



Article Taking Sides: Asymmetries in the Evolution of Human Brain Development in Better Understanding Autism Spectrum Disorder

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Abstract: Confirmation from structural, functional, and behavioral studies agree and suggest a configuration of atypical lateralization in individuals with autistic spectrum disorders (ASD). It is suggested that patterns of cortical and behavioral atypicality are evident in individuals with ASDs with atypical lateralization being common in individuals with ASDs. The paper endeavors to better understand the relationship between alterations in typical cortical asymmetries and functional lateralization in ASD in evolutionary terms. We have proposed that both early genetic and/or environmental influences can alter the developmental process of cortical lateralization. There invariably is a "chicken or egg" issue that arises whether atypical cortical anatomy associated with abnormal function, or alternatively whether functional atypicality generates abnormal structure.

Keywords: asymmetry; lateralization; hemisphericity; evolution; autism spectrum disorder

1. Introduction

1.1. Is Hemispheric Lateralization Uniquely Human?

It is difficult to understand the critical importance of lateralization and cerebral asymmetries without providing a history of its evolution ultimately arriving in neurotypical hominid evolution and how autism spectrum disorder (ASD) may manifest as a deviation in the normal maturational patterns of asymmetries in neurotypical children and adults.

Despite its asymmetry, the brain is constructed on a symmetrical basis that has been evidenced since the beginnings of Bilateria (i.e., bilaterally symmetrical animal embryos or organisms possessing mirror imaged right and left sides) dating back some 600 million years, and perhaps even earlier [1,2]. There are clear disadvantages to anatomic asymmetry that are excessive, possibly associated with limitations in motor control functions associated with the dysfunction of limbs on the affected side, as well as with the ability to process sensory information [3,4]. Alternatively, symmetry may be highly associated with limitations disadvantageous to planning complex motor activities or agency [5] and activities that permit the ineffective utilization of cerebral resources, such as in birdsong or in human language. Variations in asymmetry may represent a balance between asymmetry and symmetry or individual differences in the expression of asymmetries.

Numerous authors have presumed that cerebral handedness and lateralization are uniquely human traits [6–8]. Unfortunately, the relatively recent reports of behavioral asymmetries in non-human organisms as diverse as ants [7], mice [9], and birds [10,11] has begun to detract from this view [7,8,12]. While it is true that functions such as verbal language and opposing thumb and forefinger-precision-grip and other compound manual



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Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). skills that are represented asymmetrically in the brain are exclusively human, organisms lower on the phylogenetic scale do demonstrate both precursory asymmetries that are shared with humans.

It has been thought that the origins of human asymmetric function occurred as a consequence of a mutation in the split of hominids from the great apes [13–16]. Although it is likely the case that brain control of some tasks are lateralized and are unique to homo sapiens, we now know that cerebral asymmetry is not uniquely a human function [17].

The bodies and brains of humans, as well as most other organisms, tend to be bilaterally symmetrical with the bilaterally symmetrical state being the default condition according to Palmer [18]. Corballis [19] noted that a developing organism's midplane can be represented by two axes, the dorsoventral and anteroposterior, with none right-left, with the lateral halves being consisting of independent mediolateral axes. Since the mesolateral axes are mirror images of each other, the developed organism ought to be bilaterally symmetrical, unless it interferes with that development.

In independently moving organisms, an adaptive advantage exists for limbs that are symmetrically placed as they support more efficient linear movement as compared to movement characteristic of non-limbed organisms such as snakes [20–22]. Movement that is directional requires a front to back asymmetry with mouth and eyes placed anteriorly. On the other hand, human asymmetry is right and left. With sensory perceptual asymmetry, a significantly greater increased threat from predation would occur on the non-dominant side rendering bilateral symmetry a protective adaptation.

On the other hand, we human beings are lateralized and are quite prevalent in the evolution of organisms with bilateralization not necessarily being "cast in stone" if an organism requires asymmetry as a more effective means of adaptive function. The asymmetries of lung, heart or liver placement are asymmetrically placed possibly making the organism more optimized [23]. However, considering that the internal organs are independent of the external environment, there is less need for symmetry. Therefore, it appears that for basic motor activities and sensation, bilaterality is advantageous, especially earlier in development when motor activity and sensory feedback are the main drivers of early brain growth [24]. However, for more complex motor activity, higher level sensory processing, and for all cognitive functions such as verbal and non-verbal language, it is more advantageous to be asymmetrical. Since higher level functions become more prevalent as we go higher on the phylogenetic scale it would make sense that full asymmetry in humans emerges during development and peaks later in life when the highest levels of cognitive, motor, and sensory processing are needed [25,26].

A more recent way of viewing asymmetries was represented by Zucca and Sovrano [27], which contravened a long-held orthodoxy, in part reflecting Sperry's split-brain work and that of his students and collaborators [20,28,29], who have claimed that asymmetries are unique to the human species. Now that we know of the parallelisms between non-hominid and hominid asymmetric function, we can no longer view this as such but rather, as Corballis [30] indicates, in the context of a bilaterally symmetric body plan manifested on the basis of the selective advantage of the relation between asymmetry and symmetry.

Systematic asymmetries in human evolution were integrated into activities that are likely unique to Homo sapiens. The antecedents of these asymmetries are manifest in species other than man that include frogs [31], fish [32], birds [33], and primates [30]. Neubauer and colleagues noted the importance of the brain's asymmetrical function as necessary for effective cognitive function [34] although we do not know which parts of that asymmetry are unique to humans. Earlier studies of chimpanzees found that humans are more functionally lateralized than are other organisms. Neubauer's group found that forms of spatial asymmetry pattern, that had been thought to be unique to humans, was actually shared between humans and great apes with human asymmetries appearing to be significantly more variable contrasted with that of apes.

