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Putative neural consequences of captivity for elephants and cetaceans

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Abstract: The present review assesses the potential neural impact of impoverished, captive environments on large-brained mammals, with a focus on elephants and cetaceans. These species share several characteristics, including being large, wide-ranging, long-lived, cognitively sophisticated, highly social, and large-brained mammals. Although the impact of the captive environment on physical and behavioral health has been well-documented, relatively little attention has been paid to the brain itself. Here, we explore the potential neural consequences of living in captive environments, with a focus on three levels: (1) The effects of environmental impoverishment/enrichment on the brain, emphasizing the negative neural consequences of the captive/impoverished environment; (2) the neural consequences of stress on the brain, with an emphasis on corticolimbic structures; and (3) the neural underpinnings of stereotypies, often observed in captive animals, underscoring dysregulation of the basal ganglia and associated circuitry. To this end, we provide a substantive hypothesis about the negative impact of captivity on the brains of large mammals (e.g., cetaceans and elephants) and how these neural consequences are related to documented evidence for compromised physical and psychological well-being.

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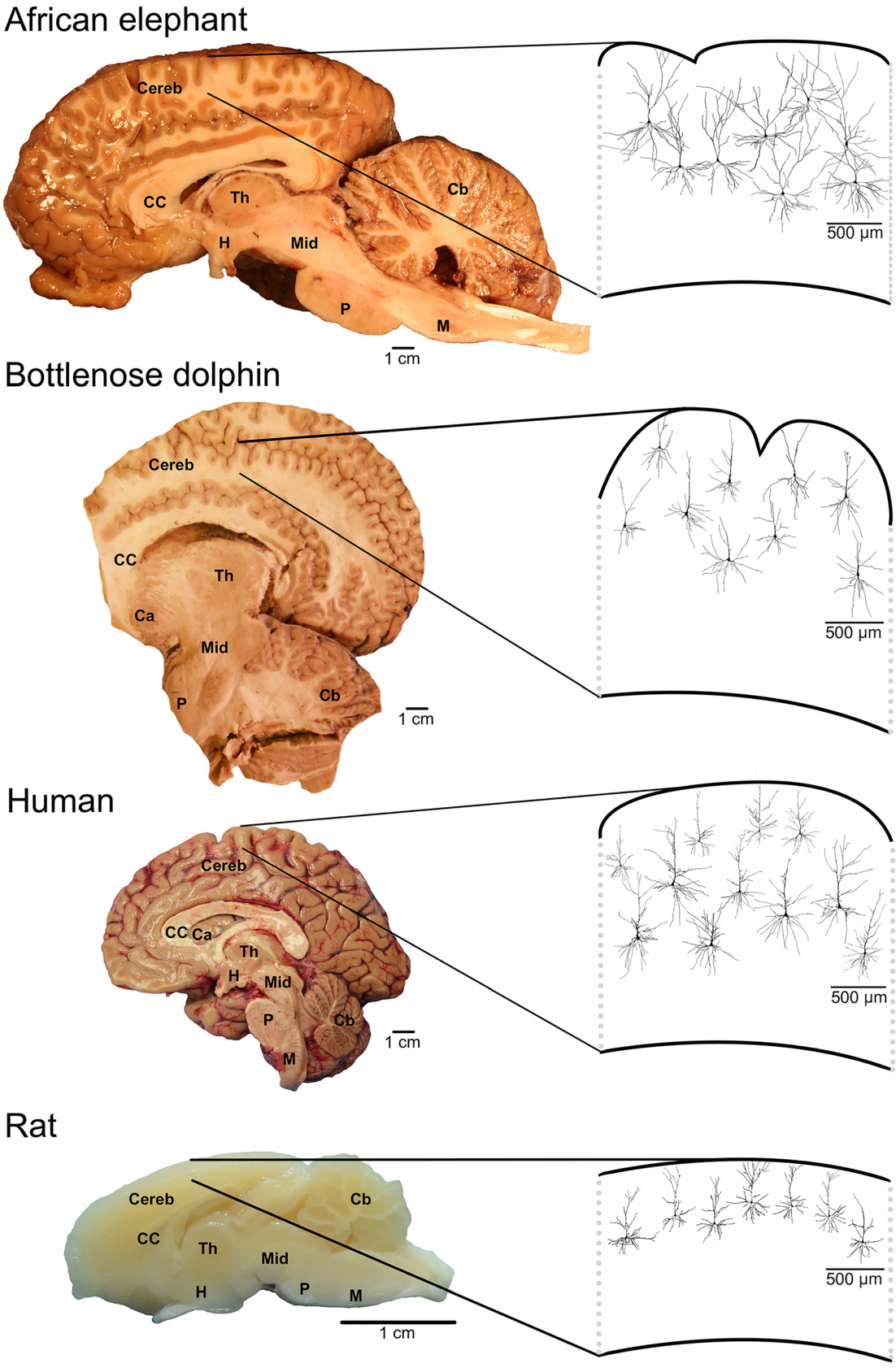
Introduction

Although some large mammals fare relatively well in captive environments (i.e., zoos and marine parks), those with extensive home ranges do not (Clubb and Mason 2003, 2007; Mason 2010). Large-brained animals with complex cognitive capacities such as elephants and cetaceans seem particularly prone to poor welfare in captive environments insofar as they do not have an adequately stimulating, natural environment. Globally, more than 3000 cetaceans and 17,000 elephants are held in captivity (Jackson et al. 2019; Riddle and Stemme 2011). In the present review, we begin by summarizing the shortcomings of captive environments and the concomitant, often stress-related clinical issues for elephants and cetaceans. Although one can directly observe the physical and behavioral manifestations of welfare in captivity, we cannot do the same for potential neural consequences. Thus, we must infer the effects on the brain from the animal's behavior, biomedical assays, and from inductive extrapolations of empirical neuroscience research. We propose several neural systems in elephants and cetaceans that are likely negatively affected by the chronic stress of captivity.

Elephants and ~75% of cetacean species, along with humans and three pinniped species, belong to a small subset of species with brain masses >700 g (Manger et al. 2013). The adult African elephant brain mass is ~5000 g (Manger et al. 2009; Figure 1). Across the ~86 species of odontocete and mysticete cetaceans, brain mass ranges from 164 g (Indus River dolphin, *Platanista minor*) to 8030 g (sperm whale, *Physeter macrocephalus*) (Manger 2006; Marino 2009). The African elephant (*Loxodonta africana*) brain contains ~257 billion neurons, three times as many as the ~86 billion neurons in the adult human brain, with ~251 billion (or 97.5%) of these neurons in the cerebellum (compared to ~69 billion in the human) and only 5.6 billion in the neocortex (compared to 16.3 billion in the human; Herculano-Housel 2009; Herculano-Housel et al. 2014).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Whole brain neuron counts in cetaceans are not available, but an unbiased stereological estimate suggests ~13 billion neurons in the minke whale cerebral cortex (Eriksen and Pakkenberg 2007). Elephant and cetacean brains are not only large in absolute size but in relative size. The elephant brain is slightly larger than expected for its body size (Roth and Dicke 2005) and the brains of many odontocete cetacean species are significantly larger than predicted by their body size (Marino 2009). Size differences aside, all eutherian mammals share the same brain components (Finlay and Darlington 1995), with many parts of elephant and cetacean brains appearing to be highly conserved in terms of neuroanatomy and chemoarchitecture, including the limbic system (Butti et al. 2015; Denver 2009; Jacobs et al. 2011, 2015; Limacher-Burrell et al. 2018; Patzke et al. 2014). Phylogenetic variations in neuroanatomy for these species are primarily related to sensorimotor specializations.

For practical and ethical reasons, options for experimentally exploring the neural consequences of a captive/impoverished environment are severely limited for mammals such as elephants and cetaceans. To date, only three African elephant brains have been perfused to allow detailed histological investigations (Manger et al. 2009). In the current review, we therefore extrapolate from experimental findings in other well-studied species (e.g., murid rodents and primates). We also offer comparisons from nonexperimental *in vivo* findings in humans and other animals who have experienced deprived environments. Our inductive conclusions about the effects of captivity on elephant and cetacean brains are based on the fact that brain structures are highly conserved across vertebrates, especially across mammals (Finlay and Darlington 1995). Moreover, substantial evidence suggests that mammalian brains employ very similar mechanisms for interacting with their environment (Lupien et al. 2009).

The clinical profiles of captive elephants and cetaceans manifest in many of the same physical and psychological perturbations as do other mammals in impoverished environments. Such similar welfare outcomes are likely to be based on common neural disruptions, which is why we hypothesize that elephants and cetaceans in artificial environments suffer neural damage. In the present paper, we review the neural consequences of impoverished environments, the effects of short-term and chronic stress on mammalian brains (specifically, corticolimbic structures), and the neural foundations of stereotypy, with a focus on basal ganglia circuitry. We argue that neural inferences from other mammals to elephant and cetacean brains are strongly supported using the logic of triangulation (Thurmond 2001), which is employed in other animal welfare assessments (Clegg and Delfour 2018). Thus, we connect the known effects of impoverished environments on brains from experimental studies in other species as well as the shared clinical profiles in impoverished environments across species to infer the effects of captivity on the brains of elephants and cetaceans.

