IMPROVING ANIMAL WELFARE THROUGH GENETIC SELECTION

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IMPROVING ANIMAL WELFARE THROUGH GENETIC SELECTION

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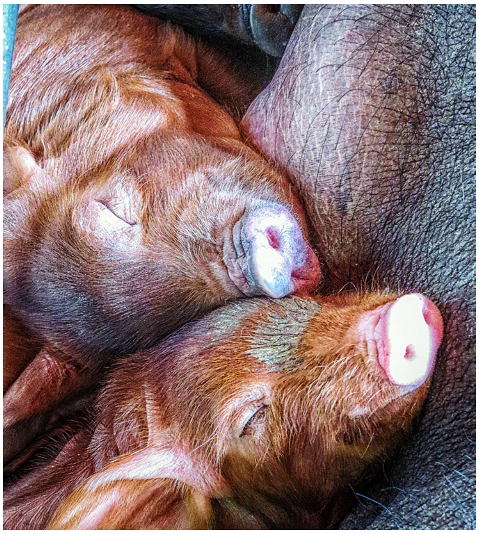

Suckling Iberian piglets. Photo by WM Rauw

In livestock species, breeding goals are aimed primarily at improvement of production traits. However, there are a number of examples where selection for high production efficiency has resulted in reduced welfare through unfavorable outcomes in health and fitness characteristics. These effects raise questions about what is ethically acceptable in animal breeding.

Welfare problems may be experienced when physiological balance is disturbed by genetic selection for high production alone, by a mismatch between the environmental challenges and the range of coping responses available to an animal, or from a mismatch between the animal's needs and their degree of satisfaction. This may be resolved by either improving the environment to support the animal, but also by providing the animal, through genetic selection, with means to adapt to the production environment.

The Standing Committee of the European Convention for the Protection of Animals kept for Farming Purposes emphasizes that breeding goals should include health and welfare. The Farm Animal Welfare Council pleas for a greater emphasis in breeding programs on traits associated with good welfare. However, although breeding goals in most farm animal species have been broadened beyond production traits to include functional traits, behavioral traits are rarely included despite their potential to improve animal production and welfare.

It is the goal of the present Research Topic to bring together experimental and theoretical research focusing on the genetics of welfare traits and the possibility to improve animal welfare through selection. This topic presents an overview of the relationship between selection for high production and livestock robustness, examples of improving robustness through the introduction of novel traits in livestock breeding, and a discussion on selection methods to address welfare issues. The discussion on sustainability of breeding practices is very alive today and will remain to be an important part of the debate in the future.

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EDITORIAL
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Editorial: Improving Animal Welfare through Genetic Selection

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Keywords: selection, genetic, welfare, livestock production, livestock improvement, sustainable agriculture, animal breeding, genetics

Editorial on Research Topic

Improving Animal Welfare through Genetic Selection

The Food and Agriculture Organization of the United Nations predicts that the projected massive global increase in demand for livestock products will continue for several decades. According to Delgado et al. (1999), it is appropriate to term the course of these events a "Livestock Revolution," which, as opposed to the Green Revolution, is driven by demand. While more precise production technologies, nutrition, and genetic selection methodologies will be successful in reducing the "yield gap," the production is limited by finite resources including land, water, and energy, thus emphasizing the need for intensification. However, this often requires additional fertilizer, water, and chemical use (Foley, 2011). Godfray et al. (2010), thus, wrote: "A threefold challenge now faces the world: Match the rapidly changing demand for food from a larger and more affluent population to its supply; do so in ways that are environmentally and socially sustainable; and ensure that the world's poorest people are no longer hungry."

Intensification of livestock production in particular includes an important additional factor to the sustainability equation: the living animal. In response to the morality of intensive livestock production, the last few decades have witnessed a greater consumer demand for organic foods and free range products, and an increased political response and research toward animal welfare issues, particularly driven by public opinion. In addition, continuous selection for high production in livestock has resulted in animals that have been shown to be more at risk for behavioral, physiological, and immunological problems. For example, in this issue, Canario et al. showed that modern 1998-type French Large White sows with high lean growth rate and prolificness at birth were less active in the first 6 h after birth and less attentive to piglets, resulting in a higher risk of piglet death than 1977-type sows. As Van Rooijen indicated, suffering may result from a loss of harmony in animals with themselves (their physiology) and with their environment (natural environment vs. intensive production systems). Therefore, it is unlikely that further intensification of livestock production practices can count on much public acceptance if no measures are taken to guarantee sustainability. "Sustainable intensification" of livestock must be defined by economic profitability through improvement of productive output, while maintaining animal health and welfare, and without compromising environmental resources during the production process. Livestock breeding programs of today and of the future must adhere to this definition; therefore, animals must be bred that are robust.

Robustness may be improved through the use of reaction norms analysis (as reviewed by Rauw and Gomez Raya) and through the inclusion of robustness traits in the breeding objective. The last few decades have seen the inclusion of functional traits such as those related to longevity, health, and fertility, in addition to production traits in selection indexes. Indeed, these traits have a clear economic value and are considered as indicators of well-being. In this issue, Strucken et al. reviewed

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the genetics that underlies the complex physiological dynamics behind the lactation cycle of dairy cattle as a new potential functional trait. Selection for a production curve that allows production without inducing an energy deficiency, by distributing the total quantity of milk per lactation more equally over time, could improve health and welfare. Kassahun et al. described admixture mapping as an approach for gene discovery of economically and medically important traits. Their work describes the potential of admixture mapping in hybrid domestic animals with divergent ancestral genomes derived from *Bos taurus* and *Bos indicus*, to search for genomic regions associated with susceptibility to bovine tuberculosis—a chronic respiratory infection in cattle.

In addition to the inclusion of functional traits, several authors discuss the feasibility of including behavioral traits in the selection criteria. For example, in this issue, Haskell et al. extensively reviewed the feasibility of including temperament traits in dairy and beef cattle selection indices. This has a clear economic value through the associations between temperament and productivity; in addition, animals that respond poorly to handling suffer negative emotional and physical experiences, resulting in reduced welfare. Including behavioral traits in the selection criteria pose a number of challenges. For example, as extensively described by Ellen et al., when animals are kept in groups, social interactions can have large positive (cooperation and mothering behavior) and negative (competition and aggression) effects on individual welfare, productivity, and health. As a result, response to selection using classical selection methods for socially affected traits may not always be optimal. Alternatively, statistical methods have been derived that capture the total genetic variation underlying a trait by taking into account both the direct genetic effect of an individual and its social genetic effect on the phenotype of its group mates. The theoretical and empirical works on social genetic effects in livestock and the application and implication of its inclusion in livestock breeding programs are extensively reviewed by Ellen et al. Selection programs to improve associative effects or social impacts of one animal on the performance of another in poultry are described by Muir et al. The authors indicate that breeding programs that involve multi-level selection, and multi-trait selection methods where one of the traits includes indirect genetic effects, will improve both production traits and animal well-being at the same time.

In 2012, the Farm Animal Welfare Council concluded that farm animal breeding companies should be congratulated for the progress made on breeding goals aimed at improving robustness and health and welfare traits. However, there are still some issues associated with high production levels resulting in poor animal welfare. With this research topic, and thanks to the generous willingness of all participants to contribute, we aimed to present examples that show that research is devoted to improve welfare in livestock through selection, which will enhance sustainability of livestock production systems in the future.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Genetic trends in maternal and neonatal behaviors and their association with perinatal survival in French Large White swine

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Genetic trends in maternal abilities were studied in French Large White sows. Two lines representing old-type and modern-type pigs were obtained by inseminating modern sows with semen from boars born in 1977 or 1998. Successive generations were produced by inter-se mating. The maternal performance of sows from the second generation was compared in farrowing crates. Video analysis was performed for the 1st h after the onset of 43 and 36 farrowing events, and for the 6 first hours for 23 and 21 events, in old-type and modern-type sows, respectively. Genetic trends were estimated as twice the difference in estimates between the 2 lines. The contribution of behavior to the probability of stillbirth and piglet death in the first 2 days was estimated as the percentage of deviance reduction (DR) due to the addition of behavior traits as factors in the mortality model. Sow activity decreased strongly from the 1st to the 2nd h in both lines ($P < 0.001$). In the first 6 h, old-type sows sat (1st parity), stood (2nd parity) and rooted (both parities) for longer than modern-type sows, which were less active, especially in 2nd parity. In modern-type sows, stillbirth was associated positively with lying laterally in the first 6 h (4.6% DR) and negatively in the 1st h (9.1% DR). First-parity old-type sows were more attentive to piglets ($P = 0.003$) than modern-type sows which responded more to nose contacts at 2nd parity ($P = 0.01$). Maternal reactivity of modern-type sows was associated with a higher risk of piglet death (4.6% DR). Respiratory distress at birth tended to be higher in modern-type piglets than in old-type piglets ($P < 0.10$) and was associated with a higher risk of piglet death in both lines (2.7–3.1% DR). Mobility at birth was lower in modern-type than old-type piglets ($P < 0.0001$). Genetic trends show that sow and piglet behaviors at farrowing have changed. Our results indicate reduced welfare in parturient modern-type sows and their newborn piglets.

Keywords: maternal behavior, piglet vitality, farrowing, genetic trend, sow

INTRODUCTION

Highly productive lean sows are affected by undesirable correlated effects of genetic selection, including modifications of behavior that affect both their own welfare as well as that of their progeny (Rauw et al., 1998; Rauw, 2007; Canario et al., 2013). In particular, a rise in the sensitivity to stressors in the physical environment is observed when intensive genetic selection for a few traits is applied (Grandin and Dessing, 2014). Sows face acute stressors when they endure a sudden change in their environment, such as the critical period of farrowing, especially in primiparous females. In pigs, the survival of progeny depends strongly on maternal care during the first days of life. Sow behavior is a major component of maternal success in terms of piglet survival and growth. Thodberg (2001) suggested that good sow maternal behavior involved limited activity in the peripartum period, but that farrowing should be preceded by a period of nest-building activity (e.g., Thodberg et al., 1999; Damm et al., 2005). At farrowing, such activity can continue although lying laterally and changing posture only infrequently is preferable to reduce the risks of stillbirth and crushing new-born piglets. At the same time, limiting changes in posture allows for easier access to the udder where piglets find warmth and colostrum (Petersen et al., 1990; Jarvis et al., 1999). Paradoxically, the development of proper mother-progeny bonding requires postural changes so that the sow can interact with the piglets (Jarvis et al., 1999; Pedersen et al., 2003).

The evolution of sow maternal behavior in response to domestication has been studied by comparing domestic sows with wild sows or wild boar × domestic sows. No trend was observed for behavior around farrowing (e.g., Jensen, 1986; Jensen et al., 1991; Horrell, 1997).

Genetic selection schemes for lean growth rate and prolificacy conducted in pig dam lines at the end of the last century led to increased piglet mortality around farrowing (Tribout et al., 2003; Canario, 2006). Since then, selective breeding programs have been successfully modified in order to limit stillbirth; however neonatal mortality remains a serious problem. Little is known about the genetic trends in sow maternal behavior associated with genetic selection for both lean growth rate and prolificacy. It is nevertheless reasonable to hypothesize that the production of larger litters requires a higher maternal investment than in the past. In 1977 Bidanel and collaborators initiated an experiment aimed at estimating genetic trends for performance in French Large White (LW) pigs over a 21-year period (1977–1998) corresponding to approximately 11 generations of selection (Tribout et al., 2010). The principle of the experiment was to use frozen semen from boars that were representative of the two populations raised at the beginning and the end of the 21-year period to inseminate modern-type sows and produce 2 lines (Smith, 1977). The next generations were produced by inter-se mating. Animals were compared in the same environment for a large number of traits. The animals from the two lines will be referred to as old-type pigs and modern-type pigs, respectively. Modifications in sow maternal performance were investigated in detail in sows from the second generation and their progeny (Canario, 2006).

The consequences of genetic selection on animal behavior have rarely been investigated, especially for traits that are difficult and time-consuming to record. Based on the above-described experimental design, we estimated whether sow behavior has been modified as a correlated response to selection for lean meat growth and prolificacy in the French Large White population. In this paper, we establish genetic trends for behaviors related to sow farrowing activity, newborn vitality, and their associations with piglet mortality in the first 48 h after birth.

MATERIALS AND METHODS

EXPERIMENTAL DESIGN

The animals were produced and raised in the INRA experimental herd of Avord (Cher). Sows were managed under a batch farrowing system, with 3 weeks interval between successive batches. Animals were cared for according to the protection of animals rules defined in the French law (Code Rural, articles R214-64–R214-71; http://www.legifrance.gouv.fr). The history of selection over the study period can be summarized as follows: until the mid-1980s, pigs were selected for growth rate, feed efficiency, and carcass leanness; in 1985, a meat quality index was introduced in the breeding goal; at the end of the 1980s, a strong emphasis was placed on improving the litter size through the generalization of so-called "hyperprolific" breeding schemes. Finally, in the mid-1990s, standard selection indexes were replaced by more accurate predictors of breeding values based on multiple-trait BLUP animal model methodology. At this time, the criterion of selection for litter size was the total number of piglets born. Management and other environmental conditions have improved progressively over the 21-year period considered, with, for instance, an increasing knowledge of nutritional requirements of animals and the generalization of artificial insemination.

The two lines (referred to as old-type and modern-type, respectively) have been produced by inseminating French LW sows born in 1998 with semen from LW boars born either in 1977 or in 1998 (Tribout et al., 2010; **Figure 1**). Three generations of old-type and modern-type pigs were then produced by inter se mating of randomly chosen old-type or modern-type boars and gilts. The difference observed between the 2 lines shows half of the genetic change. In the present experiment, sows from the 2nd generation were inseminated twice at a 12-h interval with frozen semen from boars of the first generation in first parity and with fresh semen from boars of the second generation in second parity. The maternal performance of sows and litter characteristics were recorded from August 2003 to September 2004. Sows were managed in a batch-farrowing system, with a 3-weeks interval between successive batches. They were fed 2.5–3 kg of a commercial sow diet twice daily during the whole gestation period. Approximately 1 week before expected date of farrowing, they were moved to one of the 2 farrowing units. Sows were housed in farrowing crates (1.80 × 2.40 m; space available to the sow: 0.60 × 1.90 m) on a partially slatted flooring covered with a thin floor of straw and made with solid external wooden walls (height: 0.5 m) on the four sides, so that sows could see their neighbors. As often as possible, old-type and modern-type sows were placed in neighboring farrowing crates, so that an old-type female had modern-type neighbor females. The room was lit both by natural daylight and artificial lighting maintained all around the clock. Sows were fed a commercial diet twice a day according to regular management practices and had permanent access to water from a nipple drinker. Feed was distributed at 8:00 a.m. and 4:30 p.m. Crates were cleaned daily at 8:00 p.m. Sows were daily provided with 1 kg straw, from 2 days before to 4 days after the date of farrowing, so that they had continuous access to straw during the experimental period. A water nipple for the piglets was also present, as well as a ceramic heat lamp located at the back of the sow until day 3.

From day 111 of gestation, sows were daily visited to identify signs of impending farrowing and to reduce their fear of humans. The farrowing was not induced. Birth assistance including ocytocin treatment and/or vaginal palpations was restricted to cases of extreme necessity and implied the removal of the sow from the study. Care was provided to the sows when essential to respect the general guidelines outlined in the European animal welfare regulations applicable at this time. Farrowing supervision was carried out 24 h a day. Disturbance of the sows was limited by video watching from an adjacent room. Apart from manipulation of newborn piglets that stimulate their vitality, interference with the natural farrowing process was avoided. There was no human intervention to control aggression or prevent crushing of newborn piglets. Cross-fostering was not allowed. Ear marking and tail trimming was performed on day 2 and male piglets were castrated on day 4. The onset of farrowing corresponded to the time of birth of the first piglet. Each expelled piglet was immediately caught. Its umbilical cord was cut and a blood sample taken for plasma parameter measurements. The remaining part of the umbilical cord was ligatured with a surgical silk. Subsequently, the piglet was carried to a weighing place located inside the maternity to be dried with straw and drying paper, weighed, sexed and marked on its back with a number corresponding to its birth order. Next, it was replaced in the back part of the crate, close to the vulva of its dam. Piglets were weaned at 4 weeks of age. A total of 137 litters and 1679 piglets were produced.

