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PERSPECTIVE

Oxidative stress and cognition in ecology

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Abstract

Oxidative stress occurs when the body's antioxidant system is unable to prevent reactive oxygen species from causing cellular damage, and over the last two decades, oxidative stress has received extensive attention from behavioural ecologists investigating its links with life-history traits including reproduction, growth, and immunity. Despite the breadth of studies examining oxidative stress in relation to animal behaviour, life-history, and health, the role of oxidative stress in shaping variation in the cognitive abilities of wild animals has been almost entirely neglected. Here, I discuss how oxidative damage in the brain may affect cognitive performance in the wild, both directly and by mediating links to other life-history traits. First, I outline evidence that the brain is particularly susceptible to oxidative stress and highlight medical studies demonstrating that oxidative damage impairs cognitive ability in humans and other animals. I then explore how oxidative stress may similarly affect cognition and behaviour in an ecological context, and the far-reaching consequences this could have on wild animals' lives, including their fitness. Finally, I suggest methodological tools that could clarify the role of oxidative stress in cognitive ecology and approaches that combine existing ecological assays of behaviour and cognitive performance with bio-medical experimental designs. While challenging to investigate, oxidative stress in the brains of wild animals may have profound consequences for their cognition and health, which currently remain almost entirely unexplored.

Introduction

Oxidative stress occurs when excessive cellular generation of reactive oxygen species (ROS) damages the body's cells and tissues (Finkel & Holbrook, 2000), which can lead to tissue dysfunction and other diverse pathological effects at the organismal level (Halliwell & Gutteridge, 2007). As such, an individual's capacity to prevent, minimize, and recover from oxidative stress may be a key determinant of its fitness, and following a seminal paper by von Schantz et al. (1999), there was a surge of interest amongst behavioural ecologists in understanding the extent to which oxidative stress underpins key life-history trade-offs. While the field has made substantial progress elucidating the role of oxidative stress in shaping variation in survival, ageing rates, reproduction, growth, and immunity (Alonso-Alvarez et al., 2007; Bize et al., 2008; Costantini, 2014; Costantini & Møller, 2009; Cram, Blount, York, et al., 2015; Cram, Blount & Young 2015; Dowling & Simmons, 2009; Metcalfe & Monaghan, 2013; Monaghan et al., 2009; Speakman et al., 2015), links between oxidative status and cognitive performance remain virtually unexplored by ecologists.

The paucity of ecological studies investigating whether oxidative stress can affect variation in cognition is surprising, because bio-medical studies frequently invoke a role for oxidative stress in both mild and severe cognitive impairment disorders. ROS are known to mediate neuronal death in Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and many other behavioural or cognitive disorders in humans (*Homo sapiens*) (reviewed in Rego & Oliveira, 2003). Clearly, in humans, elevated oxidative stress in the central nervous system (CNS) can have life-altering consequences for behaviour and diverse aspects of cognition, yet the extent to which this occurs in animals, and whether levels of oxidative stress seen in wild animals can alter animal behaviour and cognition sub-lethally, are unknown.

In this article, I will summarize the key components in oxidative stress physiology, and outline why the CNS is *more* likely to suffer from oxidative damage than many other tissues investigated in ecological studies of oxidative stress, as a result of four aspects of the brain and neurons' structure and function. I then suggest how oxidative stress in the brain may affect animal behaviour and cognitive performance, based on medical studies of how it does so in humans and laboratory animal model species, and how altered cognition may impact behaviour and fitness in the wild. Finally, I provide advice for researchers aiming to develop studies to investigate links

between oxidative stress in the CNS and animal behaviour and cognition, by combining cognitive performance assays from behavioural ecology with physiological measures and interventions from medical studies.

Reactive oxygen species, antioxidants, and oxidative stress

The extent to which an animal suffers from oxidative stress depends on two factors. First, elevated generation of ROS is associated with greater oxidative damage (Finkel & Holbrook, 2000). ROS are primarily generated as a by-product of oxidative phosphorylation in the mitochondrion (Balaban et al., 2005; Chance et al., 1979), but are also actively produced by a number of enzymes to serve crucial functions in cell-signalling and immune defence (Finkel, 2003; Klebanoff & Clark, 1978). ROS are highly reactive and unstable, and unless neutralized, they rapidly trigger chain reactions resulting in harmful alterations to DNA, proteins, and lipids (Ames et al., 1991; Dröge, 2002).

