]. VBM of ASD subjects has found increased total volumes of the cerebellum which correlated with TBV [73]. However, hypoplasia of posterior vermis [74–78] and reduced SA of vermal lobules (VI and VII) [75, 79, 80] were noted in a few studies. Decreases in GM in right Crus I, lobule VIII, and lobule IX of the cerebellum was reported in a meta-analysis of various VBM studies [81–83]. Others reported decreased GM in the left crus and an overall increase in GM of the cerebellum [81, 82] (see Table 1).

Corpus callosum Corpus callosum (CC) is the thick white matter tract that connects the right and left hemisphere and helps in interhemispheric communication [83]. Although increased CC volume was reported in ASD children when compared to TD subjects [84], a more

consistent finding was decreased CC size in youth with ASD compared to controls [85, 86]. Table 1 enumerates the various changes in the brain as evident from MRI and its correlation with the symptoms of ASD.

White matter abnormalities Literature suggests abnormalities in genetically programmed synaptogenesis, myelination, and pruning in children with ASD, thus compromising WM integrity [87]. Diffusion tensor imaging (DTI) is a technique of MRI which is utilized to detect changes in white matter tracts. Measures such as fractional anisotropy (FA) and mean diffusion (MD) are used to assess the directionality and diffusion of water, respectively, in a particular area of interest or voxel [88]. Therefore, DTI is used to detect structural white matter changes in ASD [89]. Ample literature suggests reduced FA indicating increased WM abnormalities, especially in the frontal and temporal lobe areas [90–95]. DTI studies found that there are more abnormalities in the long tract when compared to short tracts [95]. Abnormalities of FA and MD wad reported in right inferior, superior longitudinal fasciculi [96], and bilateral anterior thalamic radiation [96, 97]. Uncinate fasciculus, arcuate fasciculus, inferior fronto-occipital fasciculus and corpus callosum [98–100]. Evidence from the last three decades has shown left-hemispheric abnormalities and atypical hemispheric dominance in children with ASD [101–103]. Two approaches to DTI, namely, whole-brain voxel-based analysis (VBA) and the region of interest (ROI) approach, reported less overlap of such findings using the same data set. However, overall results obtained by two methods reported lesser overall brain connectivity in both long and short-range connections in ASD subjects, while corpus callosum and ventral tracts turned out to be the main connections affected [104]. Few studies revealed abnormalities in FA and MD in age-matched unaffected siblings of children with ASD as compared to TD, which represent impairment in white matter integrity suggesting that it may be a potential endophenotype [105, 106]. However, unaffected siblings exhibited less severe and fewer affected tracts when compared to children with autism [106].

Functional imaging—fMRI Functional MRI (fMRI) is instrumental in studying the functionality of neural circuits and interregional, cortico-cortical, and cortico-subcortical connectivity. ASD is considered a disconnection syndrome due to aberrant, atypical, and decreased functional connectivity as evidenced through fMRI studies. fMRI is primordial in finding the correlation of the neurocognitive abnormalities of ASD with anatomical and functional connectivity.

Task-dependent fMRI measures the region-specific deficit based on the neurocognitive task assigned to the subject. A range of region-specific deficits can be found with various tasks such as face processing, emotional processing, attention, language, imitation, and sensory and motor processing [107]. fMRI has been instrumental in studying the core features of ASD such as social cognition, language, and repetitive behavior. However, few studies reported impaired amygdala modulation rather than just hypoactivation in a social context [108].

Fusiform gyrus has been implicated in visual processing, particularly information related to faces [109, 110] and bodies [111, 112]. Possibly the most replicated finding is the hypoactivation of fusiform gyrus to facial expression [109–113]. Studies have reported hypoactivation of other areas involved in facial processing such as the amygdala and superior temporal sulcus [114]. The neurological substrate for imitation, the mirror neuron system (MNS) is dysfunctional in ASD leading to impaired imitation and contributing to communication deficit. A meta-analysis of 24 experimental studies reported hyperactivation of MNS in ASD, which might underlie the imitation impairments in these individuals [115] (see Table 2—summary of fMRI changes in autism [116–121]).

fNIRS is a non-invasive neuroimaging technology that maps the functioning of the cerebral cortex by measuring hemodynamics via absorption of light. Different light

