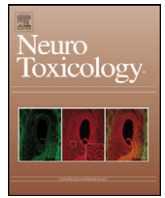




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NeuroToxicology



Commentary

Ockham's Razor and autism: The case for developmental neurotoxins contributing to a disease of neurodevelopment

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ABSTRACT

Much professional awareness regarding environmental triggers for ASD has been narrowly focused on a single possible exposure pathway (vaccines). Meanwhile, empirical support for environmental toxins as a broad class has been quietly accumulating. Recent research has shown that persons with ASD have comparatively higher levels of various toxins and are more likely to have reduced detoxifying ability, and, that rates of ASD may be higher in areas with greater pollution. This report documents that within the state with the highest rate of ASD, the rate is higher for schools near EPA Superfund sites, $t(332) = 3.84, p = .0001$. The reasons for the rise in diagnoses likely involve genetically predisposed individuals being exposed to various environmental triggers at higher rates than in past generations.

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1. Introduction

Vaccination presents a challenge to the body's defenses, and although it appears plausible that heavy metal exposure (especially at a time when the body is addressing another invasion) could pose unique challenges in susceptible individuals, currently the weight of evidence does not support a connection between thimerisol and ASD¹ (Madsen et al., 2003; Richler et al., 2006). Yet, the implications of recent findings suggest a role for toxins in a broad sense. First, persons with ASD have higher levels of various toxins compared to controls. Second, persons with certain neurobiological disorders – including ASD – appear to be more likely to have genotypes that increase harmful effects of toxins. And finally, most important to the current report, multiple studies are documenting that rates of ASD are higher in areas or populations with greater pollution/toxic exposures. Each of these three points will be reviewed as background and framework for the current report. Here, focusing on the state with the highest IDEA reported rate of ASD, it is investigated whether or not the prevalence of autism is higher near areas of identified high contamination.

1.1. Higher levels of toxins

Because it has long been understood that autism is essentially a disorder of neurodevelopment, many researchers have hypothesized that prenatal effects or very early insults play an important etiological role. The gold standard for questions such as this are research designs that measure a hypothesized independent variable prospectively and then follow the participants to see if measured levels will predict who later develops the outcome of interest. Longitudinal studies such as this are time-intensive, and there are not many that fit this criteria. However, such a study was recently reported. In a sample of Latino farm workers in California, families were first contacted during pregnancy and followed until the child was 2 years old. Pesticide levels were determined via urine analysis for both mothers prenatally and children after birth. Higher levels of pesticide metabolites predicted "significantly higher risk of PDD, with an approximately twofold increase in risk for each 10-fold increase in metabolites" Eskenazi et al., 2007, p. 796. It should also be noted that controlling for variables such as birth weight and abnormal neonatal reflexes did not appreciably lessen the effect. As a group, farm workers have higher exposure to pesticides, and this group had an overall higher rate of behaviors associated with ASD (rocking or flapping, indifference to affection, lack of eye contact). Importantly, this study suggests that when pockets of high ASD are found, it might not be due to diagnostic differences, but rather to a biologically relevant exposure. Recently, a study that had been cited by researchers (Shattuck, 2006a,b; Fombonne et al., 2006) as demonstrating that mercury

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¹ It should be noted for completeness that federal officials recently acknowledged that a child diagnosed with autism began her autism-like symptoms after multiple vaccinations given the same day aggravated a preexisting mitochondrial disorder. Some studies show that this disorder is not rare among those diagnosed with autism (Poling et al., 2006; Oliveira et al., 2007).

blood levels are NOT higher in those with ASD was found to be in error with the published results based on typographical and statistical errors by the original authors. The original numbers published in 2004 (Ip et al., 2004) as well as proper analysis of the clean data set shows a statistically significant relationship was present such that children with ASD had higher levels of blood mercury (DeSoto and Hitlan, 2007). Other studies have shown that persons diagnosed with an ASD have higher levels of various pollutants (pesticides, PCB's and solvents) than would be expected (Edelson and Cantor, 2000), and urinary markers for mercury exposure (via coproporphyrin) have been shown to be higher among children with autism by two separate lab groups (Nataf et al., 2006; Geier and Geier, 2006). Furthermore, the levels were reported to predict ASD severity in one study (Geier and Geier, 2006). A recent study by Soden et al., while not finding support for chelation as a therapeutic approach in the age of children studied, clearly showed that more children with ASD had higher levels of heavy metals (Soden et al., 2007; DeSoto, 2008). As a whole, recent research from multiple labs is demonstrating that when direct measurements of neurotoxins among those with autism are compared to those without, the levels are higher in those with an ASD.

