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The threat of global mercury pollution to bird migration: potential mechanisms and current evidence

Chad L. Seewagen[1]

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Abstract
Mercury is a global pollutant that has been widely shown to adversely affect reproduction and other endpoints related to fitness and health in birds, but almost nothing is known about its effects on migration relative to other life cycle processes. Here I consider the physiological and histological effects that mercury is known to have on non-migrating birds and non-avian vertebrates to identify potential mechanisms by which mercury might hinder migration performance. I posit that the broad ability of mercury to inactivate enzymes and compromise the function of other proteins is a single mechanism by which mercury has strong potential to disrupt many of the physiological processes that make long-distance migration possible. In just this way alone, there is reason to expect mercury to interfere with navigation, flight endurance, oxidative balance, and stopover refueling. Navigation and flight could be further affected by neurotoxic effects of mercury on the brain regions that process geomagnetic information from the visual system and control biomechanics, respectively. Interference with photochemical reactions in the retina and decreases in scotopic vision sensitivity caused by mercury also have the potential to disrupt visual-based magnetic navigation. Finally, migration performance and possibly survival might be limited by the immunosuppressive effects of mercury on birds at a time when exposure to novel pathogens and parasites is great. I conclude that mercury pollution is likely to be further challenging what is already often the most difficult and perilous phase of a migratory bird's annual cycle, potentially contributing to global declines in migratory bird populations.

Keywords Methylmercury · Migratory · Navigation · Long-distance flight · Stopover · Oxidative stress · Immunocompetence

Introduction

Mercury has become a ubiquitous, global pollutant over the past two centuries as a result of fossil fuel combustion, artisanal gold mining, and other human activities (Driscoll et al. 2007, 2013). The ability of atmospheric mercury to travel long distances before entering aquatic and terrestrial systems via precipitation or cloud water allows mercury to contaminate areas far away from its site of origin (Selin 2009; Driscoll et al. 2013). This widespread atmospheric deposition, combined with local point-source releases of mercury into air, soil, and water is exposing humans and wildlife alike to a toxin that is capable of having myriad adverse health effects (Wolfe et al. 1998; Selin 2009; Driscoll et al. 2013).

Like most contaminants, mercury generally poses the greatest risk to large-bodied, predatory animals that consume biomagnified concentrations in their prey. The most harmful and bioavailable form of mercury, methylmercury (MeHg), is most readily formed in aquatic ecosystems, placing animals that are both predatory and aquatic (or have diets of largely aquatic origin) at even greater risk (Scheuhammer et al. 2007). Dosing experiments and field studies determined toxicity thresholds and the impacts of mercury to such species decades ago, while animals at lower trophic positions and many associated with terrestrial habitats were largely overlooked for having little potential to accumulate harmful levels (Seewagen 2010). In more recent years, however, songbirds (Passeriformes) and other animals occupying low positions within food webs have been increasingly observed to have much higher mercury levels than once expected. This includes small songbirds that have invertebrate-based diets and live in terrestrial systems with no known current or historical point-source contamination

✉ Chad L. Seewagen
cseewagen@greathollow.org

[1] Great Hollow Nature Preserve & Ecological Research Center, 225 Route 37, New Fairfield, CT, USA

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(e.g., Rimmer et al. 2005, 2010). Captive dosing studies and field studies of songbirds have recently determined that at the upper range of the levels observed in the wild, mercury can exert many of the same adverse effects as it does on piscivorous waterbirds and other large-bodied non-passerines, including but not limited to altered endocrine and immune system function, behavioral impairments, and reduced reproductive success (Whitney and Cristol 2017).

Nearly all research on the effects of mercury on both passerine and non-passerine birds has focused on survivorship and endpoints related to reproduction and health despite the fact that the many negative effects of mercury seen in these contexts could also affect migration (Seewagen 2010). Migration may be a period of particularly heightened exposure to mercury as a result of hyperphagic feeding during stopovers (Klaassen et al. 2012) and protein catabolism during flight (Seewagen et al. 2016). At this same time, migrants are faced with a physically and cognitively demanding task that requires a complex interplay of physiological processes and pushes them to the limits of their abilities. Yet few studies have directly or indirectly investigated the effects of mercury on migrating birds, or considered how the negative effects of mercury on physiological processes and behaviors that are important to reproduction and health might also have important consequences for migration.

Here, I explain how some of the physiological and histological effects of mercury on non-migrating birds and non-avian vertebrates represent potential mechanisms by which mercury threatens to disrupt some of the most fundamental elements of migration, including navigation, endurance flight, oxidative balance, stopover refueling, and disease resistance. I focus on long-distance, night-migrant songbirds, but most of the potential mechanisms are relevant to any birds that engage in a form of migration that is energetically demanding and requires accurate orientation and navigation. Approximately 19% of the extant bird species on Earth are migratory, and among all birds, migratory species have experienced disproportionately steep population declines over the past century (Kirby et al. 2008; NABCI 2016). For the reasons discussed herein, I believe that mercury is likely to be further challenging what is already considered to be the most difficult and dangerous phase of a migratory bird's annual cycle (Sillett and Holmes 2002, Klaassen et al. 2014), potentially contributing to the downward population trends of many of the world's migratory bird species.

