Resilience in farm animals: biology, management, breeding and implications for animal welfare

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Abstract.   A capacity for the animal to recover quickly from the impact of physical and social stressors and disease challenges is likely to improve evolutionary fitness of wild species and welfare and performance of farm animals. Salience and valence of stimuli sensed through neurosensors, chemosensors and immunosensors are perceived and integrated centrally to generate emotions and engage physiological, behavioural, immune, cognitive and morphological responses that defend against noxious challenges. These responses can be refined through experience to provide anticipatory and learned reactions at lower cost than innate less-specific reactions. Influences of behaviour type, coping style, and affective state and the relationships between immune responsiveness, disease resistance and resilience are reviewed. We define resilience as the capacity of animals to cope with short-term perturbations in their environment and return rapidly to their pre-challenge status. It is manifested in response to episodic, sporadic or situation-specific attributes of the environment and can be optimised via facultative learning by the individual. It is a comparative measure of differences between individuals in the outcomes that follow exposure to potentially adverse situations. In contrast, robustness is the capacity to maintain productivity in a wide range of environments without compromising reproduction, health and wellbeing. Robustness is manifested in response to persistent or cyclical attributes of the environment and is effected via activity of innate regulatory pathways. We suggest that for farm animals, husbandry practices that incorporate physical and social stressors and interactions with humans such as weaning, change of housing, and introduction to the milking parlour can be used to characterise resilience phenotypes. In these settings, resilience is likely to be more readily identified through the rate of return of variables to pre-challenge or normal status rather than through measuring the activity of diverse stress response and adaptation mechanisms. Our strategy for phenotyping resilience of sheep and cattle during weaning is described. Opportunities are examined to increase resilience through genetic selection and through improved management practices that provide emotional and cognitive enrichment and stress inoculation.

Additional keywords: affective state, allostasis, animal behaviour, animal temperament, animal welfare, disease resistance, genetic selection, homeostasis, resilience, robustness, stress inoculation.

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'Well,' said Pooh, *'what I like best,' and then he had to stop and think. Because although Eating Honey was a very good thing to do, there was a moment just before you began to eat it which was better than when you were, but he didn't know what it was called.* A.A. Milne, *Winnie-the-Pooh*

1. Introduction

During its development and during later life, each animal is exposed to a diversity of stimuli arising from its internal and external environments. It is desirable for the animal's welfare, and for its commercial productivity and environmental fitness that it has a capacity to cope with these challenges and to bounce back rapidly when insults to its integrity occur. Although factors influencing the development of phenotype have been a focus of research for over a century (Strandberg 2009), the past decade has seen a substantial increase in interest in resilience

and robustness of animals to environmental effects (Klopcic *et al*. 2009; Hermesch and Dominik 2014). Resilience to the effects of parasitic disease in farm animals was first recognised 80 years ago by Clunies Ross (1932), yet, in recent years, a broader concept of resilience has emerged in animal and human sciences that encompasses not only the response of the individual to disease challenges but also the individual's response to environmental and social stressors (Russo *et al*. 2012; Wu *et al*. 2013; Hermesch and Dominik 2014). Therefore, in Section 2 of this review, we examine the biological processes whereby animals respond to signals from their internal and external environments, the influence of personality, emotion and cognitive functions of the animal on these responses, how responses to stimuli are regulated and what happens when signals are noxious or overtax the capacity of the animal to cope. Two patterns of environmental challenges are identified. The first are episodic, sporadic or situation-specific challenges

that evoke acute stress responses and accommodation via facultative learning. The second are persistent or cyclical challenges that the animal adjusts to via innate regulatory pathways. From this biological background, we examine in Section 3, the current concepts of resilience and robustness, and suggest a broader definition of resilience that encompasses the animal's capacity to cope with environmental, social and disease challenges. We propose that resilience can be described as the capacity of the animal to be minimally affected by a disturbance or to rapidly return to the physiological, behavioural, cognitive, health, affective and production states that pertained before exposure to a disturbance. In the remainder of the review, we examine approaches for managing and breeding animals to improve resilience.

2. Sensing, reacting to and coping with the environment

The interactions of an animal with its environment are central to the concept of resilience and it is the biology of these responses that are explored below. Readers with little interest in the biological concepts underlying resilience could proceed directly to Section 2.8 for a summary of this section.

2.1. Sensing environmental stimuli

Sensing the environment is the first step by which an animal becomes aware of potential threats to its integrity. More broadly, the animal interacts with its environment so it can gather resources and can express functions and activities that contribute to its life history. To engage in these actions, the animal requires information about the environment it occupies, including its internal environment. Information from these environments is gained via three main media: (1) sensors in the peripheral nervous system, which transmit information to the central nervous system via axons; (2) receptors throughout the body, which respond to chemical and hormonal stimuli and communicate with the host cell bearing the sensor, with neighbouring cells, with distant organs and with the central nervous system via autocrine, paracrine and endocrine messages that are distributed throughout the body by interstitial fluid, lymph, cerebrospinal fluid and blood; and (3) the immune system. These can be abbreviated to neurosensors, chemosensors and immunosensors.

In a broad ranging classification of neurosensors, Sherrington (1900) recognised five sense modalities: teloreception (vision and hearing), proprioception (limb position), exterioception (touch, pain and temperature), chemoreception (taste and smell) and interoception (visceral sense). Stimulation of sensors in the sense organs (e.g. eye, inner ear) or on axons in peripheral tissues (e.g. stretch receptors in the rumen wall) invokes action potentials, which convey signals via afferent nerves to the central nervous system where sensations are perceived. New sensibilities of these sensors, such as a primary taste sensibility for fat in humans (Keast and Constanzo 2015), continue to be found. Among these senses, the interoceptive sense is least well characterised. Although it was recognised by Sherrington in 1900, the neuroanatomical pathways for interoception have only been identified in recent years, and it is now considered that interoception provides a sense of the physiological condition of the entire body rather than being limited to sensing visceral

organs (Craig 2002). This interoceptive sense has also been called the homeostatic sense and may provide a sense of somatic self which, at least in humans, provides through self-awareness a sense of 'how one feels' (Craig 2002, 2003).

Immunosensors detect the presence of foreign (non-self) molecules through germ line-encoded receptors of the innate immune system and through receptors that are generated throughout life by receptor gene hypermutation in the T and B lymphocytes of the adaptive immune system. The immune system shares with other cells and organs of the body the capacity to communicate via autocrine, paracrine and endocrine pathways and is intimately linked with the autonomic nervous system (Czura and Tracey 2005; Wrona 2006). Chemosensors provide the means for cellular and organ exchange and utilisation of resources and one medium for central regulation of these functions. Importantly, the nutrient economy of the cell is not managed autonomously by the cell but is regulated via extracellular signals received predominantly via chemosensors (Fox *et al*. 2005).

2.2. Processing environmental stimuli

Sensors need stimulation for the development and ongoing expression of normal functions. Stimulation is particularly important during critical periods in the ontogeny of the sense functions (Wiesel 1982). The concept of critical periods was first developed to describe acquisition of behaviours and social skills (Scott 1962) and is applied now throughout developmental biology and epigenetics in the study of environmental influences on phenotype. For instance, a critical period is seen in the immune system where stimulation during early postnatal life develops immune capabilities and influences response characteristics expressed in later life (Kelly and Coutts 2000) that influence metabolic profiles and disease susceptibility (Tilg and Kaser 2011). The function of sense organs is adapted to an optimal range of stimulus intensity and either too low or too high a rate of stimulation of some types of sensors can have adverse effects for the animal (Wiesel 1982).

Animals respond both to quantitative and qualitative attributes of stimuli. Quantitative attributes include frequency and intensity of stimuli whereas qualitative attributes include salience and valence. The ways that tissues respond at a local level and the way the animal responds at a central level are influenced by the state of the system and by the stream of stimuli it is receiving. The stream of stimuli impinging on the animal creates a context within which an individual stimulus is nested and this context influences the ability of the animal to discriminate a single stimulus from background (the stimulus salience). Thus, context can influence the ability of the animal to attend to and respond to a stimulus. The aversiveness or pleasantness of a stimulus (its valence) is also influenced by context. For instance, the speed with which temperature changes within a constant range influences the extent of emotional and physiological responses in cattle (Desire *et al*. 2002). A detailed account of how stimulation of thermosensors in skin at a single temperature can be perceived as either pleasant or painful depending of the context of the stimulus is provided by Craig (2002). The state of the system, known as its affective state, can also influence the valence of a stimulus (Mendl *et al*. 2010),

as demonstrated in sheep (Doyle *et al*. 2010) and as described in more detail in Section 2.5.3.

Individual sensors respond to a limited range of the stimulus spectrum and thus impose an initial filter on the environmental information relayed to the animal. Additional filtration at the sensor level occurs due to sensor response characteristics such as hysteresis, refractory period, co-operativity and blockade by antagonists (Gether and Kobilka 1998; Dumont *et al*. 2002). Following stimulus sampling and filtration by the sensor, messages from neurosensors and some chemosensors and immunosensors are processed by the central nervous system. Cells in peripheral tissues also process signals from chemosensors and immunosensors. The salience and valence of a stimulus are in part attributes or qualia that arise from the animal's perception of the stimulus rather than qualities intrinsic to the stimulus or the filtered sample relayed by the sensor. Perception of a stimulus is largely a function of the central nervous system that involves integrating multiple sources of information. Tissue and immune system perception of stimulus salience and valence are also important concepts but will not be pursued here.

2.3. Regulation of responses to environmental stimuli

The need for the animal to maintain a stable internal environment in the face of environmental fluctuations was first recognised by Claude Bernard (Cooper 2008). Walter Cannon subsequently called this process of physiological regulation homeostasis (Cannon 1929). The involvement of behavioural anticipations and behavioural reactions in maintaining the internal environment was first recognised by Pavlov (1904; Smith 2008) and Richter (Woods and Ramsay 2007). With the progressive development of engineering systems during World Wars I and II to improve the targeting of weapons by use of negative feedback to correct errors, it was proposed that animals also use negative feedback to control physiological responses (Rosenblueth *et al*. 1943). In subsequent decades, negative feedback to control a physiological variable at a fixed set point became the default model of homeostatic regulation (Carpenter 2004). In fact, much more complex mechanisms of physiological regulation occur, and the inaccuracy of a set point model for describing regulation via negative feedback has long been recognised (Carpenter 2004; Cooper 2008). Rather, it is considered that physiological variables are regulated within a range, with excursions above and below the range controlled by various effector mechanisms which often act independently. Importantly, there is no error signal generated by comparison between the current value of the regulated variable and a notional target value or set point (Ramsay and Woods 2014). This model of regulation leads to the concept that the physiological variable is regulated towards a settling range or balancing range rather than a fixed point. Using thermoregulation as an example, a detailed account of the balancing point or balancing range model of regulation is provided by Ramsay and Woods (2014). These authors note that measuring a regulated variable often tells us little about the activity status of the various effector mechanisms that influence the variable. This observation can be generalised to the notion that proximate mechanisms require a different level of enquiry than the ultimate biological functions they act on (Bateson and Gluckman 2011). Thus, physiological processes can be viewed as defending critical functions of the animal, such as nutrient storage in body mass, through multiple effector mechanisms.

