SUPERIOR COURT OF THE STATE OF CALIFORNIA
COUNTY OF LOS ANGELES

NC, a minor

Plaintiff,

v.

Hain Celestial Group, Inc.; Beech-Nut Nutrition Company; Nurture, Inc.; Plum, PBC, d.b.a. Plum Organics; Gerber Products Company; Walmart, Inc.; Sprout Foods, Inc.; Ralphs Grocery Company; and DOES 1 through 100 inclusive

Defendants.

Case No. 21STCV22822
Judge: Hon. Amy D. Hogue

Department: 7

EXPERT REPORT OF DR. KEVIN SHAPIRO, MD, PH.D. IN SUPPORT OF GENERAL CAUSATION

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I. Background and Qualifications

I currently serve as Medical Director and Clinical Executive for Research and Therapeutic Technologies at Cortica Healthcare, an organization which provides comprehensive assessment and therapeutic services for children with autism and other neurodevelopmental differences. I am also a member of the Neurology staff at Children's Hospital Los Angeles and an affiliate member of the Neurology staff at Rady Children's Hospital in San Diego.

I received my undergraduate degree in Psychology and Biology, summa cum laude, in 2000 from Harvard College in Cambridge, Massachusetts. I subsequently completed a medical degree at Harvard Medical School and a Ph.D. in Psychology (Cognition, Brain, and Behavior) from Harvard University, both in 2008. After receiving my medical degree, I completed internship and residency in pediatric medicine at Boston Children's Hospital, followed by residency in neurology and child neurology at Massachusetts General Hospital. During my residency I held a position as a postdoctoral fellow in the Cognitive Neuropsychology Laboratory in the Department of Psychology at Harvard University, where I contributed to research in cognitive development and the neuroanatomical basis of language.

After residency I received fellowship training in vascular neurology at the University of California, San Francisco, and subsequently joined the faculty there as Assistant Professor of Neurology from 2013-2017. During that time, I was founding director of the Pediatric Language Clinic, a specialized clinic focusing on the evaluation of developmental language disorders and dyslexia. My research examined the effects of early injuries to the developing brain on emerging language and cognitive abilities in childhood.

Since 2016 I have collaborated in the design, execution, and interpretation of eTHINK (Evolving Treatment of Hemophilia's Impact on Neurodevelopment, Intelligence and Other Cognitive Functions). This nationwide cross-sectional study examines multiple aspects of neurodevelopment in children with hemophilia at various ages, including the contribution of hemophilia severity and management to the emergence of symptoms of autism and deficits in attention and executive function.

My current role at Cortica Healthcare is divided between clinical care and research. In my clinical capacity as Medical Director I am responsible for the evaluation, treatment, and long-term follow up of children with neurodevelopmental conditions including autism spectrum disorder (ASD), attention deficit-hyperactivity disorder (ADHD), sensory processing disorders, speech and language disorders, and disorders of motor function. This includes clinical assessment of the underlying causes of cognitive and behavioral symptoms. My research role is dedicated to evaluating the efficacy of novel treatment paradigms for symptoms of these disorders.

To date, I have been an author of 30 peer-reviewed publications, most of which focus on the neurobiology of language. I am also the author of the monograph "Evaluation of learning difficulty and cognitive delay" for the BMJ Best Practice website.

II. Charge

I have been asked to provide my opinions on the clinical understanding of ASD, its biological mechanisms, and etiology, with particular emphasis on my experience as clinician and researcher in the field of neurodevelopment and cognition. Additionally, I have been asked to provide my opinion on whether the neurological effects of exposure to certain heavy metals, specifically lead, mercury, and arsenic, correspond with the biological pathways implicated in the pathogenesis of autism. This report contains a summary of my analysis and conclusions. I reserve the right to amend this report and the analysis and/or conclusions herein in response to new information, the opinions of defendants' expert witnesses, or for any other reason. I also reserve the right to add new opinions regarding baby foods that contain lead, arsenic, and mercury and their ability to cause ASD or ADHD once this case proceeds to a stage where I will have access to information specific to the foods at issue, and whether exposure to heavy metals contained in said baby foods was a substantial contributing factor to an individual's diagnosis of ASD, ADHD, or another neurodevelopmental disorder. Finally, I also reserve the right to use demonstratives and other visual material – including animations – at any evidentiary hearing or trial in support of my opinions and testimony.

III. Summary of Opinions

- Autism is a neurodevelopmental disorder characterized by atypical social communication and interaction along with restricted and repetitive patterns of behavior.
- Symptoms of autism spectrum disorder can be identified in the early developmental period. In some cases, the emergence of ASD symptoms between 15-24 months of age occurs on a background of apparently typical neurodevelopment.
- Neurobiological studies of autism suggest that symptoms result from abnormal connectivity within brain networks. There is also strong evidence that increased oxidative stress and impaired mitochondrial metabolism contribute to nervous system dysfunction in individuals with autism.
- The prevalence of autism has been increasing in recent decades. Some, but not all, of this increase is attributable to changes in clinical definitions and surveillance. The increase in prevalence not explained by changes in classification is likely attributable to increases in risk factors that contribute to the development of autism symptoms.
- The pathogenesis of autism has a genetic component, but genetic factors cannot account fully for variability in the presentation and severity of symptoms. Epigenetic mechanisms, environmental risk factors, and gene-environment interactions also contribute to the emergence of symptoms.
- Known environmental risk factors for autism include exogenous agents that affect brain network function by altering cellular signaling and neurotransmitter release and/or by increasing oxidative stress and inflammation. These effects may occur following exposure *in utero* or within the first 2 years of life.
- Exposure to heavy metals in the early neurodevelopmental period has been shown in epidemiologic studies to correlate with reductions in intelligence, behavioral problems, and symptoms of attention deficit-hyperactivity disorder, all of which constitute cognitive processes that contribute to core symptoms of ASD.
- The mechanisms by which heavy metals affect neuronal function and development *in*

vivo and *in vitro* overlap to a significant degree with the biological pathways implicated in the pathogenesis of ASD.

IV. Prior Expert Testimony and Compensation

In the past four years I have testified as an expert witness in the following cases: Pelletier v. HHS; Huddleston v. Fiorentino, et al.; Mendoza Alcala v. Ghodisan, et al.; Marshall v. Ghaemmaghami; Camargo v. Ricci, et al.; Gerard v. Freeman, et al.; McEahern v. CVS Pharmacy; Stopper v. IHC Health; Bryce Kao Yeh v. Yuk Fan Chao, et al.; Martin v. Kaiser Permanente, et al.; Acosta v. UJ Peoria; Tompkins v. Hoag Hospital Newport Beach, et al.; Jordan v. Garg; Burman v. Talwar; Jones v. Antelope Valley; Fredette v. Dignity Healthcare.

I am being compensated for my time at a rate of $500/hr for record/literature review; $750/hr for deposition testimony; and $750/hr for trial testimony.

V. Methodology

I have approached this project using the methods, procedures, and techniques typically used by experts in my field. In reaching the opinions contained in this report I am relying upon my ten plus years of clinical experience in diagnosing and treating individuals with ASD and related neurodevelopmental differences, clinical and research experience in understanding the biological pathogenesis of ASD, and clinical and research experience in understanding how neurological injuries may produce the core symptoms of ASD. Moreover, to arrive at the conclusions in this report, I have reviewed the extensive literature – clinical, epidemiological, and toxicological – on ASD, its etiology, biological mechanisms, and risk factors, with a specific focus on whether the neurological effect of exposure to the heavy metals lead, mercury and arsenic is relevant to understanding the pathogenesis of ASD from a clinical perspective. I searched available online databases, such as PubMed and Google Scholar, for literature discussing the biological mechanisms of exposure to lead, mercury and arsenic, and the pathogenesis of ASD. The use of such databases is common in clinical and research practice. All opinions expressed in this report are held to a reasonable degree of scientific certainty.

VI. Autism: Clinical Definition and Impact

Autism or autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by core deficits in social communication and behavior. It is important to emphasize that the definition of autism is based on the presence of a cluster of psychological and developmental symptoms, and not on any specific underlying neurobiological or genetic pathology. Clinical symptoms of autism can manifest in a large number of biological conditions that affect the early development and connectivity of brain networks.

