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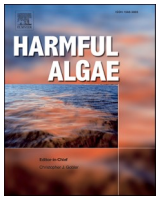

Sea lions as a natural model for charting the developmental course following in utero exposure to domoic acid

Peter F. Cook [a,b,*], Colleen Reichmuth [c], Megan E. Moriarty [d], Alissa C. Deming [e], Vanessa Fravel Hoard [f], Cara Field [f], Frances Gulland [g]

[a] Marine Mammal Science, New College Florida, Sarasota, FL 34234 USA
[b] Institute of Marine Sciences, University of California Santa Cruz, 115 McAllister Way, Santa Cruz, CA 95060 USA
[c] Long Marine Laboratory, Institute of Marine Sciences, University of California Santa Cruz, 115 McAllister Way, Santa Cruz, CA 95060 USA
[d] Office of Research, University of California Santa Cruz, 115 McAllister Way, Santa Cruz, CA 95060 USA
[e] Pacific Marine Mammal Center, Department of Conservation Medicine and Science, 20612 Laguna Canyon Road, Laguna Beach, CA 92651 USA
[f] The Marine Mammal Center, 2000 Bunker Road, Fort Cronkhite, Sausalito, CA 94965-2619 USA
[g] One Health Institute, University of California Davis, Davis, CA 95616 USA

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ABSTRACT

Domoic acid-producing algal blooms are increasing in size, frequency, and duration along the eastern Pacific coastline resulting in regular and repeated exposure of marine mammals to the toxin. Because of their prolonged gestation, large numbers of marine mammals are now encountering this excitotoxin in utero, with potential long-term developmental effects. Evidence of developmental neurotoxic effects is accumulating in California sea lions particularly, which serve as an accessible sentinel species for studying the effects of domoic acid exposure in mammals. In biomedical settings, rodent models have revealed some developmental aspects of early domoic acid exposure, including a tendency for gross neurobehavioral changes to emerge after puberty. However, rodents are altricial and have a truncated developmental course. In contrast, marine mammals are precocial and mature slowly. Further, neurobehavioral responses to domoic acid have notable differences between those in adult rodents exposed in vivariums and in free-ranging wildlife. Primate models address some of these gaps, but are limited by practical constraints. There is a clear need to establish an ecologically valid model of brain development and clinical progression of developmental domoic acid exposure in long-lived and precocial mammals. Here we present California sea lions born in wildlife rehabilitation facilities to mothers with documented domoic acid toxicosis as a promising and accessible disease model, and we provide a framework for future research. Hundreds of adult sea lions in rehabilitation centers have already taken part in veterinary assessments and experimental assays of brain and behavior, demonstrating the plausibility of careful and scalable science with these animals. We discuss preliminary work with a juvenile sea lion enrolled in a longitudinal study with repeated clinical, behavioral, and neurobiological assessment, and advocate for cohort-based studies of maternally exposed sea lions.

1. Scope of problem

Harmful algal blooms producing the excitotoxin domoic acid (DA) have increased in size, frequency, and duration over the last few decades due to complex and interactive factors including nutrient availability and ocean temperature (Anderson et al., 2021; Lefebvre et al., 2025a; Lewitus et al., 2012; McCabe et al., 2016). Filter-feeding invertebrates and fish consume the planktonic diatoms, and the toxin bioaccumulates as it moves up the food chain. Exposure in top coastal consumers is believed to be extensive, in some cases encompassing entire populations (Fig. 1). While the effects of acute and chronic DA exposure in adult vertebrate animals are fairly well understood, there are far fewer data on neurobehavioral disruption from developmental exposure, particularly in long-lived mammals. This is a critical knowledge gap, as large numbers of marine mammals are now believed to be exposed annually during gestation and through nursing (Rust et al., 2014). There is also

* Corresponding author.
E-mail addresses: pcook@ncf.edu (P.F. Cook), coll@ucsc.edu (C. Reichmuth), mmoriart@ucsc.edu (M.E. Moriarty), ademing@pacificmmc.org (A.C. Deming), vfravel@gmail.com (V.F. Hoard), fieldc@tmmc.org (C. Field), francesgulland@gmail.com (F. Gulland).