### 2.4. Adaptation to environmental change

The changing nature of environmental conditions requires continual adaptation (acclimatisation) by the animal during the course of its life. Koolhaas *et al*. (2011) suggest that physiological processes are adapted to a range of values for each environmental variable and that the capacity of the physiological response to adapt to environmental fluctuations is greater towards the centre of this range and diminishes at its periphery. Changing environmental conditions can shift the regulatory range. This is exemplified by the shift in the thermoneutral range of sheep adapted to cold (Webster *et al*. 1969) and in cattle adapted to heat (Kadzere *et al*. 2002). When animals are exposed to an increasing heat load their adaptive capacity is reduced and the cost of maintaining normal functionality is increased (Kadzere *et al*. 2002; Roberts 2007). This is seen for instance in the increased maintenance costs (Collier *et al*. 2009) and lower milk production in heat-stressed cows than in pair-fed control cows (Rhoads *et al*. 2007). At a cellular level, microRNA play an important role in reprogramming gene expression during such adaptation (Leung and Sharp 2010). Fig. 1 illustrates the increasing recruitment of adaptive responses in sheep as they attempt to control body temperature during exposure to increasing ambient temperatures.

The physiological demands of life events such as pregnancy, lactation, migration, and hibernation are coordinated by changes in hormonal activities that alter nutrient utilisation by tissues (Bauman and Currie 1980; Bell 1995; Bell and Bauman 1997). These homeorhetic changes anticipate the demands of changing tissue activities that are linked to cyclical or persistent environmental stimuli such as seasonal changes and the reproductive cycle.

2.5. Sources of variation between individuals in responses to environmental stimuli

2.5.1. Behavioural types

The individual's response to environmental stimuli is influenced by numerous factors including ontogeny, experience, genetics, age, sex, physiological status, emotional state, cognitive function and season (von Holst 1998; Cockram 2004; Veissier and Miele 2014). Furthermore, individual variation can occur at each level of the response: sensor stimulation, perception, reaction, and outcome (Moberg 2000). Within this underlying variation, an individual animal can show a consistent type of behavioural and physiological response in different challenge situations and on different occasions when exposed to a single type of challenge. When the behavioural response is consistent across time and across situations it is described as a behavioural type, temperament or personality (Sih *et al*. 2004; MacKay and Haskell 2015). A combination of genetic, physiological and cognitive attributes creates a so called behavioural architecture that supports associations between behaviour type and metabolic rate, cerebral lateralisation and response to stressors (Wolf and Weissing 2012). The position of an individual on several behavioural axes is recognised as temperament traits. Prominent axes for characterising temperament traits are frequently
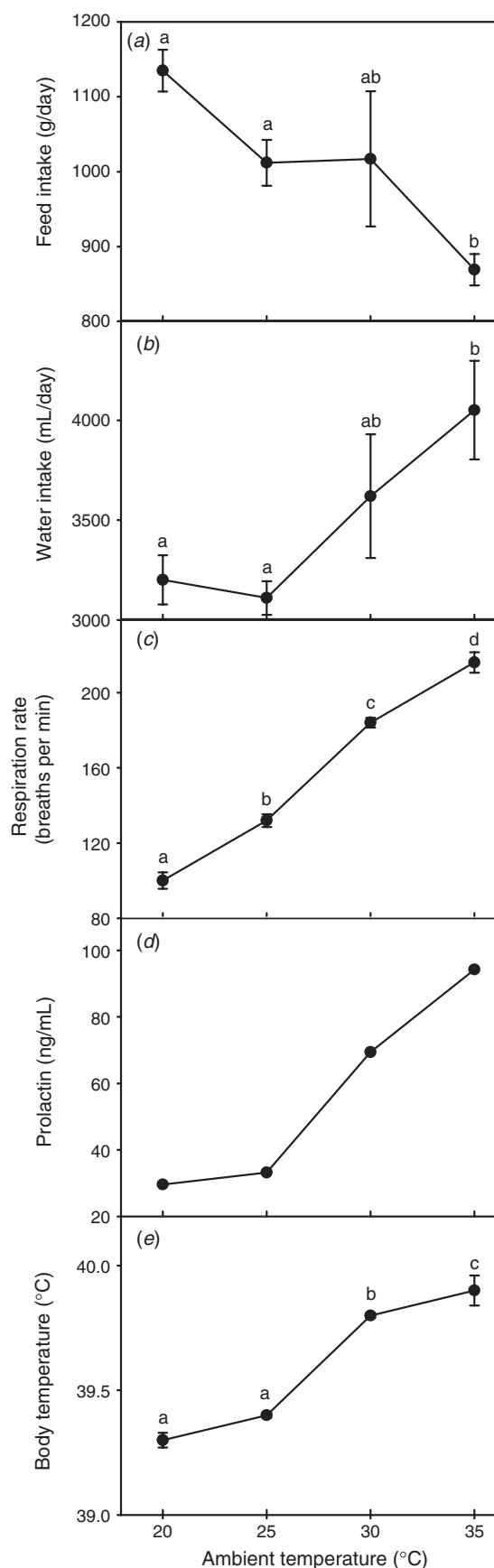
described with terms equating with bold–fearful, exploratory–neophobic, active–inactive, social–asocial, and aggressive–non-aggressive (Réale *et al*. 2007). Alternatively, temperament is sometimes described as the position on a single factor vector, for example degree of fearfulness, rather than a position on a spectrum between two behavioural antonyms (Mehta and Gosling 2008). Temperament influences several types of responses to environmental stimuli (Stamps and Groothuis 2010) and hence is likely to be one of the factors influencing resilience to potentially adverse challenges.

2.5.2. Coping styles

Correlated behavioural and physiological responses to stressful stimuli have been termed coping styles (von Holst 1998; Koolhaas *et al*. 1999). Two major coping styles to stressor challenges are proactive and reactive coping. The proactive style is associated with higher behavioural activity, elevated reactivity of the sympathetic autonomic nervous system (SAM) and higher sensitivity of the dopaminergic reward system whereas the reactive coping style displays lower behavioural activity (withdrawal, freezing, less aggression), and high hypothalamic-pituitary-adrenal (HPA) axis and parasympathetic reactivity in stressful situations (Coppens *et al*. 2010). Importantly, coping style does not equate with success in coping with stressors: the term describes the strategy or processes an animal employs when reacting to stressors rather than the outcome of the coping response (von Holst 1998). The distribution of individuals along the coping style axis can differ between populations and this distribution may have been influenced by selection of farm animals for certain production traits due to genetic correlations between the selected traits and the physiological and behavioural processes underpinning coping styles. For instance, in recent decades, genetic selection in pigs (Knap 2005) and meat sheep (Rowe and Banks 2015) has resulted in reduced carcass fat that in pigs has been accompanied by a reduction in urinary cortisol concentrations (Foury *et al*. 2009) that might also reflect a change in coping style in the selected population. Furthermore, recent studies indicate that catecholamines like adrenaline produced by the SAM during stress responses stimulate proliferation and virulence of common pathogens of farm animals (Freestone *et al*. 2008). Thus, coping style, and as we

Fig. 1. Physiological changes in Merino sheep exposed to ambient temperatures of 20°C, 25°C, 30°C and 35°C at 70% relative humidity for 5 days. Values are means ± s.e.m. of daily measurements of groups of 12 sheep. (*a*) Feed intake, (*b*) water intake, (*c*) respiration rate, (*d*) plasma prolactin, (*e*) vaginal temperature. Within a variable, ambient temperature treatments without a common letter are significantly different (*P* < 0.05). Biological adaptation at 25°C was achieved by increased respiration rate, which maintained body temperature at the level seen in sheep held at 20°C. Sheep were not able to fully adapt to the higher ambient temperatures through the behavioural response of elevated respiration rate. Consequently, body temperature and water intake increased and feed intake decreased. Prolactin levels were not statistically analysed in the form present here. With failure of the behavioural response to control body temperature, prolactin secretion was increased as part of the effector responses attempting to balance physiological variables. Data from Roberts (2007), with permission.

shall see later resilience phenotype, could be closely linked to disease susceptibility in farm animals, whereas the impact of selection for production traits on the SAM/HPA balance noted above could be contributing to increased disease susceptibility in high-production genotypes (Rauw *et al*. 1998).

Use of environmental resources can differ between behavioural types, as demonstrated by the influence of boldness/shyness on grazing behaviours in sheep (Michelena *et al*. 2009). Some differences in susceptibility to stress-related disease and some differences in reactivity to immunological stimuli have been noted between coping styles. For instance, sheep with a proactive coping style had a more protracted increase in body temperature, a greater reduction in feed intake, and a smaller increase in cortisol in response to challenge with endotoxin, which is a potent stimulator of the innate immune system, than sheep with a reactive coping style (Lee *et al*. 2014). Pigs that were classified retrospectively as proactive on the basis of aggression in a test of social confrontation together with resistance in the backtest had greater *in vivo* and *in vitro* activity of cell-mediated adaptive immunity and lower antibody responses in the humoral arm of adaptive immunity (Hessing *et al*. 1995). Interestingly, cell-mediated adaptive immunity was suppressed by weaning stress in the proactive but not the reactive pigs. In a separate study, pigs classified by the backtest as proactive also had lower antibody responses (adaptive immunity) to ovalbumin, keyhole limpet hemocyanin and tetanus toxoid than reactive coping-style pigs (Schrama *et al*. 1997). It is noteworthy that behavioural tests used in the identification of coping styles are also used to define temperament in farm animals.