Current criteria for the clinical diagnosis of ASD are described in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and include the following:

- Persistent deficits in social communication and interaction (including deficits in social-emotional reciprocity; nonverbal communicative behaviors; and the ability to develop, maintain, and understand relationships).
- Restricted, repetitive patterns of behavior, interests, or activities (e.g., stereotyped or repetitive motor movements, use of objects, or speech; insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior; highly restricted, fixated interests that are abnormal in intensity or focus; and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment). [APA 2013].

The age at which children present with symptoms of ASD is variable. Clinical definitions require that symptoms be present in the early developmental period, to distinguish ASD from adult-onset psychiatric conditions such as schizophrenia, which also impact social communication and behavior. Some research suggests that symptoms predictive of clinically relevant deficits in ASD can emerge as early as 6-18 months of age [Szatmari et al 2016]. In this age group, the caregivers or primary care provider may notice delays in speech or language development, poor eye contact, or limited interest in socializing.

By contrast, about one-fourth to one-third of children ultimately diagnosed with ASD achieve early cognitive milestones, but experience a plateau or regression of language,

communication, and/or social skills between 15 and 24 months of age. In some cases, development of social communication skills is typical or even above average prior to plateau or regression [Ozonoff et al 2011].

To meet clinical criteria for the diagnosis, symptoms of ASD must cause clinically significant impairment in social, occupational, or other important areas of functioning (such as school). However, the DSM-5 allows that symptoms may not be recognized in situations where social demands are limited, or when an individual is able to employ compensatory (masking) strategies. Individuals with subtler symptoms of autism may not receive a diagnosis until they enter the school system (or later) and may come to attention initially because of co-existing symptoms of attention problems or anxiety [McConachie et al 2005].

Across the spectrum of symptom severity, the lifelong burden of ASD can be considerable both from a financial perspective and with respect to quality of life. Individuals with autism are at higher risk for psychiatric comorbidities, as we will discuss below, but also for non-behavioral adverse health outcomes including injuries [Jain et al 2014] and increased mortality [Schendel et al 2016, Hirvikoski et al 2016]. There is a substantial impact on quality of life, which is independent of age, IQ, and symptom severity [van Heijst & Geurts 2015].

It should be noted that the DSM-5 definition of ASD, which was adopted in 2013, differs in some respects from the definition in the prior version of the DSM (DSM-IV-TR) [APA 2000] and the International Classification of Diseases and Related Health Problems (ICD-10) [WHO 1992]. These criteria require evidence of abnormal or impaired development in social use of language, reciprocal social interaction, or functional or symbolic play prior to the age of 3 years, and do not include a criterion explicitly related to disordered sensory processing, which is increasingly recognized as a key neurologic feature of autism spectrum disorders. The current diagnostic criteria are therefore somewhat broader and include individuals who might previously have received the alternative diagnoses of Asperger syndrome or pervasive developmental disorder (milder symptoms), or childhood disintegrative disorder (severe symptoms of regression in skills). It is therefore expected that estimates of the cost and quality of life impact associated

with ASD is likely to increase over time [Leigh et al 2015].

VII. Autism: Epidemiology

The population prevalence of ASD in developed countries is estimated to be around 1.5% (Baxter 2015). In the United States, rates of ASD are monitored through screening and abstraction of existing health and education records, which suggest a prevalence estimate of 1.56-1.85% [Maenner et al 2016; Christensen et al 2019; Shaw et al 2020], and through survey data collected from parents and caregivers, which give slightly higher estimates of 2.24-2.5% [Kogan et al 2018; Zablotsky et al 2019].

All of these surveillance methods indicate that the prevalence of autism has been increasing over time, with an especially marked increase in the past three decades. To some extent the apparent increase is explained by changes in case definition or survey wording, increased awareness of the diagnosis, and diagnostic substitution—i.e., the assignment of an ASD diagnosis to children who might previously have been diagnosed with other developmental disorders, learning disorders, or intellectual disability [Williams et al 2006; Fombonne 2009; Wing & Potter 2002, Zablotsky et al 2015, Shattuck, 2006]. These effects may have been especially pronounced after 2013 as the broader understanding of autism spectrum disorders reflected in the DSM-5 began to supplant more restrictive definitions that had been the standard in most prior epidemiologic studies. For example, the change in the National Health Interview Survey wording in 2014 from "Autism/autism spectrum disorder" to "autism, Asperger's disorder, pervasive developmental disorder, or autism spectrum disorder" correlated with an increase in the estimated prevalence of ASD to 2.24% from an annualized prevalence of 1.25% based on the 2011-2013 data. At the same time, the prevalence of "other developmental delay" declined from 4.84% to 3.57% [Zablotsky et al 2015].

As might be expected based on the above, much of the increase in estimated prevalence of autism can be accounted for by cases at the milder end of the autism spectrum, with less marked changes in the prevalence of severe autism with accompanying intellectual disability [Lyall et al 2019]. On the other hand, changes in clinical definitions and diagnostic substitution

alone are not likely to explain the dramatic increase from an estimated prevalence of 0.045% in 1966 [Lotter 1966] to 0.6-0.7% in the early 2000s [Fombonne et al 2005; MMWR 2007] to 2.24-2.5% today.

A consistent observation across epidemiologic studies is that ASD occurs more frequently in males than in females, especially in individuals with less pronounced intellectual disability [Fombonne 2005, Fombonne & Tidmarsh 2003]. In part this may be due to under-diagnosis of ASD in females, but there may also be a biological contribution reflected in brain differences related to sex/gender [Lai et al 2017]. Prevalence of autism does not vary significantly across racial and socioeconomic groups [Yeargin-Alsopp et al 2003], though these factors may affect access to care and resources, including appropriate diagnostic evaluations and developmental therapies.

Up to 70-80% of children with ASD also meet criteria for other, non-ASD developmental and psychiatric diagnoses [Simonoff et al 2008, Levy et al 2010, Lai et al 2014, Matson & Cervantes 2014], including about 30% with intellectual disability [Christensen et al 2016], 30-50% with attention deficits and/or hyperactivity, and at least 30% with anxiety. As many as 30% of children with ASD have epilepsy [Lukmanji et al 2019, Hyman et al 2020], likely reflecting common underlying structural differences in brain development, as I will discuss next.

VIII. Autism: Neurobiology

The clinical observation that autism spectrum disorders often co-occur with other neurological, cognitive, and behavioral differences is supported by research findings of global differences in brain architecture and metabolism in individuals with an autism diagnosis. To put this a different way, autism is a cluster of neurocognitive and behavioral symptoms that can emerge because of any of several disturbances to the structure and function of the developing brain. In contrast to focal brain lesions like stroke and cortical malformations, autism results from a more diffuse alteration in the formation of brain networks. It is not surprising, therefore, that there is significant overlap between autism and other "network dysfunctions" including sensory processing disorders, ADHD, and mood disorders [Henry & Cohen 2019, Diwadkar &

Eikhoff 2021].

A consistent feature of neuroimaging, electrophysiologic, and histologic studies of autism is the finding of atypical neural connectivity [Lai et al 2014, Boddaert et al 2009]. There is often an early, abnormal increase in brain surface area and volume between 6 and 24 months of age [Hazlett et al 2017] that appears to correlate with an increased number of neurons [Courchesne et al 2011] and a failure to refine connections within neural circuits that underly various aspects of cognition [Piven et al 2017].

The process of refinement or "synaptic pruning" during typical development depends on the experience of associations between neural activation and sensory inputs; therefore, if either the activation of neurons or the ability to process sensory inputs is disrupted, the result will be an aberration in network formation. At a cellular level, this type of plasticity depends on the activity of the N-methyl-D-aspartate (NMDA) receptor and downstream molecular pathways that are known to be disrupted in autism [Piochon et al 2016, Hansel 2018].