The captive environment for elephants and cetaceans

In their natural habitat, elephants have expansive home ranges that extend from tens to 10,000 km^2 (Bahar et al. 2018; Ngene et al. 2017), in which they typically travel ~8–12 km/day, with much greater distances common (up to ~50 km/day; Miller et al. 2016; Wall et al. 2013). Elephants engage in a variety of activities, such as socializing, caring for offspring, and foraging on a wide selection of food species (e.g., grasses, trees, bark, roots, and fruits; Dierenfeld 2006). In captivity, however, the actual size of most enclosures is in the range of only 0.017–6.937 km^2 per animal (Taylor and Poole 1998). Small enclosure size prevents elephants from moving long distances and freely interacting with a large network of conspecifics; natural foraging is replaced with a limited zoo diet. Exercise is extremely constrained, even though elephants are physically and cognitively adapted for long-distance movement over diverse substrate while actively interacting with an ever-changing, challenging environment (Poole and Granli 2009). The static environments found in captive situations preclude natural behaviors. This is especially true if the animals are restrained with chains or ropes, which is common for circus and temple elephants, and is sometimes employed in zoos for management reasons (Bradshaw 2007; Lenhardt 2006). Moreover, free-living elephants live

Figure 1: Midsagittal sections of the African elephant (*Loxodonta africana*), bottlenose dolphin (*Tursiops truncatus*), human (*Homo sapiens*), and rat (*Rattus norvegicus*) brains.
Included are tracings of superficial pyramidal neurons from the neocortex of each species. Note that the anterior portion of the frontal lobe has been removed from the dolphin brain. Traced neurons are reproduced from previous studies on quantitative neuromorphology: African elephant (Jacobs et al. 2011), bottlenose dolphin (Butti et al. 2015), human (Jacobs et al. 2018; Warling et al. 2020), and rat (Jacobs et al. 2018). Elephant brain image courtesy of Dr. Paul Manger, University of Witwatersrand, Johannesburg, South Africa. Dolphin brain image courtesy of Drs. Bruno Cozzi and Ksenia Orekhova, University of Padova, Padua, Italy. Abbreviations: Ca, caudate; Cb, cerebellum; CC, corpus callosum; Cereb, cerebral cortex; H, hypothalamus; M, medulla; Mid, midbrain; P, pons; Th, thalamus.

in matriarchal, multigenerational family groups of two to 10 adult females and their immature offspring (de Silva et al. 2011; Vance et al. 2009). Zoos, on the other hand, do not provide biologically appropriate social groups (Poole and Granli 2009) insofar as conspecific interactions are largely limited to small groups of mostly unrelated adult females and very few infants or juveniles (Clubb and Mason 2002), with some elephants even held in solitary confinement for decades (Lindsay 2017). Finally, most captive elephants are forced to interact directly in some capacity with humans, whether it is for entertainment, tourism, or religious purposes, potentially creating further stress.

Similar issues obtain for captive cetaceans who, despite routinely swimming tens of kilometers a day in the ocean (Matthews et al. 2011), are typically held in concrete tanks that are too small and too shallow to allow for any natural ranging or diving behaviors (McPhee and Carlstead 2010). Even in the largest facilities, cetaceans are kept in tanks that are ~10,000 times smaller than their natural home range (https://www.cascadiaresearch.org/projects/killer-whales/using-dtags-study-acoustics-and-behavior-southern). Such tanks are characterized by reflective, barren, smooth surfaces as opposed to naturalistic textures and substrates (Rose and Parsons 2019), creating an environment with constant, unnaturally high levels of ultraviolet radiation. As with elephants, cetaceans naturally have long juvenile periods and depend heavily on cultural learning as well as life-long support from a complex social network (O'Corry-Crowe et al. 2020). In contrast, captive cetaceans have little choice in terms of social associations and partners. Most captive groupings are artificial and unstable because animals are moved among facilities for breeding purposes (Clegg and Butterworth 2017). As with elephants, natural feeding behavior is absent in captive cetaceans, who are fed a narrow selection of dead fish/invertebrates, which are delivered in an unnatural manner (i.e., above water, thrown directly into their mouths) that requires none of the cognitive or behavioral engagement necessary in the wild. Finally, as with elephants, many captive cetaceans are trained to perform artificial behaviors and are routinely forced to interact with humans (e.g., swim with the dolphin programs; Frohoff 2018).

The clinical profiles of captive elephants and cetaceans

Because elephants have complex physical and social needs that are difficult to meet even in professionally accredited zoological institutions (Kagan et al. 2018), they suffer from high rates of behavioral and physical pathology (Lahdenperä et al. 2018). In terms of behavior, a prevalent abnormality is stereotypic behavior (Mason and Rushen 2008), which consists of aberrant, repetitive movements (e.g., limb swaying, and rocking) induced by the frustration of natural impulses (Clegg et al. 2017). It is estimated that 47–85% of elephants in zoos and 100% of those in circuses exhibit stereotypies (Greco et al. 2016; Mason and Veasey 2010; Schmid 1995). Captive elephants also exhibit hyperaggression (Harvey et al. 2018), in part because there is no opportunity for physical distancing during heighted intragroup stress (Archie et al. 2006). Medically, captive elephants suffer from both gastrointestinal diseases (e.g., impaction and colic; Greene et al. 2019) and nutritional/metabolic disorders because of their captive diet and lack of exercise (Khadpekar et al. 2020), with obesity being a serious issue (Brown et al. 2020). Across North American zoos, 74% of elephants were found to be overweight with 34% believed to be clinically obese (Morfeld et al. 2016). Skin issues (e.g., inflammation, lesions, and pressure sores) are common (Brown et al. 2020; Fowler 2006a) as are foot-related disorders (e.g., hyperkeratosis, cracked nails, and abscesses; Fowler 2001). Osteoarthritis in the feet, exacerbated by locomotor stereotypies and obesity, occurs prematurely in captive elephants and can lead to euthanasia (Issa and Griffin 2012). Finally, captive elephants are particularly susceptible to several infectious diseases (e.g., *Mycobacterium tuberculosis*, TB, the endotheliotropic herpesvirus, EEHV), which are highly contagious (Fuery et al. 2018; Mikota and Maslow 2011). TB is deadly in elephants and treatment is often unsuccessful (Lyashchenko et al. 2006). EEHV is prevalent in captive environments, particularly in young, chronically stressed, immunocompromised Asian elephants (*Elephas maximus*; Schaftenaar et al. 2010), and is now the leading cause of death for captive elephant calves (Perrin et al. 2021). These factors appear to be associated with reproductive issues (Clubb and Mason 2002; Perrin et al. 2021) and a reduced lifespan for both Asian and African elephants in captivity (Clubb et al. 2008, 2009).

Captive cetaceans also exhibit a variety of stereotypies (e.g., repetitive swimming patterns; regurgitation/reingestion of food), with the most common being oral stereotypies that result in severely worn teeth from grating them on hard surfaces (Jett et al. 2017; Ugaz et al. 2013). Some cetaceans also exhibit symptoms characteristic of depression (e.g., logging on the surface, lying motionless on the bottom of the tank, and loss of appetite; Jett and Ventre 2012). As with elephants, hyperaggression is more

common in captive cetaceans than in their free counterparts due to their severely confined living space (Lott and Williamson 2017; Marino 2020). In terms of medical issues, there are several parallels with elephants. Nutrition/metabolism disorders (e.g., insulin resistance, fatty liver disease, hemochromatosis, and hypocitraturia; Mazzaro et al. 2012; Venn-Watson et al. 2012, 2013; Zuckerman and Assimos 2009) are often linked to the captive diet (Rosen and Worthy 2018). Additionally, digestive and gastrointestinal disturbances (e.g., gastritis, ulcerations, and torsion) pose significant and sometimes fatal problems for captive cetaceans (Stoskopf 2015). Two common skin disorders in captive cetaceans are tattoo skin disease, which is caused by pox virus and is associated with immunocompromised individuals, and the potentially life-threatening diamond skin disease, caused by *Erysipelothrix rhusiopathia* (Van Bressem et al. 2018). When facilities fail to maintain levels of chlorine and ozone within strict parameters, elevated concentrations of these chemicals can cause eye damage, respiratory problems, and skin sloughing (Gage 2010). The main cause of fatality in captive cetaceans is (viral and bacterial) pneumonia (Jett and Ventre 2012). Moreover, the prevalence of infectious diseases in captive cetaceans is compounded by the routine use of antibiotics and antifungals, including frequent prophylactic administration, leading to an imbalance of microflora and an increased risk of medicinal resistance (Park et al. 2020; Reidarson et al. 2018). Such disruptions have broader health implications insofar as research in both humans and rats strongly suggests bidirectional communication (e.g., neural, hormonal, and immune) between gut microbiota and the brain, with alterations in the gut microbiome associated with chronic stress and depression (Kelly et al. 2016). Finally, as with elephants, reproductive issues (Robeck et al. 2018) and a reduced lifespan in some cetacean species have been documented (Rose and Parsons 2019).

In summary, the clinical profiles of captive elephants and cetaceans indicate that they experience a similar pattern of psychological, behavioral, and physical health issues. Many of these problems appear to be manifestations of the same kinds of neurobiological deficits demonstrated in other mammals in impoverished environments under controlled experimental conditions. Below, we examine the neural consequences of impoverished environments and the associated effects of chronic stress on the brain across several different species. In doing so, we provide support for the inference that captive elephants and cetaceans incur neurobiological damage that is similar to that documented in other animals.

