
Windows of Vulnerability: An Overview of Brain Development and Susceptibility to Environmental Contaminants

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The Developing Brain

Brain development begins very early in human gestation and continues well after birth through adolescence. It depends on a tightly orchestrated cascade of sequential and concurrent events. During development, brain cells proliferate, migrate to the appropriate location in the brain architecture, differentiate into the correct cell type, and establish connections (synapses) with nearby and distant cells in complex neuronal circuits. Myelin sheathing on the neurons begins to develop after cell proliferation and migration, and continues through adolescence. Programmed cell death (apoptosis) is important to normal brain development and occurs in two waves in prenatal and postnatal development.

Disruption of this sequence at any point during brain development can have lasting consequences for brain function later in life. The nature of the impact will depend in large part on the timing of the disruption of normal developmental events. Experimental data show that extremely short term exposures to developmental neurotoxicants can have permanent impacts on later brain function, and that the abnormalities observed after exposure to a single toxic agent may vary with the timing of the exposure.¹ The nature of the neurotoxicant, the extent of exposure, and the timing of exposure are, therefore, each important determinants of outcome.

As with fetal and child development more generally, brain development is under the control of genetic and environmental factors that interact in complex ways. Although genetic inheritance plays a prominent role in fetal brain development, environmental factors also significantly contribute to final outcomes through their direct impact on developing tissues, by alteration of signaling chemicals that are essential mediators of brain development (neurotrophins), or by modifying gene expression. Environmental factors include nutrition, pharmaceuticals, other chemicals, infectious agents, maternal illnesses, and the psychosocial context.

Mental Retardation

It must be acknowledged that the role of environmental agents in the etiology of mental retardation and associated developmental disabilities is poorly studied and understood. Strikingly little concerning this topic has been published in either the mental retardation or neurotoxicology literature. In 1987, the American Association on Mental Deficiency published a monograph entitled, “Toxic Substances and Mental Retardation.” Most of the volume discusses prenatal exposure to alcohol and lead as potential contributors to the incidence and severity of mental retardation, with an interesting chapter on fetal antigenicity and maternal immunoreactivity as a potential cause as well.

Our understanding is constrained by several factors. In general, there is little systematic evaluation of the neurodevelopmental impacts of a variety of potentially toxic agents to which people are regularly exposed. A substantial literature concerning impacts of lead, mercury, polychlorinated biphenyls (PCBs), alcohol, tobacco, and a few pesticides is the exception. For most agents with the potential for disrupting normal brain development, few data are available. Yet, these exceptions suggest that we should be pursuing this line of inquiry more vigorously since they demonstrate the vulnerability of the developing brain to toxic exposures at levels that have no discernable impacts in adults.

It is also important to note that there is no good animal model for studying mental retardation as the endpoint of interest. Some manifestations of neurodevelopmental impairment, such as learning, activity level, and memory, lend themselves to animal testing and quantitative assessment far more readily than mental retardation, which is a combination of intellectual functioning and adaptive skills.

Definitional Issues and Their Importance to Neurotoxicologic-MR/DD Evaluation

Mental retardation is a combination of sub-average intellectual functioning combined with limitations in adaptive skills like communication, self-care, home living, social skills, use of community resources, self-direction, work, leisure, health and safety.² But precise definitions may differ in some details, and these differences may have an important impact on studying the etiology of mental retardation and related disabilities. For example, the American Psychiatric Association (DSM IV) definition includes three levels of severity—mild (IQ 50-55 to 70), moderate (IQ 35-40 to 50-55), and severe (IQ below 25). The American Association on Mental Retardation (AAMR) definition, however, does not include the three categories of severity and has a cut off of IQ 70-75, rather than IQ 70, as a diagnostic criterion. Of course, the different threshold cut off value has important implications for eligibility for services. From the standpoint of understanding etiology, however, there appear to be significant differences for mild and severe mental retardation, and for that reason, the subset classifications of DSM IV are useful. Most studies of the causes of mental retardation focus almost exclusively on IQ for case identification, leaving out the adaptive factors included in the definitions.

Co-morbidities

Epilepsy, autism, cerebral palsy, low-birth weight or small for gestational age, visual or hearing disorders, behavioral problems, psychiatric disorders, and micro- or macrocephaly may be associated with mental retardation. Presumably these disorders are additional manifestations of the clinical condition of which mental retardation is a part, but how they may be related to mental retardation is not always clear.

The Causes of Mental Retardation

It is likely that a large percentage of cases of MR have more than one causal factor. At least our current understanding suggests that multiple factors play a role in many cases.³ It is important, therefore, to have a dynamic view of the individual in the context of biological, physical environmental, and psychosocial factors. A vulnerable individual may develop intellectual function and adaptive skills better or worse, depending on the nature of the environment in which he/she is situated.⁴

- Prenatal, perinatal, and postnatal factors may play a role in the development of mental retardation.
- Prenatal: genetic, teratogenic (infections—e.g. rubella, cytomegalovirus; chemical agents—e.g. alcohol), central nervous system birth defects/malformations; hypothyroidism
- Perinatal: Intrauterine events, birth trauma, anoxia (low oxygen), neonatal infections (e.g. meningitis)
- Postnatal: Viral or bacterial infections, trauma, tumors, anoxia

Frequently the cause of MR is unknown, and this is more likely in cases of mild than of severe MR.⁵ Down syndrome is the most commonly identified chromosomal abnormality associated with severe MR. A number of other genetic abnormalities, however, have also been identified, such as Fragile X syndrome. In one review of epidemiologic studies of mental retardation, fewer chromosome abnormalities and a larger percentage of cases of unknown cause were found for mild than for severe MR.⁶ Vaccination programs (e.g., rubella) and routine screening for congenital hypothyroidism and PKU have dramatically reduced the incidence of MR associated with those conditions.