Orientation and navigation

At its simplest, successful migration between breeding and wintering areas requires birds to fly in the proper direction, for the proper distance. Many species of songbirds migrate at night, navigating by cues provided by Earth's magnetic fields, the setting sun, stars, and possibly environmental odors (Holland et al. 2009; Chernetsov 2016). Nocturnal migrants can perceive Earth's magnetic fields through specialized sensory pathways that involve a magnetite-based detector in the upper beak and a light-dependent radical pair process that occurs in the eyes. Magnetite in the upper beak is thought to transmit information on magnetic intensity to the brain through the ophthalmic branch of the trigeminal nerve and provide birds with a sense of location, but not direction (Mouritsen and Hore 2012). In contrast, photoexcitation of cryptochrome molecules in the eyes of night-migrants creates a radical pair process (see Ritz et al. 2000) through which birds are believed to visually perceive the inclination of magnetic fields and thereby distinguish north from south (Mouritsen et al. 2005; Stapput et al. 2008). The signal from the photoreceptors is processed by an area of the brain known as Cluster N, which is a specialized component of the thalomofugal pathway and located in the hyperpallium and mesopallium (Mouritsen et al. 2005; Heyers et al. 2007; Mouritsen and Hore 2012). Night-migrants are not able to orient properly when radical pair formation in the eyes or the processing of that information by the brain is disrupted (Stapput et al. 2008; Zapka et al. 2009). As such, radical pair-based visual sensing of magnetic fields is a primary magnetic orientation mechanism on which night-migrant songbirds rely to reach their destination.

The hippocampus, which largely controls spatial memory in birds, is another region of the brain that is involved in navigation (landmark-based rather than magnetic) by night-migrants as well as diurnal homing pigeons (*Columba livia domestica*) (Strasser et al. 1998; Bingman and Cheng 2005). Evidence for this includes observations that within the same species, migratory subspecies have larger hippocampi and more hippocampal neurons, and perform better at spatial memory tasks than non-migratory subspecies (Cristol et al. 2003; Pravosudov et al. 2006). Also, within individual birds, migration experience may increase hippocampus volume and the number of neurons in the hippocampus. Adult night-migrant songbirds that have migrated before and therefore learned important landmarks along their route have a larger hippocampus and more hippocampal neurons than juveniles of the same species that have never migrated before (Healy et al. 1996). Similar experience-driven increases in hippocampus size have been documented in homing pigeons (Cnotka et al. 2008). Pigeons also have elevated neuronal activity in the hippocampus while they are homing, and numerous lesion studies have shown that damage to the hippocampus significantly impairs their homing ability (Shimizu et al. 2004).

Navigation is a complex cognitive behavior that is controlled by these phenotypically flexible brain regions and biophysical processes, some of which are unique to birds. It follows that any disruption of the mechanisms underlying navigation can be potentially disastrous to a migrant. MeHg is a powerful neurotoxin that readily crosses the blood-brain barrier, and at high enough concentrations, has been observed to cause demyelination, axon degeneration, and lesions in bird brains (Heinz and Locke 1976; Evans et al. 1982). Neurotransmitter function is sometimes also compromised (reviewed by Whitney and Cristol 2017). Concentrations of MeHg in bird brains are often highest in the cerebellum, the region responsible for motor learning and flight mechanics, but MeHg can sometimes reach its highest concentrations in the cerebrum (Hamilton et al. 2011), where Cluster N and the hippocampus are located. Additionally, there is evidence from mice that the mammalian hippocampus, which is homologous to the avian hippocampus (Sherry and Hoshooley 2007), is particularly susceptible to MeHg accumulation compared to other areas of the brain (Fujimura et al. 2009). It is currently unknown whether environmentally relevant amounts of MeHg are capable of damaging Cluster N or the hippocampus to an extent that would impair a bird's ability to migrate on course. However, Swaddle et al. (2017) found that zebra finches (*Taeniopygia guttata*) dosed with environmentally relevant levels of MeHg and tasked with finding hidden food performed poorly compared to control birds. Recalling the locations of stored or hidden food is a form of spatial memory in birds that is also controlled by the hippocampus (Sherry and Hoshooley 2007), which suggests that MeHg dosing partially compromised the functionality of this region of the zebra finches' brain (Swaddle et al. 2017). Moye et al. (2016) found MeHg to reduce the homing performance of pigeons, which also suggests some impairment of hippocampal function. More studies are needed to understand the effects of MeHg on the avian hippocampus as well as Cluster N, and determine whether wild songbirds are exposed to MeHg levels that are capable of impacting the brain circuits that are critical to navigation.

While little is known about the effects of MeHg on the areas of the avian brain that are involved in navigation, even less is known about the effects of MeHg on the eyes of birds. Before the brain of a night-migrant can process geomagnetic information from the visual system, the eyes must first properly react to stimuli and transmit signals to the thalomofugal pathway. The visual magnetoreception system begins with the excitation of retinal photoreceptor molecules by dim light in the blue-green spectrum, which forms radical pairs. Radical pair formation in different parts of the retina in relation to the bird's orientation to magnetic fields is thought to generate the visual signal that allows birds to "see" the magnetic fields (Ritz et al. 2000; Mouritsen et al. 2004). Cryptochromes, the primary molecules in the eye that are believed to be involved in light-dependent magnetoreception in birds, are concentrated in the ganglion cells, large displaced ganglion cells, and photoreceptors (rods and cones). Cryptochrome expression and neuronal activity are particularly high in large displaced ganglion cells during magnetic orientation (Mouritsen et al. 2004). Any physical damages to these structures of the retina or interference with neurotransmission from the retina to the brain could therefore be expected to interfere with the radical pair-based navigational mechanism of birds.