1.2. Ancestral Origins of Hemispheric Lateralization

The evolution of lateralized control of behavioral function can provide us with a window to aid in understanding the nature of human asymmetric function. Babcock [35] studied the healed injuries of fossilized trilobites. He concluded that the predatory behavior of these organisms when alive demonstrated asymmetric brain function. Babcock noted significant differences between the trauma-related scars evidenced on both the left and right of the fossilized trilobites that he studied that provided support for behavioral asymmetry in predatory behavior at the time. Trilobites crawled on the planet well over 250 million years ago during the Cambrian period. Babcock [35], therefore, provided evidence of the oldest known behavioral brain asymmetries in the fossil record.

Supporting this notion of the early origins of functional asymmetry is provided by Reisz and colleagues [36] examined the teeth and jaws in an attempt to assess the feeding patterns of a reptile of the early Permian period from between approximately 298 to 252 million years ago. They had noted that the teeth on the right jaw were significantly more eroded relative to those on the left. This indicated the existence of feeding behavior that was lateralized that favored the right jaw thereby indicating directional motor function associated with brain hemispheric laterality. They concluded that this is an example of brain-based behavioral asymmetry with both birds and mammals both demonstrating the essential characteristics of lateralization. Hirnstein and colleagues [37] asked why it is that functional cerebral asymmetries evolved at all? They proposed a hypothesis that an asymmetric brain would be advantageous for parallel processing. The noted that asymmetric control function of the brain would support significantly greater optimized function for instantaneous and parallel tasks. Hirnstein et al. [37] found that symmetrically organized participants outperformed asymmetric participants in accuracy and response times, not supporting the hypothesis of asymmetry leading to optimized function. On the other hand, Santamecchi and colleagues [38] found support for the notion that a predictor of higher intelligence can be that synchrony between primary sensory regions is reduced. Excessive degrees of asymmetry, however, may make information processing systems less optimized. There is a requirement for an effective mix of symmetry and asymmetry between the hemispheres to be able to maximize synchronized simultaneous functions in the most efficient way [39–41].

While it is not our intention to delve into evolutionary issues of brain asymmetry in depth here, the reader is referred to [42–44] for a more copious analysis. Our function is to indicate how dysfunctioning communication in asymmetric brains may play out in behavioral terms with ASD as a vehicle for explaining phenotypes. In this regard, Neubauer et al. [34] indicated that four largely independent axes support the development of functional lateralization: emotion, perception/action, symbolic communication, and decision-making. The modularization of human functional asymmetries support Neubauer and associates' [34] findings of human brain asymmetry that when compared with apes is relatively more decoupled in humans. They determined that various cerebellar areas in the posterior and anterior cerebellum concerned with symbolic communication and perception/action respectively were dominantly activated.

The findings of Neubauer et al. [34] are interesting in our discussion as the decoupling of occipital lobe and cerebellar asymmetry provides insight into the relation between cerebellar evolution in humans and its possible involvement in ASD with aberrant maturation of some children. Neanderthals, our closest extinct relatives and the great apes did not possess round cerebellums. The expansion of the cerebellum during fetal and neonatal development of the brain in Homo sapiens evolved only relatively recently. The decoupling of cerebellar and occipital asymmetry reported by Neubauer and associates may be a reflection of evolutionary changes in the patters of the cerebellum and cortex's neural connectivity that with maturational aberrations may well be represented in decoupling in basal ganglia-cerebellar pathways noted in ASD. It has also been noted that early developmental disruption of cerebellar development plays a role in autistic symptoms [45].

It had been previously suggested [46-49] that functionally asymmetric regions of the brain demonstrate less connectivity via the corpus callosum (CC) than non-lateralized brain regions. What would follow from such lateralized processing is the reduced likelihood of interhemispheric delays in conduction in the larger human brain. the expectation that larger brains grow faster and/or longer than small brains resultantly manifesting greater developmental instabilities which has been hypothesized to rerate to greater fluctuating asymmetry. Higher functions that are more lateralized are also more independent, and this is an advantage [50,51]. It also indicates that integration of these more lateralized areas of the brain are more dependent on temporal coherence [52], which is instantaneous and would therefore be faster and more efficient than simple physical connectivity provided by the CC [53]. Lateralization increases the bandwidth and the processing speed where it is needed for more the more complex cognitive functions [26,54]. This may explain why humans have a relatively small CC compared to the overall size of the brain. Having two independent hemispheres that operate in a relatively independent, yet synchronized, fashion gives significant cognitive advantage but may also reveal a potential weakness if either of these two factors, asymmetry or temporal coherence, is disrupted [55–57]. This, we think, is what may be an underlying process in ASD and in other developmental neurobehavioral disorders [58].

In both behavioral and cerebral asymmetries studied to date, a number of individuals are capable of reversing or negating their dominant sidedness, thus indicating that such asymmetries can be viewed in the process of overriding the brain and body's bilateral symmetry, allowing the evaluation of the relative advantages and disadvantages of human symmetry and asymmetry. We also note that a mixed dominance profile or delayed dominance is much more common in children that are developmentally delayed such as in those with ASD [59].

1.3. Genetic and Environmental Contributions to the Development of Human Brain Asymmetry

The genes that regulated body asymmetry are fairly well known [60], but their role in brain lateralization is less clear. The nodal complex of genes and their interaction with other genes clearly lead to body lateralization and seem to play a role in creating neuroanatomical asymmetries. It is agreed that nongenetic factors such as environmental, especially motor and sensory stimulation play the most important role in the development of brain asymmetry [61,62] with the most important factors related to the shifting of dominance from right to left over the first six years of life [62]. The genes underlying the process of shifting hemisphere dominance is not clear, but it is present to varying degrees in other species [60]. A unilateral slow wave function associated with sleep allows for one hemisphere to essentially sleep while the other hemisphere remains awake and is present in a number of species [63,64]. Dolphins, for example would drown without the ability to sleep with "half a brain" [65]. The mechanism by which this process occurs is supported by the "active" or conscious brain that is connected to the contralateral eye which remains open, and it may also work with active flippers or the contralateral fins [65,66]. This seems akin to the dominance profiles observed in humans where the dominant eye, ear, hand and foot are contralateral to the "dominant" hemisphere-the hemisphere that has greater conscious control of behavior and or memories. The same genes that regulate this in other species may have something to do with the shifting of activation during brain development that ultimately influences the brain's asymmetry of function [14,60,67]. This shifting of developmental trajectories between the hemispheres combined with environmental, non-genetic factors, such as motor development and sensory feedback along with other environmental experiences may be the most important factors leading to an asymmetric brain in humans.