Table 2 Summary of fMRI changes in ASD

Author	Task	Brain structure	fMRI findings
Lei Li et al. 2021	Resting state	Between mPFC and Bilateral amygdala	Attenuated activity
Padmanabhan et al. 2018	Resting state	Between the dmPFC and PCC/precuneus	Reduced functional connectivity
Odriozola et al. 2018	Resting state	Between the amygdala and vmPFC	Reduced functional connectivity
Fishman et al. 2018	Resting state	Between amygdala and lOG	Reduced functional connectivity
Ciaramidaro et al. 2018	Facial expressions	Amygdala, fusiform gyrus, and STS	Reduced activity
Sato et al. 2018	Eye gaze stimuli	Amygdala	Reduced activity
Lynn et al. 2018	Images of faces and cars	dmPFC and IPL	Reduced activity

mPFC Medial prefrontal cortex, *STS* Superior temporal sulcus, *lOG* inferior orbital gyrus, *vm PFC* Ventromedial prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex

absorption rates of oxy-Hb and deoxy-Hb allow the mapping of the activated and deactivated areas. In comparison with fMRI, fNIRS is low cost, portable, and tolerant to motion artifacts and electromagnetic noise [122]. fNIRS has shown abnormalities in fPFC, prefrontal cortex, TC: temporal cortex; STS, superior temporal sulcus; pSTS: posterior superior temporal sulcus; AC, auditory cortex [123–130] (see Table 3—summary of fNIRS changes in ASD).

Discussion

As mentioned above, structural and functional neuroimaging studies have shown various changes in the brain in ASD which may be translated into endophenotypes. Regrettably, many of these findings have not been consistent. Therefore, translating these findings into neural endophenotype is by far an attempt in its budding stage. Aspiring to grow such a concept may require combined efforts of ASD researchers focused on different aspects of basic, genetic, neuroimaging, and clinical research [131]. To uncover the endophenotype rooted in the genetic program of a child, neuroimaging studies shall be matched with genetic studies to bridge the gap. Such endophenotype-oriented neuroimaging research will be a huge contribution. To correlate the genetic basis to an observed endophenotype, genetic studies shall be paired with neuroimaging findings observed in syndromic ASD when compared with "idiopathic" autism or in a non-autistic population. The most compelling area of investigation is to elucidate whether the comorbid conditions in ASD are true comorbidity or a distinct endophenotype of ASD. ADHD and ASD are commonly occurring comorbid conditions with genetic overlap [132]. However, it remains to be clarified whether these co-occurring conditions are separate neural endophenotypes of ASD. Similarly, 40–50% of children with ASD have comorbid anxiety disorder treated with psychotropics [133]. Certainly, some anxiety can be considered a part of ADS core symptoms such as a preference for sameness, although it remains unclear as to when Obsessive–compulsive symptoms should be considered beyond mere repetitive behavior of ASD. Subtyping ASD phenotypes with comorbid conditions using neuroimaging (for example, studying limbic system connectivity in case of anxiety disorders) may help in the development of more targeted and effective treatment strategies. Furthermore, subtyping ASD based upon neuro-endophenotypes may help find pretreatment abnormalities, develop more personalized and effective treatment and monitor psychotropic response. One such approach would be to highlight the mitochondrial dysfunction as a cause for most psychiatric disorders. The prevalence of mitochondrial diseases is higher in the population of ASD than in general population and up to a half of children with ASD showed evidence of mitochondrial dysfunction. Insertion of mitochondrial DNA missense mutation exhibits ASD endophenotypes, including autism-like behaviors and electroencephalographic profiles, and correlates with mitochondrial abnormalities. On the other hand the alteration of the tryptophan (Trp)–kynurenine (KYN) metabolic system

Table 3 Summary of fNIRS changes in autistic spectrum disorders

Authors	Participants age in years	Task	NIRS result	Brain region
Floyd-Fox et al. [123]	< 1	Auditory and visual task with or without social factors	Activation: ASD < TD	pSTS
Fox et al. [123]	< 1	Face recognition task	Activation: ASD < TD	mPFC, Right TC
Keehn et al. [124]	< 1	resting state while listening sounds	Increased Intra- and inter-hemispheric connectivity in infants with HRA than infants with LRA at 3 months. No difference at 6 and 9 months	TC
Edwards et al. [125]		Auditory task	Activation: low-risk female: first-half > second-half high-risk female: first-half = second-half	TC
Zhu et al. [126]	9.0 ± 1.3	Resting state	Intra- and inter-hemispheric connectivity: ASD < TD	TC
Yasumura et al. [127]	10.5 ± 2.3	Stroop task Reverse Stroop task	Activation: ASD = TD	Right PFC
Xiao et al. [128]	10.1 ± 2.1	Go/No-Go task Stroop task	Activation: Go/No-go: ASD < TD Stroop: ASD = TD	Right PFC
Minagawa-Kawai et al. [129]	9.2 ± 1.8	Auditory task	Activation: TD: phonemic, left AC; prosodic, right AC ASD: prosodic, right AC	AC
Suda et al. [130]	26.4 ± 3.0	Conversation task	Activation: Negative correlation between activation and Autism Spectrum Quotient score	Left STS

The studies were ordered by ages of individuals with ASD

PFC prefrontal cortex, *mPFC* medial prefrontal cortex, *TC* temporal cortex, *STS* superior temporal sulcus, *pSTS* posterior superior temporal sulcus, *AC* auditory cortex

was also observed in patients with ASD. KYN is neuroprotective and evidence suggest its lower levels in neurodegenerative diseases and ASD. Growing evidence has revealed that mitochondria have a close link to KYN metabolism and that mitochondrial dysfunction and the activation of the KYN system contribute to the pathogenesis of neurodevelopmental disorders [134]. Thus, potential strategies of clinical neuroprotection using novel kynurenine metabolites and analogues could be a new approach toward treatment of ASD [135]. Moreover, a previous study has shown improvement in memory component of cognitive domain with KYN analogue [136].