2.5.3. Influences of affective states

The operational state of the central nervous system influences the way an animal responds to environmental stimuli. The operational state, more commonly termed the affective state, acts as both gate keeper and modulator of stimuli as they pass from afferent sensory inputs to the efferent outputs that activate the response modalities of the physiological, immune, behavioural, and cognitive systems and tissue morphology (Fig. 2). Just as the passage of light is influenced by the molecular structure and the interface angle as it traverses a prism, processing of stimuli through the central nervous system is influenced by two principal aspects of affective state, its valence and its arousal. As well as modulating outputs, valence and arousal can themselves be influenced by afferent inputs (Mendl *et al*. 2010). Two important proximate outputs of stimulus modulation by the operational state of the central nervous systems are the affects termed emotions and moods of the animal (Mendl *et al*. 2010). As well as inputs from the external environment, endogenous stimuli from the animal's internal environment provide important inputs which influence affective state. For instance, interoceptive inputs (Section 2.1) can generate positive and negative valence and the affect of homeostatic wellness (Craig 2003; Wiens 2005), and certain sensory nerve fibres provide inputs that can generate strong negative valence and the affect of pain (Shackman *et al*. 2011).

Despite longstanding interest in the expression of emotions in animals (Darwin 1965), acceptance that animals do indeed experience emotions has been slow to develop (Veissier and Miele 2014). Opinions differ on the nature of emotions, their proximate mechanisms and the ultimate functions they serve. An evolutionary role for emotions in enhancing fitness through effects on the animal's success in acquiring rewards and avoiding punishments has been proposed (Mendl *et al*. 2010). Emotions can be considered to be transient changes in affect, which can accumulate to create longer-lasting affective states such as moods (Boissy *et al*. 2007; Mendl *et al*. 2010; Boissy and Lee 2014).

A valuable insight into the nature of emotions is provided by Barrett (2012) who suggests that the named emotions such as fear, joy, and anger in humans are socially constructed concepts that are learnt as the child matures. Barrett illustrates this proposition in the following manner. Plants exist in the physical world. When viewed by humans, plants can acquire functions such as becoming a weed or becoming a flower that are not intrinsic to their biological activities as plants. The function emerges from the interaction between the physical object (the plant) and the conceptual constructs of the human agent. In like manner she suggests that in humans, the changes in the physiology, behaviour, voice and neural activity that occur during emotional reactions acquire functions through application of the learned and socially shared concepts that we know as acculturated individuals by names like fear, joy and anger. The functions of these named emotions are a property of secondary consciousness (awareness of awareness), which is a human trait that appears to not be shared by farm animals (Hobson 2009). Barrett's viewpoint has been strongly influenced by her team's own research and a meta-analysis of numerous studies, which failed to find unique neurophysiological signatures for the individually named emotions (Lindquist *et al*. 2012). Further exploration of this concept is beyond the scope of the current review, except to say that if Barrett's proposition pertains, then as animal scientists we may be forcing the observable reactions of the animal to certain environmental challenges into categories (e.g. fear, joy, aggression) that are not functionally discriminated by the animal itself. But this is not to say that Winnie the Pooh did not enjoy the anticipation of eating honey for want of a name to describe the emotion. As we shall see in Section 3, constructing the concepts of resilience and robustness carries this same risk of imposing values-based functions on characteristics of animals where biological functions might not exist.

A conceptual framework for assessing discrete emotions through behavioural testing in farm animals was introduced by Desire *et al*. (2002). These authors proposed using test paradigms controlling the suddenness, novelty, intrinsic pleasantness, predictability and controllability of stimuli, and then monitoring subsequent neurophysiological, motor and motivation reactions of the animal from which emotional reactions could then be inferred. In addition, test paradigms to assess the impact of valence and arousal dimensions of affective states on cognitive functions of farm animals have been developed (Mendl *et al*. 2009, 2010). From studies employing these test paradigms in farm animals, and from a very large body
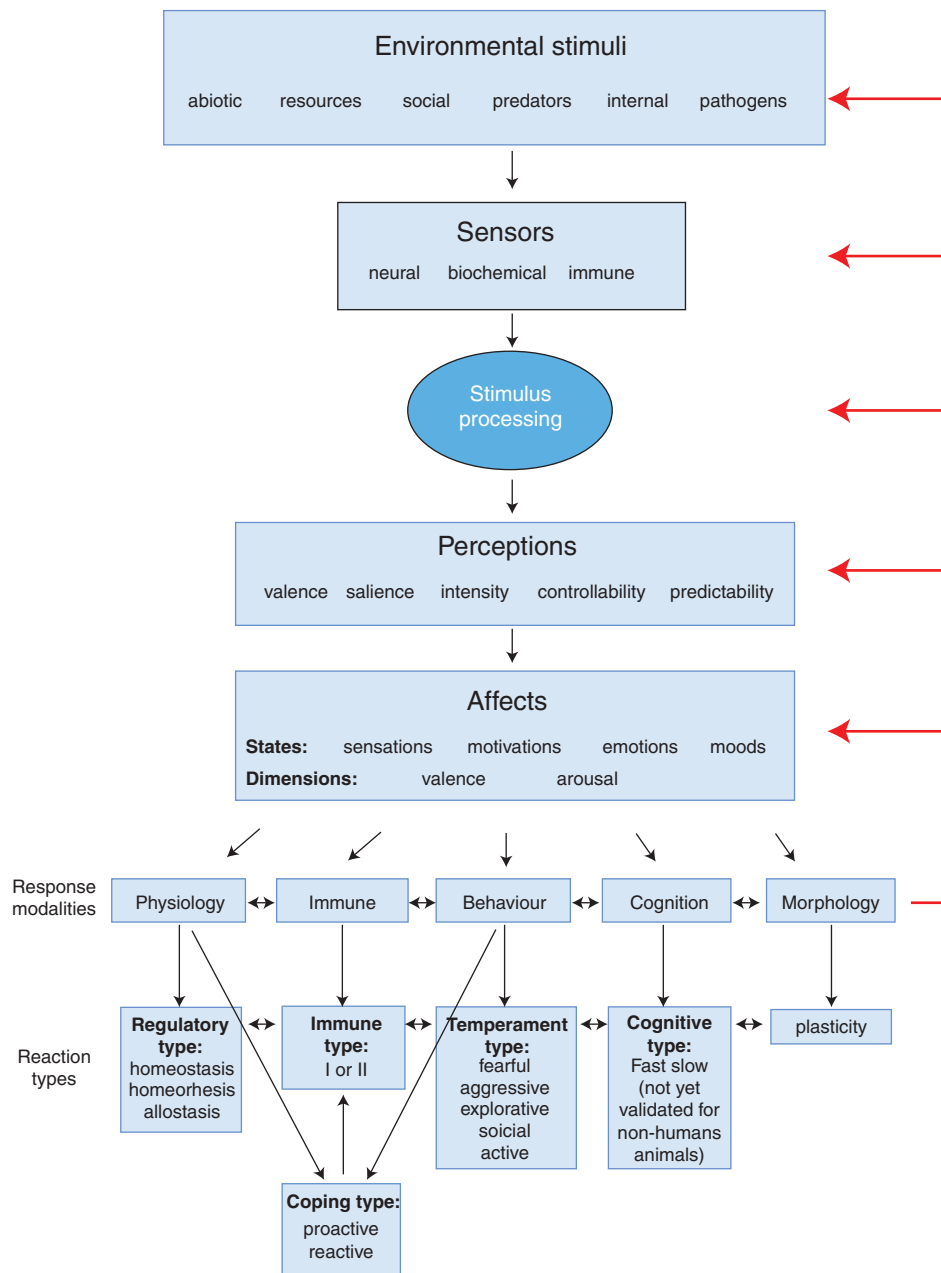
Fig. 2. A simplified representation of stimulus processing. Environmental stimuli are sensed by neural, biochemical and immune sensors. Processing of signals leads to perception of stimulus attributes including salience, valence, intensity, controllability and predictability. Perceptions modify affects which in turn modulate the response modalities activated by the stimulus. Response modalities exhibit several type reactions that can be consistently expressed across a range of stimulus situations. Interactions between response modalities and reaction types further modulate responses and provide feedback (red arrows) to affect, signal processing and sensing processes with the ultimate goal of controlling interactions of the animal with environmental stimuli.

of research in laboratory animals, several principles have emerged:

- Negative affective states can diminish cognitive functions, expression of production traits and health outcomes (Boissy *et al.* 2007; Doyle *et al.* 2011).
- Predictability and controllability of exposure to a stressor can diminish the perceived negative valence of the stressor and

subsequent magnitude and negative valence of responses (Greiveldinger *et al.* 2007, 2009).
- Anticipation can increase the hedonic value of a reward (Boissy *et al.* 2007).
- A negative affective state (frustration) can arise from failure to receive an anticipated hedonic reward or failure to fulfil a motivated behavioural drive (Greiveldinger *et al.* 2011).

- The negative value of a diminished reward is perceived to be greater than the positive value of an enhanced reward (Boissy *et al*. 2007).

Sustained adverse environmental conditions such as heat or cold, and low body mass during periods of limited feed availability or when body reserves are being used to support lactation impose substantial stress on farm animals (Bell and Bauman 1997; Collier *et al*. 2009; Sordillo and Mavangira 2014). Studies using operant conditioning show that animals will work hard to alleviate heat stress and undernutrition and suggest that these stresses create negative affective states (Roberts 2007; Roche *et al*. 2009; Stockman *et al*. 2014). The contribution of negative affective states to the impact of these common production stressors on the animal is an issue deserving more attention. Fig. 3 illustrates the behavioural demand of sheep to alleviate heat stress in an operant conditioning model. In conclusion, affective states influence the perception of stimuli as positive or negative, and also influence health, productivity, and the likelihood of the animal recovering quickly or developing adverse responses to environmental perturbations.

2.5.4. Social effects on individual responses

In social species, interactions between individuals and social isolation can be a source of stress and can influence access of the individual to environmental and social resources (Langbein and Puppe 2004; Greenwood *et al*. 2014). Position of the individual within the social structure of the group can influence physiological and immune responses and disease outcomes (Hessing *et al*. 1994; Tuchscherer *et al*. 1998; von Holst 1998). Social conflict has been used in tests of coping style in farm animals (Koolhaas *et al*. 1999; Lee *et al*. 2014) and in animal models of human resilience (Russo *et al*. 2012; Wu *et al*. 2013). Social conflict provides strong afferent inputs to affective state to influence the response modality of the individual to the stressor (Wu *et al*. 2013).

