Chapter 1
Neurotoxins and Neurodevelopment

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Developmental perspectives for understanding how neurological factors relate to overall functioning and behavior across the life span are imperative. The leading cause of neonatal mortality is birth defects (McKenzie et al., 2014), in some cases the result of exposure to neurotoxins. Even when not resulting in death, damage or insult to the developing brain or nervous system from exposure to neurotoxins can result in ramifications that range from mild to severe and are lifelong (Gilbert, Miller, Martin, & Abulafia, 2010). Consistent with a developmental framework, models of pathology should be based on what is known about typical development and underlying neurological processes (Sonuga-Barke, 2014). Additionally, the neurodevelopmental timing of the deviation or damage is important with effects on the pathogenesis of disorders in children. Because their brains are still developing, children are particularly susceptible to the deleterious effects of neurotoxins (Dietrich et al., 2005; Gilbert et al., 2010; Konijnenberg & Melinder, 2011; Lidsky, Heaney, Schneider, & Rosen, 2007). Therefore, those who work with children, expectant mothers, or families should be knowledgeable about neurotoxins and

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C. Riccio, J. Sullivan (eds.), *Pediatric Neurotoxicology*, Specialty Topics
in Pediatric Neuropsychology, DOI 10.1007/978-3-319-32358-9_1

their effects on child development in order to enhance prevention efforts, improve diagnosis, and formulate and implement research-based interventions. In each of the ensuing chapters the research specific to a class of neurotoxins is summarized, with a focus on the potential effects on neurocognitive and neurobehavioral domains.

What Are Neurotoxins?

Neurotoxins are harmful substances that damage or destroy neural tissue (Costa, Aschner, Vitalone, Syversen, & Porat-Soldin, 2004). Toxic exposure comprises contact with a large range of substances that ultimately are poisonous to one or more aspects of the neural system (Williams & Ross, 2007). Neurotoxins include environmental substances that naturally occur, manmade substances, prescribed medications, and recreational substances. Environmental and chemical teratogens, such as lead (see Chap. 8); mercury, manganese, arsenic, toluene, polychlorinated biphenyls (PCBs), and pesticides (see Chap. 7); and air pollution (see Chap. 9) can often be found in the child's environment and can be a serious threat to development (Gilbert et al., 2010; Landrigan, Lambertini, & Birnbaum, 2012; Winneke, 2007). Proximity to sources of natural gas, for example, is associated with cardiac defects and neural tube defects (McKenzie et al., 2014). Issues related to toxic effects of environmental substances received increased attention following the passage of an executive order by President Bill Clinton acknowledging children's increased vulnerability to the harmful effects of environmental toxins and the need to protect them from these risks (Executive Order No. 13045, 1997). Healthy People 2010 also included environmental quality as an important health indicator, given the contributions of poor air quality and environmental toxins to preventable illnesses (U.S. Department of Health and Human Services, 2000).

Exposure to neurotoxins may be in the form of direct interaction, as in the case of a child who chews on a toy that has been finished with lead paint or was inadvertently contaminated with pesticides. Some research indicates that the majority of exposure to neurotoxic chemicals such as lead occurs postnatally, while most of the exposure to mercury and PCBs occur prenatally. It is important to note, however, that exposure has been found to occur across the life span and can have detrimental consequences to neurodevelopment and associated behaviors (Winneke, 2007).

Environmental toxins are not the only teratogens that can have an impact on neurodevelopmental functioning. From the time of conception, the developing fetal brain is exposed to the chemical and electrical environment of the mother. Studies consistently indicate that substance use and consumption of certain medications by pregnant women place their unborn children at risk. Effects on an unborn child are indirect and occur through maternal contact or ingestion of the toxin, including prescribed medications. Medications may be prescribed to address concerns with the maintenance of the pregnancy (e.g., diethylstilbestrol [DES], thalidomide) or to address the medical status of the mother (e.g., seizure control, diabetes). A wide range of medications have been identified as disturbing the normal developmental

process in utero (Pillard et al., 1993; Titus-Ernstoff et al., 2003). With medical treatment, however, where both maternal health and child health are of concern, determining appropriate protocols and potential effects is ongoing (see Chap. 5 on antiepileptic drug effects; Chap. 6 on other psychotropic medications). A final consideration is the use of recreational and addictive substances during pregnancy, such as alcohol (see Chap. 2), stimulants including nicotine and cocaine (see Chap. 3), and opiates and marijuana (see Chap. 4). As detailed in these chapters, children who have been exposed to various recreational drugs by their mothers demonstrate increased risk for poor academic and social-emotional outcomes.