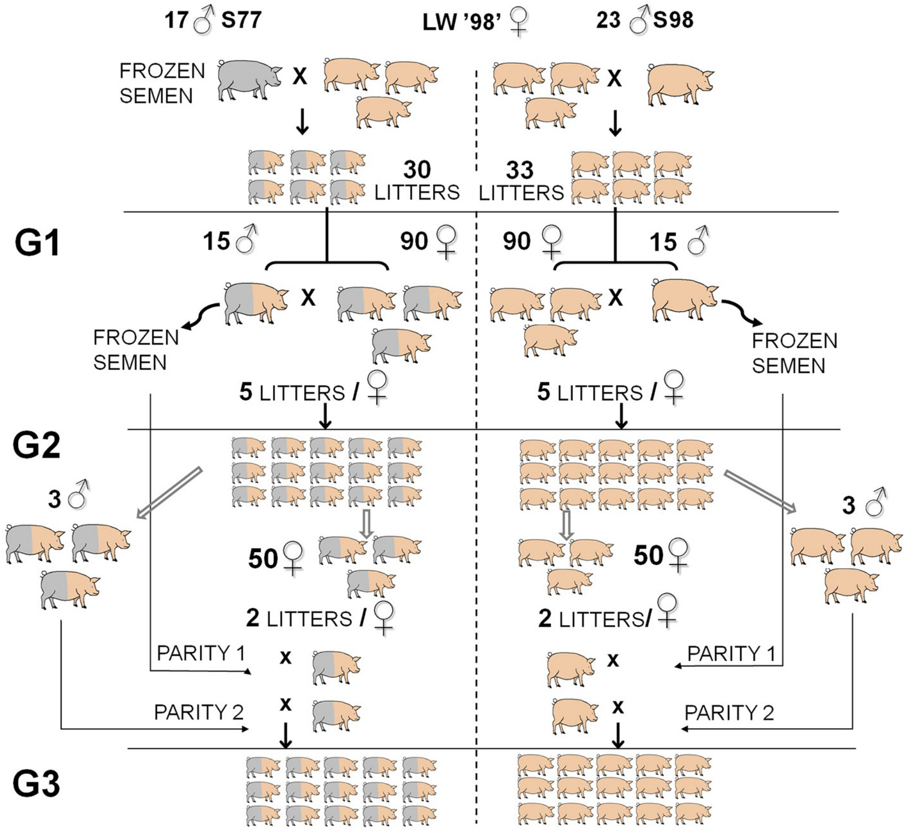

FIGURE 1 | Overview of the experimental design developed to estimate genetic trends from 1977 to 1998 in the French Large White dam population. Phenotyping of the maternal performance of old-type and modern-type lines was carried out in the first 2 parities of G2 (second generation) sows and their progeny (G3). Modified from Tribout et al. (2010).

LITTER MORTALITY TRAITS

The fine monitoring of stillbirth allowed the number of piglets born alive to be exactly known. Piglet mortality was carefully registered during the first 2 days after birth and the causes of deaths were determined by a macroscopic examination. They were classified in three categories: (1) thin piglets dying with chops palpable or visible under the skin, presumably because of starvation, were classified as weak; (2) piglets dying because of injuries caused by the sow were classified as crushed; and (3) other causes, including unidentified cause, and cannibalism.

BEHAVIORAL TRAITS

Sows from the 2 lines could not be visually differentiated. The onset of farrowing was determined on 61 and 52 farrowing events in old-type and modern-type sows, respectively. Sow and piglet behavior was recorded using 24 time lapse video (VHS Panasonic video recorder associated with DPX9 *multiplexer Advanced Technology Video*). Video tapes were analyzed by a single observer by continuous observations with speeded up watching. Behaviors were analyzed as durations and/or occurrence. Time of birth, time to first contact with the udder and time to first intake of colostrum were recorded for each piglet. First, behavioral analyses at farrowing were limited to a 6 h period beginning with the birth of the first piglet to depict finely the pattern of sow activity in the first hours and to identify the change from a period of high activity—elicited by the onset of farrowing—to a period of lower activity. A total of 23 old-type sows including 8 first and 15 second parity sows, and 21 modern-type sows including 6 first and 15 second parity sows, were compared. The behavioral traits included the sow postural activity, rooting behavior, and attention and responsiveness toward progeny. Rooting behavior was visible only during the first 4 h. The behavioral definitions for sow and piglet measurements are given in **Tables 1**, **2**, respectively. Second, sow postural activity was analyzed during the first hour after the onset of farrowing on 26 first-parity and 17 second-parity old-type sows and 23 first-parity and 13 second-parity modern-type sows.

On-field behavioral observations were also realized. Several reactions of the sow were registered by direct observations when animals were manipulated by humans. The 3 observers had trained together in preliminary trials to register the behavioral items in similar way. The behavioral reaction of the sow to first handling of a newborn piglet and at the first nose contact with a newborn piglet was quantified via postural changes and vocalizations. The catch up of piglets was a rapid action without staying stationary at the back of the crate. The initial posture of the sow was recorded. Once the piglet was taken out from

Table 1 | Behavioral measurements for the comparison of old-type sows and modern-type sows.

Behavior	Definition
VIDEO OBSERVATION	
Postural activity	
Lying ventrally	Lying in sternal recumbency, with udder not exposed
Lying laterally	Lying in lateral recumbency, with udder exposed
Sitting	Sitting continuously for at least 5 s
Standing	Standing upright, on four feet
Postural changes	All changes between the four positions mentioned above
Exploratory activity	
Rooting	Head making a scooping motion with the nose in contact with the floor (and/or straw) in a scaterring way
Maternal activity	
Piglet examination	Movement of the snout toward the approaching piglet, located at less than one piglet length from the sow snout
Piglet indifference	No visible reaction to the approaching piglet, located at less than one piglet length from the sow snout
Piglet responsiveness	Ratio of piglet examinations above trials (sum of piglet examinations and indifferences)
Piglet attentiveness	Head directed attentively to at least one piglet, located at more than one piglet length from the sow snout
DIRECT OBSERVATION	
Reaction to newborn handling	
Maximal postural change	Sows were in lateral recumbency at the beginning of the observation. The different postures corresponded to lying laterally, lying ventrally, sitting, and standing
Vocalizations	Vocalizations were registered according to the following ordered scale: 0, no grunting; 1, some isolated grunts ($n < 5$); 2, regular grunts; 3, rhythmic high intensity grunts
Reaction to first nose contact with a newborn	
Maximal postural change	Same definition as above
Vocalizations	Same definition as above
Investigation	Four ordinal categories: 0, no answer; 1, piglet calm sniffing; 2, piglet strong sniffing; 3, attempt on biting piglet
Sniffing	Piglet calm or strong sniffing
Aggressive reaction	Piglet strong sniffing, or attempt on biting piglet

Table 2 | Behavioral measurements for the comparison of old-type and modern-type newborn piglets.

Behavior (criterion)	Definition
VIDEO OBSERVATION	
Suckling activity	
Time to first udder contact (min)	Time interval between birth and first touching of the udder with nose
Time to first colostrum intake (min)	Time interval between birth and immobilization at the udder, holding a teat in mouth with rapid mouth movements for at least 5 s
Activity at the udder (#)	Number of piglets suckling (teat in mouth or massaging the udder actively)
DIRECT OBSERVATION	
Respiratory difficulty (0/1)	The piglet shows difficulties to breath normally, makes attempts to breath, with visible exaggerate movements of the mouth
Mobility at birth (class)	Evaluated at the birth weighing: the piglet 0, doesn't move at all; 1, shows some movements; 2, shows many movements to stand up or even stand up
Vocalizations at birth (class)	Evaluated at the birth weighing: the piglet 0, doesn't scream; 1, makes few vocalizations; 2, makes many vocalizations

the crate, the sow maximum posture reached and vocalizations were recorded. Piglet vitality at birth was assessed through direct observation of the individual difficulty to breath, mobility, and intensity of vocalizations while weighed in a standard box ($60 \times 40 \times 35\,\text{cm}^3$).

STATISTICAL COMPARISON OF THE LINES

Statistical analyses were performed using the Statistical Analysis System Software (SAS Institute, Inc.). Stillbirth and early mortality traits were analyzed as raw values and as the percentage of piglets born in total and born alive, respectively. If normally distributed, behavior traits were analyzed with the MIXED procedure. When binomially or Poisson distributed, they were analyzed using the GEE option from the SAS GENMOD procedure.

The general model for analyses of sow traits included the fixed effects of farrowing batch, line, parity, and the line × parity interaction, plus a sow random effect. In addition, a fixed effect of the observer was included for sow reactivity when recorded on farm. For the video data corresponding to the first hour from 79 farrowing events and the 6 first hours from 44 farrowing events, line differences were first estimated globally over the whole period of time using the model described above. Next, for the description of the farrowing pattern, analyses were carried out on a per hour basis. The model included in addition to the previous model the fixed effects of the Period of Time (PT = first to 6th h after onset of farrowing), the line × PT and parity × PT interactions. When not significant ($P > 0.10$), interactions were removed from the model. The covariance between measurements at different time intervals within the same sow was allowed to vary according to an exchangeable structure. Then, patterns of line × PT behaviors were drawn.

As regards to piglet traits, respiratory difficulty and reaction at birth were considered as binomially and Poisson distributed, respectively. The model included the fixed effects of farrowing batch, line, parity, line × parity interaction plus the random effect of the litter of birth. Udder activity was recorded on 12 litters in each line among which 11 old-type piglets and 21 modern-type piglets had no time record for the first contact with the udder and 18 piglets and 32 modern-type piglets had no time record for the first intake of colostrum. Two situations occurred: (1) these pigs did not suckle and therefore observation periods became extremely long. In such a case, they were attributed the value of 3 h; (2) in large litters, it became more and more difficult to see individual piglets reaching the udder while the number of born piglet increased. Time to first udder contact and first intake of colostrum was analyzed with a model including the fixed effects of the line, farrowing batch and a random effect of the litter of birth.

Estimates are given after a back transformation to the original scale: when having a Poisson distribution, results on the original scale were obtained via an exponential transformation and when binomially distributed, results were obtained via an $\exp(y)/(1 + \exp(y))$ transformation where y was the least square means estimate on the logit scale. The realized genetic trends from 1977 to 1998 (ΔG) and their standard errors ($SE(\Delta G)$) were estimated for each trait as proposed by Smith (1977): $\Delta G = 2 \times$ (modern-type lsmean—old-type lsmean) and $SE(\Delta G) = 2 \times SE$(modern-type lsmean—old-type lsmean).

RELATIONSHIP BETWEEN BEHAVIOR AND PIGLET MORTALITY

The piglet probability of stillbirth and the probability of death in the first 2 days of life were analyzed in each line following the methodology described by Canario et al. (2006a). The probability was assumed to follow a binomial distribution. The factors of variation considered in the model were the effect of parity and behavioral traits as covariates. Estimates were obtained from generalized linear model of the GENMOD procedure. Both behaviors during the first hour (peak of activity) and the first 4 h (larger pattern where most of the sow activity, at least in postural changes, takes place; **Figures 2–4**), were considered as explanatory variables for the risk of mortality. The sow behavior was defined as mean duration per hour, except postural changes that was defined as a frequency per hour and responsiveness as a probability per hour. These analyses allowed the contribution of each effect to the variance reduction to be evaluated and quantified with the coefficient of determination of Hosmer and Lemeshow (1989). This coefficient of deviance reduction (DR) was established using deviance differences between successive models where explanatory variables were added one by one. The level of significance of each effect was estimated according to a likelihood ratio test.

RESULTS

FARROWING PROCESS AND PIGLET MORTALITY

The distribution for time of onset of farrowing in old-type and modern-type sows is shown on **Figure 2**. The modern-type sows started farrowing more often out of the staff working hours (8–12 a.m. and 2–5 p.m.) than the old-type sows (probability of 0.66 vs. 0.46, respectively, $\chi^2 = 4.23$, $P = 0.04$). There was no line × parity interaction on this trait. In the global population, the effect of parity on the number of stillbirths and deaths in the first 2 days was not significant. Stillbirths were more numerous in modern-type litters than in old-type litters: the genetic

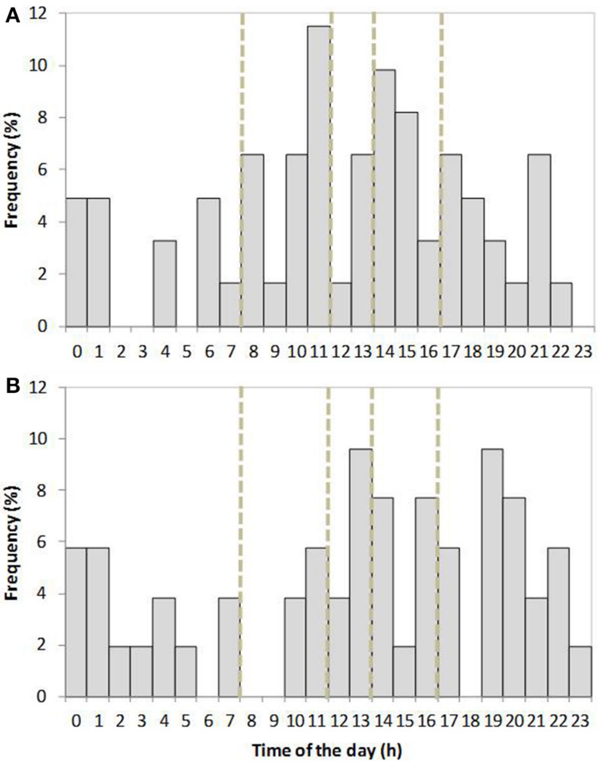

FIGURE 2 | Distribution of the onset of farrowing over the circadian period in old-type (A) and modern-type (B) sows. Periods of staff working hours are indicated with doted lines (8–12 a.m. and 2–5 p.m.), data from the first and second parities are grouped together.