The neural consequences of impoverished environments

The brain's exquisite responsiveness to its environment is a hallmark of plasticity, for better or worse, and has been demonstrated across all species examined, from insects (e.g., honeybees; Groh and Rössler 2020), to invertebrates (e.g., aplysia; Antonov et al. 2001), to a variety of mammals (Holtmaat and Svoboda 2009). Following Hebb's (1947) observation that free-roaming rats performed better on cognitive tasks than laboratory-housed rats, researchers at the University of California, Berkeley (Edward Bennett, Marian Diamond, David Krech, and Mark Rosenzweig) created a framework for exploring the neural effects of housing environments in what has come to be known as the environmental enrichment/complexity paradigm. In this basic framework, littermates are placed in one of three conditions: (1) A relatively large, *enriched/complex condition* together with several conspecifics and multiple objects/toys, which are changed frequently to provide novelty—in short, the enclosure is designed to enhance the animal's sensory, motor, and social interactions; (2) a *standard/control condition*, where several animals are housed together without opportunities to interact with stimulatory objects; and (3) an *impoverished condition*, where animals are alone in smaller cages with no opportunity for social or object interaction. It should be noted that the standard/control condition is, relative to the enriched/complex condition, also a form of impoverishment as these housing conditions constitute a continuum of environmental stimulation. Moreover, active, direct contact with conspecifics and objects in the environment is crucial; merely observing an enriched environment is not enough to promote neural changes (Ferchmin et al. 1975).

Six decades of these studies have underscored the profound functional, anatomical, chemical, and molecular effects the environment has on the central nervous system (CNS) across a wide variety of species (Table 1A). The CNS appears particularly sensitive during early development (Bogart et al. 2013), but environmentally induced changes occur across the lifespan, including in very old animals (Diamond et al. 1985), and transgenerationally (Arai and Feig 2011). Although most research of this nature has emphasized the neural benefits of an enriched environment, the impoverished environment is likewise detrimental. Impoverished rats (Katz and Davies 1984), mice (Henderson 1970), and gerbils (Rosenzweig and Bennett 1969) tend to exhibit lower overall brain weight than enriched cohorts. As brain weight decreases with impoverishment, so does cortical volume (Altman and Das 1964)

Table 1: Environment-brain interactions across species.

A. Epigenetic changes in response to environmental enrichment/impoverishment

Species	Major finding	Source
Atlantic cod fish (*Gadus morhua*)	Enriched rearing promoted social learning.	Strand et al. (2010)
Beagle dog (*Canis lupus familiaris*)	Increased brain derived neurotrophic factor (BDNF) and cognitive improvement in response to environmental enrichment and antioxidant diet	Fahnestock et al. (2012)
Cat (*Felis catus*)	Complexity of sensory environment altered morphology of synapses, resulting in enhanced responsiveness of neurons in visual cortex to stimuli.	Beaulieu and Cynader (1990)
Crayfish (*Procambarus clarkii*, *Procambarus acutus*)	Environmental enrichment enhanced rate of neurogenesis.	Ayub et al. (2011)
Human (*Homo sapiens*)	Increased dendritic complexity was associated with higher formal education levels in Wernicke's area.	Jacobs et al. (1993)
Human (*Homo sapiens*)	Training induced transient structural changes in the midtemporal region and the posterior intraparietal sulcus.	Draganski et al. (2004)
Marmoset monkey (*Callithrix jacchus*)	Complex social housing increased dendritic complexity in hippocampus and prefrontal cortex.	Kozorovitskiy et al. (2005)
Octopus (*Octopus vulgaris*)	Enriched environment promoted neurogenesis in brain areas involved in learning, memory, and sensory integration.	Bertapelle et al. (2017)
Pigeon (*Columba livia*)	Neurogenesis in prosencephalon was observed in response to enriched housing.	Melleu et al. (2016)

B. Stereotypies observed across species

Species	Major finding (Type of stereotypy)	Source
African (*Loxodonta africana*), Asian elephant (*Elephas maximus*)	Locomotor (e.g., swinging limb or trunk), whole-body (e.g., pacing), oral (e.g., bar biting), and self-directed (e.g., trunk sucking)	Greco et al. (2017)
Parrot (*Amazona amazonica*)	Locomotor (e.g., pacing, perch circles) and oral (e.g., wire chewing)	Meehan et al. (2004)
American black bear (*Ursus americanus*)	Pacing	Carlstead and Seidensticker (1991)
Orca (*Orcinus orca*)	Oral (e.g., biting and chewing hard tank surfaces)	Jett et al. (2017)
Pacific walrus (*Odobenus rosmarus divergens*)	Tusk rubbing on concrete structures	Dittrich (1987)
Rhesus monkeys (*Macaca mulatta*)	Pacing, stereotypy-related self injurious behavior	Lutz et al. (2003)
Horse (*Equus caballus*)	Crib-biting, weaving, and box-walking	McBride and Hemmings (2009)
Giraffe (*Giraffa camelopardalis tippelskirchi*)	Oral (e.g., tongue-playing, object licking, and vacuum chewing)	Baxter and Plowman (2001)

C. Enrichment-induced reductions in stereotypies

Species	Major finding	Source
African lion (*Panthera leo*), Sumatran tiger (*Panthera tigris sumatrae*)	Feeding enrichment reduced stereotypic behavior and increased nonstereotypic activity.	Bashaw et al. (2003)
Australian sea lions (*Neophoca cinerea*)	Enrichment objects reduced pattern swimming.	Smith and Litchfield (2010)
Chimpanzee (*Pan troglodytes*)	Enrichment devices (e.g., manipulable toys) reduced repetitive stereotypies.	Brent et al. (1989)
Common seal (*Phoca Vitulina*)	Enrichment devices focused on feeding/foraging significantly reduced stereotypical circling behavior.	Grindrod and Cleaver (2001)
Cynomolgus monkey (*Macaca fascicularis*)	Enriched playpen environment reduced stereotypy and autoaggression.	Bryant et al. (1988)
Giant panda (*Ailuropoda melanoleuca*)	Behavioral enrichment items significantly reduced rate and time engaged in stereotypic behaviors.	Swaisgood et al. (2001)
Giraffe (*Giraffa camelopardalis tippelskirchi*)	Feeding enrichment reduced oral stereotypies.	Fernandez et al. (2008)
Horse (*Equus caballus*)	Enriched foraging device reduced several types of stereotypic behavior (e.g., weaving).	Henderson and Waran (2001)
Parrot (*Amazona amazonica*)	Enriched cages significantly reduced locomotor and oral stereotypies.	Meehan et al. (2004)

Table 1: (continued)

C. Enrichment-induced reductions in stereotypies		
Species	**Major finding**	**Source**
Sea turtles (*Caretta caretta, Chelonia mydas*)	Enrichment devices decreased stereotypic resting and pattern swimming.	Therrien et al. (2007)
Sloth (*Melursus ursinus*), American black (*Ursus americanus*), brown bear (*Ursus arctos*)	Enriched feeding methods reduced stereotypic pacing.	Carlstead et al. (1991)

and section weight (Globus et al. 1973), even though impoverished rats tend to have greater body weight than enriched rats (Walsh 1981), a finding that parallels the obesity problem identified in many captive animals (Clubb et al. 2008).

Neocortical consequences of impoverishment

Consistent across environmental complexity studies is a significant decrease in cortical thickness with impoverishment (Diamond et al. 1967), especially in occipital cortex (Katz and Davies 1984; Møllgaard et al. 1971; Figure 2), reflecting several changes in underlying cortical neuropil. Within the cortex, capillary volume, and hence cortical blood supply, tends to be lower in impoverished rats than enriched rats (Diamond et al. 1964; Figure 2). Also, the impoverished rat brain possesses fewer glial cells, especially oligodendrocytes, than does the enriched rat brain (Altman and Das 1964; Katz and Davies 1984), which implies that cortical neurons in impoverished brains receive less metabolic and structural support than neurons in enriched brains. Both nuclear and perikaryon diameters in supragranular neurons are smaller in impoverished rats (Diamond et al. 1967). Impoverished animals exhibit dendritic systems for both pyramidal and stellate neurons that are less complex in terms of number and length, especially for more distal branches (Volkmar and Greenough 1972; Figure 2) in occipital (Sirevaag and Greenough 1985), parietal (Leggio et al. 2005), and temporal (Greenough et al. 1973) cortices for rats, and in motor cortex for deer mice (Turner et al. 2003). Marmoset monkeys (*Callithrix jacchus*) housed in standard cages for one month, compared to cohorts in complex environments, exhibited less basilar dendritic complexity in pyramidal neurons of the prefrontal cortex (Kozorovitskiy et al. 2005), which is involved in executive functions (e.g., cognitive flexibility and planning).

