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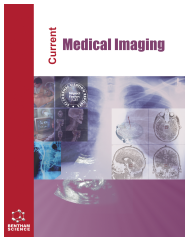

REVIEW ARTICLE

Applications of PET and SPECT in Patients with Autism Spectrum Disorder

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Abstract:

Autism spectrum disorder (ASD) consists of neurological development disorders that manifest before three years of age and affect social interactions, markedly restricting range of interests and activities, often associated with some degree of intellectual disability. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are non-invasive imaging tools to investigate the function of the brain *in vivo*. SPECT and PET studies exploring rCBF and brain glucose metabolism in patients with ASD have been performed, providing important insights into the brain regions involved in ASD. Abnormalities in serotonergic, dopaminergic, GABAergic, cholinergic, and glutamatergic systems have been suggested to contribute to the observed distorted brain circuitry associated with ASD. However, the specificity of such abnormalities needs to be fully clarified because schizophrenia and other psychiatric diseases have been shown to present with comparable changes in neurotransmitter systems. Neuroinflammation could also play a role in the development of autism. Therefore, ASD is a complicated process involving a number of factors. It is mandatory to perform more research studies to determine the molecular cornerstone of ASD and to improve our comprehension of the clinical correlates of ASD.

Keywords: Positron emission tomography, PET, SPECT, Autism, Brain, Pediatrics.

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1. INTRODUCTION

Autism spectrum disorder (ASD) consists of neurological development disorders that manifest before three years of age and affect social interactions, markedly restricting a range of interests and activities, often associated with some degree of intellectual disability [1]. Children with autism have cognitive deficits of different degrees: 30-40% have a mild delay, 40-50% have a severe or deep delay, and 10-15% have a normal intellectual level. Some individuals with ASD may be even capable of integrating into social life and having satisfying social relationships [2]. Additional features in patients with ASD may include obsessions, compulsions, catatonia, epilepsy, and changes in the sleep-wake rhythm [3].

Currently, the cause of autism spectrum disorder is unknown. However, the scientific literature agrees on a multifactorial etiopathogenesis to which genetic and environmental factors contribute. Therefore, an extremely complex picture is outlined, where it is difficult to trace a single triggering event. Moreover, in recent years, increasing attention has been devoted to epigenetics and intracellular factors that could affect the phenotype without altering the genotype [4].

The different manifestations of the autism spectrum can be divided into high-functioning autism (subjects capable of communicating verbally and endowed with normal or even superior intelligence) and low-functioning autism (subjects who are unable to use appropriate language and have insufficient mental capacity). Autism spectrum disorder includes idiopathic diseases (or primary autism), such as autism, autistic disorder, Asperger's syndrome, childhood disintegrative disorder (Heller's syndrome), and genetic subtypes (or secondary autism), such as fragile X syndrome, Rett syndrome, and tuberous sclerosis. Despite the fact that

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there are many different causes of autistic behavior, it is likely that common changes in signaling pathways can be present [5].

Recently, a whole genome association study involving over 1500 cases and controls combined from different cohorts has identified and replicated at least one locus at genome-wide significance [5]. Currently, there are over 25 different loci that may be considered autism susceptibility candidate genes (ASCG), and many more implicated loci are under investigation. Most of these are rare, Mendelian mutations, including copy number variation (CNV) or syndromic forms of autism, and only a few are due to common genetic variation. Genetic models for the etiology of ASD [5] provide a neurodevelopmental synthesis of autism that is based on altered connectivity between higher-order cortical association areas, especially anterior frontal and temporal lobes [6]. Anatomical evidence suggests that during the first three years of life, the trajectory of brain growth is elevated in ASD, with head circumference increasing from approximately normal to 10% larger than age-matched peers. During this time period, from age 2 to 4, this growth appears to localize in the frontal cortex, temporal lobes, and amygdala [7]. Patients with Fragile X and co-occurring ASD also exhibit an increase in head circumference size compared to those with Fragile X alone [8]. Diffusion tensor imaging shows that the axon tracts to these areas are disrupted [7], consistent with the notion of a developmental disconnection.

A second major model for autism pathogenesis suggests that ASD is caused by a disruption of the formation or maintenance of synaptic connections. This model is driven by the identification of the synaptic proteins NLGN3, NLGN4X, NRXN1, and SHANK3 as ASCG [9]. As predicted by this model, the gene ontology terms could suggest a significant enrichment of genes that have a synaptic function annotation.