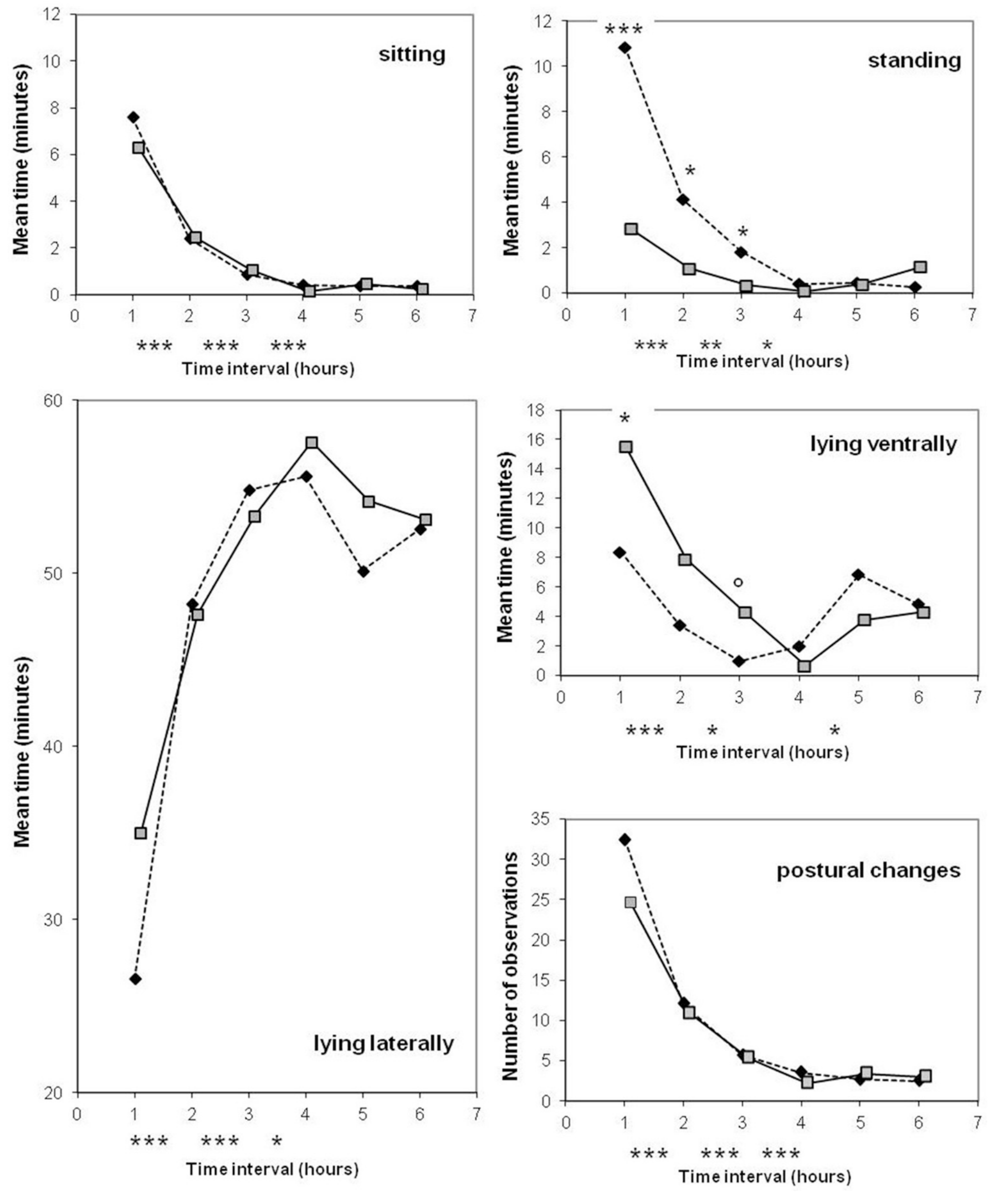

FIGURE 3 | Comparison of old-type sows (◆) and modern-type sows (■) for postural activity during the first 6 h after the onset of farrowing. Significance levels below the X axis refer to differences between successive periods of time, obtained with both lines merged together. Significance levels reported on the graph above mean values refer to lines differences: $^{\circ}P < 0.10$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

trend was $\Delta G = +1.34$ (SEΔG 0.6) stillborn piglets per litter. The number of piglets born in global, i.e., including mummified and macerated piglets was higher at second parity in modern-type litters than in old-type litters (12.3 vs. 14.6 piglets born; $\Delta G = +4.6$ (SEΔG 2.1); $P = 0.04$). No difference was detected on that trait at first parity [12.2 vs. 12.4 piglets born; $\Delta G = +0.4$ (SEΔG 2.2)]. Savaging piglets accounted for only one death in each line. On average 0.85 and 1.12 born alive piglets died per litter in the first 2 days in old-type and modern-type sows, respectively ($\Delta G = +0.54$; SE$\Delta G = 2.76$; $P = 0.43$), accounting for 6.9 and 8.5% of mortality in old-type and modern-type litters ($\Delta G = +3.2$; SEΔG 2.7; $P = 0.51$).

SOW GLOBAL ACTIVITY

Sow postural activity in the first 6 h after the onset of farrowing is depicted on **Figure 2**. Three old-type sows vs. 1 modern-type sow were totally inactive on this period of time. The interaction between line and parity tended to be significant for almost all postural traits on this 6 h frame ($P < 0.15$), so that trends are depicted per line and parity (**Table 3**). Over the 6 h period, sows spent most of the time lying (>90% of time) but the first-parity modern-type sows tended to be less agitated than their old-type counterparts. Similarly, the first-parity modern-type sows also spent less time sitting than their old-type counterparts. At second parity, sow activity was globally lower and equivalent in the

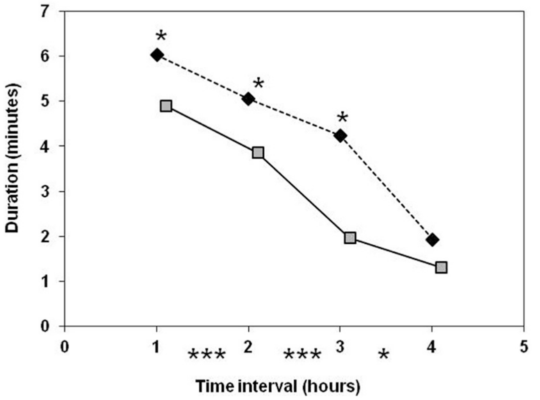

FIGURE 4 | Comparison of old-type sows (◆) and modern-type sows (■) for rooting activity during the first 4 h after the onset of farrowing. Significance levels below the X axis refer to differences between successive periods of time, obtained with both lines merged together. Significance levels reported on the graph above mean values refer to line differences: $^{*}P < 0.05$; $^{***}P < 0.001$.

two lines (46 vs. 50 min; $P = 0.60$) but the modern-type sows spent less time standing and tended to spend more time lying ventrally than their old-type counterparts. Old-type sows spent more time lying ventrally and sitting, and changed of postures more frequently at first parity than at second parity. Accordingly, the relative amount of time spent lying laterally increased in old-type sows (73 vs. 89% at first and second parity, respectively) but not in modern-type sows (83 vs. 88%).

The line differences were mainly observed in the first 3 h after the onset of farrowing. Postural activity drastically decreased with time, and lying laterally became the main position (from the 3rd h, more than 80% of each hour was spent in this posture) with a maximum reached during the 4th h (**Figure 3**). Estimates of sow postural activity in the first hour are given at the bottom part of **Table 3**. The line × parity interaction tended to be significant for the occurrence of standing position ($P = 0.06$). A significant effect of parity was detected in modern-type sows which stood less frequently, spent even more time lying laterally and were less agitated at second parity than at first parity during the first hour.

Due to the low occurrence of sow exploratory behavior, the line × parity interaction was not estimable. The two lines differed in the time spent rooting in the first 6 h and the difference was important at second parity (11.4 vs. 2.4 min in old-type and modern-type sows, respectively; **Table 4**). The old-type sows performed more rooting than the modern-type sows in the first 3 h. A drop in this activity was observed in the 4th hour (**Figure 4**).

MATERNAL BEHAVIOR

Estimates of sow maternal behavior are shown in **Table 5**. There was a significant line × parity interaction for responsiveness toward progeny when defined as occurrence, and a tendency for attentiveness when defined as duration. The probability of response to a nose contact differed between lines at second parity in favor of modern-type sows. The first-parity old-type sows spent more time watching their piglets than their second-parity and modern-type counterparts. At second parity, differences disappeared and sows from both lines spent less time in attention toward their progeny than in first parity. Responsiveness decreased with time, but modern-type sows remained more responsive than their old-type counterparts (**Figure 5**). Attention

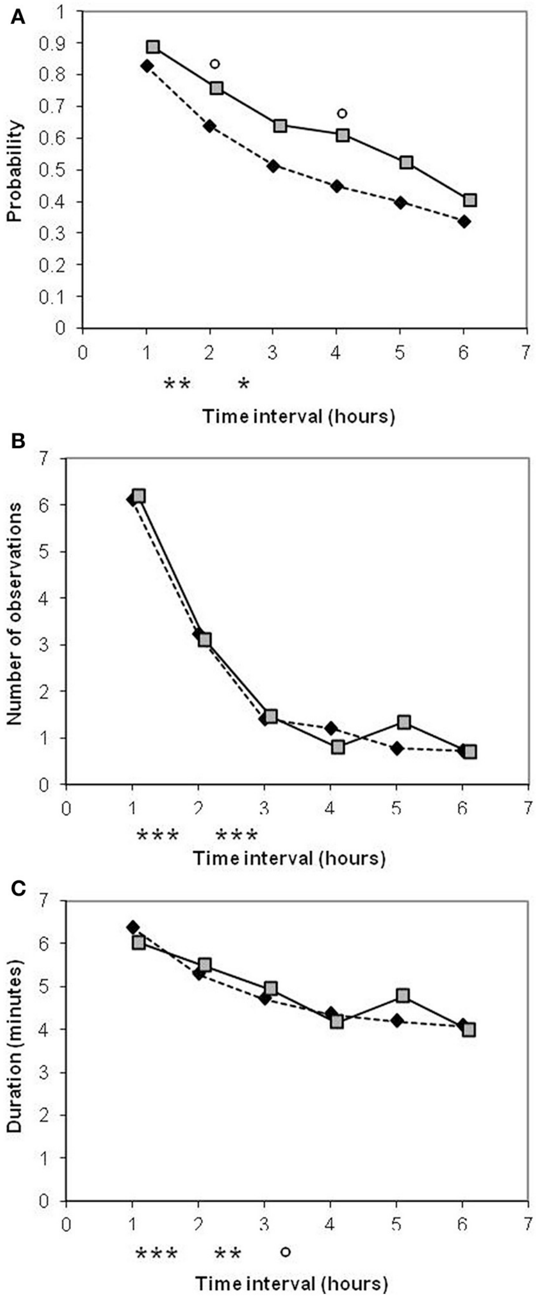

FIGURE 5 | Comparison of old-type sows (◆) and modern-type sows (■) for maternal responsiveness (A) and maternal attentiveness occurence (B) and duration (C) during the first 6 h after the onset of farrowing. Significance levels below the X axis refer to differences between successive periods of time, obtained with both lines merged together. Significance levels reported on the graph above mean values refer to line differences: $^{\circ}P < 0.10$; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Table 3 | Genetic trends for sow postural activity at farrowing.

Trait (criterion)	Parity	Old-type sows[a]	Modern-type sows	ΔG ($SE\Delta G$)[b]	Pr > |t| H0: $\Delta G = 0$[c]
IN THE FIRST 6 H AFTER ONSET OF FARROWING					
Standing (min)	1	15.9	9.5	−12.8 (3.9)	0.44
	2	19.2	5.1	−28.2 (3.2)	0.004
Sitting (min)	1	19.4 |**[d]	10.3	−18.2 (2.7)	0.05
	2	7.4	11.1	+7.4 (2.7)	0.17
Lying ventrally (min)	1	63.8 |**	41.5	−44.6 (3.3)	0.39
	2	13.1	24.9	+23.6 (2.9)	0.09
Lying laterally (min)	1	265.0 |*	293.4	+56.8 (2.2)	0.16
	2	313.8	309.7	−8.2 (2.1)	0.80
Postural changes (#)	1	85 |**	62	−46 (2.4)	0.11
	2	41	42	+2 (2.5)	0.94
IN THE FIRST HOUR AFTER ONSET OF FARROWING					
Standing (min)	1	6.0	5.2	−1.6 (2.8)	0.69
	2	4.0	3.3	−1.4 (3.2)	0.66
Standing (#)	1	1	1 |**	+0 (2.9)	0.32
	2	2	0	−4 (3.7)	0.01
Sitting (min)	1	1.4	4.1	+5.4 (4.6)	0.18
	2	2.6	1.8	−1.6 (3.7)	0.58
Sitting (#)	1	6	5	−2 (2.5)	0.34
	2	4	3	−2 (2.8)	0.38
Lying ventrally (min)	1	9.5 |*	13.5 |°	+8 (2.9)	0.27
	2	3.2	5.5	+4.6 (3.3)	0.28
Lying laterally (min)	1	37.8	33. |*	−9.6 (2.3)	0.24
	2	45.4	50.0	+9.2 (2.3)	0.45
Postural changes (#)	1	16	14 |*	−4 (2.4)	0.40
	2	9	7	−4 (2.8)	0.35

[a] *Least square means.*

[b] *Genetic trend estimated from 1977 to 1998:* $\Delta G = 2\times$ *(modern-type mean—old-type mean) and* $SE\Delta G = 2\times$ *SE (modern-type mean—old-type mean).*

[c] *Probability associated with the null hypothesis (H0):* $\Delta G = 0$ *(P-value).*

[d] *Differences between parity 1 and parity 2. Level of significance:* $^{\circ}P < 0.10$; $^{*}P < 0.05$; $^{**}P < 0.01$.

Table 4 | Genetic trends for sow exploratory behavior.

Trait (criterion)	Parity	Old-type sows[a]	Modern-type sows	ΔG ($SE\Delta G$)[b]	Pr > |t| H0: $\Delta G = 0$[c]
Rooting (#)	1	8	6	−4 (3)	0.46
	2	7	2	−10 (3)	0.0004
Rooting (min)	1	10.3	4.8	−11.0 (3.5)	0.16
	2	11.4	2.4	−18.0 (3.3)	0.001

[a] *Least square means estimated from data analyzed during the first 6 h after onset of farrowing.*

[b] *Genetic trend estimated from 1977 to 1998:* $\Delta\ G = 2\times$ *(modern-type mean—old-type mean) and* $SE\Delta G = 2\times$ *SE (modern-type mean—old-type mean).*

[c] *Probability associated with the null hypothesis (H0):* $\Delta G = 0$ *(P-value).*

also decreased with progress of farrowing. As regards to sow reactivity at first manipulation of a newborn by human, no piglet was screaming during handling. Sow's maximum posture reached was similar in the two lines: most of the sows remained in lateral position (33/36 and 30/34 in old-type and modern-type sows, respectively). However, at second parity, even if not significant, the modern-type sows tended to perform more grunts in reaction to piglet handling than their old-type counterparts ($P = 0.19$). The line × parity interaction approached significance ($P = 0.15$) and a tendency for greater vocal reaction at second parity than at first parity was observed in both lines ($P < 0.10$). The maximum posture achieved at the first nose contact between the sow and a newborn piglet did not differ. Approximately two third of the sows in each line were moving to a position different from lying laterally (15/27 and 25/36 in old-type and modern-type sows, respectively). The average vocal reaction was also equivalent between the lines (but 9/27 old-type and 22/36 modern-type sows did not grunt at all). In addition, the modern-type sows

Table 5 | Genetic trends for sow maternal behavior.

Trait (criterion)	Parity	Old-type sows[a]	Modern-type sows	ΔG (SEΔG)[b]	Pr > |t| H0: ΔG = 0[c]
VIDEO OBSERVATION SOW REACTION IN THE FIRST 6 h AFTER ONSET OF FARROWING					
Piglet responsiveness (*p*)	1	0.67 |***[e]	0.72	+0.10 (1.09)	0.21
	2	0.48	0.64	+0.32 (1.13)	0.01
Piglet attentiveness (#)	1	30 |***	18	−24 (2.59)	0.04
	2	6	10	+8 (2.73)	0.08
Piglet attentiveness (min)	1	37.9 |***	17.7	−40.4 (0.07)	0.003
	2	9.7	13.3	+7.2 (0.05)	0.37
DIRECT OBSERVATION AT FARROWING ONSET					
Reaction to first piglet handling (*N* = 36 and *N* = 34)					
Maximum posture reached (class)[d]	1 + 2	0.14	0.12	−0.04	0.88
Vocalizations (class)	1	0.15 |°	0.11 |°	−0.08 (6.44)	0.74
	2	0.52	0.77	+0.50 (2.6)	0.19
Reaction to first nose contact with a piglet (*N* = 27 and *N* = 36)					
Maximum posture reached (class)	1	1.39	1.43 |°	−0.26 (3.83)	0.92
	2	1.15	0.79	−0.72 (2.92)	0.39
Vocalizations (class)	1	1.19	0.66 |°	−1.06 (3.23)	0.21
	2	0.93	1.23	+0.60 (2.92)	0.46
Sniffing piglet (*p*)[d]	1 + 2	0.75	0.94	+0.38	0.19
Aggressive reaction (*p*)	1	0.60	0.51	−0.18	0.11
	2	0.52	0.50	−0.04	0.45

[a] *Least square means.*

[b] *Genetic trend estimated from 1977 to 1998: ΔG = 2 × (modern-type mean—old-type mean) and SEΔG = 2 × SE (modern-type mean–old-type mean).*

[c] *Probability associated with the null hypothesis (H0): ΔG = 0 (P-value).*

[d] *Due to low sample size and low occurrence of the trait, the line × parity interaction could not be estimated.*

[e] *Differences between parity 1 and parity 2. The sign for significance is attributed to the largest value. °P < 0.10; ***P < 0.001.*

tended to react less with postural change and more with vocalizations from first to second parity. Conversely, the probability of aggressive reaction to the first newborn piglet approached significance: the modern-type sows tended to have a gentler reaction than old-type sows at first parity.

NEWBORN PIGLET BEHAVIOR

Results of newborn piglet behavior at birth are shown in **Table 6**. The line × parity interaction was significant for mobility and vocalizations when put in a new environment ($P < 0.01$) and a tendency was obtained for respiratory difficulty ($P = 0.14$). Second-parity modern-type piglets showed higher difficulties to breath at birth than their old-type counterparts. At both first and second parities, modern-type piglets had a lower vitality than old-type piglets. Time to reach the udder and to the first colostrum intake were higher in modern-type than old-type piglets.