There is also evidence for abnormal brain metabolism in individuals with autism. Several studies have suggested that the neurobiology of autism is associated with increased levels of reactive oxygen species, increased lipid peroxidation, and other markers of oxidative stress [Bjørklund et al 2020], a process that leads to cellular injury through damage to proteins and DNA. Some individuals with ASD have neurobiological signs of mitochondrial dysfunction [Goh et al 2014], reflecting an alteration in energy metabolism in brain tissue.

IX. Autism: Pathogenesis

The mechanisms leading to communication and behavioral differences in individuals with autism are not fully understood. I have just reviewed how early brain development may differ in some individuals in ways that lead to the emergence of symptoms of autism. A key question, of course, is what drives those differences in brain development. The risk of autism may be rooted in genetics, but the expression of these genetic traits is modulated to a sometimes-significant degree by environmental risk factors and exposures.

Genetic Factors. A genetic contribution to ASD etiology is supported by studies estimating that the heritability of ASD is between 50-83% [Sandlin et al 2014, Bai et al 2019], and the risk of recurrence in siblings may be 3-8 times as high as the population prevalence [Sandin et al 2014, Gronborg et al 2013, Ozonoff et al 2011]. Specific rare genetic variants that markedly increase the risk of ASD include alterations in genes involved in forming connections between brain cells (e.g. *SHANK3, CNTN4*), controlling cell growth and size (*TSC1, TSC2*), and regulating the expression of other genes (*CHD2*) [Bourgeron 2015, Pinto et al 2014]. In many cases, however, the heritable component of ASD is likely to be polygenic in nature—that is to say, it is influenced by the cumulative effect of multiple common genetic variants. At least a few of these variants also probably contribute to the pathogenesis of other neurodevelopmental and psychiatric disorders, such as ADHD, bipolar disorder, and schizophrenia [Lee et al 2013], which occur more frequently in relatives of individuals with a diagnosis of ASD [Xie et al 2019, Sullivan et al 2012].

Parental and Prenatal Risk Factors. At the same time, the heritability of ASD is not 100%. To put this differently, even monozygotic twins, who share exactly the same genetic material, do not always share a diagnosis of ASD, which suggests that environmental or experiential factors must play a role in the development of symptoms. Some of these risk factors may cause direct structural injury to the developing brain, such as congenital infections. Others are thought to exert their influence through epigenetic modification, in which genes are switched "on" or "off" early in life while the nervous system is still immature, and thus affect the structure of the developing brain without any changes in the primary genetic code. Increased parental age [Lee & McGrath 2015] and maternal stress during pregnancy [Van den Bergh et al 2020, Babenko et al 2015, Beversdorf et al 2018] have been demonstrated to increase rates of autism in children, mediated in part by epigenetic mechanisms.

Stress may also lead to upregulation of the maternal inflammatory and immune response, which in turn has been linked to increased ASD risk through the effects of inflammatory mediators on the developing brain[Brown et al 2014, Zerbo et al 2016, Goines et al 2011, Han et

al 2021]. Both genetic and epigenetic factors likely increase sensitivity to detrimental effects of inflammation, reinforcing the idea that a confluence of environmental exposures can produce or exacerbate symptoms of ASD in susceptible individuals [Oldenburg et al 2020].

Exposure of the developing brain to exogenous chemicals also increases the odds of an ASD diagnosis. Historically, maternal use of medications with teratogenic properties has been known to lead to increased diagnoses of ASD in children [Newschaffer et al 2007]. More recently, large epidemiologic studies have identified increased autism risk associated with maternal exposure to antiepileptic medications [Bromley et al 2013, Christensen et al 2013, Veiby et al 2013] and beta-2 adrenergic receptor agonists [Croen et al 2011, Gidaya et al 2016], which can cross the placenta and can also be transferred through breast milk. Both classes of medication affect brain connectivity by altering neuronal excitability in response to endogenous neurotransmitters.

Certain environmental toxicants can also cross the placenta and the blood-brain barrier and alter brain development. At least eleven studies have shown that prenatal exposure to airborne pollutants is a risk factor for ASD. These include gases such as nitrogen dioxide (NO_2) and ozone (O_3), particulate matter [Volk et al 2013, Kalkbrenner et al 2010], solvents, and metals such as, lead, arsenic and mercury (which will be discussed below at greater length) [Windham et al 2006]. These have been hypothesized to disrupt brain development both directly (through deposition of particles in the developing nervous system) and indirectly (by activating the immune system or the oxidative stress response) [Kalkbrenner et al 2016], mechanisms which are supported by other studies showing associations between air pollutants and poor birth outcomes, immunologic changes, and decreased cognitive abilities [Currie et al 2009, Hansen et al 2008].

A second mechanism by which chemical exposure can lead to neurodevelopmental abnormalities is through disrupting the activity of hormones important for neurodevelopment [Schug et al 2015]. For example, maternal exposure to endocrine disrupting chemicals (EDCs), including organophosphate and organochloride pesticides, has been associated in several studies

with autistic behavior in children [Eskenazi et al 2007, Braun et al 2014, Roberts et al 2007, Shelton et al 2014].

Postnatal Risk Factors. Most of the environmental risk factors for autism that have been discussed up to this point involve prenatal exposures to either endogenous or exogenous chemicals that influence brain development. However, the development of the brain is not complete at the time of delivery, and many processes that are crucial for the development of language and social cognition continue to unfold during the first 2 years of postnatal life. Postnatal impacts on brain development may in part explain the observation of developmental regression between 15-24 months of age in up to one-third of individuals with ASD.

Among postnatal factors important in the pathogenesis of autism, studies have demonstrated that extreme premature birth and low birth weight are significant contributors to the risk of autistic behavior in later childhood [Limperopoulos 2009, Agarwal et al 2018]. This may be mediated in part by prematurity-related structural brain injury, such as cerebellar and germinal matrix hemorrhage, and in part by atypical postnatal development of brain networks involved in sensory processing [Rahkonen et al 2015].

The emergence of behavioral symptoms in children after 2 years of age may also be affected by the availability of certain nutrients crucial for early brain development. For example, some studies have demonstrated that supplementation with ω-3 and ω-6 fatty acids reduces symptoms of atypical sensory processing and autistic behavior in at least some toddlers with a history of premature birth [Boone et al 2017, Keim et al 2018, Boone et al 2019]. Abnormalities of the folate metabolic pathway, including autoantibodies to folate receptors, have been identified in some children with ASD, and symptoms in these children can be substantially improved by treatment with folinic acid [Frye et al 2020].

Finally, some environmental pollutants linked to increased risk of ASD – including heavy metals such as lead, mercury, and arsenic – may have either prenatal or postnatal effects on brain development. The Childhood Autism Risks from Genetics and the Environment (CHARGE) Study, which established a link between air pollution exposure and autism, modelled pollution

exposure by examining residential histories from conception through the child's most recent place of residence [Hertz-Picciotto et al 2006, Volk et al 2013]. Interestingly, one of the findings of the CHARGE Study was that exposure air pollution increases susceptibility to autism particularly in children with a specific variant in the MET receptor tyrosine kinase (*MET*) gene, pointing to an interaction of genetic and environmental risk factors in the pathogenesis of neurodevelopmental disorders [Volk et al 2014].

X. Heavy Metals in Neurodevelopment

It is well-established that early childhood exposure to certain heavy metals, particularly lead and mercury, are harmful to the developing nervous system, leading to neurocognitive deficits and behavioral problems [Mendola et al 2002]. More recently it has been recognized that other metals, including arsenic and manganese, are also toxic to the developing brain [Rodríguez-Barranco et al. 2013]. Heavy metals cross the blood-brain barrier, accumulate in the central nervous system, and can interfere directly with key cellular proteins.

Studies demonstrating higher levels of certain heavy metals in children with autism spectrum disorders are helpful in establishing an association between heavy metal exposure and ASD. But to establish a meaningful understanding of whether elevated metal levels are the *cause* of ASD symptoms or a *result* of behavioral disturbances in ASD (e.g., ingestion of non-food objects that may be contaminated with metals) it is important to consider these studies in conjunction with epidemiologic studies of prenatal and early postnatal exposure to heavy metals (i.e., exposure prior to ASD diagnosis), as well as basic scientific studies examining the biological mechanisms by which heavy metals interfere with the function and development of the nervous system.