Mechanisms of Impact on the Developing Child

Any disruption in the extended process of central nervous system development can affect structures or functions of the nervous system, with associated negative consequences for later developing functions and behaviors (Gilbert et al., 2010). Moreover, brain and neural development occurs in stages, with some time periods accounting for more critical development of specific functional systems (Costa et al., 2004; Jian'an et al., 2015; Stiles & Jernigan, 2010). Thus, neurotoxin exposure during different periods of development may yield very different symptoms or alterations in developmental trajectory (Costa et al., 2004; Jian'an et al., 2015; Miodovnik, 2011; Richardson, Goldschmidt, Larkby, & Day, 2015). Given the importance of communication across areas of the brain, abnormal development (or an interruption in normal development) of any one area of the brain for any reason leads to associated abnormalities at levels of functioning and can potentially affect multiple systems (Zillmer, Spiers, & Culbertson, 2008). Even for in utero exposure, timing is important.

In Utero Exposure

Effects on the fetus are likely associated with neuronal rapid cell proliferation, synaptic pruning, suppression, and neuronal cell death (i.e., apoptosis) as a result of exposure (Gilbert et al., 2010). In the early developmental stages in utero, rapid cell proliferation, differentiation, migration, and apoptosis contribute to the formation of cognitive structures and brain area specialization (Gilbert et al., 2010; Stiles & Jernigan, 2010). The rapid changes in neuronal development make in utero development especially vulnerable to the adverse effects of neurotoxins (Konijnenberg & Melinder, 2011; Rice & Barone, 2000). Research documenting negative effects has led to some pesticides, for example, being banned in the USA (e.g., dichlorodiphenyldichloroethylene [DDE]), although it is still being used in Mexico and other countries with adverse effects (Osorio-Valencia et al., 2015). Moreover, the potential for harm caused by neurotoxin exposure in utero is increased because the

blood–brain barrier is not fully developed until approximately 6 months of age, making the developmental periods before and immediately following birth especially vulnerable (Costa et al., 2004).

Childhood and Beyond

In addition to in utero exposure to neurotoxins, children and adults potentially are exposed to neurotoxins in the environment across the life span. Synaptic development, myelination, and pruning occur throughout the life span, but are especially prevalent in childhood and adolescence (Rice & Barone, 2000; Winneke, 2007). As such, children continue to be vulnerable to cognitive, behavioral, and emotional deficits that stem from neurotoxins. Disruption of synaptic pruning can adversely affect the amount of synaptic connections made and retained in the brain (Costa et al., 2004). Additionally, structural changes in grey and white matter continue into young adulthood and affect behavior (Stiles & Jernigan, 2010). Fine-tuning of neural functioning continues throughout the life span and is continuously affected by environmental contexts. It is the functioning of the neural system that sets the stage for behavior. As a result, neurotoxin exposure during these developmental periods can adversely affect brain development and manifest as various learning and developmental disorders (Rice & Barone, 2000). While there is minimal understanding of the long term effects of exposure, there is research to suggest impact on children, as well as adults.

Impact and Diagnostic Considerations

It is well established that various mechanisms can affect neural development negatively, and, as a result, alter the developmental trajectory of specific abilities, processes, and functions. Development of the brain and central nervous system starts in utero and continues through adolescence or early adulthood (Archer, Kostrzewa, Beninger, & Palomo, 2010). Individuals with neurodevelopmental disorders are those who have, or who are at risk for, limitations in some or all life activities as a result of impairments in the central nervous system (Mudrick, 2002; Spreen, Risser, & Edgell, 1995). The possible consequences and limitations range from mild to severe cognitive, sensory, motor, educational, and behavioral or psychological impairments (Mendola, Slevan, Gutter, & Rice, 2002), as well as physical effects. It is believed that developmental and learning disorders stem from disruption in brain development and function that results in negative effects on performance, ability, and achievement (Gilbert et al., 2010). Although some neural impairments may be apparent at birth, other effects are latent and do not appear until later in life or until a time where the effect is more noticeable, such as cognitive, attention, and emotional regulation deficits that

become more conspicuous as the academic and behavioral demands placed on the child increase (Costa et al., 2004; Lanphear, Wright, & Dietrich, 2005; Rice & Barone, 2000; Trask & Kosofsky, 2000; Weiss, 2000).

As already noted, different manifestations of neurodevelopmental problems are dependent on the time in development when exposure occurs (Archer et al., 2010; Costa et al., 2004; Konijnenberg & Melinder, 2011; Miodovnik, 2011; Riley & McGee, 2005; Trask & Kosofsky, 2000; Vajda et al., 2010). For example, there is growing evidence that exposure to PCBs in utero has negative consequences on cognitive abilities, executive functioning, and behavior; however, exposure to PCBs via breast milk in infancy was not found to be associated with cognitive or attentional impairments (Ribas-Fito, Sala, Kogevinas, & Sunyer, 2001; Williams & Ross, 2007). This importance of timing applies regardless of the neurotoxin.