It is well-known that single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are non-invasive imaging tools to investigate brain functions [10], including the cerebral blood flow (CBF), glucose metabolism, and a variety of neurotransmitters (receptors, transporters, or synthesis) [11]. It is important to note that in a healthy pediatric brain, glucose metabolism and perfusion are age-related, with newborns having low metabolic activity, and a peak in glucose uptake at 4 years, followed by a decrease with normal aging [12]. The mean cerebellum-to-cerebral cortex index has been shown to be high in the neonatal period, rather low between 2 months and 15 years, and thereafter somewhat identical to that observed in adults. Besides, cortical occipital indices exhibit considerable changes during the first year of life due to differences in maturation. A slight increase in fronto-occipital and temporo-occipital indices due to normal maturation of the brain must be recognized. At the subcortical level, thalamic perfusion is predominant over cortical areas up to the end of the second month. Regional cortical activity is distributed in certain patterns. Indeed, around the 40th week of gestation, the perfusion of both the parietal and occipital areas is fully visible [13]. In contrast, frontal activity remains scarcely recognizable up to the second month, but it increases to that seen in adults at the beginning of the second year [12].

The aim of this review was to provide a deeper understanding of ASD pathophysiology highlighting the contribution of molecular pathology and molecular imaging by means of the most salient findings available in the literature.

2. CEREBRAL BLOOD FLOW (CBF)

Results of molecular imaging studies have shown the presence of brain hypoperfusion in nearly 75% of ASD children [14 - 18]. Indeed, Zilbovicius *et al*. investigated the frontal cortex metabolic maturation in autistic children at pre-school age by performing a longitudinal rCBF study. The rCBF measurements were taken at two different times during their development, for *e.g*., at two and a half and four years, respectively. Children with autism aged 2 to 4 presented with transient frontal hypoperfusion, thus matching the pattern of hypoperfusion observed in younger healthy children. Since rCBF patterns in children have been shown to be related to maturational changes in brain function, the authors suggest the presence of delayed frontal maturation in childhood autism. Accordingly, such a delayed brain maturational process has been proven to correlate with clinical data and the cognitive performance of autistic children [18]. According to frontal findings, two independent groups reported significant bilateral hypoperfusion in temporal lobes related to perceptual, affective, and cognitive abnormalities of autism [17, 19]. Indeed, while limbic and parietal lobes are known to be connected to the sensory systems, the temporal regions have been shown to present strong connections to frontal areas. Besides, the observed reduction of rCBF in the auditory cortex could explain why early autistic children are frequently misdiagnosed as deaf and present with severe difficulties of communication, including verbal and non-verbal anomalies, poor lexical patrimony, inadequate verbal comprehension, presence of echolalia and pronominal inversions, and lack of communicative intentionality (Fig. **1**). The presence of hypoperfusion in the superior temporal sulcus (STS), a multimodal associative region that has strong connections to the fronto-parietal and limbic areas, could be related to the emotional and cognitive aspects of autism. Thus, the presence of temporal hypoperfusion in children with primary or idiopathic autism suggests the possibility that individuals with neurological disorders may exhibit autistic behavior as a result of dysfunction in the temporal lobe. Results of rCBF studies are consistent with the knowledge that the processing of a variety of environmental signals reaching the nervous system through the eyes and ears takes place primarily in the temporal lobe. Along with temporal cortices, the frontal areas may also have a role in the pathophysiology of ASD. Interestingly, it has been shown that perfusion in children with ASD gets worse as they get older and that age-related hypoperfusion of verbal-associated areas in the temporal and frontal lobes becomes progressively noticeable in autistic people [20].

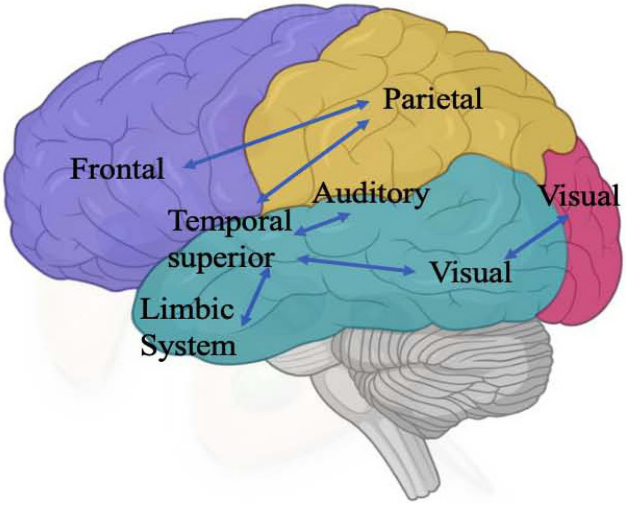

Fig. (1). Representation of cerebral pathways involved in autism disorders.

