

Conceptual Models of Neuronal Dysfunction in Autism:
Biochemical Toxins, Neuroregulation, and Implications for Neurogenesis

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Annette Ruth is a sophomore Biology and Psychology dual-degree candidate from northwest Indiana. Interested in neurology from a young age and more recently inspired by her Applied Behavioral Analysis (ABA) program work with autistic children in the South Bend area, Annette dedicates much of her time to literary research in the field of neurobiology, specifically pertaining to the potential causes of neurological dysfunction in pervasive developmental disorders such as autism. She will spend her next four semesters working on research in neuroendocrinology to augment her understanding of various hormones and external neurochemicals, their impact on neural development, and the resulting behavioral differences they produce. Annette ultimately wishes to earn an MD-PhD in pediatric neurology and to continue conducting advanced neurobiological research in autism.

Introduction

Imagine a special part of the human brain that moderates our observations and interpretations of other people's actions and our deduction of their intentions, providing essential input that governs our interactions with others. Now imagine what would happen if such a specialized brain function were impaired: the afflicted individual would not know how to interact with other people, would lack the abilities to empathize and imitate, and would fail to make eye contact. The brain's specialized cells that perform such observational and interpretational moderation are called mirror neurons, and their dysfunction among autistic individuals serves as an exemplary model of a neuroregulatory disorder. In addition, consider other neurons, such as Purkinje cells¹, and their contributions to human cognition. The sensitivity of these neurons to various biochemicals renders them exceptionally susceptible to dysfunction, thereby subtracting some essential component of cognitive capability in affected individuals. In essence, this complex of neurological conditions, consisting of various neuronal dysfunctions, ultimately constitutes autism. This concept has become the focal point of research into autism, with neurological research focusing on the mechanism of imitation in mirror neurons and the associated implications for language and working memory in relation to other neural groups. The brain's mirror neurons and their dysfunction in observational and interpretational moderation leads to the aforementioned commonly perceived symptoms characteristic to autism.

Autism's prevalence among the human population is evident, with its frequency of occurrence increasing in recent years. A six-year study by Baird and others² reported autism in one of every 333 children (0.3%) in the UK's South Thames region, and recent reports from the California Department of Developmental Services suggest that the rates of autism are increasing.³ This suggests that external factors may be changing, such as an increase in

environmental toxins. Though the precise cause or causes of autism are unknown, and the disorder has always been enigmatic due to its wide array of symptoms, a basic symptomology of autism has been established based on behavioral symptoms common to the vast majority of cases, though still with varying degrees of prominence. The widely varying behavioral symptomology, along with several notable morphological characteristics such as increased brain volume, observed among individuals with the disorder illustrates the idea of a “spectrum.” These consistent symptoms include qualitative impairment in the ability to interact socially and qualitative impairment in communication, which ranges from a delay in acquisition of spoken language, accompanied by the development of abnormal speech patterns, to a failure to ever vocalize. Repetitive, restricted, and stereotyped patterns of behavior and activities, such as rocking, hand flapping, narrow interests, and obsessive desire for a static environment are also distinctly characteristic of autistic individuals. The pervasive aspect of autism spectrum disorder (ASD) constitutes mild to significant lifelong disability, with no available effective treatment other than various forms of behavioral therapy.

These differing combinations of symptoms or cognitive levels are also found in memory function in autistic children, with a special working memory deficit in oculomotor⁴ response delay and a verbal working memory considered by some researchers to be the “core of cognitive deficit” in autism.⁵ Mirror neurons can explain the reciprocation of observational perception in understanding actions, thoughts, and emotions in others, and they are necessary for normal development of recognition, theory of mind,⁶ and language. Understanding human actions and internal states relies on both the ability of the observer to see others as being “like me” in their actions and behaviors, and also the ability to simulate these observed actions and states with the observer’s own cognitive, motor, and emotional demonstrations.⁷ This mental simulation allows

the observer to understand another person's behaviors and feelings, or to have a "theory of mind" — something of which a child with autism is incapable. For the purpose of working with a highly researched and thus more widely understood neural model, this paper discusses the neurological etiology of autism primarily based on mirror neuron physiology. However, evidence of Purkinje cell loss and dysfunction and the alteration of neuronal physiology are presented to explain the roles of various biochemicals in autism within a physiological context using specific examples.

