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# A hypothesis about how early developmental methylmercury exposure disrupts behavior in adulthood

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ABSTRACT

Events that disrupt the early development of the nervous system have lifelong, irreversible behavioral consequences. The environmental contaminant, methylmercury (MeHg), impairs neural development with effects that are manifested well into adulthood and even into aging. Noting the sensitivity of the developing brain to MeHg, the current review advances an argument that one outcome of early MeHg exposure is a distortion in the processing of reinforcing consequences that results in impaired choice, poor inhibition of prepotent responding, and perseveration on discrimination reversals (in the absence of alteration of extradimensional shifts). Neurochemical correlates include increased sensitivity to dopamine agonists and decreased sensitivity to gamma-aminobutyric acid (GABA) agonists. This leads to a hypothesis that the prefrontal cortex or dopamine neurotransmission is especially sensitive to even subtle gestational MeHg exposure and suggests that public health assessments of MeHg based on intellectual performance may underestimate the impact of MeHg in public health. Finally, those interested in modeling neural development may benefit from MeHg as an experimental model.



Nervous system development requires a delicately balanced chemical environment, one that can be disrupted by exogenous influences such as drugs or environmental contaminants. Drug exposure is voluntary in a sense, so its epidemiological pattern is restricted to intentional users. In contrast, individuals have little control over exposure to environmental contaminants when they are found in the air or the food or water supply. Lead presents a well-studied example. Because of its presence in the air and drinking water, everybody was exposed to lead in the 20th century, many at levels that, by current standards, were quit high. A striking pattern has been noted, in which an increase and then decrease in intellectual disabilities and violent crime tracked the rise and fall in environmental lead, respectively (Nevin, 2009; Reyes, 2007). The story of lead's addition and removal from the environment had been hailed as one of the most important Public Health successes of the 20th century (Domestic Public Health Achievements Team, 2011), and the argument in support of its removal was based on its behavioral toxicity (Davis et al., 1993; Gilbert and Weiss, 2006; Schwartz, 1994).

Methylmercury (MeHg), like lead, is a ubiquitous neurotoxicant. Everybody who eats fish is exposed to MeHg (Mahaffey, 2004). It is found in the highest concentration in large, long-lived predatory fish, including several marine species and fresh-water fish from contaminated water bodies. The broader lessons learned from lead apply to MeHg, even if the pattern of deficits is quite different. Effects of low-level exposure can be detected only with the appropriate behavioral (in animals) or psychometric (in humans) evaluations, but otherwise the effects will rarely appear as overt morphological changes. Because of long half-lives of elimination from the brain, there is accumulation with continued exposure, the most common scenario. The consequent nervous system damage has behavioral manifestations that are often silent, significantly delayed, and irreversible (Rice, 1996a; Weiss et al., 2002; Weiss and Reuhl, 1994). The darkest lesson, which came from Japanese experience with MeHg (Smith and Smith, 1975), is that the developing nervous system is especially vulnerable (Harada, 1995, 1968).

In the present review, we argue that MeHg exposure during rodent gestation, a developmental period that approximately models human neural development during the first two trimesters of gestation (Bayer et al., 1993; Rice and Barone, 2000), has long-lasting behavioral consequences that appear in adulthood and, in some cases, may not appear until aging. Such exposure

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produces a behavioral rigidity that appears as perseveration in discrimination reversals, disrupts the acquisition of choice as environmental demands change, and can be linked to, and may be caused by, an elevated impact of reinforcing consequences. Neural correlates include increased sensitivity to dopamine agonists, diminished sensitivity to inhibitory gamma-aminobutyric acid (GABA) agonists, and raise the hypothesis that the prefrontal cortex is especially sensitive to this developmental neurotoxicant. Since such a pattern of behavior change is only weakly correlated with changes in IQ scores, these effects suggests that a reliance on tests of academic achievement or IQ as a measure of altered development may underestimate MeHg's developmental neurotoxicity. From a scientific perspective, these data suggest that MeHg may provide an excellent experimental model by which early cortical developmental might be studied.

## 1. Why study methylmercury in the laboratory?

Fish are the sole source of MeHg exposure, and this presents a significant public health dilemma because of the well-known nutritional benefits of fish consumption (Oken et al., 2012; Ström et al., 2011). There is an extensive literature comparing adverse effects of MeHg with nutritional benefits, and the common conclusion is that large, long-lived predatory fish should be avoided (Mahaffey et al., 2011; Oken et al., 2012; Ström et al., 2011). Many of citations here represent studies of human populations, some of heavy fish consumers explicitly and others of broader populations. These investigations are important but they are necessarily correlational, and therefore contain the confounding variables and ambiguities about causality embedded in epidemiological studies. To tease out cause-effect relations, our laboratory has directly compared the benefits of fish nutrients selenium (Se) and docosahexaenoic acid (DHA) under controlled experimental conditions using prenatal and adult-onset MeHg exposure (Newland and Paletz, 2000; Newland et al., 2008).