Several other neocortical deficits related to impoverishment have also been documented. Pyramidal neurons in both occipital (Globus et al. 1973) and parietal (Leggio et al. 2005) cortex exhibit reduced spine density in impoverished rats (Figure 2). Lower spine density along the basilar dendrites of pyramidal neurons has also been observed in the prefrontal cortex of marmoset monkeys (Kozorovitskiy et al. 2005). At the synaptic level, impoverished rats have been shown to have fewer synapses per cortical neuron than their enriched counterparts, suggesting less overall synaptic activity (Sirevaag and Greenough 1985). Moreover, impoverished rats tend to have

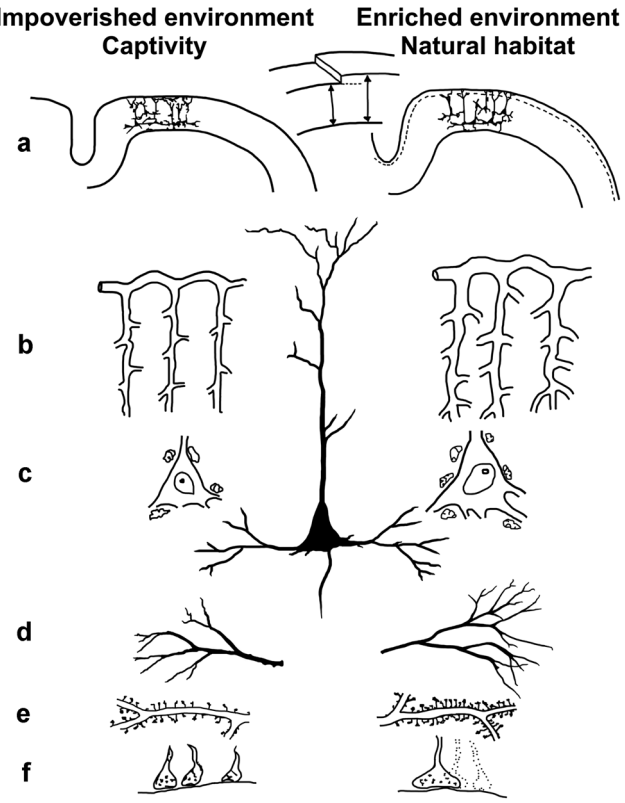

Figure 2: Different levels of the cerebral cortex affected by impoverished (captive) and enriched (natural) environments. In impoverished/captive environments, there are several cortical changes: (a) Decreases in cortical thickness, (b) smaller capillary diameter, (c) decreases in neuronal soma size and fewer glial cells per neuron, (d) less complex dendritic branching, (e) fewer dendritic spines, and (f) less efficient synapses. Image courtesy of Dr. Arnold B. Scheibel.

smaller synapses than enriched cohorts (Møllgaard et al. 1971), with significantly shorter postsynaptic opaque regions in asymmetrical synapses (Sirevaag and Greenough 1985; Figure 2). Similar findings have been documented in cat visual cortex, where the number of round-asymmetrical synapses per neuron is lower and the number of flat-symmetrical contacts is higher in impoverished compared to enriched animals, functionally suggesting that impoverished cortex may be less responsive to visual stimuli because there are more inhibitory synapses per neuron (Beaulieu and Cynader 1990).

Although experiments of this nature are not possible in humans, there are documented effects of a stimulating environment on the human brain as well. For example, as with the environmental complexity studies (Kleim et al. 1998), specific training (e.g., formal music practice) causes structural changes (e.g., volumetric increases in somatosensory and motor cortices) in the human brain (Gaser and Schlaug 2003). At the morphological level, Scheibel et al. (1990) found a positive relationship between the basilar dendritic extent in cortical pyramidal neurons and the complexity of the computational task performed by that area, a finding confirmed in subsequent studies (monkey: Elston and Rosa 1997; human: Jacobs et al. 2001). In addition, they found preliminary evidence of a positive association between dendritic complexity in the hand-finger region of primary somatosensory cortex and the nature of an individual's occupation, a relationship recently supported by neuroimaging (Lenhart et al. 2021). A subsequent study in Wernicke's area found a positive correlation between education level (seen as a form of enrichment) and dendritic extent, with university educated individuals having more complex basilar dendritic systems than those who did not complete high school (Jacobs et al. 1993). Recently, more complex pyramidal dendritic arbors in human temporal and frontal cortices have also been positively associated with intelligence (Goriunova et al. 2018). Although one cannot determine causation in such correlational studies, the nonhuman animal research indicates that the brain of an enriched animal exhibits detrimental changes (e.g., decreases in dendritic length) when the animal is put in an impoverished environment, and vice-versa, underscoring the epigenetic sensitivity of neural tissue (Diamond 1988).

The neocortex in elephants and cetaceans—potential parallels with other mammals

The experimental evidence indicates that impoverished environments have wide-reaching and damaging effects on the cerebral cortex by contributing to thinner cortical laminae, a decreased blood supply, smaller neuronal cells bodies with fewer glial cells to provide metabolic and structural support, decreased dendritic branching for synthesizing information, fewer dendritic spines (indicating fewer connections with other neurons), and smaller, potentially less efficient synapses (Holler et al. 2021). Although the neocortex of elephants and cetaceans is largely agranular (Hof et al. 2005; Jacobs et al. 2011), it is logical to expect that an impoverished environment would affect their neocortex similarly to the way that it affects that of other mammals. An agranular cortex simply represents a variation of the six-layer cortex characteristic of euarchontoglires (e.g., murid rodents and primates). Generally, cetacean neocortical neurons are morphologically very similar to those observed in other cetartiodactyls (Butti et al. 2014, 2015; Jacobs et al. 2015). Elephant neocortical neurons are similar in in overall dendritic extent to humans but tend to have fewer branches and extend more laterally than in other mammals (Jacobs et al. 2011). As is the case with other mammals, the neocortex of elephants and cetaceans exhibits a variety of complex spiny neurons, with pyramidal neurons being dominant (Butti et al. 2015; Jacobs et al. 2011). In both elephant and cetacean neocortex, aspiny interneurons appear to be highly conserved morphologically and thus similar to those observed in other eutherian mammals (Jacobs et al. 2011, 2015).

Impoverishment across other brain regions

The effects of impoverishment also extend to other brain regions. In the cerebellum, for example, impoverished/inactive rats fail to show the same increases in synaptic number along parallel fibers as do their enriched/active cohorts (Kleim et al. 1998). Similarly, in monkeys (*Macaca fasciularis*), impoverished animals do not exhibit the same dendritic growth that characterizes the Purkinje neurons of their enriched counterparts (Floeter and Greenough 1979). Although the cerebellum in most cetaceans and in elephants is much larger in both relative and absolute size compared to other eutherians (Marino et al. 2000; Maseko et al. 2012), the neuronal morphology of the elephant and cetacean cerebellum is very consistent with what has been observed in other mammals (Jacobs et al. 2014), and likely responds to impoverishment in a similar manner. The disproportionate size of the cerebellum in elephants and cetaceans, particularly in the lateral hemispheres (Smaers et al. 2018), appears to be related to its sensory acquisition and processing role and the importance of infrasound in elephants and echolocation in cetaceans for exploring the

environment (Hanson et al. 2013; Jacobs et al. 2014). It remains unclear to what extent the cerebellum also contributes to cognitive and emotional functions in elephants and cetaceans, although such functions have been demonstrated in other species (primates: Habas 2021; rats: Shipman and Green 2020).

Finally, two limbic structures are also negatively affected by impoverished environments. The hippocampal-dentate complex (or hippocampus), which is particularly sensitive to environmental influences, exhibits a lower volume in impoverished animals compared to enriched animals largely because of decreased neurogenesis (mice: Kemperman et al. 1977; pigeons: Melleu et al. 2016; rats: Veena et al. 2009). In the amygdala, impoverished rats show greater c-Fos (a gene involved in cell proliferation/differentiation following extracellular stimulation) expression in the medial nucleus following aversive training than enriched animals, suggesting they experience greater levels of stress (Nikolaev et al. 2002). Comparatively, the elephant possesses a typical mammalian hippocampus in terms of both size and architecture (Patzke et al. 2014). Although the hippocampus in cetaceans is smaller than one would expect (Oelschläger and Oelschläger 2009; Patzke et al. 2015), perhaps because of a greatly reduced olfactory system (Kishida et al. 2015), it exhibits typical mammalian subregions (e.g., dentate gyrus, hippocampus proper, and subiculum; Oelschläger et al. 2008). Moreover, despite the reduced hippocampal formation, the paralimbic region in cetacean brains is enormously elaborated (primarily by the well-developed entorhinal cortex and cortical limbic lobe) suggesting there may have been transfer and elaboration of non olfactory hippocampal functions (i.e., long-term memory and learning) to the paralimbic cortex (Marino 2015). Although this hypothesis has yet to be tested, it comports with the behavioral evidence for sophisticated cognitive functions in dolphins and many other cetaceans (Deecke 2018; Marino et al. 2008).

In terms of the amygdaloid complex, the African elephant has a well-developed amygdala similar to that observed in other mammals, although there are some specializations (e.g., enlarged anterior cortical nucleus) thought to be related to the animal's heavy reliance on olfaction (Ngwenya et al. 2011) and its affect-laden and social-empathic behaviors (Limacher-Burrell et al. 2018). The cetacean amygdaloid complex resembles that of other mammals (Oelschläger et al. 2010) but is smaller in relative size (Patzke et al. 2015). Moreover, the cetacean limbic lobe, which includes cingulate, insular, and parahippocampal cortices, is extensive with deep folds (Oelschläger and Oelschläger 2009; Oelschläger et al. 2010). It remains unclear how the relatively smaller hippocampus and amygdala affect susceptibility or resiliency of cetaceans to environmental perturbations. Nevertheless, these relative size differences do not necessarily negate the argument that their psychological functions (and those of other well-developed adjacent brain areas) are impacted by impoverished environments, as the clinical profiles would suggest.

Impoverishment at the molecular level

At the molecular level, epigenetic-related deficiencies in impoverished brains are ubiquitous (Table 2). In this regard, the chemoarchitecture of elephant and cetacean brains underscores considerable similarities across mammals. For example, the primary antibodies used in African elephant research (Maseko et al. 2013; Ngwenya et al. 2011; Patzke et al. 2014) were developed in the rabbit and work in several species (e.g., bats, drosophila, felines, ferrets, humans, mice, mollusks, pigs, rats, and squid), suggesting synapomorphic cytochemistry across a wide array of taxa. For example, quantitative distribution of gamma aminobutyric acid (GABA)-immunoreactive neurons in the Black Sea porpoise (*Phocoena phocoena*) visual cortex is similar to that observed in euarchontoglires (Garey et al. 1989). In primary visual cortex, the general typology of GABA-ergic neurons immunoreactive to calretinin (CR) is similar for bottlenose dolphins (*Tursiops truncatus*) and humans (Glezer et al. 1992). As with neuroanatomy, differences in distribution, density, and typology in neurochemical systems typically reflect specialized sensorimotor and ecological adaptations (Glezer et al. 1998; Manger et al. 2021), but they do not diminish the fundamental similarities across all mammalian brains. Finally, many studies have examined the impact of differential environments on neurotrophins, nerve growth factors (NGF), and brain derived neurotrophic factor (BDNF), all positively associated with neurogenesis, neuroplasticity, emotional resilience, and improved cognitive performance (Table 2). Underlying these findings is the fundamental, lifelong effect that the environment, including training or even a single exposure to enrichment (Ali et al. 2009), has on the expression of a large number of genes linked to neuronal structure, synaptic plasticity, and neural transmission (Rampon et al. 2000) and, by extension, an animal's emotional and cognitive functioning (Neidl et al. 2016).