Neurons exist in a variety of physical forms, each with different biochemical compositions and requirements. The multitude of possibilities in regard to their location, function, and chemical makeup allows for a hierarchy of neuronal vulnerability to a variety of chemical insults.⁸ Though research has shown that neurotransmitters such as oxytocin and vasopressin are hyposecreted or present in only precursor forms in autistic individuals, it is still unclear as to which specific neuronal groups these hormones and other neurochemicals affect. Many environmental toxins that exist in the body in minute amounts—parts per million or billion—mimic the functions of endocrine hormones, or neurotransmitters, not only during prenatal development, but also during the critical period in the first few years of life and into adulthood.⁹ By labeling the toxins with biomarkers, magnetic resonance spectroscopy can show which neuronal groups the invasive chemicals target, and therefore which domains of functionality would be impaired in an individual as a result. Understanding the precise neurological mechanism by which chemicals affect the physiology of the human body provides significant insights into the etiology of autism.

Mirror Neuron Functionality

First discovered in monkeys in the 1990s,¹⁰ mirror neurons fire both during the performance of an action and during the observation of that same action performed by another individual.¹¹ Thus, they link the observation of another's action to one's own behavior, enabling the observer to imitate that behavior¹² as well as to rapidly surmise, without the need for explicit reasoning, why the other individual might behave in such a manner.¹³ Ongoing research demonstrates that the mirror neurons' firing represents the comprehension of the action, regardless of the subject's active or passive role, rather than the physical performance of that action.¹⁴ The same team confirmed the existence of the mirror neuron function in humans and determined that those neurons are not confined to a specific region of the brain, but are spread across many areas with some in close proximity to each other. Exact brain areas were activated when study participants simply observed motor acts. According to another study involving activation of isolated brain regions, children with autism who only observed motor acts showed no mirror neuron activity in the inferior frontal gyrus, with activity in this area being inversely related to symptom severity in the social cognition.¹⁵ This finding also serves to bolster the hypothesis that a dysfunctional mirror neuron system may underlie the social deficits observed in autism. Additional primate experiments revealed that the mirror neurons' firing patterns reflect comprehension not only of the action itself, but also of that action's goal, as when food is grasped for the purpose of storage rather than for eating.¹⁶ However, regarding the act of stereotyped mimicry such as echolalia¹⁷, where no specific purpose for the actions seems apparent, mirror neurons account for difficulty in inhibiting such actions.¹⁸ In these ways, mirror

neurons show activity in relation to specific actions performed by oneself and by others, thereby creating a potential bridge between individuals' minds.

Behavioral Significance in Autism

Discovered independently in the 1940s by American psychiatrist Leo Kanner and Austrian pediatrician Hans Asperger,¹⁹ autism is a severe state of social disconnectedness that afflicts approximately 0.5 percent of American children.²⁰ Clearly, neuronal dysfunction is not altogether uncommon and can have pervasive effects on a person's functional capacity, emphasizing that the external factors responsible for this dysfunction are significant contributors to autism. Mirror neurons serve as a model of neuronal malfunction in respect to the significant cognitive deficits with which they are associated in the context of autism spectrum disorder, and thus it is important to first investigate the nature of their dysfunction. Although it seems logical enough that autism could result from a malfunction of the mirror neurons' action-and-intention comprehension system, such a conclusion could not be assumed until experimental evidence demonstrated the cause-and-effect relationship, thereby demonstrating neuronal sensitivity to insult and the magnitude of resulting physiological impairments.

