Brain Research Bulletin 198 (2023) 65–76

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Review

Prefrontal functional connectivities in autism spectrum disorders: A connectopathic disorder affecting movement, interoception, and cognition

Gerry Leisman [a,b,*], Robert Melillo [a], Ty Melillo [c]

[a] Movement and Cognition Laboratory, Department of Physical Therapy, University of Haifa, Haifa, Israel
[b] University of the Medical Sciences of Havana, Department of Clinical Neurophysiology, Institute of Neurology and Neurosurgery, Havana, Cuba
[c] Northeast College of the Health Sciencs, Seneca Falls, NY, USA

ARTICLE INFO

Keywords:
Prefrontal cortex
Autism
ASD
Retained primitive reflexes
Cognition
Self
Hemisphericity
Cognitive-motor interaction

ABSTRACT

The prefrontal cortex is included in a neuronal system that includes the basal ganglia, the thalamus, and the cerebellum. Most of the higher and more complex motor, cognitive, and emotional behavioral functions are thought to be found primarily in the frontal lobes. Insufficient connectivity between the medial prefrontal cortex (mPFC) and other regions of the brain that are distant from each other involved in top-down information processing rely on the global integration of data from multiple input sources and enhance low level perception processes (bottom-up information processing). The reduced deactivation in mPFC and in the rest of the Default Network during global task processing is consistent with the integrative modulatory role served by the mPFC. We stress the importance of understanding the degree to which sensory and movement anomalies in individuals with autism spectrum disorder (ASD) can contribute to social impairment. Further investigation on the neurobiological basis of sensory symptoms and its relationship to other clinical features found in ASD is required Treatment perhaps should not be first behaviorally based but rather based on facilitating sensory motor development.

1. Introduction

The prefrontal cortex is included in a neuronal system that includes the basal ganglia, thalamus and cerebellum (Melillo and Leisman, 2010). Most of the higher and more complex motor, cognitive, and emotional behavioral functions are thought to be found primarily in the frontal lobes (Melillo and Leisman, 2010).

There exists a direct and equal relationship between motor and nonmotor deficits of the frontal lobe in Autistic Spectrum Disorders (ASD) (Hampson and Blatt, 2015; D'Mello and Stoodley, 2015). The degree of cognitive or behavioral dysfunction correlates directly to an individual's motor dysfunction. Therefore, it is postulated that in patients with diffuse prefrontal dysfunction, the inability to inhibit movements to simple external stimuli may correlate with the inability to inhibit complex social behaviors in response to complex internal stimuli (Mahone et al., 2006; Fernández et al., 2019). If this correlation is accurate, then a motor dysfunction could result in cognitive and emotional dysfunction and vice versa. This also has powerful therapeutic implications because it should follow that improved sensory-motor function should result in improved cognitive and behavioral function of the frontal lobe.

With the relationship between cognitive and motor function related to the prefrontal regions in ASD, there exists an overlap of cognitive and motor symptoms. This relationship is based on the articulation of cerebellum, basal ganglia, and frontal lobes, which are areas of the brain recognized to control motor and nonmotor intentional and executive function (Hampson and Blatt, 2015; D'Mello and Stoodley, 2015; Fernández et. al, 2019). Most developmental disabilities including ASD have as their most common symptom, motor incoordination or clumsiness, especially of posture and gait. Impulse control, either inhibited or facilitated, and judgment disorders can all be attributed to dysfunction of this network and its control of motor and nonmotor behavior (Ketcheson et al., 2021; Su et al., 2022). This spectrum of disorders all involve disruption primarily to what is known as executive functions which are functions attributed to the frontal lobe. Striatal neurons may be involved with gating incoming sensory input to higher motor areas such as the intralaminar thalamic nuclei and premotor cortex that arise from several modalities to coordinate behavioral responses (Groenewegen et al., 2016; Haber, 2017). These varied modalities may lead to

* Correspondence to: Movement & Cognition Laboratory, Faculty of Social Welfare and Health Science, 199 Abba Khoushy Street, Eshkol Tower, Room 910 Mt. Carmel Haifa, 3498838, Israel.
E-mail address: g.leisman@alumni.manchester.ac (G. Leisman).

https://doi.org/10.1016/j.brainresbull.2023.04.004
Received 27 February 2023; Received in revised form 5 April 2023; Accepted 17 April 2023
Available online 21 April 2023

the perception of sensation resulting in motor response. The basal ganglia, like the cerebellum, is functionally connected to the premotor and motor cortices as well as to the prefrontal cortex (Mei et al., 2022).

The frontal lobe is united by five subcortical circuits represented in Fig. 1 (the frontal eye fields; dorsolateral, prefrontal, orbito-frontal and anterior cingulate cortices as well as the supplementary motor area;) with the globus pallidus, thalamus, and striatum, in functional systems that mediate executive functions, saccadic eye movements, volitional motor activity, social behavior and motivation. The necessary components for optimized executive function include the striatum, providing support for motivation; the amygdala adding emotional support; and the thalamus providing the capacity for the integration of sensory input – all under the direction of the prefrontal regions of the brain. In the basal ganglia -prefrontal circuits there are two primary loos The direct and indirect pathways usually maintain a dynamic balance. The direct pathway activates motor activity, motivation, saccadic eye movement, executive function and social behavior. The indirect pathway inhibits these functions. If there is too much influence of the direct pathway hyperkinetic behaviors, tics, manic behavior, inappropriate or social behaviors, and/or saccadic dysmetria may result. If there is excessive indirect pathway activity hypokinetic behavior may result. To help maintain this dynamic balance is the hyperdirect pathway which has two parts, the premotor area (Brodmann Areas (BA) 6, 8) only on the right hemisphere activates the indirect pathway and projects directly to the subthalamic nucleus to control unwanted motor behaviors. The second pathway of the hyperdirect pathway arises from the right inferior frontal gyrus, (BA 44, 45, 47) and activates the indirect and subthalamic nucleus to inhibit limbic, cognitive, and associative functions. Loss of this dynamic balance can explain most of the symptoms witnessed in ASD along with a right hemisphere deficit. (Melillo and Leisman, 2010).

The right hemisphere develops first in the uterus and for the first three years is highly influenced by early motor activity. If there is any altered, delayed, or abnormal motor development such as retained primitive reflexes, low muscle tone, skipped or severely delayed motor milestones this would be a main influence on underdevelopment of the right hemisphere and the indirect pathway. In ASD, the various regions under the control of prefrontal areas are not effectively synchronized with each other. Support for this notion is provided from studies of brain structure and the electrophysiology of its function, animal models and clinical studies of ASD individuals. Additional support is provided from postmortem data, structural analysis of the cortex, and the nature of neuronal connectivities (Melillo and Leisman, 2010).

We will be building on our previous work on the nature of functional connectivities in those with ASD, in particular the nature of weak long range connectivities. We also support this contention on the basis of the findings that ASD individuals demonstrate exceptional performance in detail processing; but simultaneously demonstrate impairment of motion perception, face processing and sustained visual attention besides the core social deficits. Increasing evidence supports the thinking that ASD individuals' core deficits are associated with deficits in functional connectivities within and between distributed cortical networks that reflect an orchestra playing without an effective conductor.

As previously stated, the frontal lobe is united by five subcortical circuits represented in Fig. 1 for behavioral sequalae (the frontal eye fields; dorsolateral, prefrontal, orbito-frontal and anterior cingulate cortices as well as the supplementary motor area) with the globus pallidus, thalamus, and striatum, in functional systems that mediate executive functions, saccadic eye movements, volitional motor activity, social behavior and motivation (Riveros et al., 2019). The basal ganglia-prefrontal circuits are represented in Fig. 2. The necessary components for optimized executive function include the striatum, providing support for motivation; the amygdala adding emotional support and the thalamus, providing the capacity for the integration of sensory input – all under the direction of the prefrontal regions of the brain (Rosch and Mostofsky, 2019).

In the basal ganglia-prefrontal circuits there exist two primary loops, as represented in Fig. 2. The direct and indirect pathways usually maintain a dynamic balance. The direct pathway activates motor activity, motivation, saccadic eye movement, executive function and social behavior. The indirect pathway inhibits these functions. If there is too much influence of the direct pathway hyperkinetic behaviors, tics, manic behavior, inappropriate or social behaviors, and/or saccadic dysmetria may result. If there is excessive indirect pathway activity hypokinetic behavior may result. Therefore, effective behavioral function is a direct consequence of the brain's ability to integrate and time or simply balance multiple functions especially as they relate to cognitive-motor behavior (Melillo and Leisman, 2010; Leisman et al., 2022).

To help maintain this dynamic balance is the hyperdirect pathway which has two parts, the premotor area (Brodmann 6, 8) only on the right hemisphere that activates the indirect pathway and projects

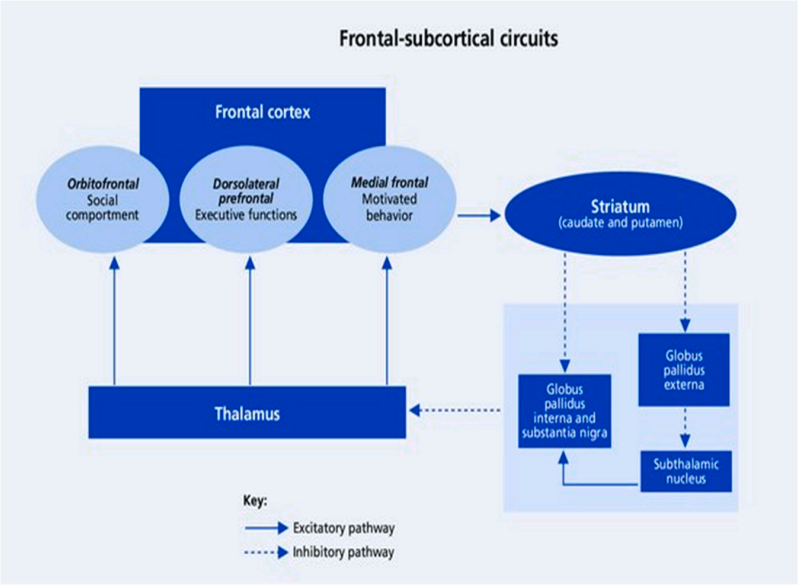

Fig. 1. Frontal subcortical connectivities related to common neurobehavioral sequelae.