## 2. The developmental window is important

The consequences of MeHg exposure depends critically upon the developmental period during which exposure occurs, and this is one of many reasons that it can serve as a model of disrupted neural development. Adult-onset exposure produces sensorimotor deficits and accumulation of mercury in, and damage to, the cerebellum and sensory and motor regions of the cortex (Castoldi et al., 2003; Gilbert and Maurissen, 1982; Harada, 1995; Heath et al., 2010). In contrast, the entire neocortex is vulnerable to pre- and perinatal MeHg exposure (Eto, 1997), suggesting that effects of developmental exposure could extend into domains mediated by that region. Moreover, exposure levels that produce toxicity are many-fold lower if exposure occurs during early development (Costa et al., 2004). For example, we have shown that chronic, adult-onset exposure produces overt neurological signs after about a year of exposure to 5 ppm of MeHg in drinking water, but not 0.5 ppm (Heath et al., 2010). In contrast, maternal exposure for only three weeks of gestation to 0.5 ppm produced subtle but irreversible effects in the adult and aging offspring, even though by all cage-side observations these animals appeared perfectly healthy. That is, exposed animals showed no neurological signs, weight loss, reproductive toxicity, or changes in physical appearance even as they showed significant, if subtle, neurotoxicity as adults (Newland, 2012; Newland et al., 2008). Such sensitivity has been reported with auditory, visual, and somatosensory deficits in monkeys (Rice, 1996b) and in behavioral studies with rodents (Bourdineaud et al., 2008; Bourdineaud et al., 2011; Castoldi et al., 2008; Liang et al., 2009; Montgomery et al., 2008; Newland et al., 2008; Onishchenko et al., 2008; Weiss et al., 2005) and are linked to disturbances in the development of the dopamine systems (Rasmussen and Newland, 2001; Reed and Newland, 2009).

Some of the behavioral effects of gestational exposure that we have reported, such as response perseveration, were affected at the lowest exposure level examined, 0.5 ppm in drinking water, yielding about 40 μg/kg/day of Hg as MeHg. This dosing regimen produced brain mercury concentrations equivalent to those experienced by many people (Newland et al., 2008). It is also relevant to public-health policy regarding MeHg exposure. The exposure level considered to be unlikely to be harmful is established by public-health agencies such as the Environmental Protection Agency or the World Health Organization after reviewing human and animal studies. These agencies extrapolate from experimental models using laboratory animals, which typically use exposures that exceed those experienced by humans, to estimate human daily intakes that are unlikely to present a significant risk. Using the Environmental Protection Agency's approach to extrapolation, the 40 μg/kg/day level described in our experimental model translates into a "reference dose" (a level unlikely to be harmful) of 0.4 ug/kg/day, which is quite close to the current reference dose of 0.1 μg/kg/day that was established in 1997 (Keating et al., 1997). This leaves little room for error. Thus, based on brain concentrations and estimated acceptable daily exposure levels, this dosing regimen models human exposure.

## 3. Methodological considerations

Rodents give birth to multiple offspring, which means that littermates experience the same uterine environment and, of course, half of their genes. When examining the impact of gestational exposure to a chemical, drug, or toxicant, this also means that assigning all same-sex littermates to a single treatment group confounds prenatal experience and genetic background with exposure. Because of this, it is poor practice to assign littermates to the same experiment, but the presence of multiple births generate creates an efficient and sensitive experimental design: assign littermates to separate studies. The litter becomes the statistical unit, but each litter can contribute to multiple experiments. Therefore, only one same-sex pup is assigned to a single experiment, although when examining sex differences some investigators treat male-female siblings as a repeated measure (Maurissen, 2010; Spyker and Spyker, 1977).

Human MeHg exposure is almost exclusively through fish consumption (Mahaffey, 2004), raising a scientific and regulatory dilemma because fish are also the source of a number of important nutrients, including selenium (Se) and the *n*-3 polyunsaturated fatty acid, DHA (Budtz-Jorgensen et al., 2007; Mahaffey et al., 2011; Rice, 2008). Our laboratory was interested in whether nutrients found in fish influenced the impact of MeHg exposure during gestation. To address this issue, we exposed pregnant rats to one of three MeHg levels, 0, 0.5 or 5 ppm in their drinking water using a full factorial design (Fig. 1). Half of the rats consumed a diet rich in a nutrient (Se or DHA) and half consumed a diet that was low. In each case, the nutrient level was within the bounds of what was recommended for laboratory rodents (National Research Council, 1995). This approach allowed us to determine whether MeHg was toxic under both dietary conditions, as would be revealed in a main effect of MeHg. A main effect of diet allowed us to identify potential benefits of Se or DHA and an interaction would reveal protection by these nutrients.

The distribution of rats to experiments is illustrated in the top left cell. The female breeders continued exposure so we could examine chronic, adult-onset exposure. Offspring were assigned to different experiments, so each experiment had only one