2.5.5. Immune response types

A dimensional model is also sometimes used to describe adaptive immune responses to antigenic stimuli. The dimensions are described as Type I and Type II immunity on one axis and the degree of immune responsiveness on the second axis. When faced with a pathogen challenge the body usually mounts an effective and efficient immune response. Some pathogens have devised means by which they enter cells of the body, classified as intracellular pathogens, whereas others remain in the environment external to cells, classified as extracellular pathogens. Elimination of intracellular pathogens generally requires that infected cells be destroyed by phagocytic and cytotoxic immune cells, the action of which can be collectively described as 'cell-mediated immune responses'. In contrast, extracellular pathogens and soluble antigens are more effectively controlled by 'antibody-mediated immune responses'. Antibodies act by binding to pathogens and soluble antigens in the extracellular environment, preventing them from damaging or entering cells and tagging them for destruction by immune cells. T-helper (T_H) cells, a type of T lymphocyte, play an important role in orchestrating adaptive immune responses by
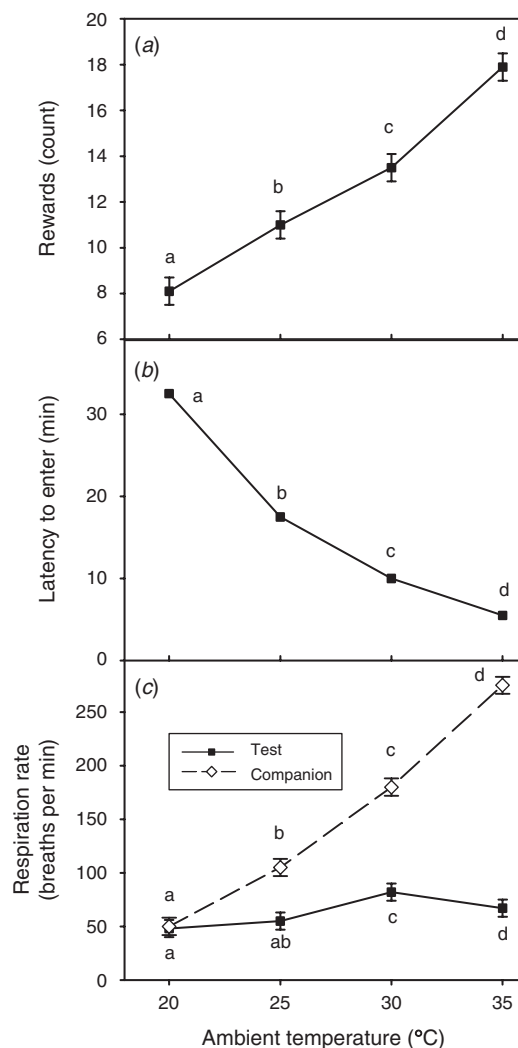

Fig. 3. The behavioural demand of sheep held at ambient temperatures of 20°C, 25°C, 30°C and 35°C and 70% relative humidity to escape to a cool chamber at 20°C and 70% relative humidity. Merino sheep ($n = 6$) were trained to press a panel to enter the cool chamber then tested at each temperature at four workloads (1, 4, 10, 25 presses on the panel to activate the door opening mechanism permitting entry to the cool chamber) in random order of test conditions. Sheep were held in the cool room for 20 min then returned to the ambient temperature pen for further testing. Companion sheep were located adjacent to the cool chamber and ambient temperature pen. (*a*) Number of entries to the cool chamber achieved during 9 h of testing at each ambient temperature for data combined across workloads. (*b*) Latency to enter cool chamber when returned from cool chamber to ambient temperature pen. (*c*) Respiration rate of test sheep performing the operant conditioning task to enter the cool chamber and companion sheep held at the ambient temperature. Respiration rates were measured five times on each animal during the test procedure. The behavioural demand to enter the cool chamber increased at each increasing ambient temperature and the latency to enter decreased. Access to the cool chamber substantially reduced the respiratory rate response to elevated ambient temperatures. Within a variable, ambient temperature treatments without a common letter are significantly different ($P < 0.05$). Data from Roberts (2007), with permission.

promoting host immune responses tailored to the encountered pathogen. Distinct populations of T_H cells, based on their function and the cytokines they secrete, were first described in mice

(Mosmann *et al*. 1986). T_H1 cells secrete Type I cytokines, including interferon-γ and interleukin-12, which largely promote cell-mediated immune responses whereas T_H2 cells produce Type II cytokines, including IL-4 and IL-5, which largely promote antibody-mediated immune responses. The existence of a similar T_H1/T_H2 paradigm has been investigated in several farm animal species including chickens (Vandaveer *et al*. 2001; Erf 2004), pigs (Schmied *et al*. 2012); (Raymond and Wilkie 2004) and cattle (Estes *et al*. 1998). Although polarised cell-mediated and antibody-mediated responses to intracellular and extracellular pathogens respectively are observed in these production animals, evidence suggests that the T_H1/T_H2 paradigm established in mice is an oversimplification of a more complex immunoregulatory framework operating in these species (Brown *et al*. 1998). Nonetheless, the Type I/Type II paradigm provides a useful framework for assessing immune responses in livestock, with strength of the immune response being the second and perhaps more important dimension to assess. Immune responsiveness influences the outcome of challenges to the animal's integrity by disease causing organisms and, as discussed in Section 3, is therefore likely to participate in the mechanisms conferring resilience.

2.6. Effects from underload and overload by environmental stimuli

Claude Bernard considered that maintenance of the internal environment was necessary for the efficient functioning of the animal (Cooper 2008). Through studies on the consequences of prolonged exposure to diverse noxious stimuli, Hans Selye proposed that animals exhibit a general adaptation syndrome that is a prelude to diseases of (mal)adaptation, which occur when resistance to the noxious stimuli breaks down (Selye 1936, 1946). The consequences of failure to adapt to a burden of noxious insults impair functioning of the animal. An enormous body of research and conceptualisation since Selye's early work has attempted to categorise the processes and quantify the costs of progression from maintenance of normal function through stages of dysregulation to final collapse. Following Selye, the early focus of stress research on physical stressors like exercise, tissue damage and toxins addressed physiological reactions and failed to recognise the biological significance of the emotional component of the animal's response to stressors. This balance was changed by the work of Mason who showed that in a stress challenge paradigm containing psychological and physical components, the greater part of the physiological response was attributable to the psychological component of the stressor (Mason 1971; Veissier and Miele 2014).

For a naïve animal exposed to a novel stressor such as a swim test in rats, responses of the SAM system and HPA axis differ from those seen in experienced rats (Koolhaas *et al*. 2011). Energy mobilisation in experienced rats more closely matches energy needs during the swim test. Importantly, response variables return to normal more rapidly in experienced rats. Behavioural changes also occur, with Norwegian rats for whom water is a natural habitat, voluntarily entering water once they become experienced with the test. This example provided by Koolhaas *et al*. (2011) illustrates the progression from non-specific to more specific responses with experience of

a stressor. The same phenomenon is seen within the immune system in which innate responses to foreign agents in naïve animals recruit a wide range of non-specific host defence reactions including fever and production of acute phase proteins and pro-inflammatory cytokines, whereas on repeated exposure the response of the adaptive immune system is better focussed on the molecular characteristics of the foreign agent and entrains fewer of the non-specific defence components of the innate immune system (Colditz 2008*a*). Energy mobilisation and changes in priorities for nutrient utilisation are prominent features of the non-specific defence response (Elsasser *et al*. 2000; Colditz 2002). Thus, defence of the animal's integrity by physiological and immune functions share a common strategy of progressing from costly non-specific responses on initial exposure to less costly responses of higher specificity and lower cost on re-exposure to the stressor (Colditz 2008*a*).

No clear boundary has been identified to denote where responses to stimuli pass from normal maintenance of physiological equilibria into the domain of stress responses. Following Mason, some authors identify a negative emotional state as indicating that a (dis)stress response has occurred (Rushen 1986; Cockram 2004). Several physiological mediators expressed during activation of innate immune responses such as pro-inflammatory cytokines, micro RNA, heat shock proteins and acute phase proteins can also be upregulated by physical and psychological stressors that have no immunological component (Colditz 2008*a*; Leung and Sharp 2010). Behavioural repertoires change as animals experience an increasing stressor load, with increasing expression of abnormal behaviours in distressed animals (Cockram 2004; Dwyer and Bornett 2004). The commonality of non-specific reactions to novel noxious stimuli perceived by neurosensors, chemosensors and immunosensors is noteworthy. We can characterise these sensors as the afferent arms of host defence. Activation of these sensors by novel stimuli recruits a broad range of responses that generally act with low stimulus specificity to protect the host. Refinement of responses through experience and learning increases the specificity of the responses for eliminating or diminishing the impact of the noxious stressors. Stimulus specificity of host defence responses can be provided by specialised behaviours, anticipatory and adapted physiological responses, by so called affinity maturation of receptors of the adaptive immune system and by cognition. A more nuanced version of Barrett's model of emotions acquiring functionality in humans might hold that the refinement of the emotional response from an initial shared pool of neurophysiological, physiological and behavioural reactions towards the named functions learned as conceptual constructs improves their utility for dealing with the context of the emotion. These refinements to the effectiveness of host defence through experience can be termed facultative learning in the sense that they are not obligate refinements. Furthermore, the refinements are not necessarily expressed in like manner or to the same degree between individuals. A question arising from this characterisation of host defence is whether a negative affective state occurring during exposure of naïve animals to a novel stressor is an innate protective reaction acting as an advantageous component of non-specific host defence, or whether (as often viewed from the perspective of animal welfare) a negative affective state is a negative outcome

whenever it occurs. From an evolutionary perspective, some negative affective states are considered to improve avoidance of threats to the animal (Mendl *et al*. 2010).

A problem when considering stress responses is to account for maladaptations where system functions settle at suboptimal or deleterious operational states in the absence of any substantial genetic lesion that might predispose the animal to the disease state. The concept of allostasis was introduced in 1988 in part to account for such lifestyle diseases and dysfunctional physiological states that develop under a sustained burden of stressors (Sterling and Eyer 1988; Sterling 2004). Although the validity of the claimed differences between allostasis and homeostasis has been energetically debated (McEwen 1998; McEwen and Wingfield 2003; Woods and Ramsay 2007; Booth 2008; Cooper 2008; Romero *et al*. 2009; Koolhaas *et al*. 2011; Sterling 2012; Ramsay and Woods 2014), the discussion has drawn attention to important aspects of physiological regulation and to changes that occur during adaptation (acclimatisation) of the individual to environmental conditions and during chronic stress. The reader is referred to the above references for a history and comparative analysis of the concepts of homeostasis and allostasis.