Despite, the need to integrate neuroimaging studies with genetic studies, the pragmatic difficulties in recruiting unaffected relatives of children with ASD besides the children themselves have made it an arduous task. Moreover, neuroimaging itself has limitations such as spatial and temporal resolution, inability to visualize microscopic changes, difficulty in training children for the procedure, and small sample size which might potentially overestimate the effect sizes. Using large-scale neuroimaging in endophenotype studies could be a daunting task in terms of cost-effectiveness and recruitment of a large number of non-autistic relatives to ensure adequate statistical power. Therefore, the possibility of large population-based studies remains bleak. Nevertheless, it is important to disentangle the complexities of the atypical neurodevelopment in ASD in the light of neuro-endophenotype research to provide greater insight into etiopathogenesis translating into better therapies.

Future research shall employ machine-learning approaches particularly suited to the search for autism biomarkers. Structural and functional MRI findings can be used to classify ASD based on the neuroanatomical changes using machine learning techniques such as support vector machines. Identification of autism biomarkers would help detect autism in infants and young children who are at increased risk of developing autism. This approach of early detection would hold good, given the body of work on the efficacy of an early intervention. Moreover, ASD is a complex disorder not linked to a single biomarker. Instead, ASD biomarkers are complex involving many genes and many neurobiological abnormalities. However, matching the genetic studies and neuroimaging studies to find conclusive neuro-endophenotypes of ASD may help. Although such a classification holds good for various clinical application several issues needs to be addressed before its use in clinical practice. The high cost of MRI, problems with image resolution, difficulty to train children to stay still, and portability are among the few issues that need to be addressed. However, these are among the few issues which can be resolved by the use of fNIRS.

Conclusions

An internal biomarker representing a set of genes is an endophenotype. The structural and functional neuroimaging changes may represent neural endophenotypes unique to ASD. However, the inconsistencies in the finding from neuroimaging could not pave the way for categorizing ASD based on neural endophenotype. Nevertheless, endophenotype-oriented research remains a hope which can help classify ASD and throw light on etiopathogenesis translating into more personalized and effective therapy. In addition, identifying the biomarkers of ASD early in the course will help change neural connectivity through early intervention techniques.

Abbreviations

ASD: Autistic spectrum disorder; DmPFC: Dorsomedial prefrontal cortex; DT: Dizygotic twins; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; GM: Grey matter; GMV: Grey matter volumes; ILF: Inferior frontal gyrus; IOG: Inferior orbital gyrus; MD: Mean diffusion; mPFC: Medial prefrontal cortex; MNS: Mirror neuron system; MRI: Magnetic resonance imaging; fMRI: Functional magnetic resonance imaging; fNIRS: Functional near-infrared spectroscopy; sMRI: Structural magnetic resonance imaging; MT: Monozygotic twins; ROI: The region of interest; TBV: Total brain volume; TD: Typically developing; SLF: Superior longitudinal fasciculus; STS: Superior temporal sulcus; VBA: Voxel-based analysis; VBM: Voxel-based morphometry; vm PFC: Ventromedial prefrontal cortex; WM: White matter; WMV: White matter volume.

Acknowledgements

This research would not have been possible without the exceptional support of our Dean Professor Mohammed Salleh Mohammed Ardawi.

Author contributions

This is a single-author review paper by me. I am responsible for the conception, design/methodology, analysis, interpretation of data, writing, reviewing, and editing of the manuscript. The author read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Since it was a survey study ethical permission was not needed. However, Institutional review board permission was obtained, questionnaire included a consent to participate and anonymity of the participants was strictly maintained.

Consent for publication

Not applicable.

Competing interests

The author declares that she has no conflicts of interest.