1.2. Genetic alleles that effect how the body handles toxins

Of the approximately 25,000 genes that provide the directions to construct a working human being, a number have been isolated that appear to have an effect on how the body deals with environmental toxins. Some of these genes that allow the body to deal with toxins have more than one allele in the human gene pool—and some alleles result in greater efficiency than others. For example, paraoxonase is associated with detoxification processes for neurotoxins such as pesticides and nerve gasses. Paraoxonase (PON) activity varies significantly across individuals, decreased PON activity means less ability to break down and remove toxins, and the genes that control PON activity come in more than one variety. Certain variants may be associated with neurological diseases such as amyotrophic lateral sclerosis, or ALS (Morahan et al., 2006; Saeed et al., 2006). This is important because although more research is needed, variants of such genes may predispose persons to neurological diseases as a result of environmental exposure. The strong relationship of ALS to a “PON gene cluster is consistent with the hypothesis of environmental toxicity in a susceptible host precipitating ALS,” and the finding is speculatively offered as a possible explanation as to why groups that have higher exposure to such toxins might have higher prevalence of the disease (Saeed et al., 2006, p. 775). The frequency of variants of PON genes is not identical across populations. Importantly, some studies have found that autistic persons have less paraoxonase activity than non-autistics (Pasca et al., 2006) and one study has found evidence that in some populations, but not in others, autism is related to PON gene variants that are less active (D'Amelio et al., 2005). Besides the PON1 genotype, genes that instruct the body regarding glutathione synthesis have been found to differ in autistic populations compared to controls (Buyske et al., 2006). Glutathione plays an important role in eliminating heavy metal toxins from the body and the null variant of the GSTM-1 gene can be expected to be less efficient at eliminating heavy metal toxins that find their way into circulation (Gundacker et al., 2007). Finally, deficiencies in functioning of the mitochondria (especially mitochondrial chain disorders) appear to result in an increased detrimental effect for even standard types of stress, which may cause affected children to regress after developing normally for a time (CDC, 2008). Such deficiencies may be more common in those with an ASD (Poling et al., 2006; Oliveira et al., 2007). It is crucial to appreciate the recency of these findings: each of the studies that

are directly addressing genetic vulnerability via genotypic differences were all reported within the last two years. It is imperative that researchers and practitioners appreciate that new information is rapidly accumulating; reviews from even 1 or 2 years ago are likely to be outdated.

1.3. Increased rates and environmental pollutant levels

Areas with the biggest increases in ASD do not appear to be randomly distributed. It might be argued that if environmental contact with neurotoxins increases the odds of autism, then the increase in ASD diagnosis over the past generation can be explained by a macro-level increase in such toxins. There is a test for this idea. The test is whether the increase in ASD is higher in areas with more pollutants. Although some researchers have denied that any actual increase has occurred (and that there has been no change in actual incidence at all), this view is predicated on the belief that practitioner behavior changed before the increase began, and that current differences in prevalence are fully due to changes in practitioner/diagnostic behavior. The initial change in prevalence began within the United States near the time of changes in the IDEA law, and the official diagnostic criteria of the DSM was slightly modified near this time as well (APA, 1994). The temporal correlation is of interest, but correlation does not necessarily imply cause.

Ideally, the hypothesis that “diagnostic changes” are the cause of the continued increase in prevalence would require a precise definition of diagnostic changes, an independent, direct measurement of diagnostic changes—and then a statistical test of this variable's ability to account for prevalence changes. The question is not if a change in diagnostic practice has occurred over the past two decades, but whether this change can account for the increase in prevalence. Autism prevalence across time in California has been analyzed as a function of changes in diagnostic practice. Results have shown that there have been changes in diagnostic behavior—these changes have been quantified and appear to account for a 67% increase in the number of diagnoses (Hertz-Picciotto and Delwiche, 2009), however as noted in the study, there has been a nearly 700% increase in prevalence. As a whole, this suggests that diagnostic changes have occurred, but do not come close to fully accounting for the observed change in prevalence. This is important, the fact of diagnostic change is not in dispute, the question is if the change in practice can account for the several-fold increase in observed prevalence.