It has also been documented that mixed or absent dominance profiles are common in neurobehavioral disorders [58,59,61] often with reversed or abnormal laterality. If the genes that regulate lateralization are malfunctioning [26,68] or if the left side of the brain becomes active first [69–71] or if the relevant genes do not create asymmetric activation during development [67,68,72] this may disrupt the normal lateralization of the brain. If one side of the brain has a shorter period of development than normal [73] or if the contralateral hemisphere comes online too soon [73] this may be associated with abnormal lateralization which can create a developmental asynchrony [74,75] and maturational delays [58,74,75]. Asymmetric development of the motor system may be associated with concomitant asymmetries in sensory exploration and activation. For example, lateralized light activation in some species can be associated with asymmetric brain connectivity and function [26,76,77].

It is thought that the brain developed to allow an organism to move more purposefully [78,79]. The ability to purposefully move allowed a choice of direction-toward or away from an object or another organism. Purposeful movement requires the anticipation of an outcome prior to the initiation of an outcome [80,81]. For this to occur, a brain is necessary rendering movement foundational for developing brains [82–84]. In the context of phylogenetic development, it can be said that with greater complexity of movement, brains tend to possess greater degrees of complexity and asymmetry [85,86].

Brain lateralization commences early in development. By ten gestational weeks (GW), Hepper et al. [87] found that human fetuses moved their right arms significantly more often than left in 85% of 72 cases examined with in utero ultrasound scanning, possibly indicating an embryonic precursor of human behavioral lateralization.

We humans have developed the most complex movements of all species-bipedalism, coincident with the most asymmetric and complex brains. Corballis [8,15,42,69] had noted that the larger brains of primates and humans associated with greater complexities of behavior is constrained by the size of the skull with asymmetry being an effective means of addressing brain complexities. Bipedal animals possess small birth canals that restrict the growth of head circumference but produce infants with a concomitant need for a complex brain. Cerebral asymmetry is one way in which brain complexity may be accommodated as asymmetry can increase the number of specialized areas of the brain. Due to the small birth canals, combined with very large heads, human infants are the most immature at birth of any species. This means that most of the development takes place outside the womb and that human brains are most dependent on environmental factors that influence brain development. This can be of great advantage, as the genes and the brains that regulate neurological development. It also is a potential source of vulnerability because if the environment or the ability to move through the environment is not optimal.

In most species, as well as in humans, genetic factors contribute to the development of asymmetric brains. Nodal genes have been reported to support the physical asymmetry of the body plan and are thought to be involved in the control of the asymmetric development of the brain. Kasprian and colleagues [88,89] noted that brain asymmetry is initiated and regulated early in fetal and neonatal development and is apparently related to asymmetric gene expression controlling cerebral hemisphericity as early as 12 GWs [88,89]. Earlier studies had consistently found that brain asymmetries were most evidenced perisylvian and temporal [90–94]. There are some studies that have identified specific genes that may be related to this asymmetry. Sun and colleagues [95] in a review of both behavioral and cerebral asymmetries, referenced a number of studies where individuals were capable of reversing or negating their dominant sidedness, thus indicating that such asymmetries can be viewed in the context of the brain's ability to override the brain and body's bilateral symmetry [96]. This offers support for the notion hat combinations of genetic and nongenetic elements can support the development of brain asymmetries. Light exposure, for example, in certain embryos may be associated with asymmetrical visual pathway development [97-99].

The literature is replete with studies that have found relationships between alterations of brain asymmetry and psychiatric and cognitive dysfunction, that have included schizophrenia [100–102], ASD [100,103,104], and language pathology [100,105]. A comprehensive meta-analysis study published back in 2001 found that schizophrenia was related to left- and mixed-handedness, especially associated with aberrations in the lateralization of the sylvian fissure and planum temporale [106]. Individuals with ASD have demonstrated differences of handedness [107] cortical structure [108], and functional lateralization for language [108,109].

Two papers concerned with the ontogenesis of lateralization (Güntürkün and Ocklenburg 2017 and Ocklenburg et al. [68,79]) have provided comprehensive reviews on body and brain lateralization. They identified genes that may control lateralization. During mammalian embryogenesis, the embryo initially develops cross an anterior-posterior axis, then followed by the development on a dorsal–ventral axis. The final break of symmetry occurs between right and left [110], The left–right body axis is controlled by a structure termed the node and which in turn is contingent upon the nodal signaling cascade [111].

2. Evolution in the Context of ASD

2.1. Evolutionary Advantages of Human Accelerated Genomic Regions in ASD

When attempting to understand the relationship between the evolution of the human brain and ASD, we can note that alterations in genetic regulatory mechanisms may be important in both ASD and in human evolution.

There have been recent reports from comparative genomic studies that have recognized small areas of the human genome common to numerous species but that were altered relatively fast during the evolutionary divergence of humans from chimpanzees. Such sequences in the genome are termed human accelerated regions (HARs) [112,113]. As our cognitive and social behaviors are so distinctive relative to other species, some investigators have concluded that alterations in HARs might be significant factors in the evolution of these traits in humans [114,115]. If significant HARs were dysfunctional or damaged, it could also be associated with impaired human cognitive and/or social functioning [115].

Additionally, autism-related genetic variants associated with ASD may have been selected as a positive alteration during the evolution of *Homo sapiens* as there may well have been a need for superior cognition. Polimanti and Gelernter [116] had performed a genome-wide study of demonstrated that inherited variants linked to ASD were found in positive selection at levels greater than that predicted on the basis of chance. The relatively high incidence of ASD that we are now observing with relatively minor effects can significantly impact on complex genetic phenotypes that could be both negative, as well as positive. Polimanti and Gelernter found that ASD variants were statistically associated with intellectual prowess. They additionally found that many of the ASD variants were molecularly associated with processes related to the creation of new neurons. The big question is why these ASD-related variants have not been eliminated by evolutionary processes. It appears that these retained variants have had a positive effect with the downside being ASD which might provide an adaptive benefit.

