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The Current State of ASD Research

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Abstract:

The rising rates of autism diagnosis among children is becoming a topic of growing interest among many arms of the research community. The most recent CDC data and statistics suggests that the prevalence of autism in the US is about 11.3 per 1000 children; this equates to about 1 in every 88 births (**CDC, 2012**). The trending increase in prevalence has increased the need for autism research greatly. So much is unknown about the nature of Autism Spectrum Disorders (ASD) that there is a seemingly endless range of subject matter for pertinent research. There is currently such a surge of autism related research being published that it is often difficult to discern what are the most significant discoveries. Investigators from many disciplines are seeking answers to questions including; possible treatments, the accuracy of current diagnostic criteria, pathology, epidemiology, economic impact, and risk factors for the disorder. This paper will review my independent study on the current state of research in ASD, media controversy surrounding autism, as well as explore future possibilities and advancements.

Pathophysiology of Autism Spectrum Disorder

Autism is not a simple diagnosis. There is no straightforward and conclusive medical test that can be done to identify the condition, however, the American Psychiatric Association's Diagnostic and Statistical Manual-IV, Text Revision (DSM-IV-TR) lays out a series of criteria for diagnosis. These criteria include abnormal social interactions, developmental delays, stereotyped behavior, and issues with language, among other signs **(First, 2002)**. The issue with this method of diagnosis is that it is subjective, and diagnostic decisions could differ

depending on the physician. This difficulty in diagnosis is compounded by the nature of autism being not a singular condition, but a spectrum of disorders ranging from mildly impaired social skills to the much more severe Childhood Disintegrative Disorder (CDD). There are currently 5 disorders classified under the umbrella of ASD. They are Autistic Disorder (AD), Rett's syndrome, Asperger syndrome, CDD, and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) **(DSM IV-TR)**.

As more information about these conditions are elucidated, even the current classification scheme is in flux. In May 2013**,** the new APA DSM-5 is scheduled for release. The proposed changes for the classification of the different ASD conditions as well as diagnostic criteria are quite substantial. For example, some experts are seeking to merge Asperger syndrome with Autistic disorder due to their similarity in long term prognosis and to reduce the possibility of misdiagnosis **(Mondre, 2011**). However, this idea is opposed by others since it may hinder the possibility of specialized treatment for each condition independently. The proposed change to the DSM states, "different research groups often uses different criteria, and quality of early language milestone information is variable" **(Klin, & Volkmar, 2005).** Rett's syndrome is also slated to be removed from the ASD umbrella since it's cause has been identified as purely genetic and it is distinct enough in its pathophysiology to be placed in a separate category. Another significant change proposed in the DSM-5 is the addition of categories of severity. These levels range from level 1, "requiring support"; to level 3, "requiring very substantial support" **(APA, 2011)**. These classifications of severity are designed to apply to all of the conditions included in the spectrum, and will make diagnosis better suited to match treatment. It is more efficient for treatment and therapy to be based on severity, and the APA expects this to streamline treatment options. However, the new, more

strict criteria proposed for the DSM-5 could potentially exclude many individuals currently classified as autistic by the DSM-IV-TR. The implications of this could become a substantial issue for families receiving money from governmental aid programs.

Many tools have been developed to help ensure proper diagnosis, but misdiagnosis remains an issue. An important step in diagnosis is distinguishing essential from complex autism. Complex autism is defined as autism compounded with physical malformations, suggesting a genetic link. This difference helps group patients not only for treatment, but the division into distinct subgroups helps "increase the power of research analysis" **(Science Letter, 2005)**. As more subgroups are identified and characterized, a clearer picture of autism will develop, as well as more specific research.

Comorbidities and Risk Factors

In order to discover the root cause of ASD, much research is directed towards studying the many comorbidities associated with ASD.These studies are useful because comorbidities with known mechanisms of pathogenesis may elucidate relationships with the mechanism of autism and other neurodevelopmental disorders, as well as identifying risk factors linked to the disease. Furthermore, it is important to distinguish symptoms of comorbidities from symptoms of ASD, since methods of treatment may differ. These associated conditions include premature birth (**Gardener, 2011**), congenital birth defects **(Hultman, 2002)**, issues with motor skills (**Matson, 2011**), a wide variety of neurological defects, seizures, chromosomal abnormalities such as fragile-x syndrome and trisomy 21 (**Morgan, 2003),** and obesity. Investigations are designed with statistical analysis to determine the relationship between these common comorbid factors and ASD. The correlation with childhood obesity is especially intriguing, since it is also a growing issue amongst children in America. A U.S. study found that 30.4% of