On the other hand, if toxic exposure is playing at least some role in the increased prevalence, then the rate of ASD should not be random: ASD prevalence should increase as environmental toxins increase. This coupling should occur both across time and across geographical region in as much as toxic exposure levels can be defined and quantified. In the past 2 years, several tests of this idea have emerged in the literature. A large study using 7540 children found that proximity to heavy pesticide use in the mother was strongly related to ASD in the offspring. The risk was strongest for mothers living closest to the greatest amount of exposure and the risk appeared specific to ASD—comparison groups included both normal children as well as mentally retarded children without ASD (Roberts et al., 2007). Autism may be more common in more industrialized areas. The difference is not explainable by differences in general diagnostic practice or medical availability, and importantly, seem to relate more to where the pregnancy occurred than where the diagnosis occurred (Kamer et al., 2004; Yurong et al., 2001; Hoshino et al., 1982). Most recently a study of the state of Texas has demonstrated that the rate of autism is higher for school districts that are near toxic releasers and the increase in ASD rate is predictable based on the distance and the amount of heavy metals released (Palmer et al., 2009). Despite the limitations of the

ecological design of these studies, findings such as this are hard to explain in terms of simple diagnostic awareness.

1.4. Current study of Minnesota ASD prevalence

In the past generation the United States, like other industrialized countries (see for example Atladottir et al., 2007), has seen the diagnoses of both classic autism and the broader category of ASD increase dramatically. By the year 2002, the nation wide increase within the United States had been widely acknowledged to have been at least a factor fourfold (see Yeargin-Allsopp et al., 2003). An analysis in the same year conducted within Minnesota, found the increase in ASD to be as high as a 14-fold increase (Gurney et al., 2003). The study by Gurney and colleagues attempted to dissect competing influences on the increase in Minnesota. Although the data rule out the type of diagnostic substitution that Shattuck (2006a,b) suggested might underlie the increase, the data were consistent with an increased attempt to count children with ASD specific behaviors. As a whole, it was concluded that changes in administrative law played some role in the increase, but the authors were careful to note that whether a true change in disease incidence had occurred could not be determined.

In 2009, a careful study of incidence within a single county in Minnesota by Barbaresi, Cooligan, Weaver and Katusic found that relying on clinical diagnosis alone results in an increased estimate of the change in incidence. Barbaresi et al. (2009) report that while the increase in clinical diagnosis increased by 22-fold, utilizing a more careful research-based methodology (reviewing information from all health care and school sourced for the entire population), the increase in incidence was found to be closer to an eightfold increase (from 5.5 cases per 100,000 in the early 1980s to 45 cases per 100,000 for the mid-1990s). Although the authors' main conclusion was focused on the discrepancy between clinical and research-based ascertainment methodology, it is at least of equal import to note that using either clinical diagnosis or a more careful research-based incidence approach, a sharp increase is observed in a circumscribed region. The results may be interpreted as further documenting that an increase has occurred—including using the more stringent research-based incidence measure. Certainly finding a range of increase between 800% and

2200% using very different methods does not lend any credence to the idea that no increase has occurred. Furthermore, the discrepancy in the size of the increase is probably best seen as an artifact of selecting the specific interval of time (grouping the years 1980–1983 and using this as the starting point). Had there been one more clinically diagnosed case in that time period – or, had the years before or after this interval been selected as the starting point – it would not have resulted in the clinical case incidence increase being significantly higher than the research-based increase. For example, careful readers may note that if one compares the years of the sharply increasing prevalence (1988 across 1997), one method shows a sevenfold increase and the other a ninefold increase in autism (Barbaresi et al., 2009). As depicted in Table 1 and Fig. 1, page 466, the data and the graph appear to demonstrate an increase in incidence regardless of the method employed to count cases. Although it is necessary to refer to the original article for full clarity—either method shows a clear, in fact almost parallel, increase in autism for Olmstead County, Minnesota.