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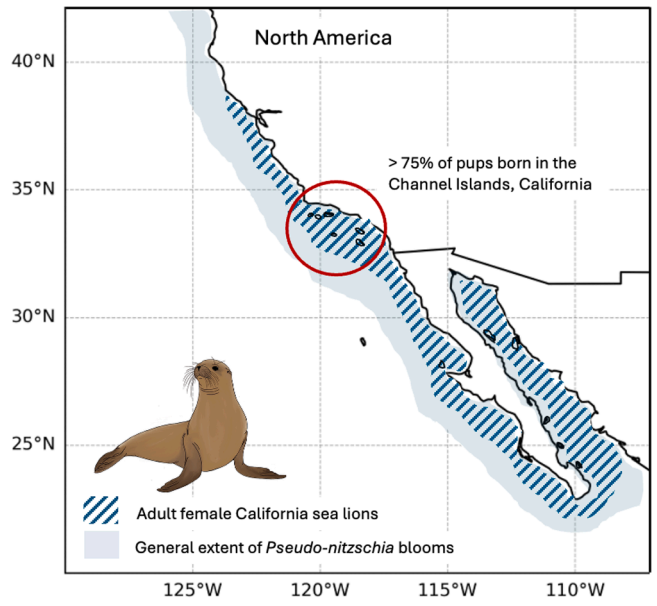

Fig. 1. Pregnant and nursing female California sea lions (*Zalophus californianus)* forage in the coastal North Pacific Ocean with movements constrained by the location of breeding colonies (Laake et al., 2018). Areas of episodic *Pseudo-nitzschia* spp. blooms encompass their foraging and pupping grounds, leading to maternal transfer of domoic acid (amnesic shellfish poison, ASP) at population scales. Illustration: R. Jones.

growing concern among public health officials regarding low-dose exposure to human fetuses *in utero*. Laboratory rodent models have illuminated specific mechanisms of neural insult at various developmental stages, but these have not generalized well to animals with extended developmental phases. Rodents are also altricial, achieving fewer developmental milestones during vulnerable in utero periods than precocial animals like marine mammals. Studies on laboratory primates have also revealed effects of domoic acid on development (Burbacher et al., 2019), yet these studies are limited by the extensive funding and specialized infrastructure required.

Thus, the basic progression of excitotoxin-related neurobiological change through puberty in long-lived mammals remains unclear. Here we argue that foundational, longitudinal research into the brain and behavior of maternally exposed California sea lions (*Zalophus californianus*) will provide an ecologically valid developmental model for understanding DA's neurotoxic effects on other less accessible marine mammals and potentially humans.

2. Domoic acid and the brain

While DA levels in commercial fisheries are now closely monitored to protect human health, this toxin continues to affect coastal sea life throughout the eastern Pacific Ocean, from shellfish and schooling fish to sea birds, sea otters, pinnipeds, and whales. Toxic exposures have been identified in all these marine taxonomic groups in recent years (Krasner et al., 2025). Domoic acid acts as a glutamate agonist similar in structure to kainic acid (Hampson and Manalo, 1998). With a high affinity for kainate and AMPA receptors, DA can lead to tonic activation of neurons, calcium influx, and apoptosis in vertebrate animals (Pulido, 2008). In the hippocampus, which has a high concentration of kainate receptors, particularly in the dentate gyrus, the over-activation of neural tissue can lead to formation of new, recursive synapses that promote a tendency toward continued over-activity and, in certain cases, cause chronic medial temporal epilepsy (Cendes et al., 1995; Ramsdell, 2007; Ramsdell and Gulland, 2014). The specific mechanisms of DA action have been carefully studied in rodent models and validated with work on wild sea lions (McClain et al., 2023), showing mossy fiber sprouting in the dentate gyrus (Bernard et al., 2007; Buckmaster et al., 2014), gross hippocampal damage (Cook et al., 2015; Goldstein et al., 2008; Gulland et al., 2002; Montie et al., 2010; Silvagni et al., 2005), and aberrant hippocampal connectivity (Cook et al., 2015, 2018).