MeHg is able to cross the blood-retina boundary. It accumulates in the retina and remains there for long periods of time relative to other tissues (Warfvinge and Bruun 1996; Fox 2015). Although the effects of this on the eyes and vision of birds do not appear to be known (aside from gross deformities in embryos and hatchlings exposed to high concentrations), the visual systems of vertebrates in general are considered to be highly sensitive to MeHg (Mela et al. 2012; Fox 2015). Wide-ranging and immediate effects of MeHg on vision have been documented in fish, amphibians, and mammals, including humans. For example, several studies have shown impaired color vision, reduced contrast sensitivity, and visual field constriction in non-human primates dosed at high levels (e.g., Burbacher et al. 2005) and in people with high degrees of occupational exposure to mercury (e.g., Canto-Pereira et al. 2005; Ventura et al. 2005). Environmentally relevant levels of MeHg have been observed to cause cellular degeneration, structural damages to membranes, morphological changes in photoreceptors, peroxidative damage, and changes in neurotransmitter activity in the eyes of vertebrates (Mela et al. 2012; Pereira et al. 2016).

Nighttime (scotopic) vision is particularly affected by MeHg because rods can fail to properly respond to light after exposure to mercuric ions (Evans and Garman 1980; Tessier-Lavigne et al. 1985; Fox 2015). Histopathological effects that environmentally relevant concentrations of MeHg have been observed to have on the rods of vertebrate eyes include cellular deterioration and morphological changes in the inner and outer segments, and discontinuity of the disc membrane with the outer segment plasma membrane (Mela et al. 2012). Resulting decreases in rod receptor potential and scotopic sensitivity have been observed in fish (Hawryshyn et al. 1982), amphibians (Fox and Sillman 1979), and mammals (Fox 2015), and therefore, can be expected to occur among avian taxa as well. Scotopic vision is of course critical to birds that are active at night, and cryptochrome-containing rods are likely to be a major site of radical pair formation during magnetic compass orientation (Solov'yov et al. 2010). It is therefore conceivable that MeHg can impede the light-dependent

magnetoreception process of night-migrants from the very first stage.

Collectively, the detrimental effects of MeHg on both the brain and the eyes of other vertebrates, along with a recent finding that mercury can interfere with magnetic alignment in turtles (Landler et al. 2017), provide reason to believe that MeHg might impair multiple aspects of the navigational system of migratory birds. As with any endpoint, the important question is whether such effects on birds could result from exposure to environmentally relevant levels of mercury. This is an entirely unstudied area of ecotoxicology and should be a research priority given the fundamental significance of navigation to migration.

Flight endurance

Migration for most songbirds and many other species of birds consists of multiple long-distance flights separated by stopovers of one or more days in between. These long-distance, non-stop flights routinely last several hours (Bowlin et al. 2005; DeLuca et al. 2015), requiring birds to sustain a high level of aerobic activity for long periods of time, and with exclusively endogenous sources of energy, nutrients, and water (McWilliams et al. 2004). Birds have evolved unique physiological abilities to meet the extreme energetic demands of migration. Chief among them is the ability to fuel high intensity aerobic exercise with fatty acids rather than carbohydrates, unlike mammals (McWilliams et al. 2004; Guglielmo 2010). Fat yields 8 to 10 times the energy of carbohydrates and protein per unit of wet mass, making it a far more economical fuel substrate for a bird to carry in flight (Jenni and Jenni-Eiermann 1998). Yet, the insolubility of fatty acids makes them difficult to transport from adipose tissue through the circulatory system and into the myocytes of flight muscles for use as energy (McWilliams et al. 2004; Guglielmo 2010). To overcome this obstacle, migrating birds substantially upregulate key enzymes and transport proteins that can mobilize and deliver fatty acids at the rate necessary to power long-distance flight (Egeler et al. 2000; McWilliams et al. 2004; McFarlan et al. 2009; Guglielmo 2010). This ability to sustain endurance exercise with extramuscular fatty acids sets birds apart from all other vertebrates, except possibly migratory bats (Guglielmo 2010).

To understand the potential impact of mercury on the endurance of migrating birds, first consider the primary steps in the fatty acid oxidation process and the important role of catabolic enzymes and transport proteins. The utilization of fatty acids to fuel migratory flights begins with the mobilization of triacylglycerol (TAG) from the adipocytes of a bird's fat stores. The TAG is hydrolyzed into non-esterified fatty acids (NEFA) by the enzyme hormone sensitive lipase (HSL), which are then bound and transported through the circulatory system and to the working muscles by plasma albumin. Very low-density lipoprotein (VLDL) produced by the liver and hydrolyzed by lipoprotein lipase (LPL) provides muscles with additional exogenous NEFA. At the sarcolemma, two transport proteins that are heavily upregulated during migration, plasma membrane fatty acid binding protein (FABP-pm) and fatty acid translocase (FAT/CD36), carry the NEFA across the membrane and into the cytosol. They join additional NEFA that are derived from the hydrolysis of intracellular TAG droplets. The NEFA are transported through the cytosol by heart-type fatty acid binding protein (H-FABP) and converted to acyl-CoA by long-chain acyl-CoA synthetase (LCACS). The acyl-CoA is subsequently converted to acyl-carnitine by carnitine acyl transferase (CAT) and then crosses the mitochondrial membrane, where it is converted back to acyl-CoA before entering the beta oxidation pathway. Finally, acetyl-CoA produced through the beta oxygen pathway is catabolized in the citric acid cycle, ultimately yielding energy in the form of ATP (McWilliams et al. 2004; Weber 2011). Meanwhile, the heightened amount of oxygen needed for these aerobic reactions is transported by hemoglobin through the bloodstream to the working muscles and then carried from the sarcolemma to the mitochondria by myoglobin (Wittenberg and Wittenberg 1989). Limitations imposed on any of these biochemical processes and the molecules involved might compromise the ability of birds to engage in the long bouts of endurance exercise that are required to successfully travel the thousands of kilometers that often separate breeding and wintering grounds.