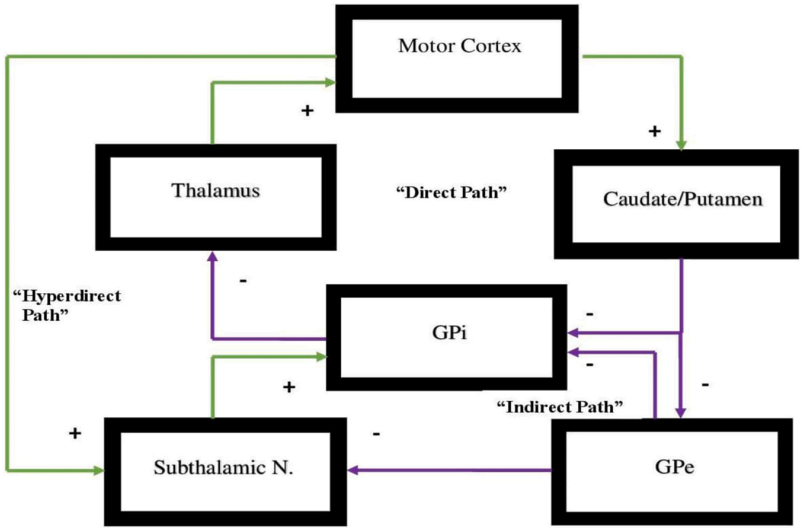

Fig. 2. Schematic of the direct vs. indirect basal ganglia pathways indicating inhibitory vs. facilitatory components of motor activity. Input from the cerebral cortex to the striatum, in the direct pathway, is related to the activation of striatal inhibitory neurons. This subsequently is associated with increases in inhibitory output that in turn projects to the globus pallidus-internal [GPi]. Subsequently, decreased inhibitory output from GPi to the ventral anterior [VA] and ventral lateral [VL] thalamic nuclei is evidenced. This, in turn, projects to the premotor cortex through excitatory pathways. Motor and premotor cortical excitation that is involved in planning and movement initiation is regulated by the direct pathway. When appropriately functioning, the indirect pathway inhibits movement when excitatory activity that is cortically generated activates inhibitory neurons in globus pallidus external [GPe]. These, as a result inhibit tonic inhibitory output neurons, are associated with decreased tonic inhibition of the subthalamic nucleus [STN], that results in increased excitatory output to GPi. Excitatory input to GPi adds inhibitory output from GPi to the thalamus. This, in turn, diminishes excitatory feedback to the cerebral cortex which, under normal circumstances, should lead to motor inhibition. The hyperdirect pathway is an exception as the striatum is circumvented with a direct link from the cortex to the subthalamic nucleus, directing excitatory projections to the GPi. The hyperdirect pathway is essential in constraining non-purposeful movement. When the system is impaired, individuals are less able to inhibit unplanned motor activity (from Leisman and Melillo, 2022).

directly to the subthalamic nucleus to control unwanted motor behaviors. The areas of Brodmann are represented in Fig. 3. The second pathway of the hyperdirect pathway arises from the right inferior frontal gyrus (BA 44, 45, 47), activates the indirect and subthalamic nucleus to inhibit limbic, cognitive, and associative functions. Loss of this dynamic balance can explain most of the symptoms witnessed in ASD along with a right hemisphere deficit (Leisman and Melillo, 2022b). The right hemisphere develops first in utero and for the first three years is highly influenced by early motor activity. If there is any altered, delayed, or abnormal motor development such as retained primitive reflexes, low muscle tone, skipped or severely delayed motor milestones this would be a main influence on the underdevelopment of the right hemisphere and the indirect pathway. In autistic spectrum disorder, the various regions under the control of prefrontal areas are not effectively synchronized with each other. Support for this notion is provided from studies of brain structure and the electrophysiology of its function, animal models and clinical studies of ASD individuals. Additional support is provided from postmortem data, structural analysis of the cortex, and the nature of neuronal connectivities.

2. Brain asymmetries and movement timing in ASD

2.1. Basis for asymmetric brain organization in cognitive-motor interaction

For movement coordination to be effective, bilateral movements require limbs to produce efficient and optimized gait. Symmetrical gait's effectiveness is a direct function of timing in the motor system associated, in part, with the effective functioning of the inferior olive and the cerebellum (De Sanctis et al., 2021; Shimada et al., 2013). The importance of the cerebellum in this context is its ability to adjust muscle tone in involuntary and voluntary movement through the descending motor pathways that are articulated with the frontal lobes. The timing signal is metronomic permitting the motor system to connect movement temporally and spatially (Ivry et al., 2002). If there was no such timing signal, then there would exist a significantly greater likelihood of uncoordinated movement. The mechanism that allows for timing the coordination of movement should also be equal bilaterally.

The timing signal generated by the "clock" needs to be distributed symmetrically in the motor system otherwise aysmmetric movements might be generated which are not infrequently observed in developmental disabilities associated with asymmetric development or in developmental or adult-onset cerebellar damage (Swinnen et al., 1993; Morishita et al., 2022). ASD as well as numerous other developmental disorders and what used to be called developmental coordination disorder (DSD) have been described as cerebellar-based developmental functional and anatomical deficits (Bruchhage et al., 2018; Brown-Lum and Zwicker, 2015). However, beyond the requirement for sensory and motor control, cognitive, behavioral and information processing functions necessitate brain asymmetry. A critical function of the human brain is the necessity for speed of response. For self-preservation, it is essential for the brain to function speedily. Redundancy is the nemesis of speed and efficiency in the human nervous system. Brain centers become deoptimized when multiple regions perform the same function. It is far more effective to have a distinct area on one side of the brain and an additional control region on the contralateral side, where on occasion they can cooperate and at times inhibit each other to minimize interference. In addition to increases in speed, accuracy and efficiency, the bicameral brain function enhances the brain's ability to accomplish more highly specialized tasks that are associated with complex brains asymmetry (Güntürkün et al., 2020).

2.2. Brain asymmetry and complexity

There exist two primary components in complexity theory, one of which being: a) differentiation. For a complex system to adequately function, diversity is a necessity (Merker et al., 2022). By definition, systems consisting of various nodes and regions controlling specialized activities are complex. With hemispheric function performing related tasks, but in different and specialized ways, there exists a requirement for a more complex brain. In comparison to other species, humans possess the most asymmetric as well as the most complex brains with a concomitant complexity of behavior. In ASD and well as with other developmental disabilities brain immaturity may be observed that is alternatively less capable of behavioral complexity or demonstrating behaviors that are less efficient in cognitive capacity (Mackie and Fan, 2016). On the other hand, skill disparity may be observed that is characteristic of individuals with developmental disabilities (Johnson et al.,

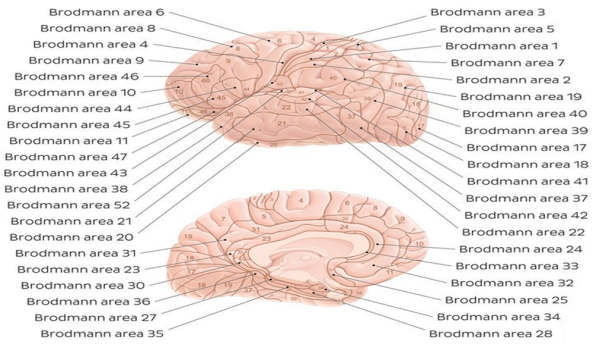

Fig. 3. Areas of Brodmann. Cerebral Cortical cytoarchitecture relate to the frontal lobes according to Brodmann. Areas 1, 2 and 3 - Primary Somatosensory Cortex, Area 4 - Primary Motor Cortex, Area 5 - Somatosensory Association Cortex, Area 6 - Pre-Motor and Supplementary Motor Cortex (Secondary Motor Cortex), Area 7 - Somatosensory Association Cortex, Area 8 - includes Frontal eye fields, Area 9 - Dorsolateral prefrontal cortex, Area 10 – Fronto-polar area (most rostral part of superior and middle frontal gyri), Area 11 – Orbitofrontal area (orbital and rectus gyri, plus part of the rostral part of the superior frontal gyrus) Area 12 – Orbitofrontal area (used to be part of BA11, refers to the area between the superior frontal gyrus and the inferior rostral sulcus), Area 13 and Area 14 - Insular cortex, Area 15 - Anterior Temporal Lobe, Area 17 - Primary Visual Cortex (V1), Area 18 - Visual Association Cortex (V2), Area 19 – (V3), Area 20 - Inferior Temporal gyrus Area 21 - Middle Temporal gyrus, Area 22 - Superior Temporal Gyrus, of which the rostral part participates to Wernicke's area, Area 23 - Ventral Posterior cingulate cortex, Area 24 - Ventral Anterior cingulate cortex, Area 25 – Sub-genual cortex, Area 26 – Ecto-splenial area, Area 28 - Posterior Entorhinal Cortex, Area 29 – Retro-splenial cingular cortex, Area 30 - Part of cingular cortex, Area 31 - Dorsal Posterior cingular cortex, Area 32 - Dorsal anterior cingulate cortex, Area 34 - Anterior Entorhinal Cortex (on the Para-hippocampal gyrus), Area 35 – Peri-rhinal cortex (on the Para-hippocampal gyrus), Area 36 – Para-hippocampal cortex (on the Para-hippocampal gyrus), Area 37 - Fusiform gyrus, Area 38 – Temporo-polar area (most rostral part of the superior and middle temporal gyri, Area 39 - Angular gyrus, part of Wernicke's area, Area 40 – Supra-marginal gyrus part of Wernicke's area, Areas 41 and 42 - Primary and Auditory Association Cortex, Area 43 – Sub-central area (between insula and post/pre-central gyrus), Area 44 - pars opercularis, part of Broca's area, Area 45 - pars triangularis Broca's area, Area 46 - Dorsolateral prefrontal cortex, Area 47 - Inferior prefrontal gyrus, Area 48 – Retro-subicular area (a small part of the medial surface of the temporal lobe), Area 52 – Para-insular area (at the junction of the temporal lobe and the insula) (Adapted from Leisman and Melillo, 2011).

2021). An additional feature of complex systems is b) integration. When specialization and differentiation exist, we can readily observe reduced complexity and rigidity of behavior. In a highly specialized and complex system, the function must be integrated efficiently so as to generate behavioral complexity. As with motor-binding mechanisms in the motor system, we also generate timing signals in the brain that support cognitive-binding, initiated by the thalamocortical system (Ribary et al., 2019; Zhou et al., 2018). This timing signal subserves the context-permitting binding in time and space and from instant to instant for numerous dedicated brain regions. If this timing mechanism is asymmetric or slow as opposed to being symmetric, that mechanism could very well inhibit the binding and integration of isolated or distant brain areas resulting in the interference with complex behavior (Lorsung et al., 2021). When there exists a deficit in specialized and complex systems "chaos" is likely to result.

2.3. The corpus callosum supporting integrated symmetric behavior and efficiencies of timing in an asymmetric system

It has been well established that sensory function in humans is significantly asymmetric, observable as right-sided sensory input and bilateral motor output. To be able to evoke a cohesive motor response, bi-hemispheric input must be integrated (Stephan et al., 2003). The corpus callosum (CC) is significantly involved in complex cognitive and well as in motor activity and in the development of specialization of brain regions (Doron and Gazzaniga, 2008). In general, the literature supports the notion that a significant relationship exists between increased interhemispheric transfer time and CC connectivities in individuals with a congenital absence of the CC and in split-brain individuals (Iacoboni et al., 2000; Mooshagian et al., 2009). In this context it should be noted that ASD individuals reportedly demonstrate significantly increased interhemispheric transfer times and reduced interhemispheric coherence (Keary et al., 2009). For a more expansive discussion on this topic see Leisman et al. (2022).

2.4. Cerebral connectivity and the corpus callosum in ASD

The CC has been depicted, as a broad and thick axonal tract consisting of fiber bundles beneath the cerebral cortex that conjoins the left and right hemispheres of the brain. Its major function is to sustain the effectiveness of inter-hemispheric communication. Those with ASD have been reported to demonstrate a smaller CC which in turn is reflective of neural underconnectivity and reductions in the synchronization patterns between brain regions (Just et al., 2004). Clinical and case studies of agenesis of the CC validate the relationship with impaired social functioning also found in ASD (Badaruddin et al., 2007; Paul et al., 2007).

In endeavoring to describe further why it is that these clinical observations exist, Belmonte et al. (2004)) and Courchesne and Pierce (2005) indicated that in ASD the primary deficits are related to reduced long-range and local over-connectivities between numerous brain systems and the frontal lobes. Superficial white matter tracts associated with CC volume and cortico-cortical fibers are reduced. When considering the aforementioned in addition to the cerebral white matter and vermis size one is able to discriminate 95% of ASD toddlers and young children from neurotypical children, as well as being able to predict developmental outcome to a significantly high degree (Bolduc et al., 2012; Dickinson et al., 2021; Leisman et al., 2022).

It has been known for some time that individuals with ASD have reportedly demonstrated fronto-striatal system dysfunction that relates to social, emotional, and cognitive behavior. These findings have been based on studies of Tower of Hanoi-type tasks, (Borys et al., 1982) Wisconsin Card Sorting tests (Landry and Al-Taie, 2016) and the results of scores on the Cambridge Neuropsychological Test Automated Battery test of frontal lobe function (Ozonoff et al., 2004; Lin et al., 2019; Seng et al., 2021). Although the reasons for the performance deficits on the tasks in ASD are not known, it has been suggested that atypical right frontostriatal networks are causally related to executive function and information integration deficits (Rinehart et al., 2001; Del Casale et al., 2022).