3. Developmental effects

Domoic acid is a proven developmental teratogen that can affect animals throughout their lifespan, from conception to old age (Costa et al., 2010; Dakshinamurti et al., 1993; Doucette and Tasker, 2016). However, the sequence of DA's neurobiological effects across developmental periods has not been comprehensively characterized, particularly in longer-lived animals. There is concern that DA may have developmental effects in humans, even at low doses (Campbell et al., 2024; Lefebvre and Robertson, 2010), leading to warnings against fish and shellfish consumption during pregnancy (Grattan et al., 2021). However, developmental studies in humans are lacking. Veterinary case studies of sea lions and a fur seal with likely maternal transfer of DA have suggested delayed onset of neurological signs, sometimes for years (Fuquay et al., 2012; Schmitt et al., 2023; Simeone et al., 2019), but the neurodevelopmental course has not been closely tracked in any of these animals. In laboratory dose-response studies of rodents, fetuses and neonates can be impacted by maternal transfer of DA (Fuquay et al., 2012; Maucher and Ramsdell, 2007), with offspring more susceptible to neural disruption from lower dose exposures than more mature animals (Costa et al., 2010; Grant et al., 2010). Early exposure to DA can lead to delayed neurobehavioral abnormalities in rodents (Levin et al., 2005; Tanemura et al., 2009). Unfortunately, current laboratory models are not well suited to explore lifespan effects in longer lived mammals (Olney, 2002). Studies of non-human primates intentionally exposed to DA and other excitotoxins during gestation may better mirror developmental course in precocial species such as marine mammals and long-lived animals such as humans (Grant et al., 2010; 2019; Petroff et al., 2019; Spitzer et al., 2016). However, as mentioned above, primate studies are hard to fund, and it is frequently impractical to follow affected offspring over long time periods.

Rodents can be more readily studied over a longer portion of their developmental trajectory, but pups are altricial with a truncated developmental time course, so these studies cannot fully illuminate potential maternal transfer effects in precocial and long-lived species. Importantly, precocial animals complete more of the early-stage synaptogenesis in utero than altricial animals (Charvet and Finlay, 2018; Kalusa et al., 2021; Workman et al., 2013), during which time excitotoxin exposure, including DA, may have more significant long-term effects on brain organization (Doucette and Tasker, 2016; Gong et al., 1995; McDonald et al., 1992). Rats spend 20–30 days in utero and reach maturity between 3 and 6 months of age. The corresponding developmental course for mice is even shorter. This contrasts with the much longer gestational intervals of humans and many other long-lived mammals, who also have a prolonged period of lactation during development post-parturition. Current rodent models of developmental DA exposure are insufficient to conclusively account for and predict all possible effects in the species of greatest concern for natural exposure.

4. Sea lions as natural models

Sea lions are a largely untapped natural model for studying extended developmental effects of in utero exposure to DA (Fig. 2). They have a large and heavily gyrified brain. They are long lived (up to 30 years) with an extended developmental course. Mothers have a prolonged gestation at 240 days (Melin, 2002) and are often naturally exposed to high levels of DA during pregnancy (Brodie et al., 2006; Goldstein et al., 2009). Their pups are born precocial in a birthing season tied to prime environmental conditions that favor harmful algal bloom development in early summer. Annual DA-producing blooms are most prevalent during late spring and summer (Mckibben et al., 2017; Smith et al.,