Various teams of researchers at the University of California, San Diego, have performed such experiments and confirmed the relationship between action and intention as mediated by mirror neurons.²¹ Surmising that the work of Rizzolatti, et al., provided clues to the neurological underpinnings of autism, Ramachandran and Oberman devised experiments to test this theory. They focused upon the mu wave, a component of the EEG trace that is characteristically suppressed whenever the subject performs a voluntary muscle movement. As Rizzolatti's team

had found with the firing of mirror neurons, Ramachandran's team found that the suppression of mu waves associated with voluntary actions also occurred when normal subjects observed others performing similar actions. However, when the autistic subjects observed those same actions, their mu waves continued unimpeded even though they exhibited normal mu suppression when they performed such actions themselves.

The Rizzolatti research team, in an attempt to gain a greater understanding of the role of mirror neurons in human imitative capabilities, observed human subjects who were watching and imitating finger movements in learning how to play the guitar.²² Both of these activities triggered the mirror neuron system, particularly when the movement had a specific goal. However, these movements were simple and practiced, leading the research team to wonder how mirror neurons would respond in learning new and complex motor acts. Monitored by functional magnetic resonance imaging (fMRI), study participants' parietofrontal mirror neuron systems became active during observation, and even more so during the participants' imitation of the chord movements. The most interesting breakthrough for memory occurred when the same brain region became active in the interim between observation and imitation. This region, called prefrontal area 46, is associated with working memory and therefore may participate in the mental assemblage of motor acts that a person is about to perform.

Children with autism, unlike their typically developing counterparts, cannot succeed in tasks requiring the retention of information in working memory, an essential feature of executive function that is necessary for flexible, future-oriented behavior, particularly in novel circumstances. If autistic individuals have mirror neuron dysfunction, researchers point out that it is reasonable to conclude that this same observed phenomenon could explain such persons' deficient working memory.²³ The mirror neuron system also includes Broca's Area, responsible

for the motor function that produces verbal communication, or spoken language. Such abnormalities in both verbal and nonverbal communication are marked impairments of those with autism, and a serious delay in language development is what often prompts families to seek a child's diagnosis. Language development is related to joint attention (JA) based on the observation that children with autism who exhibit more sophisticated language skills are also observed to more effectively share and follow the attention of others.²⁴ This indicates that JA ability serves as a predictor of language ability, as found in longitudinal studies of autistic children, where research data indicated that a greater ability to initiate and respond to JA predicts greater language skills in one year, five years, and even eight years later.²⁵ Thus, early language abilities predict social functioning, academic achievement, and psychiatric outcome in late childhood and early adulthood. This relation between abilities makes sense in light of the fact that sharing a focus of attention with other individuals enables one to acquire skills that are solely socially learned and exercised, such as language. Research also provides strong evidence through studies that teaching children with autism to engage socially and share communicative intent will improve language outcomes among those who already have these skills to some degree, rather than those who must initiate them.

In further exploration of JA dysfunction, the cognitive view of psychology comes into effect when dealing with triadic joint attention difficulties in autism, which involve a child's attention on an object through observance of an adult's indication of that object, or sharing a focus of attention. The problem for autistic children arises in the argument of the cognitive view that this capacity for JA serves as a precursor to children's later "theory of mind," in which autistic children are deficient and are consequently incapable of forming representations of both the self and the other person focusing attention on the same object. Autistic children lack this

“shared attention mechanism” and therefore cannot comprehend higher-level representations, demonstrated by the generic form, “A sees that B is looking at O” (Lopez & Moore 2000). Once again, this failure to comprehend what others perceive points to the role of mirror neurons in the “like me” recognition that others can have like experiences.²⁶ JA difficulties are an expected result of mirror neuron impairment.