Other studies have detected specific alterations in secondary autism presenting with neurological diseases. Fronto-temporal and temporo-parietal hypoperfusion was detected in autistic subjects with epilepsy. Gillberg and co-workers investigated 31 ASD children with 99m Tc HMPAO, discovering an rCBF reduction in temporal lobes. Although 16 of these patients presented with epilepsy along with autistic disorder, no differences in rCBF were found between autistic patients with and without epilepsy, thus suggesting that seizure disorder could not account for rCBF findings [21]. In contrast, Sasaki *et al*. [16] showed that patients with autism and epilepsy could present with mixed hypoperfusion patterns involving the prefrontal, anterior cingulate, medial parietal, and anterior temporal cortices. Accordingly, the study by Degirmenci *et al*. performed on 10 ASD children (7 good functioning and 3 low functioning) showed the presence of hypoperfusion in the right inferior and superior frontal, left superior frontal, right parietal, and right mesial temporal cortices, and right caudate nucleus. Indeed, hypoperfusion was also described in subcortical areas [22, 23], including the cerebellar hemisphere [24]. Reduced rCBF in thalami has been linked to repetitive, self-stimulatory, atypical behaviors, a negative attitude toward changes in routine and surroundings, and peculiar sensory interest [25]. Besides, hypoperfusion of the temporal and frontal lobes has been linked to lowered IQ in people with ASD [26]. A right-side prevalence of rCBF reduction was observed in 11 ASD children [27]. In contrast, another study showed rCBF abnormalities mainly in the left temporal and parietal lobes [28].

3. GLUCOSE METABOLISM

According to the knowledge that glucose is the primary source of energy for the brain, 18F-fluorodeoxyglucose [(18F) FDG] PET has been used to track glucose metabolism in individuals with ASD in a number of clinical states. The study of glucose metabolism in awake ASD patients during rest or participating in activities, like listening to music or performing memory or attention tests [29 - 33], showed the presence of hypometabolism in the medial prefrontal and cingulate cortices, whereas an increased metabolism was observed in the occipital and parietal cortices [29 - 33]. Results of a [18F] FDG PET study performed in 21 ASD children (17 male/4 female; mean age 8.4 years) demonstrated the presence of hypometabolism in the bilateral temporal lobe [17] and superior temporal sulcus [14, 17, 34]. With respect to this concern, autistic children are frequently misdiagnosed as deaf and present with severe difficulties in communication, possibly related to dysfunction of the auditory cortex. Indeed, it has been reported that in contrast to normal children, activation of the superior temporal sulcus is not present in ASD children when exposed to sounds, thus suggesting that complex sensory inputs are not correctly elaborated in hypometabolic areas. Results of other studies performed on adults and children with ASD have shown reduced functionality in response to speech-like sounds in speech-related brain regions, such as the left temporal cortex [14, 17]. Moreover, hypometabolism in the fronto-temporal and dorsal-anterior cingulate cortex has been found to be associated with greater social impairments in ASD patients [35]. A number of [^{18}F] FDG PET studies performed on ADS patients have also documented the presence of sub-cortical hypometabolism in the thalamus and putamen [33, 36, 37], along with a widespread brain hypermetabolism [32]. Differences in PET findings are likely to be related to study designs, patient features (age and level of functioning), and experimental conditions [38]. A comprehensive list of SPECT and PET studies performed on children with autism is summarized in Table **1**.

Table 1. Main characteristics of the PET and SPECT studies included in the review.

PET Studies in ASD	-	-	-	-
Authors	**Target**	**No. of Partecipants**	**ASD IQ**	**Major Findings in ASD**
Schifter *et al*. (1994) [39]	Glucose	ASD: N = 13	-	4/13 individuals with ASD had an abnormal FDG-PET scan
Chugani *et al*. (1996) [40]	Glucose	Infantile spasm with temporal hypometabolism: N = 18; CON: N = 10	-	Children with infantile spasms have a poor long-term outcome and the majority are autistic at follow-up (10/14)
Chugani *et al*. (1997) [41]	5-HT synthesis	ASD = 8 CON: N = 5	OABC:19-29 months	Asymmetries in the dentate-thalamo-cortical pathway have been detected in individuals with ASD compared to their siblings

(Table 1) contd.....