ASD individuals prefer repetition, predictability, and routine [117]. Those events or processes which ASD individuals single out for intense attention tend to be mechanistic and trite cognitive functioning of ASD individuals have demonstrated that they possess skill with the examination of detail. ASD individuals along the entire spectrum have relatives who disproportionately represent engineering disciplines and this across generations [118].

There exist evolutionary advantages for possessing autistic behaviors. Historically, for most of the time that *Homo sapiens* have existed they have lived as hunter gatherers necessitating observation of the predictable patterns of the movement of game and knowing how to stay safe from predators. Additionally, tools such as clovis points, the atlatl, and the production of effective projectile spears required great attention to detail in order to produce them. These behaviors certainly indicate the understanding of materials and even of physics by our forebearers. The ASD phenotype certainly had been advantageous to the ancients. In present times we may note that ASD serves as a "balanced polymorphism" or genetically based disease or disorder that would be advantageous in many respects in ways such as thalassemia which renders the individual immune from malaria if bitten by an anopheles mosquito with the cost of deterioration and death being irrelevant, as

individuals from those geographical regions died before the downside of the condition could manifest itself [119].

2.2. The Functionality of Half a Cortex at a Time

In examining species such as cetaceans we can more clearly observe and understand the function of hemispheric switching and lateralization. In marine mammals such as cetaceans there exists a need to thermoregulate [120]. As a result, these organisms are required to continuously swim so as to adjust their body temperature. Additionally, they need to constantly breathe requiring them to periodically resurface. To ameliorate the problem of breathing while asleep, one hemisphere remains active while the other is asleep [121]. The contralateral side opposite the active hemisphere sleeps while one of the organism's eyes is open thereby supporting continuous movement and hemi-attention, in turn allowing for response to potential predators. It is not only cetaceans that have this unilateral asymmetric function, but species including mallards and birds [121,122]. As numerous species possess this function, many have speculated that the relevant regulatory genes are also likely to be found in humans. We conjecture that this mechanism may be the basis of asymmetric hemispheric shifting in child development that is highly associated with cognitive abilities including self-awareness and right hemisphere-based body ownership [123], which is largely absent or reduced in ASD [124]. Actually, an analog to lateralized sleeping has been noted in humans. When we, for example, attempt to sleep in an unfamiliar place, the right hemisphere sleeps, and the left hemisphere remains active [125,126]. Actually, in humans, consciousness sits predominately in the left hemisphere as it tends to be "aware" [127]. Laterality associated with ear, eye, and foot are typically related to the "dominant" hemisphere which is also lateralized for language. There is a clear relationship and advantage to asymmetry of the brain, but this may also lead to a specific vulnerability that may lie at the core of many neurobehavioral disorders in children and adults [58].

2.3. Dancing Asymmetrically: Timing of Asymmetry and Lateralization

Asymmetric development of the hemispheres is largely a function of the timing of the expansion of the cerebral hemispheres [128]. In humans, the fetal right hemisphere develops in utero continuing for the next three years of life [128]. The left hemisphere then continues by then principally developing over the following three years, with a 20–30% advantage in developmental activity supporting the influence of non-genetic environmental factors that lead to asymmetric development of specialized functions [129]. Additionally, cerebral dominance or handedness, which is regulated by the left hemisphere in most cases, does not fully emerge until the age of three when the left hemisphere becomes dominant in development [58]. This is true for consciousness and explicit memory, which are also regulated predominantly by the left hemisphere [130]. This is a reason given why it is that we humans possess "childhood amnesia", where we typically do not remember most events before the age of three and start to form conscious memories when the left hemisphere and the hippocampus come online [131]. Before this time the right brain forms subconscious, procedural, and implicit memories [58,131].

While our focus is on the value and importance of asymmetries. Symmetric bilaterality is critical for effective sensory-motor function. It supports our ability to move in a purposeful fashion allowing symmetrical feedback supporting movement to navigate our world more efficiently. If the control of muscle tone were asymmetric, it would impede motor function rendering it significantly more uncoordinated in ways that we see after brain insult [132] or in developmental disabilities such as ASD where most impaired individuals exhibit motor coordination difficulties.

For movement coordination to be effective, bilateral movements require limbs to produce efficient and optimized gait. The effectiveness of that symmetrical gait is a direct function of motor system timing, in part the effective functioning of the inferior olive and the cerebellum [133,134]. The importance of the cerebellum in this context rests on its ability to regulate tone in voluntary and involuntary movement via the descending motor

system. This timing signal functions metronomically allowing the motor system to be able to connect movement spatially and temporally [135]. If such a signal did not exist, the result would be significantly greater for uncoordinated movement. The timing that allows for coordination of movement should also be equal bilaterally.

This "clock" that generates the timing signal needs to be symmetrically distributed in the motor system otherwise this could result in asymmetric movements oftentimes observed with developmental or adult onset damage to the cerebellum or with developmental disabilities associated with asymmetric development [136]. Numerous neurobehavioral disorders such as attention deficit hyperactivity disorder (ADHD), ASD, or what used to be called developmental coordination disorder (DSD) have been demonstrated to possess cerebellar-based developmental anatomical and functional deficits [137,138]. However, other than the need for basic sensory and motor control, behavioral, cognitive, and processing functions require brain asymmetry. One of the most important functions of the human brain is the requirement for speed of response. The brain is required to function quickly for beneficial and protective responses. An enemy of efficiency and speed in the human nervous system is redundancy. Possessing brain centers that perform the exact same job is deoptimized. It is similar to the adage, "A man with one watch always knows what time it is a man with two watches never knows what time it is". It is more efficient to have a single region on one side of the brain and another control center on the contralateral side, where, at times, they can cooperate and, at times, inhibit each other to reduce interference. Besides increases in speed, accuracy and efficiency, asymmetric brain organization increases the brain's ability to perform more highly specialized tasks that in turn is associated with the asymmetry of our complex brains [26].