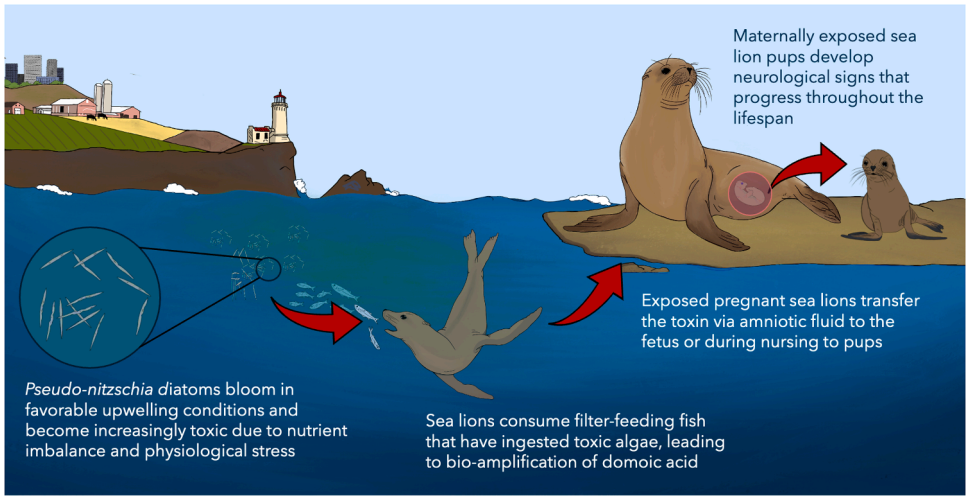

Fig. 2. Pregnant sea lions with dietary exposure to domoic acid can pass the toxin on to their pups, either in utero or after parturition via nursing. Maternally exposed pups may manifest neurobehavioral disruption throughout their lifespan. Illustration: R. Jones.

2018), thus *in utero* DA exposure is most likely during the third trimester of development. However, in the past decade, DA blooms have increasingly occurred throughout the early spring and late fall as well, suggesting potentially harmful exposure in the first and second trimesters. In rodents, neural susceptibility to excitotoxins appears to be greatest during peak synaptogenesis, which occurs post-partum (Doucette and Tasker, 2016; Ramsdell and Zabka, 2008). This susceptibility is pronounced in the hippocampus, where synaptogenesis heralds the transition from the "silent" brain to active inter-regional signaling (Hanse et al., 2009; Kerchner and Nicoll, 2008). Given that fetal sea lions presumably undergo extensive synaptogenesis during the third trimester, this may be a particularly vulnerable developmental stage for excitotoxic effects in this species. Glutamate toxicity during synaptogenesis may cause a reduction of GABAergic inhibitory inputs into the hippocampus and a related over-formation of recurrent excitatory collateral connections between hippocampal subregions. These in turn can lead to spreading excitation, activation, and seizure kindling (Martisova et al., 2012; Meldrum, 1993; Ramsdell and Gulland, 2014; Sarlo and Holton, 2021). New anecdotal evidence indicates that these early exposures in sea lions can manifest in delayed neurological signs, sometimes emerging after puberty, years after initial exposure (Krucik et al., 2023; Schmitt et al., 2023; Simeone et al., 2019). Comprehensive, longitudinal studies of these effects with regular behavioral and neurobiological testing in developing sea lions would provide novel and potentially generalizable data on how DA alters brain, behavior, and health at different developmental timepoints.

Importantly, naturalistic studies with wild animals will always be limited by uncontrolled variability. In environmental toxicology, we cannot have precise dose-response data, although trophic transfer models for ecotoxins are improving and may increasingly allow some estimation of exposure load (e.g., Lefebvre et al., 2025b). Further, genetic factors and individual and maternal health will impact development in ways that may interact with developmental toxic effects. Applying genetic and transcriptomic approaches to wild animals (e.g., Bowen et al., 2022; Esperanza et al., 2024) and assessing their relation to disease processes is newly affordable and achievable, and such studies should be pursued with sea lions. Naturalistic studies will always be complemented by careful laboratory models. However, naturalistic studies and studies of larger and longer-lived animals have been under-explored, and are uniquely suited to addressing long-term developmental impacts of environmental toxins that cannot be fully characterized in the lab (e.g., Dawson et al., 2018; Sarasa and Pesini, 2014; Yin et al., 2022). There is also an obvious ethical value in studying naturally occurring effects in accessible wild populations, as it may allow more limited and targeted use of laboratory animals.