RELATIONSHIP BETWEEN PIGLET MORTALITY AND SOW AND PIGLET BEHAVIOR

Estimates of the probability of stillbirth and death are shown in **Tables 7**, **8**, respectively.

Regarding the probability of stillbirth, the trait associated with the largest effects, i.e., time spent lying laterally during the first hour, explained 1.1 and 9.1% of DR in old-type and modern-type sows, respectively. In the first hour, time spent lying ventrally was also negatively associated with the probability of stillbirth in old-type sows (3.3% DR). Moreover, the probability of stillbirth tended to increase in piglets born from modern-type sows that realized more postural changes (2.2% DR). In the first 4 h, time spent standing was a factor of stillbirth in both lines (4.6 and 3.0% DR in old-type and modern-type sows, respectively). Sows more attentive toward their piglets had a lower probability of stillbirth in the two lines (DR of 4.7 and 4.6%). Rooting was associated with a consistent DR in the modern-type sows (4.7%). Lying laterally was a risk factor in modern-type sows (4.6% DR). The probability of stillbirth decreased with rooting and increased with lying laterally in modern-type sows. The influence of other behavioral traits on the probability of stillbirth was less than 2%.

Due to the relatively low occurrence of crushing and starvation, the two causes of mortality were not distinguished. The probability of death in the first 2 days was lowly influenced by sow behavior in the first hour but varied with the duration of standing and sitting, and the number of postural changes in the first 4 h in modern-type sows (more activity—lower risk of piglet death; 2.3–5.5% DR). In old-type sows, the probability of death decreased with sitting activity (7.6% DR) and attention to piglets (9.1% DR). The duration of lying laterally was not a factor of variation for the risk of death in any of the two lines. Sow reaction at the onset of farrowing affected the probability of death: the maximum posture reached in response to piglet handling explained 4.6% of DR in modern-type sows (more reaction—higher risk of death) and vocalizations explained 2.6% of DR in old-type sows (more grunts—lower risk of death). The probability of mortality tended to increase with sniffing of the first newborn piglet in

Table 6 | Genetic trends for newborn piglet behavior.

Trait (criterion)	Parity	Old-type sows [a]	Modern-type sows	ΔG ($SE\Delta G$)[b]	Pr > $\lvert t \rvert$ H0: $\Delta G = 0$[c]
VIDEO OBSERVATION					
Time to first udder contact (min)[d]	1 + 2	43 (6)	57 (6)	+28	0.14
Time to first colostrum intake (min)[d]	1 + 2	69 (8)	86 (7)	+34	0.16
DIRECT OBSERVATION					
Respiratory difficulty (*p*)	1	0.03	0.04	+0.02 (1.25)	0.77
	2	0.03	0.07	+0.08 (1.19)	0.01
Mobility at birth (class)	1	1.40	1.20	−0.40 (2.20)	0.02
	2	1.50	1.23	−0.54 (2.20)	0.003
Vocalizations at birth (class)	1	0.82	0.46	−0.72 (2.51)	0.01
	2	0.64	0.27	−0.74 (2.55)	0.0004

[a] *Least square means. $N = 506$ vs. 477 for respiratory difficulty; $N = 508$ vs. 488 for mobility; and $N = 500$ vs. $N = 475$ for Vocalizations at birth in old-type and modern-type lines, respectively.*

[b] *Genetic trend estimated from 1977 to 1998: $\Delta G = 2 \times$ (modern-type mean—old-type mean) and $SE\Delta G = 2 \times SE$ (modern-type mean—old-type mean).*

[c] *Probability associated with the null hypothesis (H0): $\Delta G = 0$ (P-value).*

[d] *Due to low sample size and low occurrence of the trait, the line × parity interaction could not be estimated.*

Table 7 | Association between probability of stillbirth and sow behavior.

Sows	Old-type piglets			Modern-type piglets		
Model	**Sign[a]**	**D**	**DR (%)[b]**	**Sign**	**D**	**DR (%)**
IN THE FIRST HOUR OF LACTATION *N* = 934						
(0) = intercept	+	279.26		+	296.98	
(1) = (0) + Parity	+	276.92	0.84	−	294.3	0.90
(2) = (1) + Postural changes	−	273.88	1.10	+	287.68	2.25°
(3) = (2) + Standing	−	271.54	0.85	−	282.66	1.75
(4) = (3) + Sitting	−	271.22	0.12	−	282.54	0.04
(5) = (4) + Lying ventrally	−	262.22	3.32**	−	278.84	1.31
(6) = (5) + Lying laterally	−	259.36	1.09	−	253.48	9.10***
IN THE FIRST 4 H OF LACTATION *N* = 583						
(0) = intercept	−	125.15		+	168.68	
(2) = (1) + Parity	−	123.72	1.14	+	166.70	1.17
(3) = (2) + Postural Changes	−	123.61	0.09	+	166.56	0.08
(4) = (3) + Standing	+	117.95	4.58**	+	161.62	2.97*
(5) = (4) + Sitting	+	117.94	0.01	+	161.25	0.23
(6) = (5) + Lying ventrally	−	117.55	0.33	+	158.50	1.71
(7) = (6) + Lying laterally	+	117.48	0.06	+	151.20	4.61*
(8) = (7) + Rooting	−	117.42	0.05	−	144.13	4.68**
(9) = (8) + Piglet responsiveness	+	117.06	0.31	+	144.01	0.08
(10) = (9) + Piglet attention	−	101.62	4.67**	−	137.36	4.62*

Reduction of deviance due to the addition of behavioral traits as explanatory variables.

[a] *Sign of the corresponding estimate indicates positive or negative association between stillbirth probability and the explanatory variable. D, deviance; DR, deviance reduction.*

[b] *Level of significance according to Likelihood Ratio Test (LRT) statistics. Level of significance: °$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.*

modern-type sows (3.4% DR). Both old-type and modern-type piglets with greater respiratory difficulties at birth were more susceptible to die in the first 2 days (3.1 and 2.7% DR in old-type and modern-type piglets, respectively). Mobility at birth explained a greater part of DR in old-type piglets than in modern-type piglets (2.3 vs. 1.2% DR). These analyses showed higher contributions of sow behavior than piglet behavior to the probability of mortality.

DISCUSSION

GENERAL CONSIDERATIONS

Swine behavior and welfare can be affected by genetic selection due to genetic correlations with the traits included in the breeding goal. Some genetic correlations may be antagonistic, so that the modifications in behavior may be limited. Selection on litter size has reduced the selection pressure on the formerly selected

Table 8 | Association between probability of death in the first 2 days after birth and sow and piglet behavior.

Model	**Old-type piglets**			**Modern-type piglets**		
	Sign[b]	**D**	**DR (%)**[c]	**Sign**	**D**	**DR (%)**
CONTINUOUS SOW BEHAVIOR IN THE FIRST HOUR OF LACTATION (VIDEO) *N* = 847						
(0) = intercept	–	253.02		–	256.62	
(1) = (0) + Parity	+	252.72	0.12	–	256.58	0.02
(2) = (1) + Postural changes	+	252.46	0.10	+	254.98	0.62
(3) = (2) + Standing	+	249.12	1.32	+	252.42	1.00
(4) = (3) + Sitting	+	249.12	0.00	–	252.16	0.10
(5) = (4) + Lying ventrally	+	248.92	0.08	–	250.8	0.54
(6) = (5) + Lying laterally	+	248.18	0.30	+	247.28	1.40
IN THE FIRST 4 H OF LACTATION *N* = 370						
(0) = intercept	+	108.90		+	99.18	
(2) = (1) + Parity	+	108.46	0.40	+	99.18	0.00
(3) = (2) + Postural changes	–	107.92	0.50	–	96.64	2.56*
(4) = (3) + Standing	–	107.88	0.04	–	91.32	5.51**
(5) = (4) + Sitting	–	99.72	7.56**	–	89.22	2.30*
(6) = (5) + Lying ventrally	–	99.04	0.68	–	88.74	0.54
(7) = (6) + Lying laterally	–	98.8	0.24	–	87.8	1.06
(8) = (7) + Rooting	+	98.52	0.28	–	87.74	0.07
(9) = (8) + Piglet responsiveness	–	97.24	1.30	–	87.48	0.30
(10) = (8) + Piglet attention	–	89.58	9.07***	–	87.68	0.07
OBSERVED MATERNAL BEHAVIOR *N* = 398						
(0) = intercept	–	112.38		–	133.84	
(1) = (0) + Parity	–	110.36	1.78	–	133.84	0.00
(2) = (1) + H_Max posture reached[a]	+	110.28	0.07	+	127.64	4.63*
(3) = (2) + H_Vocalization	–	107.42	2.59°	–	127.64	0.00
(4) = (3) + C_Max posture reached	–	107.26	0.15	+	127.42	0.17
(5) = (4) + C_Vocalization	+	107.1	0.15	+	127.28	0.11
(6) = (5) + C_Sniffing	+	106.06	0.97	+	122.94	3.41°
(7) = (6) + C_Aggressive reaction	–	104.52	1.45	+	121.08	1.51
NEWBORN PIGLET BEHAVIOR *N* = 990						
(0) = intercept	–	283.62		–	322.96	
(1) = (0) + Parity	–	283.34	0.10	–	322.72	0.07
(2) = (1) + Respiratory difficulties	+	274.68	3.06°	+	313.9	2.73*
(3) = (2) + Mobility at birth	–	268.34	2.31*	–	310.2	1.18°
(4) = (3) + Vocalizations at birth	+	268.04	0.11	–	309.86	0.11

Reduction of deviance due to the addition of behavioral traits as explanatory variables.

[a] *H, handling piglet reaction; C, nose contact reaction.*

[b] *Sign of the corresponding estimate indicates positive or negative association between stillbirth probability and the explanatory variable. D, deviance; DR, deviance reduction.*

[c] *Level of significance according to Likelihood Ratio Test (LRT) statistics. Level of significance: °$P < 0.10$; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.*

traits. The statistical power of the experimental design available to address behavior changes over a 21-year selection period was limited by the rather low number of animals available and the large within-line variability of behavioral responses classically reported in the literature (e.g., Koolhaas et al., 1997; Wechsler and Hegglin, 1997). Nevertheless, the power was sufficient to detect several significant differences between lines that demonstrate that selection has modified both sow farrowing activities and piglet vitality at birth.

The behavioral response also depends on conditional factors. It may be relatively less intense when observations are performed in the home environment rather than in a novel environment. In addition, sows from the two lines were placed in adjacent crates alternating old-type and modern-type sows, which tended to homogenize results between the 2 lines with the progress of lactation. However, farrowing ought to be a process experienced uniquely by each individual. We therefore expected a substantial variation in behavioral traits during this critical period that causes high acute stress in the sow and represents a challenge for newborns who must adapt quickly to extra-uterine life (Nowak et al., 2000). Human intervention was limited in order to study the biological phenomenon as objectively as possible and to evaluate the capacity of the sow to produce piglets.

Our results are in accordance with previous estimates obtained for the 2nd generation populations, in which the total number of piglets born per litter did not significantly differ between old-type sows (11.9 ± 0.5) and modern-type sows (12.7 ± 0.5) but an increase of stillbirths had been detected: +1.34 stillborn piglets per litter and +8.4% of stillbirths on average (Canario et al., 2007a). The reason for the lack of difference in litter size between the lines at both first and second parities was discussed: prenatal losses and intra-uterine crowding during late gestation were more severe in modern-type sows. The sow populations compared in the present study differed as regards to backfat depth but not in body weight at farrowing, and fatness was a large determinant of stillbirth in modern-type sows (20.3% of DR for the probability of stillbirth; Canario et al., 2007a).

In the present study, early piglet mortality was not extremely high (7 and 8.5% in old-type and modern-type sows, respectively), but substantial losses were observed previously more than 48 h after the beginning of lactation (Canario, 2006). All born alive piglets were kept under the sow, whatever the litter size. In the literature, litters with more numerous stillborn piglets have been shown to face higher pre-weaning mortality (Leenhouwers et al., 1999; Casellas et al., 2004). Accordingly, in modern-type sows, on average one piglet was lost per litter in the 2 days after farrowing. The fact that sows were maintained between fences might have prevented them from displaying the whole range of their behaviors, so genetic trends and the role of dams on the survival of their progeny might have been underestimated. Behavioral results will be discussed in connection with the welfare issues related to selective breeding, the discussion being facilitated by our results revealing the relationships with the risk of piglet mortality.

GENETIC TRENDS IN THE GLOBAL ACTIVITY OF PARTURIENT SOWS

A major rule of animal welfare is to limit pain by prevention or treatment. In conventional farming, farrowing events are routinely assisted with use of ocytocin injection to stimulate contractions and vaginal palpations to release piglets that might be blocked in the vaginal canal. In our study, human interventions at farrowing were limited to cases of extreme necessity, involving survival of piglets and in such cases, the litter was not included in analyses. In past years, several reports have suspected an increase in the duration of farrowing with selection for litter size (Rutherford et al., 2013). Although expected due to the genetic variation in this trait ($h^2 < 0.10$) and its genetic association with stillbirth (Holm et al., 2004; Canario et al., 2006b), such a trend could not be detected distinctly even in the current low-interventionist design. In global populations, even though modern-type piglets were heavier at birth (+260 g on average compared with old-type piglets), we found no distinct trend in farrowing kinetics between old-type and modern-type first-parity sows and a non-significant average increase of 0.8 h of farrowing in second-parity sows with a risk of stillbirth that increased strongly with the time elapsed from the onset of farrowing in modern-type piglets (Canario et al., 2007a).

Sows prepare farrowing several hours in advance and their activity decreases with impending parturition (e.g., Jensen, 1993). Interestingly, our results suggest that modern-type sows can postpone the onset of farrowing so as to avoid human presence. If so, this represents a fairly significant adaptation to their environment. This reaction can be interpreted as increased anxiousness of modern-type sows, which have a higher stillbirth rate when farrowing occurs during the presence of staff (Hemsworth et al., 1999; Janczak et al., 2003). Grandinson et al. (2003) found no phenotypic relationship between avoidance of humans and piglet mortality during early lactation, but a positive genetic association in favor of selection against this behavior.

At farrowing, lower reactivity facilitates the continuity of the process and thus limits birth difficulties. Lying laterally can be considered as a good behavior (Thodberg, 2001). A limited time spent in the lying posture indicates difficulties in coping with this critical event. But on the contrary, total inactivity is also indicative of farrowing difficulties. This assumption was confirmed by a positive association between the time spent lying during the first hour and the risk of stillbirth in modern-type sows. Also, Engelsma et al. (2011) estimated favorable but not significant correlations between the sows' genetic potential for piglet production and calmness around farrowing (less postural changes and lower activity). The higher contribution of the lateral lying posture to the risk of stillbirth in modern-type sows indicates that they experience greater uterine and maternal fatigues that lead to dystocia than old-type sows. The same inactivity has been observed in mice selected for lean-tissue growth rate (McPhee et al., 2001). More generally, the first 3 h after the onset of farrowing are a highly sensitive period during which the sow must adapt to motherhood.

The risks of stillbirth and neonatal death are reported to undergo little variation during the first parities (e.g., Arango et al., 2006) although Canario et al. (2006a) found a decrease in stillbirth from first to second parity in the French Large White dam population. In the study lines, the effect of parity on stillbirth was not significant (Canario et al., 2007a). Stillbirth in young sows might be related to insufficient size of the birth canal (Pejsak, 1984), especially in modern-type sows that produce heavier piglets. As regards to behavior, sows acquire maternal experience at the first parity. Multiparous sows display faster and easier behavioral adaptation than primiparous sows due to a lower susceptibility to the stress of farrowing, leading to lower reactivity (Thodberg, 2001). Such a difference due to maternal experience was detected only in old-type sows that spent more time lying laterally at second parity than at first parity during the 6-h observation period. In modern-type sows, the level of total inactivity was very high at both first and second parities, presumably in relation with the higher incidence of prenatal deaths and the higher mean piglet weight found in these sows compared with old-type sows (Canario et al., 2007a).