The second factor that determines the extent of oxidative stress is the body's protection against ROS, and a complex antioxidant system has evolved to prevent, delay, or repair oxidative damage (Surai, 2002). Intracellular antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase form the first line of defence, while a complex group of non-enzymatic compounds further neutralize ROS. Non-enzymatic antioxidants can be dietary (e.g., vitamin E) or endogenous (e.g., glutathione). Overall, these components form an integrated biochemical antioxidant network (Kurutas, 2016).

Under normal circumstances, the balance between ROS production and antioxidant protection ("oxidative balance") is maintained such that oxidative damage is minimized. However, when the production of ROS is elevated, or antioxidant defences are reduced, ROS can overwhelm antioxidant protection and cause oxidative stress. Prolonged exposure to oxidative stress can cause significant disruption to normal cell function and has been implicated in impaired reproduction and growth (in ecophysiological studies, Costantini et al., 2016, Smith et al., 2016) and in the pathogenesis of a number of diseases (in medical studies, Guzik Tomasz & Touyz Rhian, 2017, Halliwell, 2006, Rego & Oliveira, 2003).

Susceptibility of the CNS to oxidative stress

Bio-medical studies indicate that four aspects of the CNS's function and anatomy make it unusually vulnerable to oxidative stress. First, the high oxygen consumption of the brain increases the risk of ROS generation. In humans, the brain constitutes only 2% of total body weight yet it is responsible for over 25% of the total oxygen consumption (Magistretti, 1999). While the human brain is disproportionately large relative to those of other animals, oxygen consumption per unit mass is similarly disproportionate in the brains of other vertebrates (e.g., Kummitha et al., 2014). As such, mitochondrial activity (the primary source of ROS generation) is likely to be exceptionally high in brain tissue of both humans and other animals.

Second, CNS tissue contains an abundance of compounds that are both vulnerable to, and can perpetuate, oxidative damage. Lipids are particularly susceptible to peroxidation, and lipid concentrations in the brain are second only to those in adipose tissue, constituting up to 50% of brain dry weight (Hamilton et al., 2007). Polyunsaturated fatty acids (PUFA) are abundant in membrane phospholipids in the brain and nerve cells, and they contain double bonds which give up hydrogen ions during peroxidation. PUFA are particularly liable to lead to oxidative stress because peroxidation creates unstable intermediates, triggering a chain reaction that can subsequently damage structures or cause cell death (Su et al., 2019). Termination of the lipid peroxidation chain reaction can only be achieved when multiple ROS combine to form oxygen and a non-radical, or by chain-breaking antioxidants such as vitamin E (Reed, 2011). In addition to vulnerable PUFAs, the brain contains high concentrations of redox-transition metals such as copper and iron, which are crucial for neurotransmitter synthesis and oxygen transport, respectively (Desai & Kaler, 2008; Sheftel et al., 2012). These metals can catalyse the formation of highly volatile hydroxyl ROS (Lovell et al., 1998), and imbalances in copper and iron ions have been implicated in a number of neurological disorders in humans, including Alzheimer's disease (Lovell et al., 1998).

Third, in addition to high oxygen consumption and an abundance of compounds vulnerable to peroxidation, some components of the antioxidant protection in brain tissue are surprisingly weak. Glutathione is a primary antioxidant in other tissues, and catalase is a ubiquitous antioxidant enzyme found in all known organisms, yet the actions of both these antioxidants are remarkably low in the brain (Zhao, 2005). Levels of other antioxidants (e.g., vitamin C) appear to be increased in some neurons in the brain (Rice & Russo-Menna, 1997), illustrating the complexity of the antioxidant system. Nonetheless, unusually reduced levels of catalase are associated with schizophrenia (Li et al., 2006), suggesting that where the brain's antioxidant capacity is not increased in-line with its vulnerability to peroxidation and high ROS generation, cognitive disorders can arise.

Finally, the ability of the CNS to recover from cell damage is typically limited. In humans, the poor regenerative capacity of central axons compared to other cells types (including peripheral nerves) has been studied for over 100 years (Iismaa et al., 2018). While there is substantial taxonomic variation in the responses of damaged CNS cells, only amphibians exhibit substantial neurogenic activity. By contrast, rats (*Rattus norvegicus domestica*) with CNS injury show slower functional recovery than primates, including humans (Friedli et al., 2015). Across mammals and birds, limited neurogenesis, the absence of axonal regeneration and a non-permissive repair environment in the adult CNS mean that the ill-effects of cell injury or cell death, whether from trauma, apoptosis, or oxidative damage, are likely to accumulate rather than subside (Barker et al., 2018).