2.7. A summary of physiological regulation of responses to environmental stimuli

If we step outside the constraints of definitions of regulatory models such as homeostasis, homeorhesis and allostasis, the key points about physiological regulation can be summarised as follows:

- The valence and salience of stimuli (including stressors) are influenced by the context of the stimulus, and the affective state and residual adaptive capacity of the animal.
- Physiological variables are regulated towards a balancing point within a balancing range that is reflected in the typical reference intervals for variables used in clinical pathology, for example (Lepherd *et al*. 2009).
- Balance is achieved by operation of multiple effectors that defend key functionalities of the animal. For example, during thermoregulation to defend core body temperature, autonomic effectors independently modify metabolism, blood flow to skin, evaporation, and piloerection, whereas behavioural effectors influence respiration, body posture, shade seeking, and so on (Ramsay and Woods 2014).
- Regulating the internal environment comes at a cost to the animal; however, activation of physiological and behavioural effectors in anticipation of a stimulus or stressor challenge generally reduces this cost.
- Increments in the stimulus or stressor load cause decrements in the residual capacity to adapt (Koolhaas *et al*. 2011).
- Costs increase with increments of the stressor load and/or decrements of residual adaptive capacity.
- Disturbance of behavioural repertoires, expression of abnormal behaviours and prevalence of negative affective states increase with stressor load.
- Regulatory behaviours and physiological responses can be influenced by ontogeny and by recent experience.
- Learned and predictive physiological, behavioural and immune responses generally reduce costs

- Animals adapt (acclimatise) to a range of environmental conditions. Adaptation leads to a change in the environmental sensitivity of effectors, for example, thermogenesis in sheep.
- Responses can vary due to characteristics of the individual including ontogeny, behavioural type, social status, affective state, physiological state, gender, age, season, prior experience and cognitive ability.

2.8. Two response patterns

Two patterns emerge from the above description of response and adaptation to environmental stimuli. In the first class, environmental stimuli tend to be sporadic, episodic or situation-specific. Examples include challenges to the animal's integrity created by infection, social conflict and physical trauma. The stimuli can also be situation-specific such as periodic supplementary feeding or husbandry procedures. Innate responses to these stimuli such as innate immune responses and behavioural characteristics dictated by the animal's temperament can be optimised through learned coupling of environmental cues with behavioural, physiological and immune responses. Through coupling with environmental cues, the learned responses become predictive and anticipatory and prepare the animal for the impending load it will be exposed to.

The second class of stimuli are provided by cyclical or persistent characteristics of the environment such as circadian and seasonal changes in temperature, light, and pasture availability. Internal stimuli with these characteristics include stimuli associated with reproductive cycles. Environmental cues provided by these stimuli activate innate regulatory pathways such as the hormone pathways directing homeorhetic responses. Adaptation (acclimatisation) to these persistent environmental characteristics occurs principally through adjustment within the adaptive range (allostasis) rather than through facultative learning of new metabolic response patterns. Consistent with the view, we are unaware of evidence that the efficiency of homeorhetic changes is improved by experience within the lifetime of the individual.

In Section 3 we illuminate the distinction between these two classes of stimuli through the analogy of weather and climate.

The affective state of the animal and learned responses in the behavioural, immune and physiological systems influence whether an environmental challenge is perceived as noxious or benign and whether the outcome to the challenge is beneficial, such as rapid recovery from an insult, or detrimental, such as a protracted stress responses. In the next section we examine resilience and robustness to environmental stimuli and propose an approach for identifying animals with a phenotype that confers resilience to the potentially adverse impacts of the first class of environmental stimuli that are commonly experienced within the farm animal production environment.

3. Resilience and robustness

From the perspective of evolutionary biology, traits of an animal have merit in terms of their influence on the flow of genetic and non-genetic (e.g. cultural) information to subsequent generations and their contribution to environmental outcomes such as niche construction and ecological services. For animals within the care and responsibility of humans, it is economic,

ethical and aesthetic values rather than measures of evolutionary and environmental influence that are brought to the consideration of the merits of traits and the circumstances under which the animal lives. For farm animals, resilience and robustness are examples of two such conceptual constructs developed from human values. Animal welfare, which bridges aspects of resilience and robustness is an example of a third such values-based conceptual construct (Sørensen *et al.* 2001). Differentiation between the concepts of resilience and robustness is merited if different values are brought to the concepts or if some differing biological processes underpin their management through environmental manipulation or genetic selection.

3.1. Historical concepts of resilience

Clunies Ross (1932) appears to have been the first to recognise the distinction between resistance to infection, in terms of parasite numbers, and resistance to the impact of infection, in terms of host disease. Although Clunies Ross did not use the term, later studies described the latter phenomenon as disease resilience (Albers *et al.* 1987; Bisset and Morris 1996; Bishop 2012; Doeschl-Wilson and Lough 2014), which is typically defined in terms such as a capacity to maintain high productivity in the face of ongoing infection (Bisset and Morris 1996; Bishop 2012). More recently, interest in the impact of non-infectious stressors on animal performance has used the term resilience to describe these broader aspects of an animal's response to environmental challenges (Hermesch and Dominik 2014). In human studies, resilience is described in negative terms as the absence of persistent adverse behavioural, physiological, affective and cognitive outcomes following periods of extreme physical trauma, psychological stress or life threatening situations that in non-resilient individuals are linked to conditions such as post-traumatic stress disorder, depression and other psychiatric conditions (Russo *et al.* 2012; Wu *et al.* 2013).

3.2. Models of resilience in humans

Several animal models of the conceptual construct of human resilience have been developed that provide valuable insights for research into resilience in farm animals. Two aspects of resilience are identified in these models: (1) insensitivity or low sensitivity to stimuli found to be noxious by some conspecifics, and (2) adaptive responses involving neurophysiological and behavioural changes (Russo *et al.* 2012). Animal models use a range of physical (e.g. forced swim test, electric shocks) and psychosocial (e.g. social defeat) stressors and define resilience with negative terms such as subsequent absence of social avoidance, stress-induced hyperthermia, anhedonia (e.g. reduced interest in food rewards or sex), or metabolic syndrome (Russo *et al.* 2012). Interestingly, even within highly inbred strains of mice drawn from a single cohort, animals exhibiting maladaptive responses (that is, animals lacking resilience) typically comprise a substantial proportion (e.g. 30%) of the study population. This observation provides a hint that even within a highly genetically homogeneous group, a social ecology might be in operation drawing individuals into distinctive resilience phenotypes. Adverse outcomes are increased by lack of ability to control exposure to the stressor including

unpredictability of the stressor, and by exposure to some early life stressors. Conversely, resilience is enhanced by ability to predict and control exposure to stressors, by development of behaviours that reduce exposure to stressors, and by graded exposure to some stressors early in life. The latter phenomenon has been termed stress inoculation (Levine 1962). Several genetic factors influencing neuroendocrine and neurotransmitter pathways have also been identified and are discussed below.

3.3. General environmental resilience

In view of the concordance between mechanistic studies in mouse models of human resilience and the biological response pathways to environmental challenges in farm animals reviewed in Section 2, we propose a characterisation of resilience in farm animals that focuses on the outcome of exposure to infectious, social and other environmental stressors. In this synthesis, resilience can be described as the capacity of the animal to be minimally affected by a disturbance or to rapidly return to the physiological, behavioural, cognitive, health, affective and production states that pertained before exposure to a disturbance. This broader characterisation of resilience can be considered to describe general environmental resilience to distinguish it from the narrower concept of disease resilience previously used by others. This formulation encapsulates low sensitivity or lack of sensitivity to disturbances that other conspecifics can find stressful or detrimental, and values a rapid recovery when situations with negative consequences on morphological, physiological, behavioural, cognitive, health, affective or productive functions do occur. The environmental challenges linked with resilience tend to be episodic, sporadic or situation-specific challenges rather than persistent characteristics of the environment. In common with its characterisation in humans (Rutter 2012), resilience is a comparative measure of differences between individuals in the outcomes that follow exposure to potentially adverse situations. In this formulation, biological processes underpinning resilience relate to perception of stimuli and the efficacy of the short-term stress and adaptive responses that ensue in minimising the impact of the stressor. As indicated by studies on responses to environmental stressors in farm animals (reviewed in Section 2) and by studies of resilience in humans, innate mechanisms conferring resilience are likely to be found within sensor sensitivity to environmental stimuli, central processing functions and the response architecture provided by temperament, affective state, cognition, immune competence, behaviour and morphology of the animal. Facultative learning within these response modalities provides a means by which the resilience of the animal can improve with experience. Clearly, much work is needed in this area.

3.4. Resilience or robustness?

An important question arises as to the relationship between resilience and robustness. The recognition that several functional and conformation traits including health, reproduction and leg strength have deteriorated during selection for production traits in farm animals (Rauw *et al.* 1998) has led to a strong call to increase robustness through genetic selection to improve functional traits (Knap 2005; Star *et al.* 2008). The definition provided by Knap (2005)

is commonly used to characterise robustness in farm animals. The robust farm animal has the ability to express its production potential in a wide range of environments without compromising its reproduction, health and wellbeing. The environmental effects that influence expression of functional and production traits tend to accumulate within the animal over longer time frames than the disturbances that can be minimised by resilience of the animal. Furthermore, these environmental effects tend to be cyclical or persistent. An analogy for the time frame in operation here is the distinction between environmental fluctuations described as weather from those described as climate. Indeed the somewhat arbitrary time boundary between climate and weather may provide a useful boundary for identifying the temporal difference between resilience and robustness. Animals cope with short-term, episodic fluctuations in environmental conditions through acute physiological stress responses coupled with innate and learnt behaviours. When perturbations persist over longer time frames whereby the environmental conditions are better described as characteristic of the environment than as temporary perturbations, homeorhetic physiological responses enable acclimatisation and adaptation (Collier *et al.* 2009). Others describe this adaptive process as allostasis. Nonetheless, these characterisations of the temporal boundary between resilience and robustness are somewhat arbitrary and tautological. The difference between environmental factors influencing resilience and robustness are also termed as microenvironmental and macroenvironmental effects respectively (Strandberg 2009).

Two aspects of robustness are commonly pursued in animal breeding. The first quantifies robustness through consistency of trait expression despite variations in genotype and environment (Strandberg 2009). A particular focus of this aspect in animal breeding is the ability of the animal to achieve its genetic potential for production traits in environments that have greater resource constraints or a larger load of adverse environmental conditions than the environment in which the genetic merit of parents was assessed. This consistency of production performance across environments is usually identified through estimation of genotype by environment interactions and reaction norms (Bryant *et al.* 2005; Knap 2005). The second aspect addresses the biological mechanism through which trade-offs within the animal between production traits and functional traits occur and is generally approached within the framework of resource allocation theory (Beilharz *et al.* 1993). Consideration of the genetic models and mechanisms related to resilience and robustness is beyond the scope of this review.

