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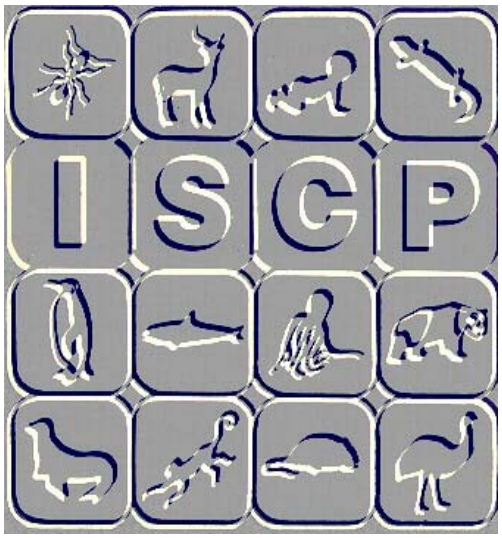

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Considerations of the Effects of Noise on Marine Mammals and other Animals

Andrew J. Wright and Lauren Highfill, ***Guest Editors***

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Noise-Related Stress and Marine Mammals: An Introduction

Andrew J. Wright and Stan Kuczaj

Marine mammals (especially cetaceans) use sound as their primary sensory input for social communication, foraging, and other vital life-processes. Background noise has the potential to interfere with these functions by masking normal sounds, and at least some noise sources have been linked to behavioral and physiological responses (with lethal and non-lethal consequences). Consequently, it is reasonable to assume that at least some acoustic sources may act as stressors (stimuli leading to a stress response) for marine mammals.

The notion that noise may act as a stressor for free-ranging marine mammals is not a new one. Several reports and reviews in both the noise and the stress literature have mentioned this possibility (e.g., Richardson et al., 1995; Fair & Becker 2000; NRC 2003, 2005; Nowacek et al., 2007). The most common conclusion in this literature is that very little is known regarding marine mammal stress responses to noise. The most common recommendation is that more data be gathered. As a result, managers have been left with little information to guide their decisions.

There are large gaps in our knowledge about the particular physiological effects that chronic, repetitive or even acute noise exposures may have on cetaceans and other marine mammals. Experiments with captive animals alone are unlikely to bridge this gap, given the ethical dilemmas that arise when one considers exposing animals to potentially harmful levels of noise. Nonetheless, we suspect that studies with captive animals will prove valuable in ascertaining the more subtle effects of noise, such as masking and interference with cognitive processing. Given the paucity of data specific to marine mammals, evidence gathered from other animal populations might constitute a baseline on which to ground hypotheses regarding the likelihood of cetaceans to experience similar stress processes.

To initiate such a transfer of information, Dokumentes des Meeres (www.sound-in-the-sea.org), as part of its ongoing project on anthropogenic noise and marine mammals, brought a number of marine mammal scientists together with a diverse range of experts from other fields to discuss the impacts of noise. The objectives of the workshop were twofold:

- to identify the potential and likely consequences of noise-induced stress for individual animals and the populations to which they belong; and
- to determine the likelihood that, and the ways in which, noise exposure may induce stress responses in marine mammals based on of what is known about the effects of noise on humans and other animals in addition to the available information for marine mammals.

These discussions are represented in two papers in this issue. The first summarizes what is known about the physiological stress response, the initiation of that response by anthropogenic noise, the importance of context (physiological, psychological and environmental) in the stress response, and the ways that noise itself can change that context (Wright et al., this issue, a). The contents of this paper are broad and it is hoped that the conclusions and findings will be of use to anyone that studies or manages any species that may be subject to disturbance by

anthropogenic activities. The second paper applies to marine mammals the concepts brought together in the first, drawing on what is known about the responses of marine mammals to noise as well as other anthropogenic activities (Wright et al., this issue, b). Important contextual considerations specific to marine mammals are also discussed, and a collection of key findings and research recommendations are offered. Finally, a summary table is provided in the appendix with examples of the various known effects of stressors on an array of animals for easy comparison.

Definitions

It became clear very early on in discussions at the workshop that the disparate fields of science often used terminology in slightly, but notably, different ways. A related issue arose from the different measures of sound in air and in water, as well as conversions between the two. The latter issue is considered by Hatch & Wright (this issue), and in more detail in the references therein. However, as the discussions surrounding the terms 'stress' and 'habituation' could have lasted for the entire duration of the workshop, participants agreed to disagree, but also to adopt a set of working definitions for the purposes of the workshop.

What is stress?

Early discussions quickly revealed that participants were using the term 'stress' in a number of different ways, as discussed by Romero (2004). These included referring to:

- the threatening[1] stimuli to which an individual is exposed;
- the physiological and behavioral coping responses to those stimuli; and
- the over-stimulation of the coping responses that results in disease.

To allow for a productive dialogue the participants decided to adopt the terminology and definitions provided in Romero (2004) to distinguish between these different meanings. Consequently, we use 'stressor' to refer to a threatening stimulus, 'stress response' to refer to the various physiological and behavioral coping mechanisms, and 'chronic stress' to refer to long-term over-stimulation of coping responses. We also use the term 'stressed' (sparingly) to refer to an individual that is already experiencing a stress response that may either be chronic or acute.

The participants adopted these as working definitions while recognizing that the biomedical community itself is debating the various terminology, with the controversial concepts of 'allostasis', 'allostatic load' and 'allostatic overload' being recently proposed by McEwen & Wingfield (2003, summarized briefly below and in more detail by NRC 2005 and Romero 2004). This adoption does not represent agreement by any participant of those definitions, simply recognition that common ground would be required as we moved forward with our discussions.

[1] Romero (2004) used 'noxious' instead of 'threatening'. However, the term noxious is often used to refer specifically to painful stimuli. Noxious stimuli will certainly provoke a stress response, but many stressors represent psychological or physiological threats in the absence of overt pain.

Allostasis

Allostasis is the maintenance of homeostasis within a changing life-cycle and environment. Animals may build up an 'allostatic load' when they must work harder and/or consume more to handle a normal life-history task (such as breeding or migration) or deal with some additional drain on their energy budget. When they are no longer able to fully offset the additional demands they enter a state of 'allostatic overload', the state in which energy requirements exceed the capacity of the animal to replace that energy from environmental resources (a 'stressed' state). Consequently, McEwen & Wingfield (2003) proposed that 'stress' only be used to refer to stimuli that require an emergency energetic response (i.e., when stimuli push the animal into a state of allostatic overload).

Allostasis does not easily consider effects without direct (if any) energetic consequences, such as loss of sleep and missed opportunity costs. As a result it is central to an ongoing debate in the biomedical world. Although this was all discussed at the workshop, the participants did not want to enter into the debate, but simply to recognize that it exists.

What is habituation?

Habituation has a specific and consistent meaning in the psychological literature: "the gradual weakening of a response to a recurring stimulus" (e.g., Domjan, 2005; Kuczaj & Xitco, 2002). Similarly, Telch, Valentiner, Ilai, Petruzzi & Hehmsoth (2000) defined physiological habituation as the "reduction of arousal that results in a disassociation between the stimulus and response propositions". It was noted at the workshop that it is possible for overt responses to weaken without an associated reduction in physiological response. It is thus not surprising that the term "habituation" has been used in a variety of ways by those who study marine mammals, partly due to the fact that this taxonomic discipline brings together scientists with a variety of different backgrounds. Furthermore, the term "habituation" is also often invoked without reference to the literature and seemingly in conflict with the use of the term in the biomedical or psychological literature (see Bejder et al., 2006). Consequently, it has on occasion been used seemingly to demonstrate the end of impact, despite the fact that the psychological literature recognizes that habituation can be a negative consequence in itself. For example, the U.S. Minerals Management Service, Alaska Outer Continental Shelf Region (MMS Alaska OCS Region), noted in their discussion of the likely effects of the planned Oil and Gas Lease Sale 193 in the Chukchi that as "other cetaceans seem to habituate somewhat to continuous or repeated noise exposure when the noise is not associated with a harmful event, this suggests that bowheads will habituate to certain noises that they learn are nonthreatening" (MMS Alaska OCS Region 2007, pp IV-105). A precise definition or source is never offered, however it is noted in the same report that certain birds "become habituated to shipping activity… and spend the summer nesting or living nearby without apparent harm" (MMS Alaska OCS Region 2007, pp IV-196). This latter comment suggests that MMS are equating a habituated animal with one that is unaffected by further exposure to the stressor concerned.

Workshop participants were generally in disagreement with the idea that a behaviorally habituated animal is unaffected by a stressor. However, they also disagreed about which specific definition of habituation should be used. Guidance was provided by Romero (2004), who presented a definition for the related term "acclimation" as to be when an animal no longer responds physiologically in the same robust manner to repeated or chronic stressors, such as repeated handling. In acclimation, the psychological context of the stressor has effectively changed: the stimulus is no longer threatening to the animal and the physiological stress response is reduced. However, it should be noted that there are situations where a reduction in behavioral response can occur without an associated reduced physiological response, as discussed in more detail by Wright et al. (this issue, a).

Psychologists will recognize that Romero's definition of acclimation is in fact the definition of habituation (albeit focused on the physiological response), and undoubtedly wonder why acclimation was preferred to habituation. Suffice it to say that some workshop participants wished to distinguish themselves from the various perceived misuses of the term "habituation" by others, especially pertaining to the management of marine mammals, and so acclimation was viewed as a less controversial term.

An organism sometimes becomes acclimated to one stimulus but then shows sensitization to a perceivably different stimulus presented at some later time (see Domjan, 2005; Romero, 2004). The acclimation process can alter the animals' physiology such that responses to novel stressors are enhanced compared to responses of non-acclimated animals. This process is known as "sensitization" or "facilitation" and it occurs frequently, although not always, as a result of acclimation. For example, if rats exposed to repeated handling are then transferred to a novel environment their physiological stress response is higher than in naïve controls (Dallman et al., 1992). In many cases, it is the sensitized response that signals pathological consequences or acclimation to repeated exposure to a stressor (i.e., researchers look for sensitization to a novel stimulus to assess acclimation to a previous, repeated stimulus). It is important to recognize that apparently calm or other non-responsive behavior does not necessarily indicate acclimation (see Beale, this issue). In addition, acclimatizing to a stimulus (e.g., an intense sound source) may reduce the stress response, but not eliminate the potential physiological damage on, for instance, hearing. Examples of this have been seen in human behavior (see Clark & Stansfeld, this issue).

Working definitions

In light of the above, participants agreed to use the following terminology and definitions (based mostly from Romero, 2004) for the purpose of the workshop. This does not necessarily reflect the preferred usage for any individual, nor establish a position in any discussion surrounding the concepts.

Stressor: a threatening or unpredictable stimulus that causes a stress response.

Stress response: the physiological, hormonal and behavioral changes that result from exposure to a stressor.

Chronic stress: a state that an organism enters when repetitive or long-term exposure to a stressor has exceeded an organism's regulatory capacities.

Context of a stressor: the physical and psychological conditions present when a stressor appears.

Acclimation: after repeated or chronic exposure to a single stressor, an animal no longer perceives the stressor to be threatening and reduces its physiological stress response. The decrease in stress response is specific to that stressor and does not generalize to other stressors as long as the animal is capable of distinguishing between them.

Sensitization[2]: when acclimation to one stressor increases subsequent stress responses to novel stressors.

"Stress hormones": a generic and non-scientific term for hormones whose concentrations change in response to stressors and are indicative of a stress response. They are divided in two main types: catecholamines (e.g., epinephrine/adrenaline, norepinephrine/norarenaline, etc.) and glucocorticoid-steroid hormones (e.g., cortisol, corticosterone, etc.). Some hormones (e.g., cortisol) have been traditionally used as indicative of stress. However, they may exhaust under repetitive stimuli and may not reflect chronic stress.

Steroid hormones: a class of hormones (including testosterone, estradiol and cortisol) typified by a four-ring structure.

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[2] We use sensitization instead of facilitation as per Romero (2004) as this is the standard term in the psychological literature.

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Endocrinology of Stress

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When an animal detects a stressor, it initiates a stress response. The physiological aspects of this stress response are mediated through two endocrine systems. The catecholamine hormones epinephrine and norepinephrine are released from the adrenal medulla very rapidly and have numerous effects on behavior, metabolism, and the cardiovascular system. This is commonly termed the Fight-or-Flight response. On a longer time scale, the glucocorticoid hormones are released from the adrenal cortex. They interact with intracellular receptors and initiate gene transcription. This production of new proteins means that glucocorticoids have a delayed, but more sustained, effect than the catecholamines. The glucocorticoids orchestrate a wide array of responses to the stressor. They have direct effects on behavior, metabolism and energy trafficking, reproduction, growth, and the immune system. The sum total of these responses is designed to help the animal survive a short-term stressful stimulus. However, under conditions of long-term stress, the glucocorticoid-mediated effects become maladaptive and can lead to disease.

Stress, as originally coined by Selye (1946), has been the subject of study for decades. It became quickly apparent that the term "stress" actually encompasses three related topics: changes/stimuli from the environment that cause "stress" (subsequently called stressors); the physiological and psychological responses to those stimuli (subsequently called the stress response); and the diseases that result from an overstimulation of the physiological and psychological responses (subsequently called chronic stress effects). Research has focused on all three of these concepts. An enormous amount is now known about what stimuli elicit which physiological and psychological responses. We also know many of the mechanisms whereby various hormonal mediators compromise organ, tissue, and cellular function (Fink, 2007). This paper will provide a brief overview of what is known about the endocrine responses to stressors. The following general information is broadly known and widely presented. Most of the information comes from the following sources (McEwen & Goodman, 2001; Nelson, 2005; Norman & Litwack, 1997; Norris, 2007; Sapolsky, Romero, & Munck, 2000) and interested readers should consult them for more detail. Specific information and individual studies are cited independently.

Although there are many hormones that have been identified as playing a role in the vertebrate stress response, two categories of hormones are thought to form the central components of the endocrine response. These are the catecholamines, epinephrine and norepinephrine (also known as adrenalin and noradrenalin) and the glucocorticoids. Together, these hormones help to orchestrate the body's stress response. How they do so is presented below.

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Catecholamine Responses

The catecholamines are a class of hormones consisting of a 6-carbon ring with a carbon side chain. The type of side chain determines the type of catecholamine and provides biological specificity. The two most important catecholamines in the stress response are epinephrine (Epi) and norepinephrine (Norepi). The catecholamines bind to specific membrane-bound G-protein receptors. When bound, these receptors initiate an intracellular cAMP signaling pathway that rapidly activates cellular responses. The speed at which these responses are activated provides the foundation for many of the catecholamine effects.

The suite of responses mediated by Epi and Norepi are commonly called the Fight-or-Flight response because they have immediate effects on increasing the readiness and activity of the animal. Upon detection of a stressor, Epi and Norepi are released by both the adrenal medulla and nerve terminals of the sympathetic nervous system. These hormones are produced beforehand and stored in secretory vesicles. Consequently, release of Epi and Norepi occurs rapidly after detection of a stressor. When coupled to the rapid activation of cellular processes through their receptors in target tissues, Epi and Norepi activate organism-level responses within seconds of detecting a stressor.

Epi and Norepi activate a number of responses, including: decreasing visceral activity and shutting down digestion; increasing visual acuity; increasing brain blood flow and arousal; increasing gas exchange efficiency in the lungs; breaking down glycogen to release glucose stores; inducing vasodilation in muscles; inducing vasoconstriction in the periphery; increasing heart rate; and inducing piloerection. This suite of responses comprises the classic Fight-or-Flight response and is designed to help the animal survive an acute threat such as an attack by a predator or conspecific competitor. They not only activate beneficial responses such as increasing alertness and providing energy to muscles, but also inhibit processes, such as digestion, that can be superfluous during an acute emergency.

Glucocorticoid Responses

Glucocorticoids are a class of steroid hormones consisting of a 4-ring carbon backbone with different hydroxyl groups and carbon side chains attached at various places around the rings. The particular side chain and where it is attached determines which steroid it is, and provides specificity for the various steroid receptors. All steroids share common precursors and common synthetic pathways and are interconverted, so that both the classic steroid hormones (e.g., testosterone) and their intermediates (that can also have biological activity) can be found both in tissues and in the blood. However, the primary steroids released in response to a stressor are the glucocorticoids (GCs): cortisol and corticosterone. Most species rely primarily upon either cortisol (e.g. fish and most mammals, including humans and marine mammals) or corticosterone (e.g. birds, reptiles, amphibians, and some rodents), although both can be found in most species and some species rely upon a

mix of the two (e.g. some rodent species). Both hormones bind to the same receptors and appear to have identical functions in their respective species.

The release of GCs results from a hormonal cascade that begins with the detection of a stressor. Areas of the brain that interpret external and/or internal stimuli (e.g. the amygdala and hippocampus) send neuronal signals to the hypothalamus (primarily the paraventricular nucleus). The cells in the hypothalamus send axon projections to the median eminence where they terminate along capillaries of a portal blood system that connects to the anterior pituitary. Once stimulated, the hypothalamic cells release a suite of hormones into the portal blood. The most important of these hormones are corticotropin-releasing factor (CRF) and arginine vasopressin (AVP – or arginine vasotocin in non-mammalian vertebrates). (Although CRF is sometimes referred to as CRH (corticotropin releasing hormone), a recent committee addressing nomenclature proposed that CRF be adopted as the appropriate name (Hauger et al., 2003) CRF and AVP travel the short distance of the portal blood system from the base of the hypothalamus to the anterior pituitary. There they bind to receptors and stimulate the release of adrenocorticotropic hormone (ACTH). ACTH is then released into the general circulation and travels to the adrenal cortex where it binds to its receptors and stimulates the production of steroid synthetic enzymes. GCs, like all steroids, are not stored once they are produced, so there is no functional difference between ACTH-induced production of GCs, and the release of GCs into the bloodstream. Thus, the increase in production rate results in increased GCs released into the peripheral circulation. This hormonal cascade from the hypothalamus to the adrenal via the pituitary is called the Hypothalamic-Pituitary-Adrenal (HPA) axis. Although other factors, such as gonadal steroids, cytokines, and the splanchnic nerve, can also directly or indirectly modulate GC secretion, the HPA axis is the primary pathway stimulating GC release in response to a stressor.

Once released, GCs travel in the peripheral circulation primarily bound to corticosteroid binding globulins (CBG). Steroids are highly lypophilic so that most GCs are bound to CBG, but unbound GCs increase dramatically during a stress response. Whether CBG functions primarily as a carrier to deliver GCs to their target tissues, or primarily as a buffer to moderate GC function, is currently under debate (e.g. Breuner & Orchinik, 2002). Once at the target tissue, GCs pass through the outer cell membrane and bind to an intracellular cytoplasmic receptor. Activated receptors then enter the nucleus and begin acting as transcription factors. Activated receptors bind to short stretches of DNA sequences called glucocorticoid response elements and act as promoters or inhibitors of gene transcription. Consequently, the end product of GC stimulation is either the production of new proteins or the inhibition of protein production. In addition, there is evidence that a membrane-bound receptor for GCs exist. This receptor is believed to mediate rapid behavioral effects of GCs. Along with GC's effects in response to a stressor, GCs vary in a circadian rhythm and are important in regulating normal physiological processes.

In contrast to Epi and Norepi, GCs are much slower at exerting their effects. The multiple steps of the HPA axis ensure a time lag between the onset of a stressor and the increase in blood GC concentrations. In general, increases in GC

concentrations cannot be detected in under 3-5 min (and occasionally longer for some species). When coupled with GCs' primary effect of altering gene transcription rates, the physiological impact of GCs begins to occur approximately 20-30 min after the onset of a stressor. If a stressor does not continue, negative feedback will generally start to reduce GC concentrations in 30-60 min, although because the newly produced proteins can continue to function, GCs' physiological effects can last considerably longer. Consequently, the catecholamines and the GCs dovetail to produce both an immediate and a longer-term response to stressors.

Although GCs alter gene transcription rates for an enormous number of genes, at the organismal level GCs can be classified as having five broad effects (Romero, 2004): increasing blood glucose concentrations; altering behavior; inhibiting growth; inhibiting reproduction; and modulating the immune system. This suite of effects is believed to help the animal recover from a stressor, shut down those systems that can profitably be delayed until the danger has passed, and prepare the animal for potential subsequent stressors. Each of these broad effects will be discussed briefly below.

The classic effect of GCs is to increase the blood glucose available to tissues involved in responding to a stressor. In fact, the name "glucocorticoids" was assigned to these hormones because of this important role, which takes two general forms. First, GCs increase blood glucose by converting protein to glycogen, thereby indirectly increasing glycogen break down into glucose by Epi and Norepi, and by stimulating the catabolism of protein to form new glucose in a process called gluconeogenesis. Second, GCs reduce the uptake of blood glucose by target tissues, resulting in higher blood glucose concentrations available to tissues involved in responding to stress. GCs do this by stimulating the internalization of glucose transport molecules from the cell surface of target tissues. Fewer glucose transporters result in less glucose utilization, the sum of which across multiple target tissues results in higher blood glucose concentrations. Tissues that need extra glucose to respond to the stressor (e.g. muscles) compensate for the GC effect and essentially have preferential access to the increased pool of blood glucose. The sum of these effects is that GCs orchestrate the allocation of energy stores during either prolonged stressors or after stressors have ended (Dallman et al., 1993).

GCs are known to alter behavior, but how they alter behavior depends upon the context in which the stressor is presented. Specific behavioral changes are difficult to predict. Although there has been an enormous amount of research on GCs' behavioral effects in the laboratory, recent research has also included studies of wild animals in their native habitats. For example, studies have shown that GCs can induce migratory activity in birds (Silverin, 1997). Depending upon the environmental context, GCs can promote a behavioral strategy of hiding and waiting out a stressor, or promote a behavioral strategy of abandoning an area and fleeing the stressor (Wingfield & Ramenofsky, 1997). The mechanisms for how GCs alter behavior are currently unknown and an active area of research, but may involve a novel membrane-bound G-protein receptor that induces rapid behavioral

effects. GCs can also induce long-term behavioral changes by having a direct effect on memory formation and consolidation in the brain.

GCs inhibit growth by blocking the secretion of growth hormone from the pituitary, decreasing the sensitivity of target cells to growth hormone, and inhibiting protein synthesis (related to GC-stimulated gluconeogenesis from protein catabolism mentioned above) (Sapolsky, 1992). This is a transient effect during acute stress responses and, because growth is a long-term process, appears to have little impact on the overall growth of the animal. Prolonged exposure to GCs, however, can result in observable inhibition of growth. In humans, the syndrome is called psychosocial dwarfism (Green, Campbell, & David, 1984). Inhibition of growth is believed to be an example of GCs shifting resources away from processes that can be postponed in order to use those resources to cope with an emergency.

GCs also inhibit reproduction (Wingfield & Romero, 2001). Vertebrate reproduction is regulated with a hormonal cascade that is similar to the HPA axis. The hypothalamus releases gonadotropin releasing hormone (GnRH), which causes the pituitary to release leutenizing and follicle-stimulating hormones (LH and FSH), which in turn stimulate gamete formation and reproductive steroid production (e.g. testosterone and estradiol) by the gonads. GCs suppress this pathway in several ways: by inhibiting GnRH release, reducing pituitary sensitivity to GnRH, and reducing the sensitivity of gonads to LH. Furthermore, GCs can reorient behavior away from reproduction. Similar to the effects on growth, GCs' effects on reproduction have little impact over the short-term, but long-term stress can cause complete reproductive shutdown. Stress has even been implicated as a factor in human infertility (Homan., Davies, & Norman, 2007; Wischmann, 2003). GCs' effects on reproduction are thought to be another example of allocating resources preferentially during an emergency.

Interestingly, the reproductive system can become resistant to inhibition by GCs in some reproductive contexts. For example, if GCs allocate resources away from reproduction, and thereby reduce individual fitness (i.e. successful production of offspring), the benefit of the reproductive system ignoring the GC signal may outweigh the cost of not responding to the stressor. In semelparous species (those that breed once and then die) such as some salmon species and several Australian marsupial rodents, death occurs in all individuals (or all individuals of one sex) shortly after breeding. The proximate cause of death is extremely high levels of GCs that catabolize essential proteins (reviewed in Wingfield & Romero, 2001). Reproduction in these animals clearly continues despite elevated GCs. Furthermore, GCs do not inhibit reproduction in many short-lived species and in older individuals, and in dominant individuals in some species where the dominant individual has a limited period with access to mates (Wingfield & Sapolsky, 2003). Consequently, susceptibility to GC-induced inhibition of reproduction is highly specific depending on the importance of continuing to reproduce in the presence of stress which may vary depending upon age, sex, stage of the breeding cycle, etc.

Finally, GCs have a broad inhibitory effect on the immune system (Spencer, Kalman, & Dhabhar, 2001). This has made GCs very important clinically and they are widely prescribed as drugs. GCs have a number of effects

on the immune system including: inhibiting the synthesis, release, and efficacy of cytokines (immune system proteins); inhibiting antigen presentation through reduced major histocompatibility complex (MHC) expression; reducing the activation and proliferation of T cells, B cells, and macrophages; lowering the circulating levels of lymphocytes; reducing lymphocyte chemotaxis; reducing the number of phagocytic cells at inflammation sites; stimulating atrophy of the thymus; and triggering the death of immature T and B cells. All of these effects lead to immunosuppression, especially with long-term GC exposure. There is some evidence, however, that GCs might enhance immune function in the short-term (Dhabhar, 2006; Dhabhar & McEwen, 1999). The reason GCs have such powerful immunosuppressive effects is not entirely clear, but it has been proposed as a mechanism to prevent overactivation of the immune system that could lead to autoimmune diseases.

Conclusion

The large suite of catecholamine and GC responses is believed to be essential in surviving stressors. Clearly, the lack of Epi and Norepi release, i.e. the Fight-or-Flight response, would be devastating during a predatory attack. Similarly, animals that lack GCs are unable to mount an effective stress response and quickly die (Darlington, Chew, Ha, Keil, & Dallman, 1990). All three hormones serve to orchestrate an organism's effective response to stressors in order to promote survival.

On the other hand, long-term or chronic release of these hormones can be detrimental. Repeated or constant activation of the Fight-or-Flight response can lead to cardiovascular disease. Similarly, individuals exposed to long-term or chronic GCs suffer from a number of diseases including diabetes, depression, psychosocial dwarfism, reproductive dysfunction, and immune suppression. Consequently, responses to acute stressors generally enhance fitness, but long-term exposure can decrease fitness. Clearly, successful long-term survival requires balancing acute release while minimizing chronic exposure.

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From Classic Aspects of the Stress Response to Neuroinflammation and Sickness: Implications for Individuals and Offspring

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Accumulating evidence suggests that exposure to psychological stressors leads to increased expression of pro-inflammatory cytokines and activation of inflammatory-related pathways in the central nervous system. Several logical predictions arise from these findings: (1) stressor exposure should produce changes in behavior that are reminiscent of acute illness; (2) administration of anti-inflammatory agents should ameliorate some behavioral consequences of stressor exposure; and (3) there should be convergence between anatomical and neurochemical pathways activated by stressor exposure and those involved in mitigating sickness behaviors. Importantly, these predictions have been tested in our laboratory across multiple stressor paradigms (footshock, maternal separation, and during acute alcohol withdrawal) using two species (rats and guinea pigs), suggesting that sickness may represent a more general motivational state that can be elicited by a diverse range of psychological challenges. Implications of these findings for understanding stress-related changes in behavior, mood and neuroinflammatory processes will be discussed with special reference to implications for the individual and reproductive fitness.

The concept of stress has suffered a long and contentious history with little agreement even today about what it entails (e.g., McEwen & Wingfield, 2003). The problem becomes particularly apparent when one tries to operationalize the term for scientific study, and even worse when one seeks to determine the impact of stress on individuals or populations. In its crudest form, the concept of stress can be broken down into three principle components which I will describe in some detail below, using what is known about central nervous system (CNS) regulation of the stress response as a lens through which consequences of stressor exposure might be viewed. The first component must be the evocative agent: the general construct of stress can be parsed into categorically distinct threats (often termed stressors), each of which may activate the major stress responsive systems to varying degrees. The *stress response*, therefore, becomes the second principle component and refers to the constellation of changes (behavioral, physiological, or psychological) provoked by the actual or perceived threat. Finally, the impact of stress exposure on the overall health of the organism (Component III) must in some way be a function of the stress response(s) that have been evoked by the stressor. As a result, stress-responsive systems have been studied extensively in biomedical research as core systems that mediate and/or modulate nearly all disease-related processes (whether infectious, traumatic or genetic in nature). Ecologists, on the other hand, are particularly interested in the impact of anthropogenic stressors on the welfare and reproductive fitness of diverse species. With that in mind, the goal

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of the following review is to help bridge the gap between these seemingly disparate fields.

The Classic Stress Responsive Systems

Two classic systems that are principally activated during times of stress are the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Though they will be discussed categorically below, it is in fact the combined effort of the SNS and HPA axis – among other critical endocrine and neural systems – that ultimately comprise an organism's response to stress. These systems are activated rapidly in response to stressful stimuli and have a broad impact on diverse aspects of physiological functioning. Indeed, many of the delayed and/or long-term consequences of stressor exposure are set into motion as a downstream consequence of the initial SNS and HPA responses. In this regard, indirect measures of SNS activation (such as increased heart rate, blood pressure, or hyperthermia) or direct measures of SNS output (plasma concentrations of epinephrine and norepinephrine) and HPA activation (corticosteroid concentrations in plasma, tissue or excrement) are often used as an index for the severity of a stressor that has been encountered. Regardless of which measure is examined, the magnitude of the stress response is best defined as 'area under the curve' whenever possible because this measure integrates peak response with duration of stressor exposure (Barnum, Blandino Jr, & Deak, 2008; Pacak & Palkovits, 2001). Note, however, that for these measures to be useful indices of the stress response, they must be (a) assessed with respect to a known baseline or non-stressed condition in the same animal or a group of conspecifics that have been otherwise treated identically; (b) evaluated in a threatening context, since pleasurable experiences such as sexual intercourse (Bonilla-Jaime, Vazquez-Palacios, Arteaga-Silva, & Retana-Marquez, 2006), euphoria produced by drugs of abuse (Goeders & Clampitt, 2002), or anticipation of palatable food (Pecoraro, Gomez, Laugero, & Dallman, 2002) also elicit profound activation of these same physiological response systems but do not fit the intuitive mold of 'stress'; and (c) considered within the context of circadian rhythms, as corticosteroids and catecholamines both evince diurnal variation. Some caution is therefore prudent in the interpretation of physiological measures that are used to infer that a given response is a manifestation of stress.

The sympathetic nervous system is a fast-acting response to stress that can be detected within seconds of stressor onset, assuming that the onset is a punctate event (i.e., one with a clearly defined beginning and end, such as detection of a predatorial attack). In other cases, SNS activation is often described as a steadily escalating 'tone', where over the course of hours, days or months (depending on the nature of the stressor), general activity of the SNS is increased, leading to increased metabolic demand and gradual wear-and-tear on physiological systems (allostatic load) that may eventually culminate into physiological failures (allostatic overload) (McEwen & Wingfield, 2003).

Mechanistically, the vital nature of SNS responses to stress is underwritten by the redundancy evident in the system. For instance, SNS activation leads to the release of the catecholamines epinephrine and norepinephrine from sympathetic

nerve terminals that innervate all organs of the body and the musculature, allowing for rapid and profound changes in whole organism physiology. Epinephrine and norepinephrine are also released from the adrenal medulla into the general circulation where it acts as an endocrine signal (i.e., affecting distal targets) that helps prolong the action of neurally-derived catecholamines. These peripheral cascades of catecholamines are regulated by autonomic structures in the CNS such as the locus ceruleus (LC), nucleus of the solitary tract (NTS), the ventrolateral medulla (VLM) and the medial amygdala. Importantly, these structures all communicate to other structures in the CNS using predominantly (though not exclusively) norepinephrine and epinephrine, and are sensitive to internal homeostatic threats (hypoxia, hypoglycemia, immune stimuli, toxin and toxicant exposure, etc). These structures (particularly the LC) receive extensive input from brain structures involved in threat perception from the forebrain, thereby regulating peripheral sympathetic outflow through descending projections that activate sympathetic chain ganglia (see Guyton & Hall, 2006) for a general overview of SNS organization and function). Together, the redundant release of catecholamines directly onto target tissues from sympathetic nerve terminals, into the general circulation and locally within the CNS produces a coordinated, whole body response to stressful stimuli.

Though activation of the hypothalamic pituitary-adrenal (HPA) axis is somewhat slower to develop (usually within 3-5 min of stressor onset), the impact of corticosteroid release from the adrenal cortex is equally profound, though on a somewhat more protracted timeline. Every nucleated cell in the body expresses corticosteroid receptors, though the relative expression of these receptors differs markedly across cell and tissue types (Spencer, Young, Choo, & McEwen, 1990) and ultimately determines organ sensitivity to corticosteroids. Corticosteroids (cortisol in humans, corticosterone in rats) are the ultimate effector of the HPA response and are the end-product of a series of hormonal secretions that are initiated by cells in the paraventricular nucleus (PVN) of the hypothalamus (Dallman et al., 1987). As a result, the hypothalamus generally, and the PVN more explicitly, receives neural input from numerous other nuclei in the CNS involved in the perception of threat (i.e., stress) and is therefore uniquely situated as a final site of integration for the stress response. From a teleological perspective, this allows diverse threats to the organism (i.e., stressors) to activate a single effector response (corticosteroid release). The stereotyped release of corticosteroids in response to diverse stressors leads to mobilization of glucose from the liver, alterations in gene expression patterns and changes in cellular metabolic activity among other far-reaching consequences, all of which ultimately promote survival in the face of diverse threats (Munck, Guyre, & Holbrook, 1984).

Sickness and Neuroinflammation as a Consequence of Stress

While SNS and HPA responses to stress occur rather quickly, these responses inandof themselves do not readily explain the diverse range of long-term consequences of stress. For instance, exposure to relatively intense stress in rodents leads to reduced food and water consumption (Deak et al., 1999a; Dess, Raizer, Chapman, & Garcia, 1988; Marti, Marti, & Armario, 1994), decreased so-

cial and sexual behavior (Retana-Marquez, Salazar, & Velazquez-Moctezuma, 1996; Short & Maier, 1993; Uphouse, Selvamani, Lincoln, Morales, & Comeaux, 2005), and reduced activity/exploration in a novel environment (Woodmansee, Silbert, & Maier, 1993). Because these changes often persist for several days following stressor termination, they cannot be explained readily at a mechanistic level by activation of the principle stress responsive systems, the SNS and HPA axis, because these responses have largely resolved by the time the behavioral adaptations emerge. It is therefore advantageous to examine physiological and behavioral processes that occur in a protracted fashion following termination of the prototypical stress responses, and these effects will be the subject of the following discussion.

When this constellation of behavioral changes is viewed from the perspective of motivation rather than as individual behavioral changes, the overall pattern of changes seems to suggest decreased propensity to engage in goal-directed behavior. For many years, the biomedical research community has likened these changes to depressive-like tendencies (Gronli et al., 2005). While this interpretation provides clarity on clinical implications of intense stressor exposure, it does little to advance our understanding of brain mechanisms underlying such widespread consequences of stress. Moreover, this interpretation would seem to violate the implicit evolutionary presumption that the stress response – and behavioral consequences that ensue – somehow act in an *adaptive* manner to promote survival.

In light of this, we prefer to view the constellation of behavioral changes observed after stressor exposure as *recuperative responses* rather than pathological ones. In doing so, it becomes immediately apparent that the collective changes in behavior observed after intense stressor exposure are strikingly similar to those observed during acute illness produced by infection, termed sickness behaviors (Hart, 1988; Kent, Bluthe, Kelley, & Dantzer, 1992a). In fact the similarities between consequences of stressor exposure and acute illness extend well beyond behavioral changes and include alterations in neurotransmitter release (A.J. Dunn & Welch, 1991), changes in cognitive function (Gibertini, Newton, Friedman, & Klein, 1995; Pugh et al., 1999), as well as changes in peripheral immune function (see Maier & Watkins, 1998 for a review). These similarities led us to propose that many behavioral consequences of stressor exposure – particularly ones indicative of a general malaise – may be aptly described as 'stress-induced sickness behaviors' (Hennessy, Deak, & Schiml-Webb, 2001). This hypothesis arose from numerous empirical findings. First of all, stress can increase the expression of pro-inflammatory cytokines in the CNS (Deak et al., 2005b; Nguyen et al., 1998), and these factors are also known to be critical for the generation of sickness behaviors precipitated by acute illness (Bluthe et al., 1999; Kent, Bluthe, Kelley, & Dantzer, 1992a; Kent et al., 1992b). Injection of lipopolysaccharide (a component of cell walls of gram negative bacteria that is often used to mimic infection) or direct administration of pro-inflammatory cytokines provokes a similar complement of behavioral changes as intense stressor exposure (Hennessy et al., 2004; Plata-Salaman & French-Mullen, 1992). Acute stress also increases expression of acute phase proteins and evokes a sustained increase in core body temperature, effects

that can persist for days following stressor termination (Deak et al., 1997). Indeed, exposure to psychological stressors produces a fever response that is commonly used as a rapid and sensitive index of SNS activation (Barnum, Blandino Jr, & Deak, 2007; Oka, Oka, & Hori, 2001). Finally, and perhaps most compelling, central administration of anti-inflammatory agents can reverse many sickness-like changes provoked by stress (Hennessy et al., 2007; Milligan et al., 1998; Schiml-Webb, Deak, Greenlee, Maken, & Hennessy, 2005). Together, these data support the view that acute illness and stressor exposure produce many similar sequelae that are coordinated through common biological pathways.

In this regard, it is interesting to note that sickness responses to infection are thought to reflect a goal-directed process (i.e., a motivational state) designed to promote recuperation, not a debilitated state for the animal (Aubert, 1999; Dantzer, 2004; Hart, 1988). Evidence to support this hypothesis comes from the simple observation that sickness behaviors are more readily observed in the home cage environment of laboratory animals (i.e., a safe haven) than in a novel environment where threats are unknown. In a very clever study, it was shown that sick dams fail to rebuild their nest and retrieve pups at normal ambient temperatures, but readily do so in a cold environment that threatens her offspring (Aubert, Goodall, Dantzer, & Gheusi, 1997). Data from our own laboratory suggest that rats exhibit normal swim behavior while sick after doses of LPS that evoke a pronounced fever and increased cytokines that persist for 2-3 days (Deak, Bellamy, & Bordner, 2005a; Deak et al., 2005c). Such plasticity of behavior during times of immunological threat supports the view that sickness itself is a goal-directed, recuperative response. Our central argument, therefore, is that intense stressor exposure is followed by a similar recuperative period, mediated by common neural mechanisms.

Mechanistically, increased expression of pro-inflammatory cytokines in the CNS is likely to be the common biological mechanism that unites the consequences of stressor exposure and acute illness (Maier & Watkins, 1998). Of the many inflammatory factors that have been identified, Interleukin-1 (IL-1) appears to be particularly inducible by stress and the hypothalamus is a key structure where such changes are prevalent (Deak et al., 2005b). It is important to note, however, that not all stressors increase expression of IL-1 in the CNS. For instance, exposure of rats to simple restraint in a Plexiglas tube, brief social defeat or insulin-induced hypoglycemia had no effect on hypothalamic IL-1, while exposure to footshock, tailshock or immobilization all elicit profound increases in hypothalamic IL-1 (Deak, Bellamy, & D'Agostino, 2003; Nguyen et al., 1998; Plata-Salaman et al., 2000; Shintani, Nakaki, Kanba, Kato, & Asai, 1995). Interestingly, if simple restraint was administered in combination with a hypoglycemic challenge or on an orbital shaker, two procedures that change both the nature and intensity of the restraint experience, then increased hypothalamic IL-1 was in fact observed (Deak et al., 2005b). To the extent that increased IL-1 can be used to more broadly infer neuroinflammation, there are several potential explanations for these findings. First of all, there may be an *identifiable threshold* of stress that is necessary to provoke a neuroinflammatory response. Though stressor intensity is a notoriously difficult construct to define operationally, stressor intensity is often inferred based on the magnitude of the corticosteroid response observed (eg. Pace et al., 2005). In this

regard, it is noteworthy to mention that increased hypothalamic IL-1 and plasma corticosterone concentrations bare little association if any (Barnum et al., 2008; Deak et al., 2005b).

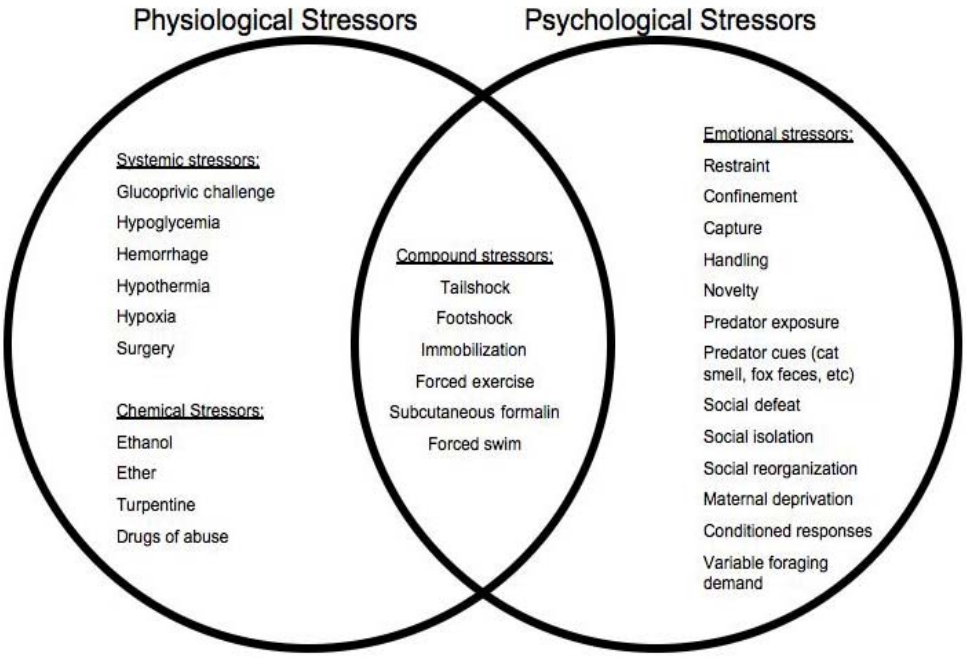

Figure 1. Venn diagrams categorizing the most commonly used stressor paradigms. Available data supports the view that most threats to mammalian species can be separated into at least two separate categories, described here as "physiological" and "psychological" stressors. Note, however, that some stressors are not readily classified into either category because the response they produce is significantly more profound than for other, more categorically distinct, stressors. To account for this, we use the term "compound stressors" to refer to stressors which fall in the overlapping portions of the Venn Diagram.

An alternative explanation for the apparent stressor-specific increases in hypothalamic IL-1 is that features of the stressors themselves are recognized in a categorically distinct fashion by the CNS and that only specific categories of stressors can activate a neuroinflammatory response. Indeed, there is general agreement among stress researchers that threats can be divided into at least two distinct categories based on the brain systems they activate (Dayas, Buller, Crane, Xu, & Day, 2001; Herman, Prewitt, & Cullinan, 1996; Sawchenko et al., 1996; Sawchenko, Li, & Ericsson, 2000). 'Psychological' stressors (also referred to as emotional, processive and neurogenic) are detected by the cognitive or perceptual apparatus of the organism and include paradigms such as restraint, novelty and predator exposure among others (see Figure 1). These stressors seem to preferentially activate forebrain and limbic structures such as the amygdala, prefrontal cortex, and hippocampus that send descending and/or lateral inputs to the PVN, thereby leading to activation of the HPA axis. 'Physiological' stressors (also referred to as physical, homeostatic or systemic), on the other hand, represent dire threats to organismic

functioning. As such, physiological stress encompasses internal threats to homeostasis such as hypoglycemia, hypoxia, hemorrhage, and immune challenge. These threats are detected largely by vital regulatory centers in brainstem autonomic nuclei including the VLM and NTS. These structures provide direct noradrenergic drive to the PVN through ascending fiber tracts, thereby leading to activation of the HPA axis (Herman & Cullinan, 1997).

Interestingly, some stressors yield brain activation patterns that do not fit neatly into the psychological or physiological categories, but instead seem to uniquely activate both sets of brain structures (Dayas et al., 2001). In this regard, if emotional and physiological stressors are opposite ends of the spectrum, then some stressors may lie more centrally because they uniquely comprise characteristics of both poles. This premise is depicted in Figure 1 where Venn diagrams are used to provide an overview of the numerous stressors employed in the laboratory setting. Note that direct empirical data is not available for all of these stressors, so stressors were arranged based on intuitive similarity to other stressors and/or the common outcomes produced by them.

To the extent that stressor intensity may be reflected by activation of quantitatively greater numbers of stress-responsive brain structures, stressors that fall in the central domain (termed 'compound stressors') would be expected to produce the most severe outcomes. From a functional neuroanatomical perspective, this would be reflected by a 'compound' drive to hypothalamic structures (particularly the PVN) because drive to the PVN would arrive from brainstem structures as well as forebrain/limbic structures. It is under these circumstances that activation of a neuroinflammatory response – indicated by increased expression of IL-1 and possibly other cytokines – is most likely to occur. Initial support for this hypothesis comes from our recent work showing that exposure to restraint in combination with a hypoglycemic challenge increased IL-1 in the hypothalamus, while neither stressor alone had any effect (Deak et al., 2005b). Whether this is due to activation of both psychological (restraint) and physiological (insulin-induced hypoglycemia) stress circuits or is a synergistic response produced by direct metabolic challenge to hypothalamic neurons (produced by insulin) during an otherwise mild stressor (restraint) remains to be determined. Regardless, the dual nature of the threat led to tell-tale signs of neuroinflammation, underscoring the potential impact for individuals when faced with multiple threats (i.e., stressors) that, if encountered individually, would otherwise have little consequence. In fact, it is likely to be the synergistic interaction among diverse threats – rather than the additive or cumulative ones – that are conceptually difficult to predict, yet represent the most profound threats to the health and vitality of all species.

The next logical question becomes, How do you get from the immediate perception of threat and activation of classic stress responsive systems (SNS and HPA axis) to neuroinflammation and a sickness-like syndrome? This question becomes particularly puzzling when one considers the prominent role of corticosteroids as counter-regulators of immune processes. That is, corticosteroids are widely known for their ability to inhibit inflammatory processes and are used clinically as a therapeutic tool to rapidly supplant inflammatory processes (Munck et al., 1984). However, the doses necessary to produce anti-inflammatory effects are typically

supraphysiological and there are numerous reports indicating that corticosteroids are necessary for normal progression of the immune response (Fleshner, Deak, Nguyen, Watkins, & Maier, 2002) and that lower doses of corticosteroids activate signal transduction pathways that promote inflammatory-gene expression. Indeed, there is compelling evidence that actions of corticosteroids (i.e, whether the effects are pro- or anti-inflammatory in nature) depend heavily on the tissue/cell types to which they bind (Sorrells & Sapolsky, 2007). With that said, removal of endogenous corticosteroids via adrenalectomy dramatically increases expression of IL-1 in the CNS provoked by stress (Nguyen et al., 1998; Nguyen et al., 2000), suggesting that corticosteroids constrain the development of neuroinflammation in response to stress. In contrast, the release of norepinephrine in both central nervous system structures and peripheral immune organs has been shown to increase the expression of proinflammatory cytokines (Blandino Jr, Barnum, & Deak, 2006; Johnson et al., 2005). Together, these findings suggest that neuroinflammatory consequences of stress may be mechanistically intertwined between the stimulatory actions of the SNS and the inhibitory influence of the HPA axis, though much work clearly remains to be done.

The Broader Impact of Stress-Related Neuroinflammation for Evolution and Ecology

Though the framework provided here focuses rather selectively on the ability of stress to increase pro-inflammatory cytokines in the CNS and its relationship to stress-induced sickness behaviors, the impact of cytokines and neuroinflammation extends well beyond an acute behavioral syndrome (summarized in Figure 2). Indeed, there are numerous laboratories examining the impact of neuroinflammation on cognitive function, mood, and affective disorders as well (Deak, 2007; Dunn, Swiergiel, & de Beaurepaire, 2005). From an evolutionary standpoint, these effects can be viewed as proximate consequences of stress insofar as they produce a readily observable and immediate impact on functioning of the individual. However, there is a broader cost to the individual that may not be immediately apparent and it is these costs that are most difficult to quantify. Because these costs are still for the affected individual (not offspring), I would suggest use of the term ‘distal consequences’ to describe them. For instance, normal aging of the CNS across the lifespan is associated with a transition to a greater pro-inflammatory cytokine balance, an effect that may be accelerated by repeated stressor exposure (Frank et al., 2006). Similarly, neuroinflammation is causally related to the development of neurodegenerative disorders such as Alzheimers Disease and Parkinson’s disease and may account for the earlier age of onset and worsening of symptoms produced by stress (eg. Whitton, 2007). Finally, our discussion has centered largely around neuroinflammation, but it is important to recognize that many of the same inflammatory-related changes are observed in other systems as well. As such, activation of inflammatory-related pathways during times of stress has been associated with the development and/or exacerbation of cardiovascular disease (Black, 2002), rheumatoid arthritis and Crohn’s Disease, as well as autoimmune disorders such as multiple sclerosis, lupus and Type I Di-

abetes. Perhaps even worse, increased IL-1 in the CNS sensitizes later stress reactivity that can be observed days to weeks later (Deak, Bellamy, & Bordner, 2005a; Johnson et al., 2002; Schmidt, Aguilera, Binnekade, & Tilders, 2003), suggesting that the impact of chronic stress across the lifespan may feed-forward into progressively more deleterious stress consequences. To this end, activation of inflammatory pathways in the CNS may more generally portend the erosion of individual health. From an ecological perspective, this would be more likely manifest as reduced longevity (due to greater susceptibility to predation) rather than full-blown disease states.

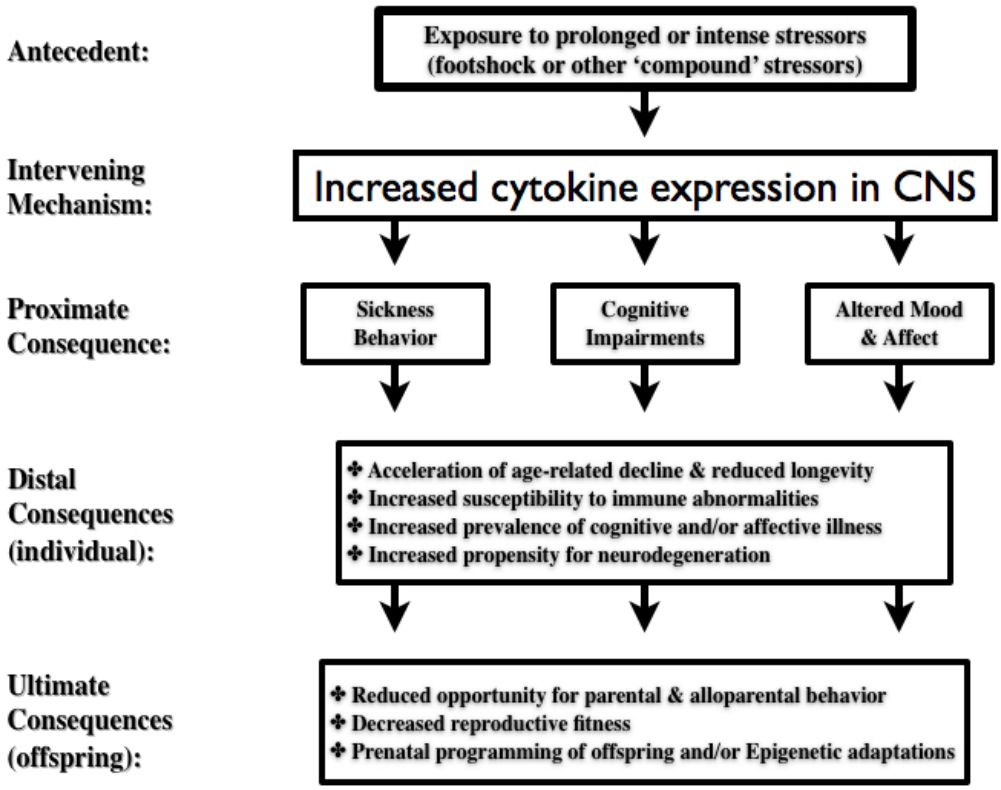

Figure 2. Schematic summary of central cytokine involvement in proximate, distal and ultimate consequences of stressor exposure.

The intrinsic or extrinsic factors that lead an individual to develop a given pathology in response to stress is not currently known in most cases. However, much the same as the ecologist is accustomed to thinking about speciation being driven by the various pressures of natural selection, the same principles may be turned inwardly towards the physiology of the individual. That is, we each possess a diverse range of organs and tissues that operate at some level of efficacy. The weakest of these organs or tissues – perhaps as a result of prior insult, developmental programming, or genetic liability – would be expected to show greater deterioration, wear-and-tear, or overt disease as a result of stress, thereby manifesting as

individual differences in stress reactivity. In the end, the disease states provoked or exacerbated by stressor exposure will undoubtedly enhance susceptibility to predation in the wild.

The impact of stress is not restricted to the individual and often extends to one's offspring as well. Such 'ultimate consequences' come in the straight-forward sense that reproductive behavior is often diminished during peak periods of stress, an effect that is also observed during acute illness, particularly for females (Avitsur & Yirmiya, 1999). Poor health associated with accelerated aging may reduce the opportunity for parental and alloparental behavior, thereby reducing social transmission of critical knowledge and skills later in life. Some of the most profound effects of stress on offspring occur by altering maternal behavior. Rat dams that spend more time licking and grooming their offspring yield litters that are more resilient to stress later in life, while maternal deprivation/neglect produces the opposite effects (Kaffman & Meaney, 2007). Similar effects have been observed in non-human primates where the amount of time the mother spends foraging predicts stress reactivity and mental health of her offspring, presumably because conditions where food is scarce or difficult to acquire lead to greater neglect of offspring (Gorman, Mathew, & Coplan, 2002; Rosenblum & Paully, 1984). As such, the impact of escalating foraging demand would be expected to have a particularly adverse impact on mammalian species where parental investment is high.

With that said, we must resist the call to view stress, stress responses or the consequences of stress in a purely deleterious manner. Recall instead that the principle stress responses (SNS and HPA axis) in addition to the inflammatory response have been highly conserved across the course of evolutionary history and therefore must provide significant adaptive benefit towards survival. For instance, exposure to acute stress has been shown to improve several aspects of wound healing and immune function, while chronic exposure to stressors can produce immunosuppressive effects (Deak et al., 1999b; Dhabhar & McEwen, 1997). These findings challenge the prevalent dogma that stress has only deleterious effects on immune function and remind us that the stress response has many adaptive qualities.