In summary, characteristics of the CNS anatomy and function make it disproportionately likely to face ROS challenge, unusually vulnerable to peroxidation by ROS, and poorly

equipped to minimize and recover from the resulting oxidative damage (Fig. 1). While most of the studies are of human physiology, the limited evidence from animals suggests these traits are generalisable across taxa.

Bio-medical evidence linking oxidative stress with cognitive performance

Cognition comprises the mental mechanisms by which individuals acquire and store information through learning and memory, appropriately process this information, and use it to change behaviour (Shettleworth, 2009). As outlined above, extensive reviews implicate oxidative stress in the pathologies of neurodegenerative and cognitive disorders in human patients (Rego & Oliveira, 2003). However, links between oxidative status and cognition are also evident in patients with mild cognitive impairments and mood disorders (Hassan et al., 2014; Savage et al., 2021; Schiavone et al., 2015), and in healthy individuals at the end of their lifespan (Glade, 2010; Hajjar et al., 2018). The role of oxidative stress in shaping cognitive abilities is therefore not limited to patients with rare, severe disorders, and may similarly affect wild animals in an ecologically-relevant way. In this section, I will outline the evidence linking oxidative stress with cognition and behaviour, principally from studies of rodent animal models.

Learning and memory

There is strong evidence from animal models that performance in learning and memory tests is impaired by oxidative stress, and improved by antioxidants. An early study in mice (*Mus musculus*) found that age-related declines in learning and memory were associated with a substantial increase in two markers of oxidative stress in the amygdala and hippocampus, regions of the brain thought to be associated with memory and learning (Liu et al., 2003). This correlative evidence was strengthened by experimental increases in two antioxidant enzymes, SOD and catalase, which almost entirely mitigated both the oxidative damage and cognitive impairments in a dose-dependent manner. Notably, the dose that most effectively reduced oxidative damage also produced the best cognitive performance (Liu et al., 2003). The finding that SOD over-expression causes cognitive improvement has since been replicated across contexts: at advanced ages, mice over-expressing SOD exhibit improved spatial and working memory compared