In lending some of the most significant symptoms to autism spectrum disorder, dysfunctional mirror neurons are pervasive in their effect on social interaction and cognitive perception of the self and others. A conjunction of two or three environmental toxins present in parts per million in the body may be responsible for such a malfunction and thus, the resulting deficits. Other than physical injury, only neurochemical insults have the ability to introduce such a severe effect on the functionality of mirror neurons. Environmental toxins, or chemical pollutants, are likely to blame as reports of autism epidemics are correlated with the presence of chemical toxins in the water supply and proximity to large industrial facilities. The human body encounters incessant environmental insults on a daily basis, though the neurological effects are usually not significant enough to produce outwardly noticeable—and therefore diagnosable—physiological dysfunction. Subsequent research will strive to identify the combinations of substances that have the most detrimental neurological impact.

Effect of Environmental Toxins on Neural Functionality

In order to comprehend the significance of neurological dysfunction in autism, one must understand that it is unclear as to whether the dysfunctions associated with this neurobiological disorder are primary in nature or if another system is malfunctioning and negatively affecting the neurobiological system.²⁷ Mirror neurons, or neurons in general, must have a distinct cause for their malfunctioning, other than a mutation occurring during a critical stage of prenatal development. Considering this, neurological disorders may be caused by neurochemical deficits or imbalances in the brain, largely originating from the environment. Research has demonstrated the significance of toxic chemicals in the environment and how they can affect neurological development. In our world, we utilize potentially harmful chemicals in industry and in household cleaning agents on a daily basis, and we bear constant exposure to various sources of radiation, so it seems only reasonable to deduce that the environment is not only outside us, but also within us.²⁸ Interestingly, there are almost 200 other diseases, disorders, and conditions that either have just become noticeable or have just developed within the last century, corresponding with the rise of manufactured chemicals, over 3,000 new drugs, electromagnetic fields, and the widespread implementation of various technologies. Thus, detoxification of our bodily systems may effectively lead to amelioration or recovery of autistic symptoms—those that impair individual performance capabilities—provided that there exists a way to repair damaged or abnormal neurological pathways. The presence of very small, even negligible, dosages of certain chemicals acting in conjunction within the body have been observed to have significant effects on fetal development. Chemicals in the environment measured at parts per billion or trillion have acted as teratogens²⁹, negatively affecting fetal neuronal circuits at critical stages in development. These chemicals that fall below safety thresholds can act upon the body by mimicking hormones and other signaling and regulating molecules.³⁰ Variation among

individuals would be due to differing degrees of sensitivity to certain hormones, as well as to altered hormonal environments.

To best illustrate the experimental findings that support what is discussed above, Herbert offers evidence from a recent study of environmental factors affecting the population of Brick Township, New Jersey, where there exists an autism cluster, or an unusually high frequency of cases.³¹ Three chemicals, bromoform, chloroform, and tetrachloroethylene, were discovered in the municipal water supply, each individually below toxic thresholds. However, in an experimental study working with *Spisula* or surf clam embryos, scientists discovered that when placed together, these three chemicals “damaged a pathway in brain development that each alone (or even in pairs) did not do.”³² More specifically, the synergistic activity of these chemicals was found to impair the functionality of neurotransmitters or receptors of the serotonergic-dopaminergic nervous system.³³ This bolsters the argument that a combination of various toxic exposures over the past century have acted upon the human population in conjunction with one another to produce harmful effects, much like the three chemical pollutants.

On a more direct physiological level, the Purkinje cell is an exceptionally large inhibitory neuron in the cerebellum that receives input from parallel and climbing fibers³⁴ at over 200,000 connections, making it not only particularly sensitive but also selectively vulnerable to changes in its environment. Local excitotoxicity in a cerebral neural cluster is likely to affect one of these pervasive Purkinje cells, increasing its susceptibility to the effects of chemical toxins. Excessive rises in intracellular calcium, associated with excitotoxicity, can cause cell death, and Purkinje cell loss in the cerebellum is one of the most consistent neurological abnormalities found in individuals with autism. However, it is not cell death that causes Purkinje cell loss, but a noted absence of gliosis, or proliferation of neural tissue that follows neural damage particularly during gestation.³⁵ Neuronal functionality among autistic persons may also be affected by other

neurotoxins such as lead and aromatic hydrocarbons like toluene, benzene, styrene, and trichloroethylene. Sources of these compounds are found in the environments of industrialized nations, along with polluted waters, dry cleaning chemicals, exhaust fumes, and chemical coatings. Considering that nearly infinite combinations of chemical influences are possible, and factoring in individual differences, this evidence suggests that treatment strategies would have to be uniquely tailored for each individual, if the specific factors affecting them could even be identified in the first place.