Table 2: Effects of impoverished environment at the molecular level.

	Major Finding	Source
Acetylcholine	Total acetylcholinesterase activity levels decreased in impoverished animals compared to enriched littermates.	Rats: Rosenzweig and Bennett (1972) Mice: La Torre (1968)
Monoamines	Impoverished rats exhibited higher densities of dopamine D1 receptors in the prefrontal cortex than animals housed in enriched environments, which correlated with higher levels of spontaneous, open field motor activity for the impoverished animal.	del Arco et al. (2007)
	Environmental enrichment appeared to increase coping behaviors because of a reduction in the release of dopamine (and acetylcholine) in the prefrontal cortex.	Segovia et al. (2009)
Noradrenaline	Lower levels observed in control mice versus enriched cohorts in the parieto–temporal–occipital cortex, as well as in the cerebellum and lower brainstem.	Naka et al. (2002)
Serotonin	Impoverished rats exhibited significantly lower expression of the gene for serotonin 1A receptors in the dorsal hippocampus, suggesting potentially less neuronal plasticity than in the more environmentally stimulated cohorts.	Rasmuson et al. (1998)
Amino acid transmitters	Reduced levels of metabotropic glutamate receptors observed in the prefrontal cortex of impoverished rats, potentially impairing cognitive functions.	Melendez et al. (2004)
	During early development in mice, an impoverished environment impeded the maturation of both gamma aminobutyric acid GABA-ergic and glutamatergic synapses in the forebrain and hippocampal regions.	He et al. (2010)
Nerve growth factors (NGF) and brain derived neurotrophic factor (BDNF)	Impoverished rats exhibited lower NGF and BDNF levels than enriched cohorts in cerebral cortex, hippocampus, basal forebrain, and hindbrain.	Pham et al. (2002)
	Levels of BDNF mRNA were lower in beagle dogs not receiving behavioral enrichment.	Fahnestock et al. (2012)
	Cell proliferation was reduced for unstimulated, control octopuses (*Octopus vulgaris*) in brain areas involved in learning, memory, and sensory integration.	Bertapelle et al. (2017)

Impoverishment and lack of exercise in the captive environment

A crucial component to an enriched environment is exercise (Basso and Suzuki 2017), which is severely lacking for captive elephants and cetaceans (Clubb et al. 2008; Morfeld et al. 2016). Exercise not only increases the supply of oxygenated blood to a metabolically expensive brain, but also increases serum neurotrophic factors and BDNF (Heisz et al. 2017; Liang et al. 2021) which, in turn, contribute to potential neurogenesis and enhanced cognitive abilities through a series of complex biochemical cascades (Horowitz et al. 2020). Moreover, exercise generally has a positive influence on the immune system, leading to a reduction in inflammatory biomarkers, and increases in antioxidant defenses (Gomes and Florida-James 2016). Finally, as reviewed by van Praag et al. (2000), exercise appears to enhance the activity of several neurotransmitter systems in rats: (1) cholinergic functioning in the hippocampus, which improves spatial learning (Fordyce and Farrar 1991), (2) opioid activity, which modulates pain (Sforzo et al. 1986), and (3) monoamine functioning (noradrenaline and serotonin), which contributes to learning and synaptic plasticity (Chaouloff 1989). One can logically expect the same exercise-related neural changes in elephants and cetaceans.

Lack of exercise and other shortcomings of the captive environment are apparent to those in the captive industry. However, zoos and aquariums cannot practically make wholesale changes to an animal's environment as can be done in laboratory settings, where general enrichment and exercise are known to reduce stress and anxiety (mice: Varman et al. 2012; rats: Veena et al. 2009), enhance memory (mice: van Praag et al. 2000), increase cognitive functions and neural plasticity (mice: Arai and Feig 2011; fish, *Gadus morhua*: Strand et al. 2010), protect against lead toxicity (mice: Schneider et al. 2001), treat developmental disorders (humans: Ball et al. 2019), and ameliorate several psychiatric and neurogenerative disorders in humans (Nithianantharajah and Hannan 2006). Instead, zoos and

aquariums engage animals in limited types of directed enrichment (Law and Kitchener 2017; Markowitz 1982) in an attempt to alleviate the specific psychological/behavioral problems arising from an impoverished environment.

Current evidence suggests that targeted, ad hoc zoo/aquarium enrichment remains insufficient for the overall neural health of mammals such as elephants and cetaceans as long as they remain constrained by standard captive conditions. Here it is worth noting a couple of additional points: natural environments appear to be better for the emotional health of rats (as measured by c-Fos activation in the nucleus accumbens) than artificially enriched environments (Lambert et al. 2016), with similar findings in humans (Lambert et al. 2015). Thus, not all types of enrichment are equally effective (Lyn et al. 2020). Moreover, transient, inconsistent enrichment can create more stress and frustration for the animal than no enrichment at all (Latham and Mason 2010). Finally, insofar as the developing brain is particularly susceptible to impoverishment induced alterations (Narducci et al. 2018), the greatest challenge is for those animals born into a captive environment, which applies to most mammals in zoos (Hosey et al. 2020).

Corticolimbic structures and the neural consequences of stress

In response to environmental stressors, all animals attempt to maintain dynamic homeostasis (Schulkin 2011). The exquisitely sensitive stress response system promotes quick activation of the body in the face of acute stress and then a return to homeostasis once the threat has abated (Sapolsky et al. 2000). In captivity, however, stress can become chronic, leading to distress or "toxic stress", which adversely affects physiological mechanisms (McEwen 2017). Three intricately interconnected systems are involved in the stress response: the nervous system, the endocrine system, and the immune system (Besedovsky and del Rey 1996). At the core of this tripartite schema is the hypothalamic–pituitary–adrenal (HPA) axis which, despite small heterospecific specializations (Atkinson et al. 2015), is highly conserved across mammals (Denver 2009; Nikolova et al. 2018). Here, we provide a simplified overview of the neural consequences when the HPA axis is chronically activated, resulting in an allostatic overload that is generally associated with poorer physical and mental health outcomes (Guidi et al. 2021).

Environmental stresses cause three, cascading linear events: (1) Corticotrophin releasing hormones are released from the paraventricular nucleus of the hypothalamus, (2) adrenocorticotrophic hormone is released from the anterior pituitary into the bloodstream, and (3) the adrenal glands release glucocorticoids such as cortisol (Lupien et al. 2009). In addition to stimulating the sympathetic nervous system to prepare the body for short-term action, glucocorticoids flow through the bloodstream into the brain where, when chronically elevated, they have complex, wide-ranging effects. These include excitotoxity mediated by excitatory amino acids (e.g., glutamate), mitochondrial dysfunction, modulation of extra- and intracellular mediators (e.g., BDNF), microglial activation, detrimental epigenetic changes, induction of neuroinflammatory processes, and apoptosis (McEwen et al. 2015; Tynan et al. 2010; Vyas et al. 2016). Three corticolimbic brain structures—the prefrontal cortex, the hippocampus, and the amygdala (Figure 3)—are particularly affected by these stress responses (Chattarji et al. 2015; McEwen et al. 2016; Vyas et al. 2016), in part because they express a high density of corticosteroid (e.g., mineralocorticoid and glucocorticoid) receptors.

Stress and the prefrontal cortex

The prefrontal cortex plays a major role in stress-related behaviors and fear extinction by exerting top-down modulatory regulation of both the amygdala and the hippocampus (Chattarji et al. 2015; Radley et al. 2015). In particular, the medial prefrontal cortex is part of a negative feedback system to regulate stress-induced HPA activation and amygdala-mediated arousal (Radley et al. 2015). During chronic stress, this negative feedback system is disrupted, resulting in downregulation of glucocorticoid receptors (Mizoguchi et al. 2003), which then results in decreased corticosteroid receptor density throughout the limbic forebrain (Radley et al. 2015). Such disruptions are associated with the pathogenesis of stress-induced neuropsychiatric disorders (e.g., depression, post traumatic stress disorder, and PTSD; Alt et al. 2010; Lecorps et al. 2021; Radley et al. 2015). Stress-induced gray matter reductions have also been documented (Nikolova et al. 2018) as well as N-methyl-D-aspartate (NMDA)-dependent decreases in apical dendritic complexity and spine density in the medial prefrontal cortex (McEwen 2016, 2017; Radley et al. 2015; Figure 3). In the orbitofrontal cortex, chronic stress has been associated with increased dendritic complexity, as would be expected in captivity due to increased vigilance (McEwen et al. 2015). Finally, prolonged stress also results in structural changes to cortico-striatal circuitry involved in decision making (Dias-Ferreira et al. 2009).