Insight into the adaptive nature of the stress response can also be gleaned by examining the evolution of the endocrine and inflammatory systems more generally. Modern evolutionary views argue that endocrine systems such as the HPA axis evolved initially from unicellular organisms where they were expressed as intracellular signaling cascades, which evolved into cell-to-cell signaling pathways in multicellular organisms, and so forth (Roth et al., 1985). Evidence for high affinity corticosteroid receptors in yeast cells (*Candida albacans*) suggests that rudimentary "HPA axes" may have followed a similar evolutionary path (Malloy, Zhao, Madani, & Feldman, 1993). Though it has not been stated explicitly, the elements of neuroinflammation discussed here are all considered to be part of the 'innate' immune response, which is phylogenetically the most ancient component of the vertebrate immune system. This evolutionary framework suggests that activation of inflammatory pathways by stress is likely to generalize across taxonomic orders, though clearly more work is necessary to test this hypothesis. Based on available data, however, it is reasonable to conclude that stress-related neuroinflammation and the sickness-like cascade that ensues must also have some adap-

tive value. To my mind, it makes good evolutionary sense that the magnitude of the recuperative response provoked by stress should somehow vary as a function of stressor intensity. Whether 'stressor intensity' in this case more aptly refers to crossing some identifiable threshold or is defined by unique features of the stress experience itself remains to be determined. Regardless, it is clear that hallmark signs of neuroinflammation can be provoked by the assembly of two threats that individually are without influence on neuroinflammation, as when hypoglycemia was combined with restraint as a unitary challenge (Deak et al., 2005b). In this regard, one might speculate that exposure to threats such as low-level toxin or toxicants from the environment might interact synergistically with, or lower the threshold for, otherwise innocuous threats (brief capture, increased foraging demand, anthropogenic noise, etc) to produce more severe consequences for the individual than would otherwise be expected from isolated threats alone. But in the end, the principles of evolution remind us once again that conservation of biological function is as prevalent as niche adaptation. It is perhaps not so surprising, therefore, that surviving a threat of significant proportion requires a period of recuperation, and that natural selection has favored a unified biological approach (i.e., sickness) as the prevailing mechanism to promote recovery.

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The Behavioral Ecology of Disturbance Responses

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Measuring the impacts of anthropogenic activities on wildlife is crucial for ensuring effective management. Animal behavior is often considered a sensitive index of impact, but its use requires detailed understanding of the context dependent decisions animals make. In this manuscript I identify a number of areas where insights from the field of animal behavior are relevant to studies of human disturbance and activity. In particular, I differentiate between disturbance effects and disturbance impacts and show how context-dependent decision-making often makes animal behavior an unreliable index of impact. I show the areas where animal behavior can be useful in quantifying minimum disturbance impact when additional information is available, and identify a number of areas where further research may help improve the management of anthropogenic activities within wildlife areas.

The effective management of human activities in wildlife areas is an important conservation issue, as the footprint of human influence continues to expand (Green, Cornell, Scharlemann & Balmford, 2005) and incidental impacts of human activities (e.g. noise and disturbance) spread into more areas (Keirle, 2002; Hatch & Wright, this issue; Weilgart, this issue). Such expanding anthropogenic activity is widely perceived to lead to negative consequences for the wildlife beyond habitat loss alone (Frid, 2003; Higham, 1998; Stevens & Boness, 2003; Taylor & Knight, 2003; de la Torre, Snowdon & Bejarano, 2000; Wauters, Somers, & Dhondt, 1997). Understanding how animals respond to noise and more generally, anthropogenic activities is fundamental to resolving potential conflicts between humans and animals (Hatch & Wright, this issue; Weilgart, this issue; Wright et al., this issue, a). There are numerous ways in which it is possible to study animal responses, but changes in an animal's behavior are often the most obvious consequences of anthropogenic activities so it is not surprising that many authors use behavioral observations to understand impacts (Fortin & Andruskiew, 2003; Nettleship, 1972). However, interpretation of the results of animal behavior studies is not always straightforward and while the study of behavior within a conservation context is to be encouraged (Sutherland, 1998) insights from the wider field of animal behavior will have direct relevance to understanding. In this paper I review a number of areas where understanding animal behavior offers insights of management importance in understanding how animals may respond to human activities. This is not an attempt to fully review the impacts of anthropogenic activities on animal behavior, but rather to highlight a few important insights that have sometimes been overlooked in conservation studies (Buchholz, 2007; Sutherland, 1998).

Animal behavior is an eclectic field with a scope that ranges from purely behavioral observation (the assessment of the amount of time an animal

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spends doing various activities, for example), through questions relating to resource allocation (how many offspring to have in a litter, how much testosterone to place in an egg, etc.) to more psychological questions of how animals perceive their environment (when in a foraging patch, how long do animals remember recent weather events, etc.) (Alcock, 2003; Buchholz, 2007). Underlying the field is an attempt to understand how animals make decisions and what the consequences of these decisions are. In this paper I will attempt to show how understanding from a number of different areas of animal behavior has implications for understanding how noise and other anthropogenic disturbance is likely to impact animal conservation and welfare, starting with the simplest observations of animal behavior.

Behavioral responses to threatening stimuli

Perhaps the most obvious of the responses an animal makes to a threatening stimulus are simple behavioral responses. It is therefore unsurprising that measuring behavioral responses such the distance at which an animal flees or first responds to human presence have therefore been widely used to address a number of related questions about the impacts of disturbance. Primary among these is the simple question: does human disturbance affect animals (Blumstein, Anthony, Harcourt, & Ross, 2003; Klein, Humphrey, & Percival, 1995; Tuite, Hanson, & Owen, 1984)? Behavioral measures have also been used when human disturbance effects are assumed and the question is more to identify which populations or species are most susceptible to disturbance (Blumstein, Fernández-Juricic, Zollner, & Garity, 2005; Tarlow & Blumstein, 2007). However, behavioral responses involve the animal making a number of different decisions, so a naïve exploration of the simple behavioral response may be inadequate.

For example, on first hearing a noise, a feeding animal may stop foraging and look around for the source. If the noise or its source is threatening enough, the animal's stress response pathways may be activated at this point, the short- and long-term physiological consequences of which are highlighted elsewhere (e.g. Deak, this issue; Romero & Butler, this issue). What an animal decides to do about this threat, however, is not fixed: it may choose to simply keep a wary eye on the threat and resume feeding, or it may flee the area to feed in a safer location. Let us assume the noise is caused by a one-off, short-term stimulus and the animal chooses to abandon the area temporarily but will return when the threat has passed. This is a short-term response to a short-term stimulus and the costs of this response are likely to fall well within the norms the animal is used to (i.e. homeostasis is maintained: Romero, 2004) so this would be an appropriate decision for the animal to make. However, if the stimulus is repeated frequently, the cost of repeated short-term responses (lost foraging time, costs of flight, etc.) may accrue meaning that an animal in the frequently disturbed environment may decide that staying put but maintaining a constant readiness to leave is less costly than fleeing. This may result in increased energetic expenditure and chronic stress with all the physiological consequences associated (Deak, this issue; Romero & Butler, this issue), but is still an appropriate decision if the costs involved in repeatedly leaving the feeding area are greater than the physiological consequences of chronic stress. If we are to accurately interpret behavioral responses to a disturbance event,

therefore, it is crucial that we understand the *context* within which an animal makes decisions.

Before continuing further, it is important to note that the *effects* of a disturbance event are not necessarily the same as the *impacts* of that disturbance event. E.G., in the first example above the effect of the one-off disturbance was to make the animal temporarily leave a feeding area, an effect that was not shown by the animal in the second example. Leaving a foraging area might be assumed to be a negative impact (as noted by Gill, Norris, & Sutherland, 2001a), but the impact is likely to be largely negligible compared with the impact on the animal subjected to repeated stimuli in the second example that showed no behavioral effect but may suffer physiological consequences. If we are interested in conservation and welfare, we are clearly much more interested in impacts than simple effects (Gill et al., 2001a; Gill, Sutherland, & Watkins, 1996; Nisbet, 2000). This crucial difference is often ignored when researchers equate effect with impact: certainly human disturbance affects animal behavior, but this does not necessarily mean human disturbance has a (negative) impact on animal conservation or welfare. The previous example illustrates one case where the behavioral measure (whether or not an animal left the area) is clearly not an appropriate index of the impact of the disturbing stimuli. More generally, Gill et al. (2001a) suggested that a lack of behavioral response may not imply a lack of fitness consequence but may instead reflect a lack of choice and Beale & Monaghan (2004a) provided an empirical test showing that such theoretical arguments translate directly to the field and concluded that it is wrong to assume that the most responsive animals are those that are most vulnerable to disturbance.

It seems that context-dependent decision-making behavior therefore limits the practical utility of recording behavioral responses as an index of the impact of stressful stimuli. I therefore consider that ignoring context and using simple behavioral measures as a direct mechanism for assessing either whether animals will suffer impacts of disturbance, or for identifying which populations or species may be most vulnerable to disturbance is seriously flawed. This, however, does not necessarily mean that behavioral measurements cannot be useful for researchers interested in impacts of human disturbance provided the context under which the behavioral decisions are made is understood and no direct link between behavioral effect and disturbance impact is assumed. For example, instead of assuming effect and impact are identical, if behavioral responses are coupled with further information on the costs of the changed behavior itself a *minimum* estimate of the cost of responding can be estimated. In the earlier example an estimate of the energetic costs of lost foraging time and energy spent moving away can be estimated and put in the context of daily energy expenditure. However, for the animal that showed no behavioral response the estimated cost would be zero but as we have already seen this animal is actually much more likely to suffer stress-related impacts than the first animal. Thus estimates of cost based on behavior alone are likely to be underestimates and if the estimated cost is low it does not mean that the impact of the stimulus is necessarily low. It is also clear that this method does not allow comparison between populations or species. If the minimum cost is put in an appropriate context where its importance can be measured against other energetic costs and it can be shown that animals are not compensating for such increased energetic expenditure (e.g. by feeding at night: Lane & Hassall,

1996), the minimum potential for negative impacts can be assessed and may be substantial (Williams, Lusseau, & Hammond, 2006).

Similarly, if the context in which decisions are made is not changed, behavioral measures can be used directly to measure the relative degree to which stressors affect individuals. However, maintaining similarity of context is challenging and variations must be strictly controlled experimentally and/or statistically. If, for example, the degree of impact caused by two different types of boat engine is of interest it may be possible to approach the same individual animals in the same location at the same time of day over a relatively short time span with the two different engines and record the behavioral responses. If one engine type consistently results in greater behavioral responses it is very likely that this engine type is perceived to be a stronger stressor than the alternative. It is crucial, however, that the context is maintained as constant as possible when assessing the impact of the two potential stressors: the individuals must be the same, in the same size group, engaged in the same activity when first approached and in the same location. If any of these variables has changed, the context in which the animals find themselves will also have changed and the results will be highly suspect unless tightly controlled statistically. Statistical control may be appropriate, for example, if the number of individuals within a group is variable and group-size alters behavioral response in a predictable manner: in such cases inclusion of a group-size variable in statistical analysis will go some way to controlling for this aspect of context.

Impacts of avoidance behavior

Perhaps the next stage of assessing the impacts of behavioral responses to threatening stimuli involves asking questions about the redistribution of animals (i.e. avoidance) that is widely observed in areas where frequent disturbances are likely (Tarlow & Blumstein, 2007; Weilgart, this issue). What is the cost to the animals of this avoidance? Does it limit population in some way?

Although not yet widely applied, resource-use based models have been used as one way of assessing the population consequences of avoidance behavior (Fernández-Juricic, Sallent, Sanz, & Rodríguez-Prieto,, 2003; Gill et al., 1996; Gill, Norris, & Sutherland, 2001b; Percival, Sutherland, & Evans, 1998). Such models develop a behavior-based model to assess the impact of human disturbance, but do not rely on directly measuring the behavioral responses animals show to human presence. Instead, they assume that animals show behavioral responses to humans but suggest that if any significant fitness costs are associated with such responses, a critical, limiting resource will be under-used. Therefore, patterns of resource use are determined instead of measuring behavior directly. If resources are under-utilized in areas where disturbance is high, human disturbance is regarded as having an impact of conservation concern. For example, Gill et al. (2001b) report a study of the effect of disturbance on the Black-tailed Godwit. They showed that, despite this species being perceived as sensitive to human disturbance, no under-use of food resources was detected, presumably either because the birds fed in the most disturbed areas at times when there were few disturbances (e.g. early mornings), or because the birds chose to use the disturbed areas once resources

were used up in undisturbed areas. They therefore conclude that although these animals appear to avoid human presence, this does not reduce the population size supported by the estuaries they studied. Similar issues have been studied using simulation models: Stillman et al. (2000) used an individual based model to show that avoidance behavior may lead to population decline and Blumstein et al. (2005) used a simple model to show that resource use may fall in disturbed areas but neither studies include context-based decision making.

Studies of resource use have so far focused on utilization of food supplies (Fernández-Juricic, Sallent, Sanz, & Rodríguez-Prieto, 2003; Gill et al., 1996; Gill et al., 2001b) and wintering habitat (Percival et al., 1998), but could also be used in relation to other resources, including breeding territories. However, such studies rely heavily on the correct identification of critical resources. If the effect of disturbance was measured on the use of the wrong resource, it would be possible to incorrectly conclude that human disturbance was not an important factor. It is possible, for example, that the utilization of food resources is unaffected by human disturbance, but that resting sites are negatively affected and the population declines because there are insufficient disturbance free areas to rest. Alternatively, it might be possible to wrongly identify human disturbance as limiting populations for similar reasons. For example, if some other external factor holds an animal's population artificially low (e.g. hunting pressure on migration) and these animals show avoidance of humans, they may not make full use of resources in disturbed areas: not all available resources are required to maintain the population so the animals never need to use the resources in more disturbed areas. However, it would be wrong to assume that this pattern of resource use provided evidence that disturbance was implicated in the low population of this species. If the population were to increase (e.g. because hunting pressure is reduced), animals might eventually decide to forage in the more disturbed areas because these previously unexploited resources are now required to maintain the increased population.

On the other hand, if animals do avoid areas with a high frequency of anthropogenic activity and under-use a particular resource or habitat, negative impacts are still not necessary consequences. For example, Mallord, Dolman, Brown, & Sutherland (2007) showed that woodlarks *Lullula arborea* avoided heavily visited habitat. This resulted in fewer individuals breeding in visited areas, but the few birds that did so were freed from competition and enjoyed increased breeding success, with the total number of fledglings from disturbed heaths approximately equal to the number of fledglings from undisturbed heaths where birds were breeding in higher densities. The overall population is therefore determined by a delicate balance between the improvement in breeding success due to density dependent effects and the reduction in habitat availability due to (inappropriate) disturbance avoidance. Whether this balance leads to a stable population or one in decline can only be determined by assessing disturbance impacts across the entire area of suitable habitat and estimating the number of animals that this could support in the absence of human disturbance. This, and especially the effect that might occur when disturbance is seasonal and otherwise perfect habitat becomes poor after animals have settled in the area (e.g. at holiday times) can be seen as forms of an ecological trap (i.e. anthropogenic activities have altered habitat quality

such that the cues an animal uses to select a habitat are no longer appropriate: (Kokko & Sutherland, 2001).

Other measures of impacts of threatening stimuli

Other methods for determining the impacts of anthropogenic stressors have recently been reviewed elsewhere and I shall not attempt this here (Tarlow & Blumstein, 2007). However, methods involving the measurement of physiological and metabolic parameters associated with stress responses are relevant to a discussion of animal behavior because they help explain how impacts may occur even in the absence of behavioral responses.

Some penguins are noted for their lack of behavioral responses to visitors, especially in areas where visitors are frequent (e.g. Nimon, Schroter, & Stonehouse, 1995; Fowler, 1999). This lack of response led to the suggestion that these birds are "habituated", a claim also made for other species (Nisbet, 2000) but, if a real phenomenon, it is more likely to refer to learned non-response as physiological acclimation seems unlikely (Wright et al., this issue). For example, Fowler (1999) studied the hormonal and behavioral responses of penguins in areas of differing disturbance. Fowler showed no difference in physiological responses between birds in medium and low disturbance plots, but found a significantly decreased hormonal response in the high disturbance areas, indicative of acclimation. However, as variation was large in the control plots but small in the disturbed plots the results suggest that, rather than birds acclimating, birds that showed high responses left the area. This is further suggested by the lower nesting density in the high disturbance plot (Fowler, 1999). Fowler also showed that average strength of the behavioral responses in each plot decreased with visitor levels, but did not examine the relationship between an individual's hormonal and behavioral responses.

Additional work on the heart-rate of kittiwakes *Rissa tridactyla* and European shag *Phalacrocorax aristotelis* with a long history of exposure to human visitors also highlighted extreme individual variation in heart-rate responses to disturbance (Beale, 2004). These studies found that even when negligible changes in behavior were observed in response to a potentially threatening stimulus, heart rate of those birds that do respond could increase by 50%. This clearly indicates that these birds are likely to be experiencing physiological stress responses which must be considered chronic in areas with frequent disturbance events. However, a raised heart-rate may itself have conservation consequences, as maintaining raised heart-rates requires increased metabolic costs which may, in turn, affect demographic parameters. I estimated an increase of 7.5 – 10% in daily energy expenditure for some individual Kittiwakes in Scotland (Beale, 2004), an increase likely to result in eventual abandonment of nesting attempts once energy reserves drop below a critical level: this is indeed the proposed mechanism linking anthropogenic activity to nesting failure in this species (Beale & Monaghan, 2004b). It is also worth noting that individualistic heart-rate responses to human disturbance again indicate the importance of understanding animal behavior, where some individuals choose to respond, and others not. Only by understanding that there are susceptible and unsusceptible individuals can the observed change in breeding success be comprehended, not by simply considering the mean response of the population.

It is, of course, important to question whether even declines in breeding success reflect an impact of genuine conservation concern. Indeed, breeding success is not necessarily a good surrogate of fitness thanks in part to density dependent effects (Frederiksen, Lebreton, & Bregnballe, 2001; Olijnyk & Brown, 1999). Moreover, breeding success is often far less important in determining populations of relatively long-lived animals than winter mortality (Russell, 1999; Weimerskirsch, Brothers, & Jouventin, 1996), a distinction likely to hold for many long-lived species. A decrease in breeding success of 9%, as observed for Kittiwakes in Scotland is, in fact, unlikely to have a major impact on the population as a whole.

Conclusions

Understanding that animals are individuals that make context-dependent decisions about how to respond to their environment results is an important insight with practical application to understanding how animals respond to anthropogenic stimuli. It is also crucial to differentiate between disturbance effect and disturbance impact. I have shown how this context-dependent decision making means the use of simple behavioral indices as a direct measure of disturbance impact is unsound, and have pointed out areas where incorporating further information can make behavior measures potentially useful. I have shown how the decisions animals make about where to feed and breed can be influenced by human activities and the consequences or otherwise this might have for the population. I have shown that in birds at least, it is clear that disturbance from anthropogenic activity can reduce breeding success even in the absence of behavioral effects. I have also shown how even physiological responses to anthropogenic activity can be individualistic, indicating that a more profound understanding of these responses also required understanding decision making behavior. Throughout, I have attempted to stress the distinction between effects and impacts, a distinction that is crucially important when making management decisions. Research on the effects of human disturbance is slowly taking account of the need to understand behavior (Fernández-Juricic et al., 2003; Gill et al., 2001b; Stillman et al., 2000), though papers continue to be published that overlook context-dependant decision-making behavior (Frid, 2003; Fortin & Andreskiew, 2003; Fernández-Juricic, Vaca, & Schroeder, 2004; Blumstein et al., 2005).

Future work on disturbance impacts is likely to be valuable and the impact of recreation on biodiversity has been identified as one of the 100 ecological questions of high policy relevance in the UK (Sutherland et al., 2006). Future efforts must distinguish between effect and impact and must adequately incorporate context-dependent decision making behavior. Although behavioral measures are inappropriate for assessing the comparative impact of disturbance on multiple species (even at the same location different species will experience the environment differently and will find themselves in different contexts), there is clearly a need to identify methods to protect multiple species (Blumstein et al., 2005). It is likely that further advances may be made through the use of individual based models that allow individuals to make truly context-dependent decisions. Further studies that identify disturbance effects at multiple levels – behavioral, physiological and metabolic

– are likely to improve understanding of disturbance impacts. Finally, I believe that more study of the behavior of people in wildlife areas is likely to offer new insights into how to manage conflicts between humans and wildlife. This aspect of human disturbance research is currently largely neglected, but must be considered a crucial part of the equation.

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A Brief Review of Anthropogenic Sound in the Oceans

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Sound in the oceans is generated by a variety of natural sources, such as breaking waves, rain, and marine animals, as well as a variety of human-produced sources, such as ships, sonars and seismic signals. This overview will begin with a quick review of some basic properties of sound waves with particular reference to differences between the behaviours of these waves underwater versus in air. A basic understanding of the physics of underwater sound is critical to understanding how marine animal acoustic signals have evolved relative to their different functions and how changes in the marine acoustic environment due to increasing anthropogenic sound in the oceans may impact these species. We will then review common sources of anthropogenic sound in the oceans. The frequency contributions of three major sources of underwater anthropogenic sound and their relative intensities will be discussed: naval exercises, seismic surveys and commercial shipping. Finally, a case study examining relative inputs to a regional noise budget, that of the Gerry E. Studds Stellwagen Bank National Marine Sanctuary, will be presented to introduce the audience to methodologies for characterizing and managing sound on an ecosystem level.

A number of reviews of anthropogenic sound in the oceans (and its effects on marine mammals) have described properties of underwater sound, outlined the differences between the transmission of sound underwater versus in air and compared acoustic characteristics associated with different types of anthropogenic sources (e.g., Hildebrand, 2005; MMC, 2007; Nowacek, Thorne, Johnston, & Tyack, 2007; NRC, 1994, 2003; Richardson, Greene, Malme, & Thomson, 1995). This paper will not attempt to provide the same detailed coverage of these topics. Instead, this paper will provide a basic introduction to the sources and physics of underwater sound for the uninitiated audience and provide references for the interested reader to gain additional information.

The reviews noted above also include thorough examination of the current scientific knowledge surrounding the effects of underwater noise on marine mammals; however, Weilgart (this issue) provides a brief overview of this material. Furthermore, natural sources of sound in the oceans will not be detailed here. This is not because these sounds do not affect marine mammals, but because management of underwater noise focuses on human contributions to the marine acoustic environment, in which sound plays important natural roles.

What Is Sound? A Primer

Sound is a compression wave that causes particles of matter to vibrate as it transfers from one to the next. These vibrations produce relatively small changes in

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pressure (compared to atmospheric pressure) that can be detected by the ear.

Depicted graphically as a sine wave, the wavelength of a sound is equal to the speed of sound divided by its frequency. Thus, high-frequency sounds have shorter wavelengths than low-frequency sounds travelling in the same medium (Figure 1). The perceived "loudness" of a sound is a function of its amplitude (i.e., how much energy it carries) or intensity (the power of the wave transmitted in a particular direction in watts per square meter) and the hearing thresholds of the receiver (i.e., listener). It should be noted that the speed of sound in seawater is the same for all frequencies, but varies with aspects of the local marine environment such as density, temperature and salinity. Due mainly to the greater "stiffness" of seawater relative to air, sound travels approximately 1,500 m/s in seawater while it travels only approximately 340 m/s in air. Boundaries between two mediums with very different sound speeds act somewhat like mirrors to all sound not striking that boundary perpendicularly. Consequently, sound does not travel well between air and the oceans.

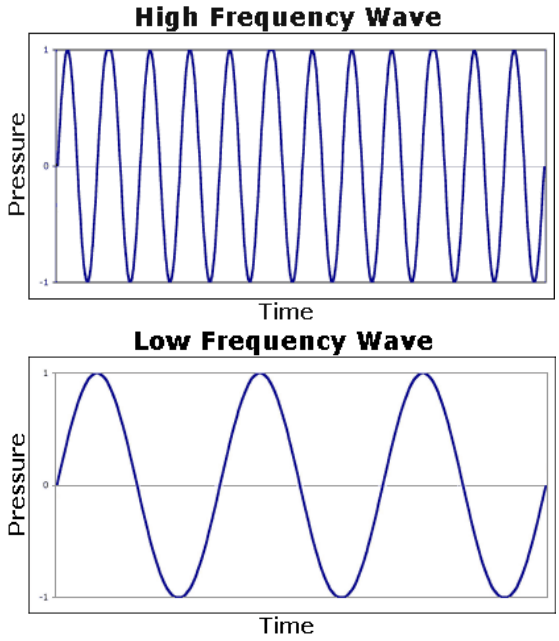

Figure 1. This diagram shows a high frequency wave (above) and a low frequency wave (below), plotted as pressure versus time. The high frequency wave has completed twelve cycles over the time shown. The low frequency wave has completed only three cycles over the same time. Diagram reproduced with permission from *Discovery of Sound in the Sea* http://www.dosits.org/ (a).

A sound's intensity is usually measured in decibels (dB), which is a relative measurement rather than an absolute measurement of wave's directional energy. Measurements in air usually reference 20 micropascals (µPa), or about the sound of a pin drop, while the standard reference in seawater is 1 µPa. Converting between sound intensities in air and water can be confusing and often the source of conflict. This is not only due to the relative nature of the decibel scale, but also the

relationship between a sound's intensity and the medium it is travelling through, in addition to the different methods for measuring the level of a sound. Sound waves with the same *intensities* in water and air when measured in watts per square meter have relative *intensities* that differ by 61.5 dB. Thus, for sounds with the same absolute *intensities* in watts per square meter, one must subtract 61.5 dB to obtain the sound's relative intensities in water referenced to 1 µPa. Reference intensities cause 26 dB of this difference, while the differences in densities and sound speeds account for the other 35.5 dB of the difference in *intensities* (Urick, 1983).

As mentioned above, there are different ways to characterize a signal's amplitude. The most common methods are to measure peak-to-peak pressure, peak pressure, and root mean squared (rms). Peak-to-peak amplitude is represented in the waveform by the entire height of the sound wave, peak pressure would be the largest displacement from the central line and rms measures the average of the pressure of the sound signal over a given duration. Due to its direct relationship to the amount of energy carried by the sound wave (i.e., intensity), the rms pressure is the most common metric used to characterize sound waves (Madsen, 2005).

As a result of the physical and measurement differences described above, sounds with equal absolute intensities in seawater and air have higher relative intensity, travel faster and go farther before they loose their energy in seawater than in air. In addition, regardless of the medium the sound is travelling through, low frequency sounds travel farther than high frequency sounds because their energy is absorbed more slowly and louder sounds travel farther than softer sounds because they have more energy to disperse over distance from the source.

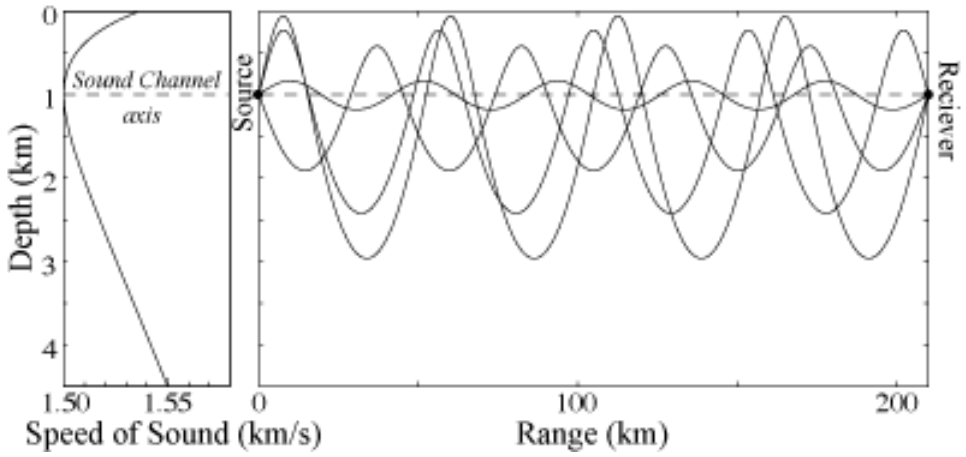

Figure 2. This diagram shows the sound channel axis. Sound speed profile from mid-latitudes is represented on the left. The paths that sound travels from a source at 1000m depth to a receiver at 1000m depth and 210km away from the source are shown on the right. Diagram reproduced with permission from *Discovery of Sound in the Sea* http://www.dosits.org/ (b) and adapted from Figure 1.1 of Munk, Worcester, & Wunsch (1995).

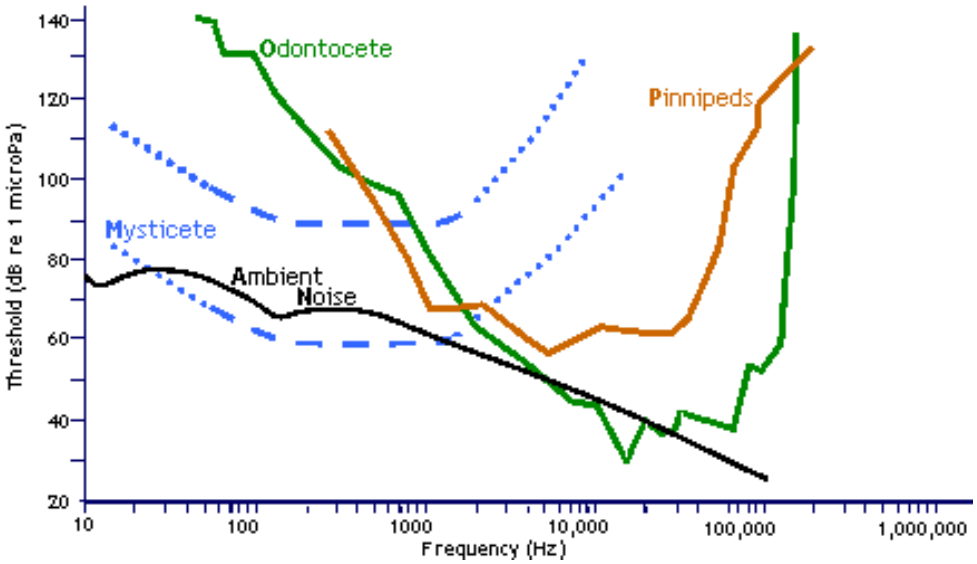

Figure 3. Estimates of the hearing thresholds for mysticetes, odontocetes and pinnipeds with ambient noise profile superimposed. The y-axis is relative intensity in underwater dB. The x-axis is the frequency of a sound on a logarithmic scale. Figure modified with permission from *Discovery of Sound in the Sea* http://www.dosits.org/ (c).

In the majority of the ocean there is often a minimum sound speed due to the predominant effects of heat from the sun and density due to depth on the speed of sound in water (salinity also plays a major role where it varies widely, such as near shore and in estuaries). The increasing sound speeds above and below this minimum tend to focus sounds like a lens at the minimum (Figure 2). Any sound travelling at about 12° or less from the horizontal are unable to escape and are refracted back toward the minimum, allowing sound to propagate much further due to a reduction in spreading and reflection and adsorption by the sea surface and sea floor. This is known as the deep sound channel, or SOFAR channel. In the deep ocean at mid-latitudes, the slowest sound speed occurs at a depth of about 800 to 1000 meters. However, the depth varies from over 1600 m in the warmest waters of the world to100 m in colder waters and can even reach the surface at the ice edge, becoming a surface sound channel.

Finally, sound is often categorized as either signal or noise. However this categorization depends heavily on the receiver (listener), who will define sounds of interest as signals and everything else that might interfere with those signals as noise. For example, Navy sonar operators would consider their sonar to be a signal, while marine mammals are likely to consider it to be noise. Concerns regarding the impacts of noise on signals must also take into account differences in species and/or individuals range of hearing. The quietest sounds, across the range of frequencies that can be heard by an individual receiver define its hearing thresholds (Figure 3).

Anthropogenic Noise

Human use of the sea, such as for shipping, military activities, oil and gas exploration, and recreation (including cruises and pleasure boating), is increasing the amount of sound that is introduced into the oceans (see Table 1). As these sounds are generally not considered to be signals by marine fauna, they will be referred here as noise. The continuing increase in anthropogenic noise in the oceans may be affecting marine life in many ways, since many marine animals have evolved to use sound as their main means to communicate, sense their surroundings, and find food underwater (Berta, Sumich, & Kovacs, 2006). As light does not travel very far in water, auditory capabilities have evolved to supplement and/or replace the use of vision for many marine animals (Bradbury & Vehrencamp, 1998). The same advantages conferred by sound relative to light underwater have led humans to deliberately introduce sound into the ocean for many of the same reasons as marine fauna: communication (e.g., sub-to-sub), feeding (e.g., fish finding sonar) and navigation (e.g., depth-finders).

The sounds produced by the range of sources in Table 1 are also highly variable, some being characterized as impulsive (such as seismic surveys) and tonal (such as sonar), comparatively loud (such as explosives) and relatively quiet (such as most fishing activities), persistent (such as shipping), short (such as winches) and very short (such as a single seismic survey pulse). Some noise sources, such as explosions, naval low frequency active sonars (LFA), some mid-frequency active sonars, high-power seismic surveying systems that are used to explore the ocean floor for oil and natural gas resources and commercial ships can all be heard over large distances, sometimes across oceans (Nieukirk, Stafford, Mellinger, Dziak, & Fox, 2004).

In general, seismic survey airguns represent the most prolific impulsive sounds introduced into the ocean by human activity. Conversely, commercial shipping is collectively making an ever-increasing contribution to the omnipresent background noise over very large spatial scales in the ocean, as well as intermittent local impacts as point sources (see below).

Many of the various sources and their characteristics have been described in previous works (e.g., Hildebrand, 2005; Nowacek et al., 2007; NRC, 1994, 2003; Richardson et al., 1995). Therefore, here we shall focus on three source types that have drawn considerable recent attention: naval exercises, seismic surveys, and commercial shipping.

Naval Exercises and Sonar

Naval activities involve a number of activities that introduce noise into the oceans, including live-ammunition training, vessel noise and explosions. However, the exercises that have been subject to the most scrutiny are those involving mid-frequency sonar operations. Around the world, mid frequency sonars have been correlated with strandings of multiple Cuvier's beaked whales in the Bahamas and have been coincident in time and space with additional stranding incidents (see Brownell, Yamada, Mead, & van Helden, 2004; Cox et al., 2006; ICES, 2005;

Weilgart, this issue). Mid-frequency naval sonar can produce sound at levels of up to 237 dB re 1uPa @ 1m mainly at frequencies between 2-8 kHz on a 2-second duty cycle repeated as needed for variable periods. The two tactical sonars most frequently used by the US Navy, AN/SQS-53C and AN/SQS-56, are focused in the 2.6 to 3.3 and 6.8 to 8.2 kHz ranges, respectively. Approximately 145 of the US Navy's ~280 ships have mid-frequency sonar capabilities, although not all of these ships utilize these capabilities at any one time. However, the US Navy is not the only military using these or similar sonars and worldwide usage is unknown.

Table 1
Types of anthropogenic noise, with example sources. Note this is not an exhaustive list.

Noise	Example sources
Sonar	Military and commercial
Marine geophysical surveys	Commercial and research
Explosions	Military exercises and testing, dynamite fishing, offshore rig decommissioning
Acoustic deterrent devices (ADDs) and acoustic harassment devices (AHDs)	Fishing activities
Winches, onboard machinery, etc.	Fishing, research, commercial activity
Vessel noise at predominantly lower frequencies	Commercial shipping and other large vessel activity (e.g., tankers, military vessels, cruise liners, etc.)
Vessel noise at predominantly higher frequencies	Smaller commercial vessels (e.g., fishing, ferries, fast ferries, recreational boating, whale-watching and research vessels, etc.) and personal water craft (e.g., jet skis)
Ice breaking and associated engine noise	Icebreakers
Acoustic thermometry of the ocean climate (ATOC) and other sounds used for oceanographical studies	Research vessels and equipment
Noise from offshore development, both during construction and operation	Dredging and other development, (e.g., oil rigs, deep-water ports, wind farms, etc.)
Noise from coastal development (including on-ice activity) both during construction and operation	Ports and harbours, sea walls, piers, bridges, aquaculture facilities, industry and residential buildings
Aircraft (under the circumstances when sound crosses into the ocean)	Helicopters, aeroplanes (especially at supersonic speeds), spacecraft, missiles and other military projectiles
Traffic noise	Traffic on bridges and coastal roads, ice-trucking (through the ice)

Concerns were also raised regarding a surface towed low-frequency active sonar system (SURTASS-LFA) that can include up to 18 projectors in a vertical array, each producing pulses up to 215 dB re 1uPa @ 1m mostly between 100 and 500 Hz. This system utilizes the deep sound channel to propagate over very large distances. Several species of mysticetes use sounds with overlapping frequencies, and also appear to utilise the deep sound channel to increase the range of their sounds (Payne & Webb, 1971). Thus, environmental impact assessments for this sonar type have focused on changes in the feeding behaviors of blue and fin whales (*Balaenoptera musculus* and *B. physalu*; Clark & Altman, 2006; Croll, Clark, Calambokidis, Ellison, & Tershy, 2001), the migratory behaviour of grey whales

(*Eschrichtius robustus*; Tyack & Clark, 1988), and the reproductive behaviour of humpback whales (*Megaptera novaengliae*; Fristrup, Hatch, & Clark, 2003; Miller, Biassoni, Samuels, & Tyack, 2000). Although low-frequency active sonars are utilized much less frequently and by fewer Naval vessels than mid-frequency sonars (i.e., in the US Navy, only 2 ships are currently capable of deploying the SURTASS LFA system), due to the long-distance propagation capabilities of these systems, they may have more subtle impacts due to masking.

Seismic Surveys

Ships undertaking marine geophysical surveys tow seismic (airgun) arrays that emit loud sounds downward to probe under the sea bed for fossil fuels. Point-source intensity estimates for airguns are difficult due to the directional nature of the source, however arrays can produce levels equivalent to 260 dB re 1 µPa @ 1m (peak), with actual in-water pressure levels reaching maximums of approximately 235-240 dB. Although the sound is focused mainly downwards, some sound is emitted horizontally. Similarly, most of the energy is below 1,000 Hz with the predominant frequencies between 10-100 Hz, but there is considerable broadband energy, up to around 15 kHz or more, that is detectible, especially at relatively close range (Goold & Coates, 2006; Goold & Fish, 1998).

Airgun signals last around 40 ms, and are repeated every 7-20 s for several hours or days. Reflection and refraction can lengthen pulse durations (up to several seconds long) at the distance of the receiver. Although seismic surveying activity is concentrated in areas with extractable petroleum or natural gas (i.e., mostly on continental shelves, although this is changing as technology advances) the low frequency nature this source type means that the signal can travel for thousands of kilometers (Nieukirk et al., 2004).

Commercial Shipping

Noise from commercial ships is highly variable, but is generally produced at levels between 160 and 180 dB re 1uPa @ 1m (Richardson et al., 1995). Ships generate noise through their propellers, motors and gears. Noise from propellers comes from the many bubbles formed in the water by the rotating propeller blades. These bubbles quickly collapse or "cavitate" creating a loud acoustic sound. The faster the propeller rotates, the more cavitation noise. The breaking bubbles produce sound over a range of frequencies and, at high speeds, these frequencies can be as high as 40,000 Hz (Bartlett & Wilson, 2002; Wenz, 1962). However, propeller noise from large ships is usually concentrated below 200Hz. Low frequency noise generated by ships contributes significantly to the amount of low-frequency ambient noise in the ocean (Wenz, 1962). Because of the increase in propeller-driven vessels, low-frequency ambient noise has increased 10-15 dB, at an average of approximately 3 dB/decade over the past 50 years (Andrew, Howe, & Mercer, 2002; Cato & McCauley, 2002; Curtis, Howe, & Mercer, 1999; McDonald, Hildebrand, & Wiggins, 2006; Zakarauskas, Chapman, & Staal, 1990).

The spatial distribution of noise from shipping is non-uniform in the world's oceans. In general, increases are more pronounced in the northern

hemisphere because of the higher shipping volumes involved (e.g., Cato, 1976; Cato & McCauley, 2002; McDonald, Hildebrand, & Wiggins, 2006). Also, the concentration of commercial traffic into shipping lanes and around ports tends to amplify vessel noise in these regions, although shallow water propagation on the continental shelf can reduce levels in some high traffic areas. Shipping noise is also directional as it moves away from the source, sometimes strongly so, thus altering the contribution of any single ship to the ambient noise depending on whether the measurement is made at the surface versus on the bottom and/or off the bow versus of the sides or stern (Gray & Greeley, 1980).

Contributions from commercial shipping are similarly variable temporally. For example, the number and size of ships entering the global maritime transport fleet continue to increase dramatically, with implications for noise due to both total input of noise and input per unit vessel. Short-sea shipping (short distance cargo hauling) is becoming more prevalent, with implications again due to additional coastal traffic. As the Arctic Ocean ice melts due to climate change, trans-Arctic paths become the best routes between Europe and both eastern Asia and western North America. Such changes are predicted to change the ambient noise profile of Arctic waters as well as introducing additional point-source noise to this area (Southall, 2005).

A Regional Case Study: The Gerry E. Studds Stellwagen Bank National Marine Sanctuary Passive Acoustic Monitoring Program

Underwater noise from ships can be evaluated at two spatial scales: as transient, relatively high intensity sounds at close range and as omnipresent, relatively low-intensity sound over great distances. The propagation efficiency of low-frequency shipping noise has led to concerns regarding possible “masking” of marine animal signals, particularly low frequency vocalizations, with possible negative effects including diminished abilities to find mates, maintain social structure, forage, navigate and/or evade predation (Erbe, 2002; Erbe & Farmer, 1998, 2000; Morisaka, Shinohara, Nakahara, & Akamatsu, 2005; Nowacek et al., 2007; Payne & Webb, 1971; Southall, Schusterman, & Kastak, 2000). Due to the long-distance propagation of shipping noise, evidence of such effects must be evaluated when animals are closely approached as well as over large spatial scales.

In 2004, the US National Oceanic and Atmospheric Administration (NOAA) Fisheries’ Ocean Acoustics Program further addressed this issue by sponsoring an international symposium on “Shipping Noise and Marine Mammals” (Southall, 2005). Symposium attendees found that prior to developing regulations and/or designing technology to mitigate shipping noise on marine mammals more research was necessary to determine the relative contributions made by identified sound sources to the total noise field. Such descriptive data gathering was also a central recommendation from an NRC (2003) report, which also stated the importance of characterizing temporal variation (e.g., annual, seasonal, monthly, and daily) and spatial variation when measuring sound fields. While the NRC Committee and the NOAA Symposium were focused globally, many of their resultant insights and recommendations can be applied at a smaller “case-study” scale to provide a more local understanding of the noise-marine

mammal issue. Insights achieved from case studies can then be used to inform the issue on national and international scales.

Such a case study is being developed within the Gerry E. Studds Stellwagen Bank National Marine Sanctuary (SBNMS or sanctuary), where collaborators are generating methodologies to merge data from passive acoustic monitoring devices with vessel tracking systems and to identify the contributions made by various classes of noise (Hatch et al., in review). The SBNMS is an "urban" marine sanctuary located to the east of Boston, Massachusetts, U.S.A. in close proximity to a densely populated coastal zone (Figure 4).

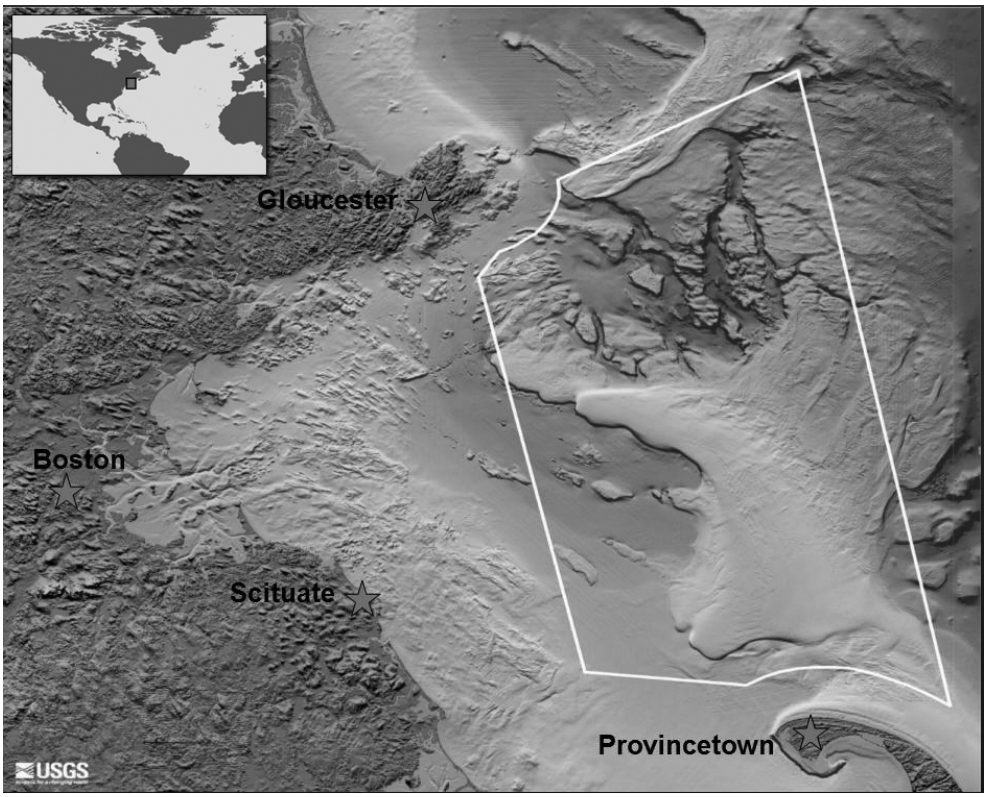

Figure 4. Location, boundaries and bathymetry of the Gerry E. Studds Stellwagen Bank National Marine Sanctuary in Massachusetts Bay off the northeast coast of the United States.

Stellwagen Bank, the central feature of the sanctuary, is home to some of the oldest and highest capacity commercial fisheries in the world and is an important feeding ground for endangered marine mammals such as the North Atlantic right whale (*Eubalaena glacialis*), humpback whale and fin whale. Because the Boston Traffic Separation Scheme (TSS) (the United Nations International Maritime Organization's recommended route for commercial vessels en route to and departing the Port of Boston) transits the sanctuary, these vulnerable marine species are at high risk of collisions with vessels and exposure to shipping noise.

Beginning in January 2005, a collaborative research team comprised of SBNMS, NOAA Fisheries' Northeast Fisheries Science Center, and Cornell

University's Bioacoustics Research Program deployed nine-ten autonomous recording units (ARUs) (Calupca, Fristrup, & Clark, 2000) to monitor the low frequency (10-1000Hz) acoustic environment of the SBNMS. Through additional collaboration with the US Coast Guard's Research and Development Center, data from four Automatic Identification System (AIS) receivers have been used to track all large commercial traffic transiting Massachusetts Bay and surrounding waters. Under the International Maritime Organization (IMO)'s current mandates, all ocean-going commercial traffic over 300 gross tons or carrying over 165 passengers, as well as all tugs and tows, are required to carry Automatic Identification System (AIS) transmitters (Federal Register, 2003; IALA, 2004). Shipboard AIS transponders transmit a vessel's position, identity and other characteristics (including but not limited to length, beam, draught, cargo type, destination and speed) as often as every two seconds.

AIS data are extracted by the SBNMS and the University of New Hampshire's Center for Coastal and Ocean Mapping using custom software written in Python (Python Software Foundation, 2007) added to the NOAA package (Schwehr, 2007). Analyses are then conducted to describe the abundance, behaviour and distribution of different vessel types over various spatial and temporal scales. Analysis of received levels at each ARU are used to compare the low frequency intensities of highly trafficked versus less highly trafficked locations of the sanctuary. Variations in received levels are then correlated with variations in vessel abundance, distribution and/or behaviour. Future research will continue to quantify the relative contribution of noise per vessel type to the sampling region's total "noise budget" (NRC, 2003). These analyses, together with synchronous year-long analyses of vocal behaviours of several endangered whale species in the SBNMS, will be used to inform management of sanctuary resources and initiate sanctuary ocean noise policy. For example, better understanding the large-scale and long-term behaviour of vessels and their acoustic footprints is currently aiding the SBNMS to quantify acoustic benefits to whales due to the recent shifting and narrowing of the Boston Traffic Separation Scheme (IMO, 2006).

Summary

Although descriptive data, including time-series data from longer-term monitoring efforts, continue to be collected and analyzed, it is clear that noise from numerous anthropogenic sources is both extensively and increasingly present within the marine environment. Technological innovation and climate change are allowing human activities to leave both deeper and larger acoustic "footprints" in the world's oceans. In response to increased accessibility and/or the growing use of remote sensing capabilities, new acoustic signals continue to be designed to address commercial, research and defense needs. In addition to purposeful use of acoustic sources, incidental noise from coastal development and vessel traffic are exposing greater proportions of marine life to increasing levels of noise. The vast majority of human-produced sources of underwater noise have intensified over a very short timeframe in evolutionary terms, providing only a few generations (at most) for species to adapt.

Experts agree that a better understanding of the relative contributors to the total ocean noise in areas of concern is needed. With its high concentrations of both acoustically-active endangered species and human activities that produce noise, Stellwagen Bank National Marine Sanctuary represents a perfect test-bed for both characterizing noise inputs and examining their impacts on marine life. Results from this highly collaborative research effort will be used to assist government agencies in fulfilling their responsibilities to identify, implement and monitor means of balancing the protective needs of marine species and ecosystems with the commercial, recreational, research and defensive needs of humans.

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Effects of Noise on Rodent Physiology

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Experiments are described in which Sprague Dawley rats were deliberately subjected to a daily 15-min white noise regime (90 dB) for 3 or 6 weeks, to determine its effects on the cardiovascular system and intestinal mucosa. In one set of experiments cardiovascular responses were monitored by radiotelemetry. Exposure to noise increased heart rate and mean arterial pressure and reduced stimulation of the parasympathetic nervous system. In the second set of experiments, one group of rats was exposed to the noise protocol for 3 weeks and a second group was not. All the rats were then anaesthetized and the small intestines of half the animals were fixed for microscopy. The remaining rats had their mesenteric microvasculature perfused for one minute with fluorescent albumin before fixing for microscopy. The rats exposed to noise showed significantly more eosinophils and degranulated mast cells in the intestinal villi than the quiet rats. In addition, the villi were swollen and the epithelial cells had widened junctions. The noise group also showed significantly more leakage of fluorescent albumin from the mesenteric microvessels. These experiments demonstrate that 90 dB white noise reduces stimulation the parasympathetic nervous system and also induces an inflammatory response in the intestinal mucosa, resulting in structural damage. These results are consistent with a stress response.

Several studies have shown that noise in animal care facilities can reach as high as 90 – 100 dB (Pfaff & Stecker, 1976; Milligan, Sales & Khirnykh, 1993). Such levels of noise can induce physiological and behavioral responses in laboratory rodents such as increased plasma corticosterone levels, reduction in body weight, decrease in gastric secretion, changes in immune response and tumor resistance, and a decrease in reproductive function. Behavioral responses include increases in total activity, grooming themselves and their cage-mates, and rearing onto their hind legs (Clough, 1982; Gamble, 1982; Sales, Wilson, Spencer, & Milligan, 1988; Milligan et al., 1993, Baldwin, Primeau, & Johnson, 2006). These changes are similar to those seen in rodents exposed to other stressful situations (Sharp, Azar, & Lawson, 2003). In spite of the evidence that noise levels in animal facilities are often high enough to produce uncontrolled physiological and psychological responses, the acoustic levels continue to be not as monitored as other environmental factors (lighting, temperature, humidity, etc).

Although noise has deleterious effects on rodent physiology, little is known about how the autonomic nervous system (ANS) is affected. Such information would indicate the state of emotional stress of the animals (Cerutti, Bianchi, & Mainardi, 1995). It is essential that the stress status of laboratory animals is monitored and controlled because stress may alter the experimental data obtained from those animals (Poole, 1997). One way of recording changes in the ANS is to measure the beat-to-beat changes in heart rate (i.e. heart rate variability, HRV). The variability is due to the changes in the activity of the sympathetic and

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parasympathetic nerves of the ANS, resulting in an alteration of sympathovagal balance. Acute social and psychological stressors affect the ANS by increasing sympathetic activation and decreasing parasympathetic activation, and these actions are reflected in changes in HRV. This article describes experiments in which groups of rats were exposed daily to a 15-min white noise regime (90 dB) for three weeks, to determine the effects of noise on the ANS (Burwell & Baldwin, 2006). Since stress responses can exert their influence by affecting ANS and endocrine output to the viscera (Mayer, Naliboff,, & Chang, 2001) further studies are described (Baldwin et al., 2006; Baldwin & Bell, 2007), in which a similar noise protocol was used to determine effects of noise on the integrity of the intestinal mucosa and mesenteric microvessels. The experimental methods are fully described in the publications cited above and just are outlined briefly here.

Method

Effects of Noise on ANS

Animals. Six male Sprague Dawley rats weighing 375 – 400 g were obtained from Charles River Laboratories (Portage, MI). Three of the rats were implanted at Charles River with PhysioTel® C50-PXT telemetry transmitters (Data Sciences International (DSI), St. Paul, MN), allowed to recover and shipped to Tucson, AZ. Upon arrival, each implanted rat was pair-housed with a non-implanted rat. No data were collected from the non-implanted rats; they served only as cage-mates for the implanted rats. Lights were on from 06:00 until 18:00. All research procedures and animal care were reviewed and overseen by the University of Arizona's institutional animal care and use committee (IACUC).

Experimental Protocol. The same animals were used throughout the experiments and were subjected to 3 or 6 weeks of daily noise, separated by 3 weeks of quiet time. The white noise stimulus consisted of a combination of frequencies from 10 Hz to 10 kHz that were electronically generated and recorded onto a CD in a 15-minute segment played between 8:00 and 8:15 each morning. The total SPL of the white noise in the animal room was 90 dB as compared with the background noise of 50 dB. On three mornings per week, telemetry data were collected before (07:50 – 08:00), during (08:00 – 08:15) and after (08:15 – 08:25) delivery of the noise. During quiet (control) periods, no stimulus was delivered and telemetry data were collected for 15 minutes sometime between 07:50 and 08:25. For three nights per week, when the rats were in their active phase, during noise experiments and quiet periods, telemetry data were collected for 15 minutes sometime between 20:00 and 21:00. Three distinct frequency ranges were identified in the power spectrum of the data: very low frequency (VLF, 0.05 – 0.25 Hz), low frequency (LF, 0.25 – 1.00 Hz), and high frequency (HF, 1.00 – 3.00 Hz). Spectral analysis of HRV in times of emotional stress shows an increase in LF power, a decrease in HF power, and an increase in the LF/HF ratio.

Statistical Analysis. Data were compared under different conditions, within the same animal and during the same observation period, using the paired Student t-test, with $p < 0.05$ considered to be statistically significant, after checking that the data passed the tests for normality and equal variance. All data are presented as mean ± standard error of the mean (SEM).

Effects of Noise on Intestinal Mucosa and Microvascular Leakage

Animals. Male Sprague Dawley rats were housed in pairs in cages as described previously (Burwell & Baldwin, 2006) in two separate identical rooms. The one intentional difference between the environments in the two rooms was that the rats in one of the rooms received a white noise stimulus (90 dB) for 15 minutes each day at the same time every day, for 3 weeks, just before the lights were switched off at 18:00. These rats are referred to as 'noise' rats. The rats in the other room

('quiet' rats) did not receive the white noise stimulus. Both rooms were chosen so that they were remote from noise-producing equipment, such as cage washers. Apart from the investigator, the animal care technician was the only person who entered the rooms. Background noise in these rooms did not exceed 50 dB. A third group of rats were housed in the 'noise' room for 3 weeks and then moved to the 'quiet' room for a further 3 weeks to determine whether noise-induced effects on the intestinal mucosa could be reversed. These rats are referred to as 'recovery' rats.

Experimental Protocol. After three weeks the animals were anesthetized for surgery (Baldwin, Primeau, & Johnson, 2006). Half of the animals from each room had their intestinal ileum prepared for light and electron microscopy in order to evaluate degranulation of mucosal mast cells, migration of eosinophils from the blood into the lamina propria, mean width of villus lamina propria and integrity of the mucosal epithelium (8 rats per group). To prepare the ileum for microscopy, the portal vein was incised for use as a flow outlet and the intestinal microvasculature was perfused at physiological pressure with physiologically-buffered Karnovsky fixative. After one hour, an 8 cm segment from the ileum was excised and fixed for one more hour. The segment was then divided into 4 portions that were incubated in 2% diaminobenzidine, post-fixed in osmium tetroxide, dehydrated and embedded in Spurrs' resin. The tissue was thick-sectioned for light microscopy and stained with 1% toluidine blue; it was also thin-sectioned for electron microscopy and stained with uranyl acetate and lead citrate. Thick sections were observed using an Axioplan microscope (Zeiss, Germany) equipped with 20x (numerical aperture 0.6) and 40x (numerical aperture 0.75; water immersion) Zeiss objectives. Thin sections were observed for electron microscopy using a model CM12 Phillips electron microscope (FEI Company, Tacoma WA).