PET Studies in ASD	-	-	-	-
Authors	**Target**	**No. of Partecipants**	**ASD IQ**	**Major Findings in ASD**
Chandana *et al*. (2005) [42]	5-HT synthesis	ASD = 117 Siblings: N = 8; Epilepsy: N = 16	Mental age <24 months	Abnormal cortical asymmetry in ASD (64/117); <5ht synthesis in ASD (58/64). Children with ASD left hemispheric asymmetry were more likely to have language impairments
Boddaert *et al*. (2005) [43]	CBF	ASD: N = 11; CON: N = 6	IQ: 43+/-21	Activation in the left middle temporal gyrus and precentral frontal gyrus
Gendry Meresse *et al*. (2005) [44]	CBF	ASD N = 45	IQ 44+/-22	Negative correlation b/w rCBF and autism diagnostic interview-R score in left STG
Chugani *et al*. (2007) [45]	Glucose	ASD: N = 12; Port-wine N = 4; CON: N = 11	Not specified	Compared to CON, the ASD group had lower glucose uptake in the cerebellum, medium temporal, AC, lateral temporal, and frontal cortices. Compared to Port-wine stain + ASD, ASD had more glucose uptake in medial temporal and AC cortices and less uptake in lateral temporal cortex
Brunelle *et al*. (2009) [34]	CBF	ASD: N = 57	-	77 ASD had lower blood flow in the superior temporal sulcus/21 had ASD along with the loss of grey matter
Duchesnay *et al*. (2011) [46]	CBF	ASD: N = 45; CON: N = 13	IQ: 45±22; DQ: 44±23	Less blood flow in the right STS and more blood flow in the contralateral post-central area
R.A. Kadwa *et al*. (2019) [47]	Glucose	ASD = 100; severe ASD = 30, and mild-moderate ASD = 70	Sensory processing abnormalities with short sensory profile	17% of children with severe ASD showed diffuse uptake in the cerebral/temporal lobe and bilateral frontal lobe uptake, and moderately low uptake in the parietal lobe (Lt>rt)
SPECT studies	-	-	-	-
Zilbovicius *et al*. (1992) [48]	CBF	ASD: N = 21; CON: N = 14	NVIQ: 36 ± 18.5, 10–75	No cortical differences between the groups
Mountz *et al*. (1995) [28]	CBF	ASD: N = 1	PIQ scores: 45, 32, 51, 70, 72, and 10	Low CBF in temporal and parietal lobes, and greater abnormalities in CBF in left *vs*. right hemisphere
Ryu *et al*. (1999) [24]	CBF	ASD: N = 23	Not specified	Less perfusion in areas, such as cerebellum, thalamus, basal ganglia, posterior parietal and temporal regions
Hashimoto *et al*. (2000) [26]	CBF	ASD: N = 22; CON: N = 10	IQ: 52.5 ± 16.2, 24–90	Low rCBF in laterotemporal and dorso-medio-frontal regions in ASD and greater in right *vs*. left temporal and parietal lobes in ASD
Ohnishi *et al*. (2000) [19]	CBF	ASD: N = 23; CON: N = 26	IQ: 48 ± 19.5 (Stanford Binet or DQ)	Low rCBF in bilateral insula, STG, and left prefrontal cortices
Starkstein *et al*. (2000) [25]	CBF	ASD: N = 30; CON: N = 14	PIQ: 30 ± 18.5	Low perfusion in the right temporal lobe, occipital lobes, thalami, and left basal ganglia
Kaya *et al*. (2002) [49]	CBF	ASD: N = 18; CON: N = 11	IQ: 56.11 ± 10.51 (Good enough IQ test)	Hypoperfusion in frontal, frontotemporal, and temporal occipital areas
Wilcox *et al*. (2002) [20]	CBF	ASD: N = 14; CON: N = 14	Complete mutism to moderately severe difficulty in language	Hypoperfusion in PFC, and hypoperfusion of speech areas in left temporal lobe and frontal areas, being more prominent with age

(Table 1) contd.....