Thus, evidence from correlation studies suggests that the chemical agents found in the environment play a role in the development of autism and that they affect neurological physiology. Other disorders, defects, and diseases, such as cancer, have similar contributing effects, as they all impart significant neurochemical effects on the body. With so many variables, to name one as a primary detrimental factor at which to begin searching proves impossible. Rather, advanced blood and biochemical analysis of affected individuals, coupled with neurological research into brain areas consistently affected among cases, should provide a starting ground for scientific investigation and should govern the direction of research interests. For example, in research, theorizing and demonstrating that autistic individuals have dysfunctional mirror neurons should prompt the following: consideration of what could cause this dysfunction on a biochemical level, a search for imbalances within the brain, and studies of the composition of tissues and body fluids to detect invasive chemicals, even in negligible amounts. This may lead to the detection of unusually high levels of certain chemicals among all or most individuals with autism, forming a positive correlation between autism and the chemical(s) in question. This finding may then turn the investigation toward the environment to look for potential local sources of these discovered toxins. In this way, immediate neurological treatment couples with promising research efforts into the specific factors that disrupt the brain's neurochemical balance.

Cerebellar Impairment

Purkinje cell loss and the dysfunction of other neurons in the cerebellum may have more pervasive effects than previously considered. The cerebellum's vast interconnection with the cerebral cortex and other regions of the brain provides evidence that it modulates various functions throughout the brain. With areas of the cerebellum found to be abnormal in autism, multiple parameters are considered likely to play a role in the disorder. The vermis³⁶ of the cerebellum modulates sensory input at the level of the brain stem, thalamus, and cerebral cortex, and when stimulated, causes hypersensitivity to touch and sound, a common symptom of autism.³⁷ Multimodal sensory neurons projecting to the vermis from the superior colliculus and back form a multisensory feedback loop, suggesting that dysfunctionality of these neurons causes the multimodal sensory integration problems and a lack of coherence of sensory information observed among autistic individuals. Areas related to communicative impairments in speech, including language delay and abnormal speech, also relate to the functionality of the cerebellum, with lesions introduced to the right cerebellum creating problems with word selection and production, resulting in dysarthria³⁸ and abnormal speech rhythm.³⁹ Interconnectivity in areas involved with attention, gaze control, and head and eye movement may be associated with the difficulty autistic persons experience with gaze, including staring into space and looking at objects from unusual angles. These areas, also involved in shifting attention, may produce the difficulties autistic individuals experience as they easily fixate upon certain trivial stimuli while ignoring others that are more important or pertinent to a given situation.

Cerebellar activation peaks when tasks are done deliberately, or with full consciousness; once performance is automatic, the cerebellum is no longer involved. This may produce hindrances on associative learning because once learning a process has occurred and specific connections have been formed such that performance no longer requires deliberate thought, the weight of cerebellar function diminishes.⁴⁰ Thus, it is likely that normal function of the cerebellum is most critical during early stages of development before significant learning takes place. This suggests that neuronal dysfunction within the cerebellum, including Purkinje cells, occurs early in development if in fact cerebellar neurons contribute to the symptomology of autism.