The effect of MeHg on the physiological processes involved in fatty acid oxidation during high intensity exercise in birds has not been investigated directly or in the context of flight endurance. However, MeHg and another highly toxic form of mercury (mercury chloride) have been found to alter the expression of peroxisome proliferator-activated receptors (PPARs; Kawakami et al. 2012; Richter et al. 2014), which are the primary regulators of lipid metabolism in birds and other vertebrates (Feige et al. 2006; Weber 2011). Among the many aspects of lipid metabolism regulated by PPARs is mitochondrial fatty acid oxidation, including the expression of key enzymes involved in the process (Feige et al. 2006; Weber 2011). Along with this, the propensity of MeHg to inactivate enzymes and degenerate other proteins by binding to thiol groups (Yadetie et al. 2013; Marasco and Costantini 2016; Ynalvez et al. 2016) raises concern that MeHg could limit a bird's capacity to mobilize, transport, and oxidize extramuscular fatty acids at a sufficiently rapid rate to fuel migratory flights.

One indication of this is that plasma proteins, and plasma albumin in particular, have been observed to significantly decrease in birds in response to high (Spalding et al. 2000a;

Hoffman et al. 2005) and environmentally relevant (Sepúlveda et al. 1999; Kenow et al. 2007) MeHg exposure. As the primary protein responsible for the delivery of fatty acids to the working muscles, significant reductions in plasma albumin could diminish a migrating bird's overall capacity to rapidly catabolize fat (Jenni-Eiermann and Jenni 1992; Jenni and Jenni-Eiermann 1998). Whether environmentally relevant levels of MeHg can reduce plasma albumin concentrations greatly enough to have an appreciable effect on a migrant's ability to deliver fatty acids from adipose tissue to the working muscles at the necessary rate is unknown, however, and in need of study.

Beyond this potential limitation on the delivery of fatty acids to the muscles, the effects of MeHg on proteins could also limit the subsequent uptake of those fatty acids by the myocytes. Of the three primary stages of exogenous fatty acid utilization (mobilization, transport, oxidation), transport of NEFA across the sarcolemma is considered the most rate-limiting step affecting an animal's capacity to power working muscles with fat (McWilliams et al. 2004). As such, reductions in FABP-pm and FAT/CD36 may be expected to have the greatest potential to deleteriously affect fatty acid utilization by, and the endurance of, migrating birds. I am unaware of any research to examine direct effects of MeHg on these critical transport proteins. However, PPARs regulate the expression of genes that control FABP-pm and FAT/CD36 (Feige et al. 2006), and alterations to PPAR expression caused by mercury (Kawakami et al. 2012; Richter et al. 2014) might therefore interfere with the substantial upregulation of FABP-pm and FAT/CD36 that is required for migration. In mice, mercury chloride was found to reduce transcription of FAT/CD36 mRNA (Kawakami et al. 2012), further raising the possibility of an adverse effect of MeHg on FAT/CD36 in birds.

Once fatty acids have been transported across the sarcolemma, H-FABP is needed to transport them through the cytosol, and LCAS and CAT are needed to convert them to acyl-CoA for entry into the beta oxidation pathway in the mitochondria. Any inactivation or reduced expression of this transport protein and the enzymes that enable fatty acids to be oxidized by the mitochondria would also potentially limit a bird's ability to utilize fatty acids to support migratory flight. While effects of MeHg on H-FABP, LCAS, and CAT in particular appear to be unknown, environmentally relevant MeHg exposure in fish has been found to inactivate acyl-CoA dehydrogenase enzymes that are involved in beta oxidation (Yadetie et al. 2013). Disruptions of mitochondrial processes by MeHg, including decreased mitochondrial oxidation and ATP production, have also been observed in other studies of fish as well as rodents (Stohs and Bagchi 1995; Gonzalez et al. 2005; Cambier et al. 2009), which suggests that the oxidation stage of extramuscular fatty acid utilization in migrating birds is likely vulnerable to effects from MeHg. Yet another way in which MeHg might limit fatty acid oxidation rate is by reducing the amount of oxygen available to the mitochondria. Birds elevate hematocrit and hemoglobin levels during migration to meet the increased oxygen demands of long-distance flight (Landys-Ciannelli et al. 2002; Morton 2002; Krause et al. 2016). Mercury is a heme inhibitor, and birds exposed to environmentally relevant and high levels have been found to have reduced concentrations of hemoglobin in their blood (as measured directly or inferred from hematocrit volume; Hoffman and Heinz 1998; Spalding et al. 2000a; Henny et al. 2002; Hoffman et al. 2009). This will constrain the oxygen carrying capacity of a bird and possibly its ability to engage in prolonged periods of high-intensity aerobic exercise, such as migratory flights (Seewagen 2010).