Luders et al. (2006) found significantly greater lateralization of the right anterior CC, the area that projects to right-handed males motor cortices. These investigators had found a greater left lateralization for motor tasks in right-handed individuals. These investigators had found that a stronger left lateralization exists for motor functions in right-handed individuals that was related to reduced fiber connections in the left hemisphere. Braun et al. (2003) as well as Saron et al. (2003) suggested on the basis of their consistent findings that there exist greater efficiencies from right to left hemispheres through the CC in neurotypical individuals with those efficiencies not noted in ASD individuals. Similar conclusions have been found by others (Valenti et al., 2020; Loomba et al., 2021). While this does not necessarily indicate dysfunction it may well be reflective of a hypothesized decreased optimized distribution of commissural connectivities.

While many investigators have concluded that the CC is highly associated with ASD, little attention has been paid to asymmetry. It is understood that the anterior CC midbody projects to the primary motor cortex (Hofer and Frahm, 2006), and from the posterior midbody of the CC to the posterior parietal cortex. We know that this region is highly

interconnected to numerous brain regions with its function being to integrate sensory and motor input from visual and somatic regions (Andersen and Buneo, 2002; Ughwanogho et al., 2022). These systems, when integrated, have connectivities supporting behavioral responsivity to the environment, in general, and sensory-guided movement planning.

Myer and associates (1998) a while back had already noted motor incoordination and deficits in tactile information processing in individuals with mid- or posterior-CC lesions. These findings have been more recently confirmed by others (Shah et al., 2021; Habata et al., 2021; Kilroy et al., 2022). Difficulties in the performance of sequential motor behavior as well as in eye-hand coordination in grasping tasks have been reported in individuals with posterior parieto-cortical (PPC) lesions (Goodale and Milner, 1992; Galletti et al., 2022). There exist numerous behaviors in individuals with ASD associated with atypical asymmetry that are reminiscent of the consequences of anterior midbody parietal lesions where motor inefficiencies are evidenced (Ghaziuddin and Butler, 1998; Randerath et al., 2017) impairments in fine motor skills (Oh et al., 2019; Dawson and Watling, 2000) motor planning and sequencing deficits (Greenspan et al., 1997; Bhoyroo et al., 2020) agency, (Mayer et al., 2020) and difficulties in responding to spoken language (Geranmayeh et al., 2012; Coslett and Schwartz, 2018). The posterior parietal cortex is involved in eye movement planning and fields of adversion, eye contact and attention in ASD may be related to the control by this brain region as well (Talanow et al., 2020).

Various right asymmetric areas of the CC (e. g. the rostral body, posterior midbody, and the splenium) have reportedly been linked with increased symptom severity in ASD. The reason is that the splenium projects to the inferior temporal and occipital lobes for face and object processing (van der Knaap et al., 2011; Lochy et al., 2019). Schultz (2005) had observed significantly reduced activity in the fusiform face area (FFA) and coincident elevated activity in the inferior temporal gyrus in ASD individuals during face processing. Associated with difficulties in social interaction in individuals with ASD, is the concomitant difficulty in facial recognition. This could, in part, explain why distinctions in the splenium between neurotypical and ASD individuals are related to deficits in social interaction. The CC rostral body's rightward asymmetry has been thought to be related to deficits in social interaction (cf. Bradshaw's fronto-striatal model (Rinehart et al., 2021; Valenti et al., 2020; Loomba et al., 2021) where abnormal lateralized frontal circuits provide a basis for the dysfunction in social and higher cognitive functions that also include social behavior. Increased asymmetry of the right posterior CC midbody is associated with significantly greater severity of symptoms which, is in turn, associated with the integration of sensory-motor input. In ASD, there exists an association with hypo- or hyper-sensory processing disorders that also are associated with repetitive and stereotypical behaviors (Baranek et al., 2006; Demopoulos et al., 2015). There exists a consistent understanding that indicates that underconnectivity and rightward cortical asymmetry interfere with the planning of movement, generate a resultant stereotypy in motor activity, can affect the control of eye movements, and disrupt effective face recognition in individuals with ASD.

Without arguing for either left or right hemisphere differences between neurotypical and individuals with ASD, there is sufficient evidence, for now already over forty years, that the essential difficulty may not be a function of lateralization but rather a functional independence of interhemispheric communication or a lack of asymmetry (for a more in-depth discussion, see Leisman et al., 2022).

3. Frontal streams in motor and sensory function in ASD

3.1. Sensory motor interaction deficits in ASD implicate the frontal lobes

In individuals with ASD there is reportedly a dysfunctioning mirror neuron system (Hadoush et al., 2019; Salimova, 2022). While the system is involved in motor planning it employs processes that are akin to the mechanisms whereby movements can be implicitly recognized. Such a system allows an individual the capacity to extract meaning or intention and emotion. These activities are reflected in the *mu* rhythm of the electroencephalogram. The sensorimotor *mu* rhythm consists of synchronized patterns of electrical activity in brain regions controlling voluntary movement (Amzica and Lopes da Silva, 2011). These patterns, as measured by EEG, are generated at between 7.5 and 12.5 Hz and mostly recorded when the body is at rest. Unlike the alpha rhythm, recorded at a similar frequency over visual cortical areas, the *mu* rhythm is evidenced over the motor cortical area. Neurotypical individuals have *mu* suppression when performing motor tasks or when imagining or when performing motor acts. In neurotypical individuals, *mu* activity suppression can be achieved in the sensory motor cortex by motor activity. However, in neurotypical individuals *mu* may also be suppressed not only by movements but through the observation of the movement of others (Amzica and Lopes da Silva, 2011). With ASD individuals, *mu* suppression is noted with self-initiated action, but not when examining the actions of others (McNaughton and Redcay, 2020).

Individuals with ASD, possess dysfunctional sensory function and sensation/perception as well as deficits in social and verbal communication skills (Hilton et al., 2007; O'Connor and Kirk, 2008; Donnellan et al., 2013). These deficits in the organization and integration of sensory stimuli underlie the aberrant responses to sensory input often noticed in ASD individuals and these may be manifested either as hypo- or hyperresponsiveness and/or in sensory self-stimulation.

The sensory processing deficits observed in ASD individuals do not affect a single sensory modality but rather numerous ones and differentially at that (Baranek et al., 2007; Tomchek and Dunn, 2007; Baker et al., 2008; Ben-Sasson et al., 2009; Lane et al., 2014). Some individuals with ASD are averse to bright visual stimulation while others who can stare for extended periods at such lights or other visual stimuli (Behrmann et al., 2006; Simmons et al., 2009). Vestibular function can likewise be affected with a hyporesponsivity that necessitates self-initiated vestibular stimulation such as rocking (Lane et al., 2022). The somatosensory tactile sense may hyper respond to touch stimuli as what has been termed tactile-defensive or aversion to being touched. These types of aberrations in ASD individuals have also been reported in auditory (Ludlow et al., 2014), proprioceptive (Riquelme et al., 2016), kinesthetic (Chen et al., 2018) and other sensations.

As most information is not processed in the brain through a single sensory channel that requires a decision for further processing or not, individuals with ASD cannot adequately process integrated sensation. Among the regions of the brain involved in multichannel sensory processing include: the superior colliculus, thalamus, and cerebellum, besides the prefrontal cortex (PFC), and the superior temporal sulcus (Ghazanfar and Schroeder, 2006).

The multiple sensation convergence model assumes that a change in neuronal firing frequency is associated with converging input from multiple sensory channels. An alternative understanding involves specific patterns of neuronal binding requiring and demanding neural coherence or the synchronization of neural signals (see Engel et al., 2012). Convergence from multiple sensory channels is supported by coherence which is, in turn, supported by the effective function of the frontal cortices with deficits in multi-modal synchronization potentially effecting multisensory processing in ASD.

3.2. Frontal and prefrontal streams in ASD

Numerous investigators have indicated the importance of the PFC in the manifestation of many of the symptoms of ASD. The orbitofrontal cortex (OFC) a prefrontal cortical region of the frontal lobes, is concerned with decision-making, cognition, and in humans consists of BA 10, 11 and 47 (Kringelbach, 2005). The OFC is a portion of the PFC that receives projections from the thalamic medial dorsal nucleus and is involved in the ability to taste and smell and in the experience of reward and decision-making (Isamah et al., 2010).

The OFC network is, in part, concerned with the integration of

sensory activity. The mPFC network, in contradistinction, controls a pathway for viscero-motor activity and projects to the brainstem. In addition, both the mPFC and OFC networks connect to both the limbic system and the thalamus (including the central striatum, nucleus acumbens, hippocampus and amygdala). These brain areas are highly associated with the ability of the individual to monitor the external environment and in generating sympathetic responses to environmental change that also includes stress responses (Öngür and Price, 2000; Ridderinkhof et al., 2004a, 2004b; Bissonette et al., 2013; Sheinkopf et al., 2019).

The Default Network (DN) of the brain is constituted by, among other regions, the mPFC, inferior temporal lobe, hippocampus, and posterior cingulate. The DN consists of a set of interacting nodes and connections to them that are concerned with "internal mentation" (i. e. the adaptative and introspective everyday mental activities. According to the internal mentation hypothesis, attention to a task deactivates the DN and reactivates with spontaneous cognition. The DN also play a significant role, according to the sentinel hypothesis, in environmental monitoring. Collectively then, the DN facilitates a cohesive internalization of oneself and environment.

Dorit Ben Shalom and D (2009) had referred to the sentinel hypothesis when she noted that there exists a positive relationship between the DN and sensory processing tasks. Hypoactivity of global attention is often witnessed in Balint's syndrome, consisting of optic ataxia, oculomotor apraxia, and simultagnosia found with bilateral parietal lobe lesions. In such cases, only one visual object can be perceived at a time, obviously distorting the gestalt and which is characteristic of those with ASD. Ben Shalom went on to hypothesize that neurotypical individuals integrate sensory information due to the mPFC at basic, integrative, and higher-order levels. It is, according to her, that the mPFC exclusively regulates integrative functions of multisensory stimuli. This, she concludes, may be the basis of sensory processing deficits in individuals with ASD in that the mPFC is dysfunctional.

With cognitive and motor functions being related to the prefrontal regions in ASD, there exists an overlap of cognitive and motor symptoms. The articulation of cerebellum, basal ganglia, and frontal lobes are areas of the brain recognized to control motor and nonmotor intentional and executive function. Most developmental disabilities including ASD have as their most common symptom, motor incoordination or clumsiness, especially of posture and gait. Impulse control, either inhibited or facilitated, and judgment disorders can all be attributed to dysfunction of this network and its control of motor and nonmotor behavior. This spectrum of disorders all involve disruption primarily of what is known as executive functions which are functions attributed to the frontal lobe. Striatal neurons may be involved with gating incoming sensory input to higher motor areas such as the intralaminar thalamic nuclei and premotor cortex that arise from several modalities to coordinate behavioral responses. These varied modalities may lead to the perception of sensation resulting in motor response. The basal ganglia, like the cerebellum, is functionally connected to the premotor and motor cortices as well as to the prefrontal cortex. (Leisman et al., 2014; Zikopoulos and Barbas, 2007).

4. Frontal streams disintegrated from the corpus callosum in ASD

We have already noted that alterations of specific frontal lobe areas have been found to have a significant effect in the manifestation of the core aspects of ASD. fMRI studies have demonstrated, for example, that the frontal lobe-based control not only of social cognition, but also of repetitive behavior, executive function, and verbal communication may be affected by dysfunctioning networks of the frontal lobes (Baron--Cohen et al., 1999; Carper and Courchesne, 2000, 2005; Chandana et al., 2005; Ohnishi et al., 2000; Luna et al., 2002; Herbert et al., 2003; Crucitti et al., 2022; Rafiee et al., 2022).