Not only are sea lions a promising theoretical model for examining extended developmental effects of early DA exposure, but the logistical pieces are in place to pursue such studies. Careful neurobehavioral work has already been conducted with large numbers of juvenile and adult sea lions in rehabilitation settings (Cook et al., 2011, 2015, 2016; de Maio et al., 2018), proving the plausibility of sea lions as a natural DA research model. Although little studied in depth to date, many young stranded sea lions with likely and verified developmental DA exposure are available each year in rehabilitation facilities. In the last two decades, large numbers of neonate and juvenile sea lions have presented to rehabilitation centers following stranding with behavioral abnormalities, including repetitive and disorganized movement and apparent confusion. DA has been implicated in these cases, in part due to spatiotemporal coincidence of strandings relative to harmful algal blooms but also due to apparent seizure activity and abnormal neurological signs. Some pups have been born to mothers under treatment for acute DA poisoning, with DA documented in maternal samples as well as in amniotic and fetal tissues or fluids (Goldstein et al., 2009; Hoard and Janech, 2019; Lefebvre et al., 2018). Many of these young sea lions exhibit electroencephalography (EEG) results unlike those found in adult females with chronic DA poisoning (Williams et al., 2023). Currently, most neonates are euthanized due to poor prognosis.

Collaborative efforts between veterinarians, rehabilitation organizations, and scientists have already successfully produced extensive neurobehavioral data on adult sea lions exposed to DA. This was possible in large part because sea lions are the most visible victims of DA poisoning – they are highly amphibious, foraging in coastal waters and frequently resting, congregating, and breeding on land in well populated areas. They feed on large fish schools that form around algal blooms. When they feed on fish schools that have been feeding on DA-producing blooms, the sea lions rapidly accumulate large amounts of the toxin, leading to acute neurotoxic effects (Lefebvre et al., 1999). Unlike most marine mammals, when sea lions are in distress they move to shore, where many sea lions with DA poisoning are observed and reported by concerned members of the public. They are then transported to wildlife rehabilitation centers, which become inundated during bloom events. Thus, sea lions are a uniquely accessible species to study the effects of this toxin (Bossart, 2011). Because of their nearshore lifestyle and large population, sea lions are considered a sentinel species for coastal ecosystem health (Hazen et al., 2019), often demonstrating the harmful effects of environmental degradation before evidence emerges in less accessible species.

To chart neurodevelopmental progression of DA signs in sea lions

exposed to domoic acid *in utero* we need to identify and monitor individuals with verified maternal exposure. Behavioral and neuroimaging studies conducted over the lifespan with such animals will uncover the timing and progression of any changes prior to adulthood that may be attributable to initial neurobiological insult from DA or its later developmental knock-on effects. These findings can be integrated with clinical monitoring to provide a comprehensive developmental timeline of the impacts of early DA exposure, and to suggest veterinary interventions and rehabilitation decisions relating to prognosis, drive future clinical research, and inform best outcome options. Such studies may also help inform models for human pregnancy exposure.

5. Time course of developmental effects

Post-partum neurodevelopment has not been extensively studied in sea lions, or, indeed, in other precocial species. However, stages of brain development are believed to proceed in a steady progression across mammalian species (Brenhouse and Andersen, 2011). Therefore we have some idea, based on prior evidence, what neurological developmental stages are likely to occur at what age in sea lions. Evidence from monkeys suggests that, as with humans, synaptic pruning speeds up prior to sexual maturity, peaks around sexual maturity, and declines thereafter (Chung et al., 2017; Zecevic et al., 1989). Female sea lions are mature between 4 and 5 years of age, so likely begin accelerated pruning around 3 years of age (Fig. 3). The potential connectivity network of the sea lion brain should be firmly established at this point. However, anecdotal evidence that neurological signs can emerge around puberty, five years of age or later, following in utero exposure, suggests that there are other factors at play, potentially including myelination and functional connectivity of frontal and medial temporal regions, which may progress quite late into development in large-brained species.