For all of these reasons, it is clear that MeHg has the potential to hinder the endurance of migrating birds by interfering with the delivery and uptake of both oxygen and fuel. Indeed, there are recent indications of this from MeHg-dosed yellow-rumped warblers (*Setophaga coronata*) that had shorter flight durations in a wind tunnel than control birds (Ma et al. 2018a) and zebra finches that were found to have significantly reduced peak metabolic rates as a result of environmentally relevant MeHg dosing (A.R. Gerson, D. A. Cristol, and C.L. Seewagen, unpublished data). Underlying causal mechanisms were not investigated in either study, however. Additional wind tunnel experiments and other approaches to determine the effects of environmentally relevant levels of MeHg on exogenous fatty acid utilization during high-intensity exercise are needed to better understand the threat that mercury pollution poses to the endurance of migrating birds. Rapid and prolonged catabolism of extramuscular fat stores is as fundamentally important to migration as navigation and orientation, and this should be another top research priority.

In addition to the physiological aspects of flight, more research is needed to investigate potential effects of mercury on biomechanics and feather development, both of which could also reduce flight efficiency and endurance. Mercury in birds can damage and accumulate at relatively high concentrations in the cerebellum (Borg et al. 1970; Hamilton et al. 2011; Scoville and Lane 2013), which is the area of the brain that controls flight and other motor skills. Environmentally relevant mercury dosing has recently been found to weaken the takeoff performance of European starlings (*Sturnus vulgaris*; Carlson et al. 2014) and the coordination of yellow-rumped warblers flying in a wind tunnel (Ma et al. 2018a), suggesting the possibility of neurological effects of mercury that could limit long-distance flight abilities of migratory birds. Increases in wing and tail feather asymmetry have been seen in some wild birds as a result of environmental mercury exposure (Evers

et al. 2008; Herring et al. 2017; but see Clarkson et al. 2012), which could increase flight costs (Thomas 1993; Hambly et al. 2004), and over long distances, conceivably shorten flight durations, lengthen stopovers, and ultimately delay arrival. These biomechanical and morphological effects of mercury on migration have yet to be tested and are important subjects for future investigation.

Oxidative stress

Fatty acid oxidation and other aerobic metabolic processes in vertebrates generate reactive byproducts that cause oxidative damage to cells. As metabolic rate increases, so does the production of these reactive species (RS) and their potential to exceed the antioxidant defenses of the animal. How migrating birds repeatedly engage in long bouts of high-intensity endurance exercise as they fly from one destination to the next and withstand the extreme oxidative challenges imposed by this behavior has recently gained an increasing amount of attention among physiological ecologists (Costantini 2008; Skrip and McWilliams 2016; Cooper-Mullin and McWilliams 2016).

RS are generated in the mitochondria when not all oxygen molecules are fully reduced to water by the electron transport chain. Some intermediates that escape the electron transport chain have an unpaired electron, making them radicals that scavenge electrons from other compounds and turn them into radicals in the process. Others undergo reactions that make them radicals after escaping the electron transport chain. Collectively, these RS can take electrons from and cause structural and/or functional damage to lipids, proteins, and DNA throughout the body unless they are counteracted by endogenous or dietary antioxidants. The fats on which birds rely to fuel their migration are particularly vulnerable to oxidative damage, further heightening the need for migrants to maintain oxidative balance en route (Skrip and McWilliams 2016).

Mercury is a well-documented cause of oxidative stress in birds and other vertebrates due to its compounding effects of generating RS, like hydrogen peroxide, while simultaneously disrupting enzymatic and non-enzymatic antioxidants, such as glutathione (GSH), superoxide dismutase (SOD), vitamin C, and vitamin E (Stohs and Bagchi 1995; Ercal et al. 2001; Ynalvez et al. 2016; Whitney and Cristol 2017). For example, GSH has been found to be negatively related to MeHg, while oxidized glutathione (GSSH) and the ratio of GSH to GSSG have been found to be positively related to MeHg in several species of experimentally dosed and free-living waterbirds (reviewed by Whitney and Cristol 2017). Henry et al. (2015) found that developmental and dietary exposure of zebra finches to environmentally relevant concentrations of MeHg caused oxidative stress, as indicated by significantly reduced SOD activity and GSH to GSSG ratio. However, markers of oxidative stress were either unrelated to MeHg or related in the opposite direction than expected in free-living tree swallow (*Tachycineta bicolor*) nestlings with low environmental exposure (Custer et al. 2006, 2008). More work on the relationship between environmentally relevant levels of MeHg and oxidative stress in songbirds is needed.

Migrating birds produce exceptional amounts of RS as a natural and unavoidable consequence of long-distance flight, and are therefore already challenged to maintain a high antioxidant capacity throughout their migration (Costantini 2008; Skrip and McWilliams 2016; Cooper-Mullin and McWilliams 2016). It therefore seems that additional RS production, coupled with the deactivation of antioxidants as a result of mercury exposure could potentially overwhelm the ability of migrants to achieve oxidative balance and avoid harmful damage. Oxidative damage has been suggested to be a proximate mechanism underlying the myriad toxic effects of mercury on a vertebrate's health, fitness, and survival (e.g., Sarafian and Verity 1991; Ali et al. 1992; Ercal et al. 2001). It stands to reason that any additional oxidative stress imposed on a migrating bird by mercury beyond that which is already levied by the metabolic requirements of long-distance flight could have pathological consequences during migration or later in life. Whether the incremental change to either side of the oxidative balance equation among migrating birds as a result of environmental MeHg exposure can be enough to cause meaningful increases in oxidative damage is an important and unanswered question.