In later experiments the presence of reactive oxygen species (ROS) was monitored in 'noise' and in 'quiet' rats by exposing a small segment of mucosa and suffusing it with dihydrorhodamine (DHR) 123 under epi-fluorescence microscopy. Niu et al. (1996) have shown that superoxide can be detected in the tissue using DHR which only fluoresces when in contact with ROS, specifically hydrogen peroxide-derived oxidants, and intra-vital digital micro-fluorography allows for quantification of oxidant production.

For the remaining animals (6 rats per group) the superior mesenteric artery was cannulated, the animals euthanized (Baldwin & Bell, 2007) and the mesenteric microcirculation was perfused for one minute with fluorescent albumin followed by fixative. The mesenteric tissue was then observed under epi-fluorescence microscopy to determine the mean number and area of leakage spots of fluorescent albumin per unit length of venule. In later experiments some of these rats were fed a special diet with increased concentrations of the antioxidants, vitamin E (10,000 IU/kg diet) and α-lipoic acid (1.65g/kg diet).

Statistical Analysis. For each parameter the Kruskal-Wallis test was applied for comparing different animals within the same group, and the Mann-Whitney Rank Sum test for comparing pairs of groups. The n was taken as the number of rats in a group and a p-value < 0.05 indicated significance.

Results

Effects of Noise on ANS

In response to white noise all 3 rats showed significant increases in HR and MAP (8% and 15%, respectively), compared to before the stimulus, and these parameters stayed elevated during the 10 minutes after the stimulus. No consistent or significant patterns were observed regarding the sympathetic nervous system (power of the LF range) in any of the rats in response to the white noise. However, an attenuation (12-13%) of the parasympathetic nervous system (power of the HF range) during and/or after the white noise was observed in all rats. Corresponding shifts in the sympathovagal balance (LF/HF ratio) were also observed during and after the white noise compared to before the stimulus. The increases in the LF/HF

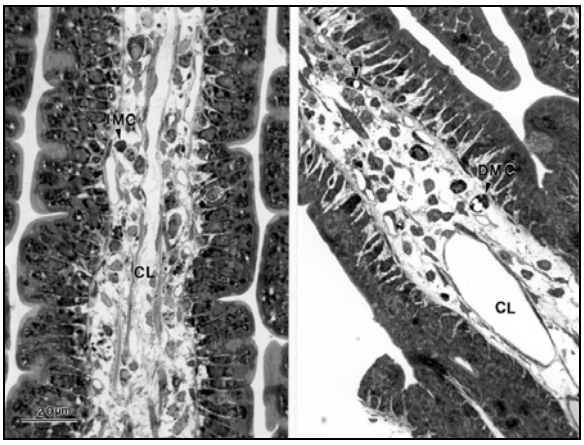
ratio were often small because the sympathetic nervous system remained relatively unchanged as the parasympathetic nervous system was attenuated.

Effects of Noise Stress on the Structure of the Intestinal Mucosa

Overall Appearance. Upon visual inspection, the small intestine of the 'noise' rats was noticeably more swollen and inflamed (hyperaemic) than seen in the 'quiet' rats. In addition, the Peyers' patches along the whole length of the jejunum and ileum were more swollen, suggesting increased activation of the immune system.

Light Microscopy. Longitudinally cut thick sections of parts of villi from a 'quiet' rat and a 'noise' rat are shown in Figures 1a and 1b, respectively. An intact mast cell (IMC), identified by its stained granules, in the lamina propria and adjacent to the central lacteal (CL) can be seen in Figure 1a. Degranulated mast cells (DMC) in the lamina propria can be seen in Figure 1b. There were significantly more degranulated mast cells per villus cross-section in the 10 villi closest to each edge of each Peyers' patch examined in 'noise' rats than in 'quiet' rats (3.95 ± 0.80 (SEM), 60 villi versus 0.35 ± 0.29, 80 villi). The Kruskal-Wallis test demonstrated that there was much greater variance between groups ($p<0.001$) than within groups ($p = 0.06$). 'Recovery' rats did not show a significant reduction in the number of degranulated mast cells, compared to the 'noise' rats (2.37 ± 0.83, 115). Similar results with degranulated mast cells were obtained when the 'noise' and 'quiet' rooms were reversed. Villi near Peyers' patches showed 2.77 ± 0.72 and 0.39 ± 0.48 for 'noise' rats and 'quiet' rats respectively. A one-way blocked ANOVA test demonstrated a significant difference between 'noise' and 'quiet' groups, but not between rooms, *per se* indicating that the data were not confounded by intrinsic differences between the rooms themselves. In villi near Peyers' patches significantly more eosinophils per villus section could be seen in the lamina propria of 'noise' rats than of "quiet" rats (9.46 ± 0.44, 60 villi versus 4.58 ± 0.38, 60 villi.)

Overall, the intestinal villi from 'noise' rats were significantly more edematous than those from 'quiet' rats, as assessed by measurements of villus lamina propria width using light microscopy. The mean villus widths of the 'noise', 'quiet' and 'recovery' groups were 57.0 ± 0.9, 39.0 ± 0.7 and 59.0 ± 0.7 μm, respectively (4 animals/group, 40 villi /animal). The distended central lymphatic vessels in villi from 'noise' rats (compare CL in Figures 1a and 1b) and the greater area of cell-free tissue indicate that the increased width of the villus lamina propria was produced by edema, rather than by increased cell growth. The villi of the 'recovery' group were just as edematous as those from the 'noise' group, consistent with the finding that the number of degranulated mast cells also remained high in this group.



a. **b.**

Figure 1. Light micrographs of longitudinally cut thick sections of parts of villi from a "quiet" rat (a) and a "noise" rat (b). The sections were stained with toluidine blue. See enlarged central lacteal (CL) in (B). Scale bar: 20 μm.

Electron Microscopy. Representative photomicrographs of the mucosal epithelium from the three groups of rats are shown in Figures 2a-c. Figure 2a demonstrates that in 'quiet' rats, the epithelial cells (E) were generally attached to each other and to the basement membrane. Very few eosinophils were evident. 'Noise' room rats, on the other hand, (Figure 2b), usually demonstrated large numbers of epithelial cells that were separating from each other and, in places, were separated from the basement membrane. Epithelial cells were considered to be separated from each other if a distinct gap could be seen between adjacent cells which extended in length from the basement membrane to the top of the cell nuclei (nearest the epithelial surface microvilli). Epithelial cells were considered to be separated from the basement if a gap appeared between the main body of the cell and the remnants of the cell adhering to the basement membrane.

Many intestinal villi contained eosinophils (EO) and partially degranulated mast cells (MC). In figure 2b an inter-epithelial leukocyte (IEL) and capillary (C) are also visible. Three weeks in the quiet room, following 3 weeks in the noise room, produced some epithelial repair (Figure 2c). Although the epithelial cells were still somewhat separated from each other, and extended long, tenuous cytoplasmic projections from their junctional aspects, the cells were rarely separated from the basement membrane.

Presence of Reactive Oxygen Species in Intestinal Mucosa

Significantly more intense DHR fluorescence was seen in the villus epithelium of 'noise' rats (58 ± 10 (SD), arbitrary units, 9 rats, 93 villi), compared to 'quiet' rats (35 ± 13, 3 rats, 55 villi), and fluorescent granules appeared in the lamina propria of 'noise' rats. These results imply that the noise-induced mucosal damage was oxidative in nature

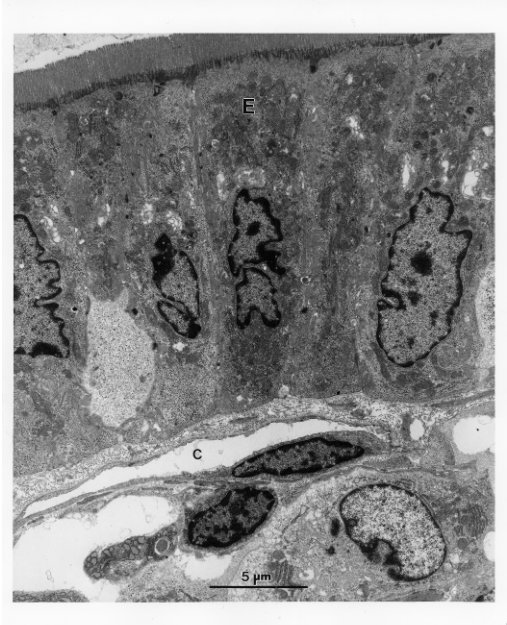


Figure 2a. Demonstrates that in "quiet" rats, the epithelial cells (E) were generally attached to each other and to the basement membrane. Very few eosinophils were evident.

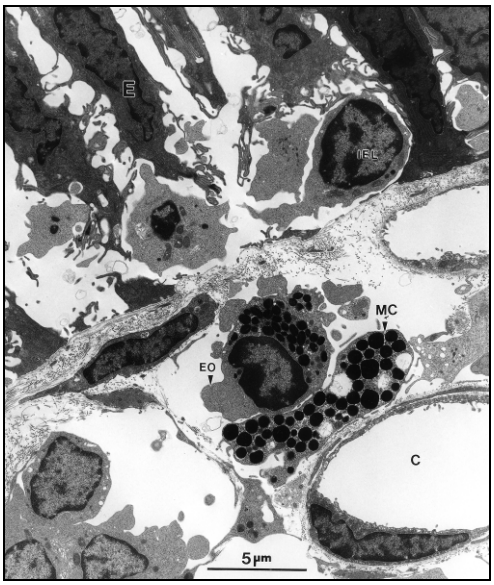


Figure 2b. "Noise" room rats usually demonstrated large numbers of epithelial cells that were separating from each other and, in places, were separated from the basement. Many intestinal villi contained eosinophils (EO) and partially degranulated mast cells (MC). In this figure an interepithelial leukocyte (IEL) and capillary (C) are also visible.

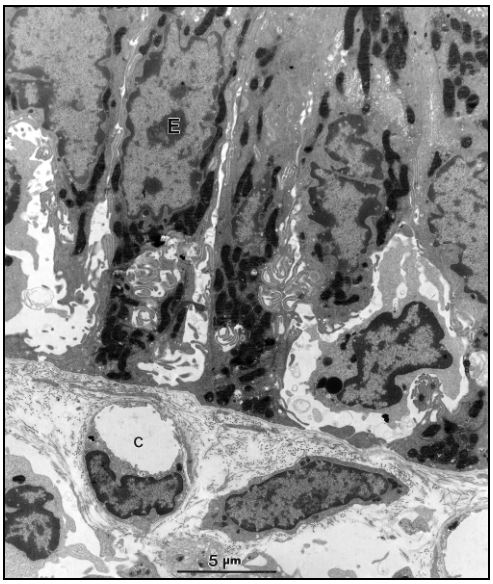


Figure 2c. Shows that three weeks in the quiet room, after 3 weeks in the noise room, resulted in some epithelial repair. Scale bars: 5 µm.

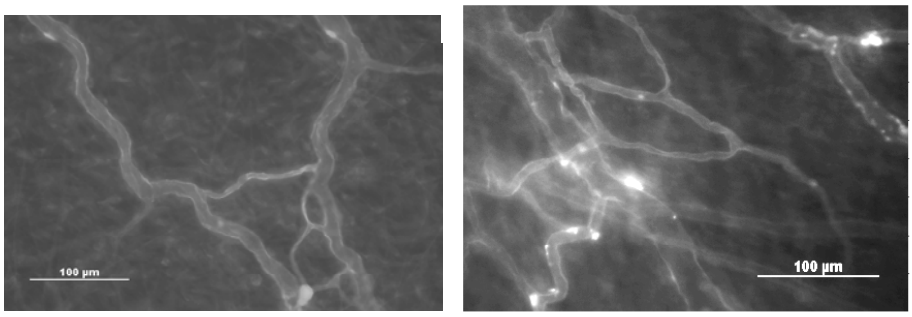
Effects of Noise Stress on Microvascular Leakage

Rats from the noise group (n=9) demonstrated significantly more leakage sites (3.84 ± 0.46 (SEM) x 10^{-3} μ^{-1}, n=95 venules) and a significantly greater leakage area per length of venule (3.20 ± 0.49 μ^2/μ), than rats from the quiet group (n=10) (1.38 ± 0.26 (SEM) x 10^{-3} $\mu^{-1}$and 0.30 ± 0.06 μ^2/μ, respectively, n=123 venules) or the recovery group (n=6) (1.40 ± 0.24 (SEM) x 10^{-3} μ^{-1} and 0.63 ± 0.16 μ^2/μ, respectively, n=108 venules). Rats from the recovery and quiet groups showed similar numbers of leaks per length of venule, but the recovery group demonstrated significantly greater leak area per venule length than the quiet group, although still significantly less than for the noise group . The percentages of venules observed that contained leaks in the noise, quiet and recovery groups were 73%, 37% and 39%, respectively. Light micrographs of typical microvascular networks from a quiet group rat and a noise group rat, after perfusion with FITC-albumin, are shown in figures 3a and 3b. Extensive fluorescent leaks are visible in the network from the noise group rat but few leaks can be seen in the network from the quiet group rat.

Mast Cell Degranulation

The mean number of degranulated mast cells per microscopic field of view (1.13 mm^2) was significantly greater for the noise group (13.75 ± 0.77) and the recovery group (12.09 ± 0.90) than for the quiet group (7.43 ± 0.36). These results

indicate that daily noise markedly increases microvascular permeability in rats, and that this change may be stimulated by mast cell degranulation.



a. **b**.

Figure 3. Light micrographs of mesenteric microvascular networks after perfusion with fluorescent (FITC)-labeled albumin. (a) Network from an animal that had not been exposed to daily noise. No leaks can be seen. (b) Network from an animal that had been exposed to daily noise. Many leaks of FITC-albumin from the venules are visible. Scale bars: 100 µm.

Antioxidants and Microvascular Leaks

Vitamin E with α-lipoic acid significantly reduced noise-induced venular leakage to fluorescent albumin although not to control levels. The quiet control animals (n=6) had a mean number of leaks per micron length of venule of 0.44 ± 0.06 (SEM) x 10^{-2} μ^{-1}, (n= 341 venules), compared to 3.05 ± 0.32 (SEM) x 10^{-2} μ^{-1}, (n= 294 venules, n=6 rats) for noise alone, and 1.04 ± 0.19 (SEM) x 10^{-2} μ^{-1}, (n= 304 venules, n=6 rats), for noise and vitamin E with α-lipoic acid. The results for leak area per micron length of venule were similar, corresponding values being 0.44 ± 0.10 (SEM) $\mu^2\mu^{-1}$, 6.60 ± 0.88 (SEM), 1.90 ± 0.51(SEM) and 2.33 ± 0.29 (SEM). Thus leak number was significantly reduced by about 66% with vitamin E and α-lipoic acid. Leak area was reduced even more, by 70% with vitamin E and α-lipoic acid.

Discussion

Exposure of rats to 90 dB white noise every day increases both HR and MAP when recorded during, and immediately after, the noise. It could be argued that the increases in HR and MAP produced by noise could have been caused by increased activity rather than by a stress response. However, that is unlikely in these experiments because apart from a startle response, lasting a second or so on the first day of the noise, very little activity was observed at this time. Thus the increased cardiovascular parameters were caused by a stress response. In this study we show that a decrease in the activation of the parasympathetic nervous system is responsible for the cardiovascular response, rather than an increased activity of the sympathetic autonomic branch. This effect is not surprising because the

parasympathetic branch is dominant when animals are asleep, as was the case when the rats were exposed to the noise. The elevations of HR and MAP seen during the daily exposure to white noise are consistent with data obtained by other investigators from rodents exposed to stressful situations, such as handling, restraint, cage-changes and injections (Sales, 1972; Kramer et al., 1993; Kramer et al., 2000; Sharp, Zammit, Azar, & Lawson, 2002; Sharp et al., 2003).

It might be argued that since the cardiovascular effects of noise only resulted in small increases in HR and BP (about 10-15% of initial values) that noise would not be a major confounding factor in rodent experiments. However, the stimuli used in these studies were only delivered once a day, at the same time every day and for short duration, unlike the audible sounds that routinely occur in animal facilities. As reported by other authors, noise levels peak many times during the day in an animal facility and contain a wide range of frequencies (Pfaff & Stecker, 1976; Sales et al., 1988; Milligan et al., 1993). Because noise levels in animal facilities tend to be poorly controlled, the cardiovascular state of the animals may also be poorly controlled and unpredictable. Although stress does not always compromise health and welfare, and in fact the stress response is necessary for survival in the wild, stress always disturbs the body's homeostasis and imposes a cost to the body, particularly when it is elicited repeatedly. This cost arises if stress-induced mediators, such as adrenal hormones, neurotransmitters, cytokines etc., are released too often.

Not only does exposure to 90 dB white noise alter cardiovascular parameters in rats; the small intestine and mesenteric microvessels become inflamed. It is not clear whether this response is mediated via the hypothalamic-pituitary-adrenal axis because accurate measures of plasma corticosterone concentrations before and during the noise could not be obtained without causing further stress to the animals. Windle et al. (1998) found that plasma corticosterone concentrations in rats varied periodically throughout the day but increased significantly in response to 114 dB noise for 10 min., if the onset of the noise coincided with the rising phase of a basal corticosterone pulse. This result suggests that the intestinal responses observed in the present study in response to noise may have been a stress response that was mediated via the hypothalamic-pituitary-adrenal axis.

The intestinal damage appeared to be oxidative in nature. Activated phagocytes, such as neutrophils, eosinophils and macrophages, are the best-recognized sources of free radicals and the intestinal mucosa of rats exposed to noise showed significantly larger numbers of eosinophils in the villi lamina propria compared to 'quiet' rats. These eosinophils were probably recruited by the presence of degranulated mast cells. Activated mast cells can release interleukin-5 (IL-5) that attracts eosinophils (28). In fact our electron micrographs often demonstrated eosinophils and degranulated mast cells in close juxtaposition (Figure 2b). The ROS and other products released by eosinophils may be partly responsible for the epithelial disruption observed near the Peyers' patches of 'noise' rats.

In summary, exposure of rodents to chronic noise appears to induce a

stress response, as demonstrated by behavioral changes and increases in HR and MAP, that is accompanied by intestinal and microvascular inflammation, possibly triggered by increased activation of the immune system.

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The Effect of Transportation Noise on Health and Cognitive Development: A Review of Recent Evidence

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Noise from transport is an increasingly prominent feature of the urban environment. Whilst the auditory effects of noise on humans are established, non-auditory effects - the effects of noise exposure on human health, well-being and cognitive development - are less well established. This narrative review evaluates recent studies of aircraft and road traffic noise that have advanced or synthesized knowledge about several aspects of adult and child health and cognition. Studies have demonstrated a moderate effect of transport noise on hypertension, cardiovascular disease and catecholamine secretion: there is also evidence for an effect on psychological symptoms but not for the onset of more serious clinically defined psychiatric disorder. One way noise may affect health is through annoyance: noise causes annoyance responses in both children and adults and annoyance may cause stress-responses and subsequent illness. Another possible mechanism is sleep disturbance: transport noise has been found to disturb sleep in laboratory and field studies, although there is evidence for adaptation to noise exposure. For children effects of aircraft and road traffic noise have been observed for impaired reading comprehension and memory skills: there is equivocal evidence for an association with blood pressure. To date most health effects have been very little researched and studies have yet to examine in detail how noise exposure interacts with other environmental stressors. In conclusion, noise is a main cause of environmental annoyance and it negatively affects the quality of life of a large proportion of the population. In addition, health and cognitive effects, although modest, may be of importance given the number of people increasingly exposed to environmental noise and the chronic nature of exposure.

Exposure to noise in the environment from transport sources is an increasingly prominent feature of the environment. The growing demand for air and road travel means that more people are being exposed to noise, and noise exposure is increasingly being seen as an important environmental public health issue.

The direct effect of sound energy on human hearing is well established and accepted. Exposure to continuous noise of 85-90 dBA (decibels, A-weighted to approximate the typical sensitivity of the human ear) can lead to progressive hearing loss and changes in threshold sensitivities (Kryter, 1985): similar damage can be caused by exposure to a smaller number of noise events, if the sound energy is great (>135 dB Lc_{pk}, Babisch, 2005) (LC_{pk} is a measurement of peak sound pressure level over a specified period). Auditory effects of noise have typically been observed in certain industrial occupations, hence protective legislation requiring hearing protectors to be worn, however, effects are also increasingly being observed due to entertainment noise from amplified music and MP3 players.

In contrast, non-auditory effects of noise on human health are not the direct result of sound energy. Instead, these effects are the result of noise as a general stressor: thus the use of the term noise not sound: noise is unwanted sound. Non-auditory effects of noise include sleep disturbance, mental health, physiological

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function, and annoyance, as well as effects on cognitive outcomes such as speech communication, and cognitive performance (WHO, 2000). These effects of noise are less well established and accepted than auditory effects.

Noise could indirectly result in poor health in several ways. Firstly, acute noise exposure directly causes a number of predictable short-term physiological responses such as increased heart rate, blood pressure, and endocrine outputs. Chronic noise exposure may cause longer-term activation of these responses and subsequent symptoms and illness. Whether acclimation of the physiological response occurs with long-term noise exposure is not certain. Secondly, these physiological responses may be activated by annoyance. Noise causes annoyance, especially if an individual feels their activities are being disturbed or if it causes difficulties with communication. In some individuals, this annoyance may lead to stress responses, and potentially to subsequent symptoms and illness. However, there is little evidence to directly support the annoyance pathway as a mechanism for non-auditory effects. Habituation[1] of behavioral or psychological responses may occur with long-term exposure for certain individuals or for certain types of behavioral responses: however, the reduction of a behavioral or psychological response may not necessarily result in the acclimation of a physiological response.

This narrative review evaluates recent studies of transport noise that have advanced or synthesized the knowledge about several non-auditory effects: namely, hypertension and coronary heart disease, stress hormones, sleep disturbance, mental health, and cognitive development: effects for children and adults are discussed. Recent years have seen several methodological advancements in the field including the use of larger epidemiological community samples; better characterization of noise measurement; and more detailed measures of health. Evidence from longitudinal studies is beginning to emerge and studies have started to examine exposure-effect relationships, to identify thresholds for noise effects on health and cognition which can be used to inform guidelines for noise exposure. There has also been a better assessment of confounding factors: noise exposure and health are often confounded by socioeconomic position, so individuals living in poorer social circumstances are more likely to have poorer health, as well as be exposed to noise. Therefore, measures of socioeconomic position need to be taken into account when examining associations between noise exposure and health. Furthermore, factors that confound physiological health outcomes such as smoking, diet, and activity levels also need to be measured and adjusted for in analyses.

Review of the Evidence

Noise Exposure Assessment

Assessments of noise exposure use established metrics of external noise exposure which indicate the average sound pressure level for a specified period

[1] Habituation is distinguished from acclimation in this paper in the following way. Habituation refers to the lessening of a behavioural or psychological response to noise, with repeated or chronic exposure: e.g. a reduction in sleep disruption or annoyance responses. Acclimation refers to the lessening of a physiological response to noise, with repeated or chronic exposure: e.g. a reduction in cortisol levels.

using dBA as the measurement unit (dBA is the unit of A-weighted sound pressure level where A-weighted means that the sound pressure levels in various frequency bands across the audible range have been weighted in accordance with differences in hearing sensitivity at different frequencies). Metrics typically employed are L_{Aeq16} and L_{day} which indicate average noise exposure (in dBA units) over a 16 hour daytime period usually 7am-11pm; L_{night} which indicates noise exposure at night (11pm-7am); and L_{dn} which combines the day and night measures to indicate average noise exposure over the 24 hour period, with a 10dB penalty added to the night-time noise measure. These metrics are usually modeled using Geographical Information Systems. Some studies measure noise exposure in the community, which is less reliable if measurements cover short time-periods. Studies have also examined exposure to maximum noise levels (e.g. L_{Amax} - maximum sound pressure in dBA units), as in pathophysiological terms it is not clear whether overall 'dose' of noise exposure is important in determining effects on health or whether peak sound pressure of events or the number of noise events might be important.

Whilst people are often exposed to sounds from more than one source, to date, studies have tended to focus upon only one type of noise exposure, such as aircraft or road traffic noise. Studies that have examined ambient noise and, thus, exposure to more than one source (e.g. Lercher, Evans, Meis, & Kofler, 2002) have not been able to attribute health effects to specific noise sources within the environment. Little is known about the effects on health of combined exposure and it is possible that combined exposure has a cumulative impact or it could be synergistic (see Nilsson & Berglund, 2001). Furthermore, noise exposure often co-occurs with air pollution, because of source-specificity, and studies have yet to explore the implications of probable interactions between noise and air pollution for human health.

Annoyance

It is beyond the limits of this paper to include a review of the effect of noise exposure on annoyance responses. Annoyance is a multifaceted psychological concept including both evaluative and behavioral components (Guski, Schuemer, & Felscher-Shur, 1999), used to describe negative reactions to noise. Annoyance is an important health effect of noise (WHO, 2000). Annoyance is the most reported problem caused by transport noise exposure and is often the primary outcome used to evaluate the effect of noise on communities. Acoustic factors such as noise source, exposure level and time of day of exposure only partly determine an individual's annoyance response: many non-acoustical factors such as the extent of interference experienced, ability to cope, expectations, fear associated with the noise source, noise sensitivity, anger, and beliefs about whether noise could be reduced by those responsible influence annoyance responses (WHO, 2000). Studies have derived exposure-effect associations for the effects of different noise sources on annoyance responses (Miedema & Vos, 1998; Miedema & Oudshoorn, 2001), finding that aircraft noise produces greater annoyance responses than road traffic noise at the same level of exposure.

Hypertension & Coronary Heart Disease

Epidemiological evidence for effects of noise on coronary heart disease and coronary risk factors in adults has been mixed. These inconsistencies may be attributable to the use of varying outcome measures, ranging from weaker self-report measures of hypertension and drug use to more objective measures of blood pressure: as well as to whether confounding factors associated with coronary heart disease such as age, gender, smoking, and body mass index have been taken into account.

Evidence for effects of transport noise exposure on hypertension and ischaemic heart disease is strengthening (Babisch, 2006a). The unique multi-centre HYENA study found increased risk of hypertension related to long-term noise exposure, for both night-time aircraft noise and daily average road traffic noise, for individuals who had lived near to one of six major European airports for five years or more (Jarup et al., 2008). The analyses adjusted for important confounders (age, gender, body mass index, alcohol intake, physical activity, education) and had a good measure of hypertension based upon blood pressure measurements, supplemented by self-reports of a diagnosis of hypertension and/or use of anti-hypertensive medication. Another recent study demonstrated an effect of aircraft noise exposure on the use of anti-hypertensive drugs around Cologne-Bonn airport, particularly for those exposed to night noise (Greiser, Greiser, & Janhsen 2007): however, no data about confounding factors was included in the analyses. A study of road traffic noise and medication use which did adjust for confounders found an effect but only for subjects between 45-55 years and for those exposed to >55 dBA L_{den} (de Kluizenaar, Gansevoort, Miedema, & de Jong, 2007). A study of over 28,000 blood pressure records from around Kadena airport in Okinawa, Japan, found a dose-response relationship between aircraft noise exposure and systolic blood pressure (Odds ratio (OR)=1.29 95% Confidence Intervals (CI)=1.13-1.47) after taking age, gender and body mass index into account: however, no effect was found for diastolic blood pressure, although a weaker measure of self-reported hypertension did show an association with noise exposure (Matsui et al., 2001). Similarly, a study around Arlanda airport in Sweden found that self-reported hypertension was more prevalent among people exposed to average aircraft noise levels of at least 55dBA (LA_{eq}) or maximum levels above 72 dBA (L_{Amax}), after taking age, gender, smoking and education into account (Rosenlund, Berglind, Pershagen, Jarup, & Bluhm, 2001). A recent Swedish study found an association between road traffic noise exposure and self-reported hypertension, after taking age, gender, smoking, occupation and house type into account (Bluhm, Berglind, Nordling, & Rosenlund, 2007): (OR=1.38 95%CI 1.06-1.80 per 5dBA increase in noise exposure). Associations were stronger for those who had lived at the address for more than 10 years and for females. However, a German study of incidence of myocardial infarction found an effect of road traffic noise only for males who had lived at their address for at least 10 years (Babisch, Beule, Schust, Kersten, & Ising, 2005). An effect of aircraft noise on incidence of myocardial infarction has also been demonstrated for individuals exposed to >50 $L_{Aeq24\ hours}$, with stronger associations found for older subjects (Eriksson et al., 2007).

Meta-analyses have established that noise has a significant effect on risk for hypertension and coronary heart disease. A meta-analysis found that for aircraft noise a 5 dBA rise in noise was associated with a 25% increase in risk of hypertension compared with those not exposed to noise (van Kempen et al., 2002). Two meta-analyses of the effect of road traffic noise exposure on coronary heart disease, where outcomes ranged from blood pressure and hypertension to ischaemic heart disease and myocardial infarction found that environmental noise above 65-70dBA was associated with a 10 to 50% increase in risk (Babisch, 2000; 2006a). A recent study estimated that 3% of the total cases of myocardial infarction in Germany are attributable to road traffic noise (Babisch, 2006b).

There is some evidence for annoyance as a possible mediating factor between noise and cardiovascular outcomes. A ten year study of nearly 4000 men from Caerphilly in Wales, found that high annoyance at baseline predicted incidence of coronary heart disease many years later but only for men who were free of chronic disease at baseline: for men with chronic disease at baseline, noise exposure but not annoyance was associated with the incident of coronary heart disease (Babisch, Ising, & Gallacher 2003). This suggests that noise annoyance may have a moderating effect on the development of coronary heart disease. A recent study of 3000 residents in a city in Serbia found that men who were extremely annoyed by traffic noise had an increased risk of reporting hypertension and myocardial infarction, compared with those not annoyed; no similar relationship was observed for women (Belojevic & Saric-Tanaskovic, 2002). However, these cross-sectional findings should be treated cautiously, as men with cardiovascular disease may be more likely to develop annoyance in response to noise. Further, longitudinal research on annoyance as a mediating factor is required.

Epidemiological evidence for effects of noise on coronary risk factors in children has been mixed, which may be due to a number of methodological problems including lack of control for confounding factors, such as parental blood pressure, as well as being limited to considering the effect of noise exposure at school (van Kempen et al., 2006). A cross-sectional study around Schiphol (Amsterdam) and Heathrow (London) airports found an effect of aircraft noise at home, as well as night time aircraft noise exposure on systolic and diastolic blood pressure for 9-10 year old children but no effect for aircraft noise at school (van Kempen et al., 2007); these findings suggest that it may specifically be aircraft noise exposure during the evening and night that affects children's blood pressure. For road traffic noise exposure, this study found that exposure at school was associated with decreased systolic and diastolic blood pressure. A study of younger children, aged 3-7 years, found an association between night-time road traffic noise exposure at home and systolic blood pressure, as well as an effect of day-time road traffic noise exposure at kindergarten (Belojevic, Jakovljevic, Stojanov, Paunovic, & Ilic, 2007). Whilst these recent studies are methodologically stronger than previous studies, additional studies focusing on the effect of different noise sources, in different settings are required before further conclusions can be drawn about noise effects on children's blood pressure.

Stress Hormones

Studies of endocrine markers of noise exposure have demonstrated conflicting results. Adrenaline, noradrenaline and cortisol, all of which are released by the adrenal glands in situations of stress, have been examined. One difficulty in studying these hormones is that salivary and urinary measures of these hormones are easily biased by unmeasured factors; studies also often have small sample sizes. Cortisol, in particular, is difficult to examine, as it has diurnal variation and is usually high in the morning and low in the evening making it difficult to measure effectively.

Evidence of effects of road traffic noise exposure on endocrine markers in adults is weak and inconclusive (see Babisch, 2003): one study found an effect of being exposed to levels above 65 dBA for raised cortisol but not adrenaline levels, although this was on a sample of only 28 individuals (Poll, Straetemans, & Nicolson, 2001). A larger study found an effect of road traffic noise on noradrenaline but not adrenaline (Babisch, Froome, Beyer, & Ising, 2001).

The findings of studies of noise effects on endocrine markers in children are similarly mixed, despite larger sample sizes. Two of the largest studies to date, examining children living near Heathrow airport in West London, found no association between aircraft noise exposure above 66 dBA L_{Aeq} and morning salivary cortisol measures (Haines, Stansfeld, Job, Berglund, & Head, 2001a), nor, in a similar study, between aircraft noise exposure above 62 dBA L_{Aeq} and twelve-hour urinary cortisol, adrenaline and noradrenaline measures (Haines et al., 2001b).

Overall, further studies on the effects of noise on endocrine responses are required. Previous studies of adults are hampered by their small sample sizes, which may reflect the unwillingness of individuals to provide biological samples. As well as inconclusive evidence, little is known about whether raised endocrine responses observed in some studies represent normal short-term responses to environmental stress or a longer-term activation of the endocrine system. There is a lack of understanding about how long-term activation of the endocrine system links to health impairment and whether endocrine responses can habituate to noise exposure is not certain.

Sleep Disturbance

Exposure to night-time noise can potentially interfere with the ability to fall asleep, shorten sleep duration, cause awakenings and reduce perceived quality of sleep (Michaud, Fidell, Pearsons, Campbell, & Keith, 2007) and could affect health in two ways. Firstly, by impacting on biological responses, such as increasing heart rate, awakenings and sleep quality, as the individual responds to stimuli in the environment (HCN, 2004). Activation of some biological responses could have long-term effects on health. Secondly, sleep disturbance can impact on well-being, causing annoyance, irritation, low mood, fatigue, and impaired task performance (HCN, 2004). In terms of noise exposure, it has been suggested that continuous noise exposure is more likely to interrupt REM sleep, whilst intermittent

noise is more likely to interfere with slow wave sleep (Passchier-Vermeer, Vos, Steenbekkers, van der Ploeg, & Groothuis-Oudshoorn, 2002).

Research on evidence for an effect of noise exposure on sleep disturbance is generally stronger from laboratory studies than from field studies. However, comparison between the findings of laboratory and field studies can be limited as laboratory studies tend to involve individuals who are not chronically exposed to noise, whereas, individuals who are chronically exposed to noise may exhibit habituation, where sleep disturbance becomes diminished, following a period of chronic noise exposure. A notable recent laboratory study tried to simulate the effect of aircraft noise exposure on sleep for 128 subjects over 13 nights (Basner & Samel, 2005). Prior to the experiment, the subjects spent a noise-free adaptation night in the laboratory, as sleep is initially affected by the laboratory setting. The experiment demonstrated a prominent first night exposure effect of noise on sleep disturbance, which wore off by the second night, which was interpreted as indicating habituation to noise exposure. On the subsequent nights no significant change in sleep structure was observed if the number of noise events and maximum sound pressure level did not exceed 4*80dB, 8*70dB, 16*60dB, 32*55dB, and 64*45dB. However, this study is still limited by having examined short-term exposure to aircraft noise, and conclusions cannot be drawn from these findings about the long-term effects of exposure to aircraft noise on sleep structure (Basner & Samel, 2005).

Overall, community studies of noise exposure, examining individuals in their homes exposed to their usual noise exposures at night, have found evidence for a direct effect of noise on sleep disturbance. However, recent reviews, assessing the strength of the evidence, differ in their conclusions. A recent synthesis of field studies concluded that there was sufficient evidence that night-time noise exposure was causing direct biological responses, at approximately 40dB SEL (Sound Exposure Level), as well as affecting well-being and quality of sleep (HCN, 2004). This report found that evidence was weaker for an effect of night-time noise on social interaction, task performance, on specific disease symptoms or on fatal accidents at work. Similarly, a meta-analysis of 24 field studies, including almost 23,000 individuals exposed to night-time noise levels ranging from 45-65dBA, found that aircraft noise was associated with greater self-reported sleep disturbance than road traffic, and road traffic noise with greater disturbance than railway noise (Miedema & Vos, 2007). This analysis also found an inverted U-shaped association between noise induced sleep disturbance and age, with the greatest disturbance being found for individuals aged 50-56 years. The study concluded that transportation noise was a widespread factor affecting sleep.

In contrast, a recent review focusing solely on aircraft noise exposure concluded that findings about noise-induced sleep disturbance differ considerably (Michaud et al., 2007). The review of five studies found little evidence for an effect of outdoor noise on sleep disturbance, whilst indoor noise was associated more closely with sleep outcomes. However, there was evidence from several studies that a greater number of awakenings occur that are either spontaneous or attributable to other noise in the home, than are attributable to aircraft noise.

The equivocal conclusions of these reviews may be because the studies are comparing studies which examine a range of outcomes ranging from more objective measures of sleep disturbance, such as polysomnography and wrist-actimetry, which measures sleep disturbance based on body movements, to subjective measures, such as self-reported sleep disturbance. The measurement of sleep disturbance is challenging, as no one physical or psychological measure is accurate or reliable. The equivocal conclusions may also reflect different exposure assessments: some studies use external noise exposure, whilst others measure noise exposure in the bedroom (Miedema & Vos, 2007).

Evidence from recent studies where change in night-time noise exposure has occurred also provides some evidence for an association between noise and sleep disturbance. Whilst a Swedish study found that a reduction in road traffic noise exposure caused by a new road tunnel was associated with improvements in sleep quality and alertness, measured by actimetry and subjective reports (Öhrström, 2002), a change in night-time aircraft noise exposure at two airports was not associated with changes in noise induced sleep disturbance (Fidell, Pearsons, Tabachnick, & Howe, 2000). Few studies have included children in studies of sleep disturbance: one study used sleep logs and actigraphy to compare the effect of road traffic noise on child and parent sleep, finding an exposure-effect relationship between road traffic noise exposure and sleep quality and daytime sleepiness for children, and an exposure effect association between road traffic noise and sleep quality, awakenings, and perceived interference from noise for the parents (Öhrström, Hadzibajramovic, Holmes, & Svensson, 2006).

In conclusion, overall, there is sufficient evidence that night-noise can disturb sleep, as well as potentially affect well-being. The field still lacks longitudinal evidence, which would enable the causal association between noise exposure and the long-term health implications of biological responses and impaired well-being, related with night-time noise exposure to be examined.

Psychological Health

Given the effect of chronic noise exposure on annoyance responses, it has been hypothesized that chronic noise exposure could have a serious effect on psychological health, as noise can cause annoyance and prolonged annoyance could lead to poor psychological health (McLean & Tarnopolsky, 1977). The effect of noise on psychological health is complicated as studies have found that poorer psychological health is also associated with greater annoyance responses (Tarnopolsky, Barker, Wiggins, & McLean 1978; van Kamp, Houthuijs, van Wiechen, & Breugelmans, 2007) and greater noise sensitivity (Stansfeld, Clark, Jenkins, & Tarnopolsky, 1985; Miyakawa, Matsui, & Hiramatsu, 2007).

Studies of adults have found that noise exposure relates to an increase in the number of psychological symptoms reported, such as symptoms of anxiety and depression, rather than to clinically diagnosable psychiatric disorders (Tarnpolsky et al., 1978; Stansfeld, Sharp, Gallacher, & Babisch, 1993). A later study examined nearly 6000 inhabitants around two military airbases in Japan, and found that those exposed to noise levels of 70 L_{dn} or above had higher rates of mental instability

and depressiveness (Hiramatsu, Yamamoto, Taira, Ito, & Nakasone, 1997). Additionally, those who were more annoyed showed higher risk of mental and somatic symptoms. Unfortunately, this study did not assess psychiatric diagnoses, but a recent study has found associations between noise exposure and psychiatric diagnoses as measured by the Composite International Diagnostic Interview (Hardoy et al., 2005), with individuals living close to an airport showing higher frequency of 'generalized anxiety disorder' and 'anxiety disorder not otherwise specified', compared with matched controls from another area. These findings need replication and unfortunately, it is not possible to distinguish cause from effect in these studies, which are all cross-sectional, measuring noise and psychological health concurrently. A longitudinal study around Schiphol airport in Amsterdam found no association between noise exposure levels and mental health either at baseline, or after the opening of a fifth runway (van Kamp et al., 2007).

Several recent studies have examined associations between noise exposure and children's psychological health. The Tyrol Mountain Study compared child and teacher ratings of psychological health for children exposed either to <50 or > 60 dBA L_{dn} (Lercher et al., 2002). Ambient noise (road and rail) exposure was associated with teacher ratings of psychological health but was only associated with child rated psychological health for children with early biological risk (low birth weight or premature birth). A study of children attending school near Heathrow airport in London also found that noise exposed children had higher levels of psychological distress (Haines et al., 2001b), as well as a higher prevalence of hyperactivity. The RANCH study, the largest study of road traffic and aircraft noise exposure on children's psychological health to date, failed to replicate an effect of either aircraft or road traffic noise on psychological distress in samples from the Netherlands, Spain or the UK (Stansfeld et al., 2005): however, the effect of aircraft noise on hyperactivity was replicated.

Overall, studies suggest that for both adults and children noise exposure is probably not associated with serious psychological illness but there may be effects on well-being and quality of life: this conclusion is limited by the lack of longitudinal research in this field. There is a need for further research, especially to establish if hyperactive children are more susceptible to stimulating environmental stressors such as noise.

Cognitive Development

It has been suggested that children may be especially vulnerable to effects of environmental noise as they may have less cognitive capacity to understand and anticipate environmental stressors, as well as a lack of developed coping repertoires (see Stansfeld, Haines, & Brown, 2000). Exposure during critical periods of learning at school could potentially impair development and have a lifelong effect on educational attainment. Whilst a recent study suggests that children may not be more susceptible to environmental noise effects on cognitive performance than adults (Boman, Enmarker, & Hygge, 2005), studies have established that children exposed to noise at school experience some cognitive impairments, compared with children not exposed to noise: tasks affected are those involving central processing

and language such as reading comprehension, memory and attention (Haines et al. 2001a; 2001b; Evans & Maxwell, 1997; Cohen, Glass, & Singer, 1973).

One of the most interesting and compelling studies in this field is the naturally occurring longitudinal quasi-experiment reported by Evans and colleagues, examining the effect of the relocation of Munich airport on children's health and cognition (Evans, Hygge, & Bullinger, 1995; Evans, Bullinger & Hygge, 1998; Hygge, Evans, & Bullinger, 2002). In 1992 the old Munich airport closed and was relocated. Prior to relocation, high noise exposure was associated with deficits in long term memory and reading comprehension. Two years after the closure of the airport, these deficits disappeared, indicating that noise effects on cognition may be reversible if exposure to the noise ceases. Most convincing was the finding that deficits in memory and reading comprehension developed over the two year follow-up for children who became newly noise exposed near the new airport.

The recent large scale RANCH study, which compared the effect of road traffic and aircraft noise on children's cognitive performance in the Netherlands, Spain and the UK, found a linear exposure-effect relationship between chronic aircraft noise exposure and impaired reading comprehension and recognition memory, after taking a range of socioeconomic and confounding factors into account (Stansfeld et al., 2005). No associations were observed between chronic road traffic noise exposure and cognition, with the exception of episodic memory, which surprisingly showed better performance in high road traffic noise areas. Neither aircraft noise nor road traffic noise affected attention or working memory. In terms of the magnitude of the effect of aircraft noise on reading comprehension, a 5dBA L_{eq16} increase in aircraft noise exposure was associated with a 2 month delay in reading age in the UK and a 1 month delay in the Netherlands (Clark et al., 2006): this association remained after adjustment for aircraft noise annoyance and cognitive abilities including episodic memory, working memory and attention. Thus, whilst aircraft noise has only a small effect on reading comprehension, it is possible that children may be exposed to aircraft noise for many of their childhood years and the consequences of long-term noise exposure on reading comprehension and further cognitive development remain unknown.

The findings of the RANCH study, along with previous findings (Haines et al., 2001b; Hygge et al., 2002) suggest that noise may directly affect reading comprehension or could be accounted for by other mechanisms including teacher and pupil frustration (Evans & Lepore, 1993), learned helplessness (Evans & Stecker, 2004) and impaired attention (Cohen et al., 1973; Evans & Lepore, 1993). It has been suggested that children may adapt to chronic noise exposure by filtering or tuning out the unwanted noise stimuli: this filter may then be applied indiscriminately to situations where noise is not present, leading to learning deficits through lack of attention.

Discussion

In summary, there is convincing evidence for non-auditory effects of noise on health and cognition for some outcomes. Evidence for the effect of aircraft noise on children's cognitive performance is strong. Evidence for health outcomes

is increasing and there is consistent evidence for a small but significant effect of transport noise on hypertension and coronary heart disease. Furthermore, there is sufficient evidence for an effect of noise on sleep disturbance. Evidence for an effect of noise on endocrine markers is weak and inconclusive, especially for adults. Health effects of noise on the endocrine system cannot yet be ruled out and further, large scale studies are required focusing on adults.

Evidence for an effect of noise on psychological health suggests that for both adults and children noise is probably not associated with serious psychological ill-health but may affect quality of life and well-being. As yet, there are no prospective studies published on the effects of noise exposure on psychological health and few studies examine psychiatric diagnoses. The conclusions from cross-sectional evidence should be treated cautiously, as individuals who are experiencing poor mental health are more likely to also evaluate the environment negatively, bringing into question the direction of causality between noise exposure and mental health.

In conclusion, noise is a main cause of environmental annoyance and it negatively affects the quality of life of a large proportion of the population. In addition, health and cognitive effects, although modest, may be of importance given the number of people increasingly exposed to environmental noise and the chronic nature of exposure. Future research needs to further develop understanding not only of the magnitude of effects and exposure-effect relationships, which can inform interventions and policy, but also needs to further consider mechanisms for the effects such as the role of annoyance, adaptation, habituation, acclimation, and coping strategies and the role these may play in non-auditory effects of noise.

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A Brief Review of Known Effects of Noise on Marine Mammals

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Marine mammals, especially cetaceans, are highly vocal and dependent on sound for almost all aspects of their lives, e.g. food-finding, reproduction, communication, detection of predators/hazards, and navigation. They are thus likely sensitive to anthropogenic noise. Sound has a large potential area of impact, sometimes covering millions of square kilometers of ocean with levels high enough to cause possible disturbance in marine mammals. There can be great variation in the reaction of marine mammals to noise, depending on such factors as species, individual, age, sex, prior experience with noise, and behavioral state. Species with similar hearing capabilities can respond differently to the same noise. Observed effects of noise on marine mammals include: changes in vocalizations, respiration, swim speed, diving, and foraging behavior; displacement, avoidance, shifts in migration path, stress, hearing damage, and strandings. Responses of marine mammals to noise can often be subtle and barely detectable, and there are many documented cases of apparent tolerance of noise. However, marine mammals showing no obvious avoidance or changes in activities may still suffer important, even lethal, consequences. Acoustically-induced strandings may displace a local beaked whale (*Ziphiidae*) population (for an extended period if not permanently) or even possibly eliminate most of its members. As beaked whales seem to be found in small, possibly genetically isolated, resident populations, even a transient and localized acoustic impact could have prolonged population consequences. Observed reactions to noise in marine mammals could theoretically result in impacts such as decreased foraging efficiency, higher energetic demands, less group cohesion, higher predation, decreased reproduction, and thus seriously impact the population. Alternatively, they may be harmless. However, noise is thought to contribute to at least some species' declines or lack of recovery (Southern resident killer whales (*Orcinus orca*), western gray whales (*Eschrichtius robustus*) off Sakhalin).

As sound travels much better than light in the oceans, many marine animals, including marine mammals, use hearing as their primary sense. Cetaceans, in particular, are heavily dependent on sound for food-finding, communication, reproduction, detection of predators, and navigation. They are therefore likely sensitive to the introduction of anthropogenic noise into their environment. Unfortunately, because sound travels further than light in water, sounds have a large potential area of impact. Low frequency sounds, such as naval Low Frequency Active (LFA) sonar and distant shipping, travel especially well and may sometimes be heard over millions of square kilometers of ocean with levels high enough to cause possible disturbance in marine mammals. Seismic surveys can raise the background noise levels by 20 dB over 300,000 sq. km. continuously for days (IWC, 2005). Human use of the sea is growing and thus increasing the amount of noise that we introduce into the oceans (see Hatch & Wright, this issue).

Several reviews have examined the various known effects of noise on marine mammals (e.g., Richardson, Greene, Malme, & Thomson, 1995; Hildebrand, 2005; Nowacek, Thorne, Johnston, & Tyack, 2007; MMC, 2007). Such efforts will not be repeated here. Instead, the intent is to provide an overview

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of the various effects that noise is known to have on marine mammals for those new to the subject. Consequently, this is not an exhaustive review. However, the examples do represent a variety of impacts including: changes in vocalizations, respiration, swim speed, diving, and foraging behavior; displacement, avoidance, shifts in migration path, stress, hearing damage, and strandings.

Especially in species as difficult to observe as cetaceans, we are limited in our ability to detect impacts. Thus, failure to find a response to noise may be more due to measuring the wrong variables or an inability to measure the right ones, rather than a true lack of response. Populations may be threatened by noise through, for instance, increased stress levels or masking, yet these effects would be difficult to detect in cetaceans, since only a handful of the ca. 84 species have population estimates that are more precise than ± 40% (Whitehead, Reeves, & Tyack, 2000). The vast majority (72-90%) of serious population declines in cetaceans would not be detected under the current population monitoring effort (Taylor, Martinez, Gerrodette, Barlow, & Hrovat, 2007). Even when responses to noise are found, the biological significance to cetacean populations is hard to discern. Usually, only short-term responses to noise are studied, for practical reasons. However, short-term effects are hard to interpret. They may be an indication of serious population consequences or they may be insignificant. Conversely, long-term population impacts may occur without dramatic or even observable short-term reactions, as has been demonstrated in bottlenose dolphins, *Tursiops* spp. (Bejder, 2005) and caribou, *Rangifer tarandus* (Harrington & Veitch, 1992). Thus, long-term studies are more useful in relating disturbance reactions to population impacts (Bejder, 2005).

Changes in Vocalizations

Increases in vocalizations may represent an attempt by the animal to overcome 'masking,' when a sound is obscured or interfered with, by background noise. Masking can both reduce the range over which signals can be heard and reduce the signal's quality of information. The following observations may or may not be attempts to compensate for masking. Beluga whales (*Delphinapterus leucas*) used specific calls more often and shifted frequencies upward when boats were near (Lesage, Barrette, Kingsley, & Sjare, 1999). St. Lawrence River belugas were also shown to increase the level of their vocalizations as a response to increases in the levels of shipping noise, an indication of a Lombard vocal response (Scheifele et al., 2005). In response to high levels of boat traffic, killer whales increased the durations of their calls (Foote, Osborne, & Hoelzel, 2004). Humpback whales (*Megaptera novaeangliae*) lengthened their mating songs during exposure to LFA sonar (Miller et al., 2000). Pilot whales (*Globicephala melas*) produced more whistles in response to military mid-frequency sonar (Rendell & Gordon, 1999), as did bottlenose dolphins (*Tursiops truncatus*) in response to boat approaches (Buckstaff, 2004).

Marine mammals have also been observed to decrease their vocalizations in response to noise, sometimes ceasing to call entirely for periods of weeks or months. This can have implications for breeding, feeding, or social cohesion,

depending on the calls affected. Decreases in "creaks," thought to be prey capture attempts, have been observed in a Cuvier's beaked whale (*Ziphius cavirostris*) in response to ship noise (Soto et al., 2006), and in sperm whales (*Physeter macrocephalus*) in response to seismic surveys (IWC, 2007). Sperm whales have also been observed falling silent when exposed to pingers (Watkins & Schevill 1975), mid-frequency military sonar signals (Watkins, Moore, & Tyack, 1985), seismic surveys, and low frequency ATOC-like[1] sounds (Bowles, Smultea, Würsig, DeMaster, & Palka, 1994). The ATOC-like sounds and perhaps seismic surveys had similar effects on pilot whales (Bowles et al., 1994), though the power to detect effects in this study was low.

Fin whales (*Balaenoptera physalus*) reduced their calling rates in response to boat noise (Watkins, 1986). About 250 male fin whales stopped singing for weeks-months over 10-20,000 sq. nm. in the presence of a seismic survey, resuming singing within hours-days after the survey ended (IWC, 2007). It is likely that there were breeding consequences of this behavior, as these fin whale calls are thought to function in mating (Croll et al., 2002).

Changes in Diving and Foraging Behavior

Marine mammals have been observed to change their surface behavior (e.g. swim speed, respiration rate, etc.) in the presence of seismic noise, with largely unknown consequences. However, if foraging dives are affected by noise, it is quite likely that there will be associated reductions in foraging efficiency. In addition to other responses, sperm whales undertook no foraging dives when approached closely by a seismic survey vessel emitting airgun noise, and reduced the number of fluke strokes and effort at more distant exposures (IWC, 2007). Similarly, in response to the nearby passage of a noisy ship, a Cuvier's beaked whale was seen to dive for shorter periods, with less time spent echolocating, in addition to a lower production of creaks as was mentioned above (Soto et al., 2006). It was suggested that the combined effects resulted in a 50% reduction in foraging efficiency (Soto et al., 2006).

Northern elephant seals (*Mirounga angustirostris*) increased descent rates and decreased ascent rates similar to an escape response, when exposed to the low-frequency noise of ATOC (Costa et al., 2003). Western gray whales reacted to seismic surveys by swimming faster and straighter over a larger area with faster respiration rates (IWC, 2007). In addition to a tendency for avoidance and less feeding across all cetaceans during seismic surveys, mysticetes generally spent more time at the surface while smaller odontocetes tended to swim faster (Stone & Tasker, 2006). More subtle responses to seismic surveys were also seen at quite large distances. For example, one study found that bowheads (*Balaena mysticetus*) displayed no avoidance or a change in calling or general activities, but were

[1] Acoustic Thermometry of Ocean Climate was an oceanographic project which broadcasted loud sounds across whole ocean basins. It continues to operate under the name NPAL, or North Pacific Acoustic Laborartory.

undertaking shorter dives with a slower respiration rate at distances up to 50-70 km away (Richardson, Würsig, & Greene, 1986; Richardson et al., 1995).

Avoidance and Displacement

Displacement from critical feeding and breeding grounds has been documented in a number of marine mammal species exposed to noise. Possibly the most striking example is the displacement of gray whales from breeding lagoons in response to industrial noise (for over 5 years: Jones, Swartz, & Dahlheim, 1994) or dredging and shipping (displaced for 10 years: Bryant, Lafferty, & Lafferty, 1984). The critically endangered population of western gray whales off Sakhalin Island was also displaced from one of their primary feeding areas by seismic survey activity (IWC, 2005; 2007).

Beluga whales appeared to actively avoid icebreakers at distances of 35-50 km, remaining away for 1-2 days (Finley, Miller, Davis, & Greene, 1990; Cosens & Dueck, 1993). Killer whales were displaced from an area for 6 years by acoustic harassment devices, or AHDs (Morton & Symonds, 2002). Humpback whales avoided seismic surveys, with resting females staying 7-12 km away, although males were occasionally attracted to the sounds (McCauley et al., 2000). In addition, sighting rates of many cetaceans in UK and adjacent waters were significantly lower, and their distance to the seismic noise source (large volume airgun array) significantly higher, during periods when the source was on in comparison to those when it was not (Stone & Tasker, 2006).

Slight, but obvious, shifts in migration paths have also been noted in several species when a noise source was placed in their migration route. For example gray whales adjusted their migration path to avoid an LFA sonar source placed inshore, but not offshore (Tyack & Clark, 1988). In addition, both gray and bowhead whales have been observed detouring around continuous industrial noise (Malme, Miles, Clark, Tyack, & Bird, 1983, 1984; Richardson et al., 1985, Richardson, Würsig, & Greene, 1990).