As I will discuss further below, it is clear that the biochemical mechanisms by which heavy metals affect development overlap with the neurobiological pathways implicated in autism spectrum disorders, particularly those important for neuronal signaling and development [Pinto et al 2014]. Many heavy metals increase reactive oxygen species and oxidative stress, or disrupt mitochondrial energy metabolism, processes implicated in the neurological disturbances

associated with ASD.

Lead. Extremely low levels of chronic lead exposure have been associated with detrimental effects on brain development, leading to the dictum that there is no safe threshold for childhood lead exposure [Lidsky & Schneider 2003]. Outcomes associated with low levels of lead exposure include reduced intelligence [Lamphear et al 2005, Surkan et al 2007], impaired executive functioning [Canfield et al 2004], behavioral problems [Braun et al 2018], and ADHD [Goodlad et al 2013].

Lead readily crosses the blood-brain barrier, and within the central nervous system it can disrupt signal transduction cascades through several cellular mechanisms. Of particular relevance in the context of autism are the findings that lead impairs signal-dependent release of neurotransmitters [Cory-Slechta et al. 1995; Goodlad, et al. 2013], inhibits function of the NMDA receptor, and increases background signaling through protein kinase C [Johnston & Goldstein, 1998], which together have the effect of reducing the strength of connections between neurons at synapses. Enhancing "synaptic noise" during critical periods of brain development may permanently disrupt the formation of networks important for sensory processing and other cognitive functions by impairing the ability to prune and refine synaptic connections.

Lead can also uncouple mitochondrial oxidative phosphorylation in the central nervous system, leading to a profound impairment of energy metabolism [He et al 2000, Holtzman & Hsu 1976]; Kim, et al. (2016), and can affect the expression of DNA binding proteins. [Schneider et al. 2012]. Such neurotoxic effects have been recognized as plausible mechanisms in the pathogenesis of ASD. [Kim et al. 2016, Smith, et al. 2018].

Finally, it has been well demonstrated in animal models that lead promotes neuroinflammation, including increased release of pro-inflammatory cytokines [Chen et al. 2019]. As I discussed above, neuroinflammation and attendant immune dysregulation in early life are recognized contributors to neurodevelopmental impairments [Oldenburg et al 2020].

Mercury. Methylmercury is an organic mercury compound that is thought to be primarily responsible for detrimental effects on the central nervous system. Early exposure to

methylmercury has been associated with cognitive deficits both in epidemiologic studies [Grandjean et al 1997, Grandjean et al 1999] and in experimental animal models [Montgomery et al 2008].

In part the effects of methylmercury on the nervous system are likely due to an increase in reactive oxygen species, which upregulate inflammatory signaling and lead to cell death. We have already reviewed evidence that oxidative stress and inflammation are key adverse biochemical contributors to the etiology of ASD. Specifically, mercury induces oxidative stress by disrupting sulfur chemistry in the brain [Garrecht & Austin 2011]. In the developing brain, methylmercury inhibits cell division and migration by blocking the organization of microtubules, interfering with receptor-mediated intracellular signaling, and promoting the blockade of neuronal calcium channels, thereby disrupting the neuronal communication needed for synaptic pruning and the formation of brain networks [Azevedo et al 2012]. Pro-inflammatory and neurotoxic effects of mercury have been observed during a wide time window in early neurodevelopment, coincident with the period of susceptibility to ASD [Pletz, et al. 2016; Garrecht & Austin 2011].

Arsenic. Exposure to inorganic arsenic during development is linked to a reduction in intelligence and cognitive function, even at levels below current safety recommendations [Tolins et al 2014, Farzan et al 2013]. Children exposed to low levels of inorganic arsenic have decreased verbal abilities, motor skills, and long-term memory [Rosado et al 2007, Wasserman et al 2014, Parvez et al 2011].

As is the case for lead and mercury, the molecular mechanism of arsenic toxicity is probably mediated both by a combination of direct effects on brain cells and neurotransmitters, and downstream effects of increased neuroinflammation. Arsenic exposure enhances production of reactive oxygen species and oxidative stress [Garza-Lombó et al 2019], leading to increased inflammation and cell death. Toxicity of inorganic arsenic has also been associated with changes in NMDA receptor expression and dysfunctional glutamate metabolism [Huo et al 2015, Ramos-Chávez et al 2015, Nelson-Mora et al 2018], as well as abnormal formation of neurons in the

frontal cortex [Zhou et al. 2018].

Dated: November 12, 2021

Kevin Shapiro, MD, Ph.D.

Dr. Shapiro Reference List

#	Author(s)	Year	Title of Article
1.	Green, et al.	2011	Reference Manual on Epidemiology (3rd Ed)
2.	Modabbernia, et al.	2017	Environmental risk factors for autism- an evidence-based review of systematic and meta-analysis
3.	Rodriguez-Barranco, et al.	2013	Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioral disorders in children: a systematic review and meta - analysis
4.	Smith, et al.	2018	Integrative bioinformatics identifies postnatal lead Pb exposure disrupts
5.	Windham	2006	Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco Bay Area
6.	American Psychiatric Publishing, Inc.	2013	Association AP. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington
7.	American Psychiatric Publishing, Inc.	2000	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR). Washington DC
8.	Lanphear, et al.	2005	Low-level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis
9.	Garrecht & Austin	2011	The plausibility of a role for mercury in the etiology of autism: a cellular perspective
10.	Pletz, et al.	2016	Dose-response analysis indicating time-dependent neurotoxicity caused by organic and inorganic mercury-Implications for toxic effects in the developing brain
11.	Zhou, et al.	2018	Postnatal low-concentration arsenic exposure induces autism-like behavior and affects frontal cortex neurogenesis in rats
12.	Tolins, et al.	2014	The Developmental Neurotoxicity of Arsenic: Cognitive and Behavioral Consequences of Early Life Exposure
13.	Rosado, et al.	2007	Arsenic Exposure and Cognitive Performance in Mexican Schoolchildren
14.	Cory-Slechta	1995	Relationships Between Lead-Induced Learning Impairments and Changes in Dopaminergic, Cholinergic, and Glutamatergic Neurotransmitter System Functions
15.	Montgomery, et al.	2008	Chronic, low-dose prenatal exposure to methylmercury impairs and mnemonic function in adult C57/B6 mice

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#	Author(s)	Year	Title of Article
16.	Grandjean, et al.	1997	Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury
17.	Lidsky & Schneider	2003	Lead neurotoxicity: Basic mechanisms and clinical correlates
18.	Chen, et al.	2019	Maternal exposure to low dose BDE209 and Pb mixture induced neurobehavioral anomalies in C57BL/6 male offspring
19.	Braun, et al.	2018	Effects of Residential Lead-Hazard Interventions on Childhood Blood Lead Concentrations and Neurobehavioral Outcomes: A Randomized Clinical Trial
20.	Agarwal, et al.	2018	Factors affecting neurodevelopmental outcome at 2 years in very preterm infants below 1250 grams: a prospective study
21.	Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators	2007	Prevalence of autism spectrum disorders --autism and developmental disabilities monitoring network, 14 sites, United States, 2002
22.	Azevedo, et al.	2012	Toxic effects of mercury on the cardiovascular and central nervous systems
23.	Babenko, et al.	2015	Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health
24.	Bai, et al.	2019	Association of Genetic and Environmental Factors with Autism in a 5-Country Cohort
25.	Beversdorf, et al.	2018	Prenatal Stress, Maternal Immune Dysregulation, and Their Association with Autism Spectrum Disorder
26.	Boone, et al.	2017	Omega-3 and -6 fatty acid supplementation and sensory processing in toddlers with ASD symptomology born preterm: A randomized controlled trial
27.	Boone, et al.	2019	Docosahexaenoic Acid and Arachidonic Acid Supplementation and Sleep in Toddlers Born Preterm: Secondary Analysis of a Randomized Clinical Trial
28.	Bjorklund, et al	2020	Oxidative Stress in Autism Spectrum Disorder
29.	Boddaert, et al.	2009	MRI findings in 77 children with non-syndromic autistic disorder