Complexity theory has two primary elements, the first of which is: (a) differentiation. To be able to engineer a complex system, diversity must exist. A system composed numerous regions that control specialized functions is by definition, a more complex system. Having two hemispheres performing similar tasks but in varied and specialized ways requires a more complex brain. Humans have the most asymmetric brains when compared with other species and also possess the most complex brains and demonstrate the most complex behavior. In ASD and other developmental disabilities, we can observe brain immaturity either less capable of complex behavior or with less efficient cognitive capacity [139]. Alternatively, we can observe a disparity of skills that is characteristic of developmental disabilities [140]. The second feature of complex systems is: (b) integration. With reduced differentiation and specialization, we invariably witness rigidity and reduced complexity. In a complex highly specialized system, specialized systems must be efficiently integrated in order to create complex behavior. In the same way that we have motor- binding mechanisms in the motor system, we likewise possess a timing mechanism signal in the brain supporting cognitive-binding, generated by the thalamocortical system [141,142]. This signal serves as the context permitting binding in space and time and from moment to moment for multiple dedicated brain areas. If this timing mechanism is slow or asymmetric rather than symmetric, that mechanism may prevent the binding and integration of distant areas of the brain thereby interfering with complex behavior [143]. The lack of integration in complex and highly specialized systems can generate "chaos".

As the development of the brain has been variously described as constituted by "complex scaffolding" of multiple types of neural processes [144] we can apply a complexity model to its normal development. First and foremost are processes that are genetically-based that are thought to be considered largely resistant to experience. These functions are designed to protect the fetal brain, direct patterns of migrating neurons, and target synaptic connectivities while also defining differentiated functions [145].

Additionally, "expectant-based" functions exist that occur when the brain is prepared to obtain specific types of environmental information–and is therefore "expectant". These mechanisms are associated with sensitive or critical periods at which time there exists a plethora of synapses, which eventually are reduced [146]. Critical periods are genetically programmed supporting the development of basic skills supporting the individual's envi-

ronmental interaction that, as a consequence, can eliminate excess synapses [147]. Synaptic pruning is controlled by competing neuronal connections [148]. The result is that inactive or rarely activated neurons are purged, and experience strengthens and maintains connections between neurons [149,150]. This gives the brain an upside-down U-shape trajectory and interference at any point can lead to brains and brain areas that are either too small or too big which both may represent immaturity of the brain. Neuroplasticity is a consequence of both timing and the individual's interactions with the environment (i.e., experience) described more fully below. As a result, severe deprivation, challenging circumstances over prolonged periods of time or other detrimental or abnormal experiences may negatively and permanently influence brain development and its structure and function [144]. Experience-dependent synaptogenesis, an additional process, results from the unique experience of the individual developmentally and even after maturation. This process occurs after the "experience-expectant" processes [151]. Therefore, each individual's brain reveals, in part, his or her unique experiential history. More importantly, "experiencedependent"-synaptogenesis is more highly represented in areas of the brain concerned with information processing associated with individual experiences [151], p. 1413. This third brain development mechanism involves numerous influences including daily social experience, as well as interventions, such as psychotherapy or occupational training.

3. Asymmetrical Brain Development in Autism Spectrum Disorders

3.1. The Corpus Callosum Supporting Integrated Symmetric Behavior and Efficiencies of Timing in an Asymmetric System

Having indicated that timing signals support the symmetric spatial and temporal function of motor activity, we know that in primates, at least, axonal processing speed relates to the evolution of hemispheric asymmetries with the development of the CC *cf.* [152]. With increasing brain size, some axonal fibers become disproportionately larger with greater conduction velocity. However, increased axonal diameters may not be large enough to offset the greater interhemispheric distance in the larger brains of primates and humans. Therefore, action potential signaling velocity across the brain through the CC is relatively delayed, which may be associated with a reduction of the speed of interhemispheric connectivity [152]. These factors could support the evolution of hemispheric specialization associated with greater brain size.

Not having had much traction since the 1970s, the work of the late Hebert Birch may be quite relevant in this regard. Birch and colleagues had noted that individuals with unilateral cerebral damage demonstrate unilateral delay in processing sensory information, with such delay being consequential for action organization. Left hemiplegic individuals demonstrated significantly longer reaction times to stimulation of the left than of the right side in contrast to controls who showed no such lateral differences in reaction time. Birch and colleagues concluded that delayed sensory information processing was associated with cerebral damage that in turn had functional consequences for awareness and perception [153–155], as well as for the organization of action [156].

We have long known that auditory, primary visual and motor function in humans is highly asymmetric manifested as right-sided sensory input and bilateral motor output. The issue of course is that bi-hemispheric input requires integration somehow to produce a cohesive motor reaction [157]. In evolutionary terms the CC is significantly involved in the control of complex cognitive activity, as well as in the specialization of brain regions [158]. In support of this notion some investigators have noted that the speed of interhemispheric communication is significantly greater as a function of greater brain size [159–163]. On the other hand, others have thought the opposite in that larger brains are associated with hemispheric slowing [164,165]. Additionally, some investigators have noted that asymmetrical brains are significantly better able to respond to simultaneously presented diverse stimuli [68,166–168]. Broadly speaking, the literature indicates that after many years of research we have been able to demonstrate a significant relationship between CC connections and increased interhemispheric transfer time in individuals with congenital

absence of the CC and in split-brain individuals [169,170]. We do note, however, that ASD individuals have been reported to demonstrate significantly increased interhemispheric transfer times [171] and reduced interhemispheric coherence.