Strandings and Fatalities

Much attention has been focused recently on acoustically-induced strandings, primarily with respect to beaked whales and military mid-frequency sonar (e.g., Fernandez et al., 2005, Cox et al., 2006). The Bahamas March 2000 mass stranding was one of the best studied of such strandings, and occurred together with naval exercises involving mid-frequency sonar. Several species of whale were found dead with injuries to their acoustic organs. The government acknowledged the fact that "...tactical mid-range frequency sonars aboard U.S. Navy ships…were the most plausible source of this acoustic or impulse trauma." (NOAA & U.S. Navy, 2001). This stranding was the only stranding for which baseline beaked whale survey data were available. Thus, it could be determined that there were no sightings of Cuvier's beaked whales for a 20 month period (May 2000 - February 2002) following the stranding, despite increased field effort in 2000 and 2001 (Claridge, 2006). Sighting rates since February 2002 appeared to be

back to those found from 1997-1999 (Claridge, 2006). The at least temporary and possibly permanent disappearance of pre-stranding known individuals seems to indicate that the affected local population of Cuvier's beaked whales was isolated from a larger population, implying that a population-level effect may have resulted from the brief transit of five naval vessels using sonar (Balcomb & Claridge, 2001; IWC, 2005). It is unknown how many whales from the local population of the species were killed during the naval exercise, but at minimum they were displaced from their former habitat. Beaked whales appear to be found in small, possibly genetically isolated, local populations that are resident year-round (Wimmer & Whitehead, 2004; Balcomb & Claridge, 2001). Such population characteristics make beaked whales particularly vulnerable to disturbance and population impacts.

Other cetacean species may also be involved in acoustically-induced strandings (see ICES, 2005), and the possibility that noise can lead to strandings and/or death in marine mammals exists beyond naval sonar. For instance, seismic noise has been implicated in a stranding of beaked whales (Hildebrand, 2005).

Hearing Damage

Noise has the potential to induce temporary hearing loss (either across the frequencies or more specific to a smaller frequency band), also known as temporary threshold shift (TTS), if it is loud or long enough in duration. In general, the higher the sound level and/or longer the duration, the more likely TTS is to occur. If exposure is prolonged or repeated or even as a result of one very loud noise event, the hearing damage can become permanent, also known as a permanent threshold shift (PTS). Experiments with captive bottlenose and beluga have, however, shown that both tonal (e.g., Schlundt, Finneran, Carder, & Ridgway, 2000) and very short duration impulsive (Finneran et al., 2002) sounds are capable of causing TTS, although the sound levels required for the impulsive sounds to do so were much higher than the 1 second tonal signals. Combining her research results along with other cited studies, Cook (2006) generally found that captive animals showed more hearing loss than similar-aged free-ranging dolphins. TTS and PTS are thought to have very similar effects on marine mammals as masking: reduction in foraging efficiency, reproductive potential, social cohesion, and ability to detect predators.

Hearing damage can kill indirectly, as in the case of humpback whales found fatally entangled in fishing gear at the same time and place as underwater explosions were occurring (Todd et al., 1996). Humpback whales in the area displayed no avoidance or behavioral reactions to the explosions, yet an unusual pattern of fatal entanglement occurred, suggesting hearing damage (if whales use sound to passively detect nets) or some other compromise to their navigation or sensory systems. Based on a good baseline of typical whale entrapment rates and patterns, it was found that entrapment rates both at the time and in the nearby area of blasting were dramatically and significantly higher, even though there were fewer fishing nets in the area (Todd, Stevick, Lien, Marques, & Ketten, 1996). Additionally, re-entrapments of the same animals occurred, something that had not happened for the previous 15 years. It is important to note that, based on the

whales' behavior, one would have incorrectly concluded that the explosions did not impact the animals, were it not for the special case of higher and unusual entanglement rates or patterns.

Noise and Stress

Although several reviews have entertained the possibility that noise induces a physiological stress response in marine mammals, there have been few studies. Romano et al. (2004) exposed a captive beluga whale and bottlenose dolphin to sounds from a seismic water gun and (for the bottlenose dolphin) 1-s, 3-kHz pure tones. They looked for various hormones in the blood, including cortisol, before and after exposure and saw changes (especially with the seismic sound) that were considered detrimental. These changes increased with increasing sound levels, and were significant. Thomas, Kastelein, & Awbrey (1990), however, did not find elevated stress hormone levels in the blood after playbacks of oil drilling platform noise to captive belugas, though their measures were less sensitive than those used in Romano et al. (2004). Miksis et al. (2001) found that heart rate in a captive bottlenose dolphin increased in response to threat sounds produced by other dolphins.

Context and Consequence

There can be great variation in the reaction of marine mammals to noise, depending on such factors as species, individual, age, sex, prior experience with noise, and behavioral state. Species with similar hearing capabilities can respond differently to the same noise (IWC, 2007). There are many documented cases of apparent tolerance of marine mammals to noise, which also demonstrate much variability. For example, bowhead whales tolerated an increase in 40 dB in seismic survey noise when feeding in summer than during the fall migration, where broadband received levels of airgun pulses corresponding to avoidance were 120–130 dB re 1 µPa (rms over pulse duration) and above (Richardson et al., 1995, Richardson, Miller, & Greene, 1999). Other examples of apparent tolerance can be found in sperm whales with seismic surveys in Norway (Madsen, Møhl, Nielsen, & Wahlberg, 2002), blue (*Balaenoptera musculus*) and fin whales with LFA sonar (Croll et al., 2001) and sea lions (*Zalophus californianus*) to AHDs (NMFS, 1996). It is not known what the consequences of this apparent tolerance are: it may represent acclimation or habituation of some kind, but may also represent an unrelenting need, e.g. for feeding or reproduction, to remain in a particular location despite exposure to noise, that could result in increased impacts from masking, hearing loss, and other potential effects, such as stress.

The observed reactions to noise in marine mammals could theoretically result in impacts such as decreased foraging efficiency, higher energetic demands, less group cohesion, higher predation, decreased reproduction, and other effects, thus seriously impacting the population as well as the individual. Alternatively, they may be harmless. However, noise is thought to contribute to at least some

species' declines or lack of recovery (Southern resident killer whales, Sakhalin gray whales; NMFS, 2002; IWC, 2007).

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Environmental Noise and Decision Making
Possible Implications of Increases in Anthropogenic Noise for Information Processing in Marine Mammals

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Recent increases in anthropogenic noise in the marine environment are a source of concern for the current welfare and future fitness of many marine mammal species. In this article I explore the specific question of how environmental noise could affect information processing. I also discuss the possible changes in behavior that would result, and how these changes could negatively impact the welfare and fitness of marine mammals. I identify two ways in which environmental noise could affect decision-making. First, environmental noise could add statistical noise to the detection of auditory signals, either masking them completely or rendering them ambiguous. Animals can respond to this problem either by moving away from the source of noise, or by altering the characteristics of their signal processing to increase the signal to noise ratio. Second, environmental noise could generate emotional states of fear or anxiety that cause biases in information processing. Anxiety is an emotion that functions as an early warning of potential threats, and is associated with a suite of changes in information processing including sensitization to stimuli potentially associated with threats, and pessimistic biases in decision-making resulting in increased risk aversion. Although these changes are clearly beneficial in the short term, chronic anxiety is likely to result in behavioral changes that will be detrimental to an animal's fitness in the longer term. Thus, there are likely to be subtle effects of noise on decision-making that have not so far been considered in relation to the effects of anthropogenic noise on marine mammal behavior.

The Problem

Anthropogenic noise has increased dramatically in the marine environment in recent years (Andrew, Howe, Mercer, & Dzieciuch, 2002; Hatch & Wright, this issue), and it is therefore important to consider how this change could affect the welfare and fitness (i.e. lifetime reproductive success) of marine mammals (Fair & Becker, 2000; Wright et al., this issue, b). Environmental noise can potentially impact the welfare and fitness of animals via a number of different mechanisms. For example, loud noises can directly damage animals' ears, and chronic exposure to moderate levels of environmental noise is associated with physiological and anatomical changes in both rats and humans that are associated with negative health consequences (Baldwin, this issue; Clark & Stansfeld, this issue; Wright et al., this issue, a). Environmental noise may also have less direct effects on behavior, and possibly also fitness, by causing alterations in information processing and consequent decision-making. These latter effects may be subtler than the direct effects of noise, however through the alterations in behavior that they cause they could be equally detrimental to animal welfare and long-term fitness. In the remainder of this article I will describe and discuss some of the effects of

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noise on information processing. I should stress at this point that there is currently very little information about these effects in marine mammals, and consequently the majority of my examples will come from studies of other more easily studied animals such as laboratory rodents and birds. However, there is every reason to expect that marine mammals should respond in similar ways to other animals when confronted with increases in environmental noise, and the limited information that we do currently have for marine mammals supports this prediction (Wright et al., this issue, b).

Information Processing and Noise

The performance of adaptive behavior relies on an animal possessing accurate information about the world (Dall, Giraldeau, Olsson, McNamara, & Stephens, 2005). Natural selection has equipped animals with the cognitive mechanisms that they need to process information and generate adaptive behavior within the environments in which they have evolved. The brain receives information about the state of the environment via the senses and about the state of the body via its own internal monitoring mechanisms. On the basis of this information, decision mechanisms in the brain generate appropriate physiological and behavioral responses.

Sound is an extremely important source of information for marine animals. The superior propagation of sound in water as compared with air, coupled with reduced visibility in the sea have led to hearing becoming an important sense in many species of marine mammals and probably also fish. For example, many marine mammals use vocalizations for both intra-specific communication and for echolocation, meaning that auditory information is crucial to activities including locating food, making foraging decisions, avoiding predators, choosing mates and social behavior. As a consequence of the importance of sound in marine mammal ecology, it makes sense that marine mammals have evolved specialized mechanisms for processing sound-related information, and that these mechanisms might be particularly sensitive to changes in environmental noise.

The term information processing refers to everything that goes on between information entering an animal via its sense organs and observed behavior (see Figure 1 for a summary). Thus, the brain can be viewed as an information-processing organ. I will discuss two routes via which environmental noise could potentially alter information processing in marine mammals.

First, environmental noise could add statistical noise to the detection of auditory signals, masking the incoming information completely, changing it in some way, or rendering it ambiguous. Second, by generating an emotional state, such as fear or anxiety, environmental noise could provoke changes in decision-making mechanisms congruent with the induced state. Below I enlarge on each of these possibilities and provide examples of the changes in behavior that might result.

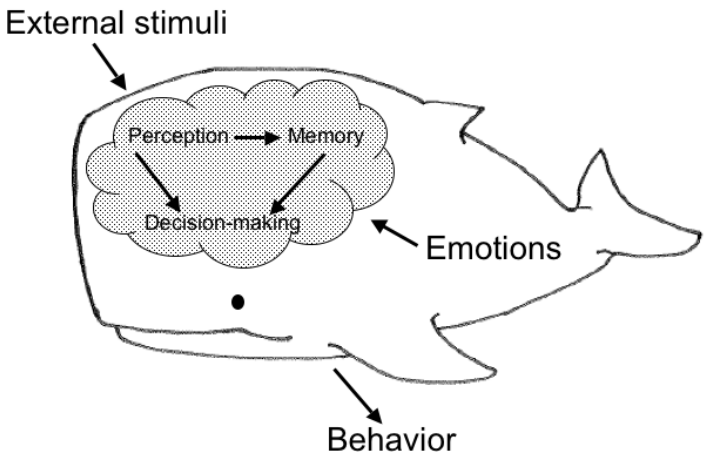

Figure 1. The basic elements of an information-processing model of behavior. Environmental noise could affect information processing in animals either by interfering with the in-coming information from the environment, or indirectly, by evoking internal emotional states such as anxiety that then bias information processing mechanisms.

Detecting Signals in Noise

Many animals face the problem of distinguishing biologically important stimuli, such as conspecific signals or returning echoes, from background noise (for a review see Brumm & Slabbekoorn, 2005). Some mistakes are inevitable, because most signals have some degree of variation associated with them, and natural environments are characterized by permanent background noise of biotic and abiotic origins. Figure 2 illustrates a typical signal detection problem in which an animal looking for a potential mate is faced with distinguishing conspecific calls from those of other species. Although I have chosen this particular example, it is important to realize that the same basic scenario could apply to discriminating any type of auditory information from background noise including returning echoes, sounds of other species and abiotic noises such as those produced by weather, seismic activity and boats. In Figure 2 both types of call are somewhat variable in frequency, as depicted by the normal distributions, and there is an area of overlap in which the two types of call cannot be distinguished on the basis of frequency alone. As a result, conspecific signals will sometimes be incorrectly ignored (misses) and calls of other species will sometimes be incorrectly identified as conspecifics (false alarms, see Table 1). Both types of mistakes have associated costs; in this example, misses will result in passing up a potential mate, whereas false alarms will result in time waste courting the wrong species and possibly infertile mating attempts. In different scenarios the costs will be different; for example in the situation where an animal has to detect the sound of an approaching boat from background environmental noise a miss could result in physical injury or even death, and a false alarm could result in prematurely leaving a good foraging patch.

The problem faced by natural selection is how to minimize the costs of misses and false alarms. Signal detection theory, originally developed in a military context to deal with the problem of identifying significant objects such as planes on noisy radar screens, can be used to quantify this trade-off (e.g. Wiley, 1994). In short, the position of the criterion for discriminating the two

types of call will depend on the relative costs of the two types of mistakes: if misses are cheap or false alarms particularly costly then it will pay to set a conservative criterion (i.e. further towards the right) and only initiate mating or stop foraging if the sound is highly characteristic of a conspecific vocalization or a boat engine, whereas if the reverse is true and misses are costly or false alarms cheap, then it will pay to set a less stringent criterion (i.e. further towards the left) and classify a wider range of signals as those of potential mates or dangerous boats. The optimal position for the criterion will depend on the specific context and the relative costs and benefits of errors versus correct responses.

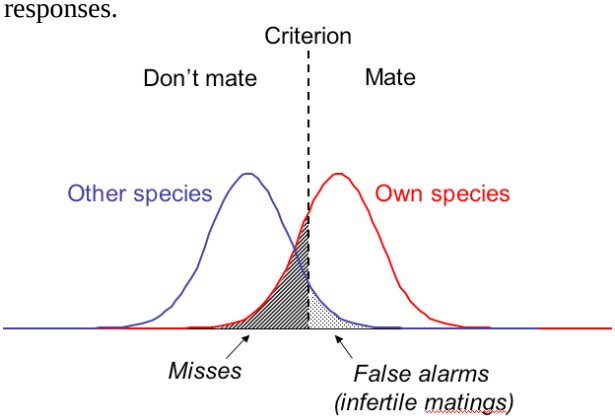

Figure 2. In this example, the x-axis describes the frequency of a call, and the y-axis describes the probability of a call of a given frequency appearing. Two probability distributions are shown: the one on the left corresponds to the calls of other species, and the one on the right to conspecific calls. The dotted line is the criterion below which calls are classified as other species and above which calls are classified as conspecific. The probability of missing a conspecific call is indicated by the hatched area, and probability of a false alarm by the shaded area.

Table 1
Types of possible response in a signal detection task.

	Signal	
Response	Present	Absent
Signal detected	Hit	False alarm
No signal detected	Miss	Correct rejection

We can use the basic framework established above to think about the possible effects of increased environmental noise on decision-making. Figure 3a shows a hypothetical example in which additional environmental noise increases the variance of the distribution of signals that should be rejected. If the criterion for rejection is unchanged (as shown in Figure 3a), then the number of misses will remain unchanged, but the number of false alarms will increase. The fitness consequences of such a change will depend on the costs of a false alarm, but if, as in the case of the above example, a false alarm translates into an infertile mating, then they could be considerable. In the most extreme cases environmental noise could completely mask biologically significant signals depriving animals of sources of information vital for their fitness.

Animals faced with an increase in environmental noise can respond in various ways to reduce the probability of errors in signal detection. Broadly speaking, either signalers can alter some aspect of their signal production to reduce the probability of errors, or signal receivers can change some feature of

their signal to reduce the probability of errors. In both cases these responses could either be adaptive plasticity within the individual, or take place by natural selection over evolutionary time. However, the long life spans and generation times of many marine mammal species may severely limit their capacity to keep up with rapid environmental changes via the latter mechanism.

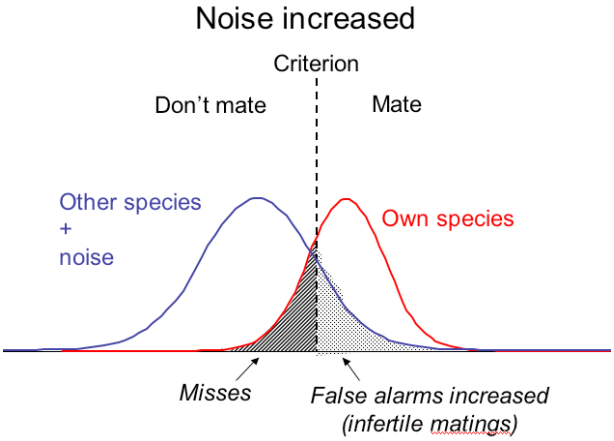

Figure 3a. Increased environmental noise makes the signal detection problem described in Figure 2 more difficult by increasing the variance of the sounds from which conspecific calls must be discriminated.

Hearing may initially appear a passive sense in which the signal receiver has little latitude for improving signal detection. However, there are a number of mechanisms involving both perception and behavior via which signal receivers can reduce the probability of errors in detection. At the behavioral level, it may be possible to improve the signal to noise ratio by moving closer to the source of a signal or away from the source of noise. At the information processing level, the signal receiver could change the criterion for classification. For example, moving the criterion to the right will serve to reduce the false alarm rate at the expense of increasing the miss rate (Figure 3b). Many perception adaptations have also been identified in species as diverse as insects, frogs, birds and bats (reviewed in Brumm & Slabbekoorn, 2005). Research on perception is usually derived from laboratory studies, making it difficult in marine mammals, however recent research on hearing in fish under noise conditions has the potential to identify the strategies used in fish (Wysocki & Ladich, 2005).

Signalers can respond by shifting the signal away from the noise by altering its frequency (Figure 3c), or sharpening the discriminability of the conspecific signal (Figure 3d), which will reduce the number of misses. An example of altering the frequency of a signal is found in urban great tits (*Parus major*), in which a correlation is observed between the amplitude of background noise and the average minimum frequency of male birds' songs (Slabbekoorn & Peet, 2003). Animals have used a number of different strategies for improving the discrimination of a signal without changing its frequency. Perhaps the most obvious way to counteract the masking effects of background is to increase the amplitude, a response referred to as the "Lombard effect". There is abundant evidence that many birds sing louder in response to increases in background noise. For example, male nightingales

(*Luscinia megarhynchos*) regulated the intensity of their songs according to the level of masking noise, thus maintaining a specific signal-to-noise ratio that is favorable for communication (Brumm & Todt, 2002). Another approach is to increase the duration of the signal or repeat the same signal more often. For example, killer whales (*Orcinus orca*) produced more easily perceived, long calls when noise from boats exceeded a threshold level (Foote, Osborne, & Hoelzel, 2004), and beluga whales (*Delphinapterus leucas*) increased the repetition of specific calls when a boat was nearby (Lesage, Barrette, Kingsley, & Sjare, 1999). It is important to realize that these compensatory strategies are not likely to be without cost. In the case of the killer whales for example, making longer calls must take either time or attention away from other important activities such as foraging, and will involve an increased energetic cost.

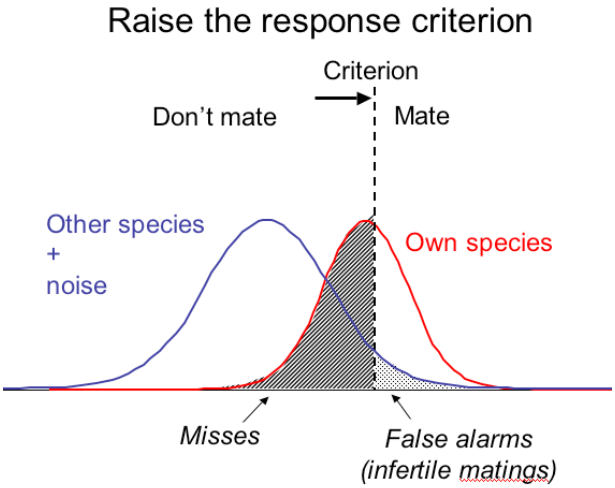

Figure 3b. Animals might respond to increased environmental noise by shifting the criterion to the right and hence reducing the possibility of false alarms at the expense of increasing the probability of misses.

Finally, both signalers and signal receivers can attempt to escape increased environmental noise either spatially or temporally. Spatial escape would involve moving to a different location where environmental noise is reduced. It is now well established that whales choose to avoid areas of high whale watching activity, and one explanation for this preference could lie in the signal detection difficulties imposed by boat noise (Wright et al., this issue, b). A major cost of using a spatial avoidance strategy is that it is likely to force animals into areas that are otherwise suboptimal. For example, whales might be forced into less good foraging areas in order to escape anthropogenic noise, which is likely to have welfare and fitness consequences. Temporal escape involves altering the timing of signaling to correspond with the time when there is least environmental noise. An example of this latter strategy was recently reported in urban robins that have shifted to singing during the night in areas where there is high traffic noise during the day (Fuller, Warren, & Gaston, 2007). Again, it is unlikely that this strategy will be without cost, because by singing at night robins may be exposing themselves to increased predation risks or depriving themselves of sleep. A possible case of temporal escape has been described in beluga whales (*Delphinapterus leucas*) that reduce their calling rate while vessels are approaching (Lesage, Barrette,

Kingsley, & Sjar, 1999). It is hard to speculate about the possible costs of this change in behavior without knowing the precise function of the vocalizations involved.

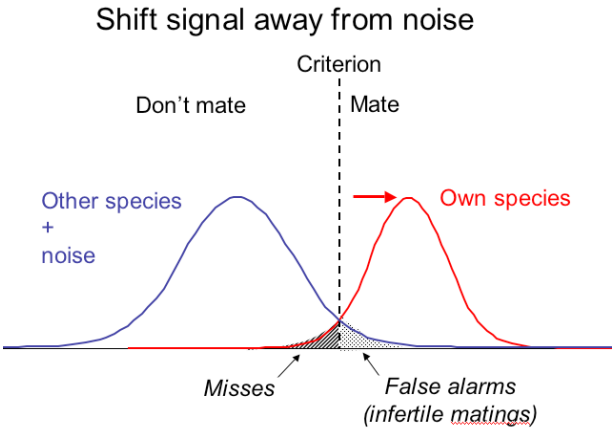

Figure 3c. Animals might respond to increased environmental noise by shifting their own signals away from the noise hence reducing the number of misses.

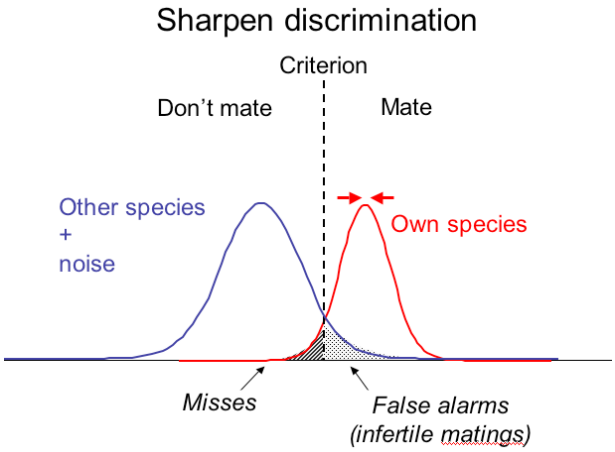

Figure 3d. Animals might respond to increased environmental noise by sharpening the discrimination of their own signals. This could be affected by reducing the variance in conspecific calls. The effect is to reduce the number of misses.

Cognitive Bias and Noise

For many animals environmental noise is an important cue that danger could be imminent. For example, many animals will rely on sound to provide them with information about the possible approach of a predator or other threat. It therefore makes sense that many animals will respond to unusual or unexpected noises with adaptive emotional reactions such as fear and anxiety. Increased levels of background noise are also associated with a stress response in humans (Clark & Stansfeld, this issue). Anxiety is an emotion that functions as an early warning of potential threats, and is associated with a suite of changes that prepare the animal for dealing with the threat. The physiological and behavioral changes that come with anxiety such as increased heart rate and vigilance are well known, however these are also accompanied by changes in information processing, referred to as "cognitive biases", that prepare the

animal cognitively for dealing with the threat (Clore & Huntsinger, 2007; Mathews, Mackintosh, & Fulcher, 1997). For example, anxious humans show selective attention to threatening words (Williams, Mathews, & McLeod, 1996), and will detect an angry face amongst a large array of neutral faces more rapidly (Bryne & Eysenck, 1995). Anxious humans are also more likely to assume a negative or threatening interpretation when presented with ambiguous stimuli such as homophones (e.g. die/dye or pain/pane, (Eysenck, MacLeod, & Matthews, 1987; Eysenck, Mogg, May, Richards, & Matthews, 1991)).

Recently, "pessimistic" cognitive biases have also been reported in non-human animals housed in suboptimal cages. For example, Harding et al. (2004) trained rats on a go/no-go task to press a lever to obtain a food reward on hearing a positive stimulus (the food-delivery tone), but to refrain from pressing the lever to avoid unpleasant white noise on hearing a negative stimulus (the noise-avoidance tone). Once trained on this task, rats were allocated to either predictable or unpredictable (depression-inducing) housing. Following this manipulation the rat were tested with non-reinforced stimuli intermediate between the food-delivery and noise-avoidance tones. The animals' anticipation of the positive and negative outcomes was estimated by measuring the probability with which they lever-pressed in response to the ambiguous tones. Rats in the unpredictable group showed fewer and slower responses than rats in the predictable group. Thus, the depressed rats showed reduced anticipation of a positive event.

We used a similar approach to ask whether European starlings (*Sturnus vulgaris*) deprived of environmental enrichment in their cages show biases in their classification of ambiguous signals (Bateson & Matheson, 2007). On the basis of the previous findings in humans and rats discussed above, we hypothesized that starlings in enriched cages should be more likely to classify ambiguous signals as being associated with a positive outcome than starlings housed in standard, unenriched cages. Starlings were trained on a go/no-go procedure to discriminate between two visual stimuli (cardboard lids of white and dark grey) associated with outcomes of a different value (palatable and unpalatable mealworms hidden underneath). Individual birds' responses to unreinforced, intermediate stimuli (various shades of grey between white and dark grey) were subsequently examined while each bird was housed sequentially in both standard and enriched cages. The probability of a bird classifying an ambiguous pale grey lid as hiding a palatable mealworm was lower in standard cages than enriched cages, but this difference was only found in birds that received enriched cages first (Figure 4). Our results can be interpreted as showing a pessimistic bias in birds that have recently experienced a decline in environmental quality (see also Matheson, Asher & Bateson, 2008).

The above studies show that animals experiencing anxiety or depression induced by poor housing conditions are more pessimistic in their interpretation of ambiguous information resulting in more risk-averse decision-making. The pessimistic animals were less ready to expose themselves to unpleasant events such as white noise or quinine-tainted food. It is reasonable to hypothesize that similar risk-averse biases may be present in marine mammals rendered anxious by recent increases in anthropogenic noise. While increased risk-aversion is an adaptive response in the face of real threats,

chronic pessimism is unlikely to be adaptive since it may cause animals to pass up opportunities beneficial to their long-term fitness.

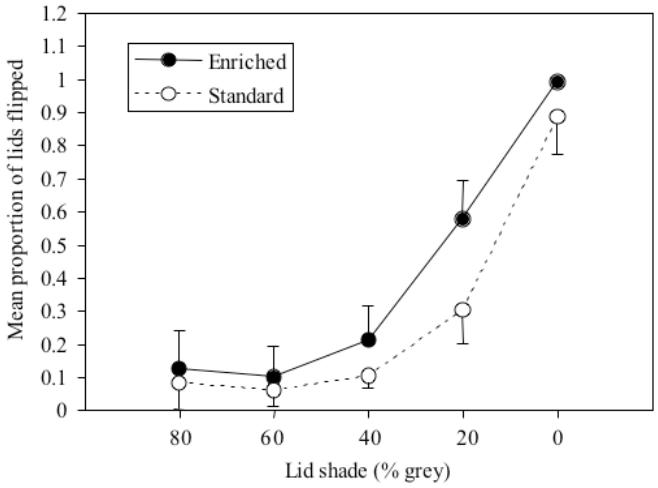

Figure 4. An example of a pessimistic cognitive bias . The x-axis shows the shade of the lid used to hide a worm. 80% grey lids were associated with unpalatable quinine-injected mealworms whereas white lids (i.e. 0% grey) were associated with palatable mealworms. Intermediate lid shades were never reinforced with either type of mealworm. The y-axis shows the proportion of times birds investigated Petri dishes by flipping off the lid (from Bateson & Matheson (2007), with permission).

Conclusions

Increases in anthropogenic noise are likely to have subtle effects on the cognition and behavior of marine mammals via at least two different mechanisms. First, noise may interfere with or mask the auditory signals available to marine mammals depriving them of important sources of information. Although evidence suggests that animals will compensate for such interference via a range of strategies, this is unlikely to be without costs. Second, noise may evoke emotional states that bring about biases in information processing and decision-making. Although these biases may have been adaptive in the environments in which the animals evolved, it is possible that they may be maladaptive in the radically different environments present in today's oceans. Further research is needed to identify the extent to which marine mammal behavior is affected by increased levels of anthropogenic noise, and to quantify the potential welfare and fitness consequences of these changes.

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The Influence of Metal Pollution on the Immune System A Potential Stressor for Marine Mammals in the North Sea

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Marine mammals of the North Sea are loaded with metal pollutants. The environmental exposure induces concentrations bioavailable to immune cells high enough to affect their function. Such an imbalance of the immune system caused by pollutants may play a significant role in the incidence of infectious diseases in marine mammals. Metals influence the function of immunocompetent cells by a variety of mechanisms. Depending on the particular metal, its speciation, concentration and bioavailability, and a number of other factors, a continuous metal exposure will result in an immunosuppression or immunoenhancement effects. Both effects were demonstrated on the cellular level in animals of the North Sea. This article reviews metal concentrations in the North and Baltic Seas particularly in tissues of marine mammals, discusses pollutants effects on health and immune functions, and underlines the still existing problem of animals living in polluted coastal areas.

The harbor (or common) seal, *Phoca vitulina*, the grey seal, *Halichoerus grypus* and the harbor porpoise, *Phocoena phocoena* are the most prominent domestic marine mammals in the Wadden Sea. Beside these species several other marine mammals occur in the Wadden Sea and adjacent North Sea as stragglers or regular visitors such as harp seal, *Phoca groenlandica*, hooded seal, *Cystophora cristata*, ringed seal, *Phoca hispida*, bearded seal, *Erignathus barbatus*, walrus, *Odobenus rosmarus*, various species of dolphins as well as large cetaceans, e.g. the minke whale, *Balaenoptera acutorostrata*, and sperm whale, *Physeter macrocephalus*. Seals living in the coastal area are strongly influenced by anthropogenic activities such as fishery, off-shore activities, habitat destruction and environmental pollution.

Since 1978 The Netherlands, Germany and Denmark have been working together on the protection and conservation of the Wadden Sea, which results in the development of the "Trilateral Monitoring and Assessment Program" (TMAP). Within this agreement the seal population is supposed to serve as a bioindicator for the Wadden Sea ecosystem. Seals are considered as indicators for medium and long-term changes in the ecosystem due to their widespread distribution over the coastal areas, their high trophic level, which results in a bioaccumulation and biomagnification of chemicals in their tissues, their long-life span and relatively late maturity including a low reproduction rate. All these factors serve to qualify harbor seals as biomarkers of chemical exposure in the Wadden Sea.

In addition, the "Seal Agreement" has been adopted, which establishes terms of research and monitoring including the monitoring of pollution and investigations on the effects of substances e.g. organochlorine compounds, metals and oil on the seal population. These terms have been specified in the "Seal Management Plan for the Wadden Sea Seal Population" which utilizes parameters such as reproduction, mortality and health status to assess the seal population and includes e.g. immunological, physiological, toxicological, pathohistological and microbiological research.

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The growth of the harbor seal population in the Wadden Sea was interrupted by a phocine distemper virus epizootic in 1988 and 2002. In this context, the influence of pollutants on the immune system has been repeatedly discussed.

Metals in the North and Baltic Seas

In the past, the North Sea ecosystem was highly loaded with both organic and metal pollutants introduced by various anthropogenic activities within the coastal zones. Until the middle of the eighties the yearly input of metal pollution caused by rivers, direct discharge, dumping at sea, atmospheric input and combustion at sea was around 340 tonnes Cd, 75 t Hg, 11.000 t Pb, 5.000 t Cr and 2.150 t Ni (Rachor & Rühl, 1990). A review on the pollution situation in the North Sea has been published by Kersten et al., 1988. Table 1 gives an overview of selected references dealing with environmental research on metals in the North and Baltic Sea.

Current studies have shown a diminishing trend in the input of pollutants into the ecosystem. The BLMP monitoring program (Bund-Länder-Messprogramm) confirmed this general tendency for metal pollutants, however it is necessary to consider this conclusion more detailed. The concentrations of Hg, Cd, Pb and Zn in water and sediment for example are still elevated compared to the "Background Reference Concentrations" which the Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) derived for the "Greater North Sea" (Schmolke et al., 2005).

The Quality Status Report of the TMAP concluded that major reductions in the input and the concentrations of metals in the Wadden Sea occurred mainly in the late 1980s until the early 1990s and continued moderately until 2002. However, local and metal specific elevated concentrations compared to the proposed background values were still frequently investigated (Bakker, van den Heuvel-Greve, & Vethaak, 2005).

Metal body burdens in the mammals of the North and Baltic Seas

Contaminants found in various marine mammal species in the North and Baltic Seas include organochlorine pollutants (Bruhn, Kannan, Petrick, Schulz-Bull, & Duinker, 1999; Hall et al., 1999; Holsbeek et al., 1999; Kleivane, Skaare, Bjorge, Deruiter, & Reijnders, 1995; Sormo, Skaare, Jussi, Jussi, & Jenssen, 2003; Troisi et al., 2000), polybrominated diphenyl ethers (Kalantzi, Hall, Thomas, & Jones, 2005; Law, Allchin, Bennett, Morris, & Rogan, 2002), perfluorinated sulfonates (Kannan et al., 2002; Van de Vijver et al., 2004) and metals (Table 2).

Table 1
Selected studies on metal concentrations in the environment of the North and Baltic Seas.

Object of investigation	Element	Location	Reference
Fish	Cd, Cu, Hg, Pb, Zn	Baltic Sea	Perttilä et al., 1982a
Fish	Cd, Cu, Hg, Pb, Zn	Baltic Sea	Perttilä et al., 1982b
Fish	As	North Sea	Falconer et al., 1983
Water (surface water)	Al, Cd, Co, Cu, Mn, Ni	North Sea	Kremling & Hydes, 1988
Sediments	As, Cd, Cu, Hg, Pb, Zn	North Sea	Chapman, 1992
Fish, Shrimp, Mussel	Hg, Se	North Sea, Belgium	Guns & Vyncke, 1992
Fish, Mussel, Sediments	Ni	Baltic Sea Gdansk Bay	Skwarzec et al., 1994
Sediments	Ag, Al, Ca, Cd, Co, Cr, Cs, Cu, Fe, K, Li, Mg, Mn, Na, Ni, P, Pb, Rb, Sr, Zn	Baltic Sea Gdansk Bay	Szefer et al., 1996
Birds	Cd, Cu, Hg, Se, Zn	North Sea, German Bight	Wenzel et al., 1996
Fish, Birds, Sediments	Organo-Sn	Polish Coast Baltic Sea	Kannan & Falandysz, 1997
Water (dissolved fraction, particulate matter)	Cd, Co, Cu, Fe, Mn, Ni, Pb, Zn	Southern North Sea	Millward et al., 1998
Fish	Hg, Cu	North Sea	Broeg et al., 1999
Sediment	Cd, Cu, Pb, Zn	North Sea, Dutch coastal zone	Laane et al., 1999
Birds	Cd, Cr, Cu, Fe, Ni, Pb, Zn	North Sea, Belgian coast	Debacker et al., 2000
Water	Co, Cu, Fe, Zn	Baltic Sea, Skagerrak	Croot et al., 2002
Sediment, Suspended particulate matter	Al, Fe, K, Mn, Pb	North Sea, German Bight	Hinrichs et al., 2002
Water (coastal water, dissolved)	Co, Cu	Western North Sea	Achterberg et al., 2003
Sediments	Ba, Cd, Cr, Cu, Hg, Ni, Pb, V, Zn	North and Baltic Sea	Breuer et al., 2004
Asteroids, Sediments	Cd, Cu, Pb, Zn	North Sea, Southern Bight	Danis et al., 2004
Water (dissolved fraction, particulate matter, surface & deeper water)	Cd, Cu, Hg, Pb, Zn	Western and Central Baltic Sea	Dippner & Pohl, 2004
Fish	Cd, Cu, Mn, Pb	North Sea, Southern Bight	Henry et al., 2004
Asteroids	Cd, Cu, Pb, Zn	North Sea, Southern Bight	Danis et al., 2006
Mussel	Cd, Cu, Ni, Pb, Zn	German Wadden Sea	Jung et al., 2006
Air, Precipitation	Hg	North Sea Area	Wängberg et al., 2007

Table 2
Summary of studies on metal concentrations in tissues of marine mammals of the North and Baltic Seas.

Species	Organ	Element	Location	Reference
Phocoena phocoena, Lagenorhynchus albirostris	B, L, M	Cu, Hg, Pb, Zn	Denmark	Andersen & Rebsdorff, 1976
Phoca vitulina	Br, K, L	Cd, Cu, Hg, Pb, Zn	German Wadden Sea	Drescher et al., 1977
Phocoena phocoena, Phoca vitulina, Phoca hispida, Halichoerus grypus, Hyperoodon ampullatus, Delphinapterus leucas	K, L, M	Cd, Cu, Hg, Pb, Zn	North and Baltic Coasts, Germany	Harms et al., 1978
Phoca vitulina	B, Br, He, K, L, Pl, Sp	Cd, Cr, Cu, Fe, Mn, Pb, Zn	Dutch Wadden Sea	Duinker et al., 1979
Phoca vitulina	Br, K, L	Br, Hg, Se	Wadden Sea	Reijnders et al., 1980
Phocoena phocoena	Br, K, L,	Cd, Cu, Hg, Pb, Zn	Scotland	Falconer et al., 1983
Phocoena phocoena, Tursiops truncates, Halichoerus grypus, Stenella coeruleoalba	B, L, M	Cd, Cr, Cu, Hg, Ni, Pb, Zn	Irish Sea	Morris et al., 1989
Phoca vitulina	L	As, Cd, Cu, Hg, Se, Zn	Norwegian	Skaare et al., 1990
Phoca vitulina, Halichoerus grypus, Tursiops truncates, Lagenorhynchus albirostris, Lagenorhynchus acutus, Delphinus delphis, Stenella coeruleoalba	L	Cd, Cr, Cu, Hg, Ni, Pb Zn	Waters around British Isles	Law et al., 1991
Phocoena phocoena, Physeter macrocephalus, Delphinus delphis, Tursiops truncatus	K, L, M	Hg	Denmark, Belgium	Joiris et al., 1991
Phoca vitulina, Halichoerus grypus, Phoca hispida	K, L	Al, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Ni, Pb, V, W, Zn	Swedish waters	Frank et al., 1992
Phoca vitulina	H, S	Cd, Hg, Pb	German Wadden Sea	Wenzel et al. 1993
Phocoena phocoena	L	Organo-Sn	Polish Baltic Sea	Kannan & Faladysz, 1997
Phocoena phocoena, Halichoerus grypus	L	Organo-Sn	Waters around British Isles	Law et al., 1998
Physeter macrocephalus	B, K, L, M	Cd, Cr, Cu, Fe, Hg, Ni, Pb, Se, Ti, Zn	Southern North Sea	Holsbeek et al., 1999
Grampus griseus, Lagenorhynchus albirostris, Delphinus delphis, Stenella coeruleoalba, Globicephala melas, Lagenorhyncus acutus, Kogia breviceps, Mesoplodon bidens, Mesoplodon densirostris, Hyperoodon ampullatus, Balaenoptera physalus, Balaenoptera acutorostrata	L	Organo-Sn	Waters around British Isles	Law et al., 1999
Phocoena phocoena, Lagenorhyncus albirostris	K, L, M	Hg	North and Baltic Coasts, Germany	Siebert et al., 1999

Phocoena phocoena	L	Cd, Cr, Cu, Hg, Ni, Pb, Se, Zn	England, Wales	Bennett et al., 2001
Phoca hispida	K, L, M	Cd, Hg, Pb, Se	Baltic Sea, Svalbard	Fant et al., 2001
Grampus griseus, Lagenorhynchus albirostris, Delphinus delphis, Stenella coeruleoalba, Globicephala melas, Lagenorhyncus acutus, Kogia breviceps, Mesoplodon bidens, Balaenoptera physalus, Balaenoptera acutorostrata	L	Ag, As, Cd, Cr, Cu, Fe, Hg, Ni, Pb, Se, Zn	Waters around British Isles	Law et al., 2001
Phocoena phocoena	K, L, K	Cd, Cr, Cu, Fe, Mn, Ni, Pb, Zn	Southern Baltic Sea, Danish and Greenland coastal waters	Szefer et al., 2002
Phocoena phocoena, Phoca vitulina, Phoca hispida	B, Br, K, L, M, S,	organo-Sn	Norwegian	Berge et al., 2004
Phocoena phocoena, Phoca hispida, Halichoerus grypus, Stenella coeruleoalba	L	organo-Sn	Polish Baltic Sea	Ciesielski et al., 2004
Phocoena phocoena	K, L, M	Cd, Cu, Fe, Hg, Se, Zn	Belgium, France, Germany (North and Baltic Sea), Denmark	Das et al., 2004
Phoca vitulina	Bl	Al, As, Be, Cd, Cr, Co, Cu, Au, Fe, Pb, Mn, Mo, Ni, Pd, Pt, Se, Ag, Sn, Ti, Zn	German Wadden Sea	Kakuschke et al., 2005
Phocoena phocoena	L	Hg, organo-Sn	Danish waters	Strand et al., 2005
Phocoena phocoena, Phoca hispida, Halichoerus grypus, Stenella coeruleoalba	L	Al, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, Ga, Hg, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Se, Si, Sr, Tl, V, Zn	Polish Baltic Sea	Ciesielski et al., 2006
Phoca vitulina	Bl	Ca, Cu, Fe, K, P, Rb, S, Se, Sr, Zn	German Wadden Sea	Griesel et al., 2006
Halichoerus grypus	Bl	Al, As, Be, Cd, Cr, Co, Cu, Au, Pb, Mn, Mo, Ni, Pd, Pt, Se, Ag, Sn, Ti, V, Zn	German Wadden Sea	Kakuschke et al., 2006
Phocoena phocoena	K, L	Cd, Cu, Hg, Se, Zn	Southern North Sea	Lahaye et al., 2007
Phoca vitulina	Bl	Al, As, Be, Ca, Cd, Cr, Co, Cu, Fe, K, Pb, Mn, Mo, Ni, Pd, Pt, Rb, Se, Sn, Sr, Ti, V, Zn	German Wadden Sea	Griesel et al., 2008
Phoca vitulina	Bl	Al, As, Be, Ca, Cd, Cr, Fe, Pb, Mn, Mo, Ni, Se, Sn, Zn	German Wadden Sea	Kakuschke et al., 2008a
Phoca vitulina	Bl	Al, As, Be, Ca, Cd, Co, Cr, Cu, Fe, K, Mn, Mo, Ni, Pb, Pd, Pt, Rb, Se, Sn, Sr, Zn	German Wadden Sea	Kakuschke et al., 2008b

B=blubber, Bl=blood, Br=brain, M=muscle, L=liver, K=kidney, S=skin, Sp=spleen, He=heart, Pl=placenta, H=hair

Most studies on metal body burdens focused on the investigation of metal concentrations in the liver, kidney or muscle, i.e. tissues available only through post-mortem examination. In living animals the choice of samples is mostly restricted to blood and hair. However, because of sampling difficulties, up to now only few studies have reported values for metals in the blood of marine mammals (Baraj et al., 2001; Caurant & Amiard-Triquet, 1995; Nielsen, Nielsen, Jorgensen, & Grandjean, 2000) and in particular for pinnipeds in the North Sea (Griesel et al., 2006; Kakuschke et al., 2005, 2006). Current studies suggested relatively high metal concentrations in living seals of the North Sea compared to human blood reference values as well as local differences in metal concentrations (Griesel, Kakuschke, Siebert, & Prange, 2008). Furthermore newborn seals in the North Sea showed high body burdens of selected metals, probably caused by a transplacental transfer from the mother to fetus or through the milk during the lactation period (Kakuschke, Griesel, & Prange, 2008a).

Metal pollutants and marine mammal health

Metals and their effects on marine mammals have been reviewed by Das, Debacker, Pillet, & Bouquegneau (2003), O'Shea (1999), and Reijnders, Aguilar, & Donovan, (1999). Nevertheless, apart from metal body burden data, only limited information is available, especially on the related health effects. Hyvärinen & Sipilä (1984) found a relationship between stillbirths of ringed seal (*Pusa hispida saimensis*) pups from Finland and the Ni concentrations in hair samples. Experimental intoxication of harp seal (*Pagophilus groenlandicus*) with methyl-Hg by daily oral intake (25mg/kg) was found to result in lethargy, weight loss and finally death (Ronald, Tessaro, Uthe, Freeman, & Frank, 1977). The corresponding blood parameters indicated renal failure, uremia and toxic hepatitis. Rawson et al. (1993) found an accumulation of lipofuscin in the liver cells of stranded Atlantic bottlenose dolphins (*Tursiops truncatus*) caused by a Hg induced inhibition of the activity of digestive enzymes, which finally results in an increased number of liver diseases. In a case study Shlosberg et al. (1997) described progressive liver damage and finally death of a bottlenose dolphin resulting from Pb intoxication. Studies on the adrenal and testicular steroidogeneses in the grey seal (*Halichoerus grypus*) and harp seals (*Pagophilus groenlandicus)* indicated altered biosyntheses caused by metal contaminants (Freeman, Sangalang, Uthe, & Ronald, 1975; Freeman & Sangalang, 1977). Methyl-Hg intoxicated harp seals showed a low level of damage of sensory cells of the organ of Corti (Ramprashad & Ronald, 1977).

Some researchers have used an indirect approach to investigate the prediction that metal pollutants result in lower resistance to diseases. The endangered population of belugas (*Delphinapterus leucas*) in the polluted estuary of the St. Lawrence River showed high concentrations of organochlorines, heavy metals, and benzo[*a*]pyrene in tissues as well as a high prevalence of tumors which suggests an influence of contaminants through a direct carcinogenic effect and/or a decreased resistance to the development of tumors (De Guise, Lagace, & Beland, 1994). Siebert et al. (1999) investigated Hg body burden and diseases in harbor porpoises (*Phocoena phocoena*) from the German Waters of the North and Baltic Seas. High Hg concentrations were associated with a prevalence of parasitic infections and pneumonia. Bennett et al. (2001) investigated harbor porpoises found dead along the coasts of

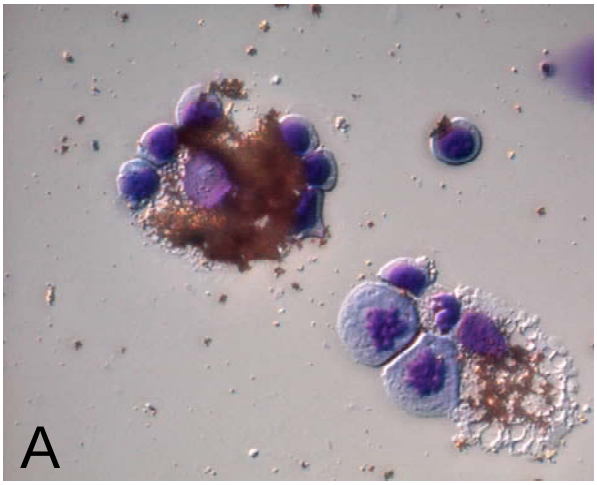
England and Wales that died as a consequence of physical trauma as well as infectious diseases. They found that the mean liver concentrations of Hg, Se, the Hg:Se molar ratio and Zn were significantly higher in the porpoises that died of infectious diseases in comparison to those who died because of a physical trauma. Similarly, Kannan, Agusa, Perrotta, Thomas, & Tanabe (2006) and Kannan, Guruge, Thomas, Tanabe, & Giesy (1998) investigated the concentrations of butyl-Sn residues and trace elements in sea otters (*Enhydra lutris nereis*) found dead along the California coastal waters. They studied otters that died due to infectious diseases as well as those that died because of other reasons. Otters that died because of infectious diseases indicated higher concentrations of butyl-Sn in comparison to those that died as a result of physical trauma. The concentrations of Mn, Co, Zn, and Cd were elevated in the diseased and emaciated sea otters relative to the non-diseased sea otters. An elevated accumulation of tributyl-Sn was also found in bottlenose dolphins (*Tursiops truncatus*) stranded along the Atlantic and Gulf coasts of Florida (Kannan et al., 1997). These relationships are substantiated by the fact that the pollution with metals may affect the immunocompetence and disrupt the immune homeostasis of free-ranging populations of marine mammals in many areas of the industrialized world.

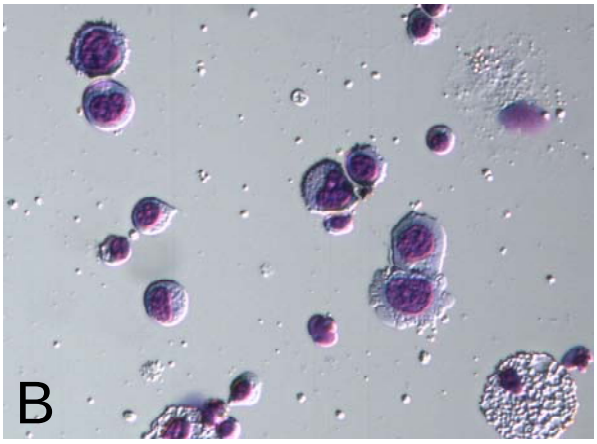
Metal influences on immune functions

Metals influence the function of immunocompetent cells by a variety of mechanisms. Depending on the particular metal, its speciation, concentration and bioavailability, and a number of other factors, a continuous metal exposure will result in an immunoenhancement or immunosuppression effects. Reviews of immunomodulation by metals in humans or laboratory animals include those of Chang (1996), Dean, Luster, Munson & Kimber (1994), or Lawrence & McCabe (2002), but metal influences on marine mammals in relation to environmental contamination have been only poorly investigated.

Immune cells such as macrophages can incorporate and store metal components, e.g. Hg and Se in mineral granules, as described for various marine mammal species (Nigro & Leonzio, 1996). In *in vitro* experiments, a similar incorporation of Ti was shown for blood macrophages of harbor seals (Figure 1a). Depending on the concentration, metals can be cytotoxic for immune cells as well as inhibit or stimulate cell functions, the latter in all probability by binding to proteins.

Killer cell activity, phagocytosis and transformation of lymphocytes have been investigated in various marine mammal species and evidence for the immunosuppression function of metal pollutants has been provided. The mitogen-induced proliferation of immune cells was inhibited by butyl-Sn compounds in several marine mammals and humans (Nakata et al., 2002). Phagocytosis and lymphoblast transformation in grey seal pups were adversely affected by Hg *in vitro* (Lalancette, Morin, Measures, & Fournier, 2003). The effects of heavy metals on beluga whale splenocytes and thymocytes *in vitro* indicate functional impairment (De Guise, Bernier, Martineau, Beland, & Fournier, 1996). Pillet et al. (2000) found a sex-dependent effect of Zn on phagocytic activity. In a study on harbor seal pups from the North Sea, lymphocyte proliferation was especially inhibited by Be, Pb, Cd and Hg in newborn pups (Kakuschke et al., 2008c). Interestingly, the susceptibility to the toxic effects of metals seems to be decreased in infant pups.





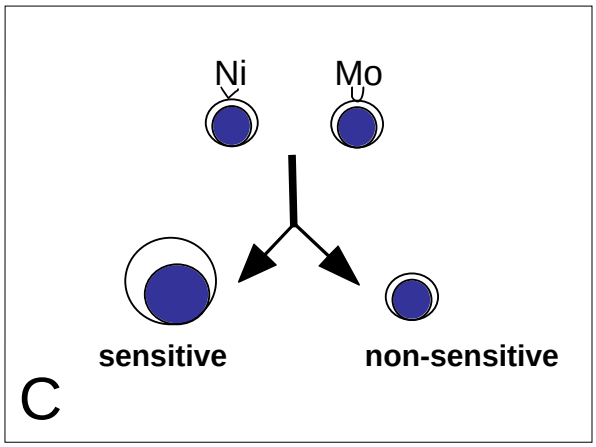


Figure 1. Morphological analysis of Ti-induced (A) and Ni-induced (B) lymphocyte proliferation. In A: two lymphoblasts, one macrophage with ingested titanium particle, and several resting lymphocytes. In B: several lymphoblasts, one macrophage, and resting lymphocytes. C: Principal transformation of lymphocytes.

In addition to immunosuppression, metal pollutants may induce immunoenhancement leading to hypersensitivity and autoimmunity. Even though the metal input into the marine system appears to have been decreasing

in recent years, low-level metal concentrations can modulate the immune system. The chronic intake of metal pollutants renders marine mammals candidates for developing hypersensitivity reactions. A lymphocyte transformation test for detecting antigen-specific metal sensitivities according to the MELISA® (memory lymphocyte immuno-stimulation assay) (Stejskal, Cederbrant, Lindvall, & Forsbeck, 1994; Valentine-Thon & Schiwara, 2003; Valentine-Thon, Sandkamp, Müller, Guzzi, & Hartmann, 2005) was used to investigate pinnipeds from the North Sea (Kakuschke et al., 2005, 2006). The method is based on the fact that lymphocytes, which have been sensitized by a certain metal ("memory cells"), transform into blasts and proliferate when they are re-exposed to this metal (Figure 1). Altogether 31 pinnipeds from the North Sea were investigated, including 13 pups and 17 adult harbor seals as well as one grey seal (Kakuschke, 2006). 13 of these 31 animals showed such a metal-specific delayed type hypersensitivity reaction. The frequency of sensitizing metals was in the order Mo > Ni > Ti > Cr, Al > Pb, Be, Sn. Furthermore, a relationship between the blood levels of metals and this immunological dysfunction was reported (Kakuschke et al., 2005).

In the case study of the grey seal the hypersensitivity reaction to Ni and Be could be validated by different approaches – the proliferation of memory lymphocytes as well as the altered cytokine pattern (Kakuschke et al., 2006). With the cytokines interleukin-2 (IL-2) and interleukin-4 (IL-4) it is possible to distinguish between T-helper 1 (Th1), IL-2 secreting cells and T-helper 2 (Th2), IL-4 producing cells (Elenkov & Chrousos, 1999). The impact of stress on the cytokine pattern was recently described for harbor porpoises from the North Sea (Fonfara, Siebert, Prange, & Colijn, 2007). Kakuschke et al. (2006) measured the mRNA-expression of IL-2 and IL-4 in grey seal lymphocytes co-cultivated with the sensitizing metals Ni and Be as well as the non-sensitizing metals Hg and Cd. Ni and Be induced the lowest cytokine expression compared to the other metals and the quotient IL2/IL4 was increased due to a strong down-regulation of the Th2 cytokine IL-4, which suggests an antigen-specific delayed-type hypersensitivity reaction with a Th1/Th2 polarization toward Th1 (Kidd 2003).