Received: 12 June 2022 Accepted: 26 October 2022
Published online: 22 November 2022

References

1. Ruggeri B, Sarkans U, Schumann G, Persico AM. Biomarkers in autism spectrum disorder: the old and the new. Psychopharmacology. 2014;231:1201–16.
2. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Pyschiatry. 2003;160:636–45.
3. Persico AM, Sacco R. Endophenotypes in autism spectrum disorders. In: Patel V, Preedy V, Martin C, editors. Comprehensive guide to autism. 1st ed. New York: Springer; 2014. p. 77–95.
4. Viding EE, Blakemore SS. Endophenotype approach to developmental psychopathology: implications for autism research. Behav Genet. 2007;37:51–60.
5. Skuse DHD, Skuse DHD. Rethinking the nature of genetic vulnerability to autistic spectrum disorders. TIG. 2007;23:387–95.
6. DiCicco-Bloom E, Lord C, Zwaigenbaum L, Courchesne E, Dager SR, Schmitz C, et al. The developmental neurobiology of autism spectrum disorder. J Neurosci. 2006;28:6897–906.
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). 5th ed. Washington: American Psychiatric Association; 2013.
8. Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol. 2007;17:103–11.
9. Freitag CM, Staal W, Klauck SM, Duketis E, Waltes R. Genetics of autistic disorders: review and clinical implications. Eur Child Adolesc Psychiatry. 2010;19:169–78.
10. Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. Am J Psychiatry. 2010;167:1357–63.
11. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med. 1995;25:63–77.
12. Bolton P, Macdonald H, Pickles A, Rios P, Goode S, Crowson M, et al. A case–control family history study of autism. J Child Psychol Psychiatry. 1994;35:877–900.
13. Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P. Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry. 2010;167:1349–56.
14. Constantino JN, Todorov A, Hilton C, Law P, Zhang Y, Molloy E, et al. Autism recurrence in half siblings: strong support for genetic mechanisms of transmission in ASD. Mol Psychiatry. 2013;18:137–8.
15. Sumi SS, Taniai HH, Miyachi TT, Tanemura MM, Kishino HH. Sibling risk of pervasive developmental disorder estimated by means of an epidemiologic survey in Nagoya, Japan. J Hum Genet. 2006;51:518–22.
16. Schaefer GB, Mendelsohn NJ, Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: guideline revisions. Genet Med. 2013;15:399–407.
17. Schaefer GBG, Mendelsohn NJN. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders. Genet Med. 2008;10:301–5.
18. Persico AM, Napolioni V. Autism genetics. Behav Brain Res. 2013;251:95–112.
19. Faizo NL. A narrative review of MRI changes correlated to signs and symptoms of autism. Medicine (Baltimore). 2022;26(101):e30059.
20. Candini M, Battaglia S, Benassi M, et al. The physiological correlates of interpersonal space. Sci Rep. 2021;11:2611.
21. Satoa W, Uono S. The atypical social brain network in autism: advances in structural and functional MRI studies. Curr Opin Neurol. 2019;32:617–21.
22. Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. Biol Psychol. 2000;54:241–57.
23. Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci USA. 2004;101:8174–9.
24. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci. 2004;24:8223–31.
25. Stoner R, Chow ML, Boyle MP, Sunkin SM, Mouton PR, Roy S, et al. Patches of disorganization in the neocortex of children with autism. N Engl J Med. 2014;370:1209–19.
26. Connors SL, Levitt P, Matthews SG, Slotkin TA, Johnston MV, Kinney HC, et al. Fetal mechanisms in neurodevelopmental disorders. Pediatr Neurol. 2008;38:163–76.
27. Courchesne E, Redcay E, Kennedy DP. The autistic brain: birth through adulthood. Curr Opin Neurol. 2004;17:489–96.
28. Raznahan A, Toro R, Daly E, Robertson D, Murphy C, Deeley Q, et al. Cortical anatomy in autism spectrum disorder: an in vivo MRI study on the effect of age. Cereb Cortex. 2010;20:1332–40.
29. Courchesne E, Pierce KS. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. IJDN. 2005;23:153–70.
30. Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J. Mapping early brain development in autism. Neuron. 2007;56:399–413.
31. Hazlett HC, Gu H, McKinstry RC, Shaw DW, Botteron KN, Dager SR, et al. Brain volume findings in 6-month-old infants at high familial risk for autism. Am J Psychiatry. 2012;169:601–8.
32. Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, et al. Early brain development in infants at high risk for autism spectrum disorder. Nature. 2017;542:348–51.
33. Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, Toth K. Rate of head growth decelerates and symptoms worsen in the second year of life in autism. Biol Psychiatry. 2007;61:458–64.
34. Zielinski BA, Prigge MB, Nielsen JA, Froehlich AL, Abildskov TJ, Anderson JS, et al. Longitudinal changes in cortical thickness in autism and typical development. Brain. 2014;137:1799–812.
35. Maximo JO, Cadena EJ, Kana RK. The implications of brain connectivity in the neuropsychology of autism. Neuropsychol Rev. 2014;24:16–31.
36. Casanova MF. Neuropathological and genetic findings in autism: the significance of a putative minicolumnopathy. Neuroscientist. 2006;5:435–41.
37. Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, et al. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. Neurology. 2001;57:245–54.
38. Sacco R, Militerni R, Frolli A, Bravaccio C, Gritti A, Elia M, et al. Clinical, morphological, and biochemical correlates of head circumference in autism. Biol Psychiatry. 2007;62:1038–47.
39. Ramoz N, Cai G, Reichert JG, Corwin TE, Kryzak L, Smith CJ, et al. Family-based association study of TPH1 and TPH2 polymorphisms in autism. Am J Med Genet Part B. 2006;141B:861–7.
40. Stevenson RE, Schroer RJ, Skinner C, Fender D, Simensen RJ. Autism and macrocephaly. The Lancet. 1997;349:1744–5.
41. Fidler DJ, Bailey JN, Smalley SL. Macrocephaly in autism and other pervasive developmental disorders. Dev Med Child Neurol. 2000;42:737–40.
42. Lainhart JE, Piven J, Wzorek M, Landa R, Santangelo SL, Coon H, et al. Macrocephaly in children and adults with autism. Am Acad Child Adolesc Psychiatry. 1997;36:282–90.
43. Lai C, Ho C, Lim C, Roger, Ho R. Functional near-infrared spectroscopy in psychiatry. BJ Psych Adv. 2017;23:324–30.
44. Hazlett HC, Poe M, Gerig G, Smith RG, Provenzale J, Ross A, et al. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Arch Gen Psychiatry. 2005;62:1366–76.
45. Carper RA, Moses P, Tigue ZD, Courchesne E. Cerebral lobes in autism: early hyperplasia and abnormal age effects. Neuroimage. 2002;16:1038–51.
46. Hazlett HC, Poe MD, Gerig G, et al. Early brain overgrowth in autism associated with an increase in cortical surface area before age 2 years. Arch Gen Psychiatry. 2011;68:467–76.
47. Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. Biol Psychiatry. 2005;57:126–33.
48. Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Lange N, Bakardjiev A, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain. 2003;126:1182–92.
49. Sato W, Kochiyama T, Uono S, Yoshimura S, Kubota Y, Sawada R, et al. Reduced gray matter volume in the social brain network in adults with autism spectrum disorder. Front Hum Neurosci. 2017;11:361.
50. Pereira AM, Campos BM, Coan AC, Pegoraro LF, de Rezende TJR, Obeso I, et al. Differences in cortical structure and functional MRI connectivity in high functioning autism. Front Neurol. 2018;9:539.