Furthermore, we found that modern-type sows were on average less active than old-type sows, which is in line with McPhee et al. (2001) who found that sows selected for lean-tissue growth rate are less active at farrowing. Genetic trends toward decreased time spent sitting (−18 min/6 h) and changing of posture (−46 postural changes/6 h) in first-parity sows and decreased standing activity in second-parity sows (−28 min/6 h and −4 times during the first hour) were estimated. Sitting can indicate stress (Dybkjaer, 1992) and possibly the sow's motivation but inability to perform nest-building activities when blocked in a crate (Hartsock and Barczewski, 1997; Jarvis et al., 2001; Thodberg, 2001). This posture was not observed beyond the 3rd hour after the onset of farrowing. The old-type first parity sows spent twice more time sitting than second parity sows, who spent more time standing and rooting. On the other hand, sitting is an ideal posture for observing piglets from a distance, as an alternative to closer contact on the ground if newborns are source of anxiety. The higher occurrence of sitting in primiparous sows confirms such a hypothesis. Standing is the more extreme postural change at farrowing. This posture is reached for maintenance activities and ground-directed activity ($r = 0.96$ and 0.86 between standing and ground-directed activity in the first 6 h in old-type and modern-type sows, respectively; $P < 0.0001$ in both cases). Also, standing allows the sow to establish motivated contacts with newborns. If this posture is not associated with the risk of stillbirth in the first hour, it becomes a substantial explanatory variable later in the farrowing process. Standing most likely favor pauses in the farrowing process and risk of hypoxia if it causes early rupture of the umbilical cord of unborn piglets. Consequently, the genetic trend toward less standing activity is positive for piglet welfare. In our study, the weight of old-type and modern-type sows did not differ at farrowing, but the modern-type sows produced heavier litters (Canario et al., 2007a). In addition, the higher frequency of postural changes in first-parity old-type sows reflects restlessness elicited by novelty (Cronin et al., 1993). The effect of parity on this trait was previously reported by Li and Gonyou in gestating sows (Li and Gonyou, 2007).

A genetic trend toward more time spent lying ventrally was observed in second-parity sows (+24 min/6 h; $P = 0.09$). Lying ventrally can reveal a discomfort as compared to lying laterally at farrowing. This posture facilitates the observation of the environment and newborns. It can therefore be important for sow-progeny bonding, as shown by the negative association between this behavior and stillbirth observed in old-type sows during the first hour. The time spent lying ventrally was higher in first- than second-parity old-type sows, thus revealing that, like sitting, it also reflects a reaction to novelty. The modern-type second parity sows may use this posture for bonding or as a compromise if farrowing is so painful or laborious that they are unable to reach a higher posture. Normally, pain should be reduced naturally via the analgesia mediated by opioids released at farrowing (Jarvis et al., 1999). Lying ventrally also means that the sows voluntarily hide their udder which complicates the first intake of colostrum. However, the observation of this posture at farrowing was not associated with a risk of death in newborn piglets.

Nesting is a sow activity that is extremely robust to domestication. It is performed even in absence of nesting materials through rooting, i.e., ground-directed activity (Jensen, 2002). When performed at farrowing, its occurrence declines rapidly with the release of oxytocin (Vestergaard and Hansen, 1984; Castrén et al., 1993), but it is sometimes claimed to be an inappropriate activity because sows are restless while giving birth (Jensen, 1993; Thodberg et al., 1999; Damm et al., 2000). Jensen (2001) suggested that rooting might continue in parturient sows that experience stress until sufficient feedback is obtained and the sow returns to homoeostasis. Also, such continuation of the activity can reflect the perception of an unsatisfactory nest environment and the willingness to improve it (Cronin et al., 1993). We found a genetic trend for decreased rooting activity in second-parity sows. However, this discrepancy between old-type and modern-type sows might merely find explanation in the greater farrowing difficulties of modern-type sows. In the present experiment, sows were supplied with a limited amount of straw. As such, rooting can be interpreted as a clue for good maternal behavior. In agreement, the risk of stillbirth increased with low rooting in modern-type sows. Genetic variability in rooting does exist: Meishan sows, often referred to as sows with a good mothering style (calm temperament), spend more time manipulating straw and rooting at farrowing than Large White sows when raised in individual pens (Rydhmer and Canario, 2014). In line with these observations, Rauw (2001) found that selected females spent less time in floor nosing activity when comparing a mice line selected for litter size with the control line.

GENETIC TRENDS IN THE MATERNAL BEHAVIOR OF PARTURIENT SOWS

The maternal behavior of sows is elicited at farrowing and is expressed through interactions with the newborns, leading to a stable relationship between the mother and her progeny. The results obtained here on maternal behavior differ according to parity. They will be discussed mainly in relation with the risk of early death. Sows often stand, turn and sniff the first piglets born (Jensen, 1986), and this behavior declines as more piglets are farrowed (Johnson and Marchant-Forde, 2009). The first-parity old-type sows tended to display a stronger reaction. But only the behavior "sniffing by the sow" was explicative of a higher risk of death in the first 2 days in modern-type piglets. The probability of aggressive reaction decreased by 18% of genetic trend in first parity sows. These elements indicate a discomfort and lesser adaptation of old-type sows to their farming conditions at farrowing. But again, the prostrate attitude of modern-type sows, although expected to be more excitable animals, may prevent fierce reactions to their newborns, especially since they are blocked in a crate.

After completion of farrowing, sows are inactive for more than 90% of the time during the first 48 h, which is an adaptive response that reduces piglet crushing (Johnson and Marchant-Forde, 2009). Early restlessness and responsiveness to piglets are correlated at the onset of farrowing ($r = 0.63$ and 0.51 in old-type and modern-type sows, respectively; $P < 0.05$). According to the literature, this behavior is correlated with the risk of crushing piglets (Wechsler and Hegglin, 1997; Damm et al., 2005). However, in the present study, postural activity within the first hours of lactation was positively associated with piglet survival in the modern-type sows only. In line with this, higher activity at farrowing may predict the sows' ability to react to piglets that become trapped when the sow lies down. Thodberg et al. (2002) found that gilts that were active during farrowing continued being so the next day. Further investigation of behavior in the first days of lactation is required to evaluate the relationships with crushing.

Grandinson et al. (2003) showed that the heritability of the sow's postural reaction to a screaming piglet on the farrowing day is low and tends to be negatively correlated with mortality at the genetic level.

McPhee et al. (2001) highlighted that sows selected for high lean-tissue growth rate are more responsive to piglets than sows selected for low lean-tissue growth rate. In our experiment, a positive genetic trend toward higher responsiveness to nose contact initiated by piglets was observed in second-parity sows (probability of +32%/6 h). This trend was explained by the decreased reactivity to piglets with parity in old-type sows, while modern-type sows maintained a high reaction at both first and second parities. Pedersen et al. (2003) suggested that sow responsiveness to newborn piglets is an indicator of good maternal care. At the genetic level, Grandinson et al. (2003) found a positive association between sow responsiveness to piglets and piglet survival in a modern-type population whereas in the present study, we found weak relations between the two traits. It is also possible that such maternal behavior helps to reduce anxiety. Indeed, Lonstein (2005) emphasized that in rats, dam-pup interactions contribute to reducing anxiety during early lactation. As a consequence, modern-type sows may be more anxious and express their anxiety behaviorally. This idea is supported by observations by Grandin and Dessing (2014) who report a more excitable temperament in pigs selected for lean growth, resulting in animals more reactive to sudden novelty. Selection for lean growth may have increased sensitivity to stress in the French Large White population, due to the negative association between lean growth and cortisol production (Mormède et al., 2011). Significant modifications of the stress-responsive systems were observed in the 2nd generation of the experiment: modern-type pigs had lower corticosteroid levels than old-type pigs (Foury et al., 2009).

An association between a sow's attention toward her newborn piglets and maternal ability was clearly established. A genetic trend toward lower attention was found in first-parity sows (−24 times and −40 min/6 h). Attention was positively associated with survival at birth in both lines and survival during the first 2 days after birth in the old-type line. This maternal behavior was not associated with a certain posture ($r < 0.32$ with the time spent in different postures in the two lines; results not shown). A more direct and easy measurement of maternal willingness is the reaction to handling of the newborns by humans. In the present study, humans were often present around the farrowing crate in the days preceding farrowing and manipulated newborns at farrowing. Although no genetic trend was found, vocalizations were related to a lower piglet death rate in old-type sows. Conversely, the intensity of vocalizations was not related to a risk of mortality in modern-type sows. Few investigations of postural reactions to the handling of newborn piglets by humans have been reported in genetic studies. Grandinson et al. (2003) found no genetic variation in the first days after farrowing, probably due to the way the test was performed.

GENETIC TRENDS IN THE BEHAVIOR OF NEWBORN PIGLETS

Piglets play a major role in their own survival after birth, and it depends largely upon the quality of their interactions with the dam. Early survival depends on both the ability of the sow to produce colostrum and her nursing behavior, as well as on the ability of each piglet to acquire a sufficient quantity of colostrum (Le Dividich et al., 2005). To their advantage, piglets are behaviorally precocious, with coordinated locomotion from birth, but they are not assisted by the sow in their teat-seeking activity (Nowak et al., 2000). Modern-type newborn piglets suffered from the greater farrowing difficulties of their dam, even more so at second than at first parity. In addition to an increased rate of stillbirth, they displayed greater respiratory difficulties due to hypoxia than old-type piglets. The modern-type piglets born later in the farrowing process were at a higher risk of stillbirth than their old-type counterparts (Canario et al., 2007a). Piglets having suffered from hypoxia at birth do not necessarily die during the birth process, but show lower vitality after birth and then lye still until they recover. If they survive, they often remain too weak to be able to suckle efficiently (Herpin et al., 1996). Vitality is beneficial to survival: sows with a higher genetic potential for piglet survival produce piglets that take shorter time to reach the udder and suckle (Knol et al., 2002). In the present study, modern-type newborn piglets were less mobile when placed in the weighing box and then, once back at the rear end of their farrowing dam, tended to be slower to access the udder and suckle for the first time. The proportion of piglets with low vitality *per se* (i.e., without breathing difficulties) was high. We demonstrated previously that modern-type piglets are less physiologically mature at birth than old-type piglets (Canario et al., 2007b). Significant differences in the body composition and physiological maturity of newborn piglets were also found between lean and fat genotypes (Herpin et al., 1993), suggesting that selection for leanness has affected piglet maturity at birth. This negative genetic trend has direct implications on the capacity of survival during early lactation. A similar conclusion was drawn by Leenhouwers et al. (2002) who found that piglets with a high genetic merit for survival were similar to piglets from genetically obese lines, with increased cortisol levels that allowed them to endure the stress of farrowing and face the difficulties of neonatal life.

As growth rate on day 1 was similar in old-type and modern-type litters (Canario, 2006), it may be assumed that the production of colostrum was similar in old-type and modern-type sows and as a consequence, that the colostrum intake of their piglets did not differ. However, modern-type sows spent longer time in a lying position which facilitated access to the udder for colostrum uptake at farrowing (i.e., with udder exposed). Several postural clues as to the old-type sows' reluctance to nurse their progeny were highlighted, especially at first parity. There was a trend for less time spent lying laterally with udder exposed during the first 6 h of lactation in first-parity old-type sows. In general, old-type sows also spent more time nest-building than their modern-type counterparts, which limited udder contact. Hence, the more favorable (inactive) behavior of modern-type sows would in some sense be beneficial to their low-vitality piglets. The higher losses observed in modern-type litters could also be due to the fact that weak modern-type piglets must access the udder within a shorter time in order to survive. Piglets must regulate their body temperature, an energy demanding process, during the time interval between birth and first colostrum intake, and this interval was increased by human manipulation. The lower maturity of modern-type piglets (Canario et al., 2007b) could be due partly to the slightly shorter gestation of modern-type sows (−0.7 ± 0.3

day; Canario et al., 2006a), which may result in a higher proportion of preterm farrowings that reduce the production of colostrum (by 40% when farrowing takes place on day 110–111 of gestation; Milon et al., 1983) and increase losses during early lactation (Casellas et al., 2004). There is growing evidence that it is important to consider the two sources of genetic variation, i.e., the dam and the piglet, to improve piglet traits (Leenhouwers et al., 2001).

CONCLUSION

This study provides an insight into the intricate interactions between maternal and newborn behavior as determinants of piglet survival in the context of genetic trends associated with the selection for lean growth rate and prolificacy at birth. The experiment was designed to assess the capacity of sow investment in piglet production. Genetic differences were obtained for the sow's activity at farrowing and suggested a higher pressure on modern-type sows. The influence of parity was more distinct in old-type sows. Genetic trends toward higher reactivity to newborn piglets were observed and related to the substantial changes on production traits. Sow behavior at farrowing was found to contribute substantially to piglet survival. Some interesting associations to consider in breeding programs were outlined, like the relationship between lying laterally during the first hours of farrowing, a higher stillbirth rate and poorer welfare in modern-type sows. The importance of sow attention toward piglets was emphasized. Piglet survival depends on the sow's capacity to farrow and the intrinsic viability of piglets. It would be interesting to analyze mother-progeny interactions during the first week of lactation to address welfare issues related to poor vitality in modern-type piglets.

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Natural and artificial selection and suffering and well-being

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INTRODUCTION

In this essay I assume the existence of subjective states of suffering and well-being (welfare is often used as a synonym for well-being) in animals (Van Rooijen, 1981). For my opinion about the relation between suffering and well-being and the study of behavior, see Van Rooijen (1997). This article will compare suffering and well-being due to natural selection and suffering and well-being due to artificial selection. As far as I know this comparison is hardly made in literature.

Lorz (1973, cited in Van Putten, 1981) has defined well-being of an animal as "Living in harmony with the environment and itself, both physically and psychologically." In a healthy animal all bodily processes are tuned in with each other. We may say that the animal is in harmony with itself (its physiology is in harmony). However, healthy animals may suffer too. For instance, because their husbandry conditions are (or have been) too remote from the natural environment to which their wild counterpart has been adapted, as may be indicated by stereotypic behavior (Van Rooijen, 1984).

During its phylogeny a species is adapted to its own natural environment. For instance, a polar bear is adapted to a polar environment. When the situation is not too extreme we may take the well-being of a polar bear in its natural situation for granted. However, a tropical bird will suffer under polar conditions. We may say that a polar bear is in harmony with a polar environment and a tropical bird with a tropical environment. In a similar way a camel is adapted to (in harmony with) an environment with little water while a whale is adapted to (in harmony with) an environment with plenty of water. When an animal is not in harmony with itself and/or with its environment we may assume that it suffers. When an animal is in harmony within itself and with its environment we may assume that it experiences well-being.

We may distinguish predators and prey animals. Companion animals (cats, dogs, guinea pigs, rabbits, birds, fish, reptiles, etc.) are sometimes predators and sometimes prey animals. Farm animals are almost exclusively prey animals (horses, cows, goat, sheep, swine, hens, turkeys, rabbits, an exception are fur animals as minks and foxes). Laboratory animals may also be one of both types: dogs and cats are predators, rabbits, mice and rats are prey animals.

SUFFERING AND NATURAL SELECTION

Wild animals may have super normal preferences, for instance, for a larger than normal egg size (Tinbergen, 1948, cited Hinde, 1966) or particular characteristics in their sexual partner. Such preferences are not fulfilled in nature because there are also other selection pressures. For instance, it would not be possible to breed too large eggs properly. Perhaps peacock females prefer males with even longer tails than in nature but such males become too easily predated. Perhaps super normal preferences may decrease the well-being, which shows that the harmony in nature is not always perfect.

Wild animals in nature may suffer from a lack of resources as territories or nesting sites. However, such a lack of resources does not result in stereotypic behavior. Perhaps the animals are in some degree adapted to such situations. In wild animals in nature variation will emerge. The genetic basis of this variation is the point of application for natural selection. Less adapted variants may suffer, but even individuals with a higher fitness may have a decreased well-being (for instance, because they have to work harder to provide food for their young than individuals with a lower fitness).

In equilibrium situations parents are on average only replaced in the next generation. Most offspring die before they reproduce. Natural selection may work by accidents and/or starvation and/or disease. This may cause suffering before the animal dies. In equilibrium situations a continuous pressure by predators on prey animals is present. As a result, in nature, prey animals may suffer more from acute stress during predation than from chronic stress. I do not know whether predators are often killed by other predators. If not this may result in chronic suffering due to hunger and disease. However, they do not seem to perform stereotypic behavior. Further, wild animals have to cope with disturbances in nature caused by man. This may cause suffering too.