The impact of human values on the concept of robustness can be seen in the approach of researchers to lactational anoestrus in high-producing dairy cows. A negative genetic correlation between milk production and reproductive performance has seen a decline in fertility as milk yield increases (Pryce *et al.* 2009). From evolutionary and physiological perspectives, lactational anoestrus can be viewed as allocating resources to the current lactation in order to improve survival of the current offspring and to protect the cow from demands of the future pregnancy and lactation while body nutrient reserves are under pressure from the current lactation (Martin *et al.* 2008), creating a so called temporal trade-off (Phocas *et al.* 2014). Attempts to

breed 'robust' cows by decoupling ovulatory activity from protective physiological regulators is driven by human values such as a management preference for an annual production cycle that matches feed availability for cows grazing at pasture with the lactation cycle (Pryce *et al.* 2009). We do not disagree with this general objective but note ethical implications such as responsibility to better manage nutrition and health (Knap 2005) and the other consequences of decoupling such as reduced residual adaptive capacity of the cow resulting from the increased metabolic load associated with higher milk production (Chagas *et al.* 2007).

3.5. Relationship between general environmental resilience and disease resilience

A second question raised by the concept of general environmental resilience is its relationship to disease resilience. Infectious agents are a very significant source of environmental challenge to animals. From studies on resistance of animals to the effects of infection, two concepts have been developed: disease tolerance and disease resilience. In farm animals, disease tolerance provides a phenotypic measure of the net impact of a given level of infection on performance whereas disease resilience is a phenotypic measure of productivity during infection (Bishop 2012; Doeschl-Wilson *et al.* 2012). The substantial biological significance of this minor semantic difference is explored in detail by Bishop (2012) and Doeschl-Wilson *et al.* (2012). The biological mechanisms contributing to these phenotypic outcomes can differ between pathogens and are not considered further here. For further details of the immune mechanisms contributing to disease tolerance the reader is referred to reviews by Glass (2012) and Ayres and Schneider (2012). A schematic relation of the terms disease resistance, disease resilience and disease tolerance to general environmental resilience is presented in Fig. 4.

4. Managing animals to enhance resilience

During life on a farm, during transport and at slaughter, farm animals are exposed to many potential stressors, which can negatively impact their physiological, behavioural, and affective states resulting in reduced production, poor health and bad welfare. A very large body of work has focussed on identifying management and environmental factors that lead to these negative outcomes in order to reduce or eliminate their effects. The preceding discussion suggests that as well as improving resilience by providing comfortable, non-threatening environments, it may be possible to enhance resilience through provision of cognitive and emotional enrichment to the animal (Wechsler and Lea 2007; Spinka and Wemelsfelder 2011; Boissy and Lee 2014). The recent progress in developing tests to assess cognition and affective states is stimulating the development of a conceptual framework for understanding how we can improve welfare and resilience through cognitive and emotional enrichment (Boissy *et al.* 2007; Boissy and Lee 2014). Boissy and Lee (2014) suggest three ways that cognitive and emotional enrichment can be achieved: (1) signalling a reward in advance, (2) providing a reward that is greater than expected, and (3) providing the animal with the ability to control fulfilment of 'wants' and 'likes'. However, experience
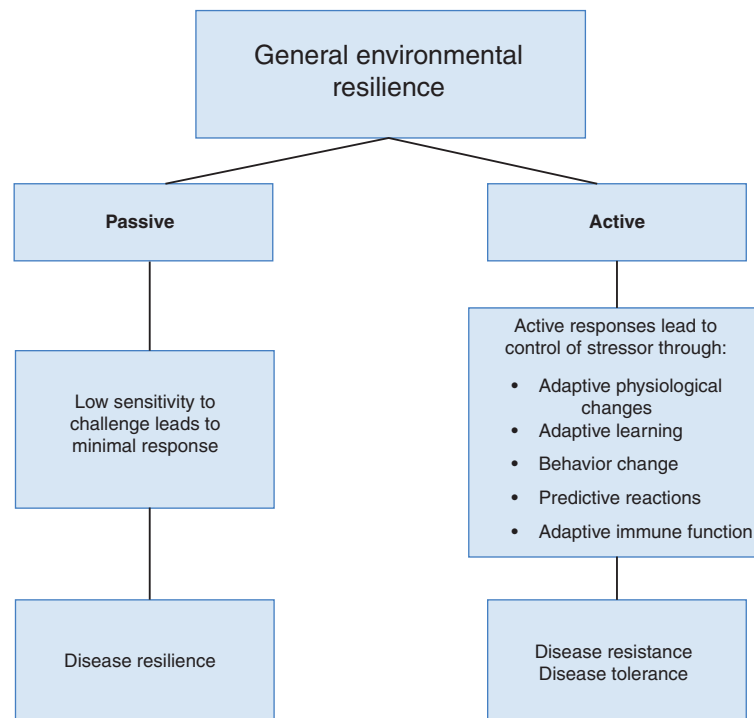
Fig. 4. Schematic relationship of the concepts of disease resilience, disease resistance and disease tolerance to environmental resilience.

of French shepherds suggests that too great a predictability of the timing of feed rewards can distract goats from engaging in normal grazing activities and reduce overall feed intake while they await the reward (Villalba *et al*. 2015). Thus, complexity in the reward structure is needed to avoid frustration from unfulfilled expectations (Greiveldinger *et al*. 2011). In contrast to using rewards to modify cognition and affect, exposing an animal to situations that provide stress inoculation and enable it to learn to control its environment has the potential to increase the animal's agency (Wechsler and Lea 2007; Spinka and Wemelsfelder 2011). Additional strategies for cognitive and emotional enrichment and for increasing animal agency are likely to be found and lead to new management methods for increasing resilience.

5. Genetic selection to enhance resilience

5.1. Defining the phenotype

A starting point for genetic manipulation of resilience is the description and measurement of desirable phenotypes. The substantial evidence discussed above suggests that a resilience syndrome can be exhibited across diverse stressor situations and thus the resilience phenotype exhibited to one stressor challenge is likely to be correlated with resilience to other stressful environmental challenges that the animal may be exposed to. This proposition will need validating as measures of resilient phenotypes are further developed for farm animals. From the definition of resilience as reduced sensitivity to potential disturbances or rapid recovery from their impact, it follows that the desirable phenotype might be most easily identified by measuring the rate of recovery to baseline and

normality of behavioural, physiological, affective, immune, cognitive or production traits following the disturbance rather than measuring the magnitude or direction of excursion of these variables while the animal attempts to cope with the stressor.

The physiological variables that change and the types of abnormal behaviours expressed can vary with the nature of the stressor and with the coping style of the animal (von Holst 1998), thus too strong a focus on measuring particular physiological response variables (for instance reactivity in the HPA axis during the stress response) or particular behaviours might characterise a phenotype that is specific to the stressor paradigm or coping style of the animal rather than be representative of the resilience syndrome. During mobilisation of defences in response to stressors, the normal dynamic range and circadian patterns of physiological and behavioural activities of the animals are reduced as defences are being forced to protect the animal. We suggest that a diagnostic signature for resilience will be more easily identified by measuring summary characteristics of response variables rather than by attempting to identify correlative relationships between the numerous labile variables that change in diverse ways in differing challenge scenarios. Thus, we advocate a predominantly outcomes-based approach to identify resilient phenotypes rather than a mechanisms-based approach.

The principle variables connoting normality are likely to differ between species and their choice will also be influenced by ease of measurement. We suggest that phenotyping be done during exposure of animals to a stressful event that is intrinsic to their management environment, and which includes a novelty component, a social component and if possible also includes a change in the pattern of exposure of animals to humans, rather

than be undertaken during exposure to an experimentally imposed stressful situation. Examples from the repertoire of management-induced stressors that could provide suitable situations for phenotyping resilience include change of housing, change of group structure, weaning, and transition to the milking parlour. We suggest that a subset of the following variables that are cognate with the chosen stressors is likely to be useful for defining resilient phenotypes.

- Core body temperature. Return to normality as defined by the time of day for and difference between maximum and minimum (i.e. normality of circadian pattern and dynamic range).
- Heart rate and heart rate variability (von Borell *et al*. 2007). The desirable outcome is normal heart rate and normal heart rate variability rather than the deviated heart rate and reduced heart rate variability seen during the change in autonomic tone that occurs during response to stressors.
- Normality of circadian ethogram and expression of behavioural complexity (MacIntosh *et al*. 2011).
- Feed intake.
- Growth rate, or principle production variable of the species.
- Immune responsiveness. Capacity to exhibit a strong immune response without excessive bias towards a Type I or Type II response to vaccines delivered during the period of exposure to the stressor.
- Normality of demeanour.
- Speed of acquisition of predictive behaviours that are cognate with positive environmental cues such as feeding or entry to the milking parlour (milk let-down).
- Normality of vocalisations.

The last three measures are included to provide information on affective state and cognitive abilities. A growing body of empirical evidence acquired from studies employing the methodology of qualitative behavioural assessment indicates that aspects of the animal's demeanour are indicative of affective state (Wemelsfelder and Lawrence 2001; Wemelsfelder *et al*. 2001; Rousing and Wemelsfelder 2006; Brscic *et al*. 2009; Stockman *et al*. 2011, 2012; Napolitano *et al*. 2012; Rutherford *et al*. 2012). Wechsler and Lea (2007) have suggested that speed with which the animal learns to respond to new environmental cues is an overlooked indicator of cognitive ability and adaptation by learning in farm animals. In view of the detrimental impact of negative affective states on cognitive functions (Mendl *et al*. 2009), measuring the speed of learning to respond to cues associated with rewards (e.g. feeding, milking) is a composite measure of learning ability and resilience of learning ability to the negative impact of the stressor. Briefer (2012) suggests that there is considerable potential to use vocalisations as measures of affective states, which seems especially pertinent in view of the increasing use of animal-borne sensor technologies, including acoustic sensors, to monitor animals in real time and to automate phenotyping (Hocquette *et al*. 2012; Greenwood and Bell 2014).

The dynamics of adverse health outcomes can be highly situation-specific such that occurrence and distribution within a group can be strongly influenced by factors other than underlying resilience (Bishop 2012). We suggest therefore that function of the immune system is better assessed through measuring responsiveness to a standardised controlled challenge from vaccination with industry relevant vaccines rather than relying on the occurrence of disease challenges during the assessment period.