autistic children are overweight, compared to 23.6% of the total population **(Curtin, 2005)**. Obesity could be secondary to autism, that is, children with ASD may have a tendency to eat more or less healthy diets, or, it could be due to a physiological relationship, such as a hormone imbalance. Relationships with related conditions such as obesity are significant targets for future research. The use of advanced brain imaging techniques such as fMRI has identified a relationship between ASD and schizophrenia. Researchers found that lower volumes of grey matter in specific brain regions such as the striatum and amygdala were common between schizophrenic and ASD patients **(Cheung, 2010)** (See Figure 1). Noticing such structural relationships and deviations could lead to more accurate diagnosis based on anatomical or histological abnormalities. Further research may prove fruitful if the disease mechanisms for the two pathologically unique conditions are related. Although many papers have been published on the subject of ASD comorbidities, there has not been much progress in identifying any distinct cause. One study states, "A number of prenatal, perinatal, and physical/motor factors appear to be associated with autism. At this point, whether these disorders have common neurodevelopmental pathways, or are to some extent causative for autism, are unknown" **(Matson, 2011).**

Along with identifying comorbidities, discovering and characterizing risk factors is also an important step in finding the cause of neurodevelopmental disorders like ASD. Research has identified a wide range of risk factors with varying degrees of significance. Many of the risk factors have to do with conditions during pregnancy and embryonic development. A Swedish case-control study on the perinatal risk factors for infantile autism found statistically significant associations with smoking during pregnancy, delivery by cesarean, low-birth weight, a low five minute Apgar score, and presence of congenital malformations **(Hultman,**

2002). The study concluded that intrauterine conditions are important to the pathogenesis of autism, and should be investigated further. Other risk factors associated with the mother's health during pregnancy have also been identified. A recent california study has identified a correlation between obesity of the mother and higher rates of autism. Obese women were found to be about 67% more likely than normal-weight mothers to have autistic children **(Tanner, 2012)**. This provides evidence to support theories of pathogenesis involving prenatal conditions. However, it is important to note that no study to date has found one distinct risk factor strongly linked to autism. It is likely that, "exposure to a broad class of conditions reflecting general compromises to perinatal and neonatal health may increase the risk". **(Gardener, 2011).**