WELL-BEING AND NATURAL SELECTION

Dawkins (1976) mentions Young (1975), who has pointed out that genes have to perform a task analogous to prediction. Dawkins writes that polar bear genes predict that the future of the unborn polar bear is going to be a cold one: "They do not think of it as a prophecy, they do not think at all: they just build a thick coat of hair, because that is what they have always done before in previous bodies, and that is why they still exist in the gene pool. They also predict that the ground is going to be snowy, and their prediction takes the form of making the coat of hair white and therefore camouflaged." (White hairs are hollow and, therefore, also a good isolation.) Animals also have a prediction about useful behavior patterns. For instance, a dog often circles around before it lies down. The function of this behavior is to create a lying place. The dog still "predicts" that it will live in an environment with vegetation. In nature animals are, thus, in some degree in harmony with themselves and their environment (as indicated by the absence of stereotypic behavior). Most of the time we may therefore take their well-being for granted. Natural selection leads to a further fine tuning of the traits of a wild species to its natural environment. That means that the wild animals become more adapted to their natural environment and this increases their well-being.

SUFFERING AND ARTIFICIAL SELECTION

To understand the situation of domestic animals under artificial conditions it is helpful to realize that these animals still predict that they will live in their natural environment. [This explains why many domestic species (horses, swine, dogs, cats, hens, etc.) easily become feral.] Not only during the ontogeny but also during adult life the environment is different from the one the animals predict; both may result in chronic stress. The ontogeny may also not be in harmony with the adult environment. This brings the animal even more in disharmony (Van Rooijen, 1982). Stereotypic behavior may occur among cats and dogs under artificial conditions (e.g., animals in shelters, animals left alone at home, animals under laboratory conditions) and among minks and foxes under intensive conditions. In farm animals under intensive conditions chronic stress is common. Perhaps, chronic stress is similar to the chronic stress experienced by psychiatric patients (Van Rooijen, 1983). Acute stress may occur in cats and dogs (e.g., visits to the veterinarian). Acute stress may also occur in farm animals. Especially during the catching of animals, but also during weaning, regrouping, castration, injections, sexing, wing clipping, beak trimming, teeth clipping, nail clipping, tail clipping, comb clipping, transportation, slaughtering, etc. Domestic animals may also be in disharmony because of their genotype:

Hybrids. Domestic species are sometimes the result of hybridization between different species or subspecies adapted to different niches. Such hybrids are sometimes not in harmony within their own physiology (for instance, neurology). Well-known examples are the hybrids between love bird species made by Dilger (1962). The parental species have different methods to transport nesting material to the nest. The hybrids are frustrated because they are hardly able to combine these methods successfully. This may decrease their well-being. More fundamental seems the frustration due to contradictory tendencies in hybrids between solitary and social species (e.g., hybrids of tigers and lions).

Inbreeding. When an inbreeding population is founded by a few individuals the number of genes present in such a population is only limited (the founder effect). This is exaggerated by genetic drift, especially when the population goes through bottlenecks. This results in a greater risk that individuals are homozygote for recessive genes that cause genetic diseases. This may decrease their well-being.

Selection for deviant traits. Many breeds are based on deviant individuals (sometimes animals with a mutation). This deviant trait is often exaggerated by selection. A deviant trait may hamper the normal functioning of an individual. The physiology of such individuals may less be in harmony. In such breeds selection toward the wild genotype may improve well-being. Hybridization of lines with the wild genotype may, therefore, often help to increase the well-being of the offspring. However, such hybridization does not help in all cases. For instance, severe feather pecking is an abnormal behavior that causes much suffering among flock mates. Indeed, wild bankiva fowl do not perform this behavior in nature but they do under suboptimal artificial conditions. In such cases hybridization with the wild genotype is not helpful to decrease suffering under suboptimal artificial conditions.

Selection for a few traits. Even if a trait is not that deviant that it hampers well-being, selection on a few traits may have the result that the physiology is no longer in harmony. This happens for instance, when hens are selected for larger eggs but are not selected for a larger cloaca width (Van Rooijen, 1983). Also animals selected for a higher weight are not in harmony when they are not also selected for stronger legs.

Selection for another generation. Broilers are selected for a large appetite. However, broiler breeders are restrictedly fed. This may imply that these animals suffer from chronic hunger.

Absence of selection pressures. When the maintenance of traits costs energy it is likely that such traits will become rudimentary when selection pressures on the trait are no longer present. This explains why animals on islands without predators may become tame. Birds and insects on such islands may, for this reason, lose their ability for flying. It also explains why some fish species living in caves where no daylight ever enters have become blind. Internal parasites like tape worms may in many respects rely on the constant conditions provided by their host. Therefore, many of the capacities which were present in the ancestors of tape worms became rudimentary during the phylogeny. Man provides farm animals also with water, food, a constant temperature, etc. This may make farm animals also lose capacities. Therefore, we may assume that animals completely adapted to the conditions of intensive husbandry become similar to internal parasites like tape worms (Van Rooijen, 1983).

WELL-BEING AND ARTIFICIAL SELECTION

Under domestic conditions, compared with natural conditions, well-being may be improved because of hygiene, veterinary care and protection against predators. Well-being may also be improved by unconscious and conscious selection. Animals which are more tolerant toward artificial conditions are less stressed under such conditions and may, therefore, have access to food and a higher fitness. This may explain why some wild species suddenly successfully invade cities. Such species become more or less domesticated. Also animals that are more tolerant toward sexual partners may have a higher fitness.

This explains why in zoos reproduction of particular species (e.g., tigers) suddenly becomes successful. Such species also become more or less domesticated. This increases their well-being.

CONCLUDING REMARKS

(1) For predators and prey animals we may conclude that the difference in acute stress in nature and under domestic conditions is not obvious.
(2) Stereotypic behavior may be an indication of chronic stress. Such behavior is more common under intensive than under traditional conditions. In nature stereotypic behavior indicating chronic stress seems absent.
(3) Animals under intensive and under traditional conditions may suffer because their physiology is not in harmony.
(4) Natural selection leads to a further fine tuning of the traits of a wild species to its natural environment, therefore, natural selection will increase well-being in the long run.
(5) Artificial selection may increase suffering but may also increase well-being. Artificial selection seems to be an important tool to decrease suffering and increase well-being in domestic animals under artificial conditions. I am of opinion that we need selection that results in animals that are more in harmony with themselves and with their environment.

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REVIEW
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Genotype by environment interaction and breeding for robustness in livestock

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The increasing size of the human population is projected to result in an increase in meat consumption. However, at the same time, the dominant position of meat as the center of meals is on the decline. Modern objections to the consumption of meat include public concerns with animal welfare in livestock production systems. Animal breeding practices have become part of the debate since it became recognized that animals in a population that have been selected for high production efficiency are more at risk for behavioral, physiological and immunological problems. As a solution, animal breeding practices need to include selection for robustness traits, which can be implemented through the use of reaction norms analysis, or though the direct inclusion of robustness traits in the breeding objective and in the selection index. This review gives an overview of genotype × environment interactions (the influence of the environment, reaction norms, phenotypic plasticity, canalization, and genetic homeostasis), reaction norms analysis in livestock production, options for selection for increased levels of production and against environmental sensitivity, and direct inclusion of robustness traits in the selection index. Ethical considerations of breeding for improved animal welfare are discussed. The discussion on animal breeding practices has been initiated and is very alive today. This positive trend is part of the sustainable food production movement that aims at feeding 9.15 billion people not just in the near future but also beyond.

Keywords: livestock production, animal breeding, genetic selection, robustness, reaction norms, phenotypic plasticity, canalization

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ANIMAL BREEDING AND ANIMAL WELFARE

Although an increase in overall meat consumption is expected in the coming decades resulting from the ever growing human population, the dominant position of meat as the center of meals is on the decline. This is motivated by religious, health, moral, and environmental considerations. Rauw (2015) reviewed the history of ethics of animal use and consumption from Pythagoras to Bentham (c 500 BC to the end of the 18th century), which describes the origins of health and moral objections to the consumption of meat. Of a much more modern origin are environmental considerations, and public concerns with animal welfare in livestock production systems; the latter particularly came about in response to the publication of Harrison's (1964) book "Animal Machines: the New Factory Farming Industry". Rapid turnover, high-density stocking, and a high degree of mechanization resulted in a public awareness of the results of intensification of livestock production practices and "factory farming" in the 60s and resulted in an increasing number of philosophical writings on animal rights from the 70s on (Singer, 2005; Stamp Dawkins, 2013). Factory farming is characterized by overcrowding, restricted movement, unnatural diets and unanesthetized surgical procedures resulting in physical pain and necessarily in reduced animal welfare (Frank, 1979). Frank (1979) suggested that intensive farming differs from factory farming in that it involves increasing productivity through better management and breeding techniques but without necessarily involving crowding and thus significantly altering the pattern of life the animal leads. However, this situation no longer applies since it became recognized that animals in a population that have been selected for high production efficiency are more at risk for behavioral, physiological and immunological problems (Rauw et al., 1998). Examples are most pronounced in populations that are selected for narrow yield goals at high intensity of selection, such as broiler chickens selected for increased body weight at a certain age (Rauw et al., 1998; Rauw, 2009). As Oltenacu and Algers (2005) write regarding dairy cattle: "[Improved production efficiency] should optimize the use of resources, increase farm profit, and reduce cost for consumers. In many European countries, yield per cow has more than doubled in the last 40 years. The dramatic increase in yield per cow is due to rapid progress in genetics, nutrition and management," however, due to the resulting fertility problems, increasing incidence of health problems, and declining longevity in modern dairy cows, "genetic selection for increased milk yield increasingly is viewed as increasing profit at the expense of reducing animal welfare."

As a result, animal breeding practices have become part of the debate that deals with issues of animal welfare and animal production ethics and at a wider scope with sustainable agriculture and livestock production. Frank's (1979) definition of intensive farming practices which do not negatively affect the pattern of life of the animals involved is now newly captured under the banner of "sustainable intensification" of livestock production, i.e., improving productive output while maintaining animal health and welfare (Gamborg and Sandøe, 2005; Charles et al., 2014). The Farm Animal Welfare Council has emphasized welfare concerns in relation to animal breeding strategies since 1992 in their reports (FAWC, 2004, 2012; MacArthur Clark et al., 2006). For example, the 1992 report on the welfare of broiler chickens reads: "Genetic selection has the potential for positive as well as negative effects on welfare. However, the selection of stock for liveweight gain and food conversion efficiency in preference to, and to the detriment of, factors necessary for the welfare of the birds should be discouraged" (FAWC, 2004). The 1998 Council Directive 98/58/EC concerning the protection of animals kept for farming purposes reads: "Natural or artificial breeding or breeding procedures which cause or are likely to cause suffering or injury to any of the animals concerned must not be practiced" (EUR-Lex, 2015). In 2000, the Sustainable European Farm Animal Breeding and Reproduction project was initiated by the Farm Animal Industrial Platform (currently the European Forum of Farm Animal Breeders); one of the aims was an agreement by breeding organizations to develop Codes of Practice (MacArthur Clark et al., 2006; Neeteson-van Nieuwenhoven et al., 2006). The main objectives of the resulting Code-EFABAR launched in 2006, a voluntary "Code of Good Practice," are to be the standard instrument for defining and maintaining good practices for farm animal breeding, and to create transparency for society (Code-EFABAR, 2006). As MacArthur Clark et al. (2006) conclude, failure to address the issues arising from bad breeding practices presents a significant risk to Governments, to the livestock industry, and to animal welfare.

HOW *SHOULD* WE BREED?

Animal production is basically an input-output system to which the first law of thermodynamics, or the law of conservation of energy, applies, in the same way as it does for any other energetic system: energy cannot be created nor destroyed, but can only be changed from one form to another. Energy in output (production, losses) requires an equal amount of energy input (eventually this comes down to food intake). In other words: an animal from a population genetically selected for increased production will only be able to realize this potential in an environment in which resources are adequately supplied (Beilharz et al., 1993; Rauw, 2009). However, while this holds even intuitively, in practice, livestock animals are often genetically selected for *increased* levels of production (output) at the same time that they are selected for *decreased* levels of energetic input (improved feed efficiency, decreased levels of fatness; Rauw, 2012). A clear example of selection practices that have resulted in a mismatch between input and output is the voluntary feed intake capacity of young sows which has been reduced as a consequence of selection for high lean growth, resulting in animals that are constrained by limited body reserves and/or limited feed intake capacity at the time of lactation when they have to support a genetically increased litter size and growth rate. As Knap (2005) writes regarding pig production: "Increasing genetic potential requires advances in animal nutrition and animal management to support its expression, but these advances have often been poorly addressed or overlooked." This results in the inability to maintain a successful balance of biological needs and consequently, inadvertently, in animals that are less robust, showing undesirable side effects of genetically improved levels of production (Siegel and Dunnington, 1997; Rauw et al., 1998; Knap, 2005).

In addition, livestock animals are required to perform in a wide variety of environmental conditions, regarding climate, housing facilities, social environment, disease pressure, and differences in feed quality and composition (Knap and Wang, 2006; Star et al., 2008; Mormède et al., 2011). The farm animal of the future is thus described as robust, adapted, and healthy (Mormède et al., 2011), i.e., having "the ability to combine a high production potential (growing or reproductive) with resilience to stressors, allowing for unproblematic expression of a high production potential in a wide variety of environmental conditions" (Knap, 2005). After Knap (2005), the literature on selection for robustness traits has increased considerably, becoming a rapidly developing key area in farm animal breeding (Knap, 2009). Knap (2009) indicates that there are two options for breeding for animal robustness, which can be implemented simultaneously in an evaluation system for performance-relevant robustness: through the use of reaction norms analysis by estimating breeding values for the environmental sensitivity of the genetic potential for production performance (indirect approach), or through the inclusion of directly measurable robustness traits in the breeding objective and in the selection index (direct approach).

This review presents a historic overview of gene by environment interactions (including the concepts of reaction norms, phenotypic plasticity, canalization, and genetic homeostasis), the applicability of reaction norms analysis in livestock production, and the feasibility of selecting for the different reaction norm parameters (the level vs the slope). The review ends with a discussion of the feasibility of directly including robustness traits in the breeding objective and selection index, a discussion of the ethical consideration of selection for robustness, and with a short synthesis of all the material discussed in this paper.

GENOTYPE × ENVIRONMENT INTERACTION: A HISTORIC OVERVIEW

The Influence of the Environment

The influence of the environment on the phenotype and on evolution was of course most famously recognized by Jean Baptiste de Lamarck in his book "Philosophie Zoologique" in his chapter (translated) "Of the influence of the environment on the activities and habits of animals, and the influence of the activities and habits of these living bodies in modifying their organisation and structure" published in 1809. Indeed his statement that "the environment affects the shape and organisation of animals, that is to say that when the environment becomes very different, it produces in course of time corresponding modifications in the shape and organisation of animals (. . .) [because] great alterations in the environment of animals lead to great alterations in their needs" has become a "truth, which, once recognized, cannot be disputed" (Lamarck, 1914). He thus recognized the continuous dynamic geological, climate, and geographic changes in the environment as opposed to a static world, and in order to adjust to these changes, organisms had to evolve (Mayr, 1972). According to Lamarck, because "nature is forced to submit her works to the influence of their environment, (. . .) this environment everywhere produces variations in them" (Lamarck in Shaner, 1927). Resulting from this, "Nature has produced all the species of animals in succession, beginning with the most imperfect or simplest, and ending her work with the most perfect, so as to create a gradually increasing complexity in their organisation, (. . .) [forming] a branching series, irregularly graded and free from discontinuity, or at least once free from it. . ." (Lamarck in Shaner, 1927). As Shaner (1927) notes, it was Lamarck who first thought of the animal kingdom as a great family tree, initiating the modern theory of evolution. However, to his disfavor, Lamarck is mostly known for his concept of inheritance of acquired characteristics formulated in his second law: "All the acquisitions or losses wrought by nature on individuals, through the influence of the environment in which their race has long been placed (. . .) are preserved by reproduction to the new individuals which arise" (Lamarck, 1914). This was similar to that proposed by Erasmus Darwin in his work "Zoonomia" published earlier in 1794: "[F]rom the first rudiment, or primordium, to the termination of their lives, all animals undergo perpetual transformations; which are in part produced by their own exertions in consequence of their desires and aversions, of their pleasures and pains, or of irritations, or of associations; and many of these acquired forms, or propensities, are transmitted to their posterity" (Darwin in Harrison, 1971). Darwin and Lamarck had failed to distinguish between the influence of the environment on individual animals (resulting in non-heritable modifications) vs. the influence of the environment on animal populations (resulting in evolution).