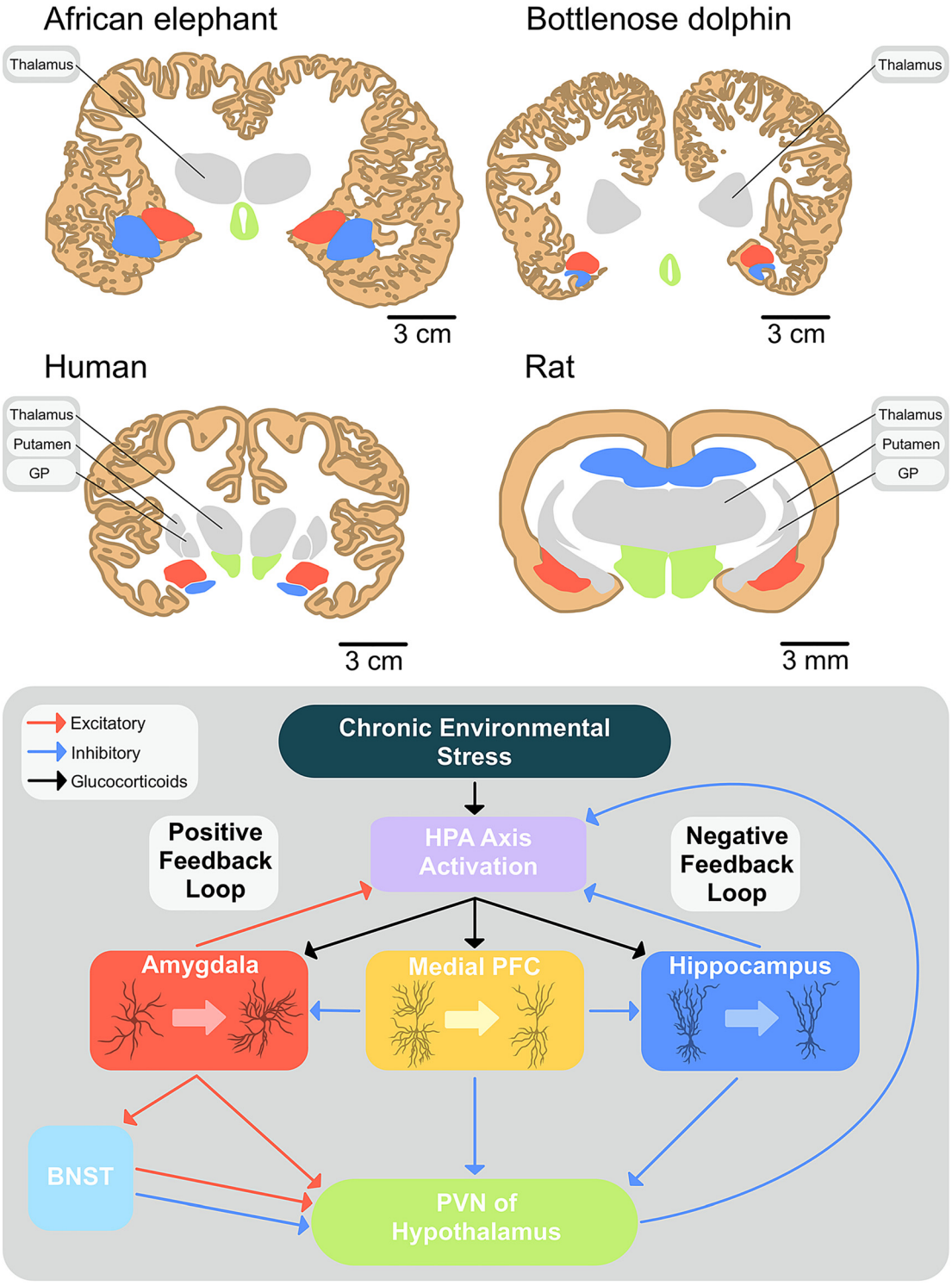

Figure 3: Schematic of hypothalamic–pituitary–adrenal (HPA) axis activation.
Coronal sections of the African elephant, bottlenose dolphin, human, and rat brains revealing major structures involved in the neural response to stress following hypothalamic–pituitary–adrenal (HPA) axis activation and the release of glucocorticoids (black arrows) from the adrenal cortex. A simplified schematic illustrates the basic structures and connections within this circuitry. Structures in the schematic are color coded to match brain cross sections—note that the medial prefrontal cortex (PFC) and the bed nucleus of the stria terminalis (BNST) are not visible in cross-sections. In addition, the entire hypothalamus is illustrated in the cross-sections rather than just the paraventricular nucleus (PVN). Major excitatory (red arrows) and inhibitory (blue arrows) projections are shown. In general, the amygdala and associated circuitry provide a positive feedback loop to activate the HPA axis whereas the hippocampus and associated circuitry contribute to a negative feedback loop to

Stress and the hippocampus

The hippocampus is especially sensitive to sustained exposure to glucocorticoids and mineralocorticoids (McEwen 2016, 2017; McEwen et al. 2015). Because mineralocorticoid receptors are more highly expressed in the hippocampus than in the prefrontal cortex (Patel et al. 2000), their activation leads to excess release of glutamate (Olijslagers et al. 2008). In turn, it has been shown in both rodents and primates that stress-elevated levels of extracellular glutamate activate NMDA receptors, which mobilizes free cytosolic calcium to toxic levels, subsequently resulting in hypoxia-ischemia, excitotoxic seizures, soma shrinkage, nuclear pyknosis, and loss of dendritic spines along with apical dendritic atrophy (Figure 3), particularly in CA3 pyramidal neurons (McEwen 2001; McEwen et al. 2016). Similar structural-functional correlates (e.g., reduction of hippocampal volume) have been documented in humans and associated with clinical depression, bipolar disorders, PTSD, and other stress-related illnesses (McEwen 2016; McEwen et al. 2016). Such stress-related damage could be particularly detrimental in cetaceans insofar as their hippocampus appears not to exhibit neurogenesis under normal conditions (Parolisi et al. 2018).

Stress and the amygdala

The amygdala, in conjunction with interconnected structures involved in autonomic, neuroendocrine, and behavioral arousal, is crucially involved in emotional processing of sensory information and regulation of emotional responsiveness, especially as related to fear (LeDoux 1994). Structurally, chronic stress contributes to long-lasting morphological changes in the amygdala in both human and nonhuman animals. Specifically, both stellate and pyramidal neurons in the basolateral amygdala (a putative locus for the storage of fear memories) exhibit increased dendritic complexity and greater spine density in response to chronic stress (Mitra et al. 2005; rats: Vyas et al. 2002; Figure 3). In contrast, neurons in the medial amygdala show stress-induced decreases in dendritic extent and spine density, a change that appears associated with reduced social interaction (mice: McEwen 2017). Volumetric changes in several corticolimbic regions (e.g., the nucleus accumbens, Reynolds and Berridge 2008), including the amygdala, also appear to positively correlate with chronic stress (Nikolova et al. 2018).

Under stressful conditions, when glucocorticoid levels are high, the baseline GABA-ergic inhibitory control exerted by the medial prefrontal cortex over the central nucleus (the major output nucleus) of the amygdala is disrupted, resulting in amygdaloid hyperreactivity to perceived environmental stressors (Skórzewska et al. 2015) with functional and structural consequences (Christoffel et al. 2011). Functionally, there is an increased fear response, prolonged HPA and sympathetic activation, increased aggression and, because of the amygdala's strong reciprocal connections with the bed nucleus of the stria terminalis (BNST), excessive anxiety (Avery et al. 2016). In humans, such dysfunctions have been associated with a variety of anxiety disorders, including PTSD, generalized anxiety disorder, phobias, panic disorders, and obsessive-compulsive disorders (Koenigs and Grafman 2009; Shin and Liberzon 2010). Amygdala hyperactivity may also increase the risk for developing the stress-related symptoms of depression (Nikolova et al. 2018). Moreover, under inescapably stressful conditions, the amygdala and the BNST, modulated by serotonergic input from the dorsal raphe nucleus, may mediate learned helplessness and conditioned defeat (Maier and Seligman 2016).

Stress for elephants and cetaceans

Because of the complex social world of elephants and many cetaceans, an issue of special relevance to the present review is the effect that social isolation has on corticolimbic structures (Mumtaz et al. 2018). In rats and nonhuman primates, chronic isolation appears to enhance HPA responsiveness to stressors (Serra et al. 2007) and increase basal cortisol levels (Hawkley et al. 2012). Stress from social isolation induces alterations in several neurochemical systems, including (1) decreases in BDNF in the hippocampus (rats: Scaccianoce et al. 2006), which is associated with increased anxiety-like symptoms in rats (Murínová et al. 2017) and several neuropsychiatric disorders in humans (Autry and Monteggia 2012); (2) reduced levels of serotonin in both hippocampus and frontal cortex, which is associated with increased aggression and depression-like symptoms (rats: Miura et al. 2002); and (3) overproduction of nitric oxide, a retrograde messenger, in the hippocampus, which is involved in excitotoxicity (mice: McLeod et al. 2001). Structural changes in response to social

reduce HPA activity. Although not shown in the schematic, the anterior BNST tends to increase HPA axis activity whereas the posterior division tends to inhibit it (Ch'ng et al. 2018). Also represented are three types of neurons and their response to chronic stress: (1) Stellate neurons in the (basolateral) amygdala, which tend to increase dendritic extent; (2) cortical pyramidal neurons in the medial PFC, which show reductions in apical dendritic extent; and (3) CA3 pyramidal neurons in the hippocampus, which undergo degeneration of the apical dendrite.

isolation have also been observed, including selective loss of prefrontal cortex volume (rats: Schubert et al. 2009). These findings are not limited to rodents and nonhuman primates. For example, decreased dendritic complexity has been documented in pallial brain regions important for the development of social/sexual preferences in socially isolated zebra finches (*Taeniopygia guttata*, Shukla and Sadananda 2021). Also, ants raised in isolation show impairment in the growth of the mushroom bodies, which are crucial for learning and memory in social insects (Seid and Junge 2016), as well as weakened immune systems (Scharf et al. 2021). Humans subjected to early socioemotional deprivation in Romanian orphanages exhibited several neural deficits, including glucose hypometabolism and white matter abnormalities in limbic and paralimbic structures (including prefrontal cortex, amygdala, and hippocampus; Chugani et al. 2001; Eluvathingal et al. 2006). Such changes may underlie some of the cognitive, behavioral, and socioemotional deficits observed in these children. Human findings of this nature underscore the importance of the early environment for shaping corticolimbic systems and the potential long-term consequences to chronic stress (Frodl and O'Keane 2013). Current human research, in fact, suggests that childhood trauma may subsequently make the adult brain more vulnerable to maladaptive stress responses (Banihashemi et al. 2020), an issue particularly relevant for long-lived, highly social animals such as elephants and cetaceans born into captivity.