Chugani's group (Muzik et al., 1998; Chugani et al., 1999; Chandana et al., 2005) had observed reduced serotonergic synthesis in the frontal lobes of ASD individuals with concomitant abnormalities of whole-brain serotonin synthesis. Serotonin, like brain derived neurotrophic factor, modulates axonal arborization (Vitalis and Parnavelas, 2003), and dysfunction in serotonin synthesis has been found to be associated with anomalies of frontal lobe connectivity (see Kumar et al., 2010).

5. Integrating the evidence for the role of the frontal streams in ASD

The understanding the role of frontal streams presented here thus far has been confirmed in postmortem studies of individuals with ASD. A significant finding revealed early in life was brain overgrowth postpartum most notable in the PFC related to a significantly large head circumference in children under three years of age. Subcortical brain regions related to sensory processing that project to the PFC that include the cerebellum and thalamus are also anatomically different in comparison to neurotypical individuals (Hazlett et al., 2005; Courchesne et al., 2011a, 2011b). A reduction in anatomical and functional connectivity was found by Nair and colleagues (2011; 2013) that affected projections between somatosensory and motor cortices and between prefrontal, parieto-occipital cortices and thalamus in ASD children. Noted by Nair and colleagues was right hemisphere-based overconnectivity between temporal and thalamic areas. The underconnectivity noted between frontal-thalamic areas directly related to symptom severity in ASD individuals (Martínez-Sanchis, 2014; Rane et al., 2015).

The thalamus serves both as an information filter for pathways projecting to the neocortex and as a relay station for sensory-motor information, thus suggesting a basis for the observed sensory deficits noted in ASD. We have noted significant relationships between the PFC and cerebellum with symptom severity in ASD individuals being a function of abnormalities of either the cerebellum, PFC or both (Carper and Courchesne, 2000; Kumar et al., 2010).

Disorders of neural connectivities as a significant portion of the variance explaining ASD allow for an integration of cognitive theories (e.g., central coherence), with neuroanatomical, neurophysiological, and a neuropsychological understanding of the basis for ASD behavior (Hughes, 2007, 2008). We have learned that there exist cortico-subcortical as well as inter- and intra-hemispheric underconnectivity in individuals with ASD. A problem that exists is that these findings co-occur with opposing data indicating hyperconnectivity (Vissers et a, 2012; Uddin et al., 2013; Kleinhans et al., 2016; Martínez et al., 2020).

5.1. Behavioral consequences in a neuroanatomical context

ASD has been most commonly viewed at as a cognitive disorder affecting primarily higher level social, nonverbal, and verbal communication. We have proposed here that instead it is primarily at its root, a sensory-motor disorder that delays the development of higher level cognitive social nonverbal skills. However, individuals with ASD also have exceptional and even gifted cognitive skills that are associated with left hemisphere function. So, it is not simply a cognitive social delay. In a pure cognitive deficit disorder there exists a classic unevenness of skills where they have clear cognitive deficits or delays associated with right hemisphere functions and advanced left hemisphere cognitive skills.

Numerous reports from comparative genomic research have noted that small areas exist on the human genome that are shared by many species but have changed relatively quickly during our evolutionary divergence from chimpanzees. Such genomic sequences are referred to as human accelerated regions (HARs) (Olson and Varki, 2003; Pollard et al., 2018). As our social and cognitive behaviors are unique in comparison with other species, some researchers have thought that HAR alterations may be significant in the evolution of these traits in humans (Doan et al., 2016; Levchenko et al., 2018). With impaired HARs, there

could well be related impairment in social and cognitive functioning (Doan et al., 2016).

Perhaps there existed an evolutionary need at times for superior cognitive skills. Autism-related genetic variants associated with ASD may have been selected as a positive alteration. Polimanti and Gelernter (2017) had found that inherited variants linked to ASD at levels greater than that predicted on the basis of chance. Polimanti and Gelernter found that ASD variants were significantly related to greater intellectual abilities. They additionally noted that many of the ASD variants were molecularly associated with processes related to the creation of new neurons. It may well be that these retained variants have had a positive effect with the negative being ASD which might provide an adaptive benefit.

This unevenness of skills is superimposed on genetic traits and exacerbated by epigenetic factors pre- and post-natally that leads to a bottom-up interference of development that ultimately creates a maturational imbalance that is reflected in the development of unevenness of skills with which they often present (for further development of this notion see Leisman et al., 2022).

5.1.1. Sensory development

The right hemisphere of the cortex develops first in utero and largely in the first three years of life (Leisman et al., 2022). Initially, a child needs to be able to communicate its basic needs nonverbally to caregivers and that includes consequences of the sensations of pain, temperature, hunger, thirst, abnormal bowel movements, or intestinal distress, fatigue, etc. Of course, primary perception and processing of this information occurs in both hemispheres in BA 3,1,2. However the final processing and response to these sensations occurs specifically in the right hemisphere (Melillo & Leisman 2015; Carmona et al., 2015; Blake, 2018). The processing of this information known as interoception primarily occurs in the right insula cortex's BA 13 (Schulz, 2016). It has been reported that children with ASD are variously deficient in internal interoception (DuBois et al., 2016). Children with ASD have unusually high threshold for pain and temperature (Yasuda et al., 2016; Duerden et al., 2015), they may not perceive hunger and thirst (Fiene and Brownlow, 2015), and sometimes have issues with failure to thrive (Keen, 2008). Others may eat or drink as a "stim" or "tic" type of behavior and not perceive when they are fully satiated. Some individuals with ASD will eat until they regurgitate not realizing they are beyond satiated, all of which is associated with deficits in interoception, and the failure to perceive basic sensory input within BA 3, 1, and 2 and in the insula cortex in the right hemisphere.

5.1.2. Attachment

The primary drive of the right hemisphere developing first is for survival and therefore attachment to other humans (Schore, 2005; Laurita et al., 2017). Human brains are, at birth, the most immature relative to other species (Leisman and Melillo, 2022). Possessing large neonatal heads birthed from mothers with relatively small birth canals requires the restriction of the growth of the brain and head in the the uterus. Human infants cannot survive alone, they must first attach to caregivers. Initially this attachment takes place through reciprocal nonverbal communication between the parents and infant. The child must be able to receive nonverbal cues and be able to respond. Initially these responses take place in the brainstem, and there exist brainstem reflexes that are connected to the muscles of facial expression (Delafield-Butt and Trevarthen, 2017). These are cranial nerve nuclei that are present in the medulla and pons initially and relate to cranial nerves that are branchial arch derivatives of cranial nerves 5, 7, 9,1 0, 11. These nerves relate to chewing swallowing, facial expression, vocalization, breath control, and head gestures that will also form the foundation of a social engagement system. Ultimately thes motor tone associated with these nuclei will come under the control of the nucleus ambiguous which is a myelinated, ventral extension of the parasympathetic nervous system. This system, over the course of the first year or so of life, will help regulate and inhibit the sympathetic nuclei and nervous system that is also found in the medulla and rostral ventral lateral nucleus, that regulates the dorsal motor nucleus of the vagus nerve, which regulates gut function (Porges, 2005; Bonaz et al., 2017). This, taken together, will support the maturation and regulation of the autonomic nervous system which will also innervate and regulate the immune system.

Children with ASD have been documented to have abnormal or delayed development of the parasympathetic nervous system (Fenning et al., 2019). An ideal way to test this hypothesis is through heart rate variability (HRV) testing and it has been demonstrated that children and individuals with autism have abnormally low HRV signifying increased sympathetic tone (Ming et al., 2005; Cheng et al., 2020). This would also relate to less nonverbal reflexive communication and reciprocation with parents and caregivers, a alack of eye contact, and lesser emotional responsivity to facial expression. All of the peripheral interoceptive information from the gut and from most of the body comes through the afferent branch of the vagus nerve and the nucleus solitarious (Bonaz et al., 2019). Its ultimate target is the insula and finally the right insula projects tot BA 13. This is the primary cortical receptive area for all interoceptive feedback. So, stimuli from the brainstem travel bottom-up to project to the insula (Barnet & Simmons, 2015). If there is a delay in the development of the brainstem and immaturity of nuclei, this delay would also affect the maturation and devolvement of the insula and especially the right insula which comes online first (Churchwell & Yurgelun-Todd, 2013). Again, this could be seen as a lesser response to basic sensory input which, as we had earlier indicated, has been well documented in individuals with ASD, as well as autonomic dysregulation and dominant sympathetic tone also well documented in ASD.

5.1.3. Socialization, attachment, and right brain emotions

As stated earlier, the primary drive for human survival is attachment to other humans. Firstly, an infant is expected to attach to its parents, and then learn to attach to other humans to become part of a social group. Throughout most of human history it is known that humans could not be expected to survive alone. The advantage we humans have had for survival was not physical strength or speed, but rather intellect and banding into to social groups that could work in a coordinated way to hunt and protect one another. This is the primary job and goal of the right hemisphere and it is the first side of the brain to come online in development. The insula is one of the most crucial structures that drives the development of the right brain. This we propose is a primary deficit in ASD, not due to damage, pathology, or genetic mutation, but simply it is related to lack of development of the social, attachment, nonverbal communication networks that commence in the brainstem. Once basic sensory, interoceptive feelings, and interoception are built on top of effectively perceived sensations, the result will be emotional awareness. The right brain emotions are mainly configured around withdrawal behavior or protection and are referred to as negative emotions. Fear, sadness, guilt, shame, embarrassment, rejection sensitivity, disgust are primary emotional responses. These emotions as we said concern protection, fear or sense of danger, disgust, ingestion, sadness, sense of loss, but also these emotions are critical to socialization. Guilt or shame allows an individual to know when they have broken a social rule. The ultimate fear and driving influence of the right brain is rejection sensitivity, fear of rejection being - in the evolutionary history of man – a death sentence. Rejection sensitivity is a right brain function (Premkumar, 2012). Most emotions are also perceived in the right insula cortex as well as other emotional networks. So, these emotions are literally built on top of networks connected to basic sensations (Zhang et al., 2019). Other right brain emotions, however, consist of love, connection, empathy, and attachment. These too are built on top of basic ssensations. With reference to empathy, known to be deficient in ASD, one cannot appreciate another person's pain unless that person feels pain. One cannot perceive the pain of another if we ourselves have not or have difficulty experiencing that pain.

Another key element in ASD involves the ability to form and

maintain relationships. Basic to maintaining relationships is interoception, being able to nonverbally communicate, understand and relate to one another. This initially requires an individual to be able to feel their own body, sensations, and emotions and then compare that nonverbally through motor expressions and proprioception thus forming the basis of reciprocal communication and social engagement. The question arises about the ASD individual for whom initial sensations and the emotions built on top of those feelings do not develop adequately. The result would be interference or complete elimination of the ability to nonverbally communicate that forms the basis of social relationships, learning right from wrong, understanding social rules, all of the things absent or impaired in ASD. We know that verbal communication in the left hemisphere commences with BA 44 and 45 and Wernicke's area BA 40, 39, 22. The right hemisphere possesses a similar nonverbal communication network. The equivalent of Wernicke's BA 40, 39, 22 in the right parietal, temporal lobe is concerned with nonverbal receptive language. The supramarginal gyrus, BA 40, among other areas responds to facial expression, BA 39, the angular gyrus, controls the response to body gestures, and BA 22, the superior temporal gyrus, responds to prosodic variation and emotional tone of voice, all significantly deficient or absent in autism. The nonverbal expression lacking or deficient in ASD would relate to the right BA 44, 45, part of the inferior frontal gyrus. Lack of facial expression and body awareness, have been well documented. But all of the networks controlling these operations that are underdeveloped commence with bottom-up development starting in the brainstem.