Treatment Prospects in Neurogenesis: Utilizing Biomarkers

The generation of new neurons largely occurs during pre-natal development, with the majority of cortical neurogenesis occurring early, or around 16 weeks into gestation. Other parts, such as the hippocampus and cerebellum, are later-developing neuronal structures that do not complete formation until after thirty-four weeks of gestation.⁴¹ However, evidence of neurogenesis in the adult brain has arisen in recent years, beginning with the discovery of active neural cell division in the amygdala and hypothalamus. Neurogenesis studies significantly increased after the development of BrdU (5-bromo-3'-deoxyuridine), a marker of cell division. Biomarkers can be imaged using magnetic resonance spectroscopy (MRS) to noninvasively detect and quantify neural stem and progenitor cells (NPCs) in the human brain, as well as to more effectively diagnose and treat neurodegenerative disorders. Essentially, biomarkers allow researchers to observe neurogenesis and monitor brain disorders.⁴² Significant differences in the

concentration of the biomarker have been found between the hippocampus and the cortex. The amygdala, a complex cerebral region that has been associated with the emotional integration of daily experiences, has also been proven as a site of neurogenesis. Because the amygdala is closely associated with the hippocampus, the increased biomarker concentration in that location is largely linked to the integration of emotional processes and neurogenesis. The hypothesis has emerged that a dysfunction in neurogenesis in the amygdala is a contributing cause of autism.

The acquisition of new social skills requires the construction of new neuronal structures, including sufficient plasticity for synaptic rearrangements.⁴³ Sociability impairments seen in autistic individuals may be caused by impaired regulation of the GABAergic system. GABA is a neurotransmitter that is released in the brain during novel experiences, and it functions along with its receptor subunit, GABAR, to mediate synaptic inhibition in the adult brain.⁴⁴ It also acts as an excitatory neurotransmitter due to the high intracellular chloride concentration in immature neurons. Thus, GABA regulation affects the amygdala's capacity to store new experiences. The amygdala also cannot properly modulate the plasticity of the corticostriatal connections in the event of dysfunctional neurogenesis. The receptor subunit composition also varies developmentally and across brain structure, with a significant decrease in GABAR density, but an increase in blood plasma GABA levels among autistic individuals. Recent studies have delved deeper into the question of how alterations in neurogenesis may affect higher and lower brain organization and functionality in autistic individuals.

A culture of pluripotent NPCs, capable of giving rise to any type of neural tissue, can model neural development when stimulated with serum from autistic children that induces neuronal cellular differentiation. This observed pattern of differentiation reflects the alterations in early neuronal development that lead to autism. Sera from autistic children were found not only

to reduce significantly NPC proliferation, but also to stimulate cell migration and synaptogenesis. With the development of network processes and synaptogenesis predominating in the brain during postnatal ontogenesis, the culture results suggest that these crucial processes are altered in autism.⁴⁵ Therefore, mirror neurons may also be affected by improper connectivity, or “wiring problems,” in the brain. Neuronal dysfunction would then stem from the neurons being incapable of sending signals to the appropriate places, rather than from problems involving the functionality of any single neuron. Neurodevelopmental alteration such as increased volumes of whole brain, the parieto-temporal lobe, and cerebellar hemisphere, as well as an abnormally large-sized amygdala, hippocampus, and corpus callosum are characteristic of autism, suggesting large-scale pathophysiological and cytoarchitectural transformations.

Neuronal proliferation, differentiation, migration, growth, and inter-structural organization may be hypersensitive to relatively minor changes in the cellular environment, such as the presence of neurotrophins and neurotransmitters, which have been found in altered amounts in the brain, cerebrospinal fluid, and blood of individuals with autism.⁴⁶ Thus, as discussed earlier, neurotoxins acting in conjunction as neurotransmitters, such as one that mimics serotonin, may lead to deregulation of neurogenesis, neuronal differentiation, axon myelination, and synaptogenesis. Altered levels of other participatory neurotransmitters, such as GABA, which is involved in neuronal integration and interneuron migration, may also result. These individual neurochemical findings stemming from the investigation of NPC cultures with autistic serum even suggest that neural hardwiring and myelination problems, all ultimately controlled by the proper functionality of neurotransmitters and specific chemicals, affect brain structure as evidenced by over- and under-connectivity and myelination of various brain regions. One study found local decreases of gray matter, or under-connectivity, in areas of the prefrontal motor

cortex belonging to the mirror neuron system, as well as malformation of neural networks in other cortical areas associated with empathy.⁴⁷ If greater NPC proliferation could be induced in affected individuals identified through biochemical testing, neurogenesis would take place under more controlled conditions, or it would be better moderated, leading to significantly improved or even corrected connectivity of neural circuitry.