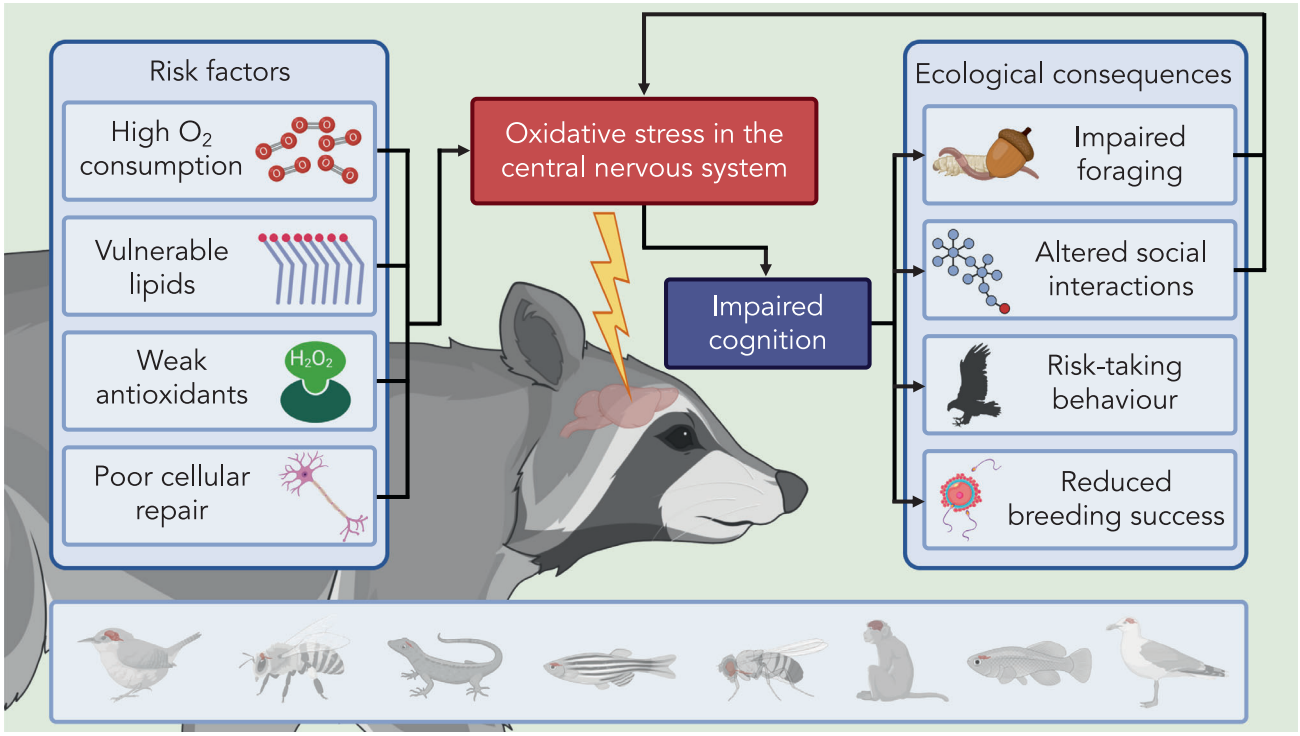

Figure 1 Schematic illustrating the putative causes and consequences of oxidative stress in the CNS of a racoon (*Procyon lotor*) and other vertebrate and invertebrate species. The high oxygen turnover, weak antioxidant protection, vulnerable lipids, and limited repair capacity of the CNS (in particular the brain itself) make these tissues disproportionately likely to suffer oxidative stress. Bio-medical data invokes a role for oxidative stress in the brain in a number of mild and severe cognitive impairments. In the wild, this could affect a range of behaviours. Those listed on the right are amongst the behaviours most likely to impact fitness. Impaired foraging and altered social interactions have the capacity to further increase CNS in the brain, by reducing antioxidant intake and elevating endocrine stress, respectively. Figure created with BioRender.com.

to wild-type mice (Hu et al., 2006; Kamsler et al., 2006). A similar study found that SOD over-expression allowed aged mice to recall maze-training more than a year later, by which time the performance of trained wild-type mice had regressed to that of naïve individuals (Levin et al., 2005).

The positive effects of SOD on learning and memory appear to generalize to several other antioxidants, and other species. In rats, vitamin E deficiency leads to poor performance in a maze test in early life, and supplementation can mitigate senescent memory declines later in life (Fukui et al., 2001; Kolosova et al., 2006). In some cases, combinations of antioxidants can prevent cognitive impairment where individual treatments do not. Aged mice given coenzyme Q and vitamin E performed better than control mice and mice on either single supplement, when faced with a suite of memory tests including maze navigation and avoidance of a familiar unpleasant stimulus (McDonald et al., 2005). Overall, the evidence indicates that oxidative stress in the CNS reduces an individual's ability to uptake and retain information about its environment in an adaptive manner. However, studies to-date are focused on rodent models and are limited to artificial captive contexts, and whether oxidative stress similarly affects learning and memory in other taxa in the wild remains unknown.

Processing information in an unpredictable or adverse environment

Animals that can successfully learn and recall information about their physical environment must also be able to process, integrate, and act on that information in an appropriate way, regardless of whether their environment is stable or changing. SOD-knockout mice showed wild-type performance in a learning trial, but were unable to complete a reverse-learning trial (Logan et al., 2019), suggesting that oxidative stress may affect behavioural flexibility in the face of a changing environment, thought to be a key component of general intelligence (Mikhalevich et al., 2017; Reader et al., 2011). Similarly, mice with elevated oxidative stress explored a novel environment less readily and with more errors, and also showed impaired motor coordination and balance (Evola et al., 2010; Forster et al., 1996; Navarro et al., 2002). Aged mice showing lipid and DNA oxidation in the hippocampus and cerebral cortex exhibited poor object recognition. In the same study, vitamin E treatment reduced lipid peroxidation, inhibited cell death, and led to recovery of cognitive abilities (Nagai et al., 2003). Together, the results of these studies suggest that oxidative stress in the CNS may impair a suite of cognitive processes, including motor skills, behavioural flexibility, and inhibitory control, culminating in an inability to respond appropriately to the physical environment.