5.1.4. Retained primitive reflexes, brainstem development potentially impacting on hemisphericity

We have indicated elsewhere (Melillo et al., 2020; Leisman et al., 2022) that in ASD, retained primitive reflexes (RPRs) exist beyond the first year postpartum and reflects the under development of right hemisphere networks. RPRs can be associated with a delay of right hemisphere development, and this may in turn lead to the left hemisphere coming online in individuals that have usually strong left hemisphere traits. This has been observed in skills such as hyperlexia where children with ASD have been documented to be able to read below the age of two (Macdonald et al., 2021). Some of the areas that underly reading ability include BA 39 and 40. Damage or dysfunction in these regions has been associated with Gerstman syndrome, a well-documented syndrome affecting the left hemisphere associated with dyslexia, dyscalculia, right/left confusion, and finger agnosia. Should these regions come online too early, one could conceive that they might inhibit development of their counterpart in the right hemisphere which should be developing first, and which should be developing nonverbal communication skills. If a child is hyperlexic that could lead to inhibition and developmental delay of the nonverbal network for reciprocal reception of facial expression, tone of voice and body gestures which is seen in ASD. Therefore, two potential contributing bottom-up factors are at play associated with a developmental interhemispheric communication deficit or functional disconnection.

In our view, the RPRs first lead to and represent a maturational delay of the brainstem. If they do not become inhibited and integrated, they represent a lack of maturation of the medulla and pons. The nuclei in those areas form the basis and foundation of all the higher sophisticated networks of the cortex. If they are delayed in maturation so too will be the networks that have yet to be developed, especially those of the right hemisphere. Since the right hemisphere develops first and the reflexes should be fully integrated by the end of the first year of life, if primitive reflexes are retained, the delay could have more of an impact on right hemisphere development and may have the left hemisphere come online too early. If the dominant left hemisphere comes online too early this can reciprocally inhibit the contralateral brainstem and the cortex and further inhibit right hemisphere development. These two factors can retard right hemisphere maturation with an infant inadequately perceiving basic sensory input and interoception, leading to lack of connection to their own bodies and sensations. This could delay development of right hemisphere emotional responsivity and ultimately delay or eliminate the primary drive of the child to attach to parents and ultimately attach to other humans and form connections simply because the networks that drive that developmental imperative are suppressed or underdeveloped. Children with ASD, to varying degrees, have little or no drive to connect to other children (Brown et al., 2022) and this is coincidently observed with overactivity of the left hemisphere networks (Mundorf et al., 2021; Wang et al., 2022).

5.1.5. Vestibular mapping

The first major sensory system to come online during fetal development is the vestibular system Bradley and Mistretta (1975); Johnson Chacko et al. (2016)). Vestibular input has a significant influence in early movement development and is directly connected to the the existence of primitive reflexes (Brandt and Dieterich, 2015; Grzywniak, 2016) and head and neck movement (Lovell, 2021). Vestibular input serves as the trigger of many primitive reflexes and support early motor development (Lovell, 2021). The Tonic Labyrinthine Reflex, Moro (also connected to sympathetic development), Asymmetric and Symmetric Tonic Neck Reflexes etc., all involve motor activity and sensory input from postural muscles and vestibular input (Gieysztor et al., 2018; Pecuch et al., 2021). An important function of early vestibular input is to assist in creating body and spatial maps. Bilateral vestibular input from otoliths and semicircular canals, as we develop our motor skills supported by primitive reflexes, activate hair receptors that generate feedback to brainstem nuclei and the cerebellum initially to help triangulate the body in space. This aids in forming a body map assisting us in placing our body in the space around us.

Initially the four vestibular nuclei located in the pons, where the initial input from the inner ear arrives, then projects to the cerebellum and ultimately up to the thalamus in the VPM,VPL and up to parietal lobe BA 3,1,2. The primary cortical reception site for vestibular input is the parietal insula vestibular cortex in the right hemisphere (Dieterich and Brandt, 2018). The posterior portion of the insula is responsible for responding to vestibular input and plays a role in building a spatial map of our bodies by the parietal lobe. This therefore assists the external environment communicate with the internal so that the infant and child can integrate both proprioceptive and interoceptive input to create an integrated "self". This sense of self, in part, resides in the right anterior insula and right anterior cingulate which communicate with the prefrontal cortex. It has been well documented that children with autism have severely underdeveloped or absent vestibular responses (Choudhery and Ansarii, 2020; Oster and Zhou, 2022). We contend in the light of this evidence that the vestibular nuclei and their connections to the cerebellum are significantly developmentally delayed and immature as RPRs retard brainstem development. This, in turn, would delay development of the midline cerebellum and connections to the thalamus and prefrontal cortex as well, as the parietal lobe. On the basis of what has been discussed, we propose that as a result of the lack of adequate input from brainstem and vestibular input, there exists a failure for the neonate, infant and child to perceive his or her body adequately, this is associated with difficulty in developing a body map in turn related to a severe form of neglect and together with lack of interoception, results in delayed self-awareness and body ownership. This penultimately delays left hemisphere-based body agency and motor control.

5.1.6. Motor planning

The most sophisticated motor planning on the phylogenetic scale is speech. A child with ASD has speech and language that is delayed for numerous reasons including: a) lack of nonverbal drive to speak and b) lack of a drive to attach to others because of lack of connection to their own bodies (Mody et al., 2018; Leisman and Melillo, 2022). Individuals with ASD possess a significant lack of sensory connection with their own bodies which affects the ability to know where their bodies are in space (Gauthier et al., 2018) and they literally cannot feel or adequately

control the facial muscles necessary for the effective production of speech, where motor planning requires extreme sensory-motor precision (Samad et al., 2015). This could explain, in part, why it is that speech impairment is observed coincident with overactivity of other left hemisphere networks. Hyperactivity, tics, and stims are all associated with overactivity of the left motor BA 4 and premotor BA 6 and their connections to the direct pathways of the basal ganglia. We see in general overactivity of the direct pathway of the basal ganglia (Subramanian et al., 2017). Llinas (2002) has described the basal ganglia as the home for all stereotypical movements and behaviors. All of these preprogrammed behaviors and movements are potentially present at birth and controlled by the basal ganglia (Herrero et al., 2002). The balance between the direct and indirect pathway is what ultimately keeps these behaviors in check and allows the cortex to ultimately choose which programs develop further and the timing of when they are inhibited or not. In children with ASD, we see that many cannot effectively control body movement. Many indulge self-stimulation interpretable as a random release of stereotypical movements and behaviors that they are not consciously controlled (Delafield-Butt and Trevarthen, 2017). Inhibition of these programs we know comes from the indirect and especially the hyperdirect pathway of the basal ganglia (represented in Fig. 2) and projected to the right hemisphere. BA 4 and 6 are the part of the hyperdirect pathway that inhibits movement, the inferior frontal gyrus BA 44, 45, 47 is the branch of the hyperdirect pathway that inhibits more emotional, cognitive, and limbic activities and stereotypical behaviors. Obsessive behaviors from the dorsolateral PFC represented as BA 46, 9 on the right, when uninhibited is associated with obsessive thoughts (Seo et al., 2016; Park et al., 2017); BA 11, 12 and the left corbito-frontal cortex, when inhibited, is associated with compulsive behavior, hypersexuality, hyperphagia, impulsivity etc., all of which are often features of ASD (Price et al., 2021).

5.1.7. Autism as a primary sensory perception and motor control dysfunction

We think that the core issues related to ASD and its repetitive stereotypical behaviors, verbal and nonverbal deficits and especially socialization and attachment deficits are primarily related to a deficit of development of right hemisphere networks that underly these issues (see Leisman et al., 2022). These deficits are brainstem related through the RPRs, which alter early movement and skew sensory perceptual feedback. This bottom-up interference impacts right brain development which commences in utero and continues over the first three years of life. The left hemisphere networks that underly verbal, motor, and some emotional behaviors come online too early and inhibit the development of the same nonverbal, sensory, and emotional networks contralaterally in the right hemisphere. We propose that ASD is not a principally a cognitive or intellectual deficit at its core, despite ASD being related to verbal language deficits. The primary language deficit we hypothesize to be a nonverbal communication deficit that commences in the right hemisphere networks in cortical regions equivalent to Wernicke's and Broca's in the left hemisphere. Hyperconnectivity of left hemisphere networks can produce both echolalia and scripting. Many with ASD demonstrate early onset hyperlexia as well as advanced mathematics and other left hemisphere-based cognitive skills. Virtually all of the advanced or savantist skills are known to be left hemisphere-based (Treffert and Christensen, 2006; Treffert, 2014).

Verbal language delay is not only a result motor planning deficits being primarily a left hemisphere skill, but it can also actually be a sensory perceptual right hemisphere-based deficit. Dysfunctioning motor and sensory feedback to the right parietal lobe and the parietal insula cortex disrupt spatial and body mapping as well as disruptions of vestibular input that produce forms of neglect and proprioception deficits. The lack of early sensory perception stimulation in the right insula can interfere with interoception, and the anterior insula and anterior cingulate do not create self awareness and body ownership, which then can lead to a deficit of agency and motor control. This loss of motor control and planning is a primary motor problem but also a sensory deficit where the individual has an impairment in perceiving his or her body position and therefore cannot reliably move their bodies readily. They are instead at the mercy of random firing stereotypical basal ganglionic programs that are recognized as self-stimulatory behaviors or tics.

6. Conclusion

The insufficient connectivity between the medial PFC and other areas distant from each other involved in top-down information processes rely on the global integration of data from multiple input sources described in this paper and would enhance low level perception processes (bottom-up information processing) as in over-focused attention to sensory details. The reduced deactivation in the medial PFC and in the rest of the Default Network during global task processing is consistent with the integrative modulatory role served by the medial PFC as has been hypothesized. We have stressed the importance of understanding the degree to which sensory and movement anomalies in individuals with ASD can contribute to social impairment. In fact, many acts are mistakenly interpreted as lack of interest, reluctance, non-compliance, and even aggressiveness when most of the demonstrated behaviors are not volitional and are secondary to the idiosyncratic sensory and movement control mechanisms. Nevertheless, further investigation on the neurobiological basis of sensory symptoms and its relationship to other clinical features found in ASD is still required to improve the understanding and quality of life for persons with ASD. Treatment perhaps should not be first behaviorally based but rather based on facilitating sensory motor development.

CRediT authorship contribution statement

Conceptualization, Writing – original draft preparation, Visualization, Investigation, Supervision, Writing – review & editing **RM:** Conceptualization, Writing – original draft preparation, Writing – review & editing. **TM:** Conceptualization, Writing – original draft preparation.

Declaration of Competing Interest

None to declare.

Data Availability

No data was used for the research described in the article.

References

Amzica, F., Lopes da Silva, F.H., 2011. Cellular substrates of brain rhythms. In: Niedermeyer, E. (Ed.), Electroencephalography: Basic Principles, Clinical Applications and Related Fields, 6th ed. Lippincott Williams & Wilkins, Philadelphia, pp. 33–63.

Andersen, R.A., Buneo, C.A., 2002. Intentional maps in posterior parietal cortex. Annu. Rev. Neurosci. 25 (1), 189–220.

Badaruddin, D.H., Andrews, G.L., Bölte, S., Schilmoeller, K.J., Schilmoeller, G., Paul, L. K., Brown, W.S., 2007. Social and behavioral problems of children with agenesis of the corpus callosum. Child Psychiatry Hum. Dev. 38, 287–302.

Baker, A.E., Lane, A., Angley, M.T., Young, R.L., 2008. The relationship between sensory processing patterns and behavioural responsiveness in autistic disorder: A pilot study. J. Autism Dev. Disord. 38, 867–875.

Baranek, G.T., David, F.J., Poe, M.D., Stone, W.L., Watson, L.R., 2006. Sensory Experiences Questionnaire: Discriminating sensory features in young children with autism, developmental delays, and typical development. J. Child Psychol. Psychiatry 47 (6), 591–601.