Stress and neuroendocrine-immune system interactions

Neuroendocrine-immune interactions are dynamic (Wrona 2006). Acute stress tends to enhance immune functions whereas chronic stress tends to inhibit them (Schedlowski and Schmidt 1996), with negative health and neural consequences (McEwen et al. 2015). Under chronic psychological or physical stress, pro-inflammatory cytokines (e.g., interleukins and tumor necrosis factors) are released by activated immune cells and can interact with multiple corticolimbic brain structures, dysregulating different growth factors (e.g., BDNF) and neurogenesis (especially in the hippocampus), several neurotransmitter systems (e.g., glutamate, serotonin, and dopamine), and neuroendocrine communication (Capuron and Miller 2011). One neural consequence under such conditions is microglia activation and a sustained release of inflammatory mediators (Leszek et al. 2016). For example, chronic stress increases the number of activated microglia in several corticolimbic regions, which can lead to neurodegeneration (mice: Nair and Bonneau 2006; rats: Tynan et al. 2010) as well as neuroinflammation that contributes to physiological, behavioral, affective, and cognitive disorders (de Pablos et al. 2014; McLeod et al. 2001).

Although there has been no direct comparative research on the neural consequences of stress in captive versus free cetaceans or elephants, existing data suggest that the immune system is negatively affected. For example, candidiasis, which is often observed in immunocompromised individuals, is relatively common in captive cetaceans secondary to stress (Ohno et al. 2019). In elephants, clinical outbreaks of salmonellosis tend to follow stress-related depression of the immune system (Fowler 2006b). Direct comparisons between captive animals and their free counterparts have also suggested weakened immune systems for some captive animals (e.g., spotted hyenas: Flies et al. 2015; zebras: Seeber et al. 2020). Biomarkers such as cortisol have also been examined to a limited degree, with acute measures indicating expected elevations in cortisol levels associated with events such as beach strandings in dolphins (Kellar et al. 2015) or transportation/relocation in elephants (Laws et al. 2007) and cetaceans (Noda et al. 2007; Spoon and Romano 2012). Notably, captive bottlenose dolphins kept in sea pen facilities that allow for ocean water flow and entry of small fish had significantly lower salivary cortisol levels than their cohorts in tanks (Ugaz et al. 2013). Similarly, not only do Asian and African elephants in larger enclosures exhibit lower glucocorticoid metabolite concentrations than their cohorts in smaller enclosures, but they also exhibit lower cortisol levels when they can access diverse enrichment options and allowed to be in compatible social groups (Brown et al. 2019). In Asian elephants, cortisol levels negatively correlate with locomotion and positively correlate with stereotypies (Schmid et al. 2001). To the extent that captivity induces stress-related immunosuppression, captive animals would thus be more susceptible not only to neuroinflammation but also to opportunistic infections and possible disruptions of fertility (Edwards et al. 2019).

Stress summary

From the neural perspective, both the PFC and hippocampus attempt to inhibit HPA activity, thus enhancing cognitive functions. However, the amygdala tends to facilitate HPA activity, potentially overriding the inhibitory mechanisms of the PFC and hippocampus, resulting in excessive anxiety and fear reactivity and, when chronically activated, inhibition of the immune system (Chattarji et al. 2015). It has been suggested that these corticolimbic structures are not only evolutionarily conserved in terms of volumetric measures, but also in terms on their functional

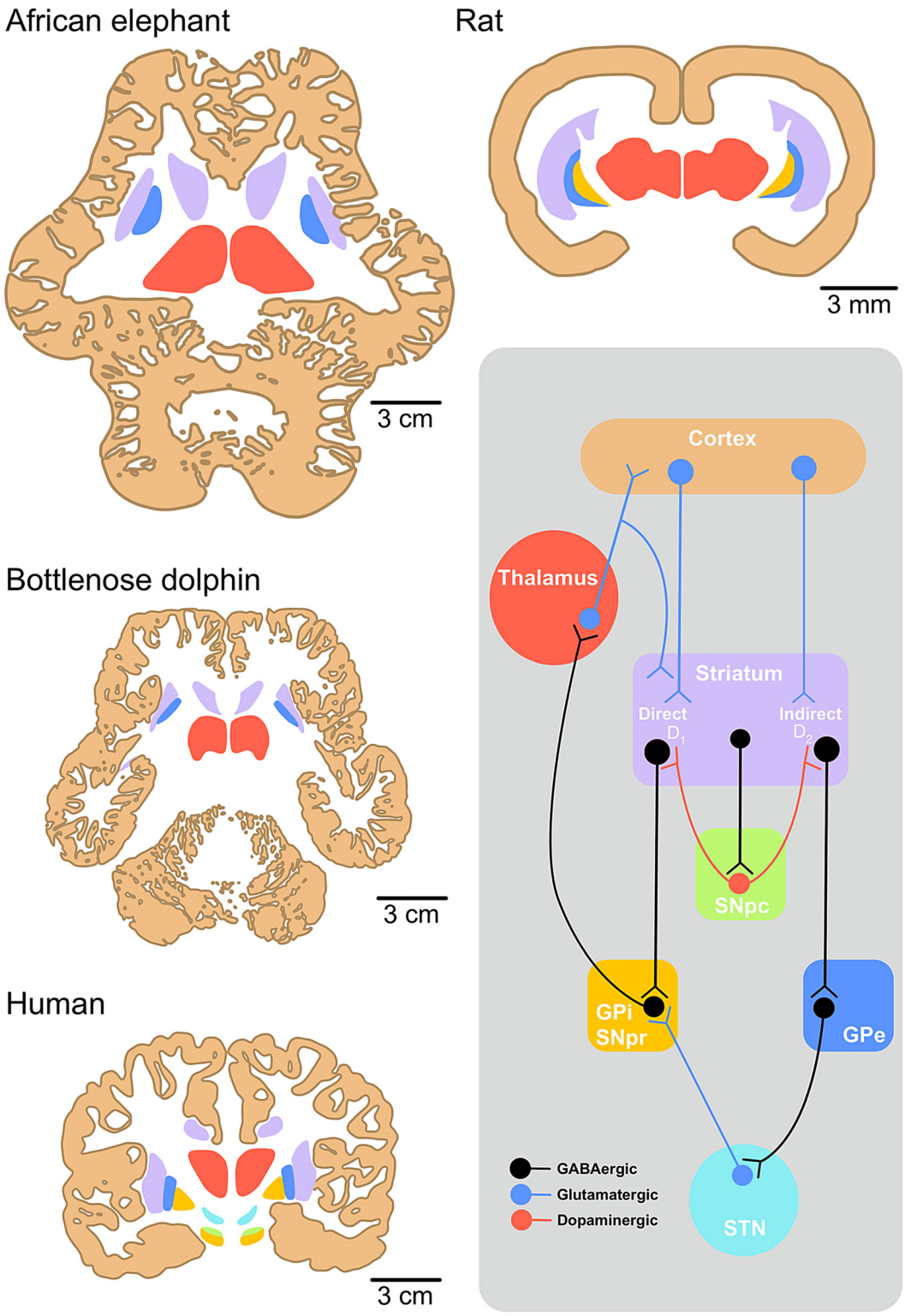

Figure 4: Schematic of brain structures involved in behavioral stereotypies.
Horizontal sections of African elephant and bottlenose dolphin brains, and coronal sections of human and rat brains revealing major structures involved in behavioral stereotypies. Not all structures are visible in all cross sections except for the human brain. A simplified schematic illustrates basic GABAergic, glutamatergic, and dopaminergic connections within this circuitry. Structures in the schematic are color coded to match brain cross sections. The direct pathway includes the following structures/projections: motor cortical areas → striatum → globus pallidus (interna)/substantia nigra (pars reticulata) → ventral anterior and ventral lateral nuclei of the thalamus → motor cortical areas. The structures of the indirect pathway are similar to those in the direct pathway with the addition of the

interconnectivity (Nikolova et al. 2018). As such, we expect that the large, complex brains of animals such as elephants and cetaceans would react to a chronically stressful environment in a similar manner as do the brains of other mammals (including humans) that have been investigated more thoroughly (Marino et al. 2020). Indeed, much of what we know about the neuropsychiatric consequences of chronic stress in humans derives from nonhuman animal models (Chattarji et al. 2015; Lecorps et al. 2021).