Frontal lobe neural pathology, becoming evident early in development through magnetic resonance imaging (MRI) evidence, suggests excess cerebral neurogenesis, as indicated by the presence of activated glia and neuroinflammatory response through additional post-mortem quantitative analysis. The frontal cortex in autism clearly appears deficient in reciprocally interacting with other cortical regions, paralleling the autistic child's inability to effectively reciprocally interact with his or her social environment.⁴⁸ Interestingly, neuroinflammatory response was also noted in the cerebellar cortices, further suggesting that lower brain systems do not receive proper integrative feedback from higher brain regions, and of those, primarily from the frontal cortex, which is responsible for this long distance cortical-cortical reciprocal activity. A positron emission tomography (PET) study in 1988 by Horwitz et al. found reduced correlative activity among brain regions, leading researchers to conclude that autism involves reduced and impaired connectivity with the lower level brain systems as well.⁴⁹ This has led to the aforementioned stipulation that local connectivity is abnormally increased while long-distance connectivity is reduced or abnormally patterned. Additionally, with the frontal lobes being the site of peak early growth pathology, macrocephaly, a physical characteristic of autism, results from the frontal cortex driving the early enlargement of brain volume. One hypothesis for this biological finding is that it stems from a reduction in neuronal pruning and consolidation of synapses during prenatal development.⁵⁰ Once more, this observed increase in brain volume

points to an increase in neurogenesis or gliogenesis, the growth pattern of both ultimately controlled by NPCs, again suggesting dysfunctional neural receptor activation on a biochemical level.

Conclusion: Implications for the Future

Physiologically, mirror neuron abnormalities produce symptoms of autism, particularly in cognitive functioning associated with language development, joint attention, and working memory, as demonstrated. Ramachandran's study suggested a link between mirror neurons' firing and mu suppression, and it demonstrated the lack of proper mirror neuron function in autistic subjects.⁵¹ Subsequently, other researchers confirmed the Ramachandran team's results and further demonstrated the dysfunctional nature of autistic subjects' mirror neuron systems. Rizzolatti spurred further investigation into the role of working memory through novel, complex imitation involving motor demonstration. The synapse between observation and imitation also demonstrated mirror neuron activity, suggesting a form of encoding. Anderson's research team performed a study that demonstrated a "theory of mind" or reciprocation at work through the correlation between joint attention and language ability,⁵² thereby confirming that yet more impairments associated with autism have their basis in mirror neuron activity in the prefrontal motor cortex. Indubitably, current authoritative research points to mirror neuron dysfunction as perhaps the greatest contributor to autism as observed in studies involving young children. The reasons for mirror neuron dysfunction must be simultaneously considered, as biochemical mechanisms are responsible for proper neuronal operation.

Biochemical evidence leads to a high probability that dysfunctional mirror neurons result from a critical chemical imbalance or from the presence of neurotoxins. Research into toxicity effects to date has involved only lower-level organisms and requires supplementary experimentation to confirm its applicability to the human brain. This remaining gap in mirror neuron investigation leaves great potential for biochemical research, as suggested by evidence arising from expansive studies that probe into the chemical functionality of other types of neurons, including those in the motor cortex. An external toxin may also be indirectly involved in the sense that it causes either hypo or hypersecretion or the deregulation of chemicals already present in the body, which may then affect the functional capabilities of mirror neurons.