Early insult from a maternally transferred excitotoxin may play out in specific ways at particular timepoints during neurodevelopment, providing different neurobehavioral research targets for charting DA's effects across extended development. As discussed previously, DA exposure during synaptogenesis (third trimester for sea lions) appears to reduce formation of inhibitory synapses in the Cornu ammonis (CA) portion and dentate gyrus of the hippocampus, contributing to the emergence of epilepsy (Martisova et al., 2012; Meldrum, 1993; Ramsdell and Gulland, 2014; Sarlo and Holton, 2021). This may lead to increased intra-hippocampal signaling, which, in turn, predicts different aberrant outcomes at each state of brain development.

The specifics of excitotoxic neurobehavioral disruption are beyond the scope of this commentary. However, we note that rodent and primate research on DA and other excitotoxins, and broad research on medial temporal brain systems and networks, suggest a range of neurobehavioral research targets for opportunistic studies of sea lions exposed in utero. Early in development, animals are unlikely to show gross accumulations of cellular damage. However, increased hippocampal excitation could promote behavioral hyperresponsivity due to the role of the hippocampus in sensory orientation (Dinel et al., 2011; Knapman et al., 2012; Rappeneau et al., 2023). In the first year or two of life, local hippocampal disruption may affect formation and refinement of whole-brain hippocampal circuits. Among the most important of these in typical mammals are prefrontal-hippocampal connections that support attention (Barbas et al., 2013; Gunseli and Aly, 2020; Li et al., 2015; Liston et al., 2011). These circuit level disruptions could, in turn, have extensive knock-on effects in later neurodevelopment as pruning (removal of underused synapses) – and myelination (insulation of important long-distance connections) – continue (Knowles et al., 2022; Meier et al., 2004; Nickel and Gu, 2018; Rappeneau et al., 2023; Zhou et al., 2008). As animals reach maturity, increased hippocampal activity may begin to result in cellular disruption and apoptosis causing gross hippocampal damage that will likely disrupt spatial and event memory (Pulido, 2008; Ramsdell and Gulland, 2014). This local damage, in turn, may have even further impact on maintenance and function of extended hippocampal circuits throughout the brain. Many of these potential changes to the brain and behavior may be subtle, particularly at first. Domoic acid-related brain damage in sea lions tends to be unilateral (Cook et al., 2015; Montie et al., 2010), which may facilitate comparisons of brain structure and function contralateral to primary insult, resulting in within-subject measures of altered neurobiology and related behavior.

6. Charting neurobiological change over time

When maternally exposed sea lions are identified and placed into long-term zoological programs, we can document changes to their brains in vivo using applications of Magnetic Resonance Imaging (MRI). Structural alterations to the brain, such as gross atrophy in the hippocampus or diffuse cell death in the temporal lobe can be quantified with straightforward high-resolution structural imaging. Inter-regional connections and white matter characteristics can be measured using diffusion tensor MRI (den Heijer et al., 2012; Förster et al., 2012; Karat et al., 2024; Miller et al., 2011; Yendiki et al., 2022). Functional connectivity alterations, related to dynamic interactions between different brain regions, can be measured with applications of blood oxygen level dependent (BOLD) MRI (Ezama et al., 2021; Holmes et al., 2014; Salami et al.,