Baranek, G.T., Boyd, B.A., Poe, M.D., David, F.J., Watson, L.R., 2007. Hyperresponsive sensory patterns in young children with autism, developmental delay, and typical development. Am. J. Ment. Retard. 112 (4), 233–245.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., Williams, S.C., 1999. Social intelligence in the normal and autistic brain: an fMRI study. Eur. J. Neurosci. 11 (6), 1891–1898.

Behrmann, M., Thomas, C., Humphreys, K., 2006. Seeing it differently: visual processing in autism. Trends Cogn. Sci. 10 (6), 258–264.
Belmonte, M.K., Cook, E.H., Anderson, G.M., Rubenstein, J.L., Greenough, W.T., Beckel-Mitchener, A., Tierney, E., 2004. Autism as a disorder of neural information processing: directions for research and targets for therapy. Mol. Psychiatry 9 (7), 646–663.
Ben Shalom, D, 2009. The medial prefrontal cortex and integration in autism. Neuroscientist 15 (6), 589–598.
Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S.A., Engel-Yeger, B., Gal, E., 2009. A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. J. Autism Dev. Disord. 39, 1–11.
Bhoyroo, R., Hands, B., Steenbergen, B., Wigley, C.A., 2020. Examining complexity in grip selection tasks and consequent effects on planning for end-state-comfort in children with developmental coordination disorder: A systematic review and meta-analysis. Child Neuropsychol. 26 (4), 534–559.
Bissonette, G.B., Powell, E.M., Roesch, M.R., 2013. Neural structures underlying set-shifting: roles of medial prefrontal cortex and anterior cingulate cortex. Behav. Brain Res. 250, 91–101.
Blake, M.L. (2018).The Right Hemisphere and Disorders of Cognition and Communication: Theory and Clinical Practice 1st Edition. San Diego, Pleural Publishing.
Bolduc, M.E., Du Plessis, A.J., Sullivan, N., Guizard, N., Zhang, X., Robertson, R.L., Limperopoulos, C., 2012. Regional cerebellar volumes predict functional outcome in children with cerebellar malformations. Cerebellum 11, 531–542.
Bonaz, B., Sinniger, V., Pellissier, S., 2017. The vagus nerve in the neuro-immune axis: implications in the pathology of the gastrointestinal tract. Front. Immunol. 8, 1452.
Bonaz, B., Sinniger, V., Pellissier, S., 2019. Vagus nerve stimulation at the interface of brain–gut interactions. Cold Spring Harb. Perspect. Med. 9 (8), a034199.
Borys, S.V., Spitz, H.H., Dorans, B.A., 1982. Tower of Hanoi performance of retarded young adults and nonretarded children as a function of solution length and goal state. J. Exp. Child Psychol. 33 (1), 87–110.
Bradley, R.M., Mistretta, C.M., 1975. Fetal sensory receptors. Physiol. Rev. 55 (3), 352–382.
Brandt, T., Dieterich, M., 2015. Does the vestibular system determine the lateralization of brain functions? J. Neurol. 262, 214–215.
Braun, C.M., Achim, A., Larocque, C., 2003. The evolution of the concept of interhemispheric relay time. The Parallel Brain: The Cognitive Neuroscience of the Corpus Callosum. MIT Press, Cambridge, MA, pp. 235–259.
Brown, M., Matson, J., Callahan, M., Tevis, C., 2022. Examining the relationship between social functioning and daily living skills in children with and without autism spectrum disorder. J. Dev. Phys. Disabil. 1–12.
Brown-Lum, M., Zwicker, J.G., 2015. Brain imaging increases our understanding of developmental coordination disorder: a review of literature and future directions. Curr. Dev. Disord. Rep. 2, 131–140.
Bruchhage, M.M., Bucci, M.P., Becker, E.B., 2018. Cerebellar involvement in autism and ADHD. Handb. Clin. Neurol. 155, 61–72.
Carmona, S., Hoekzema, E., Castellanos, F.X., García-García, D., Lage-Castellanos, A., Van Dijk, K.R., Sepulcre, J., 2015. Sensation-to-cognition cortical streams in attention-deficit/hyperactivity disorder. Hum. Brain Mapp. 36 (7), 2544–2557.
Carper, R.A., Courchesne, E., 2000. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain 123 (4), 836–844.
Carper, R.A., Courchesne, E., 2005. Localized enlargement of the frontal cortex in early autism. Biol. Psychiatry 57 (2), 126–133.
Chandana, S.R., Behen, M.E., Juhász, C., Muzik, O., Rothermel, R.D., Mangner, T.J., Chugani, D.C., 2005. Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism. Int. J. Dev. Neurosci. 23 (2–3), 171–182.
Chen, Y.T., Tsou, K.S., Chen, H.L., Wong, C.C., Fan, Y.T., Wu, C.T., 2018. Functional but inefficient kinesthetic motor imagery in adolescents with autism spectrum disorder. J. Autism Dev. Disord. 48, 784–795.
Cheng, Y.C., Huang, Y.C., Huang, W.L., 2020. Heart rate variability in individuals with autism spectrum disorders: A meta-analysis. Neurosci. Biobehav. Rev. 118, 463–471.
Choudhery, A., Ansarii, T., 2020. A systematic review study on the effects of vestibular stimulation in children with autism. Eur. J. Public Health 2 (1), 70.
Chugani, D.C., Muzik, O., Behen, M., Rothermel, R., Janisse, J.J., Lee, J., Chugani, H.T., 1999. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann. Neurol. Off. J. Am. Neurol. Assoc. Child Neurol. Soc. 45 (3), 287–295.
Coslett, H.B., Schwartz, M.F., 2018. The parietal lobe and language. Handb. Clin. Neurol. 151, 365–375.
Courchesne, E., Pierce, K., 2005. Brain overgrowth in autism during a critical time in development: implications for frontal pyramidal neuron and interneuron development and connectivity. Int. J. Dev. Neurosci. 23 (2–3), 153–170.
Courchesne, E., Campbell, K., Solso, S., 2011a. Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res. 1380, 138–145.
Courchesne, E., Mouton, P.R., Calhoun, M.E., Semendeferi, K., Ahrens-Barbeau, C., Hallet, M.J., Pierce, K., 2011b. Neuron number and size in prefrontal cortex of children with autism. JAMA 306 (18), 2001–2010.
Crucitti, J., Hyde, C., Enticott, P.G., Stokes, M.A., 2022. A systematic review of frontal lobe volume in autism spectrum disorder revealing distinct trajectories. J. Integr. Neurosci. 21 (2), 057.
Dawson, G., Watling, R., 2000. Interventions to facilitate auditory, visual, and motor integration in autism: A review of the evidence. J. Autism Dev. Disord. 30 (5), 415.
De Sanctis, P., Solis-Escalante, T., Seeber, M., Wagner, J., Ferris, D.P., Gramann, K., 2021. Time to move: Brain dynamics underlying natural action and cognition. Eur. J. Neurosci. 54 (12), 8075–8080.
Del Casale, A., Ferracuti, S., Alcibiade, A., Simone, S., Modesti, M.N., Pompili, M., 2022. Neuroanatomical correlates of autism spectrum disorders: a meta-analysis of structural magnetic resonance imaging studies. Psychiatry Res. Neuroimag., 111516
Delafield-Butt, J., Trevarthen, C., 2017. On the brainstem origin of autism: Disruption to movements of the primary self. Autism. CRC Press, pp. 119–138.
Demopoulos, C., Yu, N., Paul, L.K., Sherr, E.H., Marco, E.J., 2015. Corpus callosum in cognitive and sensory processing: insights into autism. Future Neurol. 10 (2), 147–160.
Dickinson, A., Daniel, M., Marin, A., Gaonkar, B., Dapretto, M., McDonald, N.M., Jeste, S., 2021. Multivariate neural connectivity patterns in early infancy predict later autism symptoms. Biol. Psychiatry. Cogn. Neurosci. Neuroimag. 6 (1), 59–69.
Dieterich, M., Brandt, T., 2018. The parietal lobe and the vestibular system. Handb. Clin. Neurol. 151, 119–140.
D'Mello, A.M., Stoodley, C.J., 2015. Cerebro-cerebellar circuits in autism spectrum disorder. Front. Neurosci. 9, 408.
Doan, R.N., Bae, B.I., Cubelos, B., Chang, C., Hossain, A.A., Al-Saad, S., Mukaddes, N.M., Oner, O., Al-Saffar, M., Balkhy, S., Gascon, G.G., 2016. Mutations in human accelerated regions disrupt cognition and social behavior. Cell 167 (2), 341–354.
Donnellan, A.M., Hill, D.A., Leary, M.R., 2013. Rethinking autism: implications of sensory and movement differences for understanding and support. Front. Integr. Neurosci. 6, 124.
Doron, K.W., Gazzaniga, M.S., 2008. Neuroimaging techniques offer new perspectives on callosal transfer and interhemispheric communication. Cortex 44 (8), 1023–1029.
DuBois, D., Ameis, S.H., Lai, M.C., Casanova, M.F., Desarkar, P., 2016. Interoception in autism spectrum disorder: A review. Int. J. Dev. Neurosci. 52, 104–111.
Duerden, E.G., Taylor, M.J., Lee, M., McGrath, P.A., Davis, K.D., Roberts, S.W., 2015. Decreased sensitivity to thermal stimuli in adolescents with autism spectrum disorder: relation to symptomatology and cognitive ability. J. Pain. 16 (5), 463–471.
Engel, A.K., Senkowski, D., Schneider, T.R. (2012). Multisensory integration through neural coherence. In: The Neural Bases of Multisensory Processes. Boca Raton (FL): CRC Press/Taylor & Francis; 2012. Chapter 7.
Fenning, R.M., Erath, S.A., Baker, J.K., Messinger, D.S., Moffitt, J., Baucom, B.R., Kaeppler, A.K., 2019. Sympathetic-parasympathetic interaction and externalizing problems in children with autism spectrum disorder. Autism Res. 12 (12), 1805–1816.
Fernández, M., Sierra-Arregui, T., Peñagarikano, O. (2019). The Cerebellum and autism: More than motor control. In: Behavioral Neuroscience. IntechOpen.
Fiene, L., Brownlow, C., 2015. Investigating interoception and body awareness in adults with and without autism spectrum disorder. Autism Res. 8 (6), 709–716.
Galletti, C., Gamberini, M., Fattori, P., 2022. The posterior parietal area V6A: an attentionally-modulated visuomotor region involved in the control of reach-toF-grasp action. Neurosci. Biobehav. Rev., 104823
Gauthier, S., Anzalone, S.M., Cohen, D., Zaoui, M., Chetouani, M., Villa, F., Xavier, J., 2018. Behavioral own-body-transformations in children and adolescents with typical development, autism spectrum disorder, and developmental coordination disorder. Front. Psychol. 9, 676.
Geranmayeh, F., Brownsett, S.L., Leech, R., Beckmann, C.F., Woodhead, Z., Wise, R.J., 2012. The contribution of the inferior parietal cortex to spoken language production. Brain Lang. 121 (1), 47–57.
Ghazanfar, A.A., Schroeder, C.E., 2006. Is neocortex essentially multisensory? Trends Cogn. Sci. 10 (6), 278–285.
Ghaziuddin, M., Butler, E., 1998. Clumsiness in autism and Asperger syndrome: A further report. J. Intellect. Disabil. Res. 42 (1), 43–48.
Gieysztor, E.Z., Choińska, A., Paprocka-Borowicz, M., 2018. Persistence of primitive reflexes and associated motor problems in healthy preschool children. Arch. Med. Sci. 14 (1), 167–173.
Goodale, M.A., Milner, A.D., 1992. Separate visual pathways for perception and action. Trends Neurosci. 15 (1), 20–25.
Groenewegen, H.J., Wouterlood, F.G., Uylings, H.B.M., 2016. Organization of prefrontal-striatal connections. Handbook of Behavioral Neuroscience. Elsevier, pp. 423–438.
Grzywniak, C., 2016. Role of early-childhood reflexes in the psychomotor development of a child, and in learning. Acta Neuropsychol. 14, 2.
Güntürkün, O., Ströckens, F., Ocklenburg, S. (2020). Brain lateralization: a comparative perspective. Physiological reviews.
Habata, K., Cheong, Y., Kamiya, T., Shiotsu, D., Omori, I.M., Okazawa, H., Kosaka, H., 2021. Relationship between sensory characteristics and cortical thickness/volume in autism spectrum disorders. Transl. Psychiatry 11 (1), 616.
Haber, S.N., 2017. Anatomy and connectivity of the reward circuit. Decision Neuroscience. Academic Press, pp. 3–19.
Hadoush, H., Nazzal, M., Almasri, N.A., Khalil, H., Alafeef, M., 2019. A new developed non-invasive cortical stimulation on mirror neurons in children with autism spectrum disorders. J. Neurol. Sci. 405, 94.
Hampson, D.R., Blatt, G.J., 2015. Autism spectrum disorders and neuropathology of the cerebellum. Front. Neurosci. 9, 420.
Hazlett, H.C., Poe, M., Gerig, G., Smith, R.G., Provenzale, J., Ross, A., Piven, J., 2005. Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Arch. Gen. Psychiatry 62 (12), 1366–1376.
Herbert, M.R., Ziegler, D.A., Deutsch, C.K., O'brien, L.M., Lange, N., Bakardjiev, A., Caviness, V.J., 2003. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 126 (5), 1182–1192.
Herrero, M.T., Barcia, C., Navarro, J., 2002. Functional anatomy of thalamus and basal ganglia. Child's Nerv. Syst. 18, 386–404.
Hilton, S., Hunt, K., Petticrew, M., 2007. MMR: marginalised, misrepresented and rejected? Autism: a focus group study. Arch. Dis. Child. 92 (4), 322–327.