While mirror neurons serve as exemplary models in demonstrating how the dysfunction of any one particular neuronal group may cause certain symptoms of autism, Purkinje cells demonstrate neuronal vulnerability to environmental insults, particularly chemical toxins. Biochemical toxins in the brain act upon the vulnerable Purkinje cells located in the cerebellum, which is a brain region that modulates higher-lower brain functions and interactions that, when impaired, may account for the core cognitive and linguistic deficits of autism. Future research can utilize biomarkers in labeling specific chemicals and tracking their migration through the body, including what specific neuronal groups they affect. Biochemical or hormone therapies can then be created to counter the effects of these toxins, hopefully reducing the symptoms of autism, and perhaps even eliminating them prenatally. Advances in molecular imaging and biochemical technology will guide research in mirror neuron functionality in autism toward greater prospects involving neurogenesis in treatment.

ENDNOTES

1. Purkinje cells, among the largest neurons in the brain, reside in the cerebellum and have complex connections that play an important role in motor coordination.
2. Gillian Baird and others, "A screening instrument for autism at 18 months of age: A six year follow-up study," *Journal of the American Academy of Child and Adolescent Psychiatry* 39, no. 6 (2000): 699.
3. Janet Kinnear Kern, "Purkinje cell vulnerability and autism: a possible etiological connection," *Brain & Development* 25, no. 1 (2003): 377.
4. "Oculomotor" means, literally, "eye movement."
5. Diane L. Williams, Gerald Goldstein, and Nancy J. Minshew, "The profile of memory function in children with autism," *Neuropsychology* 20, no. 1 (2006): 22.
6. Theory of mind is the ability to understand that others have beliefs, desires, and intentions that differ from one's own.
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8. Kern, 380.
9. Michael Lerner, "Autism's new paradigm: seeking answers to environmental threats," *Autism Advocate* 5, no. 1 (2006): 14.
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12. Dingfelder, 52.
13. Rizzolatti, Fogassi, and Gallese, 57.
14. Rizzolatti, Fogassi, and Gallese, 57.
15. Mirella Dapretto and others, "Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders," *Nature Neuroscience* 9, no. 1 (2006): 29.
16. Rizzolatti, Fogassi, and Gallese, 58.
17. Echolalia is the immediate and involuntary repetition of words or phrases just spoken by others.
18. Justin H. G. Williams, Andrew Whiten, Thomas Suddendorf, and David I. Perrett. "Imitation, mirror neurons and autism." *Neuroscience and Behavioral Reviews* 25, no. 1 (2001): 291.
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21. Ramachandran and Oberman, 65.
22. Rizzolatti, Fogassi, and Gallese, 59.
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25. Connie Kasari and others, "Language outcome in autism: randomized comparison of joint attention and play interventions," *Journal of Consulting and Clinical Psychology* 76, no. 1 (2008): 129.
26. Oberman and Ramachandran, 317.
27. Kern, 380.
28. Lerner, 15.
29. A teratogen is any agent, such as a virus, a chemical substance, or radiation, that causes malformation of an embryo or fetus. Some common examples are rubella, alcohol, thalidomide, and X-rays.
30. Martha R. Herbert, "Time to get a grip," *Autism Advocate* 5, no. 1 (2006): 20.
31. Herbert, 21.
32. Herbert, 22.
33. Jill A. Kreiling, Raymond E. Stephens, and Carol L. Reinisch, "A mixture of environmental contaminants increases camp-dependent protein kinase in *Spisula* embryos," *Environmental Toxicology and Pharmacology* 19, no.1 (2005): 9.
34. Parallel and climbing fibers are two types of neuronal axon branches within the brain's cerebellum. Parallel fibers arise from the numerous granule cells, which comprise nearly 50% of all brain neurons, whereas climbing fibers arise from a special region within the brain's medulla and extend through the pons to the cerebellum, where they provide essential excitatory input to motor neuron control. A Purkinje cell may connect to 200,000 or more parallel fibers but only a single climbing fiber.
35. Kern, 381.
36. The vermis is a narrow, wormlike structure between the hemispheres of the cerebellum.
37. Kern, 380.
38. Dysarthria is a difficulty in articulating words due to emotional stress or to neurological or muscular impairment.
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