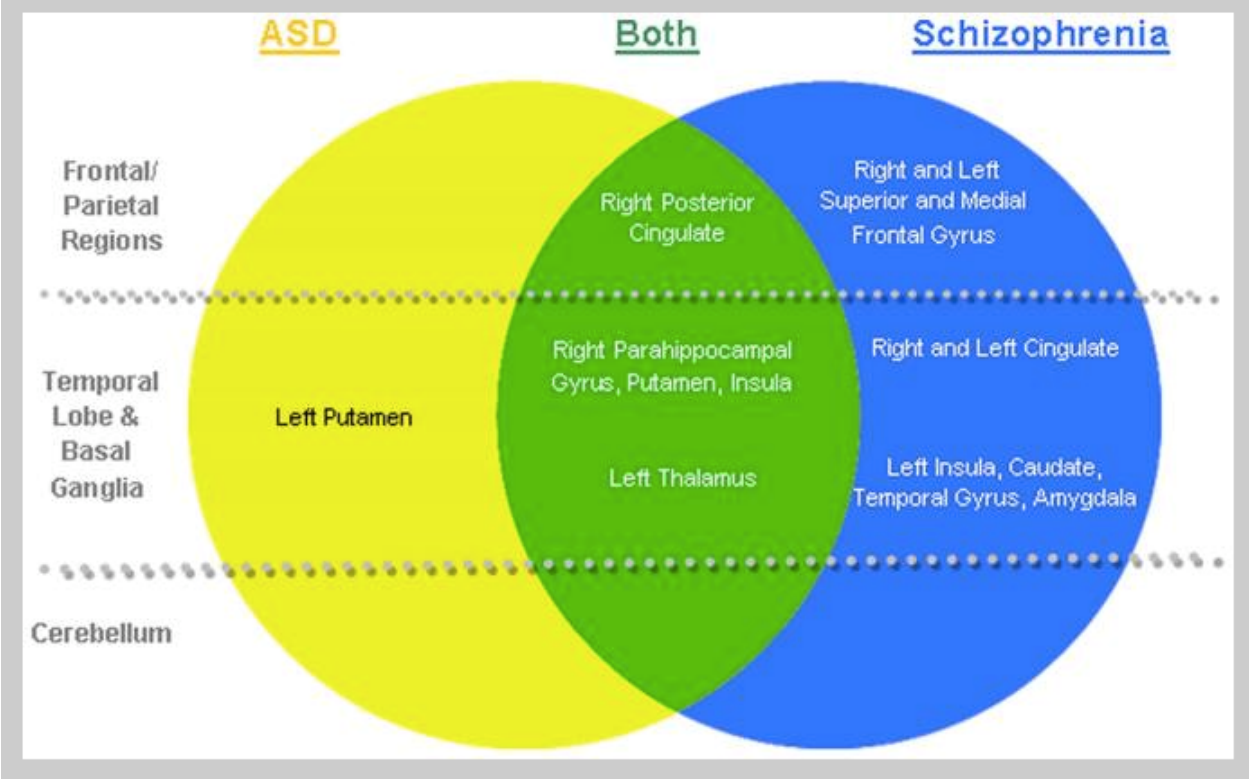

Figure 1:"Distinct and overlapping regions of grey matter deficits found in ASD and Schizophrenia". **(Cheung, 2010)**

Genetics and Neuroinformatics:

Gender association is a heavily researched topic in ASD, and for good reason. The prevalence of autism in males is significantly higher than that of females. CDC data shows that across all racial and socioeconomic groups, boys are between 4 and 5 times more likely than girls to have autism. This is a compelling statistic, driving the focus of much research. The reason for this link most likely lies in genetics, and research has suggested such. One such gene under investigation is CACNA1G, which is located in chromosome 17. A mutation in this calcium channel gene is much more common amongst males, and inheriting the mutation increases the risk of developing autism **(Genomics and Genetics, 2009).** Further investigation of CACNA1G and the identification of other related genes is important to finding the cause of autism, but much more data and samples are needed in order to accurately study the subject.

Genetic studies involving twins are very useful in revealing the heritability of traits. Studies have shown autism to have a high heritability; the concordance rate in monozygotic twins is between 60% and 90%, while it is less than 5%in dizygotic twins (**Ronald, 2006**). The study concluded,

> "When MZ (monozygotic) twins are more than twice as similar than DZ (dizygotic) twins, this suggests non-additive genetic influences such as dominance (interaction of two alleles at the same loci) and epistasis (interaction of alleles at different loci), or possible contrast effects" (**Ronald, 2006**).

Once potential gene loci are identified, more specific research on the function of those genes can take place. Until then, heritability studies such as these continue to narrow the search for a genetic component of autism.

In order to collect more genetic data on autism, an international collaborative project call the Autism Genome Project (AGP) was developed. The members of the AGP have published over 200 studies since 2003, and many breakthroughs have been made using the data collected. One such study conducted a genome-wide scan for alleles associated with autism risk, and successfully identified at least 5 new candidates **(Anney, 2010)**. Much of the AGP data is still under analysis, but it will surely produce more significant advancements and discoveries in the future.

The development of the autistic brain is a very interesting subject, with many novel research ideas stemming from it. A unique 2010 study assessed moral judgement in adults with high functioning autism (HFA) and Asperger Syndrome. They found that the subjects had difficulty assessing the severity of a transgression, which may be due to a defect in the cognitive appraisal system linked to moral reasoning **(Zalla, 2011)**. Investigations such as these allow us to see the difference between the autistic brain and a "normal" one. Some differences appear profound, while on some levels, they are indistinguishable.