Hofer, S., Frahm, J., 2006. Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion 1150 tensor magnetic resonance imaging. Neuroimage 32 (3), 989–994.
Hughes, J.R., 2007. Autism: the first firm finding= underconnectivity? Epilepsy Behav. 11 (1), 20–24.
Hughes, J.R., 2008. A review of recent reports on autism: 1000 studies published in 2007. Epilepsy Behav. 13 (3), 425–437.
Iacoboni, M., Ptito, A., Weekes, N.Y., Zaidel, E., 2000. Parallel visuomotor processing in the split brain: cortico- subcortical interactions. Brain 123 (4), 759–769, 1116.
Isamah, N., Faison, W., Payne, M.E., MacFall, J., Steffens, D.C., Beyer, J.L., Taylor, W.D., 2010. Variability in frontotemporal brain structure: the importance of recruitment of African Americans in neuroscience research. PLoS One 5 (10) e13642.
Johnson, C.N., Ramphal, B., Koe, E., Raudales, A., Goldsmith, J., Margolis, A.E., 2021. Cognitive correlates of autism spectrum disorder symptoms. Autism Res. 14 (11), 2405–2411.
Johnson Chacko, L., Pechriggl, E.J., Fritsch, H., Rask-Andersen, H., Blumer, M.J., Schrott-Fischer, A., Glueckert, R., 2016. Neurosensory differentiation and innervation patterning in the human fetal vestibular end organs between the gestational weeks 8–12. Front. Neuroanat. 10, 111.
Just, M.A., Cherkassky, V.L., Keller, T.A., Minshew, N.J., 2004. Cortical activation and synchronization during sentence comprehension 1121 in high-functioning autism: evidence of under-connectivity. Brain 127 (8), 1811–1821. Aug 1.
Keary, C.J., Minshew, N.J., Bansal, R., Goradia, D., Fedorov, S., Keshavan, M.S., Hardan, A.Y., 2009. Corpus callosum volume and neurocognition in autism. J. Autism Dev. Disord. 39, 834–841.
Keen, D.V., 2008. Childhood autism, feeding problems and failure to thrive in early infancy: Seven case studies. Eur. Child Adolesc. Psychiatry 17, 209–216.
Ketcheson, L.R., Pitchford, E.A., Wentz, C.F., 2021. The relationship between developmental coordination disorder and concurrent deficits in social communication and repetitive behaviors among children with autism spectrum disorder. Autism Res. 14 (4), 804–816.
Kilroy, E., Gerbella, M., Cao, L., Molfese, P., Butera, C., Harrison, L., Aziz-Zadeh, L., 2022. Specific tractography differences in autism compared to developmental coordination disorder. Sci. Rep. 12 (1), 19246.
Kleinhans, N.M., Reiter, M.A., Neuhaus, E., Pauley, G., Martin, N., Dager, S., Estes, A., 2016. Subregional differences in intrinsic amygdala hyperconnectivity and hypoconnectivity in autism spectrum disorder. Autism Res. 9 (7), 760–772.
Kringelbach M.L. (2005). The orbitofrontal cortex: linking reward to hedonic experience. Nature Reviews Neuroscience. 6 (9): 691–702. doi:10.1038/nrn1747.
Kumar, A., Sundaram, S.K., Sivaswamy, L., Behen, M.E., Makki, M.I., Ager, J., Chugani, D.C., 2010. Alterations in frontal lobe tracts and corpus callosum in young children with autism spectrum disorder. Cereb. Cortex 20 (9), 2103–2113.
Landry, O., Al-Taie, S., 2016. A meta-analysis of the Wisconsin Card Sort Task in autism. J. Autism Dev. Disord. 46, 1220–1235.
Lane, A.E., Molloy, C.A., Bishop, S.L., 2014. Classification of children with autism spectrum disorder by sensory subtype: a case for sensory-based phenotypes. Autism Res. 7 (3), 322–333.
Lane, A.E., Simpson, K., Masi, A., Grove, R., Moni, M.A., Montgomery, A., Eapen, V., 2022. Patterns of sensory modulation by age and sex in young people on the autism spectrum. Autism Res. 15 (10), 1840–1854.
Laurita, A.C., Hazan, C., Spreng, R.N., 2017. Dissociable patterns of brain activity for mentalizing about known others: a role for attachment. Soc. Cogn. Affect. Neurosci. 12 (7), 1072–1082.
Leisman, G., Melillo, R. (2011). The Development of the Frontal Lobes in Infancy and Childhood: Asymmetry and the Nature of Temperament and Affect. In: Andrea E. Cavanna (Ed.) Frontal lobe: Anatomy, functions and injuries. Hauppauge, NY: Nova Scientific Publishers 2011.
Leisman, G., Melillo, R., 2022. Front and center: Maturational dysregulation of frontal lobe functional neuroanatomic connections in attention deficit hyperactivity disorder. Front. Neuroanat. 16.
Leisman, G., Braun-Benjamin, O., Melillo, R., 2014. Cognitive-motor interactions of the basal ganglia in development. Front. Syst. Neurosci. 8, 16.
Leisman, G., Melillo, R., Melillo, T., Machado, C., Machado-Ferrer, Y., Chinchilla, M., Carmeli, E., 2022. Taking sides: asymmetries in the evolution of human brain development in better understanding autism spectrum disorder. Symmetry 14 (12), 2689.
Levchenko, A., Kanapin, A., Samsonova, A., Gainetdinov, R.R., 2018. Human accelerated regions and other human-specific sequence variations in the context of evolution and their relevance for brain development. Genome Biol. Evol. 10 (1), 166–188 (Jan).
Lin, C.W., Lin, H.Y., Lo, Y.C., Chen, Y.J., Hsu, Y.C., Chen, Y.L., Gau, S.S.F., 2019. Alterations in white matter microstructure and regional volume are related to motor functions in boys with autism spectrum disorder. Prog. Neuro Psychopharmacol. Biol. Psychiatry 90, 76–83.
Loomba, N., Beckerson, M.E., Ammons, C.J., Maximo, J.O., Kana, R.K., 2021. Corpus callosum size and homotopic connectivity in autism spectrum disorder. Psychiatry Res. Neuroimag. 313, 111301.
Lorsung, E., Karthikeyan, R., Cao, R., 2021. Biological timing and neurodevelopmental disorders: a role for circadian dysfunction in autism spectrum disorders. Front. Neurosci. 15, 642745.
Lovell, B. (2021). An Investigation of the Influence of a Wakeful Prone and Vestibular Activity Program on Early Infancy Motor Development (Doctoral dissertation, Victoria University) (https://vuir.vu.edu.au/43126/) Accessed 4 February 2023.
Luders, E., Narr, K.L., Zaidel, E., Thompson, P.M., Jancke, L., Toga, A.W., 2006. Parasagittal asymmetries of the corpus callosum. Cereb. Cortex 16 (3), 346–354.
Ludlow, A., Mohr, B., Whitmore, A., Garagnani, M., Pulvermüller, F., Gutierrez, R., 2014. Auditory processing and sensory behaviours in children with autism spectrum disorders as revealed by mismatch negativity. Brain Cogn. 86, 55–63.
Luna, B., Minshew, N.J., Garver, K.E., Lazar, N.A., Thulborn, K.R., Eddy, W.F., Sweeney, J.A., 2002. Neocortical system abnormalities in autism: an fMRI study of spatial working memory. Neurology 59 (6), 834–840.
Macdonald, D., Luk, G., Quintin, E.M., 2021. Early word reading of preschoolers with ASD, both with and without hyperlexia, compared to typically developing preschoolers. J. Autism Dev. Disord. 51 (5), 1598–1612.
Mackie, M.A., Fan, J., 2016. Reduced efficiency and capacity of cognitive control in autism spectrum disorder. Autism Res. 9 (3), 403–414.
Mahone, E.M., Powell, S.K., Loftis, C.W., Goldberg, M.C., Denckla, M.B., Mostofsky, S.H., 2006. Motor persistence and inhibition in autism and ADHD. J. Int. Neuropsychol. Soc. 12 (5), 622–631.
Martínez, K., Martínez-García, M., Marcos-Vidal, L., Janssen, J., Castellanos, F.X., Pretus, C., Carmona, S., 2020. Sensory-to-cognitive systems integration is associated with clinical severity in autism spectrum disorder. J. Am. Acad. Child Adolesc. Psychiatry 59 (3), 422–433.
Martínez-Sanchis, S., 2014. Neurobiological foundations of multisensory integration in people with autism spectrum disorders: the role of the medial prefrontal cortex. Front. Hum. Neurosci. 8, 970.
Mayer, A.R., Hanlon, F.M., Shaff, N.A., Stephenson, D.D., Ling, J.M., Dodd, A.B., Pirio-Richardson, S., 2020. Evidence for asymmetric inhibitory activity during motor planning phases of sensorimotor synchronization. Cortex 129, 314–328.
McNaughton, K.A., Redcay, E., 2020. Interpersonal synchrony in autism. Curr. Psychiatry Rep. 22, 1–11.
Mei, J., Muller, E., Ramaswamy, S., 2022. Informing deep neural networks by multiscale principles of neuromodulatory systems. Trends Neurosci.
Melillo, R., Leisman, G., 2010. Neurobehavioral Disorders of Childhood: An Evolutionary Perspective. Springer, New York, NY.
Melillo, R., Leisman, G., Mualem, R., Ornai, A., Carmeli, E., 2020. Persistent childhood primitive reflex reduction effects on cognitive, sensorimotor, and academic performance in ADHD. Front. Public Health 684.
Merker, B., Williford, K., Rudrauf, D., 2022. The integrated information theory of consciousness: a case of mistaken identity. Behav. Brain Sci. 45, e41.
Ming, X., Julu, P.O., Brimacombe, M., Connor, S., Daniels, M.L., 2005. Reduced cardiac parasympathetic activity in children with autism. Brain Dev. 27 (7), 509–516.
Mooshagian, E., Iacoboni, M., Zaidel, E., 2009. Spatial attention and interhemispheric visuomotor integration in the absence of the corpus callosum. Neuropsychologia 47 (3), 933–937.
Morishita, T., Timmermann, J.E., Schulz, R., Hummel, F.C., 2022. Impact of interhemispheric inhibition on bimanual movement control in young and old. Exp. Brain Res. 240 (2), 687–701.
Mundorf, A., Peterburs, J., Ocklenburg, S., 2021. Asymmetry in the central nervous system: A clinical neuroscience perspective. Front. Syst. Neurosci. 15, 733898.
Muzik, O.T.T.O., Chugani, D.C., Shen, C., Chugani, H.T., 1998. Noninvasive imaging of serotonin synthesis rate using PET and α-methyltryptophan in autistic children. Quantitative Functional Brain Imaging with Positron Emission Tomography. Academic Press, pp. 201–206.
O'Connor, K., Kirk, I., 2008. Brief report: atypical social cognition and social behaviours in autism spectrum disorder: a different way of processing rather than an impairment. J. Autism Dev. Disord. 38, 1989–1997.
Oh, H., Braun, A.R., Reggia, J.A., Gentili, R.J., 2019. Fronto-parietal mirror neuron system modeling: visuospatial transformations support imitation learning independently of imitator perspective. Hum. Mov. Sci. 65, 121–141.
Ohnishi, T., Matsuda, H., Hashimoto, T., Kunihiro, T., Nishikawa, M., Uema, T., Sasaki, M., 2000. Abnormal regional cerebral blood flow in childhood autism. Brain 123 (9), 1838–1844.
Olson, M.V., Varki, A., 2003. Sequencing the chimpanzee genome: insights into human evolution and disease. Nat. Rev. Genet. 4 (1), 20–28.
Öngür, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb. Cortex 10 (3), 206–219.
Oster, L.M., Zhou, G., 2022. Balance and vestibular deficits in pediatric patients with autism spectrum disorder: An underappreciated clinical aspect. Autism Res. Treat. 2022.
Ozonoff, S., Cook, I., Coon, H., Dawson, G., Joseph, R.M., Klin, A., Wrathall, D., 2004. Performance on Cambridge Neuropsychological Test Automated Battery subtests sensitive to frontal lobe function in people with autistic disorder: evidence from the Collaborative Programs of Excellence in Autism network. J. Autism Dev. Disord. 34, 139–150.
Park, S.E., Choi, N.G., Jeong, G.W., 2017. Metabolic abnormality in the right dorsolateral prefrontal cortex in patients with obsessive–compulsive disorder: proton magnetic resonance spectroscopy. Acta Neuropsychiatr. 29 (3), 164–169.
Paul, L.K., Brown, W.S., Adolphs, R., Tyszka, J.M., Richards, L.J., Mukherjee, P., Sherr, E. H., 2007. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat. Rev. Neurosci. 8 (4), 287–299.
Pecuch, A., Gieysztor, E., Wolańska, E., Telenga, M., Paprocka-Borowicz, M., 2021. Primitive reflex activity in relation to motor skills in healthy preschool children. Brain Sci. 11 (8), 967.
Polimanti, R., Gelernter, J., 2017. Widespread signatures of positive selection in common risk alleles associated to autism spectrum disorder. PLoS Genet. 13 (2), e1006618.
Porges, S.W., 2005. The vagus: a mediator of behavioral and physiologic features associated with autism. Neurobiol. Autism 2, 65–77.
Premkumar, P., 2012. Are you being rejected or excluded? Insights from neuroimaging studies using different rejection paradigms. Clin. Psychopharmacol. Neurosci. 10 (3), 144–154.