Stopover refueling

In between long-distance migratory flights, birds must stop to rest and refuel before they can continue towards their goal destination. Stopover refueling includes the replenishment of fat stores and the rebuilding of lean tissues that were catabolized in flight (Karasov and Pinshow 1998; Seewagen and Guglielmo 2011), usually over the course of just one to a few days in the case of songbirds (e.g., Morris et al. 1996). Most birds are under selective pressure to minimize time spent migrating and they undergo a series of physiological adjustments in preparation for migration that allow them to gain exceptional amounts of body mass in this short amount of time at each stopover site (Guglielmo 2010; Ramenofsky 2011). The physiological processes involved in fattening are under the influence of pancreatic, thyroid, and adrenal hormones, and the enzymes upon which these hormones act (Ramenofsky 2011). Of particular importance are the pancreatic hormones insulin and glucagon, which are the principal regulators of lipogenesis

and lipolysis in birds and other vertebrates (Griminger 1986; Karasov and Martinez del Rio 2007).

Migrants fatten by enlarging their gut, increasing their food intake, and selecting foods that are high in fats and carbohydrates, and have certain fatty acid composition (Pierce et al. 2004; McWilliams and Karasov 2014). Feeding stimulates secretion of insulin from beta cells in the pancreatic islet of Langerhans. The insulin stimulates activity of the enzyme adipose lipoprotein lipase (ALPL), which facilitates the deposition of circulating triglycerides into the adipose tissue for storage (Griminger 1986; Karasov and Martinez del Rio 2007; Ramanofsky 2011). Circulating triglycerides originate from dietary fatty acids or those that have been synthesized from other macronutrients by the liver (McWilliams et al. 2004). Fatty acid synthesis is fostered by malic enzyme and fatty acid synthase (Griminger 1986; Ramenofsky 2011). The reverse process of lipolysis during periods of negative energy balance is regulated by glucagon, which is triggered by hypoglycemia and stimulates the enzyme HSL to release stored fatty acids into the oxidation pathway discussed earlier (Karasov and Martinez del Rio 2007). The ratio of glucagon to insulin is therefore what largely controls whether a bird is in a state of energy storage or retrieval. Other hormones that appear to play a role in migratory fattening include corticosterone (CORT), triiodothyronine (T3), thyroxine (T4), prolactin, and possibly leptin (Ramenofsky 2011).

Stopover refueling rate is a major determinant of the overall duration of migration. Limitations on refueling rate can lengthen stopover durations, delay arrival, and reduce the energetic condition in which birds reach their breeding or wintering grounds (Lindstrom and Alerstam 1992; Schaub et al. 2008). These carry-over effects from migration to the breeding and wintering seasons can impact reproduction, survival, and possibly the population sizes of birds (Newton 2006; Norris and Marra 2007). It is therefore important to migratory bird conservation to understand whether anthropogenic changes to the environment are affecting the ability of migrants to efficiently and promptly refuel during stopovers (Mehlman et al. 2005; Klaassen et al. 2012).

MeHg is an endocrine disruptor in humans and wildlife (Dyer 2007; Tan et al. 2009), and in birds specifically, has been found to alter several hormones that are important to multiple life functions (Whitney and Cristol 2017). Effects of MeHg exposure on the endocrine system of vertebrates are widespread (Tan et al. 2009) but mainly center on pancreatic and thyroid function, including decreased hormone secretion from these organs (Soldin et al. 2008; Schumacher and Abbott 2017). Most notably, MeHg has a severe impact on pancreatic beta cell development, function, and apoptosis, which results in decreased glucose tolerance and insulin production to such an extent that it has been implicated as a contributor to worldwide increases in diabetes among humans (Chen et al. 2009, 2010; Tinkov et al. 2015; Schumacher and Abbott 2017). Insulin can also be directly compromised by the binding of mercury to its sulfur binding sites, and is among the hormones that are considered to be most sensitive to mercury (Chen et al. 2006; Rice et al. 2014).

There appear to be no published studies of the effects of MeHg on insulin production or other aspects of pancreatic function in birds, but the large body of evidence from other vertebrate taxa (Chen et al. 2006, 2009, 2010; Tinkov et al. 2015; Schumacher and Abbott 2017) suggests that similar adverse effects are likely. In the case of a migrating bird, the concern is that reduced insulin production and functionality as a result of MeHg exposure could decrease appetite and feeding intensity, and limit the stimulation of ALPL to store dietary fats consumed during stopovers. Given the nature of MeHg to broadly compromise enzyme activity (Marasco and Costantini 2016; Ynalvez et al. 2016), MeHg could also hinder energy storage by directly inactivating ALPL and other important enzymes involved in the process. MeHg exposure in fish was found to downregulate the transcription of fatty acid synthase (Klaper et al. 2008), an enzyme that catalyzes the synthesis of fatty acids and is normally upregulated by birds during migration to support rapid lipogenesis (Ramenofsky et al. 1999; Egeler et al. 2000). Inactivation and/or reduced expression of fatty acid synthase by MeHg might therefore hinder the ability of migrants to synthesize fat at necessary rates. Mercury might further limit fat storage during stopovers by reducing intestinal absorption of glucose and the activity of several digestive enzymes, as has been observed in fish (Sastry and Gupta 1980; Gupta and Sastry 1981; Sastry and Rao 1984). Each of these effects on lipogenesis and fattening would slow down a bird's overall stopover refueling rate and thereby lengthen the amount of time needed to obtain its desired departure fuel load.