Summary

The environmental exposure with metals is believed to affect marine mammal health adversely. One mechanism whereby metals can alter the health status is through modulation of immune homeostasis. Metals may change the response repertoire by direct and indirect means, which include changes in cell proliferation, phagocytosis, protein expression or other cell functions. Some resulting effects may include immunosuppression or acute as well as chronic inflammatory processes leading to hypersensitivities or autoimmune diseases. The multiple influences of metals on the immune system underline the importance of metals pollution as a potential stressor for marine mammals.

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Potential Synergism between Stress and Contaminants in Free-ranging Cetaceans

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Noise has increased significantly over the last decades in oceans, and this trend is accelerating in large part because of oil exploration and exploitation, both of which are expanding worldwide. Considered together with recent evidence that noise disturbs the behavior, echolocation, navigation and communication of marine mammals, it is likely that noise, increasingly encountered by marine mammals, will add to their allostatic load. Glucocorticoids (GCs) are the major hormones that mediate the long term effects of stress. GCs' effects depend, among other factors, on the intracellular concentrations of the various isoforms of the glucocorticoid receptors (GR). Tissue and cell-type specificity are also conferred by the presence in target cells of GR ligands such as chaperones, co-chaperones and modulatory element binding proteins whose concentrations vary according to tissue, cell types and even to the cell cycle phase. The normal regulation of GCs production in adult life relies on the normal development of the hypothalamus-pituitary adrenal (HPA) axis in uterine and early postnatal life, which in turn depends on the absence of chronic stress imposed to both the mother and newborn during these critical periods. Worldwide, cetacean populations, such as the beluga population inhabiting the St Lawrence Estuary (SLE) in Canada, are exposed to anthropogenic stressors, and are contaminated by persistent lipophilic contaminants of which many are abundantly transferred to newborns during lactation. GCs and certain organochlorine contaminants (OCs), for instance dioxin-related polychlorinated biphenyls (DRPBs), mediate their prolonged and profound effects through nuclear receptors such as aryl hydrocarbon receptors (AhR). These effects are exerted on most organs, especially on the developing brain and lymphoid organs of fetuses and juveniles and on adrenal glands of adult mammals. Multiple interactions have been demonstrated between GCs and OCs, often through interactions between their receptors. These interactions may disturb the delicate balance required by immature and adult mammals to react optimally to stressors.

Stressors elicit a fairly stereotyped response in higher vertebrates, including marine mammals. In general, the elevation of circulating GCs levels that follows exposure to various stressors – including noise - is beneficial. High GC levels become detrimental however when they occur over a long period, when the stressor is persistent or repeated (Deak, this issue; Romero & Butler, this issue; Sapolsky, Romero, & Munck, 2000; St. Aubin, De Guise, Richard, Smith, & Geraci, 2001; St Aubin & Dierauf, 2001).

The sympathetic nervous system (SNS) responds within seconds to stressors by releasing preformed catecholamines (CAs) (epinephrine and norepinephrine) from the adrenal medulla into the blood circulation. This release quickly increases heart rate and blood pressure, which is part of the acute - or fight or flight – response. These effects occur within seconds because CAs bind adrenergic receptors present in peripheral tissues. The binding triggers an

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immediate intracellular biochemical cascade through secondary messengers (Romero & Butler, this issue). When extreme, this response may kill animals and humans through CAs' toxic effects on heart muscle fibers (McEwen, 1998, 2000). In addition, within several minutes, CAs induce the production of T helper cells (Th)-1, proinflammatory (or cell-mediated immunity) cytokines (see below), probably to prepare the organism to fight bacterial invasions secondary to potential wounds.

Concurrently with CA release, hypothalamic neurons trigger indirectly the release of GCs from the adrenal glands. Hypothalamic neurons first signal the pituitary to release ACTH via the corticotrophin releasing hormone (CRH). In turn and within minutes, ACTH triggers the synthesis and release of GCs from the adrenal cortex where GCs are synthesized from cholesterol (hence their lipophilicity). GCs are then distributed indiscriminately throughout the stressed organism, and traverse the lipid-based cytoplasmic membranes of most cells. This broad distribution explains in part GCs' impact on a wide variety of cells. Each cell type, including inner ear cells (cochlea, organ of Corti), is distinguished by the presence of various isoforms of intracytoplasmic GR and other GC ligands such as chaperones, co-chaperones, and modulatory element binding proteins (heat shock protein 90 (hsp 90), immunophilins and GMEB-1 respectively), ensuring that GCs' effects are tissue and cell type specific (Canlon, Meltser, Johansson, & Tahera, 2007; De Bosscher, Vanden Berghe, & Haegeman, 2002; Horner, 2003). Elevated GC levels elicited by acute stress repress the CA-induced production of proinflammatory cytokine by Th1 cells through GR. The present review will address the potential interactions between contaminants, stress and the immune system in marine mammals at the molecular level. It will not deal with the possible role of stress on the high cancer rates seen in some populations of marine mammals (Martineau et al., 2002). The latter will be addressed elsewhere (Martineau, in preparation).

Immune system: A review

The immune system is classically divided in two major branches, innate and adaptive. The innate branch, constantly in standby alert to defend the body against microorganisms or trauma, is not antigen (Ag)-specific, and has no memory of previous encounters with microorganisms, e.g. it reacts the same way regardless of the number or extent of previous encounters. Most of those microorganisms that invade the body are quickly eliminated by the members of the innate system, monocytes/macrophages, neutrophils and natural killer (NK) cells, through acute inflammation. Acute inflammation is characterized by increased vascular permeability resulting of the action of histamine and bradykinin, but also of interleukin (IL)-1 and Tumor Necrosis Factor alpha (TNF-α). The latter two molecules, "IL-1-like cytokines", are produced by local macrophages, and are major actors of inflammation, for which they are called proinflammatory cytokines. IL-1-like cytokines also induce the expression of adhesion molecules by endothelium used by neutrophils to adhere to the walls of capillaries adjacent to inflamed sites. Interleukin (IL)-8, a molecule also synthesized by endothelial cells,

has complex effects on neutrophils, resulting in their firm adhesion to vascular walls and sequestration at the inflammatory site. Then neutrophils traverse these walls to migrate into damaged tissues which become infiltrated – and destroyed – by large numbers of neutrophils.

If acute inflammation cannot eliminate the aggressing microorganism, and/or if damages are too heavy, chronic inflammation ensues after several days. Neutrophils are progressively replaced by extensive numbers of monocytes/macrophages which engulf and kill microorganisms, and clean up tissue debris. Lymphocytes and fibroblasts accompany macrophages (fibroblasts synthesize collagen, a major component of fibrous (scar) tissue).

Simultaneously, macrophages and dendritic cells (DC) (specialized macrophages), also produce IL-12, which triggers the production of interferon (IFN)-γ by lymphocytes. In turn, IFN-γ further increases the ability of macrophages to kill microorganisms. Macrophages start presenting antigens to $CD4^+$ naïve T cells, a lymphocyte subpopulation. The IL-1 and TNF-α produced by macrophages also activate these lymphocytes, thus launching the first steps of an immune response.

In contrast to the innate branch, the adaptive branch is antigen (Ag) specific and is endowed with memory, e.g. its cellular members (lymphocytes and their products) recognize a given Ag a long time after they first encounter it. Antigen presenting cells (APCs) e.g. macrophages, dendritic cells (DC) and B cells, phagocyte foreign invaders such as bacteria, and break them down into minute fragments which are physically presented on their surface to $CD4^+$ T cells. DCs are the most efficient APCs and the most important in activating lymphocytes. On the APC surface, the Ag is presented within a cleft of certain surface proteins called major histocompatibility complex (MHC) molecules. This encounter causes undifferentiated ($CD4^+$) T cells to produce one of two distinct cytokine patterns, Th1 or Th2. The Th1 pattern, generally seen as pro-inflammatory, is directed at intracellular invaders such as viruses and certain bacteria. The Th2 pattern, broadly considered as anti-inflammatory, is central to humoral immunity (or "antibody-mediated" immunity). Antibodies are most efficient at fighting extracellular parasites such as helminthes (ex.: nematodes, cestodes, trematodes) and most pathogenic bacteria.

Th1 and Th2 are mutually antagonistic. For instance, Th1 differentiation is inhibited by IL-4, the major Th2 cytokine involved in differentiating T cells into Th2 cells (IL-4 is produced by Th2 lymphocytes, mast cells and eosinophils). The severity of tissue destruction in an organ or at a particular anatomical site during an attack by a pathogenic agent is the result of the Th1/Th2 balance prevailing at that site (with a high ratio being synonymous of severe tissue damage). A third category of T cells (T reg) has a negative regulatory effect on both Th1 and Th2 cells by the production of transforming growth factor (TGF)-β.

Which pattern will be followed depends among other factors on the type of APC (there are many types of DC and macrophages), the nature of the presented Ag, and the local relative concentrations of other cytokines. The production of IL-12 by APCs, mostly by DC, plays a central role in the differentiation of T cells into Th1 cells. Th1 cells are responsible for cell-mediated immunity; they release

cytokines among which IL-2 is central for macrophages and cytotoxic T cells ($CD8^+$) activation. Cytotoxic T cells ($CD8^+$) are lymphocytes committed in killing otherwise normal host cells infected by viruses or intracellular bacteria and abnormal host cells such as tumor cells.

Th2 cells produce a battery of cytokines (IL-4, -5, -9 and -13) that help B cell differentiating into antibodies-(IgE) producing cells. Other cytokines involved in Th1 to Th2 differentiation include CCL1 (CC- chemokine ligand 1), which plays a role in cardiovascular diseases and allergic diseases such as asthma.

IFNs are an essential part of the innate system that participates also to the adaptive system, for instance by increasing MHC proteins expression. These molecules are released in the microenvironment where they have an effect on the cells that produce them (autocrine effect) as well as on adjacent cells (paracrine effect). All those cells become protected against viral infection (interferons *interfere* with viral infection) among other effects. IFNs are classified in two groups: type I group is composed of IFN α, β and ω, which are produced by almost all cell types mainly to protect against viral infection. Their expression is partially under the control of transcription factors nuclear factor kappa B (NF-κB), interferon regulator factors (IRF)-3 and other transcription factors (IRF-3 activation itself is triggered by viral infections). Reciprocally, the expression of type I IFNs leads to IRF-3 activation, resulting in a positive feedback loop (Jonasch & Haluska, 2001).

Type II IFNs are composed of a single member, IFNγ, which plays a central role in inducing the Th1 pattern. IFNγ is produced by APCs (among which DCs are the most important), Th1 cells and NK cells. Along with IL-12, IFNγ helps differentiating T cells into Th1 cells, and the latter in turn produce more IFNγ. As importantly, IFNγ activates macrophages in at least two ways: it enhances the capacity of macrophages to kill intracellular parasites, and triggers the production of IL-12, -6 and -18 by macrophages, which further increases Th1 differentiation.

. NF-κB is a family of five transcription factors: NF-κB1 (p105/p50), NF-κB2, RelA, RelB and c-Rel, all involved in inflammation. All members form homo- or heterodimers which repress or activate the expression of a plethora of mammalian pro-inflammatory genes such as IL-1, -2, -4, -8, -12, IL-2R, and others. NF-κB1 and NF-κB2 homodimers decrease the transcription of these pro-inflammatory genes whereas RelA and RelB activate it. NF-κB members are implicated in IL-12 expression by APC, and thus are essential to Th1 differentiation. They also play a central role in innate immunity, inflammation and infection, suppression of lymphocyte apoptosis (programmed death), and DC development **(**Caamaño & Hunter, 2002). Inactive NF-κB lies in the cytosol bound to IκB, an inhibitor. Various factors such as cytokines and growth factors, or cellular stresses such as bacteria and viruses, trigger the phosphorylation of IκB, which then releases NF-κB. The latter translocates to the nucleus where, like GR and the AhR, it recognizes specific DNA sequences, appropriately named κB sequences.

Glucocorticoid receptor

GC-mediated GR activation accounts for the anti-inflammatory effects of GCs. Activated GR blocks the expression of all pro-inflammatory cytokines such as IL-1 and Th1 cytokines, leaving intact the production of "anti-inflammatory" Th2 cytokines. Thus GCs protect cells and tissues from damages inflicted by exaggerated cell-mediated Th1-type immune response (Ramirez, Fowell, Puclavec, Simmonds, & Mason, 1996; Sapolsky et al., 2000). Liganded GR also activates the transcription of anti-inflammatory proteins such as Clara cell protein 10, IL-1 receptor antagonist, lipocortin, mitogen-activated protein kinase phosphatase-1, neural endopeptidase, and serum leukoprotease inhibitor. Liganded GR activates these genes by binding DNA, specifically the GRE sequences located in the regions that control the expression of these genes.

GR-mediated repression of Th1 functions is mainly exerted through transcriptional repression of at least three pro-inflammatory transcription factors, NF-κB, IRF-3, and AP-1 (the latter is a complex made of two nuclear molecules, c-fos and c-jun). The liganded GR represses the transcription of these factors by protein-protein interactions, not by binding DNA elements. Most of these anti-inflammatory effects are mediated by interactions between liganded GR α and NF-κB. It has been hypothesized that NF-κB may compete with GR for coactivator molecules necessary for the transcription of genes targeted by both activated GR and NF-κB. These two coactivators, "Steroid receptor coactivator-1" (SRC-1) and "p300/CBP", are responsible for making gene promoters accessible to the transcription machinery by acetylating histones. Importantly, SRC-1 and p300/CBP also bind the AhR, a cellular receptor which mediates the toxicity of many contaminants. In addition, p300/CBP also binds IRF-3, suggesting that competition for coactivators could occur between GR, NF-κB and AhR (Smoak & Cidlowski, 2004; Tian, Rabson, & Gallo, 2002). IRF-3 augments IFN α and β transcription and also elevates the transcription of other pro-inflammatory genes such as Il-15 and RANTES, a chemoattractant of eosinophils and monocytes (Hiscott et al., 1999; Taniguchi, Ogasawara, Takaoka, & Tanaka, 2001). The activated GR becomes tethered to DNA-bound IRF-3, and inhibits the transcription of IRF-3 target genes (Kassel & Herrlich, 2007).

Elevation of GC circulating levels prior to exposure to loud noise protects the inner ear from audiogenic trauma and conversely, a failure to elevate GC levels prior to or during audiogenic trauma increases damages (Canlon et al., 2007). In contrast, chronic stress, which results from repeated or prolonged exposure to a stressor and leads to prolonged adrenocortical stimulation by ACTH and exposure to high GC levels, has deleterious effects on most organs, especially on the brain and the immune system (Table 1) (McEwen, 1998; Sapolsky et al., 2000; Romero & Butler, this issue). Note that sustained high levels of ACTH are correlated morphologically with hyperplasia and hypertrophy of the adrenal cortex (Ulrich-Lai et al., 2006). For instance, suicide victims, patients suffering depression and captive non human primates exposed to social stress all show an increase of adrenal mass due to chronic stress (Swaab, Bao, & Lucassen, 2005).

Table 1
Similarities between glucocorticoid receptor (GR) and aryl hydrocarbon receptor (AhR).

Characteristic	GR	AhR	Reference
Function	Nuclear receptor for endogenous hormone, glucocorticoid (released under physiological stress).	Nuclear receptor for xenobiotic. Regulate (enhance) exogenous compound metabolism.	Hahn, 2002; Escriva, Safi, Hänni, et al., 1997; Tian et al., 2002.
	Important for development		
Intracellular location	Intracytoplasmic. Ligand- activated migration to nucleus		
Constitutive ligand	hsp90		
Ligand hydrophobicity	Hydrophobic		
Other ligands	NF-κB		
Target sequence	GRE	DRE (dioxin responsive element) or Xenobiotic responsive element (XRE)	
Natural endogenous ligands	Glucocorticoids	Unknown	
Targets	Multiorgans		
Effects timescale	Prolonged		
Major immune cells targets	T cells		
Selected effects of long term ligand-mediated activation	Immune suppression (T-cell apoptosis and decreased thymus development)	T cells, B cells, dendritic cells	Kerkvliet, 2002
	CYP induction		Herold, McPherson, & Reichardt, 2006. McMillan, McMillan, Glover, et al., 2007.
	Neurotoxicity		Hahn, 2002; Wang, Faucette, Gilbert et al., 2003.
	Diabetogenic		De Kloet, Vreugdenhil, Oitzl et al., 1998; Williamson, Gasiewicz, & Opanashuk, 2005.
			Buckingham, 2006; Remillard & Bunce 2002; Matsumara, 1995.

Stress in cetaceans

Most studies carried out on captured cetaceans to measure stress-induced elevation of GCs suffer drawbacks, some of which are inherent to cetaceans: basal cortisol values are low, interindividual variations are wide, and increases in cortisol levels following stress exposure are lower than those seen in terrestrial mammals. Other drawbacks are inherent to wildlife studies: a long interval may elapse between chase/capture and sampling time, which makes difficult determining basal cortisol levels (Bossart, Reidarson, Dierauf, & Duffield , 2001; Ortiz & Worthy, 2000; St. Aubin et al., 2001; St Aubin, 2001; St Aubin & Dierauf, 2001; St Aubin, 2002 a, b). In spite of these problems, elevated cortisol levels have been associated with stressors in marine mammals and in Eastern Tropical Pacific (ETP) dolphins which are captured after the intensive chase involved in tuna fishing (Bossart et al., 2001; St. Aubin, Ridgway, Wells, & Rhinehart, 1996; St Aubin, 2002 a, b). Chased ETP dolphins showed typical evidences of acute stress such as elevated circulating GC levels, high circulating levels of glucose, decreased circulating levels of iron, thyroid hormone levels, and the presence of a typical "stress leukogram" (increased number of circulating white blood cells due to neutrophils, and decreased numbers of lymphocytes and eosinophils). Other evidences of acute stress seen in these animals were clearly deleterious, such as the observed necrosis of cardiac muscle fibers, probably due to catecholamine overload (Cowan & Curry, 2002; St. Aubin, 2002 a, b).

In porpoises (*Pocoena phocoena*), Th1 proinflammatory cytokines levels were lower and cortisol levels were higher in accidentally captured animals than in captive animals. This difference was consistent with the switch from the Th1 proinflammatory to the immunosuppressive Th2 cytokine pattern seen in response to stressors (and high cortisol levels) in laboratory animals and humans (Fonfara, Siebert, & Prange, 2007; Fonfara, Siebert, Prange, & Colijn, 2007).

Anthropogenic background noise has increased tremendously in oceans over the last decades because of increased maritime traffic and exploration for and exploitation of oil and natural gas. Cetaceans are sensitive to seismic air and waterguns used for these industrial activities (Finneran, Schlundt, Dear, Carder, & Ridgway, 2002). Papers presented in this issue and other studies indicate that both diffuse (e.g. background) and source noises impact the behavior, social communications and navigation of free-ranging cetaceans, and presumably cause stress in these animals (Aguilar Soto et al., 2006; Fair & Becker 2000; Finneran et al., 2002; Foote, Osborne, & Hoelzel, 2004; Hatch & Wright, this issue; Ridgway, et al., 2001; Schlundt, Finneran, Gardner, & Ridgway, 2000; Wright et al., this issue, b). Anthropogenic sound is likely to impact whales even in the deep ocean because it can be transported over thousands of miles, and even deep diving whales can be impacted because high hydrostatic pressures prevailing at great depth do not decrease the hearing acuity of whales (Ridgway et al., 2001). Whether high cortisol levels due to noise or to other stresses can protect whales' inner ear from noise-induced damage is of course highly speculative at this point.

Contaminants and immunosuppression in cetaceans

Some populations of cetaceans are severely affected by multiple anthropogenic stressors. Cetaceans are long lived animals which occupy top positions of the food chain, and whose body is composed of a high percentage of lipids. Thus, it is not surprising that lipophilic contaminants widespread in the food chain and resistant to metabolism accumulate at very high levels in the tissues of these animals. In addition, contaminant levels are often higher in juvenile animals than in adults because contaminants are transferred to newborns from females through cetaceans' lipid-rich milk (Hickie et al., 2000; Martineau, Béland, Desjardins, & Lagacé, l987).

The beluga whale population which inhabits the St Lawrence Estuary (SLE), Quebec, Canada, was severely reduced by hunting from about 7,800 in 1866 to a current estimate of 1,100 animals (Standard error = 300, 95 % confidence interval = 500-1,800) (Department of Fisheries and Oceans Canada, 2007). The population has failed to recover although hunting ended in 1979. Systemic examinations of stranded carcasses started in 1982 have shown that these animals are severely contaminated by lipophilic contaminants compared to Arctic beluga whales. Many of these compounds are known immunosuppressors that often target the adrenal glands, the final effectors of all stress responses (De Guise, Martineau, Béland, & Fournier, 1998; Letcher, Klasson-Wehler, & Bergman, 2000a; Letcher et al., 2000b; Martineau et al., l987; Martineau et al., 1988; Martineau et al., 2002; Martineau, Mikaelian, & Lapointe, 2003).

SLE beluga whales also suffer a variety of opportunistic infections and parasite infestations, suggesting that they are immunosuppressed. In marine mammals, contamination with DRPBs has long been associated with immunosuppression. DRPBs-induced immunosuppression has been suspected to play a role in making harbor seals (*Phoca vitulina*) more sensitive to phocine morbillivirus. These viruses killed more than 20,000 harbor seals in 1988 in the Baltic Sea. Significantly higher tissular concentrations of polychlorinated biphenyls (PCBs) were measured in striped dolphins (*Stenella coeruleoalba*) affected by the 1990-92 morbillivirus epizootic in the Mediterranean Sea, compared to concentrations observed in previous and later years. This difference led to the conclusion that DRPBs may have impaired the dolphins' immune response to the viral infection (Aguilar & Borrell, 1994). A similar association between morbilliviral infection and high OC tissular levels has been observed in common dolphins (*D. delphis ponticus*) from the Black Sea (Birkun et al., 1999).

Young harbor seals fed for 2.5 years with fish contaminated with DRPBs and other pollutants showed compromised immune functions when compared with a group of seals fed with less contaminated fish (reviewed in van Loveren, Ross, Osterhaus, & Vos, 2000). Harbour porpoises stranded in the UK showed a significant, positive association between PCB levels and the number of nematodes infecting them (Bull et al., 2006). In porpoises whose blubber showed total PCB concentration above 17 µg/g, total PCBs levels were significantly more elevated in animals dying of infectious diseases than in those dying from trauma. Below a 17 µg/g concentration, there was no correlation, suggesting that PCB-induced

immunosuppression increases the frequency of infectious diseases (Jepson et al., 2005). PCB concentrations in the SLE population are higher than this putative threshold.

Deficits in immune functions are difficult to evaluate directly in free-ranging cetaceans, largely owing to the problems associated with rapidly obtaining and processing samples in the field. A logical approach to show that the immune functions of a given population are impaired would be comparing its immune parameters to those of a control population less exposed to pollutants. Many factors render such a comparison difficult: populations unexposed to pollutants probably do not exist, the inaccessibility of some populations, which introduce variables in the time required to collect and process samples, the stress of capture, which triggers cortisol release, and genetic differences. An indirect approach - measuring a pollutant dose-response effect - allows avoiding these drawbacks. In free-ranging harbor seals, the ability of lymphocytes to proliferate when stimulated by mitogens was negatively correlated with PCB concentrations. In dolphins, increased concentrations of PCBs and DDT in blood were shown to be inversely correlated with lymphocyte responses (Lahvis et al., 1995). Another approach consists in measuring the *in vitro* response of immune cells from a presumably "normal" population to pollutants added in concentrations identical or similar to those found in the tissues of contaminated animals from the same species. The proliferative response of beluga lymphocytes to mitogens and their spontaneous proliferation are impaired *in vitro* by exposure to concentrations of p,p'-DDT and PCB 138 similar to those found in tissues of SLE beluga (PCB 138 is one of the most abundant PCB congeners present in SLE beluga tissues) (De Guise et al., 1998). Measurements of cytokine production by stimulated phocid (*Phoca vitulina*) lymphocytes similarly exposed *in vitro* to DRPBs and PAHs showed a decrease in IL-2 production, suggesting that DRPBs might impair one of the major very first steps of cell-mediated immune response (Neale, Kenny, Tjeerdema, & Gershwin, 2005).

Beluga and other marine mammals are contaminated with a complex mixture of PCB congeners, distinct compounds and their metabolites. Such mixtures affect not only lymphocyte functions but also phagocytic cells such as neutrophils and monocytes in humans, beluga and dolphins (Levin, Morsey, Mori, & De Guise, 2004; Levin, Morsey, Mori, Nambiar, & De Guise, 2005a, b; Mori, Morsey, Levin, Nambiar, & De Guise, 2006). *In vitro* exposure of phocid macrophages to PCB and PAH caused decreased IL-1β production (Neale et al., 2005).

Contaminants, cytokines and stress

Similarly to GCs' effects, DRPBs' effects are prolonged and are mediated through an intracytoplasmic receptor, the AhR, for which DRPBs have enormous affinity (Barouki, Coumoula, & Fernandez-Salgueroc, 2007) (Table 1). Similar to the GR, the AhR is widely distributed in many organs and cell types, and often has contradictory effects, depending on cell type and organ. Many of these effects are

mediated through AhR binding to NF-κB, which leads either to NF-κB activation or inhibition depending on cell type and previous cell stimulation.

Historically, the AhR was first described as a sensor of exogenous contaminants such as DRPBs and PAHs (Denison & Nagy, 2003). AhR binding to these contaminants triggers a complex cellular response resulting in increased expression of cytochrome P450 (CYP) enzymes, enzymes involved in the degradation of various endogenous and xenobiotic compounds. Like GRs, which are constantly exposed to endogenous GCs in most animals and humans, AhRs are constantly exposed to their ligands, DRPBs, because these compounds are now ubiquitous in the environment and in the tissues of animals and humans (Savouret, Berdeaux, & Casper, 2003).

In the absence of a ligand, the AhR, like the GR, rests inactive in the cytosol, bound to several proteins among which hsp90, the same ligand that binds the GR. Upon binding DRPBs, AhR dissociates from hsp90 and translocates to the nucleus, where, like the liganded GR, it binds a specific DNA sequence, the xenobiotic responsive element (XRE). The XRE is present within the promoters of multiple genes, among which CYP1A1 (Table 1). Intracytoplasmic CYP1A1 generates many highly reactive metabolites from benzo[a]pyrene (B[a]P) (these metabolites, not B[a]P *per se*, are responsible for the powerful carcinogenicity of B[a]P). Beluga and seal AhRs have been cloned, and both show a high affinity for DRPBs, comparable to that of mice strains susceptible to DRPB toxicity, and thus these species should show the same susceptibility to DRPBs toxicity (humans are less susceptible to dioxin toxicity than rodents because the human AhR shows a weaker affinity for DRPBs) (Jensen & Hahn, 2001; Kim, Hahn, Iwata, Tanabe, & Miyazaki, 2002). As demonstrated *in vivo* in laboratory rodents, AhR gene expression can be induced in presence of DRPBs. Consistent with this finding, a "dose-response" relation has been found in the livers of free-ranging contaminated Baikal seals: AhR mRNA levels were proportional to DRPBs tissue concentrations (Kim,et al., 2005).

Ligand-activated AhR can interfere with GCs' effects in many ways depending on cell type, tissue, species, and on the duration of DRPB exposure (Ruby, Leid, & Kerkvliet, 2002). In order to increase the transcription of their target genes, the AhR, GR and NF-κB must bind certain transcriptional coactivators and corepressors. Two AhR coactivators, SRC-1 and p300/CBP, also bind the GR. In addition, p300/CBP also binds IRF-3 (Servant, Grandvaux, & Hiscott, 2002; Smoak & Cidlowski, 2004; Swanson, 2002; Tian et al., 2002). Although competition between GR and NF-κB for these coactivators does not seem to be involved in NF-κB repression by GR, it is possible that, when a combination of stress, inflammation, viral infection and DRPBs occur[1], together AhR, GR and NF-κB compete for SRC-1 and p300/CBP and possibly for other transcription factors such as the GR interacting protein 1 (GRIP-1) (Kassel & Herrlich, 2007).

[1] The infection of DRBPs-contaminated cetaceans by viruses is well documented (Aguilar & Borrell, 1994; Kassel & Herrlich, 2007).

Through AhR binding, DRPBs affect macrophages, DCs, T and B cells, all actors central to innate and adaptive immunity. For instance, liganded AhR triggers the expression of pro-inflammatory cytokine genes in human macrophages, whereas it triggers apoptosis in T cells and DCs (Camacho, Singh, Hegde, Nagarkatti, & Nagarkatti, 2005; Ruby, Funatake, & Kerkvliet, 2004; Vogel, Sciullo, & Matsumara, 2007). All lymphoid organs, especially the thymus, are affected (thymus, spleen, lymph nodes). DRPBs affect B cells directly, and probably impair T cells both directly and indirectly. Dioxin exposure also results in the appearance of a T reg cell subpopulation in mice (Funatake, Marshall, Steppan, Mourich, & Kerkvliet, 2005). Together these perturbations explain that rodents experimentally intoxicated with dioxin are more susceptible to a wide variety of infectious agents.

DRPBs cause chronic inflammation (more specifically macrophage infiltration) in many organs probably because these compounds increase proinflammatory cytokines (Fan, Yan, Wood, Viluksela, & Rozman, 1997; Nyska et al., 2004; Pande, Moran, & Bradfield, 2005; Vogel et al., 2004; Vogel, Nishimura, Sciullo, Wong, & Matsumura, 2007a; Vogel, Sciullo, & Matsumura, 2007b). In primary human macrophages and in a human macrophage cell line, DRPBs increase the production of a battery of pro-inflammatory cytokines (IL-1β, B cell activating factor of the tumor necrosis factor family (BAFF), B lymphocyte chemoattractant (BLC), IRF3, CCL1, TNF-α, and IL-8) (Diaye et al., 2006; Vogel et al., 2004; Vogel et al., 2007a; b). In contrast, DRPBs seem to have severe negative effects on DCs. In mice primary DCs, dioxin decreases the nuclear translocation and binding to κB DNA sequences of NF-κB, leading to accelerated maturation and apoptosis (Ruby et al., 2004). It should be kept in mind that these experiments vary in many respects, among which the animal species, the cell type and the lack or presence of cytokine-mediated cell activation. For instance, Vogel, Sciullo, & Matsumara (2007b) used an unstimulated human macrophage cell line in which RelB and AhR cDNA were transfected, whereas in contrast, a non transfected DC line from mice, activated by TNF-α, was used by Ruby et al. (2002).

In marine mammals, DRBPs exposure seems to decrease IL-1 production by macrophages. Peripheral blood mononuclear cells (PBMC) (monocytes and lymphocytes isolated from blood) from 4 free-ranging harbor seals captured from the wild were exposed to PCB congener 169, a DRBP. This exposure significantly decreased IL1-β production. This result is in apparent contradiction with one of the above study where IL-1 β production was increased (Vogel et al., 2004). Again, many differences in the protocols used may explain this discrepancy. Firstly, no time course measurements were carried out in the seal study, e.g. phocid IL-1 was measured only after 4-hour incubation. Thus an increase in IL-1 levels would have been missed if it occurred 4 hours after exposure. This is a serious concern given that the increase in IL-1 production seen in human macrophages was detected 6 hours post exposure (Vogel et al., 2004). Secondly, the contaminant concentrations used in the two experiments were widely different: seals PBMCs were exposed to a 20-μM concentration of PCB congener 169 whereas the human macrophage cell line was exposed to 10-nM dioxin. Accounting for PCB 169 toxic equivalency

factor (0.01), phocid seal PBMCs were exposed to a dioxin toxicity level 20 times higher than that used for the human macrophages. Thirdly, PBMCs are composed of lymphocytes and monocytes. Thus decreased IL-1β production could have been due to Th1 activity by the lymphocytes present in the cell mixture because Th1 activity represses IL-1β production by macrophages. Fourth, PBMCs could have been impacted by the high plasma cortisol levels expected from capture especially considering that PBMC were isolated up to 8 h after capture (Neale et al., 2005). Finally variation in species susceptibility to dioxin toxicity may also contribute to these apparently conflicting results.

In wildlife, PCB-contaminated fish provided some of the first hints that GC and AhR cellular pathways are somewhat related. Upon capture, PCB-contaminated fish did not show the expected elevated cortisol levels that capture normally triggers in noncontaminated fish (Hontela, Rasmussen, Audet, & Chevalier, 1992; Hontela, 2005). Recent experiments carried out in fish have provided mechanistic explanations for these early observations. In contaminated fish, AhR activation decreases GC synthesis by inhibiting two key proteins involved in two rate-limiting steps of the GC synthesis, first the steroidogenic acute regulatory protein (StAR), which transports cholesterol to the mitochondrial inner membrane and second, the cholesterol side chain cleavage (P450scc or CYP11A1/scc) enzyme, which converts cholesterol to pregnenolone, the first step of cortisol synthesis. In other words, AhR-ligand contaminants hamper one of the major adaptive responses to stress. Considering that both cortisol synthesis pathways and proteins involved in GC synthesis are highly conserved in animals, most likely these findings can be applied to higher vertebrates (Aluru & Vijayan, 2006). DRPBs metabolites can also bind the GR, competing with endogenous GCs and inhibiting GC synthesis (Brandt, Joensson, & Lund, 1992; Durham & Brouwer, 1990; Johansson, Nilsson, & Lund, 1998). Moreover AhR also mediates the endocrine disruption associated with DRPBs toxicity: among other effects, liganded AhR triggers the destruction of the estrogen and androgen receptors (ER and AR) through ligation with ubiquitin (Ohtake et al., 2007). The ER, AR and GR are all members of the superfamily of nuclear hormone receptors because of the many structural and functional similarities they share. For instance, in prostate cancer patient, an AR double mutant could bind cortisol (Zhao et al., 2000). Because of these similarities, it is possible that AhR also causes GR degradation.

DRPBs adrenal toxicity

Many OCs and their metabolites also severely damage the adrenal glands, the final effector organs of stress. There are several reasons why adrenal glands are vulnerable to these compounds. The vascular supply of the adrenal cortex is disproportionately large compared to the adrenals' mass. In addition, the adrenal cortex is rich in both lipids and CYP enzymes because it synthesizes steroids from cholesterol, which explains why adrenals accumulate high concentrations of lipophilic contaminants, which are then metabolized into more toxic molecules by the CYP enzymes (Harvey & Everett, 2003).

Degenerative and proliferative changes consistent with chronic stress and DRPBs intoxication are commonly observed in the adrenal cortex and medulla of SLE and Western Hudson Bay beluga whales and the severity of these lesions increases with age in both populations. The younger age of much less contaminated control beluga whales sampled from Hudson Bay precluded a comparison of lesion severity and prevalence between age-matched groups (Lair et al., 1997).

According to existing reports, adrenocortical cysts are rare in marine mammals except in SLE beluga and white-sided dolphins (Geraci & St. Aubin, 1979; Lair et al., 1997). In white-sided dolphins, these lesions were attributed to sinusoidal blockage or hypersecretion, and were considered associated with stress related with reproductive functions since 100 % of females and only 20 % of males were affected. No lesions have been observed in the adrenal glands of other Odontocetes species beside increased medullary and/or cortical mass in Atlantic bottlenose dolphins (*Tursiops truncatus*) and harbour porpoises (*Phocoena phocoena*) with chronic stress (Clark, Cowan, & Pfeiffer, 2006; Kuiken et al., 1993). These observations suggest that the rarity of adrenal lesions in cetaceans other than beluga and white-sided dolphins is not artifactual.

Several evidences suggest that OC metabolites may cause adrenal cysts. The toxicity of OCs metabolites for the adrenal cortex such as O,p'DDD, noticed during early toxicity assessments of DDT, has long been used for the treatment of pathological adrenal cortex hypersecretion (Cushing syndrome) in both human and veterinary medicine (Hart, Reagan, & Adamson, 1973; Rijnberk, 1996). Other OC metabolites such as $MeSO_2OC$ are adrenocorticolytic in rodents, and some of these compounds, such as 3-$MeSO_2$-4,4'-DDE, compete with GRs and inhibit GC synthesis (Brandt et al., 1992; Durham & Brouwer, 1990; Johansson et al., 1998). In grey and harbor seals from the Baltic Sea, adrenocortical hyperplasia has been attributed to contamination with PCB and DDT based on epidemiological data (Bergman & Olsson, 1985; Olsson, 1994; Olsson, Karlsson, & Ahnland, 1994). In Baltic grey seals, 3-$MeSO_2$-PCB levels were highest in females with adrenocortical hyperplasia (Haraguchi, Athanasiadou, Bergman, Hovander, & Jensen, 1992), a sex distribution reminiscent of that seen in Atlantic white-sided dolphins affected by adrenal cysts.

Both SLE beluga and Atlantic white-sided dolphins are contaminated with high amounts of OCs and their metabolites (Martineau et al., l987; McKenzie, Rogan, Reid, & Wells, 1997; McKinney et al., 2006; Muir et al., 1996; Troisi, Haraguchi, Simmonds, & Mason, 1998). High blubber concentrations of $MeSO_2$-PCB and $MeSO_2$-DDE have been detected in SLE beluga. In fact, these concentrations are the highest among cetaceans, including Hudson Bay beluga (the concentrations found in SLE beluga are also higher than those found in humans exposed to PCB during the Yusho industrial accident) (Letcher et al., 2000 a, b). SLE beluga and white-sided dolphins both form abundant methylsulphones from PCBs. Thus, because of their long life span, both species may have been exposed to high levels of adrenotoxic OC metabolites for decades (Martineau et al., 2003).

There is apparent contradiction between the adrenocortical hyperplasia epidemiologically associated with $MeSO_2$-DDE in seals, and the adrenocortical

degeneration induced by these compounds in laboratory animals and possibly in SLE beluga (Brandt et al., 1992; Jönsson, Lund, Bergman, & Brandt, 1992; Jönsson, Lund, & Brandt, 1993; Jönsson, Rodriguez-Martinez, Lund, Bergman, & Brandt, 1991). Perhaps OC metabolites-mediated degeneration of the adrenal cortex alternates with ACTH-mediated regeneration since in mammals, the destruction of the adrenal cortex and/or the interference with GC synthesis normally triggers the feedback control of the HPA axis. Decreased GC levels due to adrenocortical destruction normally increase the production of ACTH by the pituitary, which leads to hypertrophy (increased cellular size) and hyperplasia (increased cell numbers) of the adrenal cortex in order to reestablish normal serum GC levels. Note that contaminant-induced damage to cortisol-producing cells has been observed in contaminated fish in the St Lawrence River (Hontela et al., 1992; Hontela, 2005; Rijnberk, 1996; Ulrich-Lai et al., 2006). Thus, it is possible that adrenal lesions affect taxonomically divergent species because of environmental exposure to similar adrenotoxic lipophilic compounds.

It is probable that the pathologic effects of ingesting low OCs'doses over decades - such as occurs in free-ranging mammals - differ from those of large single doses typical of toxicity experiments carried out in laboratory animals. SLE beluga, white-sided dolphins, harbour porpoises and Baltic grey seals are exposed to complex and different cocktails of OC compounds which generate different metabolites that alter the distribution and even the nature of each other (van Birgelen, Ross, DeVito, & Birnbaum, 1996). For instance, by contrast to cetaceans, pinnipeds have a high capacity for generating PCB methyl sulphone and have high CYP2B activity (Boon, Oostingh, van der Meer, & Hillebrand, 1994; Reijnders & de Ruiter-Dijkman, 1995; Troisi et al., 1998). The combined pathologic effects of these complex mixtures are probably not the same as those of single compounds or metabolites typically used in toxicological studies. In addition, the effects of toxic xenobiotics vary according to species, sex, genetic background, age and the developmental stage at which experimental animals are first exposed (Jönsson, Rodriguez-Martinez, & Brandt, 1995). For instance, Baltic Grey and Harbor seals contaminated in nature with OC show adrenocortical hyperplasia, a purely proliferative lesion, of which the severity is proportional to tissue OC concentrations whereas in SLE beluga in contrast, a mixture of degenerative and proliferative lesions affects the adrenal cortex (Lair et al., 1997; Olsson et al., 1994). Adrenocortical hyperplasia in harbor porpoises contaminated with OCs is not proportional to their OC tissular levels (Kuiken et al., 1993). This could be related to the relatively higher CYP2B-dependent ethoxyresorufin-*O*-deethylase (EROD) activity or other metabolic differences shared by both harbor porpoises and pinnipeds (reviewed in Martineau et al., 2003).

Conclusion

Noise is a likely source of major stress in marine mammals due to increased anthropogenic activities practiced worldwide in an industrial mode. Stress and some lipophilic contaminants exert their effects through two nuclear receptors, GR and AhR, both present in lymphocytes, and whose functions are

intertwined because they bind common ligands such as NF-κB. For instance, GCs are competed out by some PCB metabolites, and GC synthesis is decreased by AhR activation. In addition, the adrenal glands, the end producers of acute and chronic stress hormones, are themselves the target of some OC metabolites. Thus, it is safe to say that responses to stressors, acute and chronic, are disrupted by at least some OCs and /or DRBPs in contaminated marine mammals. As shown by the seemingly conflicting effects of dioxin exposure on IL-1 production by immune cells from different species, the methods used to assess mechanisms of immunotoxicity *in vitro* have to be standardized in terms of cell types employed (cell line versus primary cells; genetically engineered cells versus non genetically engineered cells; cell mixture versus pure population), duration of exposure (with time course measurements), and contaminants concentration (which should include concentrations found in wild animals) (Neale et al., 2005; Vogel et al., 2004).

Pathologists faced with the task of determining the contributing factors, or the causes of wildlife mortality, rarely have clinical information such as GC circulating or fecal levels. To compensate for this lack, adrenal and pituitary glands of dead or live animals should be examined in details because in animals and people, chronic stress and the accompanying sustained ACTH production over extended periods are expected to lead to macroscopic pathological changes in adrenal glands, of which the most obvious is probably increased mass (Clark, Cowan, & Pfeiffer, 2006; Swaab et al., 2005).

We propose that such baseline data – which could be determined on live animals, by echography or magnetic resonance imaging for instance- would help in assessing the presence of chronic stress when confronted with a declining wildlife population from which it is difficult to extract clinical data (e.g. data from live animals). Concurrently, other means of obtaining GC levels from live animals, such as measuring tissue GCs levels from skin biopsies, should be developed.

To this author's knowledge, there have been no animal toxicity studies to address the effects of stressors on the potential toxicity of environmental contaminants or therapeutic compounds. This is especially true with regards to marine mammals. Yet it is clear from this review that DRPBs can antagonize GC-mediated chronic stress responses: GCs repress the synthesis and release of all proinflammatory cytokines whereas on the contrary, at least in certain cell types, DRPBs increase expression levels of proinflammatory cytokines such as IL-1 β, TNF-α, IL-8, BAFF and of pro-inflammatory transcription factors such as IRF-3. It is also possible that AhR, GR, IRF-3 and NF-κB compete for the same coactivators, and/or that unexpected effects result from cross-talks between these receptors and transcription factors if inflammation, viral infection, DRPB contamination and chronic stress coincide temporally.

Together, the interactions between variable intracellular concentrations of GCs, GR isoforms, mineralocorticoid receptors, cytokines and co-transcription factors such as NF-κB and IRF-3 subtly modulate immune functions during stress, to avoid immune or inflammatory overreactions, or on the contrary to enhance the immune system in order to eliminate microorganisms and/or their toxins (Sapolsky et al., 2000). Any disturbance of this finely tuned system and of its development by xenobiotic compounds through AhR, or by chronic stress through

sustained high GCs levels, is likely to have undesirable consequences on the immune and inflammatory responses. Some of these outcomes might be unexpected. For instance, the inner ear relies on optimal adjustment of GCs, GR and other GR ligands (chaperones, co-chaperones, and modulatory element binding proteins) to avoid damage following audiogenic stressors. The failure to elevate GC levels in response to audiogenic trauma such as those that are likely induced by the intense sound produced by oil exploration might increase damages to the inner ear of cetaceans exposed to such noise (Canlon et al., 2007; Finneran et al., 2002; Horner, 2003).

The exposure to some OCs and to other exogenous stressors such as noise either *in utero* or during early life threatens the integrity of the immature mammalian immune system, and compromise the adaptive response to subsequent stressors. Juvenile cetaceans are often more contaminated than adults because they absorb contaminants from lactating mothers, and some OCs are especially toxic for developing organs such as thymus and brain. Thus juveniles are particularly put at risk by OC contamination and noise.

New or improved conceptual frames for stress have recently emerged (McEwen 1998, 2000; Sapolsky et al., 2000). All confer the HPA axis and its development a central role in the response to stressors. Most consider contaminants as another stressor (Romero, 2004; Sapolsky et al., 2000). Yet at least some of these stressors, DRPBs, target the adrenal glands, the very same organ whose integrity allows mammals to respond adequately to daily stressors.

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Fishery Effects on Dolphins Targeted by Tuna Purse-seiners in the Eastern Tropical Pacific Ocean

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Dolphins in the eastern tropical Pacific Ocean (ETP), particularly spotted (*Stenella attenuata*) and spinner (*Stenella longirostris*) dolphins, are subject to fishery-induced stress due to chase and encirclement by tuna purse-seiners intent on capturing the large yellowfin tuna that are frequently found associated with dolphin schools in this area of the Pacific Ocean. The direct, observed mortality of dolphins in the fishing nets has decreased over the years from several hundred thousand annually during the early 1960's when the fishing practice originated, to less than 5000 dolphins annually (thought to be a biologically insignificant level) since the early 1990s. Despite the decrease in observed mortality, the dolphin populations have not been recovering as expected. In an effort to determine whether fishery-related stress may be contributing to this lack of recovery, through unobserved effects on survival or reproduction, a variety of studies have been and continue to be conducted examining various aspects of interactions between ETP dolphins and the tuna purse-seine fishery. These studies include a review of current knowledge of stress physiology in mammals, a necropsy program to examine dolphins killed during purse-seining operations, a chase-recapture experiment, and various analyses of existing (historical) data which have led to ongoing studies of fishery effects on mother-calf pairs, ETP dolphin reproductive biology, and analyses of dolphin school composition. The effect of noise has not been addressed directly in these studies, but potentially contributes to fishery-related stress in terms of initiating the significant and prolonged evasion response typical of dolphin schools reacting to tuna purse-seiners in the ETP. Although studies completed to date have not provided a definitive answer to whether fishery-induced stress is a significant factor in the lack of dolphin stock recovery in the ETP, it is possible that at least some adults, and probably many young dolphins, are negatively affected by interactions with tuna purse-seine fishing operations.

Dolphins in the eastern tropical Pacific Ocean (ETP), particularly spotted (*Stenella attentuata*) and spinner (*Stenella longirostris*) dolphins, are frequently chased and encircled by tuna purse-seiners intent on capturing the large yellowfin tuna often found associated with dolphin schools in this area of the Pacific Ocean. The set procedure involves using helicopters to search for the disturbances caused by tuna schools feeding in association with dolphins and seabirds (National Research Council, 1992) or for bird flocks over the horizon. Once an associated tuna school has been located and determined large enough to invest the time and effort in capture, the seiner begins to set the net while 4-5 speedboats with large outboard engines are dropped off the back of the vessel to separate dolphins associated with tuna and chase them into the closing purse-seine. In an association unique to the eastern tropical Pacific Ocean (ETP), the tuna remain associated with the dolphins during the chase and capture, so that the closed and pursed seine then contains both the yellowfin tuna and the dolphins. Once the net is entirely closed

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and pursed at the bottom, a specific maneuver by the vessel ("backdown") creates a long finger of small-mesh net (the "backdown channel") on the side of the seine opposite the vessel. Many dolphins have learned to expect this maneuver (Santurtun & Galindo, 2002) and gather near the appropriate area of the seine, waiting for the channel to form. The dolphins then escape over the submerged far end of the backdown channel and quickly leave the area (Chivers & Scott, 2002).

ETP dolphins respond to an impending set by beginning to flee as soon as the tuna seiner, the helicopter, or the speedboats are perceived (National Research Council, 1992). Because the initial response tends to occur several kilometers from the vessel (Au & Perryman, 1982; Hewett, 1985), initial perception appears to be acoustic rather than visual. The dolphins respond by moving closer together and increasing their swim speed from about 1-2 m/sec to 2-3 m/sec (Chivers & Scott, 2002; i.e., doubling to tripling their previous swim speed and thereby increasing their swimming power requirement by a factor of 8 to 27 times the power required for non-chase swim speeds (Edwards, 2006)).

The chase portion of the set typically lasts 30-40 minutes (with a small percentage of chases lasting up to about 80 minutes), encirclement lasts 30-60 minutes (with a very small percentage of encirclements lasting up to about 75 minutes), and length of confinement lasts another 40-60 minutes (with a small percentage lasting up to about 90 minutes) (Myrick & Perkins, 1995), so that time from initiation of chase to release typically ranges between about 1.5 and 2.5 hours (with a potential maximum in a few sets of about 4 hours). Once the dolphins perceive that the backdown channel is ready, they swim out quickly and continue their escape by swimming at even higher speeds (3-4 m/sec) for about 90 minutes before reverting to pre-chase behaviors (Chivers & Scott, 2002). Thus, each purse-seine set experience may disrupt normal ETP dolphin behavior for at least 30-40 minutes, if the dolphin manages to escape prior to capture, and for 3-4 hours (occasionally up to 5.5 hours) if the dolphin is captured in the seine and then released.

During the early 1960s, when the seining practice originated, several hundred thousand dolphins died in tuna purse-seine nets each year, reducing the populations spotted and spinner dolphins in the ETP by 70-80% (Wade, 1994). Improvements in fishing practices and introduction of individual vessel mortality limits, as well as apparent learning by the dolphins (currently, only about 4% of encircled dolphins need assistance leaving the net during backdown (Santurtun & Galindo, 2002)), have drastically reduced dolphin deaths in tuna nets, to less than 5000 dolphins annually (thought to be a biologically insignificant level) since the early 1990s (Inter-American Tropical Tuna Commission, 2004).

However, despite this dramatic decrease in purse-seine mortality, at least two stocks, northeastern offshore spotted and spinner dolphins, have not been recovering as expected (Gerrodette & Forcada, 2005). Because fishing effort on dolphins remains high (10,000-14,000 purse-seine sets per year (Inter-American Tropical Tuna Commission, 2004)), with each spotted dolphin being chased about 11 times and captured about 3 times per year, on average (Reilly et al., 2005), it is hypothesized that indirect effects of the fishery may adversely impact ETP dolphins. This potential for ongoing adverse fishery interactions has led to a

variety of research projects addressing the possibility that fishery effects (interactions) may be contributing to the lack of population recovery through unobserved effects on dolphin survival or reproduction.

Although the issue of adverse fishery effects (in addition to direct mortality) on ETP dolphins has been of concern since the early days of the fishery (e.g., Stuntz & Shay, 1979; Cowan & Walker, 1979; Coe & Stuntz, 1980) research through the early 1990's focused primarily on reducing directly-observed mortality in the purse-seines. Once the current low level of purse-seine mortality had been achieved, research focus turned to investigating other types of fishery effects.

A major series of research projects was initiated between 1997 and 2002, in accord with mandates of the International Dolphin Conservation Program Act (IDCPA), an amendment to the US Marine Mammal Protection Act (MMPA) (Reilly et al., 2005). IDCPA-mandated fishery effects studies focused on the question "is the fishery having a significant adverse impact on ETP dolphins?" and included four related projects broadly characterized as stress studies. These included 1) a review of current knowledge of stress physiology in mammals, with emphasis on marine mammal physiology, 2) a necropsy program to examine dolphins killed during purse-seining operations, 3) a chase-recapture experiment *in situ* using a chartered purse-seine vessel, and 4) various analyses of existing (historical) data (Reilly et al., 2005). The effect of related noise was not specifically investigated as a stressor in these studies, but contributes to fishery-related stress in terms of initiating the significant and prolonged evasion responses typical of dolphin schools chased and encircled by tuna purse-seiners in the ETP (Au & Perryman, 1982; Hewitt, 1985; Chivers & Scott, 2002). The IDCPA research program also included a suite of studies to estimate current abundances, monitor environmental associations and their potential effects, and assess status and trends of these dolphin populations. Results of those studies are not covered here.

This paper summarizes results from completed studies and presents status reports for ongoing and proposed studies addressing the question of whether fishery interactions may be negatively affecting population recovery of ETP dolphins.

Completed Studies

Research Prior to the IDCPA Program

Limited data were collected prior to the IDCPA program, although the potential for fishery-related stress was recognized early in the fishery, primarily based on observations of passive-sinking behaviors by dolphins in the purse-seine nets (Coe & Stunz, 1980). These unusual behaviors suggested the possibility of "capture myopathy" (a degenerative muscle condition which can lead to delayed death, thus creating unobserved fishery-related mortality; Stunz & Shay, 1979). Subsequent examination and sampling of *Longissimus dorsi* and hypaxial muscle from 65 dolphins killed in ETP tuna purse-seines found "no evidence of myopathy" (Cowan & Walker, 1979), but this sample size is too small to

definitively eliminate the possibility of capture myopathy affecting ETP dolphins at the population level. Another study suggested that examination of adrenal glands might provide a measure of fishery-related stress (Myrick & Perkins, 1995).

IDCPA Program Research

The stress literature review summarized current knowledge about the effects of physiological and behavioral stress in mammals, and related that information to potential effects on dolphins chased and encircled by tuna purse-seiners (Curry, 1999; St. Aubin, 2002a). The review concluded that tuna purse-seine fishing activities entail well-recognized stressors in other mammals, especially wild animals, including prolonged heavy exertion, social disturbance, and disruption of normal activities such as foraging. Typical mammalian responses to such disturbances include changes in metabolism, growth, reproduction, and immune status, any of which, alone or in combination, could significantly affect survival and reproduction. Of particular concern for ETP dolphins was the observation that prolonged heavy exertion in other wild mammals can lead to capture myopathy. Although specific response levels to specific stressors differ in detail between different mammals and environments, the review found that in general, the types of stressors presented by tuna purse-seine activities may affect dolphin survival, but quantitative estimates of the magnitude of these effects are not available (Curry, 1999; Reilly et al., 2005).

The necropsy study examined various physical characteristics of dolphins accidentally killed during tuna purse-seine operations. Due to logistic difficulties, only 56 dolphins were sampled during the 3-year study, far fewer than the desired minimum (for statistical power) of 300 dolphins per stock. However, although the small sample size precluded population-level conclusions, results provided revealing snapshots of physiological conditions and characteristics of dolphins killed in the nets. Various diseases unrelated to the fishery, but characteristic of normally healthy populations of wild mammals, were found in the majority of the dolphins (Cowan & Curry, 2002). Lymph nodes indicated normal, active lymphoid systems (Romano, Abella, Cowan, & Curry, 2002a). Heart, lungs and kidney contained lesions directly linked to death by asphyxiation, possibly resulting from an overwhelming alarm reaction leading to death by cardiac arrest (Cowan & Curry, 2002). Tissue abnormalities presenting as patchy fibrous scars in heart muscle and associated blood vessels may have formed previously in response to excess secretion of stress hormones, possibly indicating prior stress responses (e.g., possibly to fishery activity or predation attempts), although the direct cause and physiological consequences of the lesions could not be determined (Cowan & Curry, 2002). Opportunistic samples of skeletal muscle showed cell damage similar to that in heart muscle, indicative of a degree of capture myopathy that could lead to unobserved mortality in some cases (Reilly et al., 2005).