Rafiee, F., Rezvani Habibabadi, R., Motaghi, M., Yousem, D.M., Yousem, I.J., 2022. Brain MRI in autism spectrum disorder: Narrative review and recent advances. J. Magn. Reson. Imaging 55 (6), 1613–1624.
Randerath, J., Valyear, K.F., Philip, B.A., Frey, S.H., 2017. Contributions of the parietal cortex to increased efficiency of planning-based action selection. Neuropsychologia 105, 135–143.
Rane, P., Cochran, D., Hodge, S.M., Haselgrove, C., Kennedy, D., Frazier, J.A., 2015. Connectivity in autism: a review of MRI connectivity studies. Harv. Rev. Psychiatry 23 (4), 223.
Ribary, U., Doesburg, S.M., Ward, L.M., 2019. Unified principles of thalamocortical network dynamics: a framework for typical/atypical functional connectivity. Magn. Signals Dyn. Cortical Netw. 543–570.
Ridderinkhof, K.R., Van Den Wildenberg, W.P., Segalowitz, S.J., Carter, C.S., 2004a. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cogn. 56 (2), 129–140.
Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., Nieuwenhuis, S., 2004b. The role of the medial frontal cortex in cognitive control. Science 306 (5695), 443–447.
Rinehart, N.J., Bradshaw, J.L., Moss, S.A., Brereton, A.V., Tonge, B.J., 2001. A deficit in shifting attention present in high-functioning autism but not Asperger's disorder. Autism 5 (1), 67–80.
Riquelme, I., Hatem, S.M., Montoya, P., 2016. Abnormal pressure pain, touch sensitivity, proprioception, and manual dexterity in children with autism spectrum disorders. Neural Plast. 2016.
Riveros, R., Bakchine, S., Pillon, B., Poupon, F., Miranda, M., Slachevsky, A., 2019. Fronto-subcortical circuits for cognition and motivation: dissociated recovery in a case of loss of psychic self-activation. Front. Psychol. 9, 2781.
Rosch, K.S., Mostofsky, S., 2019. Development of the frontal lobe. Handb. Clin. Neurol. 163, 351–367.
Salimova, K.R., 2022. Neurophysiological correlates of impaired development in Autism Spectrum Disorder (ASD). Biol. Bull. Rev. 12 (2), 140–148.
Samad, M.D., Bobzien, J.L., Harrington, J.W., Iftekharuddin, K.M. (2015, November). Analysis of facial muscle activation in children with autism using 3D imaging. In 2015 IEEE International Conference on Bioinformatics and Biomedicine (BIBM) (pp. 337–342). IEEE.
Saron, C.D., Foxe, J.J., Simpson, G.V., & Vaughan, H.G. (2003). Interhemispheric visuomotor activation: Spatiotemporal 1147 electrophysiology related to reaction time. In E. Zaidel & M. Iacoboni (Eds.), The parallel brain: The cognitive neuroscience of 1148 the corpus callosum, 2003 (pp. 171–219), MIT Press.
Schore, A.N., 2005. Attachment, affect regulation, and the developing right brain: Linking developmental neuroscience to pediatrics. Pediatr. Rev. 26 (6), 204–217.
Schultz, R.T., 2005. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int. J. Dev. Neurosci. 23 (2–3), 125–141.
Schulz, S.M., 2016. Neural correlates of heart-focused interoception: a functional magnetic resonance imaging meta-analysis. Philos. Trans. R. Soc. B Biol. Sci. 371 (1708), 20160018.
Seng, G.J., Tseng, W.L., Chiu, Y.N., Tsai, W.C., Wu, Y.Y., Gau, S.S.F., 2021. Executive functions in youths with autism spectrum disorder and their unaffected siblings. Psychol. Med. 51 (15), 2571–2580.
Seo, H.J., Jung, Y.E., Lim, H.K., Um, Y.H., Lee, C.U., Chae, J.H., 2016. Adjunctive low-frequency repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex in patients with treatment-resistant obsessive-compulsive disorder: a randomized controlled trial. Clin. Psychopharmacol. Neurosci. 14 (2), 153.
Shah, A., Jhawar, S., Goel, A., Goel, A., 2021. Corpus callosum and its connections: a fiber dissection study. World Neurosurg. 151, e1024–e1035.
Sheinkopf, S.J., Levine, T.P., McCormick, C.E., Puggioni, G., Conradt, E., Lagasse, L.L., Lester, B.M., 2019. Developmental trajectories of autonomic functioning in autism from birth to early childhood. Biol. Psychol. 142, 13–18.
Shimada, H., Ishii, K., Ishiwata, K., Oda, K., Suzukawa, M., Makizako, H., Suzuki, T., 2013. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. Gait Posture 38 (2), 203–208.
Simmons, D.R., Robertson, A.E., McKay, L.S., Toal, E., McAleer, P., Pollick, F.E., 2009. Vision in autism spectrum disorders. Vis. Res. 49 (22), 2705–2739.
Stephan, K.E., Marshall, J.C., Friston, K.J., Rowe, J.B., Ritzl, A., Zilles, K., Fink, G.R., 2003. Lateralized cognitive processes and lateralized task control in the human brain. Science 301 (5631), 384–386.
Su, W.C., Amonkar, N., Cleffi, C., Srinivasan, S., Bhat, A., 2022. Neural effects of physical activity and movement interventions in individuals with developmental disabilities–a systematic review. Front. Psychiatry 13.
Subramanian, K., Brandenburg, C., Orsati, F., Soghomonian, J.J., Hussman, J.P., Blatt, G. J., 2017. Basal ganglia and autism–a translational perspective. Autism Res. 10 (11), 1751–1775.
Talanow, T., Kasparbauer, A.M., Lippold, J.V., Weber, B., Ettinger, U., 2020. Neural correlates of proactive and reactive inhibition of saccadic eye movements. Brain Imaging Behav. 14, 72–88.
Tomchek, S.D., Dunn, W., 2007. Sensory processing in children with and without autism: a comparative study using the short sensory profile. Am. J. Occup. Ther. 61 (2), 190–200.
Treffert, D.A., 2014. Savant syndrome: realities, myths and misconceptions. J. Autism Dev. Disord. 44 (3), 564–571.
Treffert, D.A., Christensen, D.D., 2006. Inside the mind of a savant. Sci. Am. Mind 17 (3), 50–55.
Uddin, L.Q., Supekar, K., Menon, V., 2013. Reconceptualizing functional brain connectivity in autism from a developmental perspective. Front. Hum. Neurosci. 7, 458.
Ughwanogho, U.O., Taber, K.H., Chiou-Tan, F.Y., 2022. Special anatomy series: Updates in structural, functional, and clinical relevance of the corpus callosum: What new imaging techniques have revealed. J. Int. Soc. Phys. Rehabil. Med. 5 (3), 81.
Valenti, M., Pino, M.C., Mazza, M., Panzarino, G., Di Paolantonio, C., Verrotti, A., 2020. Abnormal structural and functional connectivity of the corpus callosum in autism spectrum disorders: A review. Rev. J. Autism Dev. Disord. 7, 46–62.
Vissers, M.E., Cohen, M.X., Geurts, H.M., 2012. Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. Neurosci. Biobehav. Rev. 36 (1), 604–625.
Vitalis, T., Parnavelas, J.G., 2003. The role of serotonin in early cortical development. Dev. Neurosci. 25 (2–4), 245–256.
Wang, C.G., Feng, C., Zhou, Z.R., Cao, W.Y., He, D.J., Jiang, Z.L., Lin, F., 2022. Imbalanced gamma-band functional brain networks of autism spectrum disorders. Neuroscience 498, 19–30.
Yasuda, Y., Hashimoto, R., Nakae, A., Kang, H., Ohi, K., Yamamori, H., Takeda, M., 2016. Sensory cognitive abnormalities of pain in autism spectrum disorder: A case–control study. Ann. Gen. Psychiatry 15, 1–8.
Zhang, Y., Zhou, W., Wang, S., Zhou, Q., Wang, H., Zhang, B., Wang, X., 2019. The roles of subdivisions of human insula in emotion perception and auditory processing. Cereb. Cortex 29 (2), 517-5.
Zhou, H.Y., Cai, X.L., Weigl, M., Bang, P., Cheung, E.F., Chan, R.C., 2018. Multisensory temporal binding window in autism spectrum disorders and schizophrenia spectrum disorders: A systematic review and meta-analysis. Neurosci. Biobehav. Rev. 86, 66–76.
Zikopoulos, B., Barbas, H., 2007. Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. Rev. Neurosci. 18 (6), 417–438.