PET Studies in ASD	-	-	-	-
Authors	**Target**	**No. of Partecipants**	**ASD IQ**	**Major Findings in ASD**
Steiner *et al*. (2003) [50]	CBF	Autism: N = 60; Atypical autism: N = 13; AS: N = 11; CON: N = not specified	Not specified	No significant differences between the groups
Ito *et al*. (2005) [22]	CBF	ASD: N = 16; CON: N =5	IQ: 94.7 ± 14.4, 76–126	Significant hypoperfusion in temporal cortex, and abnormal laterality in temporal, thalamic, and hippocampal regions
Burroni *et al*. (2008) [27]	CBF	ASD: N = 11; CON: N = 8	Not specified	Low CBF, and right to left asymmetry, especially in temporo-parietal areas
Degirmenci *et al*. (2008) [51]	CBF	HFA: N = 7; LFA: N = 3; (i): N = 5; (ii): N = 23; (iii): N = 15 (i) children with normal brain perfusion, brain CT or MRI and EEG; matched by age for autism group; (ii) 1st degree relatives of 8 individuals with autism in study (*e.g*., mother, father, and siblings); (iii) sex- and age-matched CON for 1st degree relatives	High- and low-functioning individuals, but IQ not specified	Abnormalities in brain perfusion found in caudate nucleus, frontal, temporal and parietal cortex in ASD, as well as 1st degree relatives
Sasaki *et al*. (2010) [52]	CBF	ASD: N = 15	IQ: 35–85; DQ: 15–58	Pattern of low blood flow in PFC, medial frontal cortex, AC cortex, medial parietal cortex, and anterior temporal lobe
Yang *et al*. (2011) [23]	CBF	Autism: N = 14; AS: N = 9; CON: N = 8	Not specified	Low rCBF in bilateral frontal lobe and bilateral basal ganglia in ASD; low rCBF in bilateral frontal, temporal and parietal areas, as well as the cerebellum, and asymmetry of hemispheric hypoperfusion
Gupta and Ratnam (2009) [53]	CBF	ASD: N = 10; CON: N = 5	IQ: 49 ± 12	Hypoperfusion in frontal and prefrontal areas, subcortical areas, as well as generalized hypoperfusion
Xiao-Mian *et al*. (2005) [54]	DAT	ASD: N = 10; CON: N = 10	Not specified	Low DAT binding
Makkonen *et al*. (2008) [55]	SERT and DAT	ASD: N = 15; CON: N = 10	IQ: 70–79 (Leitner method)	Low serotonin transporter (SERT) binding in medial frontal cortex
Makkonen *et al*. (2011) [56]	DAT	ASD: N = 13; CON: N = 10	Not specified	DAT binding being lower with age in ASD but more in control. Patients who responded to fluoxetine treatment had less DAT binding.
Mori *et al*. (2012) [57]	GABAA	Autism: N = 9; AS: N = 15; CON: N = 10	IQ < 70 (N = 7); IQ > 70 (N = 17)	Low binding in superior and medial frontal cortex in ASD
Zhao *et al*. (2014) [58]	CBF	Autism: N = 55	Not specified	Improved blood flow in prefrontal lobe and visual cortex following acupuncture treatment

4. SEROTONIN (5-HT)

The neurotransmitter 5-HT plays a regulatory role in brain development by modulating neuronal migration and synaptogenesis [59]. A study by Schain and colleagues first reported the presence of elevated whole blood 5-HT in ASD patients [60]. Besides, results of pharmacological studies showed that serotonin transporter (SERT) binding capacity is reduced in ASD adolescent patients and selective 5-HT reuptake inhibitors (SSRIs) may control some repetitive behaviors in post-pubertal ADS individuals [61, 62]. Concerning molecular imaging, the 5-HT network is the most common neurotransmission system investigated in ASD patients by SPECT and PET [63]. Results of [11C] methyl-L-tryptophan (AMT) PET studies investigating the 5-HT synthesis have shown the presence of abnormalities (*e.g*., local cortical increase or decrease) in 5-HT synthesis and asymmetries in the dentate-thalamo-cortical pathway in ASD individuals compared to their siblings [41]. Age-related changes in 5-HT synthesis have been considered atypical in individuals with ASD. Indeed, the decreases in 5-HT synthesis commonly observed in siblings between the ages of 5 and 14 years are not reported in ASD patients, thus suggesting serotonergic impairment during development [64]. Abnormalities of the dentate-thalamo-cortical pathway in ASD children have been suggested to be related to language dysfunction [42].

The serotonin synthesis in non-autistic children before the age of five has been reported to be higher than that in adults and to decline towards the adult values over time. In contrast, the serotonin synthesis in children with autism was found to be approximately one-third lower than in normal age-matched controls during the first 5 years and to progressively increase up to 15 years, reaching values 1.5 times lower than those observed in normal adults [64]. Accordingly, decreases in 5-HT2A receptor and SERT in various brain regions have been reported, including the cingulate cortex, the medial prefrontal cortex, the thalamus, and temporal and parietal lobes in ADS patients [55, 65 - 68]. It was concluded that decreased SERT binding and serotonin synthesis are likely to reflect the maturation of fewer serotonergic nerve terminals and a sparse serotonergic synapse density in individuals with autism during the early phases of their life [55].