51. Pappaianni E, Siugzdaite R, Vettori S, Venuti P, Job R, Grecucci A. Three shades of grey: detecting brain abnormalities in children with autism using source-, voxel- and surface-based morphometry. Eur J Neurosci. 2018;47:690–700.
52. Lo YC, Chen YJ, Hsu YC, Tseng WI, Gau SS. Reduced tract integrity of the model for social communication is a neural substrate of social communication deficits in autism spectrum disorder. J Child Psychol Psychiatry. 2017;58:576–85.
53. d'Albis MA, Guevara P, Guevara M, Laidi C, Boisgontier J, Sarrazin S, et al. Local structural connectivity is associated with social cognition in autism spectrum disorder. Brain. 2018;141:3472–81.
54. Gibbard CR, Ren J, Skuse DH, Clayden JD, Clark CA. Structural connectivity of the amygdala in young adults with autism spectrum disorder. Hum Brain Mapp. 2018;39:1270–82.
55. Aylward EH, Minshew NJ, Goldstein G, Honeycutt NA, Augustine AM, Yates KO, et al. MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. Neurology. 1999;53:2145–50.
56. Schumann CM, Barnes CC, Lord C, Courchesne E. Amygdala enlargement in toddlers with autism related to severity of social and communication impairments. Biol Psychiatry. 2009;66:942–9.
57. Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH, et al. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J Neurosci. 2004;24:6392–401.
58. Haznedar MM, Buchsbaum MS, Wei TC, Hof PR, Cartwright C, Bienstock CA, et al. Limbic circuitry in patients with autism spectrum disorders studied with positron emission tomography and magnetic resonance imaging. Am J Psychiatry. 2000;157:1994–2001.
59. Raymond GV, Bauman ML, Kemper TL. Hippocampus in autism: a Golgi analysis. Acta Neuropathol. 1995;91:117–9.
60. Xu Q, Zuo C, Liao S, Wang YL. Abnormal development pattern of the amygdala and hippocampus from youth to adolescent with autism. JOCN. 2020;78:327–32.
61. Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, et al. Brain structural abnormalities in young children with autism spectrum disorder. Neurology. 2002;59:184–92.
62. Piven J, Bailey J, Ranson BJ, Ardnt S. No difference in hippocampus volume detected on magnetic resonance imaging in autistic individuals. J Autism Dev Disord. 1998;28:105–10.
63. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 1990;13:266–71.
64. Utter AA, Basso MA. The basal ganglia: an overview of circuits and function. Neurosci Biobehav Rev. 2008;32:333–42.
65. Hollander E, Anagnostou E, Chaplin W, Esposito K, Haznedar MM, Licalzi E, et al. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biol Psychiatry. 2005;58:226–32.
66. Estes A, Shaw DW, Sparks BF, Friedman S, Giedd JN, Dawson G, et al. Basal ganglia morphometry and repetitive behavior in young children with autism spectrum disorder. Autism Res. 2011;4:212–20.
67. Thabault M, Turpin V, Maisterrena A, Jaber M, Egloff M, Galvan L. Cerebellar and striatal implications in autism spectrum disorders: from clinical observations to animal models. Int J Mol Sci. 2022;23:2294.
68. Voelbel GT, Bates ME, Buckman JF, Pandina G, Hendren RL. Caudate nucleus volume and cognitive performance: are they related in childhood psychopathology? Biol Psychiatry. 2006;60:942–50.
69. Langen M, Durston S, Staal WG, Palmen SJ, van Engeland H. Caudate nucleus is enlarged in high-functioning medication-naive subjects with autism. Biol Psychiatry. 2007;62:262–6.
70. Hardan AY, Kilpatrick M, Keshavan MS, Minshew NJ. Motor performance and anatomic magnetic resonance imaging (MRI) of the basal ganglia in autism. J Child Neurol. 2003;18:317–24.
71. Qiu AA, Adler MM, Crocetti DD, Miller MIM, Mostofsky SHS. Basal ganglia shapes predict social, communication, and motor dysfunctions in boys with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2010;49:539–51.
72. Ito M. Control of mental activities by internal models in the cerebellum. Nat Rev Neurosci. 2008;9:304–13.
73. Hardan AY, Minshew NJ, Harenski K, Keshavan MS. Posterior fossa magnetic resonance imaging in autism. JAACAP. 2001;40:666–72.