Some temperament traits are likely to be correlated with resilience and are likely to be a valuable component of a resilience breeding goal. It is thought that domestication has increased the threshold of behavioural responses to aversive environmental stimuli rather than led to loss from the behavioural repertoire (Price 1999; Canario *et al*. 2013), with increases in the thresholds for expression of fearfulness and fear of humans being particularly important (Mignon-Grasteau *et al*. 2005). With the inclusion of a novel environment (e.g. change of housing, change of feed type), a social stressor (e.g. mixing, weaning) and presence of humans in the situation under which resilience is phenotyped, there should be an opportunity for the influence of temperament traits on resilience to be expressed. Additional direct measurements of temperament undertaken outside the period of resilience phenotyping could also be valuable, although the extent of desirable associations between temperament and resilience still need to be ascertained.

When performance traits such as immune responsiveness, production and learning ability are measured during the response to a stressor, the measured trait is influenced by a combination of the underlying genetic potential for performance of the trait and by sensitivity of the trait to the impact of the stressor. Using the example of disease resilience to gastro-intestinal parasites, Doeschl-Wilson and Lough (2014) have noted that for accurate estimation of resilience of the performance trait to the stressor, performance should also be measured in the absence of the stressor as well as in the presence of the stressor so that the decrement in performance due to the effect of the stressor can be estimated. This limitation may be more pertinent to persistent stressors such as infections that are not cleared by host defence reactions than to transient stressors.

Measurement of the resilience syndrome would be improved by phenotyping resilience in a broad range of acute environmental challenge situations so that reaction norms can be used to assess the situational sensitivity of resilience (Knap 2005; Dingemanse *et al*. 2010) rather than using a single situation as we propose here.

5.2. The role of immune responsiveness in general environmental resilience

When exposed to a pathogen challenge, both active and passive responses make important contributions to the animal's general environmental resilience, defined in terms of their capacity to be minimally affected by the disease challenge and rapidly return to a normal health status.

Although the Type I and Type II arms of the adaptive immune system work together to protect the host, negative genetic and phenotypic correlations between an animal's ability to mount antibody-mediated and cell-mediated immune responses have been reported in dairy cattle (Hernandez *et al*. 2006; Thompson-Crispi *et al*. 2012*b*). The strength of this negative association may differ between species, but this observation is important to consider when breeding for resistance to a specific disease. Breeding animals resistant to a disease largely controlled by cell-mediated immune responses in the host may inadvertently

increase their susceptibility to diseases largely controlled by antibody-mediated immune responses and vice versa. In support of this concept, an inverse relationship between antibody production and phagocytic cell function has been reported in Biozzi mice selected for high and low antibody production (Hale and Howard 1981) and in cattle selected for resistance or susceptibility to *Brucella abortus* (Price *et al*. 1990). Although the importance of breeding strategies targeting resistance to specific diseases of economic importance, such as internal parasites in sheep (LeJambre *et al*. 1971) and mastitis in dairy cattle (Heringstad *et al*. 2000) is acknowledged, we suggest that breeding strategies should also incorporate selection for general disease resistance as manifested by an animal's ability to mount both cell-mediated and antibody-mediated immune responses to diverse antigens (Wilkie and Mallard 1999).

When deciding in selective breeding strategies whether to target disease resistance, disease tolerance or disease resilience as the basis for improving animal health, many factors need to be considered. For example, disease resistance and disease tolerance are generally negatively correlated, therefore individuals identified as susceptible to disease tend to be more tolerant, and conversely, individuals with resistant genotypes tend to be less tolerant (Raberg *et al*. 2007). It is also known that the host mechanisms and genes underlying disease resistance, disease tolerance and disease resilience differ, and have varied impacts on the evolving pathogen (Simms and Triplett 1994). Such factors highlight the importance of considering the preferred final outcomes for both the host and pathogen when establishing selection strategies to improve animal health. When developing strategies to improve the environmental resilience of livestock in Australian production systems through improved animal health, the approach taken by our team has been to target general disease resistance following the strategy first proposed by Wilkie and Mallard (1999). Selection for general disease resistance through selection for enhanced immune responsiveness was targeted because in many cases of infectious disease it is critical to eliminate the causal agent in order to prevent mortality and unintended pathogen transmission to the environment and hence to other hosts. Furthermore, animals identified as having enhanced general disease resistance are likely to be resistant to a wide range of pathological agents.

Many genes contribute to the general immune responsiveness of the animal (Kelley *et al*. 2005), which can be assessed as a quantitative trait by measuring responses to test antigens (Wilkie and Mallard 1999). This was first demonstrated among livestock species in Yorkshire pigs, where measures of innate and adaptive immunity (both cell-mediated and antibody-mediated) were combined to generate estimated breeding values for general immune responsiveness and to rank boars and gilts as high, intermediate and low immune responder (IR) phenotypes for use in future breeding programs (Mallard *et al*. 1992). This strategy aimed to simultaneously improve the ability of animals to mount both antibody- and cell-mediated adaptive responses, and as a consequence, enhance general disease resistance. Pigs classified as high IR using this strategy were found to have superior antibody responses to test antigens and several commercial vaccines (Wilkie and Mallard 1999), a lower frequency of non-responders when vaccinated with inactivated

influenza vaccine (Wilke *et al*. 1998) and higher antibody avidity for target antigen (Appleyard *et al*. 1992), relative to their intermediate and low IR counterparts. Although such findings provided overwhelming evidence that selection using this strategy successfully enhanced the general immune responsiveness of selected pigs, when challenged with *Mycoplasma hyorhinis*, high IR pigs displayed more severe arthritis than low IR pigs, suggesting that high IR phenotype pigs may be more prone to generating inflammatory responses (Magnusson *et al*. 1998). It is noteworthy however, that in the same study, high IR pigs were found to have less severe peritonitis, less severe pleuritis and an enhanced ability to produce serum antibody against *M. hyorhinis*.

More recently, research efforts have been focussed on developing protocols to assess general immune responsiveness in dairy cattle (Mallard *et al*. 2015), beef cattle and sheep (Hine *et al*. 2015). Although testing protocols developed to assess general immune responsiveness in these species have not incorporated measures of innate immunity to date, it is well recognised that strong adaptive immune responses are underpinned by strong innate immune responses. Associations between the immune responsiveness phenotypes of individual dairy cows and their incidence of disease have been investigated on large-scale commercial farms in North America (Thompson-Crispi *et al*. 2012*a*). Results showed that the incidence of several common diseases of dairy cattle, including mastitis, displaced abomasums and retained fetal membranes were observed more frequently in average and/or low IR cows as compared with high IR cows in the same herd. This strategy, to assess general immune responsiveness, has been used to investigate the influence of hybrid vigour on general immune responsiveness in purebred and crossbreed dairy cattle (Begley *et al*. 2009; Cartwright *et al*. 2012), the influence of age and pregnancy status on general immune responsiveness in dairy heifers (Hine *et al*. 2011), leukocyte populations in high and low IR dairy heifers (Hine *et al*. 2012) and the influence of geographical location on immune response profiles of Canadian dairy cattle (Thompson-Crispi and Mallard 2012). We conclude that a high level of general immune responsiveness in both Type I and Type II arms of the adaptive immune system has the capacity to improve the resilience of animals to diverse disease challenges.

5.3. Candidate genes for resilience

Research in mice and humans has identified several gene polymorphisms in the neuroendocrine and neurotransmitter pathways involved in stress, reward and learning responses to stressors that differ between resilient and susceptible phenotypes. Better characterisation of resilient phenotypes in farm animals should provide the opportunity to look for similar gene differences in these species. Genes and pathways of interest include: neuropeptide Y gene; CRH receptor 1 gene and FK binding protein 5 gene (HPA axis); catechol-O-methyltransferase gene (noradrenergic and dopaminergic pathways); dopamine transported gene and dopamine receptor genes (dopaminergic pathway); promoter region of serotonin transported gene and serotonin receptor genes (serotinergic pathway); brain-derived neurotrophic factor gene; and the fatty acid amide hydrolase

gene (endocannabinoid pathway) (Wu *et al.* 2013; Dincheva *et al.* 2015). The gene associated with porcine stress syndrome provides an extreme example of the potential for single gene effects to influence stress responsiveness and resilience (O'Brien *et al.* 1993).

5.4. Group performance

The influence of social factors on the response of the individual to stressors suggests that some aspects of resilience will be influenced by group characteristics. Thus, genetic selection for resilience may benefit from selection on performance of the group rather than the individual (Muir 2005), especially where social stressors are likely to be a major cause of environmental stress to farm animals (Muir 1996; Bergsma *et al.* 2008; Bolhuis *et al.* 2009). Genetic models to disentangle direct and social effects have been developed by Bijma *et al.* (2007). The potential for social ecological factors within a group to evoke a non-resilient phenotype in some individuals irrespective of their genotype also needs consideration.

5.5. Our approach to phenotyping sheep and cattle for resilience

Our team is currently assessing resilience using weaning in sheep and beef cattle and introduction to the milking parlour in dairy heifers as the management-induced stressor situations during which animals are phenotyped (Hine *et al.* 2015). In the majority of Australian production systems, breeding groups of sheep and beef cattle are run at pasture, with a low level of interaction with humans. Progeny are typically handled once or twice before weaning. During these handling events the routine husbandry procedures of castration, earmarking and primary vaccinations against common diseases of livestock are performed. At weaning, beef calves are usually held in an open air stock handling facility for 7–10 days, fed high quality hay and introduced to small quantities of pelleted rations. During this time they are moved through the forcing yards and stock race several times to familiarise them with human interactions and restraint, and to receive secondary or boost vaccinations where required. A comparable practice is increasingly being used for weaning lambs. The procedure termed yard weaning leads to greater ease in handling the livestock. Progeny are usually returned to pasture after weaning. In the beef industry, a portion of the progeny is often transferred to a feedlot several months after weaning to be finished for slaughter. Yard weaned calves have improved health outcomes and faster growth rates during feedlot finishing than calves weaned without the yard weaning procedure (Fell *et al.* 1998, 1999; Colditz *et al.* 2006; Walker *et al.* 2007).

Our resilience phenotyping procedure is being performed on genotyped progeny from genetic benchmarking programs in the sheep, beef and dairy industries. A typical procedure involves immunologically challenging animals at the commencement of yard weaning (lambs and beef calves), or introduction to the milking parlour (dairy heifers), and subsequently measuring both cell-mediated and antibody-mediated immune responses to vaccine components in order to assess the general immune responsiveness of individual animals while exposed to a management-induced stressor. Other phenotypic measures made on individual animals during the testing procedure include temperament assessment using flight speed testing (Burrow *et al.* 1988) and or crush/restraint score (Grandin 1993), liveweight change over the yard weaning or induction period and stress responsiveness to the management-induced stressor. Stress responsiveness is assessed by measuring changes in serum haptoglobin levels induced by the management-induced stressor each animal is exposed to during the testing procedure (Slocombe and Colditz 2005). Current work is focussed on investigating associations between these various resilience component traits, important production traits and animal health and welfare outcomes to guide the development of selection tools for farmers aiming to improve the environmental resilience of animals in their production system.