Selective serotonin receptor inhibitors have been used to target the SERT and treat the symptoms of ASD. The iodine-123-labeled N-(2-fluoroethyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane [(123I) nor-β-CIT] is a radioligand that selectively binds the SERT. Makkonen *et al*. [55] used (123I) nor-CIT SPECT to assess the availability of SERT in youngsters with ASD. They found that SERT binding was considerably reduced in ASD patients compared to controls in the medial frontal cortex, midbrain, and temporal lobes, thus suggesting that autistic people could present with a reduced SERT binding potential. Results of (11C)-labeled trans-1,2,3,5,6,10-hexahydro-6-[4-(methylthio) phenyl] and (11C) (+) McN-5652) pyrrolo-(2,1-a) isoquinoline PET studies have revealed a significantly less SERT binding in the total brain in adults with high-functioning autism compared to controls. These results are supported by another PET study with (11C)-labeled trans-1,2,3,5,6,10-hexahydro-6-[4-(methylthio)phenyl]pyrrolo-(2,1-a)isoquinoline [(11C)(+)McN-5652] showing a significantly less SERT binding in the brain of adults with high-functioning autism compared to controls [67]. In previous findings [65, 66], decreased SERT binding in thalamic nuclei has been found to be associated with repetitive and obsessive behaviours, while the decreased binding in the anterior and posterior cingulate cortices has been found to be linked to altered social cognition. Although further efforts are needed to provide more insights into the role of SERT in ADS, it has been shown that repetitive behaviours can be controlled with the aid of selective 5-HT reuptake inhibitors (SSRIs), mainly in people with post-pubertal ADS [64, 69].

5. DOPAMINE (DA)

Dopamine (DA) is involved in a number of functions, such as social reward and social motivation [70]. Attention deficit hyperactivity disorder (ADHD), tics, and anxiety have been linked to the DA transporter (DAT1) genotype in genetic investigations on people with ASD [71].

The (18F)-labeled fluorodopa [(^{18}F) DOPA] is an L-DOPA analog radioligand that can be used to assess the DA synthesis. Results of (^{18}F)DOPA PET study performed by Ernst and co-workers [72] discovered that drug-free ASD patients accumulated less [(^{18}F)DOPA] in the anterior medial PFC than age-matched healthy controls, thus suggesting that prefrontal dopaminergic deficiencies could account for the cognitive impairment in ASD. In the 2-carbomethoxy-3- (4-fluorophenyl) tropane (11C-WIN-35,428) PET study conducted by Nakamura [67], 20 patients with high-functioning autism and 20 age-matched controls were compared for DA transporter binding. The authors found that the autistic group presented an increased DA transporter binding in the orbitofrontal cortex, which is known to have a strategic role in the emotional network. Accordingly, it has been suggested that impulsive and aggressive behaviors in ASD could be related to hyperactivity of the dopaminergic orbito-frontal-limbic circuit [73]. Results of a SPECT study with a dopamine transporter imaging agent, namely ^{99m}Tc-TRODAT-1, reported a whole-brain increase in dopamine transporter binding in autistic children and no increases in the striatum/cerebellum ratio [54]. Accordingly, no differences in striatal dopamine transporter binding have been found in a SPECT study with the dopamine and serotonin transporter radioligand, namely (123I) NOR-B-IT [55]. Taken together, the results of these studies suggest that a dopaminergic dysfunction in frontal cortical regions rather than in the striatum could be responsible for the observed cognitive impairment in children and adults with autism.

6. GABA RECEPTOR BINDING STUDIES

There is evidence that gamma-aminobutyric acid (GABA) is the most common inhibitory neurotransmitter in the central nervous system and it acts on GABA-A and GABA-B receptors. However, GABA-mediated signaling is also known to exert strong control over important developmental processes, such as cell division, neuron differentiation, and circuit

amplification [74]. Emerging evidence suggests that altered GABA-mediated signaling could be involved in the pathogenesis of autism by an impairment of excitation and inhibition processes [75, 76]. Mori *et al*. [57] investigated the function of GABA-A receptors in ASD children by 123I-iomazenil (123I-IMZ) SPECT. Results of this study showed that the ASD group presented with a significantly reduced 123I-IMZ concentration in regions linked to the cognitive theory of mind, such as the superior and medial frontal cortex, compared to the control group. Accordingly, results of the 18F-flumazenil (18F-FMZ) PET study performed on 28 high-functioning ASD adults [77] showed the presence of changes in GABA concentrations, which were region- and sex-specific.