3.2. Cerebral Connectivity and the Corpus Callosum in ASD

We have described the CC as a thick and broad axonal tract that is comprised of a bundle of fibers underneath the neocortex that links the right and left hemispheres of the brain. Its principal function is to support effective communication between the cerebral hemispheres. There is much support for the notion that the smaller size of the CC in ASD reflects neural under-connectivity with an effect in turn associated with reductions in the patterns of synchronization between regions of the brain [172]. Clinical reports of CC agenesis support the notion that the resultant impairment in social functioning possess commonalities with ASD behaviors [173,174].

3.3. Corpus Callosum Asymmetry

In attempting to explain why these clinical associations are present, Belmonte et al. [175] and Courchesne and Pierce [176] argued that fundamental deficits in ASD are associated with diminished long-range connectivities between the frontal lobes and other brain systems, and to local over-connectivity within the frontal lobes. According to these investigators, superficial white matter tracts associated with cortico-cortical fiber enlargement and CC volume are reduced. One can discriminate between neurotypical and approximately 95 percent of autistic toddlers and young children on the basis of deviations between groups of cerebral white matter and cerebellar vermis size. This would allow an accurate prediction of the developmental outcome of high or low function among the autistic children. It appears that persons with ASD have been reported and long been known to demonstrate dysfunction of fronto-striatal systems associated with cognitive, emotional and social behavior based on neuropsychological testing that has included the Wisconsin Card Sorting test [177] Tower of Hanoi-type tasks [178], and the CANTAB measuring frontal lobe function [179]. While the reasons for the deficits in performance are not apparent it has been intimated that executive function deficits could be associated with an atypical right lateralized fronto-striatal brain networks that are dysfunctional in information integration [180] with differences in asymmetrical functional connections having been noted as having associations with the mechanisms of ASD.

Luders et al. [181] demonstrated significantly greater right lateralization of the anterior CC, the area projecting to the motor cortices in right-handed males. They had determined that there exists a stronger leftward lateralization of motor functions in right-handers associated in turn with a reduction in left interhemispheric fibers connections. Braun and colleagues [182,183] reported consistent findings that suggested that motor transfer is more efficient from the right to the left hemisphere via the CC in neurotypical individuals, but no such relationship has been reported with ASD individuals. The absence of a relationship in ASD individuals does not necessarily imply impairment, but rather can result in a hypothesized reduced effective distribution of commissural connectivities.

Numerous investigators have theorized that the CC is a structure highly associated with the symptoms of autism, but with little attention paid to asymmetry. We know that the anterior mid body of the CC projects to the motor cortex [184], with projections to the posterior parietal cortex from the posterior mid-body of the CC. This area is highly interconnected, and its function integrates sensory and motor input from visual and somatic areas [185]. As a result of the integration of these systems, these connectivities can subserve sensory guided movement planning and behavioral responsivity to the environment.

Studies that have examined individuals with posterior or mid-CC lesions have reported movement incoordination [186], and in tactile information processing [187]. Patients with posterior parietal cortex (PPC) lesions display difficulties in the permanence of action sequences, as well as in the performance of hand and eye movement when grasping [188]. Some of these behaviors in ASD connote an atypical symmetry of the posterior and ante-

rior mid-body which may well be associated with the motor inefficiencies so often noted in ASD [189], impairments in fine motor skills [190], motor planning and sequencing deficits [191], agency [5], and difficulties in responding to spoken language [192]. As a region of the posterior parietal cortex is involved in fields of aversion and eye movement planning, attention and eye contact in autism may be associated with this brain region as well.

Rightward asymmetry of numerous regions of the CC (e.g., the posterior mid-body, rostral body and the splenium) have been found to be associated with increased ASD symptom severity. The explanation is clear in that the splenium projects to the inferior temporal and occipital lobes significant for object and face processing. Schultz [193] has demonstrated significantly decreased activity in the fusiform face area (FFA) and a concomitant increase of activity in the inferior temporal gyrus during face processing in ASD. Impediments in facial recognition in ASD are highly associated with difficulties in social interaction and could in part explain why differences in the splenium between ASD and neurotypical 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 [194]) which indicates that frontal circuits that have been abnormally lateralized can serve as a basis for deficits in social, behavioral, and higher cognitive functions. Stronger rightward posterior mid-body CC asymmetry is related with significantly greater symptom severity with its responsibility in part of integrating sensory0motor input. ASD is associated with hypo- or hyper-sensory processing abnormalities also being related to repetitive and stereotypical behaviors [195]. The body of literature on this topic intimates that rightward brain asymmetry and underconnectivity may interfere with movement planning, stereotyped movement patterns, eye movement control, and face recognition and possibly may affect other aspects not infrequently evidenced in ASD.

3.4. Cerebral Asymmetry in Autism

There exists argument in the neuropsychological literature that claims involvement of either the right [56,103,196] or the left hemisphere [197] in the manifestation of the expressed characteristics and deficits in ASD. A principal symptom of autism is impairment in both expressive and receptive language [198,199]. This dysfunction could be evaluated relatively early in a child's neurobehavioral development and has led many to conclude that ASD is highly associated with left hemisphere deficits.

On the other hand, Children with ASD have been reported by some investigators [103] to largely develop a right-biased cortical organization for right-hemisphere information processing. If one were to assume that the right hemisphere functions in its appropriate fashion in ASD with a functional suppression of the left cerebral hemisphere, and, as a result, information would largely be right hemisphere processed, to which the ASD child would orient and ultimately assimilate so as to build cognitive schemata, and then analytic language skills in children with ASD would be absent, and such functions as visual-spatial processing and musical skill would be preserved cf. [33,58].

Much was suggested in the early 1970s that is beginning to currently gain support. Turkewitz [200] found that neonates responded more consistently to right-sided mouth and face touching touch by turning to the right compared to left-sided touching. However, infants who had scored low on Apgar testing at birth tended to not demonstrate a clear preference for the side of stimulation. Additional support that has been known for some time and with recent confirmation [201] had noted that most of the autistic children studied demonstrated enlargement of the left ventricle. Colby and Parkinson [202] found that the frequency on non-righthandedness for the autistics was 65% whereas it was 12% for the normal. Failure in the normal developmental processes of lateralization can be taken as a sign of brain dysfunction.