Minnesota is of special interest because according to IDEA data, it is the state with the highest rate of children having an ASD diagnosis. In Minnesota, like many states, there is no formal requirement that a licensed clinician or physician diagnose a child as having autism for them to categorize as ASD by a school district (although most are). Instead, a team meets to determine if ASD is the best diagnosis for educational purposes. The team includes a specialist in autism and often a psychologist. DSM-IV criteria are used. Although it is reasonable to assume that precise diagnostic procedures vary slightly from one team to another, this is not tantamount as showing these differences relate to differences in prevalence estimates. To the author's knowledge, no attempts have been made by proponents of the theory that diagnostic differences have caused the increase in autism to test the hypothesis; i.e., there is little data provided by these proponents that measure actual diagnostic practice, and to my knowledge none that show such variables are able to account for the differences in prevalence rates observed.

Conversely, if the rate within a population has increased as a result of exposure to known neurodevelopmental toxins—then the rate should be highest in areas with the highest level of contaminants. And this can be tested.

Table 1

Important autism findings documented by at least three independent lab groups that a viable theory should be able to explain.

Finding	Lab groups reporting/replicating ^a
High heritability estimates (last 10 years based on twin concordance studies)	Hoekstra et al. (2007): $H = .57$ Taniai et al. (2008): $H = .73$ for males, $H = .87$ females. Ronald et al. (2008): $H = .36$ – $.87$
Some form of decreased toxin-reduction capacity in ASD	James et al. (2004) Pasca et al. (2006) Poling et al. (2006)
Specific genes related to detoxification are seen more commonly in ASD	Serajee et al. (2004) James et al. (2006) Buyske et al. (2006)
Higher average toxic levels in autistic individuals	Edelson and Cantor (2000) Nataf et al. (2006) Eskenazi et al. (2007)
Significant differences in concurrently measured within-study ASD incidence	Hoshino et al. (1982) Oliveira et al. (2007) Kamer et al. (2004)
Increased rates associated with sources of contaminants	Roberts et al. (2007) Palmer et al. (2009) DeSoto (current report)
Rise in the reported prevalence of autism outside North America	Baker (2002) Gillberg et al. (2006) Atladottir et al. (2007)

^a Several findings above have additional replications not listed in the table (see text), but at least three replications by independent researchers are often assumed to reflect a genuine finding.

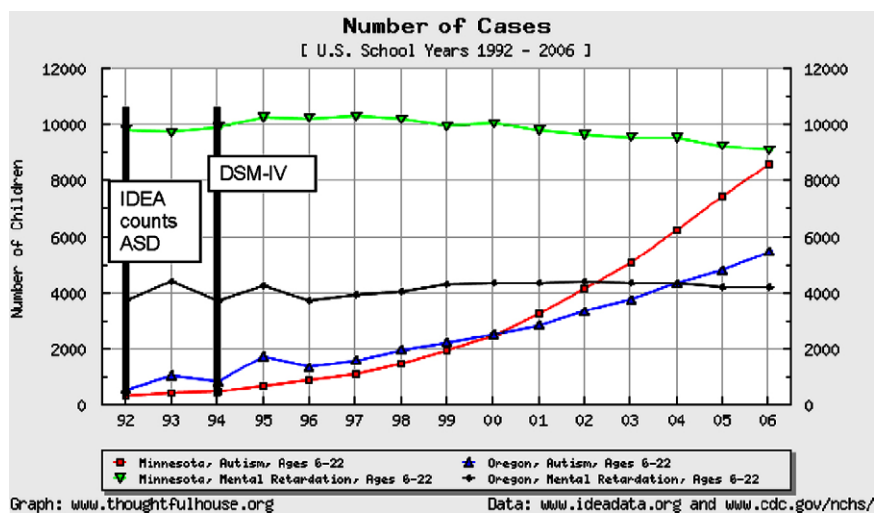


Fig. 1. Two states with highest reported autism prevalence, as reported by public schools, are Minnesota and Oregon. For comparison, the rates of students receiving services for mental retardation are included for these states. The IDEA required schools to report ASD as a diagnosis starting for the school year 1992, and there was a slight revision in autism diagnostic criteria in the edition of DSM that came out in 1994.