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#	Author(s)	Year	Title of Article
30.	Bourgeron	2015	From the genetic architecture to synaptic plasticity in autism spectrum disorder
31.	Braun, et al.	2014	Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and -5 - year -old children: the HOME study
32.	Bromley, et al.	2013	The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs
33.	Brown, et al.	2013	Elevated maternal C-reactive protein and autism in a national birth cohort
34.	Canfield, et al.	2004	Impaired neuropsychological functioning in lead-exposed children
35.	Christensen, et al.	2013	Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism
36.	Christensen DL, et al.	2019	Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 4 Years - Early Autism and Developmental Disabilities Monitoring Network, Seven Sites, United States, 2010, 2012, and 2014
37.	Courchesne, et al.	2011	Neuron number and size in prefrontal cortex of children with autism
38.	Croen, et al.	2011	Prenatal exposure B2-adrenergic receptor agonists and risk of autism spectrum disorders
39.	Currie, et al.	2009	Air pollution and infant health: Lessons from New Jersey
40.	Diwadkar & Eichkoff	2021	Brain Network Dysfunction in Neuropsychiatric Illness: Methods, Applications, and Implications
41.	Eskenazi, et al.	2007	Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children
42.	Farzan, et al.	2013	In utero and early life arsenic exposure in relation to long-term health and disease
43.	Fombonne	2009	Epidemiology of pervasive developmental disorders
44.	Fombonne & Tidmarsh	2003	Epidemiologic data on Asperger disorder
45.	Frye, et al.	2020	Treatment of Folate Metabolism Abnormalities in Autism Spectrum Disorder

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#	Author(s)	Year	Title of Article
46.	Garza-Lombo, et al.	2019	Arsenic-induced neurotoxicity: a mechanistic appraisal
47.	Gidaya, et al.	2016	In utero Exposure to B-2-Adrenergic Receptor Agonist Drugs and Risk for Autism Spectrum Disorders
48.	Goh, et al.	2014	Mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder: evidence from brain imaging
49.	Goines, et al.	2011	Increased midgestational IFN-y, IL-4 and IL-5 in women bearing a child with autism: A case-control study
50.	Goodland, et al.	2013	Lead and Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms: a meta-analysis
51.	Grandjean, et al.	1999	Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years
52.	Gronborg, et al.	2013	Recurrence of autism spectrum disorder in full-and half - siblings and trends over a time: a population-based cohort study
53.	Han, et al.	2021	Maternal immune activation and neuroinflammation in human neurodevelopmental disorders
54.	Hansel	2018	Deregulation of synaptic plasticity in autism
55.	Hansen, et al.	2008	The effect of ambient air pollution during early pregnancy on fetal ultrasonic measurements during mid-pregnancy
56.	Hazlett, et al.	2017	Early brain development in infants at high risk of autism spectrum disorder
57.	He, et al.	2000	Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitochondrial permeability transition pore
58.	Henry & Cohen	2019	Chapter 5 - Dysfunctional brain network organization in neurodevelopmental disorders
59.	Hertz-Picciotto, et al.	2006	The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism
60.	Hirning, et al.	1988	Dominant role of N-type Ca2+ channels in evoked release of norepinephrine from sympathetic neurons
61.	Holtzman & Hsu	1976	Early effects of inorganic lead on immature rat brain mitochondriam respiration

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#	Author(s)	Year	Title of Article
62.	Hyman, et al.	2020	Identification, Evaluation, and Management of Children With Autism Spectrum Disorder
63.	Johnston & Goldstein	1998	Selective vulnerability of the developing brain to lead
64.	Kalkbrenner, et al.	2010	Perinatal exposure to hazardous air pollutants and autism spectrum disorder at age 8
65.	Kalkbrenner, et al.	2014	Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence
66.	Keim, et al.	2018	W-3 and W-6 Fatty Acid Supplementation May Reduce Autism Symptoms Based on Parent Report in Preterm Toddlers
67.	Kogan, et al.	2018	The Prevalence of Parent-Reported Autism Spectrum Disorder Among US Children
68.	Kortenkamp	2011	Are cadmium and other heavy metal compounds acting as endocrine disrupters?
69.	Lai, et al.	2014	Autism
70.	Lai, et al.	2016	Imaging sex/gender and autism in the brain: Etiological implications
71.	WHO	1992	The ICD-10 classification of mental and behavioral disorders: Clinical descriptions and diagnostic guidelines
72.	Lam, et al.	2016	A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder
73.	Cross-Disorder Group of the Psychiatric Genomics Consortium, et al.	2013	Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs
74.	Lee & McGrath	2015	Advancing parental age and autism: multifactorial pathways
75.	Limperopoulos	2009	Autism spectrum disorders in survivors of extreme prematurity
76.	Lotter	1966	Epidemiology of Autistic Conditions in Young Children
77.	Lukmanji, et al.	2019	The co-occurrence of epilepsy and autism: A systematic review
78.	Lyall, et al.	2017	The Changing Epidemiology of Autism Spectrum Disorders

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#	Author(s)	Year	Title of Article
79.	Maenner, et al.	2020	Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016
80.	McConachie, et al.	2005	Can a diagnosis of Asperger Syndrome be Made in Very Young Children with Suspected Autism Spectrum Disorder?
81.	Mendola, et al.	2002	Environmental factors associated with a spectrum of neurodevelopmental deficits
82.	Nation, et al.	1989	Effects of combined lead and cadmium exposure: Changes in schedule - controlled responding and in dopamine, serotonin, and their metabolites
83.	Nelson, et al.	2017	Gestational exposure to inorganic arsenic (iAs3+) alters glutamate disposition in the mouse hippocampus and ionotropic glutamate receptor expression leading to memory impairment
84.	Newschaffer, et al.	2007	The Epidemiology of Autism Spectrum Disorders
85.	Ozonoff, et al.	2011	Onset pattern in autism: correspondence between home video and parent report
86.	Pervez, et al.	2011	Arsenic exposure and motor function among children in Bangladesh
87.	Pinto, et al.	2014	Convergence of genes and cellular pathways dysregulated in autism spectrum disorder
88.	Piochon, et al.	2016	LTD - like molecular pathways in developmental synaptic prunning
89.	Piven, et al.	2017	Toward a conceptual framework for early brain and behavior development in Autism
90.	Rahkonen, et al.	2015	Atypical sensory processing is common in extremely low gestational age children
91.	Ramos-Chavez, et al.	2015	Neurological effects of inorganic arsenic exposure: altered cysteine/glutamate transport, NMDA expression and spatial memory impairment
92.	Roberts, et al.	2007	Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in California Central Valley
93.	Sandin, et al.	2014	The familial risk of Autism

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#	Author(s)	Year	Title of Article
94.	Schug, et al.	2015	Elucidating the links between endocrine disruptors and neurodevelopment
95.	Shattuck	2006	The contribution of diagnostic substitution to the growing administrative prevalence of autism in US special education
96.	Shaw, et al.	2020	Early Identification of Autism Spectrum Disorder Among Children Aged 4 Years - Early Autism and Developmental Disabilities Monitoring Network, Six Sites, United States, 2016
97.	Shelton, et al.	2014	Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study
98.	Simonoff, et al.	2008	Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population - derived sample
99.	Sullivan, et al.	2012	Family history of schizophrenia and bipolar disorder as risk factors for autism
100.	Surkan, et al.	2007	Neuropsychological function in children with blood lead levels <10 microg/dL
101.	Szatmari, et al.	2016	Prospective Longitudinal Studies of Infant Siblings of Children With Autism: Lessons Learned and Future Directions
102.	Van den Bergh, et al.	2020	Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy
103.	Veiby, et al.	20013	Early child development and exposure to antiepileptic drugs prenatally and through breastfeeding: a prospective cohort on children of women with epilepsy
104.	Veiby, et al.	2013	Exposure to antiepileptic drugs in utero and child development: A prospective population - based study
105.	Volk, et al.	2013	Traffic - related air pollution, particulate matter, and autism
106.	Volk, et al.	2014	Autism Spectrum Disorder: Interaction of Air Pollution with the MET receptor tyrosine kinase gene
107.	Wasserman, et al.	2014	A cross - sectional study of well water arsenic and child IQ in Maine school children
108.	Williams, et al.	20006	Systematic review of prevalence studies of autism disorders