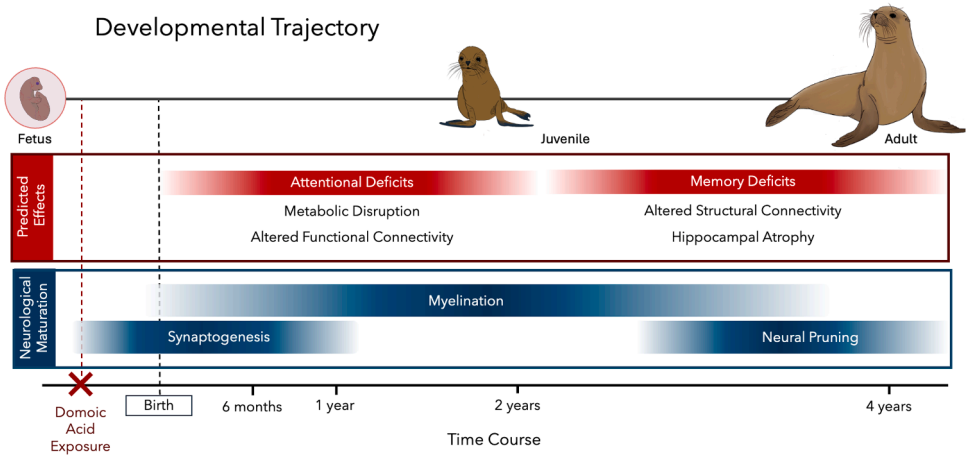

Fig. 3. Potential course of neurodevelopment and associated disruption from DA exposure in sea lions. As precocial mammals with long gestation, sea lion fetuses are believed to undergo extensive synaptogenesis in the third trimester. This may be a particularly vulnerable period for brain development, and associated neurobiological changes may affect metabolism and brain connectivity longitudinally, with behavioral ramifications. In addition, they have a fairly extended post-parturition/pre-maturity period during which early synaptic changes may influence myelination and pruning. Illustration: R. Jones.

2014; van den Heuvel and Hulshoff Pol, 2010). Regional metabolic disruptions of the sort seen in early epilepsy (Cattani et al., 2014; Huo et al., 2014; Mattson, 2017) can be measured with arterial spin labeling (ASL) MRI (Telischak et al., 2015). We have previously measured structural and functional alterations in hippocampal brain networks in adult sea lions that align with what has been observed in other species intentionally exposed to excitotoxins in laboratory studies (Cook et al., 2015, 2018), and have recently published a suite of imaging and associated veterinary handling protocols for acquiring high-quality structural, functional connectivity, structural connectivity, and perfusion MRI from living sea lions (Cook et al., 2021).

Using these established tools, it should be possible to discern divergence points in sea lion development, when typical structure and function of specific brain regions and networks are altered, potentially due to early DA exposure. This will support an emerging understanding of the mechanisms and time course of long-term neurological disruption. More broadly, we can use longitudinal findings from individual sea lions to build models of neurodevelopmental course of DA exposure in long-lived and precocial species. Such findings fit neatly into a One Health perspective, and would also suggest new avenues for research into the effects of increasingly common excitotoxins across ecosystems.

7. Opportunistic pilot research

In January 2025, our research group began conducting pilot studies along the lines discussed here, with a verified *in utero* DA exposed young sea lion in managed care at the University of California Santa Cruz Long Marine Laboratory. This individual was born at the Pacific Marine Mammal Center in Laguna Beach, CA on June 13, 2023 to a wild stranded adult female with confirmed acute DA toxicosis. The pup was apparently healthy during early development and at nine months old, brain imaging with MRI showed no obvious neurological damage. However, at 11 months old, this young sea lion started to exhibit neurological abnormalities including focal seizures. Medical management of seizures was initiated, and given poor release prospects, she was transported to Long Marine Lab for long-term managed care. Since joining the program, this sea lion has been under close veterinary supervision and has participated in typical husbandry and health training. She has completed multiple behavioral assays and a suite of comprehensive in vivo neuroimaging assessments to examine structural, organizational, functional, and metabolic changes to her brain (Fig. 4). Similar brain and behavior data will be integrated with health data to provide a detailed picture of her condition over time. Findings from this pilot case study with confirmed DA exposure exclusively during gestation will be used to develop and refine neurobehavioral assays for use with other developmentally exposed animals across a range of settings. With enough subjects we'll be better able to illuminate the population-level effects and potential risks of developmental exposure to excitotoxins in marine mammals. The interdisciplinary team working with our pilot animal, which links wildlife veterinarians with experts in animal behavior and neurobiology, suggests a translatable model for how to practically acquire and integrate neurodevelopmental and clinical data with other large, wild animals.