2. Methods

2.1. Prevalence estimates

District ASD rates for the 2007–2008 school year were obtained from the Minnesota department of education. The number of children who are receiving services for an ASD in comparison to the total number of students enrolled in the district was used to determine district prevalence. The prevalence is expressed as a ratio of one in X number of students who were receiving disability services for ASD in a school district. Minnesota had 336 type 1 school districts that range from 104 to 22,000 pupils. Each school district was treated as an independent measure of prevalence. Only type 1 school districts were included, charter school districts and other specialized schools were not included. A few districts with very high ASD rates were a result of one or two students residing in a very small district. To avoid undue influence on a region's prevalence by one or two pupils, districts that had an expected frequency (based on national prevalence estimates) of four or fewer and had an ASD rate above the 90th percentile (12 school districts) were simply averaged with the adjacent school district to which they shared the largest border. District prevalence ranged from 1 in 40 to 1 in 666, and a few smaller districts with enrollments less than 550 had zero cases.

2.2. EPA Superfund sites

Superfund is the environmental program that addresses hazardous waste sites that are found to be a significant threat to human health. Once a site is identified, it undergoes formal assessment which includes a hazardous ranking system scoring. Sites with the highest scores are recommended to the National Priority List (NPL). Minnesota sites that are part of the NPL were obtained from the EPA (EPA, 2008) and latitude and longitude coordinates were obtained for each location, and GIS software was used to plot these locations so that distances between Superfund sites and school districts could be calculated. The U.S. Department of Health and Human Service's Agency for Toxic Substances and Disease Registry (ATSDR) provides a Completed Exposure Pathway site count report. The report is based on the number of sites that a substance has been detected and incorporates ATSDR's health assessments and consultations. The list can be considered as reflecting the most frequent contaminants of exposure. The full list

and rankings are publically available, but frequent toxins found at NPL Superfund include: Lead, Arsenic, Trichloroethylene, Tetrachloroethylene, Benzene, Cadmium, Chromium and Mercury (ATSDR, 2007).

Based on the idea that ASD rates have increased partly due to changes in average exposures to neurotoxic substances at key times in development, it was expected that school districts near serious sources of environmental contamination would have higher rates of ASDs than school districts where there were no highly toxic sites near. Although it seems reasonable that prenatal exposure is of importance, and that some families would move from one district to another after a birth occurred (so that where a child was gestated might not always be the same as where the enroll in school), if exposure to toxins (prenatally or in early childhood) is playing any causal role in the increase in diagnosis that has been observed over the last generation, then proximity to a NPL Superfund location should serve to increase the observed prevalence.

Specifically, it was hypothesized school districts (using the centroid latitude and longitude point) that had one or more NPL Superfund sites within a 10 mile radius would have higher rates of ASD than those that had no NPL sites within a 10 mile radius. The geographic centroid for each school district was determined using ArcGIS software. Next, ArcGIS was employed to determine which school district centroids are located within a 10 mile radius of EPA Superfund sites.

2.3. Statistical methods

A list of school districts that had at least one NPL Superfund site within a 10 mile radius was constructed, and a list of school districts that did not have a NPL Superfund site within 10 miles was also constructed. The reported ASD prevalence rate for the two lists was compared using an independent sample *t*-test, with equal variances assumed.

3. Results

There were 288 school districts that did not have a NPL Superfund site within a 10 mile radius. The mean ASD rate for these districts was one case per 132 pupils. There were 46 districts that had one or more NPL Superfund sites within a 10 mile radius. The mean ASD rate for these districts was 1 case per 92 pupils. Fig. 1