WHY CONSIDER DEVELOPMENTAL NEUROTOXICANTS AS A “CAUSE” OF MENTAL RETARDATION?

A sizeable literature describing the impacts of alcohol, lead, mercury, and PCBs on the developing brain identifies the potential role of environmental agents in the etiology neurodevelopmental disorders, including mental retardation. In most cases, fetal exposure to these agents must be relatively large in order to cause mental retardation. Other manifestations of impaired brain development are also common, such as hyperactivity, learning and memory disorders, or behavioral abnormalities.

ALCOHOL AND TOLUENE

Studies of people with fetal alcohol syndrome or fetal alcohol effects show that the IQ distribution curve is shifted significantly to the left and includes individuals with severe to moderate mental retardation.⁷ Risks of fetal alcohol syndrome depend on the size, pattern, and timing of fetal exposures. Genetically determined variations in maternal metabolism of alcohol also influence the likelihood of fetal alcohol syndrome, since one of the metabolites of alcohol, acetaldehyde, is thought to be an important contributor to the condition.⁸ Maternal nutritional status and other substance abuse are important additional factors to consider.

Maternal exposure to toluene, another organic solvent, is also associated with pregnancy outcomes that resemble fetal alcohol syndrome, and the term “fetal solvent syndrome” is now sometimes used. Glue or gasoline sniffing during pregnancy can result in significant fetal toluene exposures with defects similar to those seen with alcohol, including mental retardation.⁹

PCBs

In the late 1960s and early 1970s two episodes of accidental human exposure to PCB- and furan-contaminated rice oil in Japan and Taiwan resulted in tragic developmental effects in children born to exposed mothers.¹⁰ The developing fetus was much more sensitive than mothers and numerous abnormalities were observed, including low birth weight, hyperpigmentation, swollen gums and eyelids, and mental retardation among some of the most highly exposed. Subsequent studies show that hyperactivity, learning and behavioral problems, as well as IQ deficits, are seen in children exposed to PCBs during fetal development.^{11 12}

METALS

Mercury and lead are two heavy metals that can also disrupt normal brain development via a variety of mechanisms. Large exposures to mercury, such as occurred in Minamata Bay in Japan, may cause mental retardation in the most highly exposed. (see P. Davidson paper) Early life exposures to lead can also reduce IQ and cause learning and behavior problems.¹³ Weiss emphasizes that exposure to neurotoxicants must be considered in the total psychosocial context of an individual or community where exposure to a variety of other factors may have negative impacts on brain development and function.¹⁴ The total incremental impact of lead exposure in a disadvantaged community, for example, may be substantially greater than the same exposure in an advantaged community, where the IQ distributions may differ by as much as 15 points in the two groups.

ADDITIONAL QUESTIONS AND CONCERNS:

Unfortunately, most industrial chemicals to which people are regularly exposed from consumer products or as environmental contaminants have not undergone neurodevelopmental testing. A large database addresses the impacts of lead, mercury, PCBs, alcohol, and smoking. A few additional chemicals have undergone initial animal testing and a few preliminary observations in human populations are available for some pesticides.¹⁵ For most chemicals, however, very little information is available.

Although it has been known for many years that untreated congenital hypothyroidism can result in severely impaired brain development, recent studies show that even mild untreated maternal hypothyroidism can have neurodevelopmental consequences, including lower IQ, in their children.¹⁶ Some PCB research has focused on disruption of normal thyroid hormone levels and interference with normal thyroid hormone function during development.^{17 18} This line of investigation has raised new concerns about other chemical compounds that may disrupt normal brain development through similar mechanisms.

Some brominated flame retardants (PBDEs) that are used in a large number of consumer products have properties that are similar to PCBs, though they have not been as well studied. Animal testing, however, shows that PBDEs can interfere with normal thyroid hormone function and with normal brain development leading to hyperactivity and deficits in memory and learning in adults.¹⁹ Other chemicals that alter thyroid hormone levels or hormone function may be anticipated to have similar effects. Although current human exposures to PBDEs are not of the same magnitude as those that cause effects in test animals, studies in the US and Europe show that PBDE levels in human fatty tissue have been rapidly rising in recent years.²⁰ Some European countries have taken initial steps to limit PBDE exposures, based on biomonitoring trends. In the US no such action has yet taken place, though legislation that would place restrictions on some PBDEs has been introduced in California.

Issues for Discussion

Though studies of the association of neurodevelopmental toxicants with mental retardation are limited, available data suggest that fairly large exposures are necessary in order to serve as a primary cause of the outcome. To what extent, however, do smaller exposures with incremental impacts on IQ or other measures of neurological function have increased significance in individuals whose intellectual function and adaptive skills are compromised by other unrelated factors? This issue has been raised by Weiss in the past and is the basis for his contention that the impacts of neurodevelopmental toxicants must be considered in the total psychosocial context of individuals and communities.

What is the importance of maternal nutritional factors in fetal brain development and what are the potential interactions of neurodevelopmental toxicants with nutritional deficiencies during critical windows of development?

Do the relative importance of prenatal and postnatal nutritional factors and interactions with neurotoxicants differ?

Endnotes

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