The Chase Encirclement Stress Study (CHESS) examined physiological and behavioral responses of ETP dolphins to repeated chase and encirclement (Forney, St. Aubin, & Chivers, 2002). During a two-month period, schools of spotted and mixed spotted/spinner dolphins were located, chased and encircled by

a chartered tuna purse-seine vessel using fishery-typical techniques (Forney et al., 2002). Individual dolphins were sampled, tagged and subsequently released with the rest of the captured dolphins. Radio-tagged focal dolphins were followed by a NOAA research vessel, and attempts were made over the following days to recapture the focal dolphin(s) and any associates. CHESS studies included analyses of blood parameters (standard veterinary blood panels, with particular focus on exertion-related enzymes and stress hormones), immune function, thermal condition, behavior, and reproductive parameters, with the intention of determining serial changes through time with repeated recaptures. Initial (first capture) samples were collected from several dozen dolphins, but recaptures were limited because tagged dolphins generally separated from their original school rather than remaining associated. Blood was obtained from 61 dolphins, 53 of which were assumed to be first captures; the remaining 8 samples were collected from dolphins recaptured 1-3 times. In general, these limited sample sizes precluded drawing population-level conclusions about effects of chase and capture. However, a number of important observations relevant to the basic objective were made, and these are summarized below.

Immune function was normal in all blood samples, with no notable abnormalities in the captured or recaptured dolphins (Romano, Keogh, & Danil, 2002b). Hormone and enzyme analyses provided strong evidence for activation of an acute stress response and muscle injury due to exertion (St. Aubin, 2002b). Samples from animals chased for 20-30 minutes exhibited mild muscle damage (consistent with lesions observed in the Necrospy Study samples) (St. Aubin, 2002b). Blood changes were not sufficient to cause life-threatening capture myopathy in any of the animals examined, but individuals differed greatly in overall stress response (St. Aubin, 2002b). Some dolphins showed much more dramatic elevations in hormones, enzymes, and other metabolic indicators, implying a wide variety of responses in the natural population (St. Aubin, 2002b).

The potential for heat stress, particularly in pregnant females required to maintain blood flow to the uterus, placenta and fetus regardless of body temperature, was evaluated by examining thermal photographs of skin surface temperatures after chases of more than 75 minutes (Pabst, McLellan, Meagher, & Westgate, 2002). Heat flux increased during chase for one of two tagged individuals, but core body temperatures were stable for all but one of 48 sampled dolphins, indicating that ETP dolphins are able to regulate body temperature despite elevated swim speeds during chase.

As observed in previous studies (e.g., Scott & Cattanach, 1998), dolphin school dynamics were highly fluid so that associations of individual dolphins were quite variable (Chivers & Scott, 2002). The passive-sinking behavior seen during the 1970s (Coe & Stunz, 1980) was not evident, although rafting behavior (vertical position with head out of the water) still occurred in some dolphins (0 to 8.5 % of the individuals in the net) at some times prior to backdown (Santurtun & Galindo, 2002). In 77% of sets, dolphins were observed circling outside the purse-seine, and overall, it was evident that ETP dolphins are now familiar with the purse-seine procedure and can anticipate backdown for release from the net (Santurtun & Galindo, 2002).

With extremely limited data, it was impossible to determine any effect of capture or recapture on reproduction. No fetal loss was observed, although there were modest decreases in levels of progesterone and testosterone in the two animals analyzed after successive recaptures (St. Aubin, 2002b). Nine females with relatively large calves were captured during at least one set. Three females originally captured with relatively large calves were recaptured with the same calf in subsequent sets, including one pair chased seven times and recaptured four times, and two pairs chased and captured twice. These recaptures indicate that larger calves are capable of remaining associated with their mothers during sets. However, developmental issues indicate that smaller calves (less than 1 year postpartum) may have more difficulty remaining associated with the mother during fishery activities (Noren, Biedenbach, & Edwards 2006; Noren & Edwards, 2007; Noren, Biedenbach, Redfern & Edwards 2007).

Historical biological data were examined in a number of ways, including: 1) to determine whether dolphin behavior differs relative to level of recent fishing effort (Mesnick, Archer, Allen, & Dizon, 2002); 2) to compare the demographic and reproductive parameters of spinner dolphins schools in 1988-1993 vs. 1998-2000 based on aerial photographs taken during NMFS research cruises (Cramer & Perryman, 2002); 3) to estimate the energetic cost to dolphins of purse-seine set evasion (Edwards, 2002); 4) as contributing data for a review of all available information on physiological and behavioral development in dolphin calves (Noren & Edwards, 2007); and 5) to compare the number of lactating females versus the number of nursing calves killed in the same sets (Archer, Gerrodette, Chivers, & Jackson, 2001; Archer, Gerrodette, Chivers, & Jackson, 2004). The results of the latter studies have led to the current focus on fishery effects on ETP dolphin mother-calf pairs and reproductive biology.

Mesnick, Archer, Allen, & Dizon (2002) found that spotted and spinner dolphins (the target species) exhibited more ship evasion and avoidance than did non-targeted dolphin stocks in areas with greater fishing effort. Chivers & Scott (2002) found that escape from tuna purse-seine sets involves prolonged and high-speed swimming (at least 90 minutes at 3-4 m/sec) in addition to the typical 60-100 minutes involved in chase and encirclement (Myrick & Perkins, 1995), bringing the total time of typical set involvement to 3-4 hours, including 2-3 hours of elevated swim speeds. Cramer & Perryman (2002) found that the proportion of calves in schools was not related to the species composition or number of conspecifics in the school, but was significantly lower in more recent years compared to earlier years. Edwards (2002) found that that additional energy costs of evading purse-seine sets are probably not important for adult ETP dolphins, but may present a significant burden to small nursing calves (and potentially their mothers). Archer et al. (2001) found far fewer calves than expected from the number of lactating females killed in tuna purse-seine nets, suggesting that at least some of the calves become separated from their mothers during tuna purse-seine sets in the ETP and that subsequent unobserved calf mortality is a potentially important issue. Noren & Edwards (2007) found that physical limitations of small dolphin calves coupled with behavioral independence of mothers may cause

mother-calf separation during tuna purse-seine set evasion, particularly with calves less than a year postpartum.

Despite limited sample sizes, IDCPA studies identified a number of fishery-related effects on ETP dolphins that could be contributing to stress-related injury and/or unobserved mortality (Reilly et al., 2005). These include 1) moderately elevated stress hormones (catecholemines) and enzymes in live-captured dolphins, indicative of muscle damage; 2) evidence of past (healed) muscle and heart damage in necropsy specimens (dolphins killed in the fishery), 3) fatal heart damage in virtually all necropsy specimens, possibly related to elevated catecholamines, 4) prolonged response to set activities, including post-release as well as during chase and capture, and 5) separation of mothers and calves. Although the effects observed in live-captured animals were all sub-lethal, differences in individual reactions to stressors could lead to more critical responses in some animals compared to others (St. Aubin, 2002b).

Research Subsequent to the IDCPA Program

Following discovery of the significant discrepancy between mortality of lactating females and nursing calves (Archer et al., 2001), additional research quantified the "calf deficit", determining that 75-95% of lactating females killed in tuna purse-seine sets are killed without an accompanying calf (Archer et al., 2004). Given the importance of the mother-calf bond to calf survival, and the potential for mating failure, fetal resorption or abortion in response to fishery activities, research subsequent to the IDCPA has focused on effects that fishery interactions may have on ETP dolphin mother-calf pairs, reproduction and calf survival.

Mother-calf research has focused on factors that can be expected to affect the proximity of mothers and calves during attempted evasion of purse-seine sets, with particular emphasis on the swimming behavior known as drafting in echelon position whereby the calf positions itself slightly above and behind the mother's midsection (Norris & Prescott, 1961). Mathematical and aerodynamic modeling of movement forces (Weihs, 2004; Weihs, Ringel, & Victor, 2006) and empirical kinematic analyses of swimming motions of bottlenose dolphin mothers and calves from birth through two years postpartum (Noren et al., 2006, Noren et al., 2007) both confirmed and quantified the significant hydrodynamic advantages (decreased cost of swimming and/or increased velocity) enjoyed by dolphin calves swimming in echelon, as well as the hydrodynamic disadvantages (decreased swim performance and increased swim effort) suffered by dolphin mothers (Noren, 2007). Mother dolphins swimming in echelon swim only about half as fast at mothers swimming independently (Noren, 2007), while 0-1 month calves in swimming echelon experience a 28% increase in average swim speed, 22% reduction in fluke stoke amplitude, and 19% increase in distance per stoke compared to calves swimming independently (Noren et al., 2007). Neonate dolphin calves can gain up to 90% of the thrust needed to move through the water alongside the mother at speeds up to 2.4 m/sec (Weihs, 2004), while mean and maximum swim speeds of 0-1 month old calves swimming independently were only 37% and 52% of adult speeds, with adult levels not achieved until at least one

year postpartum (Noren et al., 2006). Stroke amplitude and distance covered per stroke were also significantly lower than adult levels for independently swimming calves during the first year postpartum. Lower size-specific swim speed in 0-3 month olds compared to calves older than 10 months indicated that factors other than size (e.g., underdeveloped physiology) act synergistically with small body size to limit independent swim performance in dolphins during ontogeny (Noren et al., 2006). The modeling studies also revealed the importance of precise positioning for effective drafting, and included an observation of disrupted drafting when a neonate calf lost coordination during a respiratory leap attempted during escape-speed swimming in the ETP (Weihs, 2004). The importance of drafting for remaining associated with adults is illustrated by energetics modeling of swim speed duration capacity of independently-swimming (non-drafting) ETP spotted dolphins. Neonate spotted dolphins require 3.6 times more power per kilogram of muscle than an adult, to swim the same speed, and have a burst maximum speed of about 3 m/sec compared to an adult's 6 m/sec (Edwards, 2006). Even at two years of age, spotted dolphin calves must produce about 40% more power per kilogram of muscle than an adult to swim a given speed. Loss of the drafting advantage due to high-speed, fast maneuvering swimming during evasion of tuna purse-seine sets appears to be a significant and plausible source for the observed calf deficit.

Ongoing swimming kinematics research, not yet completed, includes estimation of the cost to mother dolphins of swimming with near-term pregnant morphology. Future modeling work should include estimation of the limits to drafting by dolphin calves in terms of speed and maneuvering during evasion of tuna purse-seine sets. Ongoing research on reproduction and survival includes development and application of methods to determine pregnancy rates of ETP dolphins from progesterone analyses of blubber biopsies taken *in situ*, and estimation of fetal mortality rates in ETP dolphins, based on biological samples collected during the 1980s from fishery-killed specimens.

Conclusion

In general, studies of fishery effects on ETP dolphin physiology, behavior, and population dynamics indicate that adult dolphins chased, encircled, and released during tuna purse-seine sets experience acute, intense stress during the event but most appear to recover from this experience, though some may develop long-term sequelae such as vascular and muscle lesions, reproductive failure, or reduced survival. Because even a relatively small fishery-induced decrease in reproduction or survival could lead to the observed failure of population recovery for ETP dolphins (e.g., Gerrodette & Forcada, 2005), it is possible that fishery effects on adults remain an important factor in the observed lack of population recovery The estimated calf deficit suggests that the purse-seine fishing procedure may be disrupting mother-calf associations in the ETP, and the studies of calf physiology, behavior, and swimming characteristics suggest that nursing calves not reunited with their mothers are not likely to survive. Incorporating age-based likelihoods of calf separation and subsequent mortality into population dynamics models that include age-specific fishery encounter rates is being investigated as a

tool to evaluate these potential effects of fishery activity on calf survival and subsequent population dynamics.

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The Long-term Consequences of Short-term Responses to Disturbance Experiences from Whalewatching Impact Assessment

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Studies often use behavioral responses to detect the impact of given disturbances on animals. However, the observation of these short-term responses can often lead to contradicting results. Here we describe studies focusing on the impacts of whalewatching to show how the biological relevance of short-term responses can be inferred from contextual information. They showed that short-term behavioral responses could have long-term consequences for individuals and their populations using information about variation in response magnitude with exposure levels, long-term population biology data, and multiple response variables. They showed that the added energetic constraints of the responses can impair life functions and lead to influences on vital rates with the potential to affect population viability. Individuals will manage disturbances as another ecological variable and will assess its costs in relation to other energetic trade-offs associated with the occupancy of the habitat in which the disturbance takes place. This can lead to rapid shift in tactics to cope with the disturbance, such as shift from short-term avoidance tactics to long-term habitat abandonment. When individuals cannot elude proximity to the disturbance, their fitness is reduced as observed through reduced reproductive success. These studies provide mechanisms to inform the US National Research Councils' Population Consequences of Acoustic Disturbance framework in which the influence of noise impact of on marine mammal conservation can be studied.

Many studies are now highlighting that what we perceive as short-term responses to disturbances can have unforeseen consequences for the life history of individuals exposed to those disturbances and the dynamics of their populations (Coltman et al., 2003; Cooke & Schramm, 2007; Lusseau, Lusseau, Bejder & Williams, 2006a; Proaktor, Coulson, & Milner-Gulland, 2007). These consequences can occur at an ecological scale with for example added energetic constraints from the responses influencing the homeostasis of individuals. They can also occur at an evolutionary scale. For example, selective harvesting can influence the genetic make-up of populations by selectively removing individuals with similar traits that are highly heritable (Coltman et al., 2003). These impacts influence the viability of populations, either by decreasing their fitness or by decoupling the populations from the environment in which they evolve because disturbances become a driving force for the life history of individuals at either of the temporal scales.

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In excess of 700 to 1000 cetacean populations routinely interact with tour boats (Hoyt, 2001). The potential impact of interactions between cetaceans and tourist vessels has been studied for more than 20 years (Baker & Herman, 1989; Corkeron, 2004). Over this period a wide variety of short-term effects has been detected on many species (Au & Green, 2000; Bejder, Dawson, & Harraway, 1999; Blane & Jaakson, 1995; Hastie, Wilson, Tufft & Thompson, 2003; Lusseau, 2006; Nowacek, Wells, & Solow, 2001; Williams, Trites, & Bain, 2002). These include changes in respiration patterns, variation in path directedness and other short-term behavioral alterations resulting from apparent horizontal and vertical avoidance tactics (Frid & Dill, 2002). However, it has been difficult to move from the description of short-term changes, which sometime appeared contradictory, to a more comprehensive understanding of the biological relevance of these impacts (Corkeron, 2004). Indeed interpreting behavioral responses outside the biological and ecological context in which they are studied has been shown to be uninformative (Beale & Monaghan, 2004; Bejder, Samuels, Whitehead & Gales, 2006a; Gill, Norris, & Sutherland, 2001).

Recent studies show that these short-term avoidance tactics can lead to biologically significant effects which can have long-term consequences for individuals and their populations (Bejder, 2005; Bejder et al., 2006a; Bejder et al., 2006b; Foote, Osborne, & Hoelzel, 2004; Lusseau, 2005; Lusseau, Slooten, & Currey, 2006b; Williams, Lusseau, & Hammond, 2006). These latter studies have taken a multi-contextual approach to elucidate the mechanisms linking short-term avoidance tactics to long-term impacts. Using comparisons between control and impact sites and long-term life history data they have revealed how whalewatching disturbance, a chronic intermittent stressor, had short-term effects on the lives of cetaceans which lead to long-term consequences for the viability and fitness of individuals and their populations. Whalewatching refers here to interactions between vessels and both dolphins and whales. Here we use three examples to highlight these mechanisms. We argue that this work is paving our understanding of principles governing the impacts of human activities on cetaceans. In particular, research in the effects of whalewatching can contribute significantly to a better understanding of the transfer functions in the Population Consequences of Acoustic Disturbance (PCAD) model (National Research Council, 2005).

Methods

We undertook studies on bottlenose dolphins (*Tursiops* sp.) at two sites: Shark Bay, Australia (Bejder et al., 2006a) and Fiordland, New Zealand (Lusseau, 2004). We will also present work carried out in collaboration with other authors on killer whales (*Orcinus orca*) off Vancouver Island, Canada (Williams et al., 2006). In Shark Bay, immediate responses to controlled vessel approaches were evaluated at both control and impact sites, depending on whether whalewatching occurred at those sites or not. Observed effects were related to long-term dolphin photo-identification records, reproductive rates and cumulative exposure measures to vessels (Bejder, 2005; Bejder et al., 2006a; Bejder et al., 2006b). In a similar fashion, we measured immediate behavioral responses of individuals and schools of bottlenose dolphins to boat interactions in Fiordland in two populations that were exposed to different levels of boat interactions. These two populations, one residing in Doubtful Sound and another whose home range centers on Milford Sound, are exposed to similar ecological conditions but are distinct. We then related these responses to long-term habitat use and reproductive success in relation with the rate of exposure to these disturbances (Lusseau, 2003a; Lusseau, 2003b; Lusseau, 2004, 2005; Lusseau et al., 2006a; Lusseau et al., 2006b). The Fiordland study also benefited from a natural experiment in that we made predictions regarding the consequences of increased tourism

levels in Doubtful Sound following the results of the study (2000-2002) that were tested after tourism intensity did increase in subsequent years (2003-2007).

Results

Shark Bay, Australia

In Shark Bay, dolphin abundance was compared within adjacent tourism and control sites, over three consecutive 4.5-year periods wherein tourism levels increased from zero (1988-1993), to one (1993-1998), to two (1998-2003) dolphin-watching operators. As the number of tour operators increased from one to two, there was a significant average decline in dolphin abundance (14.9%; 95% CI = -20.8 to -8.23), approximating a decline of one per seven individuals in the tourism site. In contrast, abundance in the adjacent control site, which was not used by tour boats, did not change significantly (Bejder et al., 2006b).

Additionally, the behavioral response of dolphins to experimentally controlled boat interactions was quantified at two sites: the impact site mentioned above, and another control site, located 17km away from the impact site, that had similar ecological features. The movement of dolphins became more erratic during interactions and dolphin schools tightened. However, the effect size was smaller at the impact site (Bejder et al., 2006a), which traditionally would have been explained as a sign of "habituation". However, in the light of the abundance study, it is more parsimonious to infer that individuals left at the impact site could afford to respond as much as others at the control site, because of reduced fitness. Indeed, the reproductive success of females in this area was linked to their cumulative exposure to boat interactions (Bejder, 2005).

Fiordland, New Zealand

The Milford Sound population was exposed to approximately seven times more tourism traffic than the Doubtful Sound population (Lusseau, 2004). Interactions affected behavioral budget in a similar fashion in both fiords leading to significant increased time spent travelling and decreased time spent resting (Lusseau, 2003a, 2004). They also increased the duration of travelling bouts, leading to added energetic challenges for individuals with less relative energetic stores (i.e., females and especially females with calves or pregnant). These added costs were apparent in that females tended to have different avoidance strategies than males, undergoing vertical avoidance strategies only when the boat interaction intrusiveness was such that it was highly likely to lead to injuries to non-avoiding individuals (Lusseau, 2003b).

While tourism exposure was much higher in Milford Sound than Doubtful Sound, the time spent interacting with boats in both fiords was similar (Lusseau 2004). This was linked to an avoidance of Milford Sound by dolphins during seasons with high tourism traffic (boat traffic was the only oceanographic predictor of residency pattern: $r = –0.814$, $p = 0.021$, Lusseau, 2005). In addition, when dolphins visited the fiord they avoided location with high boat traffic at peak traffic hours ($r =–0.888$, $p = 0.0018$, Lusseau, 2005). There was a linear relationship between boat traffic and dolphin-boat interaction pattern until the average time elapsed between two interactions reached 68 minutes (Lusseau, 2004; Lusseau et al., 2006b). Beyond this point,

dolphins switched from a short-term behavioral avoidance strategy to long-term avoidance strategy (habitat displacement) because the former strategy was no longer beneficial (Lusseau, 2004). Tourism activities affect only a portion of the home range of the Milford Sound population. Therefore, habitat displacement is a possible tactics for the individuals to manage the impacts. In contrast, tourism activities are pervasive throughout the home range of the Doubtful Sound population. We predicted that if boat interactions were to intensify and pass the 68-minute threshold, the population could only cope by decreasing its reproductive success (Lusseau et al., 2006b). Once boat traffic increased beyond the 68-minute threshold, the population suffered a dramatic decline in abundance (Currey, Dawson, & Slooten, in press; Lusseau et al., 2006b), passing from 67 to 56 individuals in a very short period. There was also a drastic significant decline in reproductive success with an increase in neonatal/stillbirth deaths (1994-1999: stillbirth presence: 2/5 years, stillbirth rate: 0.13 stillbirth/year; 2000-2007: 6/7 years, 0.34 stillbirth/year; randomization tests respectively: $p=0.044$ and $p=0.043$ (Lusseau et al., 2006b) and overall calf survival rate (Currey et al., submitted). This decline in calf survival could explain solely the population decline (Currey et al., submitted).

Vancouver Island, Canada

This study showed that boat traffic was also significantly affecting the behavioral budget of northern resident killer whales (Williams et al., 2006). They reduced foraging opportunities and increased travelling time. However, a simple bioenergetic model showed that while the behavioral effect size was greater for travelling than for foraging, the loss in foraging opportunity was leading to a greater energetic cost, by decreasing energy intake by 18%. In contrast, the added energetic cost of increased activities was only leading to a 3 to 4% increase in energy output for individuals (Williams et al., 2006). This showed that the biologically significant impact of boat interactions principally focused on food intake for this population. Such studies can help us prioritize management actions to minimize the biological significance of the impact. In this example, preventing boat interactions while whales are foraging will have a disproportionately greater influence on the overall impact of whalewatching than other restrictions would. Therefore establishing no-boat zones around foraging hotspots would be an ecologically and economically sensible measure (Lusseau & Higham, 2004).

Discussion

Results presented here indicate biologically significant impacts of an apparently benign human activity, i.e., watching whales and dolphins. The success of detecting population level effects was based on long-term population monitoring and the availability of information on the variation in vessel exposure between individuals, sites, and populations. The influence of these impacts on population viability can be inferred using the dose response relationships these studies describe. Early individual-based models show that these impacts are highly likely to endanger the viability of small populations which have restricted immigration/emigration because of the increased cumulative exposure they incur (Lusseau et al., 2006a).

The consequences of energetic challenges

The published studies we present here show that increased energetic challenges, either as added travelling costs or reduced foraging opportunities, can lead to reduced fitness for individuals. If such challenges occur too often, individuals shift into long-term avoidance strategies when possible by avoiding the degraded areas. However, such long-term decisions have to be balanced with other costs and benefits to leave a habitat degraded by whalewatching or leave a school exposed to whalewatching. These trade-offs lead to non-linear relationships with a rapid shift into long-term strategies when short-term tactics are no longer beneficial. This highlights that these behavioral systems, like other complex systems, can be shifted from one basin of attraction to another quite rapidly (van Nes & Scheffer, 2007). Individuals that cannot leave degraded habitat have reduced fitness leading to, at least, reduced reproductive success. This shows that at the population-level these shifts in basin of attraction may not always lead to evolutionary stable solutions.

Modeling population-level consequences

This described link between whalewatching disturbance exposure and reproductive success and survival probability can be used in agent-based simulations to define the likelihood that these effects can endanger the viability of exposed cetacean populations (Lusseau et al., 2006a). More importantly, the uncertainty surrounding the estimated dose-response curves can be incorporated in these models, so that its influence on the likelihood populations will remain viable can be accounted (Lusseau et al., 2006a). Agent-based simulations provide a tool to disturb artificial individuals in a population in a realistic manner because the rules of interactions (timing, duration, number of interactions, temporal variation) can be informed by empirical data. Unsurprisingly, these models illustrate how small populations, with restricted immigration and/or emigration, are less likely to survive even low levels of whalewatching exposure (Lusseau et al., 2006a). That is because such features increase the cumulative exposure to disturbance per capita. In addition, once the population starts to decline, restricted immigration means that exposure per individual intensifies, precipitating the population in an extinction vortex (Lusseau et al., 2006a).

Insights for the PCAD model

These studies provide templates to inform the PCAD model (Figure 1). The highlighted studies bring valuable insight into the three transition functions of the PCAD model. They show that repetitive short-term behavioral change can influence life functions by imposing additional costs to the energetic budget of individuals. The resulting impact on individuals will vary with the life history of the targeted species. In some instances, decreased energy intakes will predominantly drive the impact of the responses, while in others it may be the added energetic cost of transport.

Impacts on life functions can affect vital rates. These studies show that the influence of these changes on vital rates is non-linear, their impact shifting abruptly around a threshold. At this stage, whalewatching studies only provide a mechanistic function in an energetic framework. Other life functions may be

impaired, such as socializing, and those impacts can also have influences on vital rates, such as reproduction rate. Much work is needed to understand the principles governing these mechanisms that will be highly species-specific.

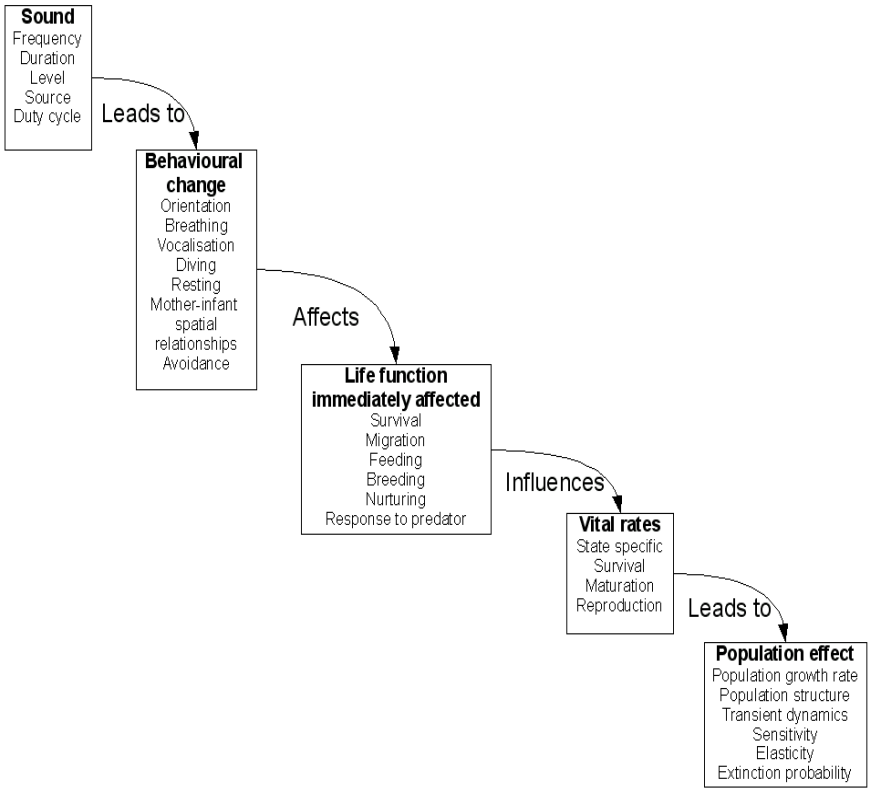

Figure 1. Modeling population-level consequences. Printed as modified from the Population Consequences of Acoustic Disturbance model developed by the US National Research Councils (National Research Council, 2005) with permission from the National Academies Press, Copyright 2005, National Academy of Sciences.

Finally, as it has been shown in the case of other anthropogenic impacts (Slooten, Fletcher, & Taylor, 2000), the alteration of vital rates can lead to influences on the viability of populations. This will depend on the resilience of the population's carrying capacity and therefore small, closed population are highly likely to be more prone to extinction under these scenarios.

Conclusion

We have shown here that there is high propensity for individuals to have context-specific responses to disturbances. It is also expected that human activities will have disproportionate influences on different individuals depending on their current fitness and life history strategy (Lusseau, 2003b; Munch & Conover, 2003; Perez-Tris, Diaz, & Telleria, 2004). If the impacts of these activities are significant enough to select against sensitive individuals, these disturbances may also influence the evolutionary dynamics of populations since the predisposition for risk-taking behavior may be heritable

in many species (Brick & Jakobsson, 2002; van Oers, Drent,, de Goede, & van Noordwijk, 2004). This population-level adaptation could result in lower observed effect size of disturbance. Such variation can be interpreted as the population "habituating" to the disturbance when in fact the population is reacting to this disturbance in several dimensions. This conclusion highlights the need for contextual information to define the biological relevance of observed short-term effects and the danger of interpreting these effects out of context.

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Adaptive Management, Population Modeling and Uncertainty Analysis for Assessing the Impacts of Noise on Cetacean Populations

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Population modeling is now widely used in threatened species management and for predicting the impacts and benefits of competing management options. However, some argue that the results of models must be used with caution, particularly when data are limited. This is important, as even the simplest models would generally require more data (and knowledge) than are available in order to have complete confidence in model predictions. In particular, population models often suffer from a lack of data on demographic rates, spatial distribution, dispersal, management responses, habitat correlations and the magnitude of temporal variations. A number of authors identify behavioral and physiological responses of animals to anthropogenic noise. Assessing population level impacts of noise on cetacean populations is essential to understanding how noise impacts on the future viability of marine mammal populations. This assessment will be particularly challenging due to the difficulties associated with identifying a clear link between behavioral responses of animals and physiological impacts, observing and measuring changes in cetacean population parameters and the long lag-times over which population changes manifest in long-lived species. The urgency of the conservation situation for many of these socially important species demands immediate action, despite pervasive uncertainty. Adaptive management provides a coherent framework for action and continuous improvement under uncertainty. I review the elements of adaptive management and discuss the role of population modeling in that context. I discuss Bayesian approaches to enhancing inferential power and reducing uncertainty in model parameter estimation. I then review approaches to characterizing irreducible uncertainty with Monte Carlo methods and sensitivity analysis and conclude with a brief discussion of formal decision tools available to assist with decision making under severe uncertainty. I propose that urgently needed action should not be postponed due to uncertainty and that adaptive management provides a coherent framework for instituting immediate action with a plan for learning.

Of primary interest to conservation practitioners is the degree to which human activities (such as anthropogenic noise) induce physiological and behavioral responses (e.g., a prolonged stress response) that ultimately manifest in changes to population dynamics such as reduced yearly survival and fecundity (collectively referred to as *vital rates*), and metapopulation dynamics such as immigration and emigration rates. More specifically, it is possible that anthropogenic noise may impact on marine mammal populations through direct physiological impacts leading to reduce survivorship and fecundity, or indirectly through changed behavior such as interrupted or altered foraging, mating or migration patterns (see Bateson, this issue; Beale, this issue; Deak, this issue; Lusseau, this issue; Romero & Butler, this issue; Wright et al., this issue, a. There

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is mounting evidence that anthropogenic noise will result in population level impacts on marine mammal species, but substantial uncertainty about exactly how anthropogenic noise impacts will manifest. This is a common situation in conservation and natural resource management. In most situations we lack information about the magnitude of anthropogenic impacts and the efficacy of ameliorative actions on vital rates and metapopulation dynamics, as well as how they interact with environmental influences. Data on 'natural' demographic rates are also often lacking making inference about the population-level impacts of noise particularly challenging.

While such uncertainties are pervasive in conservation science, attempts at dealing with uncertainties in decision making have been largely ad-hoc and few applications utilize formal decision theory. However, some principles of decision making under uncertainty are articulated in the literature (Holling, 1978; Walters, 1986; Walters & Holling, 1990) and coherent approaches to management and decision making under uncertainty have recently emerged (Dorazio & Johnson, 2003; Nichols & Williams, 2006). Bayesian approaches to dealing with uncertainty due to imperfect knowledge and data have long been available but are only now becoming more widely used by ecologists and conservation biologists (Dorazio & Johnson, 2003; Ellison, 2004; McCarthy, 2007). There are a rising number of practical examples of formal decision making in conservation and natural resource management (Gerber et al., 2005; Hauser, Pople, & Possingham, 2006; Johnson & Williams, 1999; McCarthy & Possingham, 2007; Moilanen & Wintle, 2006; Regan et al., 2005), and the number of people trained to implement formal decision techniques is increasing. The synthesis of adaptive management principles, Bayesian approaches to characterizing and reducing uncertainty, and formal decision protocols may provide the basis for improved transparency, efficiency and robustness of conservation management under uncertainty. However, there are few examples of the successful integration of these approaches in practical applications of adaptive conservation management. Here I review aspects of uncertainty analysis and experimental management of threatened species populations and propose a framework for learning about the population-level impacts of noise-related stress effects.

Management under uncertainty: The adaptive management framework

Because uncertainty is pervasive in conservation management it is not appropriate to use uncertainty as an excuse for inaction (Bruntland, 1987), as inaction often results in deleterious environmental and biodiversity outcomes (Stern, 2007). Postponing decisions and changes to management because evidence for environmental harm is inconclusive or because impacts are not yet perfectly measured may be a highly sub-optimal strategy for conservation and should be weighed against the costs and benefits of various alternative actions. Adaptive management has been proposed as a paradigm for management under uncertainty and continuous improvement (Johnson et al., 1997; Linkov, Satterstrom, Kiker & Bridges, 2006a; Walters, 1986; Walters & Holling, 1990). Adaptive management can be loosely defined as management with a plan for learning. Under adaptive

management a range of management actions are prescribed at each time step that have the dual purpose of achieving management goals and facilitating learning about the system under management and the relative performance of management strategies. Adaptive management may be described in four steps (Figure 1);

i) identification of management goals, constraints and performance measures;
ii) specification of management options;
iii) identification of competing system models and model weights; and
iv) allocation of resources, implementation of management actions and monitoring of management performance.

The integration of 'implementation of management actions' and 'monitoring' emphasizes that monitoring is central to management and not an optional extra.

Modern interpretations of adaptive management based on adaptive optimization encourage an iterative approach to decision making (also known as 'state-based' decision making; Nichols & Williams, 2006). The act of determining management actions (strategies) for a discrete period of time that are optimal with respect to one's belief and uncertainty about the state of the system, as well as one's predictions about how the system will respond to management is intuitive though not always simple to achieve (see Allan and Curtis, 2005; Stankey et al., 2003, 2005). Indeed, it is not necessary that managers adopt formal optimization methods when implementing adaptive management as long as there is a plan for learning and a willingness to adapt management decisions in light of evidence that is collected through management experiments. Adaptive management is appealing in that it explicitly acknowledges that the decision being made is subject to substantial uncertainty and may change in the next time step depending on what is discovered (learnt) in the intervening period. It doesn't require the completion of an experiment before a change to management can be instituted; rather it identifies the best decision to be taken now, based on what is believed about the state of the system and what has been discovered to date through previous monitoring and research. Adaptive management is well suited for managing systems in which changes take a long time to become apparent and definitive experiments are not possible in reasonable timeframes. Formal adaptive management helps to identify an immediate course of action despite substantial uncertainty. It also helps to clarify the role of monitoring as a process for reducing uncertainty and ranking the performance of management in ameliorating impacts.

One of the most challenging aspects of decision making in natural resource management is the process of identifying and setting management objectives, especially when multiple stakeholders hold conflicting or competing objectives (Step **i** in Figure 1). Environmental management requires decisions makers to integrate heterogeneous technical information with values and judgment. Methods for eliciting and reconciling competing objectives, such as multi-criteria decision analysis (MCDA; Figueira, Greco, Ehrgott, 2005) provide a basis for tackling this challenge. MCDA also provides a coherent way of integrating various forms of uncertainty (epistemic uncertainty, subjectivity, semantic ambiguity; Regan et al., 2001) with social preferences in the decision process. The methods and tools reviewed in the paper (adaptive management, Bayesian approaches, population modeling) are important tool for characterizing and reducing uncertainty that feed

into the decision making process. However, they do not make decisions *per se* because decision making is, necessarily, a social process that involves competing decision priorities. The common purpose of MCDA methods is to evaluate and choose among alternatives, based on multiple criteria using systematic analysis that overcomes the limitations of the unstructured individual or group decision making (Figueira et al., 2005). The aim of MCDA is to facilitate decision makers' learning about and understanding of the problem as well as about organizational preferences, values and objectives. MCDA can guide decision makers in identifying a preferred course of action through exploring these issues in the context of a structured decision analysis framework. MCDA framework may be integrated with adaptive management (Linkov et al., 2006a, b) as well as with Bayesian methods and population models. A detailed review of MCDA and associated methods is beyond the scope of this article. Here I focus primarily on approaches to characterizing and where possible, reducing uncertainty with efficient modeling and learning strategies. I recognize that these are aspects of the larger problem of dealing with uncertainty and social preferences in decision making.

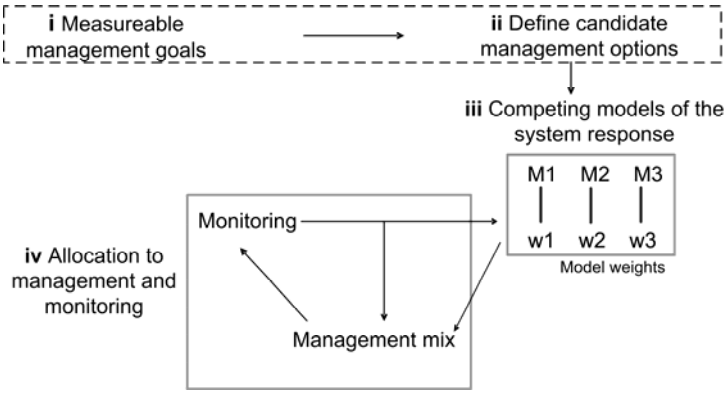


Figure 1. Adaptive management (reproduced from Figure 1, Duncan & Wintle, 2008, © with kind permission of Springer Science+Business Media); an approach to management under uncertainty with a plan for learning. The dashed-line box indicates steps that require elicitation of social preferences. Updating of models can include updating of individual model parameters (e.g. Dorazio & Johnson, 2003) and/or updating of model weights (e.g. Box 2, Johnson et al., 1997).

Population models, impact assessment and adaptive management

Adaptive management of threatened species requires the specification of a model (or competing models) of species' responses to impacts and management intervention. The role of models in adaptive management is twofold. Firstly, models help to characterize uncertainty and formalize competing views about population dynamics, and the manner in which populations respond to anthropogenic influence and interact with natural environmental processes. Secondly models are useful for making predictions about the likely impacts of future (or proposed) management actions, allowing managers and stakeholders to rank competing management options. Under adaptive management, competing

models are iteratively assigned credibility based on the observed response of species to management over time. Population models have been used in both terrestrial and marine systems to evaluate the long-term population consequences of competing management options (Box 1; Akcakaya, Radeloff, Mladenoff & He, 2004; Taylor & Plater, 2001; Wade, 1998; Wintle, Bekessy, Pearce, Veneir & Chisholm, 2005).

Box 1. The use of population modeling to rank management options: The wedge-tailed eagle and plantation conversion in northeastern Tasmania, Australia.

Bekessy et al. (in review) utilized dynamic landscape metapopulation models (DLMP: Akcakaya et al., 2004; Wintle et al., 2005) to assess the landscape-level impacts of plantation conversion on the viability of the wedge-tailed eagle in the north-east region of Tasmania. DLMP were fitted in the software package RAMAS Landscape (Akcakaya et al., 2004). The process of developing DLMP models may be broadly described in 4 steps (Wintle et al., 2005): (1) building a habitat model; (2) developing a model of population dynamics; (3) linking these models in a metapopulation model; and (4) building a forest-dynamics model and linking it to the metapopulation model to evaluate management options.

Bekessy et al. (in review) were able to use the DLMP framework to provide predictions about the future (160- year time horizon) wedge-tailed eagle population size in north eastern Tasmania under a range of forest management and plantation conversion scenarios including: (1) no logging (only 'natural fire disturbance'); (2) native forest harvesting only; and (3) native forest harvesting with extensive plantation conversion (~50% of total forest extent). Results of DLMP models were summarized using the expected minimum population size (EMP: see main text). The results of the DLMP risk assessment process indicated that all anthropogenic disturbance scenarios generated an EMP that was approximately half that of the no-logging scenarios (Fig. 1.1), but that there were no appreciable differences between native harvest-only and conversion scenarios for this particular species. This was thought to be because the primary limiting resource for the species was the availability of nesting habitat that only occurs in old, relatively undisturbed forest on sites with large trees, and that these conditions were approximately equally compromised by native forest harvesting and plantation conversion.

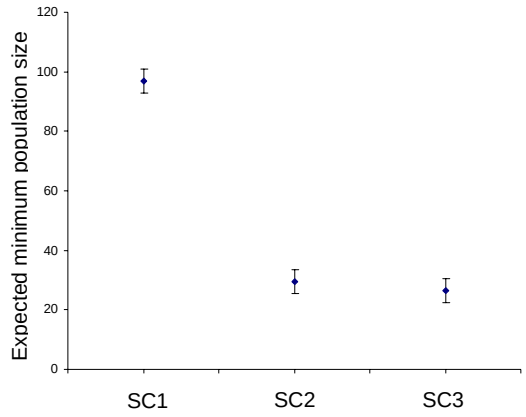


Figure 1.1. Expected minimum wedge-tailed eagle population sizes over a 160-year time horizon under three management scenarios (SC1 = no logging or plantation conversion, SC2 = only native forestry logging with natural regeneration, SC3 = native forestry with natural regeneration and approximately 30% plantation conversion). Error bars represent the 95% confidence interval on the mean EMP (this should not be confused with a 95% prediction interval for EMP). EMP may be interpreted as there being a 50% chance of the population falling below the stated level at some time over the next 160 years.

However, predictions of population models are subject to substantial uncertainty in parameter estimates (Ludwig, 1996). The standard approach to quantifying and representing such uncertainty is through Monte Carlo simulation. Monte Carlo methods are widely used for simulating the behavior of various physical and mathematical systems. Monte Carlo simulation of population models involves randomly sampling parameter values from a distribution of possible values over a number of 'iterations'. For example, when conducting Monte Carlo simulations for a population model, the value of the adult yearly survival parameter at *each time step* might be selected from a beta distribution with a mean set at the best estimate of yearly survival and a variance determined by analyzing long-run variation in yearly survival of the species. Often it is the variance of such parameters that is hardest to determine. A single iteration of the model provides a single possible trajectory for the species. Over numerous iterations, a distribution of predictions is derived that represents the predictive uncertainty in expected population trajectory attributable to parameter uncertainty and the more general effects of environmental stochasiticity. For more information about Monte Carlo sampling in population models, see Burgman, Ferson & Akçakaya (1993).

In order to test the sensitivity of model predictions to particular assumptions, one may conduct a sensitivity analysis. There are several different approaches to conducting a sensitivity analysis including random sampling or systematic perturbation of parameter values and analysis of how variation in a given parameter influences model predictions. A common approach to sensitivity analysis involves systematically adjusting individual parameters by a set amount (e.g. +/- 20%), while keeping all other parameters at their estimated mean value, and observing the magnitude of change in model predictions that arise. If the predicted change in expected population size is substantial for a small change in a particular parameter, then the model is said to be 'sensitive' to that parameter. Sensitivity analysis may be used to assess sensitivity of tail risks as well as expected population sizes. Sensitivity analysis is may be used to priorities research into vital rates or environmental parameters to which population projections are most sensitive.

McCarthy & Thompson (2001) proposed the now widely used metric 'expected minimum population size' (EMP) as an appropriate quantity of interest derived from population viability analysis. EMP is calculated by taking the mean of the smallest population size that occurred at over the simulation period for each Monte Carlo iteration of the model. The EMP is useful in ranking scenarios as it provides a good indication of the propensity for population decline but is less sensitive to model assumptions than the metrics *risks of decline* or *risk of extinction* (McCarthy & Thompson, 2001). One particularly useful property of EMP is that it can be used to delineate between management options for species that have almost no probability of going extinct under any option. The sensitivity of the model to a particular parameter, or the sensitivity of the species to a particular management option may be defined in terms of EMP (Wintle et al., 2005):

$$S_i = (\mathrm{EMP}_i - \mathrm{EMP}_b)/\mathrm{EMP}_b \times 100,$$

where S_i is the sensitivity of model i (the model being investigated), EMP_i is the expected minimum population size of the model i, and EMP_b is the expected minimum population size of the base model. The base model usually represents the model for which parameter estimates are all 'best' estimates or the model representing the default (or current) management. Sensitivity calculated in this way provides an indication of both the magnitude and direction (positive or negative) of the change in EMP.

Despite the prevalence of substantial uncertainty, modeling may be useful in challenging stakeholders and managers to clearly state their belief about species population dynamics and the magnitude and mechanisms of anthropogenic impacts. Models represent testable hypotheses that may be improved and updated as new data or knowledge comes to hand. As data are gathered, updated models may begin to provide predictions that are more broadly trusted by managers and stakeholders. In data-poor situations, it is important to make the most of available expertise or 'collateral' data. That is the topic of the next section.

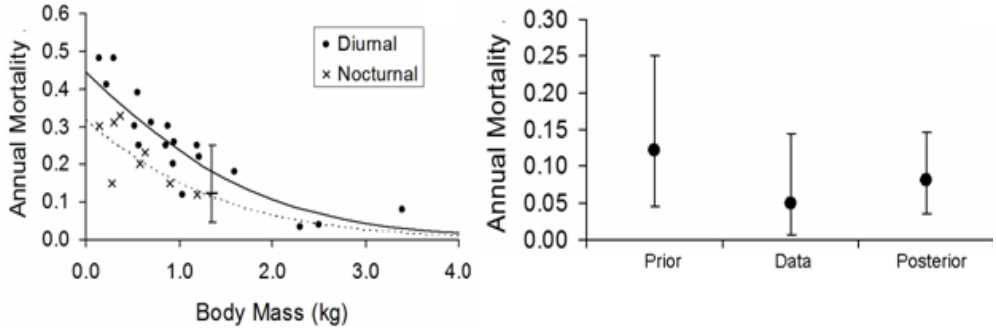
Bayesian approaches to inference

Ecological data are often expensive, time consuming and difficult to collect. Unlike in the physical sciences, the design of the definitive experiment that proves or disproves a theory can seldom be achieved in ecology and conservation. Ecological inference is largely a process of synthesizing disparate data and the results of inconclusive experiments to update knowledge and make the best possible decision. Ecological inference is primarily concerned with estimation of parameters and the weighting of competing hypotheses (models) rather than the rejection or acceptance of null-hypotheses (Anderson, Burnham & Thompson, 2000; Burnham & Anderson, 2002; Ellison, 2004; Johnson, 1999). Bayesian approaches to inference are particularly well suited to the synthesis of disparate information, parameter estimation and multi-model inference (Ellison, 2004; Harwood, 2000; McCarthy, 2007; Wintle, McCarthy, Volinsky & Kavanagh, 2003). Multi-model inference and iterative updating of knowledge (beliefs) are strengths of the Bayesian approach to inference. Ferson (2005) provides an excellent review of the criticisms of Bayesian approaches to inference and decision making, focusing on the use of prior information that is central to the Bayesian method. He identifies concerns about the contraction of uncertainty that arises when highly divergent distributions (i.e. prior and data) are combined with Bayes theorem. There are non-Bayesian alternatives to integrating multiple sources of information (e.g. meta-analysis; Sutton, Jones, Abrams, Sheldon & Song, 2000) and conducting multi-model inference (Burnham & Anderson, 2002), though they are regarded as theoretically less coherent by some authors (Link & Barker, 2006). A full review of the philosophical and practical differences between Bayesian and alternative analytical methods is beyond the scope of this paper. I also consider that the 'controversy' over Bayesian and non-Bayesian methods to be somewhat over-played and to be largely irrelevant here. However, warnings about Bayesian methods should not be ignored because, as is the case for all statistical methods, naïve applications of Bayes theorem can be dangerous. In the following two

sections I discuss two important functions of Bayesian inference in model-based management of threatened species. In the first section I discuss Bayesian approaches to reducing uncertainty through integration of alternative data sources and expert knowledge. In the second section I describe the role of Bayesian updating for iteratively assigning plausibility to competing management models under adaptive management.

Bayesian approaches to reducing uncertainty with prior data and expert opinion

Under adaptive management of noise-effects on cetaceans it is necessary to generate hypotheses and models that describe both the impacts of noise on cetacean population parameters as well as the value of proposed noise mitigation or management strategies. This can be particularly challenging in the absence of definitive studies or models that measure such processes, as is currently the situation with the case in point. McCarthy (2007; pg 134) provides an excellent example of how to develop informative prior information about the value of a poorly measured parameter (in this case, the yearly mortality rate of powerful owls in southeastern Australia). McCarthy utilized a regression of body mass on mortality rate using data for a range of (better studied) raptors from around the world. In his analysis McCarthy demonstrates the use and value of a model-based prior when making inference based on an extremely sparse data (in this case, one observed mortality in 35 observation years: Figure 2).



a. b.

Figure 2. a) Annual mortality of raptors versus body mass for diurnal (solid line) and nocturnal (broken line) raptors. The prediction and prediction interval for the powerful owl, based on the regression for other owls, is shown as the dashes and vertical bar. b) Annual mortality of powerful owls showing the prior based on other species' mortality estimates (a), the data on powerful owls and the posterior estimate (circles are means and dashes delimit 95% CIs) [reproduced with permission of Michael McCarthy and Cambridge University Press].

Box 2. Using Bayes' theorem to assign credibility to competing models with monitoring data; the management of Mallard ducks.

Models that predict a system response to management actions are needed to optimize management decisions (Nichols & Williams, 2006). Typically, multiple competing views (opinions, hypotheses) about how a system will respond to management exist and these views can be formalized as competing models. The plausibility of competing models may be assessed by comparing their predictions to data obtained from monitoring. In developing an adaptive management strategy for Mallard duck harvest, Johnson *et al*. (1997) describe a process of updating belief about the plausibility of competing models based on Bayes' theorem, such that the plausibility of a given model given the newly observed data (D) is:

$$\Pr(M_i \mid D) = \frac{\Pr(D \mid M_i)\Pr(M_i)}{\sum_{j=1}^{s} \Pr(D \mid M_j)\Pr(M_j)}, \qquad \text{(eq 1)}$$

where $\Pr(M_i \mid D)$ is known as the 'posterior probability' or 'weight' of model M_i (i.e. the degree of belief in M_i *after* considering the available data). $\Pr(D|M_i)$ is the likelihood that a given set of data would be observed if M_i were true, $\Pr(M_i)$ is the prior probability assigned to model M_i and the denominator represents the sum across the products of prior probabilities and likelihoods for all competing models including model M_i.

Models describing duck population responses to hunting pressure are central to the sustainable management of duck harvests. Managers of Mallard ducks use equation 1 to iteratively update their belief in competing models as yearly monitoring data are collected (Johnson et al., 1997; Johnson & Williams, 1999; USFWS, 1999). Various scientists and stakeholders hold alternative views about how duck hunting impacts on duck population dynamics. Debate focused on whether population growth would compensate for harvest mortality (compensatory mortality vs. additive mortality) and whether reproductive success would be strongly or weakly linked to habitat availability (strong vs. weak density dependence). In developing an adaptive management system for duck hunting, competing views were summarized as four models of duck hunting population response: 1) additive mortality (am), strong density-dependent recruitment (sdd); 2) additive mortality, weak density-dependent recruitment (wdd); 3) compensatory mortality (cm), strongly density-dependent recruitment; and 4) compensatory mortality, weak density-dependent recruitment (USFWS, 1999).

The implication of strong density dependence and compensatory hunting mortality is that higher hunting quotas may be sustainable. More conservative harvesting may be warranted if density dependence is low and hunting mortality is not compensated by increased reproductive success and a reduction in other forms of mortality. Table 2.1 shows how model probabilities were updated with duck population monitoring data over the years 1995 - 1999. Note that prior to the collection of monitoring data in 1995, all models shared equal prior probability [i.e. $\Pr(M_i) = 0.25$]. As monitoring data were collected and compared against the predictions of the four competing models, it rapidly became apparent that the compensatory mortality hypothesis was not supported by the data as hunting had a substantial impact on overall survivorship estimates. The data provided slightly more support for strong density dependence than weak.

Table 2.1
Trends in probabilities for competing hypotheses of Mallard population dynamics taken from USFWS (1999) [model probabilities have been rounded to two decimal places].

Year	'95	'96	'97	'98	'99
Model (defined above)					
1 (am, sdd)	0.25	0.65	0.53	0.61	0.61
2 (am, wdd)	0.25	0.35	0.46	0.39	0.38
3 (cm, sdd)	0.25	0.00	0.00	0.00	0.00
4 (cm, wdd)	0.25	0.00	0.00	0.00	0.00

The above example illustrates how it is possible to derive parameter estimates where little or no data are available. Approaches to eliciting Bayesian estimates of parameters from experts where no data can be obtained are analogous to those described in this simple example (see Martin et al., 2005; McCarthy, 2007 on soliciting subjective priors). A similar analysis might be initiated to develop parameters that describe the survival and fecundity of species in other situations, such as whales under various noise exposure/management scenarios. The approach outlined above is a logically coherent approach to extrapolating, for example, noise-related impacts from other mammals to cetaceans. The degree to which this approach works depends on whether the responses in question (e.g., behavioral, physiological, psychological, etc.) are highly conserved between species. For example, stress response physiology does appear to be highly conserved between species (see Deak, this issue; Romero & Butler, this issue) and thus would be a good candidate for this approach.

Bayesian updating in adaptive management. Adaptive management encourages a formal process of iteratively updating degrees of belief in competing hypotheses (models) in light of evidence collected through monitoring. There is usually substantial uncertainty about how a species will respond to management intervention, or indeed, the ecological/biological processes that mediate that response. It is common for different experts to support qualitatively different models of ecological processes. Qualitatively different management strategies usually imply different views about how species and environmental processes interact with human and natural disturbances. When appropriate experts support qualitatively different models, it implies substantial uncertainty about the best approach for achieving desired management outcomes. When such uncertainty exists (and is acknowledged), there is value in implementing management options that will facilitate learning about the relative merits of competing models and ultimately the best long-term strategies for achieving management goals. In some instances, data and expert opinion may favor some models over others. When this is the case, formal methods for weighting competing models may be utilized (Box 2; Burnham & Anderson, 1998; Wintle et al., 2003). Competing model weights may be used to assist in the allocation of effort between competing management options. If there is no substantial evidence in favor of one model over another, then uninformative (equal) model weights may be appropriate until further evidence arises that provides support for one model over others (Box 2).

Conclusions

At first glance, the range of tools and the technical aspects of formal decision making may serve as a disincentive to engage in adaptive management. Here I have focused on techniques for making predictions, characterizing uncertainty, and learning about effective ways to manage threatened species. There are substantial components of the decision making process, such as reconciling competing objectives and social utilities that I have not dealt with in detail. While there are technical challenges to all decision analysis methods, the advantages gained in terms of transparency, repeatability and stakeholder trust far outweigh

the technical overheads. In short, dealing with uncertainty in conservation and natural resource management is a difficult challenge that necessitates sophisticated methods. The number of examples of adaptive management and formal decision theory applications occurring in conservation and environmental management are gradually increasing, though much un-chartered territory remains. A systematic method of combining quantitative and qualitative inputs from scientific studies of risk, cost and cost–benefit analyses, and stakeholder views has yet to be fully developed for environmental decision making (Linkov et al., 2006a). Management of threatened cetacean populations and the acute and chronic impacts of noise will involve numerous sources of uncertainty. This highlights the need for systematic approaches to learning and decision making. I encourage cetacean conservation managers to embrace the principles and tools of adaptive management as a means to efficient use of scarce conservation resources and better long-term conservation outcomes.

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Anthropogenic Noise as a Stressor in Animals: A Multidisciplinary Perspective

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Consequences of extreme noise exposure are obvious and usually taken into some consideration in the management of many human activities that affect either human or animal populations. However, the more subtle effects such as masking, annoyance and changes in behavior are often overlooked, especially in animals, because these subtleties can be very difficult to detect. To better understand the possible consequences of exposure to noise, this review draws from the available information on human and animal physiology and psychology, and addresses the importance of context (including physiological and psychological state resulting from any previous stressor exposure) in assessing the true meaning of behavioral responses. The current consensus is that the physiological responses to stressors of various natures are fairly stereotyped across the range of species studied. It is thus expected that exposure to noise can also lead to a physiological stress response in other species either directly or indirectly through annoyance, a secondary stressor. In fact many consequences of exposure to noise can result in a cascade of secondary stressors such as increasing the ambiguity in received signals or causing animals to leave a resourceful area, all with potential negative if not disastrous consequences. The context in which stressors are presented was found to be important not only in affecting behavioral responses, but also in affecting the physiological and psychological responses. Young animals may be particularly sensitive to stressors for a number of reasons including the sensitivity of their still-developing brains. Additionally, short exposure to stressors may result in long-term consequences. Furthermore, physiological acclimation to noise exposure cannot be determined from apparent behavioral reactions alone due to contextual influence, and negative impacts may persist or increase as a consequence of such behavioral changes. Despite the lack of information available to managers, uncertainty analysis and modeling tools can be coupled with adaptive management strategies to support decision making and continuous improvements to managing the impacts of noise on free-ranging animals.