Evidence suggests that oxidative damage in the CNS is equally as central in dysfunctional responses to the social environment as it is the physical environment. Studies involving experimental induction of stressful social environments in mice, rats, and zebrafish (*Danio rerio*) have indicated that the resulting anxiety-like behaviours and cognitive impairment are likely mediated by neuronal damage and cell death caused by oxidative stress (de Carvalho et al., 2019; Lehmann et al., 2019; Patki et al., 2013; Solanki et al., 2017). Both physiological deficits and behavioural symptoms can be ameliorated by antioxidant treatment (Lehmann et al., 2019; Solanki et al., 2017). Given the varied ways in which anxiety-like behaviours can manifest (Belzung & Griebel, 2001), oxidative stress has the potential to mediate dysfunction across a broad suite of behaviours in individuals facing adverse social environments. Oxidative stress may also cause individuals to respond inappropriately even in the absence of adverse social conditions: selected lines of mice with weak antioxidant protection display enhanced aggression to conspecifics (Costantini et al., 2008). In short, oxidative stress may both generate social adversity and exacerbate its ill-effects.

Ecological evidence linking oxidative stress with cognitive performance

Our understanding of links between oxidative stress and cognition in non-model species under ecological conditions is severely hampered by a shortage of studies. In many cases, it is difficult to infer whether oxidative stress is the cause or result of a given behaviour, because experimental manipulations and transgenic lines are not feasible. Nonetheless, there is growing evidence that links between oxidative stress and behavioural and cognitive variation evident in bio-medical studies are generalisable beyond humans and rodent models.

Oxidative stress appears to similarly impair learning and memory in non-rodent species. In zebrafish, oxidative damage to proteins and lipids in the brain is associated with age-related declines in problem-solving performance (Ruhl et al., 2016). In the same species, exposure to pro-oxidant pollution caused an upregulation in the expression of antioxidant genes, but this was not sufficient to prevent substantial increases in lipid peroxidation in the brain, which were associated with marked declines in the ability to socially learn a predator escape response (Attaran et al., 2020). A comparative analysis revealed that bird species with larger brains showed lower circulating markers of oxidative damage, consistent the hypothesis that larger brains must coevolve with an improved resistance to oxidative stress (Vágási et al., 2016).

Bio-medical evidence that increased oxidative stress can cause changes in impulsivity, flexibility, and exploration in rodent models is also supported by ecological studies of animal personality. In alpine marmots (*Marmota marmota*), blue tits (*Cyanistes caeruleus*), and greenfinches (*Carduelis chloris*), greater antioxidant protection was associated with suites of behavioural traits including exploration, boldness, reduced neophobia, and higher activity levels (Arnold et al., 2015; Costantini et al., 2012; Herborn et al., 2011). Together, these results suggest that enhanced antioxidant protection may allow individuals to more rapidly explore novel environments and effectively process and respond to the associated information. Importantly, causation has not been in established in these findings, and it remains unclear whether variation in oxidative status leads to, or results from, variation in personality.

How oxidative stress-impaired cognition could affect behaviour and fitness in the wild

In its broadest sense, cognition comprises animals' abilities to gather and retain information from their environment and use it to decide what to do, and any significant impact of oxidative stress on these abilities in the wild is likely to have widespread consequences for their behaviour, life-history, and fitness. Although no studies have directly investigated how cognitive differences associated with oxidative stress affect performance in the wild, extensive evidence suggests that variation in cognition affects outcomes in profound ways, and even mild forms of the cognitive impairments driven by oxidative stress outlined above in bio-medical studies are likely to have wide-ranging consequences for animals in the wild. In insects, studies demonstrate that those that learn more effectively show enhanced foraging efficiency (Raine & Chittka, 2008), resulting in more rapid growth and better investment in offspring (Dukas & Bernays, 2000; Papaj & Rausher, 1987). Learning capabilities similarly enhance insects' ability to locate other resources in the environment including mates, shelter, and suitable locations for egg-laying, as well as helping them avoid harmful substances and predators (reviewed in Nieberding et al., 2018). Captive whitetail damselfish (*Pomacentrus chrysurus*) that had learned to fear predators showed greater survival after release than those that had not learnt (Ferrari et al., 2015), and grey mouse lemurs (*Microcebus murinus*) that demonstrated greater problem-solving performance subsequently gained more weight during the harsh dry season (Huebner et al., 2018). Finally, cognitive ability may also be relevant to contests, by affecting participants' abilities to assess the contested resource, relate their competitive abilities to those of their opponent, and develop fighting strategies (Reichert & Quinn, 2017).