74. Murakami JW, Courchesne E, Press GA, Yeung-Courchesne R, Hesselink JR. Reduced cerebellar hemisphere size and its relationship to vermal hypoplasia in autism. Arch Neurol. 1989;46:689–94.
75. Courchesne E, Yeung-Courchesne R, Hesselink J, Jernigan T. Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med. 1988;318:1349–54.
76. Courchesne E, Townsend J, Akshoomoff NA, Saitoh O, Yeung-Courchesne R, Lincoln AJ, et al. Impairment in shifting attention in autistic and cerebellar patients. Behav Neurosci. 1994;108:848–65.
77. Carper RA, Courchesne E. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain. 2000;123:836–44.
78. Allen G. The cerebellum in autism. Clin Neuropsychiatry. 2005;2:321–37.
79. Courchesne E, Campbell K, Solso S. Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res. 2011;1380:138–45.
80. Saitoh O, Courchesne E. Magnetic resonance imaging study of the brain in autism. Psychiatry Clin Neurosci. 1998;52:219-S222.
81. Duerden EG, Mak-Fan KM, Taylor MJ, Roberts SW. Regional differences in grey and white matter in children and adults with autism spectrum disorders: an activation likelihood estimate (ALE) meta-analysis. Autism Res. 2012;5:49–66.
82. Yu KK, Cheung C, Chua SE, McAlonan GM. Can Asperger syndrome be distinguished from autism? An anatomic likelihood meta-analysis of MRI studies. J Psychiatry Neurosci. 2011;36:412–21.
83. Stoodley CJ. Distinct regions of the cerebellum show grey matter decreases in autism, ADHD, and developmental dyslexia. Front Sys Neurosci. 2014;8:92.
84. Kilian S, Brown WS, Hallam BJ, McMahon W, Lu J, Johnson M, et al. Regional callosal morphology in autism and macrocephaly. Dev Neuropsychol. 2008;33:74–99.
85. Anderson JS, Druzgal TJ, Froehlich A, DuBray MB, Lange N, Alexander AL, et al. Decreased interhemispheric functional connectivity in autism. Cereb Cortex. 2011;21:1134–46.
86. Frazier TW, Hardan AY. A meta-analysis of the corpus callosum in autism. Biol Psychiatry. 2009;66:935–41.
87. Shukla DK, Keehn B, Müller R. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. J Child Psychol Psychiatry. 2011;52:286–95.
88. Catani M. Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. Curr Opin Neurol. 2006;19:599–606.
89. Jou RJ, Jackowski AP, Papademetris X, Rajeevan N, Staib LH, Volkmar FR. Diffusion tensor imaging in autism spectrum disorders: preliminary evidence of abnormal neural connectivity. Aust N Z J Psychiatry. 2011;45:153–62.
90. Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL. White matter structure in autism: Preliminary evidence from diffusion tensor imaging. Biol Psychiatry. 2004;55:323–6.
91. Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol. 2005;15:225–30.
92. Lee JE, Bigler ED, Alexander AL, Lazar M, Dubray MB, Chung MK, et al. Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. Neurosci Lett. 2007;424:127–32.
93. Sundaram SK, Kumar A, Makki MI, Behen ME, Chugani HT, Chugani DC. Diffusion tensor imaging of frontal lobe in autism spectrum disorder. Cereb Cortex. 2008;18:2659–65.
94. Kumar A, Sundaram SK, Sivaswamy L, Behen ME, Makki MI, Ager J, et al. Alterations in frontal lobe tracts and corpus callosum in young children with autism spectrum disorder. Cereb Cortex. 2010;20:2103–13.
95. Shukla DK, Keehn B, Smylie DM, Müller R. Microstructural abnormalities of short-distance white matter tracts in autism spectrum disorder. Neuropsychologia. 2011;49:1378–82.
96. Koolschijn PC, Caan MW, Teeuw J, Olabarriaga SD, Geurts HM. Age-related differences in autism: the case of white matter microstructure. Hum Brain Mapp. 2016;38:82–96.
97. Haigh SM, Keller TA, Minshew NJ, Eack SM. Reduced white matter integrity and deficits in neuropsychological functioning in adults with autism spectrum disorder. Autism Res. 2020;13:702–14.
98. Dawson G, Warrenburg S, Fuller P. Cerebral lateralization in individuals diagnosed as autistic in early childhood. Brain Lang. 1982;15:353–68.