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#	Author(s)	Year	Title of Article
109.	Wing & Potter	2002	The epidemiology of Autistic Spectrum Disorders: is the prevalence rising?
110.	Xie, et al.	2019	Family History of Mental and Neurological Disorders and Risk of Autism
111.	Yeargin-Allsopp, et al.	2003	Prevalence of Autism in a US Metropolitan Area
112.	Zablotzky, et al.	2015	Estimated Prevalence of Autism and Other Developmental Disabilities Following Questionnaire Changes in the 2014 national Health Interview Survey
113.	Zablotzky, et al.	2019	Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009 - 2017
114.	Zerbo, et al.	2016	Maternal mid - pregnancy C - reactive protein and risk of autism spectrum disorders: the early markers for autism study
115.	Levy, et al.	2010	Autism spectrum disorder and co - occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States
116.	Matson & Cervantes	2014	Commonly studied comorbid psychopathologies among persons with autism spectrum disorder
117.	Lucchini, et al.	2014	Neurofunctional dopaminergic impairment in elderly after lifetime exposure to manganese
118.	Kim, et al.	2016	Low - level lead exposure and autistic behaviors in school - age children
119.	Hirvikoski, et al.	2015	Premature mortality in autism spectrum disorder
120.	Jain, et al.	2014	Injuries among children with autism spectrum disorder
121.	Leigh & Du	2015	Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States
122.	Oldenburg, et al.	2020	Genetic and epigenetic factors and early life inflammation as predictors of neurodevelopmental outcomes
123.	Schendel, et al.	2016	Association of Psychiatric and Neurologic Comorbidity With Mortality Among Persons With Autism Spectrum Disorder in a Danish Population
124.	van Heijst & Geurts	2014	Quality of life in autism across the lifespan: a meta - analysis

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#	Author(s)	Year	Title of Article
125.	Zhang & Cao	2021	Epigenetic Remodeling in Innate Immunity and Inflammation
126.	CDC	2017	Mercury Factsheet
127.	CDC	2017	Arsenic Fact Sheet
128.	CDC	2021	Health Effects of Lead Exposure
129.	WHO (World Health Organization)	2018	Arsenic
130.	WHO (World Health Organization)	2021	Lead Poisoning
131.	WHO (World Health Organization)	2017	Mercury and health
132.	EPA	2021	Arsenic Compounds
133.	EPA	2021	Learn about Lead
134.	EPA	2021	Health Effects of Exposure to Mercury

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CURRICULUM VITAE

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Home Address:	4212 Grimes Place Encino, California 91316 Voice: 617-669-8527 Email: kevin.shapiro@gmail.com

EDUCATION

1996-2000	Harvard University	AB (summa cum laude), Psychology and Biology
2001-2008	Harvard University	PhD, Psychology (Cognition, Brain and Behavior)
2003-2008	Harvard Medical School	MD, Medicine
2008-2011	Harvard University	Postdoctoral Fellow, Cognitive Neuropsychology
2008-2010	Boston Children's Hospital	Resident, Pediatrics
2010-2012	Brigham and Women's Hospital and Massachusetts General Hospital	Resident, Child Neurology
2012-2013	Massachusetts General Hospital	Chief Resident, Child Neurology
2013-2014	University of California, San Francisco	Clinical Fellow, Vascular Neurology

PRINCIPAL POSITIONS HELD

9/2017-present	Cortica – Advanced Therapies for Autism and Neurodevelopment	Director of Pediatric Neurology; Director of Research and Therapeutic Technologies
7/2014-9/2017	University of California, San Francisco and UCSF Benioff Children's Hospital	Assistant Professor of Neurology; Director, Pediatric Language Clinic
10/2020-present	Children's Hospital Los Angeles	Medical Staff, Neurology

LICENSES AND CERTIFICATION

2011	Massachusetts Physician License
2013	California Physician and Surgeon License
2013	Diplomate, American Board of Psychiatry and Neurology (Neurology with Special Qualifications in Child Neurology)
2014	Diplomate, American Board of Psychiatry and Neurology (Vascular Neurology)

HONORS AND AWARDS

1997	John Harvard Scholarship	Harvard College
1997	Detur Prize	Harvard College
2000	Psychology Faculty Prize	Harvard University, Faculty of Arts and Sciences
2000	Joseph L. Barrett Award	Harvard University, Bureau of Study Counsel
2003	Sackler Scholarship in Psychobiology	Dr. Mortimer and Theresa Sackler Foundation
2004, 2005	Committee on Undergraduate Education Teaching Award	Harvard University, Faculty of Arts and Sciences
2006	Norfolk District Medical Society Scholarship	Massachusetts Medical Society
2008	Dr. Sirgay Sanger Award	Harvard Medical School

PROFESSIONAL MEMBERSHIPS

2003-2004	Cognitive Neuroscience Society
2003-2007	Society for Neuroscience
2003-present	Massachusetts Medical Society
2008-present	Academy of Aphasia
2008-present	American Academy of Neurology
2012-present	American Heart Association
2014-present	Child Neurology Society
2019-present	International Society for Autism Research

SERVICE TO PROFESSIONAL ORGANIZATIONS

2016-present	International Pediatric Stroke Society	Member, Outcomes Subgroup and Pediatric Stroke Neurobehavioral Outcomes and Questionnaire Working Group

SERVICE TO PROFESSIONAL PUBLICATIONS

2002	Journal of Neurolinguistics	Guest Editor
2001-present	Brain, Brain and Language, Cerebral Cortex, Cognition, Cognitive Neuropsychology, Cognitive Neuroscience, Cortex, JAMA Internal Medicine, JAMA Neurology, Journal of Child Neurology, Journal of Cognitive Neuroscience, Journal of Neurolinguistics, Language and Cognitive Processes,	Ad hoc referee

Neuroimage, Neuroimage: Clinical, Pediatric Neurology, Scientific Reports

INVITED PRESENTATIONS – INTERNATIONAL

2001	Scuola Internazionale Superiore di Studi Avanzati, Cognitive Neuroscience Sector, Trieste, Italy	Lecturer
2002	Universitat de Barcelona, Departament de Psicologica Bàsica, Barcelona, Spain	Lecturer
2002	20th European Workshop on Cognitive Neuropsychology, Bressanone, Italy	Plenary Speaker
2008	Programa de Doctorat “Ciència Cognitiva i Llenguatge”, Barcelona, Spain	Lecturer
2014	Hospital São Paulo, Universidade Federal de São Paulo, Brazil	Grand Rounds Speaker
2014	Hospital Israelita Albert Einstein, São Paulo, Brazil	Grand Rounds Speaker
2016	Instituto do Coração do Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Brazil	Grand Rounds Speaker
2016	34th European Workshop on Cognitive Neuropsychology, Bressanone, Italy	Symposium Organizer

INVITED PRESENTATIONS – NATIONAL

2015	Department of Neurology, Massachusetts General Hospital, Boston, MA	Grand Rounds Speaker
2015	Harvard Medical School Michael J. Bresnan Child Neurology Course, Cambridge, MA	Lecturer
2016	Burke Medical Research Institute, White Plains, New York	Grand Rounds Speaker
2016	Department of Pediatrics, Cornell University, New York, New York	Invited Speaker
2017	National TACA Autism Conference, Costa Mesa, California	Invited Speaker
2018	AutismOne Conference, Lombard, Illinois	Invited Speaker

INVITED PRESENTATIONS – REGIONAL AND OTHER

2006	Athinoula A. Martinos Center for Biomedical Imaging, Harvard University, Boston, MA	Invited Speaker
2012, 2013	Department of Neurology, Massachusetts General Hospital, Boston, MA	Lecturer