Besides arguing for either right or left hemisphere differences, there is significant evidence, for now already over forty years that the problem may not be either right or left dominance but rather a functional independence of interhemispheric communication. In other words, a lack of asymmetry may be present, when, in fact, there should be asymmetric function of the two hemispheres.

The majority of neurotypical individuals demonstrate cortical asymmetry usually manifested in the form of left occipital and right prefrontal protuberances [203]. A number of studies have investigated brain asymmetry is individuals with ASD with mixed results. One study by Hier and associates [204] examined asymmetries in the parieto-occipital region in a sample of 4- to 27-year-olds with ASD with an additional cohort of individuals with intellectual disability. It had been noted that the ASD cohort demonstrated more than twice the incidence of reversed occipital asymmetry (i.e., right greater than left) then did the other groups. Other investigators [205] did not find that children and young adults with ASD demonstrated significantly more occipital asymmetry than did normal adults. The studies that have examined prefrontal asymmetry [205] found no higher rate of asymmetry in people with ASD when compared with normal adults [205]. Tsai and colleague [206], on the other hand, noted that the children that they investigated with ASD had been classified at a significantly higher rate in demonstrating either frontal or occipital equal potentiality when compared with healthy right-handed adults. In contradistinction, the right prefrontal protuberances being greater than left and the left occipital protuberances being greater than right have reportedly been found in approximately 70 percent of right-handed adults [207]. Reversed asymmetries have been reported more frequently by a factor of four in individuals with developmental language dysfunction [208].

There is evidence as a basis on which to conclude that the developmental and genetically supported processes of cerebral asymmetry may create an ideal template for lateralized function development with alterations from the template predisposing the individual with ASD to develop atypical patterns of lateralization. As indicated earlier, atypical patterns of language lateralization have been reported in individuals with ASD [56], with reversed or reduced asymmetry for language having been consistently reported *cf.* [205]. Atypical brain asymmetries may be associated with very early aberrant cortical development [209].

Hardan and colleagues [210] had performed a morphometric study of the total CC volume in children with autism. They found reductions in CC total volume and several of its subdivisions in ASD children. The CC alterations in their investigation are consistent with midsagittal area tracings of decreased CC size in ASD. These findings are consistent with a hypothesis of dysfunctional connectivity with possible decrease in interhemispheric communications. Bartha-Doering and colleagues [211] found evidence that the CC is directly linked to language network connectivity and underlines the excitatory role of the CC in the integration of information from both hemispheres. There have been numerous studies on the role of CC aberrant lateralization in ASD that have been extensively reviewed by Valenti and colleagues [212] that when taken together relate to ASD symptom production in general and can be viewed as a descriptor of hemispheric connectivity. CC abnormalities can account for the characteristically poor functional connectivities noted in ASD. In their review, Valenti and colleagues, evaluated studies employing diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) that examined the contribution of the CC in structural and functional brain connectivity in individuals with ASD. A principal objective of functional and structural connectivity studies has been to determine the anatomical correlates of ASD. Among these findings have included reduction in the volume of the CC—a consistent finding in autistic brains. Additionally, functional connectivity studies have demonstrated atypical activity during working memory, social cognition, and in executive function tasks in individuals with ASD with all of these studies contributing to better understanding the CC's role in the manifestation of deficits noted in ASD. The role that the CC development has on the hemispheric specialization of language is not well understood. Hinckly and colleagues [213] employed magnetoencephalography (MEG) in patients with congenital agenesis of the CC. These individuals were given tests of verb generation and picture naming during the MEG procedures. Tests of hemispheric dominance found significant reductions of lateralized function (i.e., an increased chance of right hemisphere dominance or bilaterality) in ASD when contrasted with neurotypical

children. The results were observed to be more profound in cases where there was a complete agenesis of the CC. Behavioral measures of verbal intelligence were positively correlated with laterality. These results support the hypothesis that functional specialization in development of the brains of childhood is supported by the CC. By extension, the loss of this mechanism is related to verbal deficits.

Cermak and associates [214] performed a scoping review of studies of brain regions associated with language performance ASD individuals. They noted consistencies across studies that examined asymmetries, with negative associations between right brain regions and language in ASD individuals compared to positive associations between left brain regions and language in neurotypical individuals without ASD symptoms. Their review also found significantly greater rightward asymmetries in ASD offering support the literature review by Lindell and Hudry [215] that found a relationship between rightward asymmetry and poorer language abilities in ASD.

Yet another view on the subject of hemisphericity issues in ASD is a burgeoning literature indicating a principal suppression of the right hemisphere in favor of the left, which we favor [216]. Since diversity in a population adds to evolutionary fitness there are clear advantages to having some people be right hand dominant and others left with a clear advantage to right hand dominance. Any trait that is to be preserved, promoted, or eliminated is based on how it effects evolutionary fitness. Evolutionary fitness can be defined on the basis of whether or not it leads to a likelihood of procreation and survival of the species. It is thought that ASD, schizophrenia, and bipolar disorder have a genetic basis; however, there is no single genetic mutation that has been found to be associated with the majority of cases. However, from and evolutionary fitness perspective it would seem that each one of these disorders would reduce the evolutionary fitness of the species. ASD and schizophrenic individuals do not typically have offspring and in bipolar disorder there is a 5 x greater suicide rate [217].

Therefore, clearly from an evolutionary perspective these individuals appear to be disadvantaged. On the other hand, these disorders are still quite prevalent and seem to be increasing in frequency. The only explanation would be that there are underlying traits associated with these disorders that at one level may also impart a great advantage. However, too much of this trait can become disadvantageous. ASD and schizophrenia may be related to an "intellect trait" with family members of these individuals tending to be highly intelligent. Simon Baron Cohen has shown that autism occurs more often in families of physicists, engineers, and mathematicians [218]. He had also noted that there exist clusters of ASD individuals around areas heavily involved in the IT industry. A significant number of parents of children with autism have themselves not been diagnosed with autism but do possess similar cognitive skills and behaviors, albeit not as pronounced. This is also true for siblings of individuals with autism. Too much of one type of trait may give advantage to that trait but may also be associated with a deficit of another trait. For instance, increases in logical, linear type thinking may be associated with lower sociability. Baron Cohen thinks that in ASD individuals possess an excessive maleness trait associated with increased systemization ability in autism and decreased empathizing ability. However, we alternatively can be viewed this as hyperfunctioning of the left hemisphere in autistic individuals.