It was Erasmus' grandchild Charles who successfully challenged the inheritance of acquired characters in individuals when he recognized the influence of the environment on evolution of animal populations, resulting from natural selection in the struggle for existence. But as to how variations were produced on which natural selection could act, he wrote: "I have hitherto sometimes spoken as if the variations—so common and multiform in organic beings under domestication, and in a lesser degree in those in a state of nature—had been due to chance. This, of course, is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the cause of each particular variation" (Darwin, 1869). In an aim at answering this question of the origin of variation, he developed the hypothesis of pangenesis based on modifications and amplifications of earlier existing theories. Each unit of living tissue continually produced minute particles or "gemmules" at each stage of its development which would multiply and develop themselves into new cells and which were transmitted from parents to offspring via the reproductive organs (Geisen, 1969). This idea is similar to that proposed far back in antiquity by Hippocrates: "For the seed comes from all parts of the body, healthy seed from healthy parts, diseased seed from diseased parts" (Hippocrates in: Zirkle, 1946). However, not different from Lamarck, it was still a naïve conception of transmission of personal qualities as the heritable elements to the progeny.

Reaction Norms and Phenotypic Plasticity

This approach to heredity was very different from the first controversial but accurate model by Mendel, first published in 1865 but not seriously considered until 1900, introducing "elements" of inheritance. These elements were later coined "genes" by Johannsen in 1909 and recognized as a segment of a chromosome after the discovery of the structure of DNA by Watson and Crick in 1953 (Portin, 2002). The discovery of Mendelian inheritance resulted in a temporary popularity of discontinuous "saltations" by mutations as the primary mechanism of evolutionary change as opposed to Darwin's concept of evolution through natural selection acting on small continuous variations (Sarkar, 1999). Woltereck (1909), in order to prove Darwin right, studied phenotypic variation of continuous traits in morphologically distinct pure-line strains of Daphnia species subjected to variations in environmental factors. Plotting the response curves of the phenotypes (relative head height) of the different strains to the environmental variation (nutrient level) showed that the resulting *reaktionsnorm* (reaction norm, or standard pattern of the response curve) was different in the different strains (Woltereck, 1909; Sarkar, 1999). In his understanding, the genotype of an animal was synonymous to the shape of this curve, i.e., the reaction norm, and thus constituted the unit that was inherited, resulting in hereditary change. Johannsen, who had proposed the term "genotype" as the "sum total of all the "genes" in a gamete or in a zygote" agreed that "[t]he very appropriate German term "Reaktionsnorm" used by Woltereck is, as may be seen, nearly synonymous with "genotype," in so far as the "Reaktionsnorm" is the sum total of the potentialities of the zygotes in question. (. . .) [It] emphasizes the diversity and still the unity in the behaviour of the individual organism; certainly, the particular organism is a whole, and its multiple varying reactions are determined by its "genotype" interfering with the totality of all incident factors, may it be external or internal. Thence the notion "Reaktionsnorm" is fully compatible with the genotype-conception" (Johannsen, 1911). However, he did contest that Woltereck's observations disproved evolutionary saltations since he held that continuous transitions exhibited by phenotypes, as expressed in the reaction norm, result from discontinuous saltations in the genotype, i.e., through mutations.

Three years later, Nilsson-Ehle, discussed the "acclimatization or adjustment" to the climate by plants, i.e., "the plant's ability to change their characteristics in one way or another such that it thrives in a new environment" (Nilsson-Ehle, 1914, quote translated from Swedish). Referring to a particular example of a 10-year study by Bonnier (1894), who described the adaptation of individual plants of the same genotype (cuttings of the same seedlings) to the climate at different altitudes in the Alpes and the Pyrenees with respect to their size, color, and shape, he concluded (translated from Swedish): "Summarizing all experience in this area, then you can also say that the climate's influence can hardly be explained in a purely causal-mechanical way. One has to, as (. . .) even Johanssen explicitly holds, count with the organisms' ability of self-adjustment or self-regulation, the appropriate reaction norm. This plasticity, depending on various external conditions, is in fact neither easier nor more difficult to interpret then the organism's appropriate characteristics at all." Nilsson-Ehle is by many recognized as being the first scientist to use the word "plasticity" ("plasticitet," Nilsson-Ehle, 1914, p. 549) to describe the effect of the environment on the phenotype of an organism (Fuller, 2003), however, it was Bonnier himself who proposed it ("plasticité") some 10 years earlier based on his own work that Nilsson-Ehle had referred to (translated from French): "The influence of the climate of the Alpine region is not only visible in the modification of the diverse exterior characteristics; it also has a profound effects on the development and the nature of the different tissues of the organism, each affected to a more or lesser extent. (. . .) Among the plants that support the climate change, from the plain to high altitudes or vice versa, some show almost complete modifications the first year, whereas others only show the beginning of transformation after 10 years. Therefore, all the degrees of plasticity are possible, depending on the species considered" (Bonnier, 1895).

By 1918, Fisher had introduced a method that allowed for the separation of different causes of variability: "It is therefore desirable in analyzing the causes of variability to deal with the square of the standard deviation as the measure of variability. We shall term this quantity the Variance of the normal population to which it refers, and we may now ascribe to the constituent causes fractions or percentages of the total variance which they together produce" (Fisher, 1918). At the time he considered that the variation due to environment was nihil (probably less than five percent) and that most of the variation instead was due to ancestry, Mendelian segregation and dominance. Although later he did reconsider the environment as a possible source of variation and with it the relationship between environmental and heritable variation when he first presented the "analysis of variance" table (Fisher and Mackenzie, 1923; Tabery, 2008), the effect of the environment really created a potential complication for assessing the relative importance of heredity and so it was to be considered and then either dismissed or eliminated or at least minimized by experimental design (Tabery, 2008; Strandberg, 2009). Not for Lancelot Hogben, however, who further developed his thoughts on the relationship between differences of genetic constitution and the external environment in the process of development. He thus recognized three different sources of variability: genetic, environmental, and that which "arises from the combination of a particular hereditary constitution with a particular kind of environment," or Genotype × Environment interaction (Hogben, 1932; Tabery, 2008).

Canalization

Meanwhile, in the Soviet Union, the concept of the reaction norm was further developed in the 1920s, such as resulting from the work of Dobzhansky on the "abnormal abdomen" mutation of Drosophila *funebris* (Sarkar, 1999). Much in line with Johannsen, he held that it was the entire reaction norm that was inherited and that mutation resulted in a change in this norm of reaction (Nicoglou, 2014). Subsequently, Schmalhausen (1949; originally published in Russian in 1938) clearly recognized the influence of the environment on the evolution of the reaction norms: different environments will expose different portions of the reaction norm that will be subjected to natural selection, whereas the portions not exposed, or no longer exposed when the environment changes, will be subjected to drift. Changes in the environment eventually result in adaptive modifications that will again "stabilize" into new adaptive phenotypic response curves. The reactivity of the reaction norms, stabilized by means of processes of autoregulation through underlying reactions, would thus be buffered or "canalized" into a more specific optimal norm (Schmalhausen, 1949; Pigliucci, 2001). This idea is similar to that proposed (independently) by Waddington a few years later (1942): "The main thesis is that developmental reactions, *as they occur in organisms submitted to natural selection*, are in general canalized. That is to say, they are adjusted as to bring about one definite end-result regardless of minor variations in conditions during the course of the reaction. (. . .). The canalization, or perhaps it would be better to call it the buffering, of the genotype is evidenced most clearly by constancy of the wild type." The constancy of the wild type was recognized earlier by Darwin (1869) when he wrote observing a "much greater variability, as well as the greater frequency of monstrosities, under domestication or cultivation, than under nature."

Since canalization thus reduces the phenotypic *expression* of variation, it can actually result in the undetected accumulation of selectively neutral underlying genetic variation and mutation accumulation, a concept that is extensively discussed by Schlichting (2008). In other words, the genotype "absorbs" a certain amount of its own variation such as that resulting from new mutations ("genetic canalization") or that resulting from environmental perturbations ("environmental canalization"; Waddington, 1942; Pigliucci, 2001).

Genetic Homeostasis

Lerner (1954) coined this ability of a Mendelian population of organisms to equilibrate its genetic composition and to resist sudden changes "genetic homeostasis", as grounded in the concept of physiological homeostasis proposed earlier by Cannon (1932) (Hall, 2005). Thus, canalization of a character can be equated with homeostasis of that character. In effect, "[b]y insensible gradations this *functional homeostasis* merges with physiological reactions which result in *developmental homeostasis.* (. . .) A given repertory of functional and developmental homeostatic mechanisms is, of course, determined by the norm of reaction of each genotype" (Dobzhansky and Levene, 1955). And, similar to physiological homeostasis, straying away from the limited variety of possible reaction norms established in evolution under the control of natural selection would result in death (Dobzhansky and Levene, 1955). Although Lerner's genetic homeostasis was described for Mendelian populations and not for individuals, he argued that it was brought about by the same mechanisms as those which underlie the other forms of homeostasis (Dobzhansky and Levene, 1955). It was implied that Darwinian fitness, resulting from homeostatic adjustment through self-regulation to environmental or genetic disturbances, was manifested by true heterosis or hybrid vigor (Woolf and Markow, 2003). And hybrid vigor, in turn, was considered to be a consequence of heterozygosity, as first proposed independently by Shull and East in 1908, and after by Dobzhansky in 1950. Dobzhansky proposed that it was particularly *coadapted* heterozygosity that was a component of Darwinian fitness, referring to polygene complexes which have become mutually adapted by natural selection in the course of evolution; however, some years later he concluded that heterozygosity may produce higher fitness even without prior coadaptation (Woolf and Markow, 2003). Lerner (1954) also emphasized the heterozygote buffering advantage associated with coadapted polygenic systems resulting from evolutionary history, especially in natural populations, although he also indicated that heterozygosity at a single locus (or coadapted homozygosity in self-fertilizing plants) and epistasis may play a role in determining adaptation (Woolf and Markow, 2003). In addition, he held that no population can afford to maintain too many heterotic loci or blocks simultaneously (Lerner, 1961).

Phenotypic Plasticity vs Canalization

According to Lerner (1954), the superior buffering ability of heterozygotes at complex multigenic systems would serve two important functions: it would allow for individuals with combinations of phenotypic properties that are expressed near the optimum (canalization), while at the same time it would result in genetic variation, although "hidden" in the phenotypes, and potential plasticity (Woolf and Markow, 2003; Hall, 2005). As Dobzhansky and Levene (1955) note, homeostasis does not prevent the development from switching from one of the historically established paths to other established paths, as long as they remain within the canalized norm. The ability of the organism to follow any of these paths (or to change paths) is, in fact, highly adaptive. This emphasizes the complementary relationship between the processes of canalization and plasticity. Indeed, as given by Waddington (1953) and Dobzhansky and Levene (1955), homeostasis does not imply a stationary state but a dynamic (plastic) stability (canalization); "homeostasis is brought about by changes in some processes which result in stability of other processes." And following Cannon (1932): "Constancy is in itself evidence that agencies are acting, or ready to act, to maintain this constancy." Schmalhausen (1949) considered that those animals that are best in responding adaptively to changes in the environment (i.e., those with highest plasticity) while simultaneously best withstood environmental perturbations (i.e., those with highest canalization) would be favored by natural selection (Willmore et al., 2007). Also Bradshaw (1965), in a key contribution to the field, emphasized the adaptive value and evolutionary significance of plasticity, in particular in plants since they are not able, as animals are, to evade adverse conditions: plasticity of certain characters may lead to homeostasis (canalization) of others (Bradshaw, 1965). An example of a plastic mechanism in animals that results in overall robustness (phenotypic stability) is protein turnover, which is responsive to various physiological and developmental scenarios, and provides the flux that is necessary for metabolic regulation and adaptation. Because it is involved in maintenance of homeothermy, reproduction, development, the repair of damaged tissue, maintenance of the immune system, combating infection, and the nutritional/physiological status, a high turnover rate may improve robustness by improving the ability of an animal to adapt to new dietary and physiological conditions (Baldwin et al., 1980; Rauw, 2012). Also plasticity in the functioning of the hypothalamic–pituitary–adrenal axis, which is the most important stress-responsive neuroendocrine system and shows large differences across species, breeds and individuals, has been found to improve robustness through its effects on metabolism, the immune system, inflammatory processes and brain function (Mormède et al., 2011).

Bradshaw (1965) proposed that plasticity of a character can be (a) specific to that character, (b) specific in relation to particular environmental influences, (c) specific in direction, (d) under genetic control, and (e) radically altered by genetic selection. According to Via (1993) and De Jong (1995), "plasticity can be produced either by environment-specific gene expression or by allelic effects that vary across environments."

REACTION NORMS ANALYSIS IN LIVESTOCK PRODUCTION

De Jong (1995) defined the reaction norm as the total pattern of expression of a character along a continuous gradient,

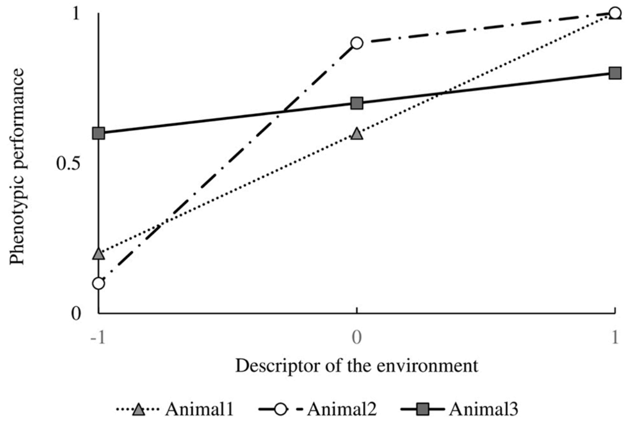

FIGURE 1 | Phenotypic performance of three different (imaginary) genotypes as a function of an environmental gradient at values −1 (an unfavorable environment), 0 (a "neutral" environment) and 1 (a favorable environment).

and plasticity as the difference in character value between environments, i.e., the first derivative of the function in that environment. When the environment cannot be described along a continuous gradient, than it will be mandatory to describe the phenotypic expression as a series of character states, i.e., values as points on the curve. However, when the environment can be described by a continuous variable, it is possible to describe a character by a function (the reaction norm) and use the function values, coefficients and derivatives for traits (De Jong, 1995). Although reaction norms are mostly described as linear relationships, they can take any shape. **Figure 1** presents phenotypic character states of three different (imaginary) genotypes as a function of an environmental gradient at values −1 (an unfavorable environment), 0 (a "neutral" environment) and 1 (a favorable environment). Animal 1 shows a steady increase in phenotypic performance when the environment improves. Animal 2 increases its phenotypic performance slightly when the environment becomes more favorable, however, it is particularly negatively affected when the environment becomes more challenging. Animal 3, as animal 1, shows a steady increase in phenotypic performance when the environment improves, but at a slower rate.

Reaction norms analysis in animal breeding involves quantification of resilience of phenotypic values of production performance expressed by a genotype or by various genotypes across a gradient of a descriptor of the environment (Knap, 2005). Intuitively it holds that an abundant environment will result in a better production performance whereas a restricted environment will depress production. It is proposed that an animal (a genotype) that is best at maintaining its production across this gradient is more robust (i.e., less sensitive) because it has a greater ability to adapt to environmental fluctuations. It is clear from the description that this method is not much more specific than the trait it aims to measure, but it does visualize what robustness represents: a combined production ability (y-axis, the level) and environmental adaptability (x-axis, the slope) trait that can be described in different ways depending on how the variables along the axes are quantified. For example, along the x-axis, environmental factors affecting animal production can be thought to include disease exposure, social stress, stocking density, temperature, nutrient quality, feeding regime, etc. In addition to the ability to maintain production performance, the animal in question will need to be healthy with a sufficient welfare, as it can only be considered robust when its production is qualified as "unproblematic." In order to include this last part in the analysis, a multi-dimensional representation could be imagined, not only including production traits measured across a gradient of a descriptor of the environment, but also health and welfare traits measured across a gradient of the environment or of the production response.