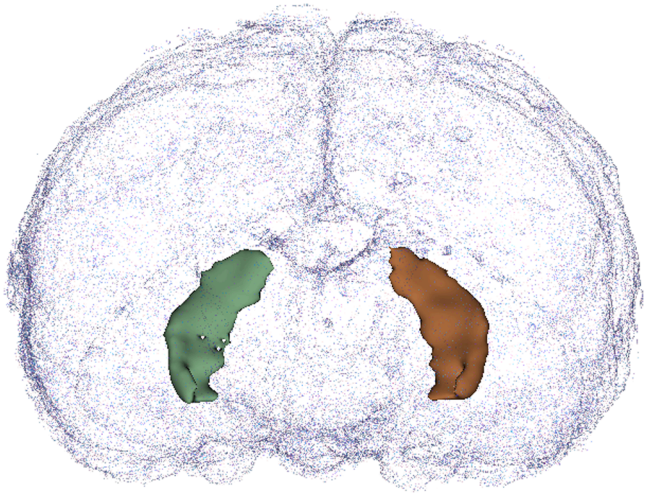

Fig. 4. 3D volumetric representation of right (green) and left (red) hippocampus in developmentally exposed sea lion. With repeated imaging, any regional changes in regional brain volume can be charted over time and compared to other animals.

8. Future directions

Harmful algal blooms are a growing problem worldwide, and, despite decades of careful laboratory research, large holes remain in our understanding of how exposure to associated toxins affects different species across the lifespan. The pieces are in place to address many of these knowledge gaps head-on by exploiting opportunistic neurobehavioral models drawing on naturally exposed, young wild animals. These models will lack the careful dose-response control of typical laboratory studies, but will benefit from heretofore missing ecological validity. Such studies complement and round out existing laboratory models.

Systematic study of opportunistically obtained sea lions with confirmed developmental exposure to DA will provide a meaningful longitudinal dataset for evaluating clinical and neurobiological change. Such data will support a generalized understanding of DA's developmental effects in long-lived and precocial animals, and, even more broadly, a new practical model for examining the effects of environmental excitotoxins across species. Studies of exposed wild-born animals would benefit from longitudinal comparisons to captive-born animals with "clean" neurological profiles. However, studies of affected animals will be highly informative on their own, as many of the neurobehavioral changes of interest involve systems moving in retrograde–brain region volumes and connections becoming weaker or more disrupted, as opposed to stronger and more coherent, and behavioral capabilities degrading as opposed to improving over the course of development.

Carrying out these long-term studies will require funding cross-disciplinary research with opportunistically identified animals across an array of interrelated settings, including the wild, veterinary rehabilitation centers, and zoological facilities. This will require close working relationships among regulatory agencies, veterinary medicine specialists, animal care specialists, and brain scientists. Such collaborations are complicated but possible, and can be highly productive. As environmental degradation continues across ecosystems and regions, One Health approaches to studying affected wild animals are needed more than ever, in addition to more traditional laboratory model species studies. By integrating these naturalistic exposure studies with the growing body of research on harmful algal blooms and ecosystem change, we will increase our understanding of the complex relationships among wildlife, humans, and our shared environment.

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CRediT authorship contribution statement

Peter F. Cook: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Colleen Reichmuth:** Conceptualization, Writing – original draft, Writing – review & editing. **Megan E. Moriarty:** Conceptualization, Writing – original draft, Writing – review

& editing. **Alissa C. Deming:** Conceptualization, Writing – review & editing. **Vanessa Fravel Hoard:** Conceptualization, Writing – review & editing. **Cara Field:** Conceptualization, Writing – review & editing. **Frances Gulland:** Conceptualization, Writing – review & editing.

Declaration of competing interest

None of the authors of this manuscript claim any competing interests.

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Data availability

No data was used for the research described in the article.

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