99. Jeong JW, Kumar AK, Sundaram SK, Chugani HT, Chugani DC. Sharp curvature of frontal lobe white matter pathways in children with autism spectrum disorders: tract-based morphometry analysis. Am J of Neuroradiol. 2011;32:1600–6.
100. Haruhisa O, Yuta YA, Takashi I, Chieko K, Junya F, Motoaki N, et al. White matter alterations in autism spectrum disorder and attention-deficit/hyperactivity disorder in relation to sensory profile. Mol Autism. 2020;11:77.
101. Dawson G. Lateralized brain dysfunction in autism: evidence from the halstead-reitan neuropsychological battery. J Autism Dev Disord. 1983;13:269–86.
102. Escalante-Mead PR, Minshew NJ, Sweeney JA. Abnormal brain lateralization in high-functioning autism. J Autism Dev Disord. 2003;33:539–43.
103. Kleinhans NM, Müller R, Cohen DN, Courchesne E. Atypical functional lateralization of language in autism spectrum disorders. Brain Res. 2008;1221:115–25.
104. Hoppenbrouwers M, Vandermosten M, Boets B. Autism as a disconnection syndrome: a qualitative and quantitative review of diffusion tensor imaging studies. Res Autism Spectr Disord. 2014;8:387–412.
105. Barnea-Goraly N, Lotspeich LJ, Reiss AL. Similar white matter aberrations in children with autism and their unaffected siblings: a diffusion tensor imaging study using tract-based spatial statistics. Arch Gen Psychiatry. 2010;67:1052–60.
106. Jou JR, Reed HE, Kaiser MD, Voos AC, Volkmar FR, Pelphrey KA. White matter abnormalities in Autism and unaffected siblings. J Neuropsychiatry Clin Neurosci. 2016;28:49–55. https://doi.org/10.1176/appi.neuropsych.15050109.
107. Casanova MF, El-Baz AS, Suri JS. Imaging the brain in autism. Springer nature publication. 2013. http://www.springer.com/biomed/book/978-1-4614-6842-4.
108. Dichter GS. Functional magnetic resonance imaging of autism spectrum disorders. Dialogues Clin Neurosci. 2012;14:319–51.
109. Weiner KS, Grill-Spector K. The improbable simplicity of the fusiform face area. Trends Cogn Sci. 2012;16:251–4.
110. Rokem A, Takemura H, Bock AS, Scherf KS, Behrmann M, Wandell BA, et al. THE visual white matter: the application of diffusion MRI and fiber tractography to vision science. J Vis. 2017;17:4.
111. Peelen MV, Downing PE. Selectivity for the human body in the fusiform gyrus. J Neurophysiol. 2005;93:603–8.
112. Suchan B, Denise A, Bauser S, Busch M, Schultle M, Gronemeyer D, et al. Reduced connectivity between the left fusiform body area and the extrastriate body area in anorexia nervosa is associated with body image distortion. Behav Brain Res. 2013;241:80–5.
113. Nickl-Jockschat T, Rottsch C, Thommes J, Schneider F, Laird AR, Fox PT, et al. Neural networks related to dysfunctional face processing in autism spectrum disorder. Brain Struct Funct. 2014;220:2355–71.
114. Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. Trends Cogn Sci. 2000;4:267–78.
115. Chan MMY, Han YMY. Differential mirror neuron system (MNS) activation during action observation with and without social-emotional components in autism: a meta-analysis of neuroimaging studies. Mol Autism. 2020;11:72.
116. Li L, He C, Jian T, Guo X, Xiao J, Li Y, et al. Attenuated link between the medial prefrontal cortex and the amygdala in children with autism spectrum disorder: evidence from effective connectivity within the "social brain. Prog Neuropsychopharmacol Biol Psychiatry. 2021;111:110147.
117. Padmanabhan A, Lynch CJ, Schaer M, Menon V. The default mode network in Autism. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017;2:476–86.
118. Odriozola P, Dajani DR, Burrows CA, Gabard-Durnam LJ, Goodman E, Baez AC, et al. Atypical frontoamygdala functional connectivity in youth with autism. Dev Cogn Neurosci. 2019;37:100603.