The effects of neurotoxin exposure can be diffuse and affect all areas of function as well as global neurocognitive and neurobehavioral outcomes. Alternatively, the effects may be more focal and affect only specific functional systems and outcomes. For example, exposure to toxic chemicals and environmental agents has been linked to decreased intelligence, psychomotor and language deficits, inattention, aggression, and hyperactivity (Henn et al., 2012; Lin et al., 2013; Perera et al., 2006; Rice & Barone, 2000; Winneke, 2007). Regardless of whether the substance is alcohol, opiates, cocaine, or nicotine, the associated deficits in self-regulation, attentional control, overreactivity, and excitability have been noted (Bandstra, Morrow, Anthony, Accornero, & Fried, 2001; Bard, Coles, Platzman, & Lynch, 2000; Molitor, Mayes, & Ward, 2003). Overall, it is estimated that at least 3 % of developmental disorders may stem from exposure to neurotoxins, while 25 % may be attributed to the interaction between neurotoxins and genetics (National Research Council, 2000).

Moderating Factors

Maturation theory posits that functional asymmetry of the cerebral hemispheres develops with age, beginning at conception, and is influenced by environmental events and stimulation (Boles, Barth, & Merrill, 2007). Sonuga-Barke (2014) posited the critical role of environment with an emphasis on stress exposure and the social-ecological context. Stress and risk in this context is generally considered the social sphere (i.e., family interactions, resources) in which the individual functions. Known risk factors include low socioeconomic status, family violence, and low parental intelligence (Williams & Ross, 2007). With some forms of exposure, males seem to be more susceptible to effects as compared to females (e.g., Evans et al., 2015). As such, overall functioning is not only the result of the integrity of brain function, but that brain function is influenced by (and influences) environmental/social contexts. Hence, the context in which the individual functions is of importance.

Genetic Contribution

Genetic contributions may serve as a predisposition or diathesis that can be altered or modified for better or worse by environmental stimulation or exposure (Asbury, Wachs, & Plomin, 2005; Pennington et al., 2009; Schmidt, Polak, & Spooner, 2005). Due to genetic variation, people vary in their susceptibility to damage after exposure to neurotoxins (Gilbert et al., 2010; Meador et al., 2013). A child who already has a genetic predisposition to low intellectual functioning may face even more substantial cognitive deficits if exposed to a neurotoxin, compared to another child without that genetic predisposition. For women taking various medications research suggests increased vulnerability as a function of genotype (Meador, Baker, Cohen, Gaily, & Westerveld, 2007). Additionally, neurotoxins have been found to alter gene expression (Gilbert et al., 2010; Landrigan et al., 2012). Specifically, these gene modifications can result in deficits in cognitive and developmental function (Gilbert et al., 2010). Furthermore, some evidence suggests that disorders such as autism, attention deficit hyperactivity disorder, and other developmental and behavioral disorders stem from a combination of genetic factors and environmental triggers, including neurotoxin exposure (Archer et al., 2010; Konijnenberg & Melinder, 2011; Landrigan et al., 2012; Riccio, Sullivan, & Cohen, 2010). Similar to the interactions seen between neurotoxins and environmental factors, genes can shape the likelihood and expression of neural damage.

Stimulation

While neuropsychology embraces the idea that the integrity of the neurological system determines behavior, there is evidence that environmental factors, including failure to stimulate particular areas of the brain, will impact functioning (Zillmer et al., 2008). Throughout childhood and adolescence, there are critical, specific windows of time where certain developmental events must occur to have the most impact (Mundkur, 2005). If the child is not exposed to the developmental experience during this time period, they may not develop normally or the critical experience will have a reduced effect. For example, if a child hears very little spoken language in the first few years of life, they may have underdeveloped language abilities, which they may be unable to recover from or improve upon (Mundkur, 2005).

Additionally, environmental factors can increase or diminish the scope of the damages caused by neurotoxin exposure (Cory-Slechta, 2005; Cory-Slechta et al., 2013; Gilbert et al., 2010; Weiss, 2000). For example, negative environmental experiences, such as stress associated with low socioeconomic status or abuse, have been found to exacerbate the effects of neurotoxin exposure (Cory-Slechta, 2005; Cory-Slechta et al., 2013; Konijnenberg & Melinder, 2011). On the other hand, positive experiences and environmental components, such as higher socioeconomic status, enrichment programs, and parental support can attenuate neurotoxic damage (Cory-Slechta et al., 2013). Humans may be exposed to neurotoxins across the life span, while the toxicity and manifestations of the exposure are determined by a variety of

negative and positive environmental factors (Cory-Slechta, 2005; Trask & Kosofsky, 2000; Weiss, 2000). Overall, whether neurotoxin exposure occurs or not, stress and environmental factors play a large role in the development of a variety of cognitive and behavioral disorders. Thus, two different children exposed to the same neurotoxin may experience divergent outcomes based on the interactions among these genetic and environmental factors.