Cognitive abilities are likely to be particularly important in the face of human-induced rapid environmental change, and an animal's ability to maintain a healthy CNS oxidative status may govern, to some degree, their ability to learn to avoid harmful human cues and profit from new opportunities. Anthropogenic environmental change brings about an enormous wave of novel cues, which animals must learn, remember, and respond to in an appropriate manner. The fitness stakes of doing so are high, and animals must either adapt or perish in the face of man-made structures in their natural habitats, changing climates, and urbanization (Greggor et al., 2014; Lee & Thornton, 2021). Links between oxidative stress and cognition may be relevant to conservation strategies, if, for example, pro-oxidant pollution impairs cognition and limits animals' abilities to learn to avoid harmful man-made environments (Greggor et al., 2014).

Oxidative stress as a mediator of life-history trade-offs with cognition

While enhanced cognition can confer survival and fitness benefits (Ashton et al., 2018; Hollis et al., 2011; Maille & Schradin, 2016), the development and maintenance of the CNS is costly and cognition appears to be traded-off with other life-history traits. For example, selection-line experiments for brain size or cognitive ability led to reduced longevity and fitness (Burger et al., 2008; Kotrschal et al., 2013), and in humans, cognitive performance is traded off with reproduction and physical activity (Longman et al., 2017; Ziomkiewicz et al., 2019). The role of oxidative stress in mediating life-history trade-offs between growth, immunity, and reproduction has been a major focus in eco-physiology for over a decade (Monaghan et al., 2009; Speakman et al., 2015), yet oxidative stress has not been invoked as a mediator of trade-offs involving cognition. Given the costs of maintaining the CNS, its sensitivity to oxidative damage, and extensive evidence that CNS oxidative stress impairs cognition, it is plausible that the costs of enhanced cognition may arise (at least partially) because of the damaging effects of elevated ROS production and the re-allocation of limited antioxidants to the CNS. If oxidative stress does mediate the costs of cognitive performance, the trade-off could be partially alleviated by dietary antioxidants. Individuals with greater cognitive abilities frequently have enhanced foraging success (Hollis et al., 2011; Katsnelson et al., 2011), raising the interesting possibility that costly investment in cognition may, to some degree, pay for itself (Catoni et al., 2008).

How to study oxidative stress and cognition in ecology

How to measure oxidative status in the CNS

Oxidative status is a complex and multi-faceted physiological state, and a comprehensive assessment of it is challenging to achieve even before considering the difficulties presented by studying the CNS of wild animals. As detailed elsewhere, measurement of both oxidative damage products and antioxidant protection provides a more comprehensive picture of an animal's oxidative status (Costantini & Verhulst, 2009; Hõrak & Cohen, 2010). Given that destructive sampling is likely impossible for studies of wild vertebrates, most studies will likely rely on circulating markers of oxidative status. Next-generation brain-imaging technology could offer the ability to non-destructively estimate oxidative stress in a captive context (Belaïch et al., 2017), but this technology may not yet be applicable to ecological studies.

A key first step in the non-destructive estimation of CNS oxidative stress in wild animals will be to test the extent to which circulating markers of oxidative status are correlated with those in the brain. Studies of both humans and animals suggest some markers of oxidative status in blood are correlated with those of multiple other tissue types, suggesting that these markers may represent measures of systemic oxidative status (Margaritelis et al., 2015; Veskoukis et al., 2009). However, other markers vary across tissues, and while correlations have been found between blood and skeletal muscle, kidney, liver, and heart tissue, the CNS has thus far been neglected in these studies and there is a clear need for further work. Encouragingly, endocrinologists have identified

correlations between hormone measures in the blood and the brain, which have yielded important insights including, for example, that blood drawn from the jugular vein is more indicative of the brain physiology than blood from peripheral veins (Newman et al., 2008). Furthermore, by comparing steroid levels in blood entering the brain (in the carotid artery, or other peripheral blood) with those in blood leaving the brain (in the jugular vein), researchers were able to estimate steroid hormone production in the brain (Newman & Soma, 2011; Saldanha & Schlinger, 1997). Similar analysis of jugular blood, either in isolation or contrasted with peripheral blood, could provide valuable estimates of the generation of oxidative damage products and the consumption of antioxidants in the brain.