Physiological responses to stressors and the consequences for an individual or a population have been debated in various arenas, partly because they are studied by scientists from widely different disciplines. Here we summarize the knowledge acquired over the recent decades in different disciplines ranging from animal physiology to human psychology. Noise is a ubiquitous stimulus with the potential to act as a stressor, which has been growing in intensity in the oceans over recent decades. Paradoxically however, the effects of noise on the health and wellbeing of humans, terrestrial animals and, most recently, marine animals remain controversial. This paper provides an overview of the physiological responses to various stressors in humans and animals across various scientific fields and their consequences. We also summarize the current state of knowledge about these responses with specific regard to noise in humans and laboratory animals. Then, we extrapolate from this overview to fill some of the gaps concerning the physiological responses induced by noise in humans and free-ranging animals, highlighting marine species as they often rely heavily on acoustical communication as light does not travel far in water (Hatch & Wright, this issue). The importance of the context in which stressors are presented is also emphasized. Finally, we attempt to identify how and to what extent noise affects the health, wellbeing and viability of wildlife populations. Working definitions of several terms related to "stress" used throughout this paper are presented in Wright & Kuczaj (this issue).

Noise levels and exposure to those levels are measured differently in air and water. The reasons for this are varied, complex and beyond the scope of this paper. More information can be found in Clark & Stansfeld (this issue) and Hatch & Wright (this issue).

Physiological Stress Responses

Pathways of response

Two major systems are known to be involved in stress: the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. These systems are activated very rapidly and have broad impacts on diverse aspects of physiological functioning. The concerted effort of these and other critical endocrine and neural systems ultimately comprises an organism's response to a stressor (see Deak, this issue; Romero & Butler, this issue). Indirect measures of SNS activation (e.g., increased heart rate, blood pressure, or hyperthermia) or direct measures of SNS output from the adrenal medulla (plasma concentrations of catecholamines – epinephrine and norepinephrine) and HPA activation (corticosteroid concentrations in plasma, tissue or excrement) are often collectively or individually used to indicate the severity of a stressor. Importantly, "stress responses" can also occur to stimuli that are merely arousing, such as sexual activity (see Deak, this issue). Thus to avoid misinterpretation of physiological and behavioral measures observers should take into consideration baseline information and should verify the presence of a threatening context to determine whether the observed changes actually reflect a stress response and not arousal *per se*.

The SNS response to stressors can be detected within seconds of the perception of a punctate stressor (i.e., one with a sharp onset). However, many stressors are not punctate but rather develop over a long period. In the cases of these building stressors, the SNS activation is often described as a steadily escalating "tone" where general SNS activity increases relatively slowly over the course of hours, days or months, leading to escalated metabolic demand and gradual wear-and-tear on physiological systems that may eventually culminate into physiological failures (see Deak, this issue). These contrasting SNS responses make it particularly difficult to identify a causal relationship between anthropogenic noise and SNS response because anthropogenic noise arises across a wide range of time frames. Noise can be punctate, such as occurs in seismic survey blasts, or noise can gradually increase over a given area and persist for extended periods (if not permanently), such as is the case with the increase in ambient noise throughout the world's oceans resulting from shipping traffic. In the latter situation, the major stressor is unlikely to be the noise itself, unless levels cross some threshold of tolerability, but rather the increasing masking (i.e., the "drowning out" of a signal in the noise) of mating calls, social communication, echolocation of prey and other important signals.

Development of the response by the HPA axis is somewhat slower than that of the SNS response, but its impact is just as profound, albeit on a somewhat more protracted timeline. Immediately upon perception of a stressor a chain of events in the HPA axis triggers the production of glucocorticoids (GCs: e.g., corticosteroid) by the adrenal cortex (see Deak, this issue; Romero & Butler, this issue). The stress hormones are then quickly released into the bloodstream (usually within 3-5 min after activation by stressor onset) where they are rapidly distributed throughout the body to initiate a systemic response to the threat (Romero & Butler,

this issue; Sapolsky, Romero, & Munck, 2000). This can be problematic for researchers as it limits the time during which they can gain valid information on GC levels, as an animal's blood GC levels rises very quickly after the individual perceives the threat of capture, regardless of whether it is yet in hand or not.

In general, the more intense the stressor, the greater the amount of GC released. Once the stressor ends, GC levels return to baseline concentrations as a consequence of both the ending of the stimulus and GC negative feedback on the pituitary gland and hypothalamus (see Romero & Butler, this issue). If the stressor persists or occurs at frequent intervals the animal becomes chronically stressed (how frequent depends upon the stressor). This is generally manifested as a long-term increase in GC secretion due to two mechanisms: repeated secretion in response to repeated stressors and a failure of GC negative feedback (Dallman & Bhatnagar, 2001).

Consequences of the stress response

GCs (both independently and in combination with other components of the stress response) cause a variety of behaviors in free-living animals that are heavily context dependent (see Deak, this issue; Romero & Butler, this issue). However, the broad effects of GCs are to shift the animal away from normal life-history behavior to emergency behaviors (see Romero & Butler, this issue). Examples include increasing activity, the scattering of a group, shifting behavior from reproduction to feeding, and abandonment of breeding territories. These behaviors are adaptive in natural environment in the short-term, but may become maladaptive in response to novel human disturbances and/or repeated or chronic exposures.

Detrimental physiological effects can also appear if the stressors remain, or additional stressors are presented, prolonging the GC response over an extended period. A number of pathological effects appear after 2-3 weeks, which are very consistent across species studied (mainly in captivity: see Romero & Bulter, this issue). These include, but are not limited to, diabetes, immune suppression and reproductive malfunction. In fact, the assault on reproductive function is threefold, involving prolonged behavioral changes, such as reorientation of the individual's behavior away from reproduction, psychological effects, such as decreases in libido, and physiological impairment of reproduction (see Deak, this issue; Romero & Butler, this issue). Interestingly, in many human couples seeking artificial conception, the underlying infertility is induced by being stressed (Homan, Davies & Norman, 2007; Wischmann, 2003).

Other long-term consequences of persistent high GC levels include accelerated aging and a slow disintegration of body condition (see Romero & Bulter, this issue). It is clear that accelerated aging in combination with decreased reproductive function presents a double-blow to the fitness of an individual. There are obvious implications for the population if such effects are widespread, but more subtle consequences also exist (see Deak, this issue; Romero & Butler, this issue). For example, if cultural exchange from one generation to the next is limited by the shortened lifespan and premature death of the older generation, certain skills

or valuable information (e.g., regarding a reliable watering hole in times of drought in elephants) may be lost.

One further example of the consequences of persistently elevated GC levels is psychosocial dwarfism (Green, Campbell & David, 1984), a rare but documented inhibition of growth in human children due to altered growth hormone function (see Romero & Butler, this issue). It appears possible (although speculative at this point) that prolonged high levels of GCs may explain why sperm whales (*Physeter macrocephalus*) in the Gulf of Mexico (GoM) are significantly smaller than others elsewhere in the world (Jaquet 2000). Humans have very extensively used the Gulf ever since the discovery of the Mississippi River: activity that has continuously intensified.[1] The apparent dwarfism in the resident sperm whales might be a symptom of the heavily stressed state of the animals due to that activity. This condition would probably not be the result of exposure to noise alone, but rather the cumulative action of noise with various other stressors such as reduced prey availability and contaminants. Genetic differences and other factors might also be involved.

GCs can also have toxic consequences for neurons (i.e., cause neuron death) in the very young brain, which is probably why GC responses to stress are attenuated during the perinatal period (Sapolsky, 1992). Only severe stressors elicit GC release by the newborn during this time, such as parental deprivation or neglect, possibly as a consequence of parental/alloparental poor health (for any reason), or maternal separation, perhaps due to increased foraging times. The period of attenuation extends up to about a week or two postpartum in rats, but its length is not known in many other species, including marine mammals. If the mother is exposed to severe stressors however, GCs may be passed to the offspring through the placenta or in milk, circumventing this attenuating mechanism. The damage caused by exposure of the young brain to GCs produced by the mother alone can have profound and permanent consequences for the offspring, including sensitizing them to stressors, that is increasing their GC response, later in life (Kapoor, Dunn, Kostaki, Andrews & Matthews, 2006). Such changes can last at least to young adulthood and may be permanent, introducing the specter of potential generational effects.

Once this attenuation period ends, the still developing brain may then be very susceptible to neurological damage and re-programming as a result of exposure to high GC levels, whatever the source. Consequently, while reasonably mild stressors can lead to mild and temporary stress responses in adult animals, similar exposure in very young animals, either directly (e.g., brief handling of neonates, for not more that 2-3 minutes per day) or indirectly (e.g., through a "stressed" mother), has the potential to elicit long-term, if not permanent, consequences for the individuals resilience to stressors.

Long-term consequences of a prolonged or repeated stress response may also be present in individuals of any age due to ways that GCs instigate changes in

[1] For more information on human activity in the GoM see the EPA Gulf of Mexico Program website (http://www.epa.gov/gmpo/about/facts.html#maritime), Lynch & Risotto (1985) and Melancon, Bongiovanni & Baud (2003).

the body. In order to have any effects GCs, like other steroids, must first pass through the cell wall. Once inside the cell nucleus, GCs bind with their receptor and they rewrite protein construction priorities (i.e., reprogram the expression of various genes). These revisions can persist long after high GCs levels have ceased circulating in the blood, thus long after the removal of the stressor. This persistence combined with the rapid activation of both the SNS and HPA axis responses means that many of the delayed and/or long-term consequences of stressor exposure are induced as a direct consequence of the initial perception of even a brief punctate stressor.

Effects of combining stressor types

The brain appears to classify threats as being processive (psychological) or systemic (physiological) in nature (see Deak, this issue). Psychological stressors include threats like predators, while physiological stressors include immediate and severe threats to physiological homeostasis, such as hypoglycemia (low blood sugar, specifically glucose). Importantly, some stressors appear to activate brain systems involved with both classes of stressors and it is these "compound" stressors that appear to produce the most direct outcomes for CNS functioning and overall health (see Deak, this issue).

Either exposure to a single very intense acute stressor, or the cumulative impact of numerous stressors across time, can ultimately lead to expression of sickness-like behavior, which is thought to be a symptom of neuroinflammation (Deak, this issue). For example, separation of a young guinea pig from its mother produces psychological stress (separation anxiety) and the offspring immediately begins to run around and vocalize. However, after an hour of exertion (physical stress), the young guinea pig stops that behavior, shuts it's eyes, curls up and looks sick (Schiml-Webb, Deak, Greenlee, Maken & Hennessy, 2006). This response can be reversed by giving drugs with potent anti-inflammatory properties (Schiml-Webb, Deak, Greenlee, Maken & Hennessy, 2006). It is possible that the stress response and illness may have co-evolved as both are responses to threats (see Deak, this issue).

Normal aging is associated with greater expression of pro-inflammatory factors in the CNS (see Deak, this issue), so that risk of neuroinflammation increases with age. Repeated stressor exposure also leads to inflammatory responses as well as to accelerated aging as discussed above, creating an escalating combination of effects that can lead to increased incidence of neurodegenerative disorders and other critical problems that normally only arise later in life (see Deak, this issue).

Maladaptation of the stress response

Generally speaking, physiological responses to acute stressors promote survival in the face of diverse threats and are therefore viewed as being adaptive. Survival is promoted principally through a preferential re-allocation of resources (blood flow, glucose utilization, cognitive and sensory acuity, etc). The increase in

catecholamines associated with the acute fight-or-flight response has distinct energetic and immune consequences for the individual. The effects of GCs are more prolonged in nature and probably evolved as a mechanism to sustain behavioral and physiological responding to stressors of longer duration. The transient expression of sickness-like behavior after stressor cessation probably represents an adaptive period of recuperation that is necessary to reinstate normal levels of cognitive and behavioral function to pre-stress levels (Deak, this issue). With prolonged or repeated stressor exposure, however, neuroinflammatory consequences of stress can become maladaptive, leading to compromised neuronal function, greater susceptibility to infection (Dhabhar & McEwen, 1997), and ultimately reduced reproductive fitness (see Deak, this issue).

Likewise, failure to mount a GC response can lead to the inability of the animal to continue to respond appropriately to a stressor, subsequently resulting in death (see Romero & Butler, this issue). This failure might be due to over-stimulation from either chronic or intense acute stressors that could have shutdown GC production through negative feedback, and possibly also depleted some of the various precursor molecules and biosynthetic enzymes necessary to produce the GC molecule. Alternatively, a prolonged response or exposure to a persistent stressor, such as pollutants, may have caused damage to the adrenocortical tissue where GCs are produced (Hontela, Rasmussen, Audet, & Chevalier, 1992; Martineau, this issue). Functional abnormalities of chronic stress are not restricted to GC effects. They can also result from catecholamines. For example, long-term activation of the fight-or-flight response across the life span can lead to coronary dysfunction and disease (see Romero & Butler, this issue), an effect that may involve vascular inflammation as an intermediate mechanism (Black, 2002, 2003).

In general, the physiological stress response and the consequences thereof described above are highly conserved between species, including fish, birds and mammals, although the exact basal levels of GCs and other stress hormones are fairly variable from one individual, population or species to another (see Deak, this issue; Martineau, this issue; Romero & Butler, this issue). However, not all stimuli are actually stressors. The distinction is largely a matter of perception by the animal/human. Experience immediately prior to a stimulus plays an important role in the nature and intensity of an animal's response to that stimulus. For example, a very slowly increasing stimulus is easily acclimated to and only becomes a stressor once it exceeds some threshold. Similarly, the stress response is initiated only when events are worse than those expected by an animal (Levine, Goldman & Coover, 1972). Conversely, if a stimulus decreases in frequency or magnitude, the individual perceives an improvement in situation and the stress response will decline, even if the individual is still being subjected to an unpleasant stimulus. Complicating the matter further, the expectation of an unpleasant stimulus may in itself initiate the stress response. Furthermore, acute stressors that normally last a short time (such as predator attacks, dominance interactions and storms) may become chronic stressors if they occur often enough or persist.

Context and Behavioral Responses

Context is thus extremely important in the overall expression of a response to a potential stressor. Innumerable factors combine to form the context: environmental factors, such as season; recent history of incidence of the particular stimulus including intervals (i.e., prior experience); maturity, age, sex and other life history factors; inter- and intra-specific variation (genetic and propensity) including individual sensitivities, resilience and personality; condition (e.g., well-fed or hungry); other stressors currently acting upon an individual (e.g., infection, chemical exposure, etc.); predictability of stressor exposure; behavioral context (e.g., what the animal is doing when subjected to the stimuli); current psychological state (e.g., anxious, optimistic); and social structure.

Behavioral responses as an indicator for stress effects

While many of the above contextual factors may influence the onset and/or magnitude of a physiological stress response, the response itself is reasonably consistent once activated. However, an observed response does not necessarily reflect the magnitude of the impact actually experienced by the animal (Beale, this issue; Beale & Monaghan, 2004; Bejder, Samuels, Whitehead & Gales, 2006; Gill, Norris & Sutherland, 2001; Harrington & Veitch, 1992; Lusseau 2004; NMFS, 1996; Stillman & Goss-Custard 2002; Todd, Stevick, Lien, Marques & Ketten, 1996).

For instance, behavioral reactions may be influenced by the psychological state of the individual. All behavioral decisions (whether conscious or not) are the product of information processing systems within the animal's brain. Stressors, including noise, and their associated emotional states, such as anxiety and depression, may influence this processing in a number of ways. First, anxiety is essentially an early warning system for the fight-or-flight response, and as such is associated with a suite of adaptive changes in cognition. Attention shifts towards awareness of possible threats and ambiguous information is interpreted more pessimistically (see Bateson this volume). These effects may be subtle and reversible, but may significantly affect the actions of an animal while they persist. For example, captive European starlings (*Sturnus vulgaris*) exposed to the stressor of being housed in barren cages may become more pessimistic and risk-averse in their interpretation of cues associated with food rewards. This pessimism is seen in a shift towards preferring safe foraging options, avoiding riskier but potentially more rewarding sites (Bateson & Matheson, 2007; Matheson, Asher & Bateson, 2008). Similar biases induced by other stressors could therefore result in changes in the spatial or temporal pattern of foraging behavior, with knock-on consequences for the fitness of the animals exposed. These changes in behavior also have the potential to place animals in situations where additional stressors could occur, such as food deprivation, or arrival in a novel environment due to avoidance efforts.

Physical condition can also influence behavioral responses. For example, well-fed animals may take fewer risks than their hungry counterparts, preferring a certain food reward over a more variable (i.e. risky) alternative (Caraco et al., 1990). Consequently, these individuals may also appear to be more sensitive to disruption, fleeing from a disturbance source at much greater distances. Conversely, a starving or sick animal may not display any observable response, as they may simply not be able to afford to react behaviorally: this is the only good feeding habitat in the area. Similarly, the well-fed animal may eventually be forced to return to its foraging ground when it becomes hungry, regardless of the potential threats. In this case, the change in behavior reflects a change in the physiological status of the animal.

However, such apparent increases in tolerance have often been used to argue that animals are "habituating" to the source and are thus no longer impacted by it (see below). On the contrary, any individuals (such as the hungry animal described above) remaining in a location in the face of potential danger may be subjected to one or more potential stressors. They may therefore display a number of physiological and epidemiological responses consistent with a stress response. For example, kittiwakes (*Rissa tridactyla*) in Scotland show an increase in heart rate in response to human disturbance. This cardiac reaction has been estimated to increase daily energy expenditure by around 7.5-10% for some individuals, despite a long history of exposure to disturbances in the area (see Beale, this issue). This increase in daily energy expenditure is sufficient to result in eventual abandonment of nesting attempts once energy reserves drop below a critical level.

In summary, a lack of behavioral response could be either because there is no stress felt, or because the animal can't afford, or is not able, to respond overtly. Likewise, a strong behavioral response to a stressor, or a high level of observed response in a population, may mean that the stimulus is a particularly horrible stressor that is to be avoided at all costs, or it may imply that there is very little, if any, cost of responding to the stimulus, even though it may amount to no more than a minor irritation. Thus, given that animals make decisions (consciously or subconsciously) about how and/or whether or not to respond to a stimulus on the basis of their current context, this context must be known to biologists in order to accurately interpret the response intensity to a given stressor. As acquiring this knowledge is fraught with enormous difficulties in practice, it may not be possible at all to make such a determination simply from behavioral observations (see Beale, this issue). However, if such information is cautiously coupled with additional data (e.g., through the application of resource-use models), behavioral measures may allow the absolute minimum cost associated with responding to a stressor to be assessed (see Beale, this issue). Also, behavioral reactions observed in longitudinal studies can be, to some extent, placed in the context in which they occur (such as population abundance trends, residency patterns, season, etc.: e.g., Bejder et al., 2006; Lusseau 2005). These multi-scale approaches can also provide a framework to infer the synergistic costs of multiple stressors (natural and anthropogenic).

Likewise if the context in which decisions are made is not changed between two stressor exposures, behavioral measures can be used directly to

measure the relative degree to which the stressors affect individuals (see Beale, this issue). However, maintaining similarity of context is challenging. Many factors, such as passing predators, changes in prey abundance and distribution (even on a very local scale), and recent experience of any and all other stressors, can be difficult to measure especially in the marine environment. If such experimental approaches are not feasible, these contextual factors need then to be included as model co-factors or accounted for in other ways. One exception occurs if the behavioral responses to a given type of stimulus remain great regardless of the context, which would indicate unambiguously that the species involved attempts to avoid that type of noise at all costs.

Acclimation

The term "habituation" is often used loosely to describe animals "getting used to" a stimulus, with various broad implications. However, "habituation" is often invoked without reference to the literature and seemingly in conflict with the use of the term in the biomedical or psychological literature (see Bejder et al., 2006). To avoid confusion, we shall use the term "acclimation" or "acclimatization", meaning that an animal no longer produces a physiological stress response in reaction to a stimulus (Romero, 2004; Wright & Kuczaj, this issue and references therein). Animals can only truly acclimate in this way to stimuli that they perceive to be the same from one instance to the next, as well as non-life threatening (Romero, 2004; Wright & Kuczaj, this issue and references therein).

Acclimation is more likely to occur with frequently repeated, predictable exposures and can be lost if enough time passes between exposure events. This may explain why laboratory results for acclimation are more consistent than observations in the wild, as what appears to be repeated exposure in the "real world" may not be predictable or perceived as precisely the same by the animal. Chronic stimuli obviously meet the exposure frequency criteria required for an animal to acclimate, however animals may still lose acclimation if the exposure ends and there is enough time before the next exposure begins. The magnitude of exposure is also a consideration, because, in general, the greater the stress response initiated by a stressor, the less likely an animal is to acclimate to it, to the point where animals never acclimate to serious stressors.

In summary, animals will acclimate quicker to stimuli that are perceived to be smaller potential threats than those representing larger possible threats. However, acclimation only eliminates or reduces the stress response. It does not prevent other effects produced by a stimulus, such as hearing loss and masking that result from noise, as well as any stress response that these effects might subsequently induce. Similarly, acclimation also opens the possibility for sensitization, where the animal may produce an enhanced stress response when exposed to a new or different stressor.

Additionally, some uncertainties remain even within the narrower definition of "acclimation" as some humans can continue to perceive a noise as annoying or stressful without physiological responses or vice versa. Also, it's not

clear exactly how similar a sound must be for animals to cease to be able to tell them apart: e.g., different boats may sound very different.

Determining Cumulative Effects

We have already discussed above the potential for one stressor to influence the impacts of a subsequently applied stressor through the alteration of the context of exposure. Accurate prediction of all the potential cumulative and synergistic effects requires a reasonable knowledge of all the various contextual factors for each exposure and is thus not an easy proposition. However, at the most basic level it seems reasonable to conclude that the addition of new stressors is likely to increase the stress response, a concept that has some support in the literature (see review by Dallman & Bhatnagar, 2001).

The cumulative effects of multiple stressors can be estimated in this way through use of the concept of allostasis (see summary in Wright & Kuczaj, this issue; and discussion in Romero, 2004: Box 1 and references within), which suggests that all the various energetic demands that would be placed on an individual can be added up to see if that individual would be able to cope with them (i.e., maintain an allostatic load) or not (i.e., go into allostatic overload). Allostasis is currently a contentious idea in the biomedical world, a debate that goes beyond the scope of this paper. Suffice to say that the use of the concept of allostasis to investigate the cumulative effects of various stressors requires a working knowledge of the size of the energetic demands generated by each stimulus, which is clearly lacking for many species. This is not to say that energetic models cannot be useful in the management of the cumulative effects of various stressors on species where such data are limited, for example marine mammals (e.g., Lusseau, 2004). Rather energetic models are indicators of minimum possible energetic costs because of the various assumptions involved and the limited knowledge of the possible non-linear synergistic interactions between stressors.

Initial efforts to begin considering such non-linear synergistic interaction could be based on the two broad categories of stressors defined earlier, psychological, or processive, and physiological, or systemic, stressors. These categories should be considered because the simultaneous exposure to stressors belonging to each category increases the likelihood of having a severe impact on the individual. For instance, rats exposed to either simple restraint or hypoglycemic challenge show no evidence of neuroinflammation, while rats exposed to both challenges showed profound neuroinflammation (Deak, Bordner, McElderry, Bellamy, Barnum, & Blandino, 2005). Given that neuroinflammation may be a harbinger of adverse long-term health outcomes of stressor exposure, these data indicate that a categorically distinct, synergistic response can be provoked when otherwise innocuous events are combined. This may have profound implications for animals in captivity, which may be exposed to a wide variety of both physiological and psychological stressors such as confinement in a small environment, handling (especially in marine species, where handling is often

accompanied with at least partial removal from water), and the noise and activities of the public, staff, and/or researchers.

Even if both the different types of stressors and their cumulative energetic demands are accounted for, it may still not be possible to predict the overall effect of multiple stressors on an individual because lab-based studies have shown that multiple stressors interact in unpredictable ways to alter GC release, either increasing or decreasing circulating GC levels (see Dallman & Bhatnagar, 2001). Context or the influence of context may also vary unpredictably. Consequently, efforts to determine cumulative and synergistic effects of multiple stressors on animals, though important to pursue, should be undertaken cautiously.

Noise-Induced Stress Responses

Some of the known effects of noise in animals include audiogenic seizures and increases in serum cholesterol levels (Clough, 1982), intestinal inflammation (Baldwin, Primeau, & Johnson, 2006), and increased adrenal weights due to overproduction of adrenal hormones caused by a prolonged stress response (Ulrich-Lai, et al., 2006). Stress responses induced by loud or sharp noises have even lead to cannibalism of neonates, as well as a generally decreased reproductive performance in mice (Michael Rand, pers. comm.).

The stress response with its various effects and impacts has been studied to some extent in rats and humans exposed to noise. For example, laboratory rats exposed daily to short periods of white noise exhibited a variety of conditions consistent with the onset of a physiological stress response after around 2 weeks, becoming more pronounced at 3 weeks (Baldwin, this issue). These conditions included inflammation of the intestinal mucosa and the mesenteric microvessels, degranulation of mast cells in the intestinal mucosa, migration of eosinophils into the wall of the intestine, and oxidative damage. Additionally, exposed rats groomed excessively and had redness around eyes and neck. After a recovery period of 3 weeks, the noise-exposed rats displayed some characteristics similar to unexposed controls, but other characteristics remained similar to pre-recovery conditions, indicating that some pathological effects continued to persist even after removing the noise exposure (Baldwin, this issue).

In humans, noise causes a number of predictable short-term physiological responses such as changes in hormone levels. However, little is known about how these might combine to have long-term consequences on health (see Clark & Stansfeld, this issue). Furthermore, specific evidence of chronic noise effects on adrenaline, noradrenaline and cortisol levels in humans is weak and inconclusive, suffering from various experimental difficulties (see Clark & Stansfeld, this issue). However, there is stronger evidence for a positive association between chronic noise exposure and both hypertension (i.e., raised blood pressure) and coronary heart disease (CHD), including some significant increases in myocardial infarction (i.e., heart attacks) associated with exposure to occupational, road traffic and aircraft noise.

There are indications that some of these effects on health may be mediated through annoyance, itself a psychological stressor (see Clark & Stansfeld, this

issue). In addition, noise exposure (or the annoyance it causes) has been associated with increased reporting of psychological and somatic symptoms in affected populations, but not with more serious clinically diagnosable psychiatric disorders such as anxiety and depressive disorders. This suggests that noise is probably not associated with serious psychological illness, but may affect well-being and quality of life (see Clark & Stansfeld, this issue). However, there have been no longitudinal studies in this area.

Noise may disturb sleep in humans as well, which may in turn have consequences for performance, mood and health. However, it appears that, with regards to sleep disturbance, naïve exposure (i.e., no prior experience) is a very important factor. Regardless of the mechanisms involved, these various effects may contribute to the increase in mortality observed in one study of industrial noise, with additional job-related stressors potentially acting cumulatively with the noise (see Clark & Stansfeld, this issue).

The greater expression of noise-related impacts in workers with higher job-related stressors is one example of the importance of contextual factors and cumulative exposure on the strength of response and ultimate outcomes from exposure to noise or any other stressor. Various other contextual factors are also important in humans in ways that are similar to the influence of prior experience on the physiological stress response of animals (see Clark & Stansfeld, this issue). For example, individuals with poor psychological health prior to exposure to noise reported greater annoyance (Tarnopolsky, Barker, Wiggins, & McLean, 1978), showing that individual psychological traits determine how annoying noise is.

Children may be more vulnerable to the effects of environmental stress as they have less cognitive capacity to understand and anticipate environmental stressors, in addition to lacking well-developed coping repertoires (Stansfeld, Haines, & Brown, 2000). Studies have consistently found that chronic noise negatively affects children's learning and cognitive abilities, and are beginning to indicate an effect on hyperactivity, although evidence for an increase in psychological symptoms is mixed and inconclusive (see Clark & Stansfeld, this issue). Recovery of some of these deficits may be possible if noise exposure ends, but noise could potentially impair child development, resulting in lifelong effects on both educational attainment and health. Longer exposures are known to cause larger and more persistent effects on physical health and are also likely to generate larger cognitive deficits and bigger effects on psychological health (see Clark and Stansfeld, this issue). Furthermore, the consequences for educational attainment are more likely to be long-lived or permanent if exposure overlaps with the closure of any learning window or opportunity (e.g., until a child leaves school).

Acclimation to noise

Given the above considerations on acclimation to stressors in general, apparent behavioral tolerance of noise cannot be automatically interpreted as true physiological acclimation. Instead, apparent behavioral tolerance could be the result of different contexts, such as an overwhelming need for an individual or a population to remain in the area, the absence of alternative habitats, the prohibitive

costs associated with avoidance, or even that the animal might already have reduced hearing at the frequencies of the stimuli. Learning alone (i.e., without an associated reduction in physiological response) might also simulate acclimation to noise. In addition to the above mechanisms, an apparent increase in behavioral tolerance at the population level can arise if the most sensitive animals in the population have already left the area (e.g., Bejder, Samuels, Whitehead, & Gales, 2006). One other possibility is that rapid "natural" selection may have taken place, through the death of either the most sensitive individuals and/or the ones that are most prone to maladaptive alarm/escape responses (for some possible examples of these in marine mammals see Wright et al., this issue, b). The possible long-term costs and benefits of behavioral tolerance as a result of any of these mechanisms are unknown, although the action of either selection or emigration will clearly reduce the number of animals in the local population.

If an animal spends a considerable amount of time reacting to human disturbance, it may be fatigued and not willing or able to evade a potential threat and thus may appear to have acclimated when in fact it has not. Likewise, the apparently quick development of tolerance to disturbances in humans (e.g., aircraft noise in most people sleeping near airports) may not translate into free-ranging animals because animals must remain aware of predators, while humans in contrast are largely spared threats of this kind. Humans also benefit from prior knowledge that the noises can be reliably associated with passing aircraft or road traffic and that these things are unlikely to indicate an imminent threat.

The matter is complicated further still by the concept of "tuning out", a type of filter for chronic, but changing, noise as is seen in humans (see Clark & Stansfeld, this issue). Consider that many patrons in a bustling restaurant largely filter out the general noise of employee activity and the conversations of other diners. This filtering does not prevent other effects, such as masking and hearing loss. Furthermore, it is not clear how much people or animals might perceive the noise as changing. For example, many of the abovementioned diners would look up if they hear a waiter breaking a plate or a glass.

Masking, psychology and behavior

Acoustic signals become ambiguous when they are hard to discriminate from other sounds. Increased environmental noise thus augments the ambiguity of incoming information by either reducing hearing capacity through hearing damage (temporary or permanent) or through masking by increasing background noise levels. Hearing damage persists after exposure (even if only temporarily) and affected animals can do little to compensate for the loss during that time. On the other hand, animals can employ several strategies to limit the ambiguity created by masking (see Bateson, this issue).

One option, physical avoidance, is to leave the noisy area for somewhere quieter. Avoidance strategies are not likely to be feasible for the majority of chronic or high-incidence noises. This is especially true for marine life exposed to ambient noise generated by shipping, which dominates background noise at low frequencies in many of the world's oceans, particularly in the northern hemisphere.

A second option, available if noise is not continuous, is to cease communicating during periods when noise levels are highest. For example, urban European robins (*Erithacus rubecula*) switch to nocturnal singing in areas with high daytime noise (Fuller, Warren & Gaston, 2007). However, such evasive behaviors could again place animals in situations where they will encounter new stressors. In the above example, nocturnal singing could lead to an increased risk of predation by exposure to, or attraction of, nocturnal predators. In any case, temporal and special avoidance strategies can only be employed if the temporal distribution of the noise is predictable.

A third tactic available to animals is to change one or more characteristics of their acoustic signals, such as length, frequency, amplitude, or other acoustic features, to increase their transmission probability in a noisy environment. Beluga whales (*Delphinapterus leucas*) for instance can increase the amplitude of their signals in response to increasing background noise, a response known as the Lombard effect (Scheifele, Andrew, Cooper, Darre, Musiek, & Max, 2005). Humans speaking loudly in noisy situations are employing this option, but will eventually become hoarse and may temporarily lose their voice. It is not known what kind of consequences long-term use of signal-change strategies may have for animals, however increasing the amplitude of a sound uses more energy and therefore carries some additional cost.

The fundamental ability of an animal to actually alter its signals may also be limited, physiologically, anatomically, or by age. Many songbirds, such as the chaffinch (*Fringilla coelebs*), have a narrow window of time in early life in which their brains are particularly receptive to acquisition of new vocal patterns such as song. A few species, such as mockingbirds (*Mimidae*) and European starlings, continue to learn new vocal patterns after this period, while other singers show only limited variation from the parental song after early learning (for a review see Catchpole & Slater, 1995). Similarly, there are indications that bottlenose dolphins (*Tursiops truncatus*) may be able to learn at any time (e.g., Watwood, Owen, Tyack, & Wells, 2005) and male humpback whales (*Megaptera novaeangliae*) are known to change their songs repeatedly throughout their lives (see Noad, Cato, Bryden, Jenner & Jenner, 2000; Payne, Tyack, & Payne, 1983). However, very little is known about the abilities of most other marine species, especially marine mammals that use low frequencies, to acquire new vocal patterns throughout their lifetimes.

In any case, while altered signals may propagate further or be more distinct in the face of increases in ambient noise than unaltered ones, the potential usefulness of signal alteration is limited by the extent to which signals continue to be recognized by the intended receiver. This is especially important when the calls are involved in species recognition, perhaps for mating or maintaining social structure, which may further reduce the extent that these calls can be changed. Alteration of signals may also be problematic in species that communicate over long distances (such as mysticetes – baleen whales), because two animals may be subjected to very different ambient noise profiles. This means that the optimum signaling strategy in the immediate acoustic environment of the signaler may be

very different from the best option given the noise profile in the immediate area of the signal receiver.

Signal alterations are also not an option for animals that hunt using passive acoustics (i.e., eaves-dropping on their prey). Consequently, there will be many occasions when the only option available to an animal will be to alter its responses to incoming sounds. For example, animals can alter their thresholds for responding to incoming sounds that they receive, be they communication signals or sounds made incidentally by prey, predators, or con-specifics (see Bateson, this issue). If increases in masking noise make it harder to discriminate important signals from other irrelevant sounds, then animals may adapt to this situation in different ways, including:

1) Lowering their threshold for a sound to be identified as a particular type of signal, thus increasing their probability of falsely identifying signals as related to mates, prey and/or predators. Possible results include chasing after objects or organisms that are neither prey nor a mate, or fleeing from things that are not a predator (or other threat). This has consequences in terms of increased energetic costs.
2) Increasing their threshold for a sound to be identified as a particular type of signal, thus decreasing their probability of identifying a signal related to a mate, prey and/or a predator. Possible results include increased missed opportunity costs (e.g., passing up on possible prey and potential mates) or increasing the risk of predation if predators are missed.

In summary, animals have a range of options available for mitigating the adverse effects of environmental noise on their use of acoustic information. However, it is important to assess the potential fitness costs of any observed adaptation. Costs may arise from increased energetic expenditure, increased risk of predation, or lost opportunities for feeding or mating. All of these sources of cost could potentially be associated with increased risks of a physiological stress response occurring as animals struggle to adapt to function in a noisy environment.

Management Issues

The stress effects from noise that are of the greatest interest to managers are those that ultimately have consequences for survival and fecundity rates (*vital rates*). Population level impacts are potentially catastrophic but highly uncertain, providing some grounds for a precautionary approach. However, as uncertainty is pervasive in ecology and conservation management, various tools have been developed that attempt to characterize and deal with such uncertainty in decision making processes (see Wintle, this issue). In particular, adaptive management and Bayesian modeling approaches offer some promise (see below and Wintle, this issue).

Management under uncertainty: A general framework

Adaptive management can be loosely defined as management with a plan for learning (Wintle, this issue). The sequential actions in the process of adaptive management should have the dual purpose of achieving management goals and facilitating learning about both the system under management and the relative performance of management actions. Effective adaptive management requires simultaneous implementation of multiple competing hypotheses and/or management actions that are iteratively updated through concurrent assessment and evaluation with monitoring data. Hypothesis generation and modeling may be based on existing data and/or expert opinion.

Adaptive management is appealing as it explicitly acknowledges that the decision being made is subject to uncertainty and may change in the next time step depending on what is discovered (i.e., learned) in the intervening period. Notably, the completion of an experiment is not required before a change to management can be instituted. This allows a more rapid response that is particularly well suited for managing systems in which changes take a long time to become apparent.

Population modeling and scenario analysis

Adaptive management of anthropogenic impacts on any species requires the construction of a model (or competing models) of species' responses to those impacts and any management intervention. Population models have been used in both terrestrial and marine systems to evaluate the long-term population consequences of competing management options (Akçakaya, Radeloff, Mladenoff & He, 2004; Taylor & Plater, 2001; Wade, 1998; Wintle, Bekessy, Pearce, Veneir, & Chisholm, 2005). Predictions of population models must be treated with caution as most population models require numerous assumptions and are themselves subject to substantial uncertainty. Despite the prevalence of uncertainty, modeling may be useful in challenging stakeholders and managers to clearly state their belief about species population dynamics and the magnitude and mechanisms of anthropogenic impacts. Models represent testable hypotheses that may be improved and updated as new data or knowledge comes to hand. As data are gathered, updated models may begin to provide predictions that are more broadly trusted by managers and stakeholders. In data-poor situations, it is important to make the most of available expertise or "collateral" data.

Bayesian approaches to inference

It is not easy or cheap to collect ecological data and definitive results are rare. Bayesian inference provides a coherent approach to synthesizing and making the most of disparate ecological data and/or expert opinion. McCarthy (2007 and summarized in Wintle, this issue) utilized a novel Bayesian approach to estimate the mortality rate of powerful owls (*Ninox strenua*) by combining very sparse observation data with predictions from a regression of body mass on mortality rate data for a range of other raptors. This approach provides a sound template for

analyses of other species that are characteristically difficult to study, including marine mammals. Expert opinion can (and should) be used in ecological studies, however it is very important that it is integrated in analyses appropriately (see Martin, Kuhnert, Mengersen, & Possingham, 2005 and McCarthy, 2007 on soliciting subjective priors for Bayesian estimates).

Once parameters have been estimated, population models may then be used to evaluate the long-term population consequences of competing management options (Akçakaya, Radeloff, Mladenoff, & He, 2004; Wintle, Bekessy, Pearce, Veneir, & Chisholm, 2005). However, any predictions arising from such a model would, at first, be compromised by substantial uncertainty in the parameter estimates. To address this, sensitivity analyses should be undertaken to identify the parameters and assumptions in the model that most strongly affect its predictions. These assumptions should then become the focus for adaptive management plans for learning.

Conclusions

It is clear that the debate surrounding physiological stress responses, behavior, welfare and anthropogenic noise are going to continue for some time. To provide some focus we offer the following points as particularly noteworthy findings and recommend that scientists and managers take them into consideration when planning research and in assessments of environmental impact of noise.

1. Noise can act as a stressor. A single source of noise can result in a range of interwoven stressors. The various potential impacts of signal masking by noise illustrate this. The cascade of interwoven stressors that can be triggered by noise and masking includes separation anxiety, anxiety arising from ambiguous information, and hypoglycemia from loss of foraging opportunities, which can all in turn lead to other consequences as discussed earlier. Even when the noise itself may not lead directly to effects arising from the stress response, animals may create their own stressors through maladaptive efforts to avoid the noise. Similarly, physical injuries resulting from noise exposure may also act as additional stressors.

2. Short-term stress responses cannot be presumed to have only short-term consequences, especially when considering cumulative effects.

3. There is great potential for synergistic effects to arise through exposure of an animal to noise cumulatively with other stressors.

4. Context, especially the predictability of the stimulus and available response choices, is a very important (and possibly the most important) factor in mediating the overall stress response. For example, very young animals and fetuses are likely to be particularly susceptible to stressors, due to the effects of stress hormones on the developing brain. Thus, while

single or infrequent exposures alone may not produce long-term effects in adults, they may produce long-term consequences in young, still-developing animals. Unfortunately, such impacts will be very hard to detect in wild animals, especially in species that are hard to observe constantly, such as marine mammals.

5. It is impossible to determine the physiological and psychological responses of an animal to a stressor based on behavioral observations alone. Changes in an individual animal's behavior (or lack thereof) cannot be related to actual physiological and psychological impact without extensive investigation of the context. Behavioral changes in context are best understood and controlled in captive situations where exposure rates, environmental conditions and other factors are documented over long periods of time. However, the extrapolation of results from captive animals to the responses of wild animals should be done very cautiously given the large contextual differences (i.e., captivity and training vs. wild and free ranging) and the potential for high ambient noise levels to alter the baseline in the captive environment. Such contextual information is not generally available when assessing the possible correlations between acoustic stimuli and behavioral change in the wild. Collecting this information presents a considerable challenge, especially in the marine environment, although it is not impossible. Impact assessment studies need to specifically incorporate long-term and large-scale contextual information in their experimental design. Current short-term studies are generally failing to correctly assess the impacts of noise. Studies that have incorporated contextual information have led to a better understanding of disturbance impacts in other human-wildlife interactions. Without such contextual information it cannot be assumed that lack of a behavioral response means that no physiological stress response has occurred, or conversely that a behavioral response indicates the occurrence of a physiological stress response. In the latter case there may still be negative consequences for the animal if the behavioral response is maladaptive, involves a detrimental increase in energetic expenditure or exposes it to other threats.

6. By definition, acclimation requires consistency between non-severe repetitive exposures (including context) to sounds that are (near-) identical as perceived by the receiver. Conversely, repetitive exposure to different types of sounds (in frequency, intensity and other acoustic characteristics) cannot result in acclimation. Furthermore, animals cannot and will never acclimate to (contextually) severe stressors as these always, by definition, represent a threat. These reasons probably explain why few studies have shown acclimation occurring in the wild. Therefore, it should be assumed that animals have not acclimated to a sound, until proven otherwise. Although humans might be able to "tune out" more generalized noise sources such as road noise, health effects of exposure to such noise can

still arise (see Clark & Stansfeld, this issue). Tuning out can have its own detrimental consequences as individuals may over-generalize that ability to other sources, which may result in that individual ignoring sounds that are important to them, such as those produced by a predator.

7. While physiological acclimation to noise in the wild appears likely to be uncommon, it is clear that many animals have the capacity to learn to react behaviorally in a specific way to a generalized set of sounds. For instance, a whale might learn not to react behaviorally to noise from all types of engines because they are have proven to be non-threatening to date. As the specific repeated experience required to induce physiological acclimation has not occurred, the whale may still initiate a stress-response to the sounds of a passing ship, priming the animal to react in the case that this particular noise is different. To date, however, the evidence that non-human animals have genuinely learned to reduce or eliminate behavioral responses to human disturbance is largely anecdotal. Regardless, generalized learning may also explain similar reductions in behavioral responsiveness to a given stressor at the population level. However, it is difficult to separate the action of such learning from a number of other possible mechanisms, including the mortality or displacement of the most susceptible individuals, gradual changes in the context in which a population find itself, and selection for adaptive responses occurring over several generations.

8. The considerable effects of relatively short periods of noise in the lab must be taken into consideration when interpreting the results of experiments undertaken with animals in captivity (see Baldwin, this issue). Most animals in captivity will have been exposed to relatively high levels of noise on a regular basis, due to feeding or other husbandry activities, machinery noise or other general facility operations. These effects, in addition to the increased sensitivity of developing brains to the effects of GCs, may partially explain why attempts to breed some animal species in captivity have not been successful.

9. Epidemiological studies in humans have been more consistent in demonstrating effects of noise on health and psychological wellbeing than on the physiological stress response. This might be explained if the epidemiological effects arise from cumulative effects over a long timeframe. Also, inconsistencies in the studies of the human physiological stress response to noise exposure may be due to (unknown) contextual elements that have not been accounted for.

10. Managing the impacts of noise on animal populations is likely to require an adaptive strategy to address the substantial uncertainties arising from a poorly understood stressor, especially in data-poor species such as many marine mammals. In situations of severe uncertainty, models can be useful

decision tools, not only because they make assumptions explicit, but also as they allow the stakeholders to explore the importance of those various assumptions. Adaptive management of noise impacts should be accompanied by well-planned long-term studies that address key uncertainties about the population level impacts of noise on the species concerned. Careful extrapolation of data from other species using appropriate analytical methods may provide a basis for developing actions to reduce noise impacts. Such actions would be refined as better, species-specific data come to hand.

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Do Marine Mammals Experience Stress Related to Anthropogenic Noise?

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Sound travels much further than light in the marine environment. As a result, marine mammals, especially cetaceans, rely heavily on sound for many important life functions, including breeding and foraging. This reliance on sound means it is quite likely that exposure to noise will have some detrimental effects on these life functions. However, there has been little application to marine mammals of the knowledge available in other species of stress responses to noise and other stressors. In this paper we begin to integrate what is known about marine mammals with the current knowledge gained in terrestrial mammals about stress physiology, specifically considering physiological and psychological context and thus also cumulative and synergistic impacts. We determined that it is reasonable to extrapolate information regarding stress responses in other species to marine mammals, because these responses are highly conserved among all species in which they have been examined to date. As a result, we determined that noise acts as a stressor to marine mammals. Furthermore, given that marine mammals will likely respond in a manner consistent with other species studied, repeated and prolonged exposures to stressors (including or induced by noise) will be problematic for marine mammals of all ages. A range of issues may arise from the extended stress response including, but not limited to, suppression of reproduction (physiologically and behaviorally), accelerated aging and sickness-like symptoms. We also determined that interpretation of a reduction in behavioral responses to noise as acclimation will be a mistake in many situations, as alternative reasons for the observed results are much more likely. We recommend that research be conducted on both stress responses and life-history consequences of noise exposure in marine mammals, while emphasizing that very careful study designs will be required. We also recommend that managers incorporate the findings presented here in decisions regarding activities that expose marine mammals to noise. In particular, the effects of cumulative and synergistic responses to stressors can be very important and should not be dismissed lightly.

As sound travels much better than light in the ocean (Urick, 1983) many marine animals, including marine mammals, use sound instead of light to gain information about their environment (Popper, 2003; Richardson, Greene, Malme & Thomson, 1995; Tyack & Miller, 2002). Cetaceans (whales, dolphins and porpoises) in particular are heavily dependent on sound to find food, communicate (including for reproduction), detect predators and navigate. Increasing mechanized use of the sea, such as for shipping, military activities, oil and gas exploration, and recreation (including cruises and pleasure boating), is increasing the amount of noise that humans introduce into the oceans, sometimes over very large distances (for details and discussion, see Hatch & Wright, this issue).

As cetaceans (as well as other marine mammals) are primarily acoustic animals, it appears likely that they will suffer more from exposure to noise than other species, including rats and humans - both species for which there is some information available about the consequences of noise exposure. It is reasonable to assume that marine mammals' reliance on sound has led to the evolution of a number of adaptive mechanisms to deal with natural noise, but whether those mechanisms are sufficient to compensate for the comparatively recent advent of anthropogenic ocean noise is uncertain (see Bateson, this issue; Weilgart, this issue). For example, cetaceans may have developed various strategies that are better than those employed by terrestrial species at averting or handling the problems created by masking (i.e., the drowning out of a signal of interest by noise). Regardless, their ability to cope with noise will still have limits. Indeed, anthropogenic underwater noise is a novel environmental element for marine mammals and some species have been exposed to it for only one generation (e.g., bowhead whale, *Balaena mysticetus*). This is a very short period in terms of

evolutionary time, making it very unlikely that any marine mammals have developed appropriate coping mechanisms (Rabin & Greene, 2002).

Here we attempt to increase our understanding of the effects of sound on marine mammals through the application of the current state of knowledge about noise, physiological stress and the influence of context, as outlined in Wright et al. (this issue, a) and detailed further in the other papers in this issue. Wright et al. (this issue, a) and the references therein should thus be considered the source for information included in this document unless other sources are cited. Working definitions for the terminology related to 'stress' are provided by Wright & Kuczaj (this issue).

Review of known effects of noise in marine mammals

Marine mammals have demonstrated various responses to specific noise exposures ranging from changes in their vocalizations (shifts in frequency, becoming silent, etc.) and displacement or avoidance (including shifting their migration paths) through alterations in their diving, swim speed, respiration or foraging behavior, to hearing damage and strandings (see Appendix 1). Weilgart (this issue) provides a summary of the known effects and the references therein offer additional details.

Hearing damage is not discussed here, as this is not a result of a noise-induced stress response. However, it should be noted that ear damage and other physical injuries would, if not immediately fatal, act as a variety of stimuli/stressors in their own right, each with the potential for producing a stress response. Thus, sound may generate both auditorily-mediated (i.e., heard) stimuli/stressors and non-auditory (i.e., those not directly resulting from sound perception through the ear) stimuli/stressors.

Noise and Stress in Marine Mammals

Two studies to date have investigated the physiological stress response to noise in captive marine mammals. Thomas, Kastelein & Awbrey (1990) exposed four captive beluga whales (*Delphinapterus leucas*) to playbacks of drilling noise but found no changes in blood adrenaline and norarenaline ("stress hormones", also known as epinephrine and norepinephrine) levels measured immediately after playbacks. Romano et al. (2004) exposed captive bottlenose dolphins (*Tursiops truncatus*) and a beluga whale to sounds from a seismic water gun and (for the bottlenose dolphins only) 1 s, 3 kHz pure tones and observed detrimental changes in some of the various hormones in the blood (for more details, also see Weilgart, this issue). However, the small sample sizes of these studies, their use of captive animals and other technical limitations mean that extrapolation of their results to wild animals should be done with caution (as recommended by Thomas, Kastelein & Awbrey, 1990). Additionally, there may have been some level of response to background noise levels that were not accounted for in the baseline measurements (see Baldwin, this issue).

It should also be noted that the epidemiological studies undertaken in humans examining physiological effects such as hypertension and coronary heart disease have been more consistent and conclusive than those considering the various stress hormones (see Clark & Stansfeld, this issue). Accordingly, it appears to be possible for noise to cause effects consistent with prolonged exposure to a stressor, such as hypertension and coronary heart disease, without necessarily displaying a consistent increase in stress hormones, such as glucocorticoids (GCs), and other metrics.

Three specific examples of the effects of sound on marine mammals are considered here in greater detail: the stranding of beaked whales (*Ziphiidae*) in association with military sonar exercises; the effects of shipping noise on beaked whale foraging and communication; and the various effects on the energy budget of odontocetes (toothed cetaceans) from disturbance due to whalewatching activities. Disruptions caused by whalewatching are likely to result from a combination of the actual presence of the whalewatching vessels as well as their noise. However, the effects of whalewatching and those of noise from moderately distant shipping are similar in many respects (see Lusseau & Bejder, this issue; Weilgart, this issue), suggesting that noise is probably the predominant source of impact of whalewatching. Furthermore, playback experiments have demonstrated that vessel noise alone can elicit responses in at least some species (e.g., manatees, *Trichechus manatus*: Miksis-Olds, Donaghay, Miller, Tyack & Reynolds, 2007).

Beaked whale strandings

Beaked whales have repeatedly mass-stranded a few hours to days after naval maneuvers during which military ships used midrange frequency sonar (Fernandez et al., 2005; Hildebrand, 2005)[1]. These whales were consistently affected by a new syndrome, never described in marine mammals prior to these events, consisting of extensive fat and gas bubble emboli: an ensemble of lesions most similar to decompression sickness in human divers (Fernández et al., 2005; Jepson et al., 2003). It is clear that the severity of emboli is the direct cause of death and that the constant temporal and spatial coincidence with naval exercises involving sonar designates these exercises as the cause of this new syndrome (Fernandez et al., 2005; Hildebrand, 2005). Recent studies have qualified beaked whales as the deepest diving mammals (down to 1.8 km: Tyack, Johnson, Aguilar Soto, Sturlese & Madsen, 2006) and have shown that these animals typically

[1] With regards to the debate over the frequency of strandings coincident with such activities, it should be noted that the discovery of just one dead body from a wild population is widely accepted in terrestrial biology to be always indicative of a wider problem, as it is easy to miss carcasses (p14-15 in Wobeser, 1994). This is likely to be even more true with marine mammals, where dead animals can be quickly scavenged upon, carried away by strong currents, or sink beneath the waves if they float at all. Deep diving marine mammals, such as beaked whales, that die at depth may be prevented from rising to the surface at all due to inhibition of decay-induced floating by the increased hydrostatic pressure (Allison, Smith, Kukert, Deming & Bennett, 1991). There are also fewer potential observers that are much more widely scattered than in terrestrial environments.

(although not always) follow a highly stereotyped diving pattern. This pattern consists of a deep dive followed by progressively shallower dives, apparently similar to the decompression stops used by human divers to avoid decompression sickness, although this is not necessarily their function (Tyack et al., 2006). Tyack et al. (2006) instead argued that the collapse of the whales' lungs at depth alleviates the need for such decompression dives.

In either case, behavioral disturbances, such as a startle or flight response, that disturb this highly stereotyped diving pattern, may overwhelm or circumvent the normal nitrogen buffering physiology of beaked whales and trigger the formation of nitrogen bubbles (i.e., 'the bends'), with the ultimate outcome being death from gas embolism and/or hemorrhage (see Cox et al., 2006; Tyack et al., 2006). While this remains the predominant theory, the physiological processes by which it occurs are still unknown (Cox et al., 2006) and other causes of death have also been suggested (see review by Rommel et al., 2006). For example, it has been hypothesized that instead of or in addition to indirect action via behavior disturbance, the navy maneuvers may directly induce the formation of nitrogen bubbles through a process termed "rectified diffusion" (Crum & Mao, 1996; Houser, Howard & Ridgway, 2001).

Additional support for the flight hypothesis is found in the similar response to novel sounds observed in other cetacean species. For example, Nowacek, Johnson & Tyack (2004) exposed foraging North Atlantic right whales (*Eubalaena glacialis*) tagged with a Digital Acoustic Recording Tag (DTag: Johnson & Tyack, 2003) to vessel noise, whale social sounds, silence, and a synthetic signal designed to alert the whales to the presence of vessels and thus reduce ship-strikes. Five out of six whales exposed to the alert signal responded by abandoning their foraging dive prematurely and executing a shallow-angled, high power (i.e., significantly increased fluke stroke rate) ascent and continued to swim at shallow depths, surfacing only to breathe, for the duration of the exposure: an abnormally long surface interval. This response was elicited by alarm sounds at received levels as low as 133 to 148 dB re 1 µPa at 1000 Hz. None of the whales exposed to ship noise playbacks responded at all.

There is also some indication that a stress response may be at least partly involved in reactions of beaked whales to military exercises involving sonar. Intracellular globules composed of acute phase protein have been found in the cells of six out of eight livers examined from beaked whales stranded in association with such exercises (tissue decay prevented detailed examination in nine others; Godinho/Fernandez, unpublished data). The globules are also found in the cytoplasm of hepatocytes in a range of examined cetacean species that stranded for many different reasons, including animals that are known to have died in 'very stressing' circumstances (e.g., anthropogenic interactions, such as bycatch; pathologies; or heat shock; Godinho et al., 2005). For example, globules have been seen in 26 of the 27 livers examined from bycaught harbor porpoises (*Phocoena phocoena*) in one study, with the only negative result being a neonate, possibly because of its immature metabolism (Godinho et al., 2006). Furthermore, only 7 of the other 11 examined porpoises that stranded for other or unknown reasons were

positive (Godinho et al., 2007; Godinho, unpublished data). It is acknowledged that live stranding itself is also likely to be an intense stressor.