Considerations for Prevention and Intervention

When introduced prenatally, exposure may be time limited, yet these substances can have both indirect and direct effects on children across their lifetime. At the same time, there is continued risk across the life span of exposure. Research findings have led to some changes in environmental policy as well as health care. For example, many pesticides are no longer considered acceptable and modifications to air exchange systems are being made. With increased knowledge of the effects of drugs on the developing fetus, there is considerable caution exercised with regard to the use of medications of any type by pregnant women (Bercovici, 2005; Meador, 2002), as well as decreased exposure to environmental toxins of the mother.

Due to neuroplasticity, it is important that deficits due to neurotoxic exposure are detected early in life. Neuroplasticity refers to the brain's ability to change structurally and functionally in response to experience (Mundkur, 2005; Rice & Barone, 2000). Early experience can have a large impact on the development and pruning of synapses, which can affect memory, cognition, and behavior (Mundkur, 2005). Early detection of brain and nervous system deficits is imperative so that intervention effects can be maximized due to the high neuroplasticity of the child brain (Mundkur, 2005; Quattlebaum & O'Connor, 2012; Westrup, 2013). The sooner the interventions are implemented, the more the functional and behavioral gains made and sustained for a longer period of time (Quattlebaum & O'Connor, 2012; Westrup, 2013).

Early intervention is also essential due to the economic impact of developmental, cognitive, and behavioral disorders (Bales, Boyce, Heckman, & Rolnick, 2006; Quattlebaum & O'Connor, 2012; Weiss, 2000). According to a study by Landrigan, Schechter, Lipton, Fahs, and Schwartz (2002), the annual cost in the USA of lead poisoning induced cognitive impairments, intellectual disabilities, autism, and cerebral palsy stemming from environmental pollutants has been estimated to be $50 billion. These estimates do not even include the costs of neurotoxic exposure to drugs and medications or the annual expenditures for other deficits that stem from neurotoxin exposure (e.g., fetal alcohol syndrome). Cognitive and intellectual impairments can result in a reduced workforce, higher medical costs, and a greater need for enrichment programs in schools and communities, all of which can create an economic burden (Weiss, 2000). Additionally, behavioral and psychological deficits can increase crime and incarceration rates and medical expenditures (Weiss, 2000). These global economic costs do not even consider the individual monetary costs to the family or the emotional and psychological toll that neurodevelopmental, cognitive, and behavioral deficits can produce.

Conclusion

Levy (2015) argued that carbon monoxide pollution and associated effects on neurodevelopment constitute a public health concern. This continues to be the prevalent assertion across disciplines of psychology, medicine, and public health and reflects both increased awareness of neurotoxins and increased use of substances, prescribed and otherwise. In the past 30 years, there has been continued advancement in technology with increased ability to examine brain structures using multiple methods (Williams & Ross, 2007); however, what is known about the effects of toxic exposure is still limited. With advanced capability for functional imaging methods and consideration of the physical and chemical environment, there is hope for greater insight and information about the potential risks. At the same time, this increased technology will yield a better understanding of brain behavior in relation to neurodevelopmental disorders (Berkelhammer, 2008). Additionally, with hundreds of thousands of manmade and natural chemicals, future research must focus on identifying potential neurotoxins and their effects on development (Goldman et al., 2004; Miodovnik, 2011; Szpir, 2006; Trask & Kosofsky, 2000). Greater identification of neurotoxic chemicals may aid in decreasing the incidence of neurodevelopmental, behavioral, and psychological disorders that stem from neurotoxic exposure and reduce economic costs.

Another area for future research includes investigating the environmental and genetic factors that can either increase or ameliorate the effects of neurotoxin exposure (Trask & Kosofsky, 2000). These features can aid in intervention and maximize outcomes, as well as provide targets for preventive measures, such as parent training. Furthermore, as noted by Sonuga-Barke (2014), what continues to be evident is the lack of identified developmental pathways that lead to pathology or disorder. Greater knowledge about the specific effects of various neurotoxins on the developing brain can aid in the creation of targeted interventions (Trask & Kosofsky, 2000; Williams & Ross, 2007). Moreover, there is a need for research that centers on identifying evidence-based approaches for early intervention for children (or adults) exposed to toxins as opposed to waiting until the effects fully manifest. More targeted and effective interventions can reduce the economic costs of neurotoxin exposure and maximize human potential. Although research efforts move the fields of cognitive and social neuroscience forward, there is still a long way to go. The remainder of this volume explores the current state of knowledge regarding the academic and psychosocial outcomes associated with neurotoxin exposure, and highlights current gaps in the literature that will set the stage for future research.

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