Urine samples provide a promising non-invasive method of measuring oxidative status, which may permit studies that would otherwise be impossible due to the difficulties of capturing and blood-sampling some species. Urine sampling may be the only option for such species, but it should also be considered even where blood-sampling is feasible, for welfare reasons and because the stress of capture and restraint can lead to confounding changes in physiology. Indeed, laboratory studies have measured oxidative status in urine for decades (Cathcart et al., 1984), and some relevant markers can be *more* stable in urine than in blood (Il'yasova et al., 2012). Two recent studies successfully measured markers of oxidative status in urine samples from wild primates, demonstrating the feasibility of this approach in ecological studies under difficult conditions at remote field sites (Melvin et al., 2022; Thompson et al., 2019). Careful consideration is needed to measure (and, where necessary, control for) environmental sample contamination, variation in urine concentration, diurnal fluctuations in markers, and sample stability both before and after freezing (Melvin et al., 2022). Furthermore, the degree to which urinary markers reflect CNS physiology, or systemic oxidative status, requires assessment. Such validation may not be possible in the focal species, but could more easily be carried out on captive or laboratory animals.

Invertebrates offer the opportunity to study links between oxidative stress and cognition in greater detail, because animals can be sacrificed. Furthermore, associations identified in invertebrates may be generalisable in taxa where destructive sampling is not possible, because aspects of cognition and neurophysiology are evolutionarily conserved across invertebrates and vertebrates (Grillner & Robertson, 2016; Morand-Ferron, 2017). Oxidative stress-mediated effects on cognition could impact a variety of traits and behaviours in insects and other invertebrates, including foraging, social interactions, inter-species interactions, predator avoidance, and mate choice. A number of species are emerging as model systems for studying invertebrate cognition, including butterflies, bees, ants, crickets, and flies (Gorostiza, 2018; Menzel, 2014; Toure et al., 2020). Many of these same species have been used in ecological studies of oxidative stress (Archer et al., 2013; Beaulieu et al., 2015; Simone-Finstrom et al., 2016), yet to my knowledge no study has investigated links between oxidative stress and cognition in insects.

How to manipulate oxidative status

Experimental manipulation will be a key tool in clarifying any causal links between variation in oxidative status and cognitive performance. An animal's oxidative status can be manipulated in three ways. First, the administration of pro-oxidant compounds can increase the oxidative burden and promote oxidative stress, which would be predicted to reduce cognitive performance. I advise against this approach, because the use of these compounds in wild vertebrates is ethically problematic, and it is challenging to evaluate the true cognitive ability of animals exhibiting generalized sickness behaviours and low motivation.

Second, the administration of supplemental antioxidants can reduce the natural occurrence of oxidative damage, potentially enhancing CNS health and cognitive performance. The antioxidant system is complex and inter-connected, and pharmacological administration of a single antioxidant can, in some cases, disrupt the system causing *increased* oxidative damage (Bowry et al., 1992), so caution is advised when developing treatments. Supplemental antioxidant treatments can either be general or targeted to brain tissue. General treatments aim to reduce the systemic oxidative burden on a study animal, without necessarily directly altering CNS physiology. If such treatment enhances cognitive abilities or otherwise affects behaviour, further work would be needed to understand the precise mechanism by which the treatment's consequences arise. Feasibly, improving overall oxidative status may permit greater allocation of endogenous antioxidants to the CNS, by relaxing life-history trade-offs mediated by oxidative status. A number of general antioxidant treatments have been developed and used in ecological studies, with results indicating a reduction in systemic oxidative stress, and these could readily be applied to research questions investigating links between oxidative balance and cognition or behaviour (Giraudeau et al., 2013; Orledge et al., 2012; Sebastiano et al., 2018). Alternatively, treatments could be developed that attempt to improve oxidative status in the CNS directly. Initial biomedical studies found that the efficacy of antioxidant therapies in treating severe neurodegenerative diseases in human patients is limited (Neves Carvalho et al., 2017), but this may be because the patients' cognitive abilities were already severely impaired. A critical consideration of antioxidant treatment is the ability of the compound to cross the blood–brain barrier, which some antioxidants can (reviewed in Pinto et al., 2020) while others cannot (Gilgun-Sherki et al., 2001).