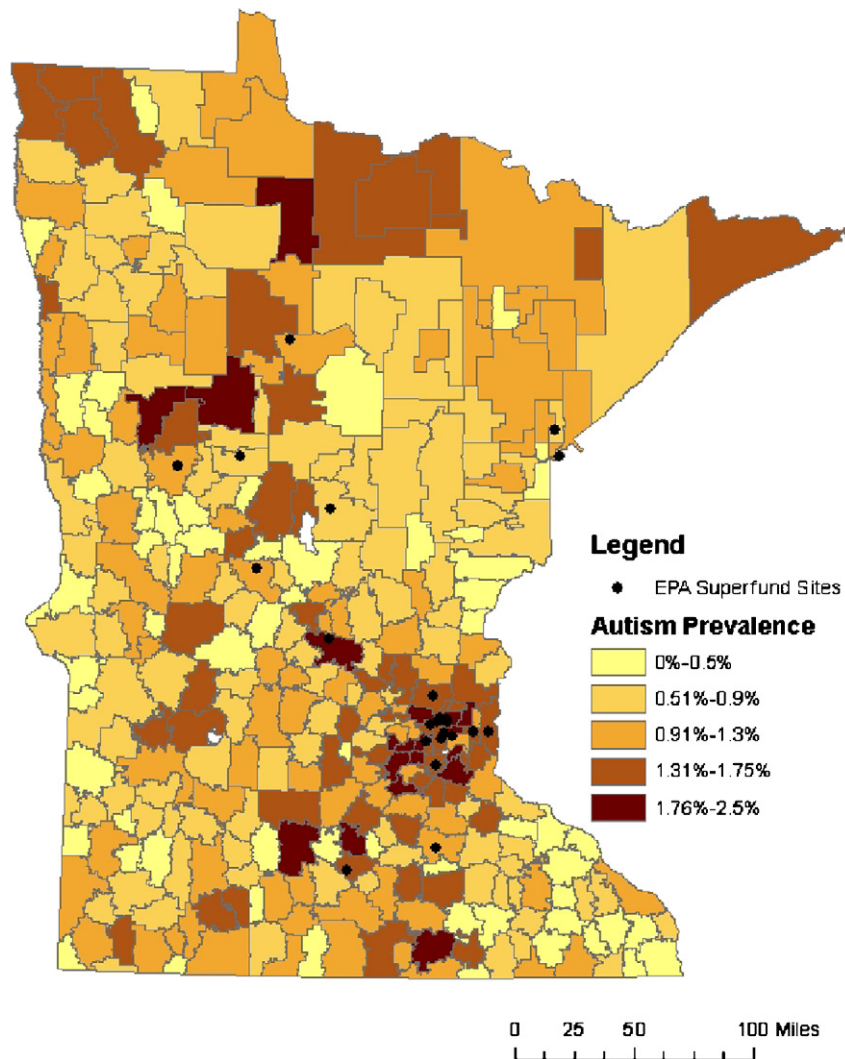


Fig. 2. Minnesota school district rates of Autism, as provided by Department of Special Education, and EPA Superfund site locations.

depicts the rate of ASD in school districts in relation to the location to EPA NPL Superfund site locations.

Overall, there was a significantly higher ASD prevalence among districts near a NPL site, $t(332) = 2.53$, $p = .01$, as hypothesized.

There were relatively few school districts within a 10 mile radius of such a site (14% of the districts). To get a more even division and to be sure that the effect was a general effect, an identical procedure was conducted using a 20 mile radius. Ninety-seven districts had one or more sites within a 20 mile radius. The result did not change. There was a significantly higher ASD prevalence among districts near a NPL site, $t(332) = 3.84$, $p = .0001$. Overall, it appears that the absence of highly polluted sites within a 10 or 20 mile radius affords some protection against the otherwise high rate of ASD observed in Minnesota school districts.

4. Discussion

These results do not support the idea that differences in prevalence rates are solely due to differences in diagnostic practice. Rather, these results suggest that prevalence rates vary in a way that can be predicted by environmental characteristics. These results fit well with very recent research that shows that ASD rates are higher in California where pesticide use is very high (Roberts et al., 2007), and with research that shows in Texas, rates are higher near toxic releasing industries (Palmer et al., 2009).