119. Fishman I, Linke AC, Hau J, Carper RA, Müller RA. Atypical functional connectivity of amygdala related to reduced symptom severity in children with autism. J Am Acad Child Adolesc Psychiatry. 2018;57:764-774.e3.
120. Ciaramidaro A, Bolte S, Schlitt S, Hainz D, Poustka F, Weber B, et al. Transdiagnostic deviant facial recognition for implicit negative emotion in autism and schizophrenia. Eur Neuropsychopharmacol. 2018;28:264–75.
121. Sato W, Kochiyama T, Uono S, Yoshimura S, Toichi M. Neural mechanisms underlying conscious and unconscious gaze-triggered attentional orienting in autism spectrum disorder. Front Hum Neurosci. 2017;11:339.
122. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage. 2012;63:921–35.
123. Fox SE, Wagner JB, Shrock CL, Tager-Flusberg H, Nelson CA. Neural processing of facial identity and emotion in infants at high-risk for autism spectrum disorders. Front Hum Neurosci. 2013;7:89.
124. Keehn B, Wagner JB, Tager-Flusberg H, Nelson CA. Functional connectivity in the first year of life in infants at-risk for autism: a preliminary near-infrared spectroscopy study. Front Hum Neurosci. 2013;7:444.
125. Edwards LA, Wagner JB, Tager-Flusberg H, Nelson CA. Differences in neural correlates of speech perception in 3-month-old at high and low risk for autism spectrum disorder. J Autism Dev Disord. 2017;47:3125–38.
126. Zhu H, Fan Y, Guo H, Huang D, He S. Reduced interhemispheric functional connectivity of children with autism spectrum disorder: evidence from functional near infrared spectroscopy studies. Biomed Opt Express. 2014;5:1262–74.
127. Yasumura A, Kokubo N, Yamamoto H, Yasumura Y, Nakagawa E, Kaga M, Hiraki K, Inagaki M. Neurobehavioral and hemodynamic evaluation of Stroop and reverse Stroop interference in children with attention-deficit/hyperactivity disorder. Brain Dev. 2014;36:97–106.
128. Xiao T, Xiao Z, Ke X, Hong S, Yang H, Su Y, et al. Response inhibition impairment in high functioning autism and attention deficit hyperactivity disorder: evidence from near-infrared spectroscopy data. PLoS ONE. 2012;7(10):e46569.
129. Minagawa-Kawai Y, Naoi N, Kikuchi N, Yamamoto J, Nakamura K, Kojima S. Cerebral laterality for phonemic and prosodic cue decoding in children with autism. Neuro Report. 2009;20:1219–24.
130. Suda M, Takei Y, Aoyama Y, Narita K, Sakurai N, Fukuda M, et al. Autistic traits and brain activation during face-to-face conversations in typically developed adult. PLoS ONE. 2011;6:e20021.
131. Ecker C, Murphy DD. Neuroimaging in autism-from basic science to translational research. Nat Rev Neurol. 2014;10:82–91.
132. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. J Child Psychol Psychiatry. 2008;49:535–42.
133. Vasa RA, Carroll LM, Nozzolillo AA, Mahajan R, Mazurek MO, Bennett AE, et al. A systematic review of treatments for anxiety in youth with autism spectrum disorders. J Autism Dev Disord. 2014;44:3215–29.
134. Tanaka M, Szabo A, Spekker E, Polyak H, Toth F, Vecsei L. Mitochondrial impairment: a common motif in neuropsychiatric presentation? The link to the tryptophan-kynurenine metabolic system. Cells. 2022;11:2607.
135. Tanaka M, Spekker E, Szabo A, Polyak H, Vecsei L. Modelling the neurodevelopmental pathogenesis in neuropsychiatric disorders. Bioactive kynurenines and their analogues as neuroprotective agents-in celebration of 80th birthday of Professor Peter Riederer. J Neural Transm (Vienna). 2022;129:627–42.
136. Martos D, Tuka B, Tanaka M, Vecsei L, Telegdy G. Memory enhancement with kynurenic acid and its mechanisms in neurotransmission. Biomedicines. 2022;10:849.

Publisher's Note