The mechanism for the accumulation of acute phase proteins and the function that they have in the organism are not clear and there are various theories. For example, one hypothesis is that the vascular compromise (e.g., resulting from live-stranding) leads to acute liver congestion, which has been observed in 17 different cetacean species, that could in turn prevent the proteins from leaving the cell, where they thus accumulate and the globules are formed (Godinho et al., 2005; Godinho/Fernandez, unpublished data). However, for reasons not yet known, the globules in the above study vary both within and between species, as shown by electron microscopy and inmumohistochemistry (Godinho et al., 2007).

Hypoxia may also become a compounding issue for any marine mammal exposed to a stressor at depth, because oxygen consumption increases dramatically with increased heart rate as a result of release of catecholamines (adrenalin/epinephrine and noradrenalin/norepinephrine) through activation of the sympathetic nervous system (SNS: see Deak, this issue, Romero & Butler, this issue). The increase in heart rate is usually associated with a corresponding increase in respiration; however this is not possible at depth. This additional oxygen demand during pronounced SNS activation could therefore be particularly problematic for deep divers that are already living right on the physiological edge. Beaked whales are thought to be diving beyond their aerobic limits (Tyack et al., 2006; Aguilar Soto et al., 2006) so additional oxygen demands could force them to cut their dives short. Regardless, the combination of a psychological stressor (extreme noise that is perceived as threatening) with a more direct physiological stressor (fat and gas emboli or hypoxia) may have some potentially deleterious consequences (see Deak, this issue). Such a combination may have contributed to beaked whale deaths recorded in the mass strandings or unobserved at sea, as well as negatively affecting the health and fecundity of survivors of the events.

Although it is possible that a stress response contributed directly in some way to the lethal consequences resulting from exposure of beaked whales to military exercises involving sonar, it remains most likely that the fatalities resulted from the whales' flight response. In understanding this subtle difference, it is useful to consider the three successive stages of adaptation to insult (i.e., a stressor) presented by Selye (1946): alarm reaction; stage of resistance; and stage of exhaustion. An animal may respond at the very initial stages of a stress response (alarm) by fleeing (i.e., flight arising from the SNS response). If this action removes the animal from exposure to the stimulus then it may only lead to a short GC response (resistance), if any at all (see Deak this issue, Romero & Butler, this issue). However, if the flight response is lethally mal-adaptive, as appears to be the case with beaked whales and military sonar exercises, the exposure may still result in death, just not as a consequence of 'stress' *per se* (as in 'chronic stress' – exhaustion). It might also be possible that flight responses are increased if a stimulus is not only psychological, but also noxious (i.e., painful) by the direct effect of the noise pressure on the tissues and/or ear.

Shipping and masking of signals of importance for cetaceans

Shipping is most likely the main overall source of man-made noise in the marine environment (NRC, 1994, 2003) and masking has been identified as the primary auditory effect of vessel noise on marine animals (Southall, 2005). Most concern on this subject has traditionally focused on mysticetes (baleen whales), which communicate at the low frequencies typically associated with shipping noise (e.g., Payne & Webb, 1971). Consequently, it is noteworthy that ambient noise levels in the deep ocean at low frequencies have increased by 10-15 dB over the past 50 years due to motorized shipping (see Hatch & Wright, this issue, a and references therein). However, there is increasing evidence that modern ship noise can reach higher frequencies (e.g., up to 30 kHz: Arveson & Venditis, 2000; up to 44.8 kHz: Aguilar Soto et al., 2006) at distances of at least 700 m (Aguilar Soto et al., 2006). For example, there is a recording of a passing vessel on a DTag attached by suction cups to a Cuvier's beaked whale (*Ziphius cavirostris*) that demonstrates clearly that ship noise can mask ultrasonic vocalizations of odontocetes (Aguilar Soto et al., 2006). The high-frequency components of shipping noise may also be increasing due to the trend toward faster ships (Southall, 2005), because broadband cavitation noise (including the higher frequencies) generally increases with vessel speed (Arveson & Venditis, 2000).

Masking predominantly results from noise at similar frequencies to the signals of interest, although there may be some masking effects from "out-of-band" frequencies. Considering only in-band masking, the measured increase of up to 15 dB in low frequency noise due to shipping will greatly reduce the maximum functional range for signals in that band (Au, 1993). Similarly, calculations made be Aguilar Soto et al. (2006) demonstrated that the maximum communication range at frequencies used by Cuvier's beaked whales would be reduced by 82% (to 18% of its normal value) when exposed to a 15 dB increase in ambient noise at these frequencies, as was observed in the above-mentioned recording of a passing vessel. They also determined that the effective detection distance of echolocation clicks would also be reduced by 58% (to 42% of their normal range). Furthermore, if the current trend observed at low frequencies were applied to the higher frequencies component of ship noise, leading to a further increase of 15 dB by 2050, beaked whale communication at those frequencies would be reduced by 97% (to only 3 % of their 1950 maximum range) with each passing vessel (Aguilar Soto et al., 2006).

It is important to note that these calculations are based on observed increases in noise at high frequencies from a single passing vessel, that noise profiles from ships are highly variable and that high frequency noise attenuates much more rapidly than low frequency noise (see Hatch & Wright, this issue), limiting the area over which Cuvier's beaked whales would be affected. However, the trend towards faster boats, producing more cavitation and thus noise at higher frequencies, should also be considered. Furthermore, marine mammals that predominantly use low frequencies (e.g., baleen whales) may suffer similar reductions in the effective range of communication and other signals over much larger areas with additional reductions nearer a passing vessel. At the very low

frequencies used by many mysticetes (e.g., under 200 Hz), masking may occur in the majority of the oceans, especially in the northern hemisphere (see Hatch & Wright, this issue). Consequently, it would not be possible for these species to employ an avoidance strategy (see Bateson, this issue; Wright et al, this issue, a) because of the omnipresence of increased background noise from ships.

This reduction in effective distances for communication will almost certainly be associated with an increase in the ambiguity of information received. The reception of ambiguous signals can act as a stressor and/or potentially lead to consequences such as missed mating opportunities and unidentified predators (see Bateson, this issue). These consequences can be especially problematic for animals that are already compromised in some way (see Wright et al., this issue, a). For example, a whale that is already in a state of chronic stress is more likely to interpret ambiguous information pessimistically and act accordingly, such as not chasing as many possible prey items or wasting energy avoiding more possible predators.

Whalewatching and energy budgets

Interactions between boats and cetaceans are known to have a number of effects on marine mammals, although they may not even be consistent among different groups within the same species (see Lusseau & Bejder, this issue). For example, in Doubtful Sound, New Zealand, female bottlenose dolphins (*Tursiops* spp.) responded linearly to increased disturbance intensity (increased intrusiveness of boat interactions) by increasing dive duration (Lusseau 2003). Conversely, the males almost immediately adopted an avoidance strategy by substantially increasing their dive duration, but then did not increase it further with increasing interaction intrusiveness. There are a number of possible reasons for this difference between males and females, including the fact that energetic demands and consequences differ between the sexes (e.g., reproduction). Whatever the reason, it may be that the males' avoidance strategy spares them from higher noise exposure and disturbance rates, limiting their physiological stress response. Alternatively, the males may be falling into an ecological trap and the females may be better off if the physiological stress response is actually quite limited and they can still continue to forage effectively.

Although difficult, it is possible to estimate the energetic consequences of behavioral alterations and other avoidance strategies (see Lusseau and Bejder, this issue). For example, increases in time spent traveling and decreases in time foraging in northern resident killer whales (*Orcinus orca*) in response to disturbance by whalewatching traffic led not only to a relatively small (although not necessarily inconsequential) estimated increase in energetic demands of 3%, but also to a estimated reduction in energetic intake of 18% (Williams, Lusseau & Hammond, 2006). It should be noted that these are minimum estimates, as any costs associated with a stress response (physiological or psychological) or as a consequence of masking would be in addition to these figures.

Dolphins have been observed apparently shifting from short-term avoidance (local behavioral) to long-term avoidance (habitat displacement)

strategies in response to passing a threshold of disturbance from tourist boats (see Lusseau & Bejder, this issue). Presumably, at the point where this behavioral switch occurred, the dolphins determined in some way that the various costs associated with remaining in the disturbed habitat had become larger than the potential benefits. Consequently, when either habitat value is very high or habitat displacement is not an option (e.g., because boat interactions occur throughout the home range of the population), the costs of short-term avoidance strategies can accumulate and have serious implications for the population's viability. Alternatively, habitat displacement can also be very costly, as new habitats may have to be found or fought for, and knowledge of the area (e.g., prey locations) may have to be learned anew, the reduced habitat awareness potentially acting as a stressor in the meantime.

In either case, the various changes in the energy budget of an animal can, in turn, have a number of additional consequences. If the animal is still consuming more energy than it is using, it can continue to survive and grow, although unquestionably it will be less able to deal with anything that places additional energetic demands upon it, such as disease, migration and reproduction. As any remaining energetic surplus diminishes, a number of significant effects may begin to appear. For example, if the energy and resources available to a parent limits natal and/or parental investment, there will be various consequences for the health of the offspring (see Wright et al., this issue, a). Ultimately, if the animal is not able to consume enough energy to meet the increased demands, then it will begin to metabolize its lipid stores before it slowly starves to death or is forced to leave the area. In marine mammals the largest lipid store is the blubber layer, the mobilization of which will concurrently lead to an increase in contaminant levels in the blood (see Cumulative and Synergistic Effects). It should also be noted that hypoglycemia is a very powerful threat to homeostasis (i.e., a large stressor) that leads to rapid activation of stress responsive systems.

Something akin to the above may be occurring in both Shark Bay, Australia and Doubtful Sound, New Zealand. In Shark Bay a significant 15% decline in the relative abundance of dolphins was observed in an area where dolphin-watching activities occur, while a similar decline was not observed in an adjacent control site free from whalewatching activity (Bejder et al., 2006). In Doubtful Sound, the rate and frequency of perinatal deaths have significantly increased and the population abundance has decreased concurrently with a significant and substantial increase in the number of boats as well as the number of trips per boat (Lusseau, Slooten & Currey, 2006). The costs associated with boat interactions are such that females have to maintain homeostasis by reducing energetic investment in the only extrinsic factor they can manipulate: reproduction. It is not known how the males are faring in comparison.

Cumulative and Synergistic Effects

If context is important in controlling how noise induces stress responses in marine mammals and the various potential consequences thereof, it is crucial to consider the other potential stressors and anthropogenic activities that may be

influencing marine mammals at any given time. We will not go into detail about the various possible additional anthropogenic stressors here, as the U.S. Marine Mammal Commission (Reeves & Ragen, 2004) provided an effective summary of the majority of other threats to marine mammals. Its annual reports also provide more information (MMC, 2007 and previous).

The following threats will almost certainly contribute in one way or another to a reduction in the condition of individuals (i.e., an increase in the "allostatic load"), which might, among other things, make them more susceptible to other potential stressors, including noise. As mentioned above, a reduction in the overall condition can also influence the psychological outlook of an animal (see Bateson, this issue). Although acting primarily on individuals, the impacts of these stressors may filter up to the population level if they affect an individual's survival or fecundity. These threats include:

- climate change and other ecosystem-wide change;
- habitat loss or degradation through coastal and offshore development, fishery activity (including due to a reduction in available prey), inland development (that results in material washing downriver either immediately or over an extended period as a consequence of a change in land-use, such as clearing forests), etc.;
- disease;
- toxic algal blooms ; and
- contaminants (especially adrenocorticotoxic contaminants: see Martineau, this issue).

Several other threats may also induce stress responses in individual marine mammals. However, they generally result in removal of an individual from the wild (either through mortality or permanent capture). Consequently, these other threats do not usually contribute to any existing stress response an animal may be experiencing prior to an exposure to noise, but are more likely to act cumulatively with noise-related stress effects at the population level. These include:

- fisheries bycatch;
- ship strikes;
- whaling; and
- dolphin drives.

It is also possible for exposure to noise (through a stress response or other means) to make individuals more susceptible to any of the above additional threats, including the generally lethal ones. For example, Nowacek et al. (2004) concluded that the alarm stimuli mentioned previously were poor options in attempts to mitigate vessel collisions with North Atlantic right whales, since the reaction of most animals in the study likely placed them at greater risk of vessel collision. Consequently, it is very important for managers to consider this conclusion when making decisions regarding the introduction of other novel sounds into the habitat

of this highly endangered and declining species (Carretta et al., 2007), especially as the entire range for the species (the coasts of southern Canada to northern Florida) is an area that has a high concentration of shipping traffic.

Additionally, marine mammals, especially deep divers, are often thought to be pushing their physiological and anatomical limits as part of their normal behavior. They often subject themselves to considerable pressures as well as large changes in pressure on a regular basis, all while holding their breath for prolonged periods. The hypothesized anaerobic diving in beaked whales discussed above is one example of this. Another would be the bone damage seen in sperm whales (*Physeter macrocephalus*), which is thought to be a manifestation of the "bends" (Moore & Early, 2004). Such extreme conditions and related injuries could potentially be acting as additional injury stressors in their own right and might thus make marine mammals more susceptible to cumulative effects with other stressors, especially those thought to be mainly psychological in nature (see Deak, this issue).

Although information is generally lacking about how exposure to noise may ultimately affect marine mammals, it is possible to draw from the available information on how they respond to exposure to other stressors. Consequently, the following discussions examine the various effects of two of the most common threats to marine mammals: contaminant loads, with examples from pinnipeds and belugas; and interactions with fisheries, with an example from tuna-dolphin sets. These examples also provide some insight into the possible physiological and psychological condition that marine mammals might be in when exposed to noise (i.e., context), thus indicating potential pathways for cumulative interactions with noise exposure.

Contaminants

Marine mammals are especially susceptible to the effects of contaminants due to their high trophic level in the food web, long-life span, relatively late maturity and low reproductive potential. Many contaminants (or their metabolic products) bioaccumulate, meaning that they are found at increasing concentrations in the tissues of animals that occupy higher trophic positions. This process can lead to very high concentrations in long-lived adults or in newborns, when lipophilic contaminants are transferred from the mother through milk (see Martineau, this issue). This is because much of the contaminant load is stored in the blubber layer, which is partially metabolized for milk production (see Martineau, this issue). In many marine mammals, the first offspring stands to receive the highest dosage as the mother might have been bioaccumulating for many years before the first offspring is born, while only accumulating contaminant loads for a year or two in between pregnancies (Beckmen, Blake, Ylitalo, Stott & O'Hara, 2003). The blubber layer is also metabolized during periods of fasting or starvation (including times of migration, such as in mysticetes, or reproduction, such as in many pinnipeds), delivering the contaminant load to the fasting animal.

While contaminant loads compromise animals and are often associated with increased occurrences of various pathological conditions, different

contaminants can have very different effects. For example, some organochlorine compounds (OCs), such as dioxin-like polychlorinated biphenyls (PCBs), can cause apoptosis (i.e., self-destruction) of T-cells in the same way that a GC stress response does. Dioxin-like PCBs (and their metabolites) are also known to interfere with the size and effectiveness of the GC response (see Martineau, this issue). Other OCs metabolites, such as DDT's, are known to damage the adrenal cortex (see Martineau, this issue), which is also involved in the stress response.

Many substances (or groups of substances) may have a range of effects (see Kakuschke & Prange, this issue). For example, studies have linked high metal burdens with a large variety of impacts in marine mammals ranging from lower resistance to diseases, through harmful influences on the liver, kidney, central nervous system and reproductive system, to stillbirths. Metals also impair immune cell function through a number of mechanisms. Depending on the particular metal, its chemical bond, concentration, bioavailability and a host of other factors (including the age of the animal), the result can either be immunosuppression or immunoenhancement leading to hypersensitivity and autoimmunity (see Kakuschke & Prange, this issue). Studies on marine mammals from the North Sea have demonstrated a relationship between pollutant exposure and infectious disease mortality (Jepson et al., 2005). Higher levels of contaminants were also found in seals that died during the Phocine distemper virus epizootic that interrupted the increase of the harbor seal (*Phoca vitulina*) population in the Wadden Sea (Hall et al., 1992).

One population that may be particularly at risk from cumulative effects of noise and contaminants is the beluga whale population of the St Lawrence estuary. These beluga may already be quite compromised as they live in a historically highly polluted area (Fox, 2001; Lebeuf & Nunes, 2005; Lebeuf, Noëla, Trottier & Measures, 2007; Martineau, Béland, Desjardins & Lagacé, 1987; Muir et al., 1996; Muir, Koczanski, Rosenberg & Béland, 1996). For example, immunosuppressive contaminants most likely led to a high susceptibility to infections by opportunistic bacteria (i.e., bacteria that are part of the usual bacterial load in many animals and are not usually pathogenic) reported in the population (Martineau et al., 1988). High levels of shipping activity in the area is also exposing the whales to noise, with the imminent construction of a liquefied natural gas (LNG) terminal and planned natural gas exploration in the estuary set to raise noise levels further. As stressors related to contaminant loads are predominantly physiological and those related to noise are likely to be mostly psychological, increasing exposure to either also increases the risk of sickness-like conditions developing in the whales (e.g., neuroinflammation: Deak, this issue).

Tuna-dolphin fishery

The yellowfin tuna (*Thunnus albacares*) purse-seine fishery targets dolphins in the eastern tropical Pacific Ocean (ETP), as the tuna schools are associated with the dolphins. It should be noted that this makes it a somewhat unusual example of fisheries interactions, as marine mammals are not often targeted directly. However, there are a relatively large number of studies into the

effects of the ETP tuna fishery upon the dolphins, which is why it was selected as an example here.

Edwards (this issue) describes the process of chase, capture and release that the ETP dolphins are subjected to by the fishery. High mortality rates in the early days of the fishery (see Edwards, this issue) substantially reduced abundance in the two dolphin species most often involved (northeastern offshore spotted, *Stenella attenuata*, and eastern spinner, *S. longirostris*) to 20% - 30% of pre-fishery (1960) levels (Wade, Reilly & Gerrodette, 2002). Despite the substantial reduction of mortality rates to sustainable levels in 1990 due to the implementation of new fishing procedures, the populations do not appear to be recovering (Edwards, this issue; Gerrodette & Forcada, 2005).

Fishery-related stress responses (e.g., acute stress responses, “heat stress”, etc.) became a suspected limiting factor in both of the most commonly targeted species, as the number of sets (i.e., the number of times dolphins are disturbed, chased and potentially captured) has not decreased (see Edwards, this issue). The role of capture myopathy (a disease complex involving muscle damage that is associated with the combination of intense physical exertion and physiological stress effects of capture or handling, and which can in some cases have immediate or delayed fatal consequences: Spraker, 1993) in the lack of recovery is yet to be fully determined for a number of reasons (see Reilly et al., 2005). However, it seems possible that detrimental sub-lethal consequences arising from each individual’s stress response are playing an important role at the population level, at least through the more sensitive animals (see Edwards, this issue).

Great concern also surrounds the separation of calves from their mothers during fishery evasion, as the subsequent potential for unobserved calf mortality if not reunited promptly with their mother is quite high (Noren & Edwards, 2007). Even if calves are reunited, or do not suffer separation in the first place, there may still be serious consequences resulting from the experience. Neonates and young calves will be particularly sensitive to GCs because their brains are still developing, like all young mammals with immature nervous systems (see Romero & Butler, this issue). The purse-seine set experience, which appears to represent a severe but intermittent stressor to the ETP dolphins, may therefore have quite significant non-lethal effects on young calves. These would result from the double dose of GCs arising from the massive influx transmitted to them via the mother’s milk as a consequence of her physiological stress response, combined with those produce by their own stress responses. These excessive stress-chemical loads have the potential for generating both acute neurological damage and long-lasting neurological re-programming in any nursing calves involved in evasion of a tuna purse-seine set in the ETP (see Sapolsky, 1992).

The various studies investigating fishery-related stress effects in ETP dolphins (e.g., changes in blood and muscle chemistry; damage to various organ systems, etc.: Reilly et al., 2005) illustrate the wide variety of impacts that can accompany an escape response (possibly acoustically-initiated) to an impending threat. At the present time, it is impossible to determine whether physiological effects of the whole chase/capture/escape experience are either short- or long-lived.

In general, physiological effects related to the stress response are likely to be reasonably short-lived for otherwise healthy adults in situations where even fairly intense natural stressors (e.g., predation attempts) occur only once every few weeks (see Dallman & Bhatnagar, 2001). Although the rate of occurrence may be similar in the ETP dolphins (see Edwards, this issue), surviving calves and fetuses in utero may still suffer a range of long-term impacts as they are exposed to maternal cortisol (if not also their own) each time their mother has been stressed during the chase-hunt, as discussed above. Some of these impacts may persist until the animals are adults and can include the development of an abnormal stress response system (e.g., Kapoor, Dunn, Kostaki, Andrews & Matthews, 2006). However, adults could also be affected as the chase process is characterized by an intensity and duration never encountered in nature (e.g., predators get tired and remain silent in contrast to motor vehicles). The set attempts likely involve both physiological and psychological stressors, such as noise and intense exercise, which may lead to sickness-like conditions in the exposed individuals (see Deak, this issue). Furthermore, the extent to which the stress response is involved in the initiation of capture myopathy has not yet been identified (see Reilly et al., 2005). The potential also exists for some serious cumulative impacts in dolphins of any age if they are in any way compromised prior to attempted purse-seine sets.

Acclimation in Marine Mammals

There is very little (if any) evidence of acclimation (as defined in Wright & Kuczaj, this issue) in marine mammals in the wild, although this does not mean that it does not occur. Many references to “habituation” have not demonstrated that the observed reduction in behavioral response is associated with a reduction in the physiological stress response and processes other than acclimation may explain the results (see Wright et al., this issue, a). For example, the observed reduction in behavioral responses of ETP dolphins when in the purse-seine net (i.e., originally they appeared to panic, but now seem to wait relatively passively until released), could indicate acclimation, but more likely indicates learning, and/or natural selection instead. It is important to recognize that these processes can change behavior in adaptive ways that nevertheless continue to be accompanied by a full internal physiological stress response.

Thus, apparent behavioral tolerance of noise in marine mammals cannot be automatically interpreted as acclimation (see Beale, this issue). However, there has been little opportunity for adaptation to noise to occur through natural selection in many marine mammals because of their long lifespans (except if there are lethal consequences of exposure to the stimulus: see below). This is especially true in large whales, as the increases in noise in the oceans may have occurred in a single lifetime. Consequently, an observed reduction in behavioral responses in marine mammals may often reflect a learning process, whereby repeated exposures to a stressor leads to reduced or altered behavioral responses, but not necessarily reduced physiological responses. The animals learn either how to behave to reduce any negative effects or that the stressor is not as noxious as it first appeared. However, the stimulus is still perceived as a stressor. It is then possible that this

information and any associated behaviors are conveyed to the next generation through cultural transmission.

With regards to the apparent acclimation in ETP dolphins to capture by the purse-seine the tuna-dolphin fishery, it is important to separately consider the capture by itself, as well as the whole purse-seine set experience collectively. It is unlikely that physiological acclimation to the whole purse-seine set activity occurs for several reasons. First, most ETP dolphins are only chased about once per month (and captured less often still; see Edwards, this issue) which is probably not often enough to lead to acclimation given the probable size of the stressor involved (although these catch frequency estimates are merely averages: some dolphins will evade sets more often, some will evade less often). Second, the dolphins still respond to capture efforts by fleeing immediately upon perception of an impending set (which, as an aside, is the cause of capture myopathy in free-ranging ruminants: Spraker, 1993). Third, they still engage in prolonged escape behavior after getting out of the net (also involved in capture myopathy: Spraker, 1993). Fourth, ETP dolphins in the more heavily fished areas exhibit escape reactions in response to all approaching big boats while responding less to vessels not approaching them directly (Au & Perryman, 1982; Hewitt, 1985), even though the combination of sounds that signal an approach are unlikely to be identical due to vessel and engine variety. Fifth, the number of ETP dolphins has been severely reduced. Finally, the social structure of the dolphins appears to have changed since the onset of the fishery as the average school size has decreased. Although the last two pieces of evidence do not necessarily reduce the likelihood that acclimation is at work, they suggest that other explanations for any tolerance displayed may be more likely, such as half a century of selective pressure (approximately four generations in these species: Myrick, Hohn, Barlow & Sloan, 1986).

It may be that the dolphins have acclimated somewhat to their temporary capture in the purse-seine nets, although the frequency of exposure remains a major issue (i.e., it may not occur frequently enough for acclimation to take place). Consequently, it appears more likely that the dolphins' relatively calm behavior reflects learning or selection, rather than acclimation. Furthermore, the dolphin's prolonged escape response after release from the net also implies that the animals have not acclimated to either capture or the full set experience. For example, it may be that, having experienced enough sets to realize that there is nothing they can do until the backdown maneuver (see Edwards, this issue), the dolphins may have learned to behave more calmly in the net, although they are very likely not internally calm at all. In comparison, learning to ignore the chase is unlikely as the result is uncertain: there is the possibility of either escape or capture.

As mentioned above, selective pressures may also be involved, fuelled by variation in individual susceptibilities to in-net mortality, the stressors of chase and capture, and possibly also capture myopathy. These factors, in combination with the fact that fishermen actively target larger schools, may have very quickly selected for dolphins that aggregated in smaller groups and behaved most appropriately to the sets. Consequently the reduction in apparent agitation in the net could be a result of the massive and efficient loss of the more sensitive individuals (potentially through unobserved capture myopathy in addition to direct

mortality in the net). Given the dramatic reduction in abundance, it appears reasonable that the remaining dolphins are those best 'suited' to surviving purse-seine sets.

Similar processes are also at work in modern fisheries. Observed effects include a reduction in the average size of collected fish, due to slower growth rates (within any given species), because only larger fish are big enough to be legally captured (see Conover & Munch, 2002). Under those conditions, fish that mature at a smaller size (either by growing slower or maturing earlier) have a selective advantage. However, smaller breeding animals may also have less resources and energy available to invest in reproduction, which could explain the associated reduction in egg size (Conover & Munch, 2002).

North Atlantic right whales

There are several possible explanations for the reactions of North Atlantic right whales to shipping noise and alarm sounds as discussed above (Nowacek et al., 2004). Two of the most likely are: 1) the whales have not learned to react to ship noise sounds appropriately (i.e., by swimming away), while they do not distinguish alarm sounds from those emitted by possible predators, such as killer whales; and 2) the whales have acclimated, wrongly, to continuous ship noise so that they do not react even at levels likely indicating danger of collision, while they do react to novel noise sources such as alarm sounds.

It is therefore no surprise that the following statements (which we demonstrate below are likely incorrect), with their associated management ramifications, are common in attempts to further understand why right whales do not appear to use sound to avoid ship strikes: 1) North Atlantic right whales appear to have "habituated" to ship noise, thus increasing the numbers and/or types of vessels in their coastal habitat does not constitute a potential threat to this endangered species; and/or 2) North Atlantic right whales have "habituated" to ship noise thus introduction of other industrial sounds to their coastal habitat does not constitute a potential threat to this endangered species.

If indeed right whales have actually acclimated to the constellation of low-frequency dominant sources in their environment, then the probability of a stress response occurring as a direct result of repeated exposure to industrial and vessel noise may be decreased. However, masking and signal discrimination would continue to create problems for right whale communication efficiency (and thus may indirectly lead to a stress response). In fact, the occurrence of ship strikes and entanglements in right whales may indicate that there is so much noise (or the noise has caused enough hearing damage) that the whales are unable to hear or locate anything except the loudest of sounds.

If acclimation is not occurring and a repeated and/or continuous stress response is being maintained by right whales due to a high incidence of exposure to acoustic and other stressors, then the observed lack of behavioral response in right whales may be due to various other factors. First, their physiological response to vessel noise exposure may not result in changes in behavior. Second, the animals may be less likely to respond if they are in poor overall health, perhaps as

chronically stressed individuals (see Beale & Monaghan, 2004). Third, any changes in behavior that do occur may be too subtle to have been detected, or have not been correctly identified (and thus recorded) by researchers due to a lack of understanding regarding the context for those changes. Finally and perhaps most likely, the whales just can't afford to react to ship noise as it happens all the time in the area they have to be in, so they carry on regardless (e.g., they have learned not to respond to the noise).

Given the lack of evidence for acclimation in this situation and in studies of other animals, as well as the discussion of acclimation above and in Wright et al. (this issue, a), it seems quite unlikely that North Atlantic right whales have acclimated, as defined, to loud sources of low frequency sound in their environments,. Consequently, the likelihood that the apparent tolerance is due to one or more of the other possible reasons needs to be considered in efforts to manage anthropogenic impacts on the species.

Conclusions

It is clear that noise can act as a stressor to marine mammals. If marine mammals react in a similar manner to other animals (including mammals) that have been studied in controlled circumstances, repeated and prolonged exposures to stressors (including or induced by noise) will be problematic for marine mammals of all ages. The resulting extended stress response may then lead to a range of issues including, but not limited to, suppression of reproduction (physiologically and behaviorally), accelerated aging, and sickness-like symptoms. Acclimation to such exposures seems unlikely for a number of reasons, including differences in the perceived stimuli, changing context, time-scales, etc. Examples of apparent "habituation" may instead indicate selection, or learning without acclimation. Learned responses, like acclimation, are highly dependent on the predictability of stimuli. However, learned responses, like other possible mechanisms of adaptation but unlike acclimation, may or may not reduce the magnitude of the physiological stress response.

Regardless, acclimation or some other apparent tolerance of a noise may have various pernicious effects, such as limiting the ability of the animals to react to actual threats. These may, in some cases, have lethal consequences (e.g. right whales' lack of reaction to ship noise, possibly resulting in collisions), but the majority of knock-on outcomes are likely to be physiological (e.g. dolphins approaching acoustic pingers, risking receiving noise levels with the potential to cause temporary hearing impairment, also known as a temporary threshold shift – TTS) or psychological (e.g., annoyance) effects that are not immediately lethal. However, physical injuries and other consequences of noise exposure may then act as additional stressors upon marine mammals. For example, if masking leads to increases in information ambiguity, or group or mother-calf separation, animals may suffer from anxiety as a result. Masking by increasing noise levels would be roughly analogous to a human trying to see through increasingly dirty glasses. Eventually, the lack of reliable acoustic information prevents marine mammals, especially cetaceans, from 'seeing' their environment, essentially leaving animals

blind. Confounding the issue further, maladaptive efforts to avoid a noise can also indirectly lead to detrimental outcomes for marine mammals.

In addition to the myriad possible affects from noise exposure that can all interact together, it is important to consider the potential cumulative effects of multiple anthropogenic stressors. For example, should the energy balance of a marine mammal become negative (due to disturbance or disease, etc.) lipids and the lipophilic contaminants stored within them are mobilized from the blubber. The release of these contaminants into the circulation not only constitutes *de facto* a second exposure to the individual concerned during a period of nutritional challenge, but mothers also expose newborns through transfer in milk (Martineau, Béland, Desjardins & Lagacé, 1987; Tornero et al., 2005; Wells et al., 2005). Affected animals would then be less able to respond sufficiently or appropriately to any additional stressors.

Further contextual complications may be involved in beaked whales and other deep diving marine mammal species, as their normal behavior may put them already at the limits of their physiological capabilities. Cumulative and synergistic effects can be assessed in different ways, but any such assessment should be undertaken very cautiously as synergistic effects can be very unpredictable. The following hypothetical chain of events illustrates the complexities of cumulative and synergistic effects in which noise-related stress may have deleterious consequences for a marine mammal.

A young male sperm whale in the Gulf of Mexico is exposed to nearby shipping noise and experiences a stress response. This response is more extreme than it would otherwise be as the young animal was exposed in utero and immediately after birth to high GC levels transferred through the placenta and milk from its mother, when she was undergoing a stress response. Despite a flight response sending the whale to the surface, the animal is lucky and avoids a potentially lethal ship strike. After repeated non-lethal exposures to that (or similar) sounds, the whale learns that the noise is not followed by any serious immediate consequences and so it stops responding behaviorally. Despite this, the animals GC levels remain high, because it has not acclimated to the passing ships and also because of its altered HPA axis. The resulting GC levels cause slow growth. If a ship passes nearby, the whale might experience TTS and/or the disruption of sleep, as well as interference in communication and foraging resulting from the masking. From time to time these problems annoy or agitate the whale and produce their own stress responses, depending on the exact situation.

As it ages, the sperm whale builds up a contaminant load over and above the dose it received as a calf from its mother. It also begins to suffer from bone damage related to diving. Frequent exposure to a variety of anthropogenic noise sources continues to disrupt foraging efforts and begins to directly affect its body condition and psychological outlook. A compromised immune system allows an infection to take hold and the whale begins to lose weight. Blubber is metabolized and the whale is exposed to the mobilization of its contaminant load. A seismic survey begins in the area and the resulting total exposure over the next several days exhausts the supply of components for GC production and pushes the combination of psychological and physiological stressors beyond a certain threshold, resulting

in neuroinflammation and other sickness-like conditions. In the face of this worsening condition, the sperm whale beaches itself and dies with no particular cause of death apparent.

Many of the effects discussed in this paper can be incorporated into population viability assessments and other models used by managers in their decision making process. There are a small number of studies in marine mammals where controls have been appropriately established that are beginning to provide some of the information required for this. However, for the majority of marine mammals, accounting for these effects will require some assumptions about the implications of the various stress responses on fecundity and survivorship, as the data that concern these parameters are not available. Fortunately, extrapolation from data in other species (and possibly even from other animal groups) appears reasonable, because the physiological stress response is highly conserved across the many different species that have been studied to date.

In addition to the more general conclusions and findings offered by Wright et al. (this issue, a) pertaining to stress responses to noise, we suggest that the following findings and recommendations (presented in no particular order) are especially important with regards to marine mammals. We propose that marine mammal managers and scientists consider these findings and specific recommendations when planning research or management actions (e.g., in assessments of environmental impact).

Findings

1. "Stress" is a very important concept to consider in managing the impacts of anthropogenic activities on marine mammals, yet definitions vary greatly among specialists as well as laymen. There is also much confusion over the use of the related term "habituation" (see also Wright et al., this issue, a).

2. Given the physiological, psychological, behavioral and ecological information presented, considered and discussed in this issue, the conclusions that have been drawn from them, and the other findings presented here, it is reasonable to assume that anthropogenic noise, either by itself and/or in combination with other stressors, can reduce the fitness of individual marine mammals and decrease the viability of some marine mammals populations.

3. The physiological stress response is highly conserved among those animal species in which it has been studied (including a few marine mammal species: e.g., Martineau, this issue) and thus extrapolation to marine mammals is reasonable.

4. Very young individuals (and fetuses) are particularly sensitive to the neurological consequences of the stress response and can suffer permanent neurological alterations as a result. Similarly, deep diving marine mammals may be particularly sensitive to noise as a stressor given that many marine mammal species are thought to live close to their physiological limits.

5. Acoustic masking may act in several ways to induce stress responses in marine mammals. These may include but are not limited to: reducing the range of signals important for communication and finding of prey; reducing the clarity of received signals; and inducing anxiety and annoyance. These combine with potential effects on foraging efficiency and social cohesion, with possible subsequent effects on reproductive success and survivorship.

6. Scientists need to study stress responses in marine mammals and their epidemiological and psychological consequences. Most immediately, classical stress measures will be needed to marry the extrapolations from studies in other animals with observed behavioral responses. Such studies will be complex and require defining concepts such as "need" and "risk" in terms of the decision making process in the often highly developed brains of marine mammals. Adequate techniques to obtain physiological data (e.g., heart rates, cortisol levels, adrenal morphology and other information) are also required. Implicitly, these various techniques should be the least invasive as possible to minimize additional stressors. It is also very important to include a comparison or control group (i.e., mammals not exposed) or baseline data (i.e., data from animals before they became exposed). However it is acknowledged that non-exposed populations of marine mammals are likely to be quite rare.

Research Recommendations

1. Efforts should be made to collect information on the dynamics of stress-related chemicals (particularly cortisol) in cetaceans and other marine mammals. Collection from blood plasma may not currently be practical for assessing the effects of most stressors, given that animals would generally need to be captured, which is a complex task when handling large marine mammals. Currently available methodologies that do not require capture involve the collection of feces from free-ranging animals (either after visual detection or through the use of the canine sense of smell: Hunt, Rolland, Kraus & Wasser, 2006), or the collection of mucus expelled during exhalation (Hogg, Vickers, & Rogers, 2005). The time between exposure to a stressor and the increase in cortisol levels in the various samples need to be considered. The period from stressor exposure to increased cortisol levels is very short in blood samples. In contrast, cortisol levels in samples from feces will be averaged between bowel movements, and those from samples of respiratory mucus exhaled with a breath are likely to take 10-15 minutes or more to reflect the impact of a stressor. Cortisol levels in fecal and mucosal samples are likely to be more variable than in blood samples, but the less invasive collection methods are less likely to trigger a stress response of their own, allowing the techniques to be used to study the effects of other stressors, such as noise. Such investigations would need to be carefully constructed, with well-designed controls. Efforts should acknowledge that is not possible to distinguish between acute and chronic stress responses in blood, fecal and mucosal

samples without a time-series. It should also be noted that animals often expel fecal matter as part of a sympathetic response when they become stressed. In addition, GC levels are fairly variable from one individual to another, so baselines will be needed for each individual against which to measure relative stress levels.

2. Opportunistic collection of information about the level of stress-related chemicals from various tissues and stores in stranded and bycaught animals should also be undertaken. Investigations should also be made to see if it is possible to obtain these chemicals from skin and/or blubber. If so, the amounts in the blubber may be long-term average levels, providing indication of cumulative stress responses for marine mammals over the long-term. However, there is some active exchange between the blubber and the blood, so levels of stress-related chemicals in the different layers of the blubber may reflect shorter-term averages, although there may also be high variability both between and within species. Post mortem examinations of stranded marine mammals should also record other pathologic effects related to exposure to stressors. For example, the size and weight of, as well as the presence of any lesions on, the adrenal glands should be noted. Chronic stress leads to chronic stimulation of the adrenal cortex by adrenocorticotrophic hormone (ACTH). In turn, ACTH chronic stimulation results in adrenocortical hyperplasia (increased number of cells) or hypertrophy (increased size of cells) necessary to allow for sustained overproduction of GC and possibly catecholamines. These morphological changes are seen grossly as increased size and weight of the adrenal glands (Clark, Cowan & Pfeiffer, 2006; Dorovini-Zis & Zis, 1987; Lair, Beland, De Guise & Martineau, 1997; Nemeroff et al., 1992; Ulrich-Lai, Figueiredo, Ostrander, Choi, Engeland & Herman, 2006). Furthermore, the presence of acute phase proteins in different organs, such as the liver or skin, could indicate recent exposure to an intense stressor. This could also provide important information on “normal” background levels of the proteins in different species, which would be very useful in developing further studies on the evaluation of stress response in marine mammals.

3. Skin biopsies, sampled from live cetaceans with minimal disturbance, have yielded unique information about genetics and contaminants (Fossi et al., 2004; Hobbs et al., 1998). Not only is skin a major target organ for cortisol (and thus cortisol is present in the skin) but skin is also a site of cortisol synthesis (Slominski, Wortsman, Tuckey & Pau, 2007). Measurement of cortisol levels in skin biopsies carried out on free-ranging cetaceans should be explored, although the possible effects of any chase and handling required to obtain the samples needs to be considered. It may also be possible to obtain this information through collection of sloughed skin from the water in the wake of a whale, which could largely circumvent this problem.

4. Given that studies on cortisol in humans have generated mixed results, efforts should also be made to study epidemiological effects in marine mammals, especially in the wild.

A Strategy for Managing the Impacts of Noise on Cetaceans in the Face of Uncertainty

Based on the available evidence, a non-trivial negative impact of noise-related stress responses on vital rates is expected for many marine mammals, especially cetacean species, although there is still substantial research needed to determine the magnitude of impacts. The Bayesian approach outlined by Wintle (this issue) is likely to be viable, logical and coherent in quantifiably extrapolating noise-related impacts from other mammals to cetaceans, given the highly conserved nature of stress physiology.

There are clearly grounds to justify initiating an adaptive noise mitigation strategy based on the available evidence and theory concerning the impacts of both acute and chronic noise on humans and terrestrial mammals, as well as the sparse data available on cetacean noise impacts. Potential noise exclusion zones should be identified as a matter of urgency. However, in order to commence the learning cycle, it is essential to measure vital rates under both noisy and noise-excluded management conditions so that the specific benefits of noise exclusion/mitigation can be better understood. Until an adequately stratified study of cetacean vital rates under various levels of noise impacts can be established, the value of noise mitigation efforts will be clouded by uncertainty. It is acknowledged that this will be a difficult and lengthy task.

A detailed description of a suitable management and monitoring strategy to assess the impacts of noise and noise mitigation on cetacean vital rates is beyond the scope of this issue. However, some general recommendations to those managing the impacts of noise on marine mammals can be made. We recommend that:

1. An expert working group should be convened with the specific goal of identifying noise impacts on cetacean (or other marine mammal) vital rates, using all available data and systematically integrating knowledge of impacts from other species.

2. Areas suitable for broad-scale noise exclusion/reduction should be identified.

3. Where possible, environmentally similar areas that cannot have noise exclusions/reductions should also be identified.

4. Based on the results of expert working groups, models should be developed to predict likely population responses to noise mitigation strategies.

5. Levels of noise should be closely monitored and measurement of cetacean vital rates initiated in all locations.

6. The relationship between noise level and cetacean vital rates may then be updated and predictions about future gains modified to reflect the new information.

7. Monitoring of vital rates should be maintained to enable better decisions about future allocation of mitigation efforts.

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Appendix 1

The following table compares some of the scientific evidence for physiological, psychological and behavioral responses to various stressors with some of the known behavioral effects of noise in marine mammals and other species. It should not be considered an exhaustive list. It should also be noted that authors contributed predominantly to the rows in which they had expertise. This has given rise to different application of the columns "mechanisms', 'observations' and 'consequences'. For example, in some cases a physiological stress response is listed as a consequence, while in others the whole response is, or elements of it are, listed as either a mechanism and/or an observation. These inconsistencies highlight the diverse approaches in the various disciplines and may arise from the different methodologies available to the scientists in the various fields and from one species to another. They should therefore not necessarily be interpreted as inconsistencies in the actual results. Finally, some of the potential impacts resulting from noise exposure discussed in this and other papers in this issue have been added to many of the marine mammal entries as possible consequences. Items in italics are uncertain and those marked '*???*' are unknown.

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
General	Chronic/cumulating acute non-specific (e.g., contaminants, predators, etc.)	Chronic GC response.	Increased GC levels prior to eventual fall-off.	Chronic: Disregulation of glucose and metabolism; Stress-induced dwarfism; Behavioral changes (context dependant); Reproductive disruption (psychological and physiological); Immune-suppression.	McEwen & Goodman, 2001; Sapolsky, Romero & Munck, 2000
Guinea pigs	Maternal separation	*Probable increase cytokine expression?*	See consequences.	Initial anxiety followed by 'sickness'.	Hennessy et al., 2007
Lab rat	Footshock	Increase cytokine expression and microglial activation and CNS.	See consequences.	'Sickness' behavior, Neurodegeneration.	Deak, Bellamy & D'Agostino, 2003; Nguyen et al., 1998; Plata-Salaman et al., 2000; Shintani et al., 1995
Lab rat	White noise (experimental)	Release of corticosterone; Intestinal inflammation; Microvasular damage; Transient increase in blood pressure.	Redness around eyes and on back of neck. Also see mechanisms.	Non-selective molecular exchange intestine-blood stream leading to septicemia.	Baldwin, Primeau & Johnson, 2006; Baldwin & Bell, 2007; Burwell & Baldwin, 2006; Windle et al., 1998

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
Humans	Aircraft noise, road traffic noise, community/ambient noise and occupational noise	Physiological responses: Hypertension; Coronary heart disease (CHD).	Increased systolic BP or hypertension diagnosis; Increased rates of CHD.	Problems with hypertension leading to heart disease; CHD; Annoyance.	Babisch, 2006; van Kempen et al., 2002; Babisch, 2000
Humans	Aircraft noise, road traffic noise, community/ambient noise and occupational noise	Physiological responses in adults and children: Stress hormones in the endocrine system (cortisol, adrenaline, noradrenaline).	Increased levels of these hormones being measured in urine and saliva.	Evidence linking stress hormone levels to health impairment is lacking but raised levels may impact of peripheral vascular system; Annoyance.	Babisch, 2003 (meta-analysis)
Humans	Aircraft noise, road traffic noise, community/ambient noise and occupational noise	Sleep disturbance.	Increased awakenings due to noise exposure; Taking longer to fall asleep; Evidence that habituation (as defined by Clark & Stansfeld, this issue) to exposure occurs.	Performance effects; Mood effects; Health effects associated with sleep disturbance; Noise during sleep may also stimulate heart rate; Annoyance.	Basner & Samel, 2005; HCN 2004; Miedema & Vos, 2007
Humans	Aircraft noise, road traffic noise, community/ambient noise	Psychological health.	Dose-response relationships between aircraft noise and depressiveness in adults; Some child studies have found increase reports of poor psychological health but others haven't.	Poor psychological functioning, wellbeing, quality of life.	Haines et al., 2001; Haines et al., 2001; Hiramatsu et al., 2000; Lercher et al., 2002; Stansfeld et al., 2005
Humans	Aircraft noise, road traffic noise, community/ambient noise	Children's cognition.	Impaired reading and short-term and long-term memory.	Impact on children’s learning and schooling.	Clark et al., 2006; Haines et al., 2001; Haines et al., 2001; Hygge, Evans & Bullinger, 2002; Stansfeld et al., 2005
Wedge-tailed eagle	Forestry operations *(chainsaw noise??)*	Fleeing.	Nest abandonment.	Breeding failure (for that year).	Mooney & Holdsworth, 1991; Mooney & Taylor, 1996

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
Robin	Ambient Noise	*Masking?*	Nocturnal Singing.	Increased risk of predation; Sleep deprivation.	Fuller, Warren & Gaston, 2007
Starlings	Barren cages	Anxiety.	Risk averse foraging.	Reduced intake of food.	Bateson & Matheson, 2007; Matheson, Asher & Bateson, 2007
Turnstones	Human presence	'Decision' based on context.	Variable alert and evasive depending on context.	Probably minimal (in this case).	Beale & Monaghan, 2004a
Kittiwake	Human presence	*Sympathetic responses?*	Variable: Elevated heart rate; Sleep/Awake proportion.	Variable: Increase nest failure (debatable long-term impact).	Beale & Monaghan, 2004a, 2004b
Wood lark	Human presence	'Decision' based on context.	Variable: nest selection; Disturbance avoidance.	Complicated: Potentially population level effects.	Mallord et al., 2007
Seals	Pollutants	Immunmodulation by metal (pollutants); Activation and/or suppression of lymphocyte reactions; Influence on cytokine expression.	See consequences.	Immunological dysfunction like hypersensitivity or immunosuppression; Changes in susceptibility to infection diseases.	Bennett et al., 2001; De Swart et al., 1996; Kakuschke et al., 2005; Kakuschke et al., 2006; Lalancette et al., 2003; Pillet et al., 2000; Ross, 2002; Siebert, et al., 1999
Cetaceans (15 different species)	Live stranding	*Vascular compromise?*	Accumulation of acute-phase proteins in hepatocytes; Acute liver congestion.	Unclear.	Godinho et al., 2005
Beluga	(Mutagenic) Pollutants	Activation and/or suppression of lymphocyte reactions; Consistent with GC and/or toxic effects of contaminants; Effects of mutagenic pollutants; PCB toxicology.	See consequences.	Immunological dysfunction in vitro & in vivo; Increase opportunistic bacterial infection; Adrenal cortex degeneration/proliferation; Cancer; CYP induction.	Buckingham, 2006; De Kloet et al., 1998; Escriva et al., 1997; Hahn, 2002; Herold, McPherson & Reichardt, 2006; Matsumara, 1995; McMillan et al., 2007; Remillard & Bunce, 2002; Wang et al., 2003; Williamson, Gasiewicz & Opanashuk, 2005

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
Eastern Tropical Pacific (ETP) dolphins	Purse-seine fishery (Acoustic cues associated with imminent capture attempt)	Set evasion.	Increased swim speed (2-3 m/sec); Leaping out of the water to breathe; Evasive maneuvering; Likely separation of mothers and young calves.	Energetic cost; Physiological stress response; School (social) disruption; Foraging disruption, Calf separation, Calf mortality, Capture myopathy.	Edwards, 2002, 2006; Myrick & Perkins, 1995; Noren & Edwards, 2007; Noren, Biedenbach & Edwards, 2006; NRC, 1992; Reilly et al., 2005; Weihs, 2004
ETP dolphins	Fishery capture	Wait for release.	Relatively calm milling and schooling in section of net far from vessel and close to section of net section where backdown channel will form.	Reduced net entanglement – therefore reduced in-net mortality; Interrupted social and foraging activities.	Edwards, 2002, 2006; Myrick & Perkins, 1995; Noren & Edwards, 2007; Noren, Biedenbach & Edwards, 2006; NRC, 1992; Reilly et al., 2005; Weihs, 2004
ETP dolphins	Release from purse-seine	Escape.	Prolonged (90 minutes) high speed (3-4 m/sec) escape swimming.	Energetic cost; Physiological stress response; School (social) disruption; Foraging disruption, Calf separation; calf mortality; Capture myopathy.	Edwards, 2002, 2006; Myrick & Perkins, 1995; Noren & Edwards, 2007; Noren, Biedenbach & Edwards, 2006; NRC, 1992; Reilly et al., 2005; Weihs, 2004
Harbor porpoise	Bycatch	*Suffocation?*	Accumulation of acute-phase proteins in hepatocytes; Death.	Death by suffocation.	Godinho et al., 2006
Marine mammals	Tonal/impulsive noise	Temporary Threshold Shift (TTS) in hearing.	TTS.	Compromised food-finding, navigation, and communication; Increased risk of predation	Finneran et al., 2002; Kastak et al., 1999; Schlundt et al., 2000
Cetaceans	Seismic surveys	*???*	Lower sighting rates; Avoidance of seismic array; Less feeding.	Energetic consequences.	Stone & Tasker, 2006
Coastal odontocetes	Chronic intermittent boat interactions	Flight response.	Behavioral budget alteration.	Reduced reproductive success; Decreased population viability; Habitat displacement.	Bejder, 2005; Bejder et al., 2006; Lusseau, 2004; Lusseau, Slooten & Currey, 2006

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
Coastal odontocetes	Boat interactions	Masking.	Reduce foraging time.	*Decreased survival rates?*	Erbe, 2002; Lusseau et al., submitted; Williams, Lusseau & Hammond, 2006
Small odontocetes	Seismic surveys	*???*	Faster swimming.	*Energetic consequences?*	Stone & Tasker, 2006
Bottlenose dolphins	Boat approach	*Masking of signals of interest for social communication and foraging?*	Higher whistling rate.	*Time/energy costs?* *Information ambiguity?*	Buckstaff, 2004
Beaked whales	Shipping noise	Masking of signals of interest for social communication and foraging.	High noise levels.	*Energetic consequences?* *Information ambiguity?*	Aguilar Soto et al., 2006
Beaked whales	Military exercises	Gas and fat embolism (hypothesis).	Atypical mass stranding (land and/or sea); Gas and fat embolic pathology.	Individual deaths; Possibly local population displacement or death.	Fernández et al., 2005; Jepson et al., 2003
Beaked whales	Shipping noise	*???*	*Activation of evasion mechanisms??*	Possible change in diving behaviour leading to reduction in foraging efficiency; Reduction in communication range.	Aguilar Soto et al., 2006
Killer whale	High boat traffic	*Masking of signals of interest for social communication and foraging?*	Increased call length.	*Time/energy costs?* *Information ambiguity?*	Foote, Osborne & Hoelzel, 2004
Killer whale	Acoustic Harassment Devicess	*???*	Long-term avoidance of area.	*Time/energy costs? Loss of opportunity for foraging, social interaction, mating?*	Morton & Symonds, 2002
Beluga	Boat noise	*Masking?*	Shifted frequencies; Used different call types.	Energetic/time/predator/prey costs; *Information ambiguity?*	Lesage et al., 1999
Beluga	Seismic like noise	*???*	Increased stress hormone levels.	*Immunity/illness consequences?*	Romano et al., 2004

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
Beluga	Icebreaker noise	*???*	Avoidance and flight at long ranges.	*Time/energy costs? Loss of opportunity for foraging, social interaction, mating?*	Cosens & Dueck, 1993; Finley et al., 1990
Pilot whales	MF sonar	*Masking?*	Increases in whistles.	*Time/energy costs?*	Rendell & Gordon, 1999
Sperm whales	Pingers	*???*	Fell silent.	*Compromised foraging or communication?*	Watkins & Schevill, 1975
Sperm whales	MF Sonar	*???*	Fell silent.	*Compromised foraging or communication?*	Watkins, Moore & Tyack, 1985
Sperm whales	Seismic surveys	*???*	Fewer creaks; No foraging dives near seismic vessel; Reduced fluke strokes and effort.	*Compromised foraging?*	IWC, 2007
Pilot, sperm whales	Low frequency pulses (similar to Acoustic Thermometry of Ocean Climate – ATOC – signals)	*???*	Decrease in vocalizations.	*Compromised foraging or communication?*	Bowles et al., 1994
Pilot, sperm whales	Seismic surveys	*???*	Decrease in vocalizations.	*Compromised foraging or communication?*	Bowles et al., 1994
Mysticetes	Seismic surveys	*???*	Avoidance; More time at surface; Fewer animals feeding.	*Time/energy costs? Reduced foraging?*	Stone & Tasker, 2006
Blue whales	Long range shipping noise	Masking.	Shifting frequency of call; May be some amplitude increase.	*Reduced mating opportunity?*	Croll et al., 2001; Payne & Webb, 1971
Fin whales	Seismic surveys	*???*	Suspension of vocalizations for weeks/months.	*Reduced mating opportunity?*	IWC, 2007
Fin whales	Boat noise	*???*	Decrease in vocalizations.	*Reduced mating opportunity?*	Watkins, 1986
Gray whales	Industrial noise, dredging and shipping	*???*	Long-term displacement of breeding area.	*Reduced mating opportunity?*	Bryant, Lafferty & Lafferty, 1984; Jones et al. 1994

Animal	Stimulus	Mechanisms	Observations	Consequences	Sources
Gray whales	Low frequency active (LFA) sonar (inshore)	*???*	Shift in migration path.	*Increased predation?* *Greater mother-calf/group separation??* *Anxiety?*	Tyack & Clark, 1988
Gray whales	Seismic surveys	*???*	Displacement out of primary feeding area; Faster respiration; Faster, straighter movement over larger areas.	*Reduced foraging?* *Time/energy costs?*	IWC, 2005, 2007
Gray whales and bowheads	Industrial noise	*???*	Shift in migration path.	*Increased predation?* *Greater mother-calf/group separation??* *Anxiety?*	Malme et al., 1983, 1984; Richardson et al., 1985; Richardson, Würsig & Greene, 1990
Bowheads	Seismic surveys	*???*	Shorter dives and lower respiration rates at as much as 50-70 km away.	*Widespread reduction in foraging?*	Richardson, Würsig & Greene, 1986
Humpbacks	LFA sonar	*???*	Mating songs lengthened.	*Long-term mating/energetic/time consequences?*	Fristrup, Hatch & Clark, 2003; Miller et al., 2000
Humpbacks	Seismic surveys	*???*	Avoidance; Occasional attraction prior to swimming away.	*Compromised foraging or breeding?*	McCauley et al., 2000
Humpbacks	Explosions	*???*	Greater entrapment in fishing gear	Often death.	Todd et al., 1996
Northern elephant seals	ATOC	*???*	Increased descent and decreased ascent rate in dives; Escape response.	*Reduced foraging?* *Time/energy costs?*	Costa et al., 2003

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