Recent studies by authors who have argued against the apparent increase in prevalence reflecting any real increase in incidence have recently documented the increase has not abated (Schechter and Grether, 2008; Fombonne, 2008). Fombonne noted that the rate of ASD increase has been steady; compared to the prior years the increase “did not attenuate” for the years 2004–2007 (Fombonne, 2008, p. 15). In fact, autism has been steadily increasing since the early 1990s, as depicted in Fig. 2. If the increase were due to changes in the DSM (APA, 1994) or to changes in IDEA law that were introduced for 1992, it seems likely that the initial increase would be lessening. After all, there have been no significant changes in the DSM for 14 years, and the IDEA categories were shifted 16 years ago.

4.1. Limitations

A weakness of the current study is that although it is likely that toxic exposure during gestation is of import, information on where families lived during the pregnancy of the child is not known. U.S. Census Bureau data suggests that approximately 15% of the population moves in a given year. However, a majority of these moves are to another residence within the same county. Furthermore, the mobility rate is higher for singles than for families (U.S. Census Bureau, 2001). Thus, most of the families with children likely lived in the same county for several years.

Nonetheless, future studies attempting to predict rates of autism as a function of environmental pollution should seek to collect information on where the pregnancy occurred whenever possible.

An additional weakness is the correlational nature of the relationship that is being reported. Essentially, there appear to be more cases of ASD diagnosed near highly polluted areas. However, such an association could result from a third variable, such as proximity to urban centers. For example, it might be that families affected by autism might choose to relocate to an urban area that might have a wider range of services to offer. Although such an explanation cannot explain the overall pattern of results reported in the literature (Kamer et al., 2004; Yurong et al., 2001; Hoshino et al., 1982), it could play a role in the association here reported between ASD prevalence and proximity to EPA Superfund locations. Future research could address this using place of birth and by specifically including highly polluted rural areas. Recent research has found an association between heavy metal pollution and developmental delay in rural areas specifically (Aelion et al., 2008), and future research should be conducted that considers ASD prevalence in rural-only areas to avoid this potential confound. Controls for age of parents and/or family SES would also strengthen the design of a future study.

Given research showing that acquired metabolic abnormalities in the parents have an inherited impact on offspring, it seems likely that a fruitful avenue for future research will focus on epigenetic mechanisms for environmental effects (see discussion in James et al., 2006). Autism is a disease of neurodevelopment: it is generally understood that something goes amiss during brain development that leads to the set of behaviors that becomes recognized as autism. Although autism is largely genetic, it is also clear the etiology is not fully explainable by classical genetics since the concordance rate for genetically identical MZ twins is not 100% (Santangelo and Tsatsanis, 2005). Something about the environment is also playing an etiological role. Researchers at the University of Arkansas have published a series of careful studies showing that ability to detoxify environmental toxins is lessened in autistic versus control subjects (see James et al., 2008 for an overview). Similar results have been found by Ming et al. (2005), Yao et al. (2006), and Zoroglu et al. (2004) in that all document a decreased ability to handle toxic insult in groups of autistic persons. A team at Rutgers has found evidence that the certain genotypes related to glutathione production are more common in Autistic groups (Buyske et al., 2006) and some evidence exists that other genes important for dealing with neurotoxic effects occur with different frequencies in ASD populations and their mothers (Williams et al., 2007). As reviewed above, a number of these genes appear to be facultative, in that their activity is affected by environmental exposures.

As documented here, the state with the highest rate of IDEA-reported ASDs has higher rates in areas near highly polluted areas, and living far from sources of toxic pollution appears to be associated with a relatively lower rate of ASD. As a whole, the data that has been published since 2005 suggest that classical genetic vulnerability predisposes certain persons to experience the particular set of missteps during neuronal development that result in the behaviors labeled as autism. One possible model for development of ASD includes epigenetic mechanisms activated by environmental toxins (and/or pathogens). One or more environmental prompts experienced by a predisposed individual at the right time in development could then “pull the trigger” and instigate one or more specific errors in neurodevelopment. Such a model is consistent with key findings that have emerged in the past 3 years as depicted in Table 1.

A long held standard of evaluating competing theories is parsimony. A single theory that explains multiple findings is superior to circuitous explanations that require untestable

assumptions. It is hard to imagine how the set of findings could be more easily explained than including an etiological role for environmental toxins.

Conflict of interest statement

None.

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