We think that it is a misconception that children with autism demonstrate left hemisphere deficits as some are not able to speak, and there is a certain percentage of the autistic population that do possess deficits in verbal language. However, many of those with autism have significantly more severe nonverbal communication deficits related to underdevelopment of the right hemisphere. Even those that are non-verbal in many cases show savant level left hemisphere skills. We propose the reason that they may not be able to speak is that a significant developmental delay of the right parietal lobe and insular cortex in turn delays their abilities of interoception and bodily spatial perception, as well as delaying the development of "body ownership" and self-awareness, in turn being associated with deficits in agency and the ability to move and control the motor planning necessary for speech and language. The reason that ASD is increasing in frequency is that the trait underlying it provides great advantage especially in a world moving more toward technology and left-brain skills as noted by Ian McGilchrist [219]. Based on the fact that there are genes that are thought to regulate the development of the left and right hemisphere separately [220,221] it would make sense that there are those that are more right or left hemisphere dominant and that like all other traits these traits would fall on a spectrum where at the most extreme end, the intellectual advantage goes over the edge of an "evolutionary cliff' and that this, coupled with extreme deficits in other functions manifest collectively as extremely well developed and significantly underdeveloped abilities lead to ASD. This can explain the typical unevenness of skills characteristic of almost all neurobehavioral disorders [58] but especially autism. It also could be explained by the hyperconnectivity seen with short range connections and the under-connectivity all seen in ASD.

3.5. Environmental Influences on Synaptogenesis and the Corpus Callosum in General and on Asymmetry in ASD in Particular

With the orderly process of asymmetric hemispheric development in humans, the right hemisphere develops first in utero and continues for the first three years postpartum. Next, the left hemisphere becomes more predominant in development during the following three years. It is during these three years there exists a 20–30% advantage in developmental activity that supports an asymmetric development of specialized functions [58]. Environmental stimulation, the most active hemisphere, and the most active afferents are the principal means for shaping hemispheric function [58]. We had earlier noted that many organisms have a mechanism that allows one hemisphere to sleep while the other hemisphere remains active. The side of the body opposite to the active hemisphere including the eye remain open and active to allow for continued movement and awareness of any danger. Since many species have this ability, the genes that regulate this function are most likely present in humans as well. We think that this mechanism may be at the root of this hemispheric shifting during development that being the single most important factor in developing lateralization of function and the unique level of cognitive ability, especially self-awareness, that humans possess. In general, the left hemisphere is invariably consciously "aware". Hand, foot, eye and ear dominance are usually associated with the "dominant" hemisphere which is most often the left hemisphere which is also the verbal hemisphere. There is a clear relationship and advantage to asymmetry of the brain, but this may also lead to a specific vulnerability that may lie at the core of most neurobehavioral disorders in children and adults.

Postnatal neuronal differentiation may be influenced by experience and be one means by which parenting can shape brain development. Rats, for example, raised in enriched conditions demonstrate increased dendritic spine density, greater dendritic arborization, and significantly more synapses per neuron in various brain regions of animals raised in stimulus reduced environments. cf. [222] Additionally, investigators have found that increases in dendritic length are highly associated with increased cortical thickness that has been found in rats raised in highly stimulating environments [222]. There also exists evidence that enriched environments have a significant positive effect on the development of white matter [223], on the CC, and on selenium myelinization [224], which is discussed more fully in the next subsection. Rhesus monkeys raised in enriched environments also demonstrate bigger corpus calosa [225]. In many of these studies, the enriched environment relates to more active or complex movement and increased sensory stimulation in these animals relates to increased and more complex movement which, in turn, drives sensory exploration and stimulation, which may also relate to early human development. In humans, for example, extensive piano practice beginning in childhood is associated with increased cerebral white matter [226] Rat studies suggest that experience effects on myelination appear to be associated with early neurological development, as mature rats raised in enriched environments do not demonstrate experiential effects of myelination [227]. If

the same principle is applicable to humans, it could denote that there exists a critical period during which parenting because a significant variable in affecting brain asymmetry.

Early environmental influences on development may both improve normal performance, as well as negatively affect it. Stresses encountered early in development, including fetal development, that may be either cognitive or physiological, may order developing neural networks to evoke cascading effects continuing into later development, that may restrict the child's adaptive flexibility to challenging and novel situations. As a result, abnormal stresses at a given stage in the developing brain impedes: the creation of new structures and functions, negatively influence the form of later-emerging structures, allow for the construction of structures that are not normally demonstrated, and/or limit the use and expansion of structures and functions that had appeared earlier [228], p. 1428. Resultantly, there exist numerous means by which brain development can become inappropriate, with significant differences between individual fetuses, neonates and children in their resilience to adversity, whether it is due to violence, poverty, parental neglect and abuse or severe discipline.

4. Conclusions

Confirmation from structural, functional, and behavioral studies agree and suggest a configuration of atypical lateralization in individuals with ASDs. The research reviewed suggests that patterns of cortical and behavioral atypicality are evident in individuals with ASDs. Importantly, the present review emphasizes that atypical lateralization is common in individuals with ASDs.

On the basis of the research reviewed, we can better understand the relationship between alterations in typical cortical asymmetries and functional lateralization in ASD. We have proposed that both early genetic and/or environmental influences can alter the developmental process of cortical lateralization. There invariably is a "chicken or egg" issue that arises whether atypical cortical anatomy is associated with abnormal function or, alternatively, whether functional atypicality generates an abnormal structure. Simply stated, we do not know.

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