Stereotypies and neural dysregulation

Stereotypies are common human and nonhuman responses to chronic stress. In humans, although clinical definitions of stereotypy vary (Edwards et al. 2012), repetitive motor dysfunctions (e.g., hand flapping and head nodding) have been documented in several conditions: Autism spectrum disorder (Langen et al. 2014), primary complex motor stereotypies (Singer 2013), frontotemporal dementia (Mendez et al. 2005), neurodevelopmental disorders (Wilkes and Lewis 2018), Rett syndrome (Temudo et al. 2007), and schizophrenia (Morrens et al. 2006). Children with a history of early institutional care are more likely to exhibit stereotypies, underscoring the influential role of the environment during early development (Bos et al. 2010). In nonhuman animals, such behavioral stereotypies are seldom if ever observed in nature (Boorer 1972), but have been consistently documented in many captive animals beyond murid rodents (Table 1B).

Imaging studies in humans implicate nucleus size, connectivity, and structural variation with restricted repetitive behaviors (Wilkes and Lewis 2018), and have revealed positive correlations between enlargement of the caudate and putamen with the severity of stereotypic behaviors (Langen et al. 2014). However, the fundamental neural synapomorphy across eutherians allows for much more detailed (e.g., pharmacological, surgical, genetic) explorations in animal models (Langen et al. 2011b; Péter et al. 2017). The circuitry involved in motor control and stereotypies is complex. At the neural center of this circuitry is the basal ganglia (or corpus striatum), one of the largest subcortical structures in the cerebrum (Figure 4). Both elephants and cetaceans possess all components of the basal ganglia found in other vertebrates (i.e., caudate, putamen, and globus pallidus) as this is a highly conserved system crucial for integrative functions (Oelschläger et al. 2008). These structures also show the typical mammalian topographic relationships to each other and to adjacent structures (Cozzi et al. 2001; Oelschläger and Oelschläger 2009). In cetaceans, the corpus striatum, involved in motor and reward systems, is prominent in size (Oelschläger et al. 2008) with a histological organization similar to that observed in other mammals (Oelschläger and Oelschläger 2009). Through a series of reciprocal connections with the cerebral cortex, the basal ganglia select and orchestrate appropriate cortical activity for a given situation. To this end, three parallel corticostriatal loops appear to be involved in this process: (1) Sensorimotor (involved with motor output, including stereotypies), (2) associative (involved with cognitive processing and impulsivity/rigidity), and (3) limbic (involved with motivations and obsessions/compulsions; Langen et al. 2011a). A fourth, hyperdirect loop, has also been proposed which, in concert with the subthalamic nucleus, acts to shut down basal ganglia output (McBride and Parker 2015).

Direct and indirect motor control pathways

Within the sensorimotor loop, which is most closely linked to stereotypic behavior, there are two parallel pathways, both of which are modulated by dopaminergic input from the substantia nigra pars reticulata. The *direct* (striatonigral) pathway is a double inhibitory system (McBride and Parker 2015) that ultimately *activates* motor programs (Figure 4). Functionally, dopamine from the substantia nigra (pars compacta) acts on D1 receptors in the striatum to enhance excitatory input from the cortex. This increases GABAergic inhibition of both the globus pallidus (interna) and substantia nigra (pars reticulata) which, in turn, remove inhibition from the thalamocortical projections to motor cortices, thereby activating motor programs. In contrast, the *indirect* (striatopallidal) pathway is a triple inhibitory system that normally *inhibits* motor programs (Figure 4). However, when dopamine from the substantia nigra (pars compacta) acts on D2 (instead of D1) receptors in the striatum, it reduces (rather than enhances) excitatory input from the cortex. This decreases GABAergic inhibition of the globus pallidus

subthalamic nucleus: motor cortical areas → striatum → globus pallidus (externa) → subthalamic nucleus→ globus pallidus (interna)/substantia nigra (pars reticulata) → ventral anterior and ventral lateral nuclei of the thalamus → motor cortical areas (Calabresi et al. 2014; Langen et al. 2011b; Lewis et al. 2006). Abbreviations: D_1 and D_2, dopamine receptors; GPe, globus pallidus externa; GPi, globus pallidus interna; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; STN, subthalamic nucleus. Schematic is adapted from Gao and Singer (2013).

(externa) which, in turn, increases the amount of inhibition on the subthalamic nucleus. Increased inhibition of the subthalamic nucleus reduces its ability to excite the globus pallidus (interna) and substantia nigra (pars reticulata). Less activity in these two structures translates into greater disinhibition (i.e., more excitation) of thalamocortical projections, and more subsequent activity of motor programs.

The striatum and associated circuitry are thus tasked with evaluating the processed information received from diverse cortical areas and determining the context appropriate motor output for the given situation (Balleine et al. 2007). Normal movement depends on a delicate balance between the direct and indirect pathways, which are interconnected with other neural systems (e.g., mesolimbic). Several neurotransmitter systems influence these pathways (Gao and Singer 2013; Lewis et al. 2006), with dopamine and serotonin appearing to be the most crucial. Overactivation of striatal D2 receptors, for example, tends to suppress the indirect pathway, allowing stereotypical behaviors to emerge (McBride and Hemmings 2005). Moreover, the dopaminergic system itself appears to be modulated by serotonin, especially when stereotypies are stress induced (Langen et al. 2011b). Chronic stress also creates heightened dopamine sensitivity in the nucleus accumbens, which is part of the mesolimbic pathway associated with motivation (Cabib 2006). Under such conditions, overactivation of the nucleus accumbens may enhance the selection of specific behavioral sequences, contributing to the emergence and maintenance of spontaneous stereotypies (Poirier and Bateson 2017).

Environmental deprivation and social isolation have repeatedly been shown to dysregulate these motor control pathways in several species, resulting in stereotypies (rats: Hall et al. 1998; primates: Martin et al. 1991; horses: McBride and Hemmings 2005; and pigs: Sharman et al. 1982). By extension, environmental enrichment appears to rebalance activity in these pathways, thus at least partially ameliorating or even preventing the emergence of stereotypies (Table 1C). These effects have been documented in both human and nonhuman animals, underscoring common neural mechanisms (Garner et al. 2003). At the neural level, enrichment has multiple effects on these motor control systems. In the subthalamic nucleus and globus pallidus, both part of the indirect pathway, significant enrichment-related increases in neuronal activity and dendritic spine densities appear to attenuate stereotypies (mice: Bechard et al. 2016). Environmental enrichment appears to prevent stereotyped behaviors by increasing metabolic activity (as measured by cytochrome oxidase) in the motor cortex, the striatum, and the nucleus accumbens (mice: Turner et al. 2002). The prevention of stereotypies has also been linked to increased BDNF in the striatum resulting from enrichment (mice: Turner and Lewis 2003).

Stereotypies summary

Although the underlying neural mechanisms are not immediately obvious, the presence of stereotypies in captive animals, including elephants and cetaceans, reflects the neural attempt to cope with an impoverished environment and the resulting detrimental effects of chronic psychosocial stress (Cabib 2006; Poirier and Bateson 2017). What remains unclear is whether the observed stereotypies are the result of temporary pharmacological dysregulation or permanent structural damage (Cabib 2006).

Conclusion

The evidence reviewed here supports the hypothesis that captive elephants and cetaceans sustain impoverishment-related neural deficits and dysregulation similar to what has been documented in other species. Insofar as it is not possible to conduct the same kinds of experimental and functional neuroimaging studies in elephants and cetaceans as in other mammals, we have relied upon the method of triangulation to make inferences about the effects impoverished/captive environments have on elephants and cetaceans. Two of the three points in the triangle are known for captive elephants and cetaceans. First, they exhibit behavioral patterns and physical abnormalities similar to other mammals in impoverished environments. Second, they possess very similar, highly conserved, neurobiological systems as do other mammals for responding to impoverishment and chronic stress. Therefore, we infer the third point, namely that elephants and cetaceans sustain neurobiological insults from living in confined, artificial environments. When elephants and cetaceans are in impoverished environments, their brains likely are affected in a manner similar to all other species that have been examined under similar conditions. The evolutionary continuity in neural structures that exists across eutherians also strongly supports this conclusion.

To the extent that captive elephants and cetaceans experience poor welfare and insofar as our hypothesis about neural damage is valid, there are a couple of options available going forward. First, our hypothesis would be better addressed with neuroanatomical data on captive and free-ranging elephants and cetaceans. There are several brain bank collections for primate brains (e.g., The Primate Brain Bank, The UCLA Brain Bank) and one that includes dolphin specimens (e.g., Michigan State University's Brain Biodiversity Bank). These kinds of efforts would be amplified and made more scientifically substantive, and facilitate more

comparative analyses, if zoos and marine parks regularly contributed well-preserved postmortem brains to these projects. Unfortunately, there is currently little transparency or sharing of scientific information between many zoos/marine parks and the scientific community.

Second, insofar as most captive elephants and cetaceans cannot be "rewilded" for scientific and ethical reasons, the case can be made for transferring them to authentic sanctuaries, where they may live in a more natural environment. There are, for example, two elephant sanctuaries in the U.S. (https://www.pawsweb.org/; https://www.elephants.com/) and others around the world (e.g., https://globalelephants.org/overview/). Currently there is only one cetacean sanctuary in Iceland and it is housing only two beluga whales (https://belugasanctuary.sealifetrust.org/en/). Although more research is clearly needed, authentic sanctuaries report improved physical and psychological health in elephants after their arrival, including decreased frequency or extinction of stereotypies, reduced aggression toward keepers, muscle tone gain, and formation of social bonds between elephants with different social histories, including elephants who were abused, traumatized, or solitary for decades (Buckley 2009; Derby 2009). In closing, current evidence strongly suggests that zoos and marine parks currently provide impoverished environments that exact a neurobiological toll on elephants and cetaceans. Although systemic changes that address these welfare problems may be far off, continued scientific exploration of these issues appears warranted.

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