GOVERNMENT AND OTHER PROFESSIONAL SERVICE

2017	United States Food and Drug Administration Blood Products Advisory Committee	Temporary Voting Member

COMMUNITY AND PUBLIC SERVICE

2013-present	International Neurology Foundation/Centro Internacional en Neurociencias and Hospital José María Velasco Ibarra, Tena, Ecuador	Volunteer Child Neurologist
2016-present	Health4TheWorld	Lecturer
2017-present	Partners In Health/Hôpital Universitaire de Mirebalais, Haïti	Visiting Faculty in Neurology
2017-present	Médécins Sans Frontières	Senior Specialist Consultant

RESEARCH AWARDS – PAST

2014-2019	National Institute of Neurologic Disorders and Stroke KS12 NS001692 “Translating Discoveries in Neurological Diseases of Infancy and Childhood”	Trainee
2005-2008	National Institute of Neurologic Disorders and Stroke F30 NS50906 “Cortical Correlates of Noun and Verb Deficits in Aphasia”	Principal Investigator
2005-2010	National Institute of Deafness and Communication Disorders R01 DC006842 “Cortical Organization of Noun and Verb Processing”	Consultant

PEER REVIEWED PUBLICATIONS

1. Bolshoy A, Shapiro K, Trifonov EN, Ioshikhes I. Enhancement of the nucleosomal pattern in sequences of lower complexity. Nucleic Acids Res. 1997 Aug 15; 25(16):3248-54. PMID:9241237
2. Shapiro K, Shelton J, Caramazza A. Grammatical class in lexical production and morphological processing: Evidence from a case of fluent aphasia. Cogn Neuropsychol. 2000 Dec 1; 17(8):665-82. PMID: 20945200
3. Shapiro K, Caramazza A. Sometimes a noun is just a noun: comments on Bird, Howard, and Franklin (2000). Brain Lang. 2001 Feb; 76(2):202-12. PMID: 11254259
4. Shapiro KA, Pascual-Leone A, Mottaghy FM, Gangitano M, Caramazza A. Grammatical distinctions in the left frontal cortex. J Cogn Neurosci. 2001 Aug 15; 13(6):713-20. PMID: 11564316
5. Shapiro K, Caramazza A. Language is more than its parts: a reply to Bird, Howard, and Franklin (2001). Brain Lang. 2001 Sep; 78(3):397-401. PMID: 11703064
6. Shapiro K, Caramazza A. Grammatical processing of nouns and verbs in left frontal cortex? Neuropsychologia. 2003; 41(9):1189-98. PMID: 12753958
7. Shapiro K, Caramazza A. The representation of grammatical categories in the brain. Trends Cogn Sci. 2003 May; 7(5):201-206. PMID: 12757821

8. Shapiro K, Caramazza A. Looming a loom: Evidence for independent access to grammatical and phonological properties in verb retrieval. J Neurolinguistics. 2003 MarchMay; 16(2-3):85-112.
9. Oliveri M, Finocchiaro C, Shapiro K, Gangitano M, Caramazza A, Pascual-Leone A. All talk and no action: a transcranial magnetic stimulation study of motor cortex activation during action word production. J Cogn Neurosci. 2004 Apr; 16(3):374-81. PMID: 15072673
10. Shapiro KA, Mottaghy FM, Schiller NO, Poeppel TD, Flüss MO, Müller HW, Caramazza A, Krause BJ. Dissociating neural correlates for nouns and verbs. Neuroimage. 2005 Feb 15; 24(4):1058-67. PMID: 15670683
11. Shapiro KA, Moo LR, Caramazza A. Cortical signatures of noun and verb production. Proc Natl Acad Sci U S A. 2006 Jan 31; 103(5):1644-9. PMID: 16432232
12. Cappelletti M, Fregni F, Shapiro K, Pascual-Leone A, Caramazza A. Processing nouns and verbs in the left frontal cortex: a transcranial magnetic stimulation study. J Cogn Neurosci. 2008 Apr; 20(4):707-20. PMID: 18052789
13. Hyde DC, Winkler-Rhoades N, Lee SA, Izard V, Shapiro KA, Spelke ES. Spatial and numerical abilities without a complete natural language. Neuropsychologia. 2011 Apr; 49(5):924-36. PMID: 21168425
14. Willms JL, Shapiro KA, Peelen MV, Pajtas PE, Costa A, Moo LR, Caramazza A. Language-invariant verb processing regions in Spanish-English bilinguals. Neuroimage. 2011 Jul 1; 57(1):251-61. PMID: 21515387
15. Shapiro KA, Moo LR, Caramazza A. Neural Specificity for Grammatical Operations is Revealed by Content-Independent fMR Adaptation. Front Psychol. 2012; 3:26. PMID: 22347206
16. Shapiro KA, Bové RM, Volpicelli ER, Mallery RM, Stone JH. Relapsing course of immunoglobulin G4-related pachymeningitis. Neurology. 2012 Aug 7; 79(6):604-6. PMID: 22843267
17. Pisano T, Numis AL, Heavin SB, Weckhuysen S, Angriman M, Suls A, Podesta B, Thibert RL, Shapiro KA, Guerrini R, Scheffer IE, Marini C, Cilio MR. Early and effective treatment of KCNQ2 encephalopathy. Epilepsia. 2015 May; 56(5):685-91. PMID: 25880994
18. Shapiro KA, McGuone D, Deshpande V, Sadow PM, Stemmer-Rachamimov A, Staley KJ. Failure to detect human papillomavirus in focal cortical dysplasia type IIb. Ann Neurol. 2015 Jul; 78(1):63-7. PMID: 25893423
19. Papinutto N, Galantucci S, Mandelli ML, Gesierich B, Jovicich J, Caverzasi E, Henry RG, Seeley WW, Miller BL, Shapiro KA, Gorno-Tempini ML. Structural connectivity of the human anterior temporal lobe: A diffusion magnetic resonance imaging study. Hum Brain Mapp. 2016 Jun; 37(6):2210-22. PMID: 26945805
20. Shapiro KA, Kim H, Mandelli ML, Rogers EE, Gano D, Ferriero DM, Barkovich AJ, Gorno-Tempini ML, Glass HC, Xu D. Early changes in brain structure predict language outcome in children with neonatal encephalopathy. NeuroImage: Clinical 2017 15:572-580. PMID: 28924555
21. Beber B, Mandelli ML, Santos MA, Binney R, Miller B, Chaves M, Gorno-Tempini ML, Shapiro K. A behavioral study of the nature of verb-noun dissociation in the nonfluent variant of primary progressive aphasia. Aphasiology 2019; 33(2):200-215.
22. Sturm VE, Datta S, Sible IJ, Holley SR, Watson C, Rah E, Meyer M, Pakvasa M, Mandelli ML, Caverzasi E, Miller ZA, Shapiro KA, Hoeft F, Hendren R, Miller BL, Gorno-Tempini ML. Enhanced visceromotor emotional reactivity in dyslexia and its relation to intrinsic salience network connectivity. Cortex 2021 Jan;134:278-295. PMID: 33316603.
23. Caverzasi E, Mandelli ML, Hoeft F, Watson C, Meyer M, Allen IE, Papinutto N, Wang C, Gandini Wheeler-Kingshott CAM, Marco EJ, Mukherjee P, Miller ZA, Miller BL, Hendren R, Shapiro KA, Gorno-Tempini ML. Abnormal age-related cortical folding and neurite morphology in children with developmental dyslexia. NeuroImage: Clinical 2018 Mar 14; 18:814-821. PMID: 29876267
24. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018 Jul 19;379(3):215-255. PMID: 29766750
25. Giudice C, Rogers EE, Johnson BC, Glass HC, Shapiro KA. Neuroanatomical correlates of sensory processing deficits in children with neonatal arterial ischemic stroke. Developmental Medicine Child Neurology 2019 Jun;61(6)667-671. PMID: 28924555
26. Buranahirun C, Walsh KS, Mrakotsky C, Croteau SE, Rajpurkar M, Kearney S, Hannemann C, Wilkening GN, Shapiro KA, Cooper DL. Neuropsychological function in children with hemophilia: A review of the Hemophilia Growth and Development Study and introduction of the current eTHINK study. Pediatr Blood Cancer 2019 Oct 8:e28004. PMID: 31595670
27. Rafay MF, Shapiro KA, Surmava AM, deVeber GA, Kirton A, Fullerton HJ, Amlie-Lefond C, Weschke B, Dlamini N, Carpenter JL, Mackay ML, Rivkin M, Linds A, Bernard TJ. Spectrum of cerebral arteriopathies in children with arterial ischemic stroke. Neurology 2020 Jun 9;94(23).