7. ACETYLCHOLINE

It is known that acetylcholine (ACh) is a neurotransmitter located at the neuro-muscular junction where two types of ACh receptors are present, namely nicotinic and muscarinic. The cholinergic system is described as an "action system" because it is responsible for attentional and behavioural responses to surrounding stimuli [78].

The role of acetylcholine deficits in autism has not been explored so far. However, a report of neuropathological abnormalities in cholinergic neurons located in the basal forebrain of patients with autism has generated interest in the study of acetylcholine. Because the cholinergic system has proven to play a pivotal role in cognitive abilities, it has been hypothesized that a dysfunction of this network could underlie the cognitive deficits (*e.g*., attention and learning) often seen in patients with autism [62]. Accordingly, post-mortem studies on autism patients have revealed a significant decrease in the number of nicotinic and muscarinic receptors in the parietal cortex and cerebellum [79, 80]. Furthermore, several drugs have been developed to counteract the brain-wasting that occurs in patients with Alzheimer's disease due to a reduced central ACh activity by increasing the time-life of Ach in the synaptic cleft. From these premises, researchers have begun to investigate the use of acetylcholinesterase inhibitors, including donepezil [81, 82], galantamine [83], and rivastigmine tartrate [81] in autism. Results of pharmacological investigations with acetylcholinesterase inhibitors have shown a reduced autistic symptomatology overall in adult patients as well as decreased aggressiveness and inattention in ASD children [81, 82, 84]. Accordingly, results of studies performed on animal models of autism provide further evidence that acetylcholine is likely to have a driving role in the attentional and social problems observed in ASD [85]. Finally, a PET study examining the cholinergic system in ASD patients regulated by the acetylcholine mimic radioligand N-(11C) methyl-4-piperidyl acetate [(11C)MP4A] showed that adults with autism have a deficiency in cholinergic innervation in the fusiform gyrus [86].

8. GLUTAMATERGIC SYSTEM

Glutamate has been shown to be the main excitatory neurotransmitter in the brain and have a strategic role in neural plasticity. ASD has been linked to Shank 3 gene deficiency, which codes for the postsynaptic scaffold protein found in glutamatergic neurons [87]. Results of a recent study with 18F-3-fluoro-5-[(pyridine-3-yl)ethynylbenzonitrile [(18F)FPEB] PET for metabotropic glutamate receptor-5 density provided evidence that adults with ASD have significantly high levels of metabotropic glutamate receptor 5 in the cerebellum and postcentral gyrus if compared to those in the typical development group [88]. The cerebellum plays a key role in the integration of sensory and motor inputs required for dexterous movement [89]. Morphological changes in the cerebellum of subjects with autism have been identified, including a reduced cerebellar volume, altered Purkinje cell density, and abnormalities in deep cerebellar nuclei [89]. Thus, it has been suggested that abnormalities in glutamate signaling in the cerebellum could be responsible for the observed dysfunction of somato-sensorimotor-cerebellar circuit, possibly leading to the motor and cognitive impairments associated with autism. Furthermore, autistic symptomatology has proven to positively correlate with (18F) FPEB binding in the precuneus, which is known to be a crucial region within DMN. This result has led to the hypothesis that the excitatory/inhibitory imbalance of glutamatergic transmission within DMN could also participate in the pathophysiology of ASD.

9. PET IMAGING OF NEUROINFLAMMATION

There is evidence that the IMMUNE system could play a role in the pathophysiology of ASD. The 18-kDa translocator protein can exhibit minute changes in expression, which can be detected by the radiotracer 11C-PBR28 [90]. The roles of TSPO include apoptosis, steroidogenesis, neuroinflammation, energy production, cell metabolism, and oxidative stress [91]. Using 11C-PBR28 PET-MR, Zürcher *et al*. [92] reported significantly decreased TSPO levels in the precuneus/posterior cingulate cortex, insular cortex, and bilateral, temporal, angular, and supramarginal gyri in young male adults with ASD when compared to those of age- and sex-matched controls. The authors reported that reduced TSPO in ASD could be a result of an altered functionality in glia, neurons, and endothelial cells. However, more efforts are required to fully clarify the precise mechanisms underlying the aberrant TSPO expression in ASD.