Third, and currently most promisingly, experimental treatments can promote the expression of endogenous antioxidant defences, rather than providing supplementary antioxidants. For example, resveratrol, curcumin, and fumarates have been shown to activate the transcription factor Nrf2 which regulates a suite of endogenous antioxidant enzymes (Neves Carvalho et al., 2017), resulting in enhanced antioxidant protection and robust positive effects on patients with neurodegenerative disorders (Bomprezzi, 2015; Calabrese et al., 2012). Similar treatments effectively deployed in ecological studies would provide an ideal way to test whether oxidative stress affects cognition and behaviour.

Box 1. Outstanding questions

- Are circulating and urinary markers of oxidative status correlated with those in the brain?
- Does investment in life-history traits, or demanding cognitive tasks, elevate oxidative stress in the brain?
- Can dietary antioxidants improve oxidative status in the brain?
- Is there individual variation in susceptibility to brain oxidative stress? What are the correlates of this susceptibility, and is it heritable?
- Are there consequences of oxidative stress in the brain in terms of boldness, impulsivity, neophobia, social interactions, risk-taking, learning, memory, and behavioural flexibility? If so, what are the consequences for ecologically-relevant behaviours including foraging, finding a mate, maintaining social status, avoiding predators and pathogens?
- Is oxidative stress in the brain particularly harmful in specific contexts, including variable or human-altered environments?
- Is resilience to oxidative stress in the CNS increased during the early life, when learning is particularly important for development?
- Can oxidative stress in the developing brain cause lasting cognitive impairments?
- Does oxidative stress in the brain increase late in life? Is this associated with late-life declines in cognitive abilities?

How to measure variation in cognitive performance in the wild

Comprehensive guidance for assaying animals' cognitive performance has been provided elsewhere (Boogert et al., 2018), but briefly, there are three pitfalls that studies should avoid. First, single trials of cognitive performance offer relatively unreliable information. Repeated measures provide a better representation of the consistency of individual differences in cognitive performance, which both strengthens estimates of cognitive abilities, and can provide information about how variable individuals are. Second, measures (even if repeated) of performance at a single task are vulnerable to noise and the risk that the task may in fact not measure meaningful variation in cognitive performance. In addition to assaying an animal's ability to spontaneously solve a task (one of the most commonly used cognitive tests), studies should measure other aspects of its cognition and behaviour including, for example, learning, memory, impulsivity, and boldness. Finally, standardizing or statistically accounting for potential confounding influences of hunger, breeding status, and age will limit the effects of non-cognitive factors.

How to design studies to test links between oxidative status and cognition in ecology

I suggest three general approaches for tackling key unanswered questions regarding the role of oxidative stress in shaping variation in cognition and behaviour (Box 1). First, longitudinal studies of both cognitive performance and oxidative balance reduce the effects of noise and thus represent a more accurate picture of individuals' health and cognition, and provide opportunities to relate within-individual changes in oxidative status to changes in behaviour. However, I urge caution as correlative studies may mask costs and trade-offs, because higher quality individuals might be expected to show both stronger oxidative status and enhanced cognitive performance. Second, experimental manipulation of oxidative status, as discussed above, will allow researchers to identify any causal links between oxidative stress and performance at cognitive tasks both in captivity and in the wild (Cauchoix et al., 2017), as well as with social network position, reproductive success and survival. Finally, studies of animals in their early-life (including the prenatal phase) provide an opportunity to test whether oxidative stress in the developing CNS has organizational effects on behaviour and cognition that continue later in life. Evidence suggests that variation in conditions and physiology during the early life can have disproportionate effects on later-life reproduction, survival, and oxidative physiology (Blount et al., 2003; Lindström, 1999), but the degree to which early-life exposure to CNS oxidative stress affects subsequent cognitive ability and later-life fates remains unknown.

Conclusion

Oxidative stress has received extensive attention from ecophysiologists, but work linking it with life-history traits has thus far all but neglected cognition. The brain is uniquely susceptible to oxidative damage, which can be associated with both mild and severe declines in cognitive abilities in humans and laboratory model species. Avoiding oxidative stress in the CNS may also affect antioxidant budgets and thus mediate trade-offs with other life-history traits. In the wild, such effects would have far-reaching consequences for behaviour and fitness. Oxidative stress could therefore provide a mechanistic basis for behavioural and cognitive variation in the wild that can be studied without complex genetic and neurological techniques.

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Conflict of interest

The author declares that no competing interests exist.

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