The effects of MeHg on other hormones in birds that are involved in fattening are more equivocal. For example, multiple studies have found baseline concentrations of CORT in birds to be positively associated with environmental mercury exposure or dosing, while just as many have found the opposite or no relationship at all (reviewed by Whitney and Cristol 2017). The thyroid hormone, T3, which controls gene transcription for the malic enzyme that facilitates the synthesis of fatty acids from other macronutrients, was negatively related to total blood mercury levels in free-living tree swallow nestlings (Wada et al. 2009). T4, which is a thyroid hormone that has been found to increase with migratory readiness in songbirds (Wingfield et al. 1997), was also reduced (Wada et al. 2009). Conversely, T3 and/or T4 had no relationship with mercury levels in free-living lesser scaup (*Aythya affinis*; Pollock and

Machin 2009) or great blue herons (*Ardea herodias*; Champoux et al. 2017). Baseline levels of prolactin, a pituitary hormone that stimulates feeding and lipogenesis (Goodridge and Ball 1967; Ramenofsky 2011), were not related to blood mercury concentrations in snow petrels (*Pagodroma nivea*; Tartu et al. 2015), but additional studies in birds appear to be lacking. In fish and rats, exposure to MeHg decreased prolactin gene expression and production (Richter et al. 2014; Maués et al. 2015), while other studies on non-avian taxa have found MeHg to increase prolactin levels possibly by interfering with the dopaminergic system that inhibits prolactin secretion (Carta et al. 2003; Tan et al. 2009). Much more research will be needed to understand the effects of mercury on these other hormones that are involved in migratory fattening.

Along with its potential effects on the physiological aspects of fattening, it is possible that mercury exposure could cause behavioral changes that would reduce a migrant's stopover refueling performance (Seewagen 2010, 2013). For example, at high levels, mercury has been observed to suppress appetite and the motivation to forage in birds (Bouton et al. 1999; Spalding et al. 2000b; Evers et al. 2008). High levels of mercury have also been associated with lethargy and ataxia (e.g., Borg et al. 1970; Bouton et al. 1999; Evers et al. 2008, but see Swaddle et al. 2017), including a study that found that mercury dosing reduced the accuracy and rate at which rock doves (*Columba livia*) pecked at food (Evans et al. 1982). Reduced activity levels and impaired motor skills would be expected to hinder foraging efficiency during migration stopovers, when prompt location and acquisition of food is a requisite for rapid refueling.

Most of these studies have involved mercury levels that are above those normally observed in most free-living migratory songbirds, however, and it is therefore uncertain whether environmentally relevant levels of mercury can cause the kinds of behavioral changes that would impair the abilities of songbird migrants to refuel effectively. Only two studies have investigated the effects of mercury on the stopover refueling rates of birds. One found no relationship between total blood mercury concentration and plasma triglyceride level (an indicator of refueling rate) in northern waterthrushes (*Parkesia noveboracensis*) at an autumn stopover site in New York, USA (Seewagen 2013). It was concluded that either the mercury levels of the birds were low enough to have no detectable effect on foraging behavior, or food was plentiful enough at the site that birds were not challenged to an extent that would reveal differences in their foraging abilities. The other found mercury to be negatively associated with refueling rate in one (*Geothlypis trichas*) out of the four songbird species studied during fall and none out of the same four songbird species studied during spring at a stopover site in Florida, USA (E. Adams, personal communication). Similar studies on a range of bird species and in other stopover habitats are needed and encouraged in order to clarify whether exposure of free-living birds to environmental mercury can interfere with their refueling performance and ability to maintain their migratory schedule.

Immunocompetence

The avian immune system represents a series of coordinated physiological processes among macrophages, B lymphocytes, and T lymphocytes that protect a bird against the pathogens and parasites encountered in its environment (Sharma 1991). Relative to sedentary species, migratory birds are likely to have greater exposure to novel parasites and pathogens because their migrations take them through multiple geographic areas of the world, each with different climates, ecosystems, and biological communities (Møller and Erritzøe 1998; Figuerola and Green 2000; Altizer et al. 2011). The high densities at which migrants can occur at stopover sites may also increase contact with pathogens and the transmission of disease (Altizer et al. 2011). Migration may therefore be a particularly critical time in a migrant's annual cycle at which to maintain a robust immune system. Contrary to this expectation, however, immune function in birds appears to be suppressed during migration (Owen and Moore 2006, 2008; Nebel et al. 2012; but see Hasselquist et al. 2007). This may be the result of an intentional and adaptive reallocation of energy from immune responses to flight and stopover refueling (Norris and Evans 2000) or an unavoidable impact of high intensity exercise on the immune system (Buehler et al. 2010; Nebel et al. 2012). In any case, this reduction in immunocompetence at a time when exposure to novel pathogens and parasites is likely to be at its highest makes migrants even more vulnerable to disease. Differing abilities of individual birds to manage the energetic tradeoff between mounting immune responses and engaging in migratory activity, and successfully defend themselves from infections during migration, may be a major contributor to migration mortality that acts to limit transmission by removing infected individuals from the population (Altizer et al. 2011; Risely et al. 2018).

Any additional factors that suppress immunocompetence in birds are likely to compound these effects of migration on the immune system and further challenge the ability of migrants to stay healthy. Immunotoxic effects of mercury have been documented in several vertebrate taxa, including birds. Waterbirds and poultry exposed to high levels of mercury have been observed to experience histological changes in the thymus, bursa, and spleens, suppressed antibody responses, decreased B-cell proliferation, and altered heterophil:lymphocyte ratios (Thaxton and

Parkhurst 1973; Bridger and Thaxton 1983; Spalding et al. 2000a; Kenow et al. 2007; Whitney and Cristol 2017). The small number of studies that have been conducted on songbirds, either living in mercury-contaminated environments or dosed with environmentally relevant levels of mercury, also generally point towards a negative effect of mercury on their immune system (Hawley et al. 2009; Lewis et al. 2013; but see Caudill et al. 2015).