10. THERAPY

The majority of ASD treatments used today are psychological and behavioral. Nevertheless, there are still no proven pharmaceutical therapies for the primary symptoms of ASD. The oxytocin has been recently proposed as a possible pharmacological treatment for ASD [93]. Researchers discovered that oxytocin improved the functional connectivity of the default mode network (DMN) [94, 95]. Using resting-state functional MRI, researchers found that oxytocin augmented the functional connectivity of the DMN [96] and cortical-striatal circuits [12]. 6-week intranasal administration of oxytocin increased the functional connectivity between the anterior cingulate cortex and dorsal medial prefrontal cortex in ASD patients [96].

Lefevre *et al*. [97] examined the therapeutic impact of oxytocin on the serotoninergic system in ASD patients using 2′-methoxyphenyl-(N-2′-pyridinyl)-p-(18F) fluoro-benzamido-ethylpiperazine [(18F) MPPF] PET for 5-HT1A receptors. They discovered an oxytocin-serotonin interaction in the

controls that was not present in the ASD patients. Hirosawa *et al*. [98, 99] studied the serotonergic regulation after long-term treatment of oxytocin in ASD patients using (11C)-3-amino-4-(2-[(dimethylamino) methyl] phenylthiobenzonitrile [(11C) DASB] PET for SERT availability. Following oxytocin delivery, the authors observed significantly increased (11C) DASB binding in the left inferior frontal gyrus and striatum in patients with ASD. Given that ASD patients could present with both an increased frontal-striatal brain dopaminergic pathway due to oxytocin-based therapy, further studies are needed to understand the interaction of oxytocin with the dopaminergic system [12, 100].

Additionally, medications affecting neurotransmitter systems, like serotonin or dopamine, may alter the way how glucose is metabolized in particular regions, possibly lessening the symptoms of ASD. Despite the lack of evidence supporting the use of SSRIs for ASD in children, several studies recommend the use of fluoxetine and selective serotonin receptor inhibitors to reduce the severity of core behaviors associated with ASD.

In a small sample of people with ASD (N = 6), the authors of a pilot (^{18}F) FDG PET study observed that regional metabolic rates increased following therapy in the anterior cingulate gyrus, medial and orbitofrontal area, and striatum. It is interesting to note that these metabolic adjustments were followed by a decline in anxiety and obsessive and compulsive behaviors [101]. Therapeutic medications may alter or normalize glucose metabolism, which may have a positive impact on behaviour.

A (^{18}F) FDG PET study examined the therapeutic potential of deep brain stimulation for an ASD patient exhibiting self-harming behaviors [102]. Two years after deep brain stimulation of bilateral nucleus accumbens, the authors documented a reduced glucose metabolism in the occipital and pre-frontal cortex coupled with symptomatic improvement. Furthermore, the volumes in these areas were reduced along with the decline in glucose metabolism. These findings suggest that ASD patients who engage in life-threatening self-harming behaviors may have organic lesions linked to structural and functional changes, and that deep brain stimulation can affect these lesions.

CONCLUSION

Impairment of several neurotransmission systems (*e.g*., serotonergic, dopaminergic, GABAergic, cholinergic, and glutamatergic) may contribute at different levels to the observed dysfunction of brain circuitry underlying ASD. The specificity of brain regions involved in the ASD network has not yet been fully clarified because schizophrenia and other psychiatric diseases have been linked to similar changes in neurotransmission, thus suggesting that a common pathway may underlie different psychiatric disorders. Neuro-inflammation and altered glucose metabolism may also play a role in the development of autism. Therefore, ASD is likely to be a rather complicated process that requires a deeper comprehension of neurological correlates to improve the pharmacological approaches for the functional adjustment of both clinical symptoms and relapse of pathological behaviors. With this concern, emerging evidence suggests that oxytocin and selective serotonin receptor inhibitors (*e.g*., fluoxetine) could be possible treatments to improve symptomatology linked to anxiety or obsessive and compulsive behaviors. Besides, the potential of acetylcholinesterase inhibitors, including donepezil [81, 82], galantamine [83], and rivastigmine tartrate [81], has also been investigated. Acetylcholinesterase inhibitors have been shown to reduce autistic symptomatology overall and to decrease aggressiveness and inattention in ASD children. Nevertheless, further studies are needed to investigate the therapeutic choices for patients with ASD.

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CONFLICT OF INTEREST

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