PMID:32457211

28. Felling RJ, Rafay MF, Bernard TJ, Carpenter JL, Dlamini N, Hassanein SMA, Jordan LC, Noetzel MJ, Rivkin MJ, Shapiro KA, Slim M, deVeber G. Predicting recovery and outcome after pediatric stroke: results from the International Pediatric Stroke Study. Ann Neurol 2020 Mar 25. PMID: 32215969
29. Castilla-Valmanya L, Selmer KK, Dimartino C, et al. Phenotypic spectrum and transcriptomic profile associated with germline variants in *TRAF7*. Genet Med 2020 Jul;22(7):1215-1226. PMID: 32376980

REVIEW ARTICLES

1. Shapiro K, Caramazza A. The role and neural representation of grammatical class. J Neurolinguistics 2002 May-September; 15(3-5):159-170.

BOOKS AND CHAPTERS

1. Caramazza A, Shapiro K. Language categories in the brain: Evidence from aphasia. In: Belletti A, editor. Structures and beyond: The cartography of syntactic structures. Vol. 3. pp. 15-38. Oxford, UK: Oxford University Press; 2004.
2. Shapiro K, Caramazza A. The organization of lexical knowledge in the brain: the grammatical dimension. In: Gazzaniga M, editor. The cognitive neurosciences III. Cambridge, MA, USA: MIT Press; 2004.
3. Caramazza A, Shapiro K. The representation of grammatical knowledge in the brain. In: Jenkins L, editor. Variation and universals in biolinguistics. Amsterdam, NL: Elsevier, 2004.
4. Shapiro K, Hillis A, Caramazza A. The semantic representation of nouns and verbs. In: Hart J, Kraut M, editors. The neural basis of semantic memory. Cambridge, UK: Cambridge University Press, 2007.
5. Shapiro KA, Caramazza A. Morphological processes in language production. In: Gazzaniga M, editor. The cognitive neurosciences, 4th ed. Cambridge, MA, USA: Cambridge University Press; 2009.
6. Shapiro KA, Buonanno F. Stroke and vascular neurology. In: Sims KB et al., editors. Handbook of pediatric neurology. Philadelphia, PA: Lippincott, Williams & Wilkins; 2013.
7. Shapiro KA, Heidary G. Neuro-ophthalmology. In: Sims KB et al., editors. Handbook of pediatric neurology. Philadelphia, PA: Lippincott, Williams & Wilkins; 2013.
8. Spinelli EG, Gorno Tempini ML, Shapiro KA. Speech and Language Disorders. In: State MW et al., editors. Genes, circuits, and pathways in clinical neuropsychiatry. San Diego, CA: Elsevier; 2016.

CONFERENCE ABSTRACTS

1. Shapiro K, Caramazza A. The status of grammatical category information in lexical production. British Psychological Society, Cognitive Section, Essex, United Kingdom, 6-9 September, 2000.
2. Caramazza A, Shapiro K. Comprehension failure in agrammatic Broca' s aphasia: implications for theories of the neural representation of grammatical processes. 20th European Workshop on Cognitive Neuropsychology, Bressanone, Italy, 20-25 January, 2002.
3. Shapiro KA, Moo LR, Caramazza A. Cortical signatures of noun and verb production. Society for Neuroscience, San Diego, United States, 23-27 October, 2004.
4. Shapiro KA, Cappelletti M, Fregni FF, Caramazza A, Pascual-Leone A. Patterns of noun and verb processing in the frontal lobes. Society for Neuroscience, Washington, D.C., United States, 12-16 November, 2005.
5. Shapiro KA, Costa A, Daley TM, Moo LR, Caramazza A. Cortical organization of grammatical category knowledge in bilingual speakers. Society for Neuroscience, Atlanta, United States, 14-18 October, 2006.
6. Shapiro KA, Bové RM, Volpicelli ER, Stone JH. Relapsing course of IgG4-related pachymeningitis. American Academy of Neurology, New Orleans, LA, 22-27 April, 2012.
7. Shapiro KA, Huynh MA, Bove RM, Cincotta SL, Ellenbogen JM. Delayed imaging findings in delayed posthypoxic leukoencephalopathy. American Neurological Association, Boston, MA, 7-9 October, 2012.
8. Shapiro KA, Buonanno F. Isolated bilateral carotid arteritis presenting with stroke in childhood. International Child Neurology Congress, Foz do Iguaçu, Brazil, 4-9 May, 2014.

9. Shapiro KA, McGuone D, Stemmer-Rachamimov A, Staley KJ. Human papillomavirus infection is not causally related to focal cortical dysplasia type IIB. International Child Neurology Congress, Foz do Iguaçu, Brazil, 4-9 May, 2014.
10. Espinosa P, Fee D, Swartz K, Ortiz-Prado E, Pobolish HR, Shapiro K, Baumann R, Vasquez B, Del Pozo PE, Dworetzky B. Decreasing the epilepsy treatment gap in the developing world: The epilepsy medical mission to the Amazon rain forest in Tena, Ecuador, report 2009-2015. American Academy of Neurology, Vancouver, BC, 15-21 April, 2016.
11. Shapiro KA, Kim HS, Mandelli ML, Ferriero DM, Glass HC, Barkovich AJ, Xu D. Early changes in brain structure predict language outcomes in children with neonatal encephalopathy. Pediatric Academic Societies, Baltimore, MD, 30 April-3 May, 2016.
12. Shapiro KA, Watson C, Mandelli ML, Wilson SM, Gorno-Tempini ML. Left hemisphere activation for language despite congenital absence of the left arcuate and superior longitudinal fasciculi. European Workshop on Cognitive Neuropsychology, Bressanone, Italy, 23-27 January, 2017.
13. Malta de Sá M, Fullerton H, Shapiro KA. Early-onset cerebrovascular disease and smooth muscle dysfunction associated with a novel Mylk1 mutation. International Stroke Conference, Houston, TX, 21-24 February, 2017.
14. Zhang Y, Garcia-Reyes K, Brown I, Castillo M, Shapiro K, Luddington L, Rawlings-Fein M, Espinosa P, Dillon W, Rehani B. Ecuador international educational project in neuroradiology. American Society of Neuroradiology, Long Beach, CA, 22-27 April, 2017.
15. Giudice C, Rogers EE, Johnson BC, Glass HC, Shapiro KA. Sensory deficits in neonatal arterial ischemic stroke: neuroanatomical correlates. Pediatric Academic Societies, San Francisco, CA, 6-9 May, 2017.
16. Buranahirun C, Walsh KS, Mrakotsky C, Croteau SE, Rajpurkar M, Kearney S, Hannemann C, Wilkening GN, Shapiro KA, Cooper D. An update on cognitive and behavior function in children and young adults with hemophilia: a 25-year journey from the Hemophilia Growth and Development Study to the current eTHINK study. National Hemophilia Foundation, Orlando, FL, 11-13 October, 2018.
17. Shapiro KA, Jaska S, Shankula S, Hattangadi N, Marco EJ, Goh S. Sensorimotor therapies improve core symptoms of autism spectrum disorder. International Child Neurology Congress-Child Neurology Society, 2020.
18. Marco EJ, Steele MC, Copeland BC, Gerdes MR, Silvers E, Shapiro KA. Assessing cranial electrotherapy stimulation (CES) benefits in a clinical cohort. International Child Neurology Congress-Child Neurology Society, 2020.

OTHER CREATIVE ACTIVITIES

1. "Evaluation of learning difficulty and cognitive delay" (monograph for BMJ Best Practice website)