The Wakefield Study and Other Media Controversy

In 1998, the medical journal *The Lancet* published Dr. Andrew Wakefield's study suggesting a link between the commonly administered measles, mumps, and rubella (MMR) vaccination, and autism (**WAKEFIELD, 1998**). Although his findings were eventually debunked and he was banned from practicing medicine in 2010, the consequences of his fraudulent research still echo today. Dr. Wakefield proposed that the trivalent MMR vaccination, usually given between 1 and 4 years of age (the same time frame that symptoms of ASD become apparent), overwhelmed the immune system leading to a condition he called "Autistic enterocolitis". While this was a valid hypothesis that could certainly warrant further

investigation, Wakefield's methods and motives were so flawed and perverted that no valid conclusions could be drawn from them. He even admitted to paying children at his son's birthday party for blood samples (**Dyer, 2007**). When Dr. Wakefield's research was first exposed to the general public, it ignited a fear of not only the MMR vaccine, but of vaccinations in general. By 2004, 10 of the 13 other authors on the controversial study had since removed their affiliations with the findings, and *The Lancet* published a retraction on the article, citing it as "unethical" **(Hope, 2004).** Unfortunately, by the time the study was retracted, the damage had already been done. Many parents in the U.K and U.S began opting not to vaccinate their children, with their decisions being supported by sensational media and ill-informed celebrities such as American actress and anti-vaccination activist Jenny McCarthy. Vaccination rates in the UK dropped to as low as 61%, far below the WHO recommended 90% **(Murch, 2003)**. As a result, herd immunity began to lose it's effect, and children began contracting illnesses such as Measles and Mumps at a much higher rate across the UK. These illnesses seem almost archaic to the developed world, mainly because vaccination has all but eradicated them, yet, due to misdirected fear, children were not well protected against them.

Since the public defamation of Dr. Wakefield, the medical research community has been more cautious on the subject of faulty research, but unfortunately, the media is not so scrupulous. In 2011, a research study reviewing the current body of autism research presented a theory for the pathogenesis of autism that proposed residual human DNA from the fetal cells used in production of the chickenpox vaccine led to inflammation of the brain and thus autism **(Ratajczak, 2011)**. This theory, while only supported by one citation of a personal communication, see **(Ratajczak, 2011)**, was only proposed as such in the study. However, when CBS news reported on the study **(Attkisson, 2011)** fear of vaccines surged again in the

US. Even if it was unintentional, widespread fear of safe vaccinations is not a desirable outcome of any news report.

These controversies have shown the significant impact that the media is capable of producing, practically overnight. The media has the ability to steer public opinion and thus has an extremely strong influence in the direction of research. The power of sensationalizing science led to the the now infamous Wakefield study. When parents opt to not vaccinate their children, they are often not making an informed decision for their child's beneficence, as the illnesses immunizations are proven to prevent are more damaging than the potential side effects in almost all cases. Furthermore, only a few specific vaccinations, such as the MMR and Chickenpox vaccine, have even had a *suspected* risk for autism, but parents often ignore jabs altogether hoping to protect their children. In order to help educate families of autistic children, the american non-profit ASAT (Association in Science for Autism Treatment) was formed. Since its establishment in 1998, ASAT has been providing education to families and parents in order to prevent the use of "fad" treatments without scientific support, and has advocated against sensationalized media claims. Fear is a powerful motivator, and the media has a responsibility to make clear distinctions between theory and fact in order to both fulfill their obligations as a news outlet and to prevent misguided panic.

Treatment:

Even though the cause of ASD is still unidentified, it is still essential to investigate possible treatments for the condition. Because the physiologic mechanisms of autism are unclear, this is a very difficult task. There are still, however, a number of investigational approaches to treatment available. Currently, the most effective and used treatment for autism is behavioral therapy **(CDC website, 2010).** Many methods exist, but most of them focus on

teaching specific skills using reinforcement. These methods aim to asses the difficulties children with autism have, including verbal behavior and communication, social interactions, motor skills, and integration with groups. These behavioral therapies are also highly modifiable to accommodate for the variable spectrum of severities and diversity of symptoms among autistic individuals. The National Institute for Mental Health (NIMH) recommends that behavioral therapy start as soon as diagnosis. For these non-drug treatment options to be maximally effective, they must be carefully tailored and constantly modified on an individual basis. This often means an entire team of health care specialists become involved, which can create stress for the parents and families of children with ASD. Parents of autistic children often struggle coordinating appointments, tests and assessments, as well as normal education, in a balance most beneficial for their child.