High energy activities are harder to sustain when the immune system is challenged. In migrating birds, pathogen infections have been observed to result in shortened flight distances, lowered stopover refueling rates, delayed arrival, and even reduced chances of survival (Van Gils et al. 2007; Risely et al. 2018). Any additional dampening of the immune system by mercury may therefore increase the likelihood and severity of infections during migration and the consequences of that for migration performance and survival. To what degree, if any, that mercury accumulation in free-living migratory birds can reduce migration performance or survivability by suppressing immune function has yet to be investigated, however, and warrants attention.

Conclusion

Although very few studies have yet to directly investigate the effects of mercury on migration, there is an abundance of information about the physiological changes that can occur in non-migrating birds as well as non-avian taxa to suggest that mercury poses a significant threat to bird migration in many ways (Fig. 1). The broad ability of mercury to inactivate enzymes and compromise the function of other proteins to which it binds is perhaps the mechanism by which mercury has the strongest potential to disrupt so many of the physiological processes that make long-distance migration possible. In just this way alone, mercury might interfere with magnetic compass navigation, flight endurance, oxidative balance, and stopover refueling.

Hindrance of any of these fundamental aspects of migration will inherently weaken migration performance, possibly to the extent that the likelihood of survival is reduced. Previous studies of the effect of mercury on survival, which have been limited to long-lived migratory waterbirds and tree swallows, have failed to find any strong evidence that environmentally relevant mercury exposure significantly reduces survivorship (reviewed by Whitney and Cristol 2017). Recent work by Ma et al. (2018a), however, found mean mercury levels in blackpoll warbler (*Setophaga striata*) and American redstart (*Setophaga ruticilla*) feathers grown during the post-breeding period and retained until the following year to be higher among birds during autumn than among conspecifics returning in the spring, suggesting that mercury may have contributed to migration mortality in these species. Although the pattern was not observed in all five of the species examined, the two species in which there was an apparent culling effect of mercury were also the species with the longest (i.e., most challenging) migrations. In blackpoll warblers, the species with the most extreme migration of any Neotropical migratory songbird (DeLuca et al. 2015), average mercury levels of feathers grown during the breeding season were 50% lower among the cohort of birds returning in the spring than among those that departed the previous autumn. This apparent removal of individuals with the highest mercury burdens from the population sometime between the onset of autumn migration and return in spring indicates that

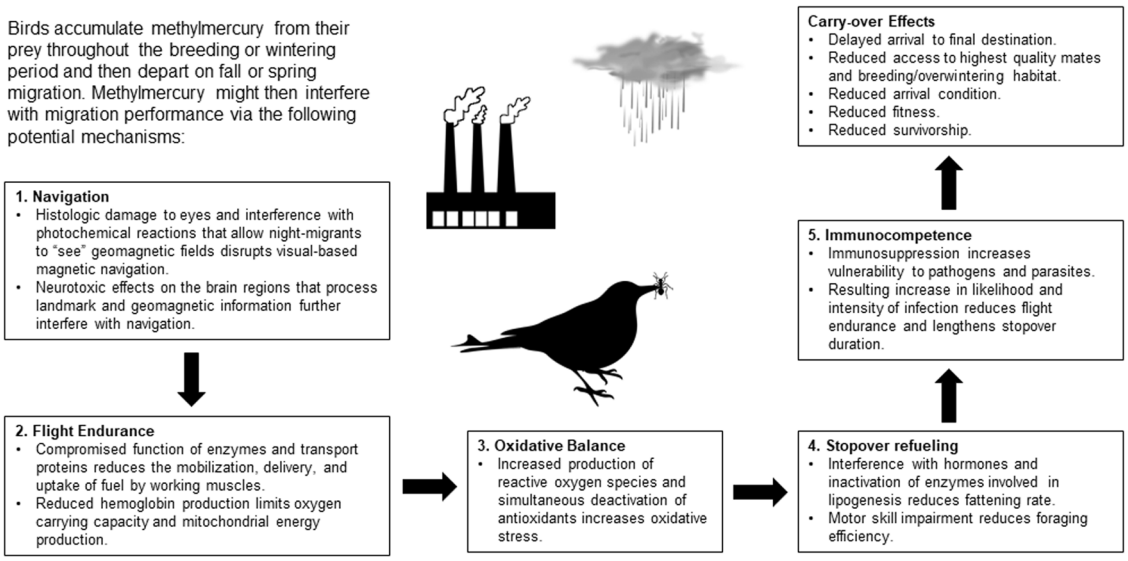

Fig. 1 Conceptual diagram of potential mechanisms by which methylmercury might hinder the migration performance of birds

mercury accumulation may have affected their migration performance, perhaps by compromising their ability to navigate properly, fly efficiently, meet the energetic demands of long-distance flight, withstand oxidative damage, refuel efficiently, and/or avoid sickness and predation. As a fuller picture of mercury's threats to birds emerges, future investigations will hopefully test these potential mechanisms by which this widespread and persistent environmental contaminant might affect the most vulnerable phase in the annual cycle of one fifth of all bird species.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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