5.6. Will selection for resilience improve robustness?

Persistent environmental challenges from poor design of facilities, poor stock management and climatic extremes pose a substantial burden on the welfare and productivity of animals. The capacity of the animal to adapt to less extreme aspects of infrastructure, husbandry and climate is also likely to have been reduced through diversion of nutrients to production traits, in accord with resource allocation theory. The extent to which adaptability to short-term environmental challenges confers long-term benefits on performance of functional and production traits remains to be seen; however, it seems likely that the mechanisms enabling adaptation to short-term perturbations (resilience) might differ from the mechanisms enabling adaptation to persistent environmental (robustness). Some potential similarities and differences between resilience and robustness are outlined in Table 1.

6. Resilience and animal welfare

The concept of animal welfare developed by the World Organisation for Animal Health (2014) is commonly used to describe welfare. It states: 'Animal welfare means how an animal is coping with the conditions in which it lives. An animal is in a good state of welfare if (as indicated by scientific evidence) it is healthy, comfortable, well nourished, safe, able to express innate behaviour, and if it is not suffering from unpleasant states such as pain, fear, and distress. Good animal welfare requires disease prevention and veterinary treatment, appropriate shelter, management, nutrition, humane handling and humane slaughter/killing. Animal welfare refers to the state of the animal; the treatment that an animal receives is covered by other terms such as animal care, animal husbandry, and humane treatment'.

Short-term challenges to the animal can reduce its welfare. Managing the animal so that its experience of the environment improves its ability to adapt, and breeding for resilience traits should help lead to better welfare outcomes. Nonetheless, as noted by others, selection for resilience, adaptability and robustness in farm animals should not be viewed as a substitute for good housing, good management and fitting the genotype of the animal to the production environment (Star *et al.* 2008; Fraser *et al.* 2013; Ferguson 2014). Rather, selection for resilience can be seen as a continuation of the genetic change associated with the process of domestication that has been

Table 1.   Characterisations of similarities and differences between resilience and robustness

	Resilience	Robustness	Comments
Approximate time frame for expression	Less than a few weeks	More than a few weeks	Disease resilience and disease resistance can take longer than 2 weeks to develop due to pathogen and immune response kinetics. Ambiguous whether disease resistance and disease resilience are better described as resilience or robustness traits
Pattern of environmental stimuli	Episodic, sporadic, or environment-specific	Cyclical: 1. External environment: e.g. circadian, seasonal, 2: Internal environment: e.g. reproductive cycles (oestrus, pregnancy, lactation) Persistent: Characteristics of the environment consistent across generations	–
Biological basis	Reduced sensitivity to environmental challenges or better adaptive activity of stimulus response pathways	Reallocation of resources away from production traits towards functional traits. Lower sensitivity of genotype to environment	The effect of ongoing domestication to reduce environmental sensitivity may be acting on both resilience and robustness (Price 1999)
Mechanisms of adaptation and acclimation	Environmental cues provided by sporadic, episodic or location-specific stimuli are learned through experience and linked to predictive behavioural, physiological and adaptive immune responses	For an individual, the expression of genetically programmed regulatory pathways are adjusted within the adaptive range of the pathway to match the environmental load. Across generations, adaptive range changes to match new cyclical or persistent characteristics of the environment	See Koolhaas *et al.* (2011) for a discussion of adaptive range. Protective responses conferring resilience are optimised through facultative learning within the lifetime of the individual. Responses conferring robustness are effected via innate physiological regulatory pathways (see Section 2.8 for details)
Effect on adaptive capacity	Improved due to lower or shorter impact of stressors on resilient animals leaving more buffer for coping with subsequent stressors	Reduced due to functions of the robust animal continuously operating near the limit of their adapted range leaving less residual adaptive capacity	By decoupling physiological protective mechanisms from expression of functional and production traits, selection for robustness might move animals closer to the resource boundary leaving less reserve capacity for coping with environmental change
Regulatory mechanisms	Homeostasis	Homeorhesis, allostasis	The terms homeostasis and allostasis are used here in the sense employed by Sterling and Eyer (1988), which is strongly contested by many physiologists (see text for discussion)
Impact on energetic efficiency of the animal	Improved due to less time spent in energetically demanding stressed state. Little requirement for genetically determined reallocation of resource use priorities across generations to improve resilience	Possibly reduced due to lower efficiency when functions of animals operate further from their environmental optima. Efficiency influenced by genetically determined resource allocation between production and functional traits	Reduced environmental sensitivity of the robust animal leads to less optimisation to the environment. Generalist versus specialist dilemma. Costs of resilience measured as phenotypic costs of host defence (Colditz 2008*b*). Costs of robustness modelled through resource allocation theory
Gene effects	Some single nucleotide polymorphisms may have a large effect on susceptibility as found in human and mouse studies	Preponderance of small additive genetic effects on pathways regulating functional and production traits	–

	Resilience	Robustness	Comments
Benefits	Improved welfare	Improved production and welfare	Compensatory production mechanisms (e.g. compensatory growth) may recoup short-term production costs of resilience
Risks	May need to select for resilience of group to account for social ecology of resilience	1. Higher management inputs required to manage animals with lower residual adaptive capacity. 2. Lower productivity of primary productive trait as more resources allocated to performance of functional traits	1. A contradiction is implicit in the two aspects of robustness in that more equitable distribution of resources to functional traits may increase rather than reduce environmental sensitivity (e.g. need for higher quality feed). 2. Benefits from improved health could counter proximate cost of temporarily redirecting resources to host defence during challenge periods
Human value domains	Ethical motives are greater than economic motives	Economic motives can be greater than ethical motives	–

occurring over several millennia (Price 1999; Mignon-Grasteau *et al*. 2005; Canario *et al*. 2013).

A challenging concept arising from work on physiological regulation and affective states in animals and from work on resilience in rodent models and humans is the importance of what can be termed negative experiences in maintaining the dynamic responsiveness of the animal and in shaping its capacity to cope with challenges (Korte *et al*. 2007; Russo *et al*. 2012; Wu *et al*. 2013; Bastian *et al*. 2014). This leads to a formulation of good welfare that includes nurturing the capacity of the animal to cope with challenges that are intrinsic to its life history and that cannot be eliminated by other aspects of good housing, good breeding, good husbandry, good disease control and good climatic environment. Thus, a proximate cost to the animal from controlled exposure to situations that invoke short-term negative effects could be necessary for the ultimate benefit of good whole-of-life welfare outcomes. The positive value of negative experiences is encapsulated in the concept of stress inoculation (Levine 1962).

7. Conclusions

Interactions with the environment expose the animal to beneficial and threatening situations. The animal's perception of environmental stimuli is influenced by historical events, its contemporary status, and the behavioural, cognitive and immune attributes of the animal. The animal can learn from experience to anticipate stimuli and minimise their impact by predictive adaptive behaviours and predictive physiological responses. Stimuli lacking predictability and controllability generally have more adverse effects on the animal than predictable and controllable stimuli. Thus, the animal can learn to modify its exposure to the environment and its reactions to the environment so that the future occurrence of negative experiences is minimised, although when the animal is in a negative affective state when exposed to a noxious stimulus its capacity to learn from that event is compromised. Temperament and behavioural traits of the animal can also

influence its perception of the valence of stimuli and influence subsequent reactions. Correlated behavioural and physiological reactions to environmental challenges have been termed coping styles. Two prominent styles are proactive and reactive coping. These styles describe the strategy of the animal for dealing with a challenge rather than the success of the outcome of its response to that challenge.

The concept of resilience differs between species (e.g. humans versus non-human animals) and between disciplines. We characterise resilience as the capacity of the animal to return rapidly to its pre-challenge state following short-term exposure to a challenging situation. Resilience is a comparative measure of differences between animals in the impact of a challenge. Resilience can arise due to lower sensitivity or better adaptability to the challenge and be improved through learnt responses. It is likely that resilience of an individual is a trait expressed consistently across diverse challenge situations, although the mechanisms by which animals achieve resilience may differ between individuals.

The concept of robustness of animals addresses both consistency of phenotype across environments and competition for resources between functional and production traits. Resilience tends to be expressed in response to environmental challenges lasting a matter of days whereas robustness is a consequence of longer lasting environmental conditions. Thus, resilience relies particularly on the reaction of the animal to stressors, whereas robustness is influenced by the capacity of the animal to adapt (acclimatise) to persistent characteristics of its environment. In animals selected for elite performance, the functional and production traits may be operating near their limits of adaptive capacity resulting in reduced residual capacity for arbitrage between production, defence and function. Some differences between resilience and robustness are open to somewhat arbitrary definition. A provisional characterisation of differences between resilience and robustness is presented in Table 1.

We suggest that for use in farm animal production, the resilient phenotype can be characterised by the rate of return of key variables to the pre-challenge or normal state that is

achieved through low sensitivity or an enhanced ability to overcome the challenge, rather than by measuring the dynamic changes in variables within stress response pathways during reaction to the challenge. To minimise the need for additional animal handling, challenge situations could be based on routine management events in the life of the animal such as weaning, change of social grouping, transition to the milking parlour or change of housing. It is desirable for the challenge situation to include elements of novelty, social stress and interaction with humans.

Ignoring stress response mechanisms in identifying the resilient phenotype entails a risk and a benefit. Focussing on resilience outcomes rather than resilience mechanisms carries a risk that negatively correlated mechanisms compete in achievement of the resilience outcome and that individuals achieve resilience by employing one of two or more discrete strategies rather than bits of each. Coping style provides an analogy here. Thus, selection based solely on the resilience outcome without considering underlying mechanisms could be impeded if different individuals expressing the resilience outcome are employing different negatively correlated mechanisms to achieve that outcome. A benefit of focusing on outcomes is that progress might be made without first unravelling the underlying mechanisms. Of course, this is a perennial dilemma in animal breeding.

The realisation that stress responses increase disease susceptibility not only through suppression of host defence functions but also through stimulation of pathogens by host-derived catecholamine mediators of stress responses suggests that improving resilience of farm animals could provide multiple benefits for their health.

Advances in research on affective states and cognition in farm animals suggests that resilience might be improved with little management cost or effort by providing animals with environments and activities that provide cognitive and emotional enrichment. In addition, controlled exposure to negative experience might provide stress inoculation that makes animals more resilient to challenges that are intrinsic to their life history and production environment. An increased focus on breeding and managing animals for improved resilience should contribute to ongoing improvements in animal welfare.

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