. It is estimated that the average lifetime cost of care for an individual with autism is $3.2 million (Rubenstein, 2006). This translates to an approximate expenditure of $35 billion per year for all of those with autism in the US. Given the economic stress that the current trending increase in the prevalence of autism is creating, the government has taken an increased interest in ASD research and epidemiology. A massive surveillance project, called ADDM (Autism and Developmental Disabilities Monitoring network) was initiated in 2000 by the CDC. The ADDM network has since expanded to 14 monitoring sites across the country, including a data coordinating center at Michigan State University. This is the network that compiles the data for the literature accepted national statistics on autism prevalence. Increased funding would allow more data collection sites and more accurate data. Aside from government programs, many non-profit agencies, medical systems, and interest groups contribute as well. An example of a more local organization striving to do so is the Michigan

Institute for Neurological Disorders, or MIND. Organizations like MIND help patients and parents of patients to create a network of therapists and physicians that are working together to individually cater to each patient.

Behavioral therapy, while it is the best available treatment, is not the only option available for ASD. Some of the symptoms associated with autism can include violence, aggression, excessive energy, and self mutilation. For this reason, ADHD drugs, antidepressants, antipsychotics, and seizure medications are used, often in combination, to alleviate these symptoms. It is important to note that none of these address the root cause of autism, and are only used in an off-label fashion to treat symptoms. The use of these drugs can complicate or benefit therapy due to the behavior modification they can cause, and it is ideal to keep their use to a minimum, since the neurophysiology of autism is not well understood. There are also dietary treatments such as gluten free diets in use by many parents, and supported by high profile social figures, to manage autism, while there is little scientific evidence to support these methods **(Alpert, 2007)**.

Autism is often thought of as a childhood disease, and not much emphasis is placed on treating adults with ASD. This assumption is not accurate since autism is a neurodevelopmental disorder that, while it may change in presentation, is usually a life-long condition. It is important to address the different needs of adults with ASD so that they can receive effective treatment. Public schools will provide education for persons with ASD until the age of 22 (**NIMH)**, but after that age, options are limited depending on the severity of the condition. Individuals with high functioning autism can often live on their own with minimal assistance, and government programs can provide financial assistance to those who choose to

do so. People with more severe disabilities can still thrive in environments such as "skill-development homes" and supervised group living.

Autism, in the current understanding, has no cure, and is a life-long affliction. Because of this, treatment can be very costly for parents of autistic children. On average, medical expenses for individuals with ASD are 4.1 to 6.2 times greater than in those without the condition **(CDC, 2012).** On top of higher general medical costs, behavioral therapy, which is essential especially in younger individuals, cost $40,000 to $60,000 a year **(CDC, 2012).** Because of the high economic pressure put on families, a streamlined and effective treatment program should be initiated as early as possible. In order to properly design a treatment regimen, accurate diagnosis is essential, especially because of the "spectrum" nature of the disorder.

Conclusions:

The search for the cause of ASD has only recently bloomed in the research community, and while many projects have been published and others are underway, actual productive advancements have been slow, but steady. With all of the potential for discovery, the field is becoming more and more attractive for researchers. ASD research has also become popular because of the relatively large amount of money available. Since 1997, when the National Institute of Health created the Autism Coordinating Committee (NIH/ACC), autism research has had growing support with increasing government funding. Since autism affects so many, it is one of the few diseases that has strong fundraising through interest groups to finance research. If this surge of support plays out, an exponential amount of research is on the way. Collaborations such as the Autism Genome Project as well as other projects in brain mapping and neuroinformatics show strong potential since there is some emerging evidence that the

cause of autism may be structurally related on the cellular level. Breakthroughs in other fields, such as genetics, neuroscience, and embryology all contribute to our understanding of the autistic syndromes. But where else should researchers look for answers?

Since many of the characteristics affected by autism are uniquely human, animal models are often not useful. The only source of data in from the affected individuals themselves, and the ones most in contact with them. More reliable diagnosis will allow for more effective surveillance and data collection in the upcoming years. With this data, more accurate estimates of the true prevalence of ASD can be defined, and more cost effective and practical treatment and assistance programs can be developed. If prevalence is really growing at the rate CDC data shows, an increasingly significant portion of the population has some type of ASD, and society must adapt to accommodate. It is important for members of the medical and research community to stay well informed to avoid unnecessarily repeating studies, and to help contribute to the general pool of knowledge. Cooperation amongst experts is essential. It may be years, or it may be decades until the etiology of autism is truly understood, but the constant progress and dedication from the research community is driving the quest for understanding.