In plants, a particular individual genotype can be represented by identical clones, however, in animal breeding, the reaction norm of an individual "genotype" (often the sire) can be approximated by its offspring which is spread across a wide environmental range, usually through AI (Knap, 2009). The following three sections give an overview of the use of reaction norms analyses today in dairy cattle, beef cattle, and pigs. The aim of these sections is to review how x- and y-axis traits are formulated in these different livestock species, and to indicate some of the results that followed from the analyses.

Reaction Norms in Dairy Cattle

The reaction norms method has been mostly applied to dairy cattle, which can count on large numbers of daughters for each sire that are producing at a wide variety of herd environments at which a wide variety of characteristics are recorded. This wide range of available production characteristics facilitates investigation of a descriptor of the environment as a continuous variable instead of being limited to describing the environment as discrete classes, i.e., as a series of character states. Zwald et al. (2001), Fikse et al. (2003), and Calus and Veerkamp (2003) describe several continuous climate and herd management characteristics that can be used as descriptors of the environment, such as "mean peak yield" and "persistency" as an overall measure of the quality and intensity of the management system, "days to peak yield" reflecting differences in dry cow management and health and nutrition programs, "herd size" as an indirect measure of differences in facilities and treatment of cattle, "day of calving" as a variable that could separate rotational grazing herds with seasonal calving from other types of herds that feature year-round calving, "percentage of animals with completed lactations" as a measure to explain differences in culling strategies between farms, "fat:protein ratio" as a measure of the feeding system, "body condition score" as a measure of the ability of management to tune the feed intake to the energy requirements of the animal, and a temperature and humidity indicator as a measure of the heat stress on cows. As Calus and Veerkamp (2003) indicate: "Potentially a large number of environmental parameters could be defined, but parameters used (. . .) were chosen because they: (1) reflect management and environment, (2) are obtainable from the available data, (3) are continuous rather than categorical (. . .), and (4) are not too strongly correlated with each other."

Strandberg et al. (2000) used the herd-year effect as a general measure of a complex of environmental values to which they linearly regressed 305-d protein yield and days open to estimate breeding values in Nordic dairy cattle (Finnish Ayrshire, Norwegian Dairy Cattle, and the Swedish Red and White Breed). Crossing of reaction norms indicated reranking in the presence of genotype × environment interactions for both traits. Calus et al. (2002) performed a random linear regression of 305-d heifer protein production on herd-year-season in Dutch Holstein Friesian dairy cattle. The level of the reaction norm had such a great impact that the slope had very little influence on the total breeding value, and no genotype × environment interaction was observed. They suggested that another more environmental-specific parameter or defining another scale for the environmental parameter might contribute to increase the influence of the slope. In addition, they suggest that non-linear reaction norms might explain sire variance better. Ravagnolo and Misztal (2002) estimated the genetic component in heat tolerance for non-return rate in Holstein cows using an animal linear model augmented by a random regression on a temperature-humidity index. They observed a negative, unfavorable genetic correlation between merit for milk yield and non-return rate at 90 days after first insemination but indicated that simultaneous selection for improving both traits is feasible. Kolmodin et al. (2002) regressed first lactation 305-d protein production and days open on the herd-year average in Nordic dairy cattle (Danish Red Dairy Breed, Finnish Ayrshire, Norwegian Dairy Cattle, and the Swedish Red and White Breed). They evaluated three different reaction norm models: (1) a random regression on an environmental variable, (2) a regression model including the level and the slope of the reaction norm of the sire, and (3) an extension of model (2) to include a set of regressions on a second environmental variable. The models were similar in both the level and the slope. Results showed that the genetic parameters changed over environments, and that a significant variation for the slope of the norm resulted in little reranking of sires, except between extreme environments. Fikse et al. (2003) regressed 305-d milk yield on fifteen environmental parameters in Guernsey-sired cows (from Australia, Canada, United States, and the Republic of South Africa). Nine parameters had a significant effect and results indicated that reranking of animals may occur in extreme environments. Calus and Veerkamp (2003) estimated breeding values for milk, fat, and protein yield and percentage, of daughters by applying a random regression on various values of environmental parameters for each sire in Dutch dairy cattle (mostly Holstein-Friesian and Meuse-Rhine-Yssel). Twelve of fourteen environmental parameters gave significant reaction norms, but reranking hardly occurred across environments. Hayes et al. (2003) investigated the magnitude of genotype × environment interactions of milk, protein, and fat yield from a random regression on four different environmental descriptors in Australian Holstein-Friesian dairy cattle. Interactions were observed for average herd protein yield and temperature humidity index. Bryant et al. (2006) investigated the environmental sensitivity of Holstein Friesian and Jersey dairy cattle and their crosses for 2-year milk, fat and protein yields in relation to the range of herd milksolid yields (as a proxy for feeding level) in New Zealand using first and second degree polynomial regression functions. Their results indicated that Holstein Friesians originating from overseas (mostly from North America), exhibited higher levels of production (level) but also higher environmental sensitivity (slope) than Holstein Friesians from New Zealand and Jerseys. The overseas Holstein Friesians, which are selected in an environment where high levels of concentrate are offered and high levels of production are achieved, improved their ranking in a high production level environment, whereas New Zealand Jerseys, which are selected in pasture-based, low production level environments with high levels of environmental heterogeneity due to the variable nature of pasture supply, improved their ranking in a low production level, grassland-type environment. Haile-Mariam et al. (2008) regressed not only milk production traits (milk, fat, and protein yield and percentage) but also fertility traits (calving interval, calving to first service interval, 25-d non-return rate at first service, and pregnancy rate) and survival to the next lactation on the environmental descriptors "level of herd milk production," temperature-humidity index, and herd size in Australian Holstein-Friesian dairy cattle. There was no evidence for the presence of a large genotype × environment interaction that resulted in economically significant reranking of bulls. Shariati et al. (2007), fitting a reaction norms model to first test-day records for first lactation milk, protein, and fat of Danish Holstein cows, reported the presence of genotype × environment interaction, but with a small effect on reranking of candidates for selection. Streit et al. (2012) applied reaction norm random regression sire models to corrected test day records for milk, protein, and fat yield and somatic cell score as a function of herd test day solutions as environmental descriptors in German Holstein dairy cattle. Results indicated the presence of minor genotype × environment interactions which did not result in reranking of sires.

Reaction Norms in Beef Cattle

Corrêa et al. (2010) evaluated differences in sire genetic values by a reaction norms hierarchical model for post weaning gain in response to estimates of contemporary group effects in Brazilian Devon cattle. They reported the existence of genotype × environment interaction. Most reranking of sires happened in restrictive environments, indicating that importing genetic material should be carefully assessed when the selection conditions of the animals in the exporting countries are greatly superior to local production environmental conditions. Pégolo et al. (2009) assessed genotype × environment interaction for 450-day adjusted weight and body weight gain in Brazilian Nelore cattle using a random regression reaction norms model on heard-year and herd-year-season-management groups, and heard-year-season-management group solution estimates. The models generated consistent parameter estimates. Important genotype × environment interactions were found with low genetic correlations among extreme environments, indicating a significant reranking of sires in different environments. Mattar et al. (2011) investigated the presence of genotype × environment interactions for long-yearling weights of Brazilian Canchim cattle using reaction norms of the trait as a response to a "contemporary group" effect that combined year and season of birth, sex, genetic group of dam, herd at weaning and long-yearling, and feeding regimen from birth to weaning and from weaning to long-yearling. Their results showed that all animals increased their performance with the environmental improvement, that there was some reordering of genotype ranks, and that there existed variability in phenotypic plasticity. Cardoso and Tempelman (2012) investigated alternative linear reaction norms models for post-weaning body weight gain to a "contemporary group" effect of herd-year-season-sex-management subclasses in Brazilian Angus cattle. They observed genotype × environment interactions and possible reranking, and furthermore concluded that environmental sensitivity of imported North American Angus bulls was significantly larger than that of local Brazilian Angus sires which tended to be more robust to environmental changes. Santana et al. (2013) determined the presence of genotype × environment interaction for birth weight, weaning weight, postweaning weight gain and yearling scrotal circumference in Brazilian composite beef cattle from reaction norms taking the environmental covariate of the reaction norms (the contemporary group) as the environmental descriptor. A genotype × environment interaction was observed and reranking of animals and it was concluded that it can be important to include phenotypic plasticity in the breeding goal.

Reaction Norms in Pigs

Reaction norms in pig production are scarcely described. Knap and Su (2008) estimated linear reaction norms of total litter size at birth as a function of routine herd-year-season effects in two PIC lines of pigs and their cross. Daughters of sires were spread over North and Latin America, Europe, Asia and Australia, providing for a wide range of environmental effects of a climatic, nutritious, management-related and infectious nature. Environmental sensitivity showed a progressively lower genetic component with increasing data volume, and progressively less frequent reranking of genotypes across the environmental range. Consequently it was recognized that reaction norms analysis is indeed a demanding process, requiring large data volume and a wide environmental range in order to produce meaningful results (Knap and Su, 2008).

Reaction Norms for Behavior and Welfare

So far, a behavioral reaction norm as suggested here previously has not been applied in livestock production, however, Sih et al. (2004) proposed that behavior can be included in phenotypic plasticity and reaction norms models. Similar, Dingemanse et al. (2009) describe that animal responsiveness (behavior) can be described as a function of environmental variation (context), and that this can be considered a complementary aspect of the individual phenotype. Examples given are the relationships between parental provisioning rate and offspring begging intensity, between dispersal behavior and wind velocity, or between anti-predator behavior and predation risk (Dingemanse et al., 2009). In addition, animal personality is suggested to express itself as a coping strategy that is consistent across contexts (Koolhaas et al., 1999); Sih et al. (2004) refer to such suites of correlated behaviors in an individual as "behavioral types," which show consistency in behavior across multiple situations. This behavioral consistency may be represented by the individual behavioral response as a function of a stimulus that can vary across a gradient, as an index of its behavioral stability (Sih et al., 2004; Dingemanse et al., 2009). Personality does not imply that each individual is necessarily completely consistent in behavior, such that variation in plasticity may be observed between individuals and populations (Dingemanse et al., 2009). Coping styles are important in livestock production as they form general adaptive response patterns that have genetically evolved in reaction to everyday challenges and are thus closely related to individual adaptive capacity and vulnerability to stress-related disease (Koolhaas et al., 1999). Dingemanse et al. (2012) used the reaction norms approach to estimate the quantitative genetics parameters of the exploration behavior of an open-field of over 1000 offspring of two populations of wild-caught three-spined stickleback fish. They found heritable variation and population differences in both the average level of exploration and behavioral plasticity.

Examples in livestock production of environmental gradients can be thought to include group size and composition, temperature, photoperiod, environmental enrichment, but might also include production parameters such as growth rate or milk production. Smiseth et al. (2008) described behavioral reaction norms to investigate parent-offspring conflict and co-adaptation. They indicate that behavioral interactions can include other questions where the expression of traits depends upon the behavior of other individuals, "encompassing the whole field of animal communication," such as aggression related to competition for resources. A similar analysis may be applicable to social interactions in livestock production systems.

Selection for Increased Production, Against Environmental Sensitivity

The breeding value as estimated from reaction norms analysis is built up of two parts: the environment-independent part (the level), and the environment-dependent part (the slope; Calus et al., 2002). Thus, the ideal reaction norm in animal production has a high level and a flat slope (Strandberg et al., 2000). According to De Jong (1995), the level and the slope are genetically correlated; however, this does not necessarily mean that separate genes for plasticity and trait mean exist.

Su et al. (2006) indicate that in reaction norms analysis a linear relationship between the phenotypic expression of a given genotype and the covariate representing a particular environmental effect is assumed, which is approximated by using the mean phenotypic performance in the appropriate environment, without the need to know the actual covariate. However, the variance among phenotypic means of production environments includes a genetic component, resulting in overestimation of the variation of environmental values, even in a random mating population. In addition, computer simulation indicated that it results in an underestimation of variance components associated with the slope, and an overestimation of the variance components associated with the level. Instead, they suggest a more satisfactory alternative by inferring environmental values simultaneously with the other parameters in the model using a Bayesian Markov Chain Monte Carlo approach, which was shown to lead to estimates of parameters with no detectable bias and with smaller mean squared errors. To account for a scale effect on residual variances in reaction norms models such that larger environmental effects are associated with larger residual variances, Cardoso and Tempelman (2012) proposed two alternative extensions to the model to allow for heteroskedastic residuals: an exponential function and a best fitting environmental classification model; the latter seemed to provide a better fit than the exponential function.

Lillehammer et al. (2007, 2009) described a different approach by investigating not the effects of genotypes but the effects of single genes in response to environmental variation using quantitative trait loci (Lillehammer et al., 2007) and single nucleotide polymorphisms (Lillehammer et al., 2009). This is important since QTLs and SNPs with an environmental interaction can be hard to detect even though they have a large average effect. In the SNP analysis they report a genetic correlation between general production and environmental sensitivity from 0.55 to 0.88, indicating that most genes should affect the level and the slope in the same direction. This supports earlier work by Kolmodin et al. (2002) who observed that animals with genetically high production tended to be more sensitive to changes in the production and fertility environment, and by Kolmodin et al. (2003), who studied the effect on environmental sensitivity (the slope) of selection for high phenotypic value (the level) in combination with a continuously improving environment in a simulation study. They detected a significant selection response, suggesting that environmental sensitivity will increase with selection for high phenotypic values. These observations were also supported by later work, for example by Knap and Su (2008), who indicated that the very precisely estimated correlation between the intercept and the slope was extremely high: "Hence, irrespective of genetic effects, the performance of sows with a high reproductive capacity is practically always highly sensitive to environmental disturbance. [The same pattern applies to] the genetic level; [it is clear] that for litter size, the performance of high-potential genotypes (and of high-capacity sows) will likely come down strongly when environmental conditions become unfavourable." However, because of the low heritability of the slopes, environmental sensitivity would be increasing at a slow rate.

The negative correlation between high levels of production and increased environmental sensitivity can result from resource allocation patterns described by Beilharz et al. (1993). Resource demanding physiological processes show trade-offs resulting from limits in the resource availability, food intake and digestive capacity and/or limiting resource allocation patterns which typically result in a genotype × environment interaction. Animals that are genetically driven to produce at high levels may need to reallocate resources away from other process, leaving the animal lacking in ability to respond to other demands, such as coping with disease and stress. This will consequently result in an animal that is more sensitive to environmental fluctuations (Rauw, 2009). Indeed, Friggens and Van der Waaij (2009) indicate the single-trait limitation of the reaction norms approach and developed resource allocation models, based on the model of Van der Waaij (2004), providing a framework for a multi-trait definition of robustness. This model explicitly examines the partition of resources between different life functions and provides a framework for exploring trade-offs. The equations allow for relating total fitness to environmental variation and resource availability, defining plasticity in terms of more than one trait. This is more biologically meaningful since adaptation to environmental change is essentially a process that results from a combination of physiological mechanisms (Friggens and Newbold, 2007). However, as reviewed by Friggens et al. (2013), the challenge of linking prediction of nutrient partitioning to its consequences on health, reproduction, and longevity is only recently being addressed, and so far the models developed, for the most part, remain research models that need to be further developed to be applied in the field.

As Kolmodin et al. (2003) notes, high sensitivity may be beneficial when the environment is highly controllable and predictable, since the benefit from improvements of, for example, management and feeding would be substantial, while the risk of environmental deterioration, causing drastic reductions in levels of production, would be relatively low. However, since populations of animals with high production potential will be more dependent on highly controlled environments this may be of ethical concern. Lillehammer et al. (2009) indicate that their results show that a small fraction of the genes affect only production (the level) or only environmental sensitivity (the slope). In addition, even a category of possible selection gene candidates was found that affects production and environmental sensitivity in opposite directions. Such genes would facilitate selection for increased production and robustness at the same time.

DIRECT INCLUSION OF ROBUSTNESS TRAITS IN THE BREEDING OBJECTIVE

The second option for breeding for animal robustness is the direct approach, which encompasses the inclusion of directly measurable robustness traits in the breeding objective and in the selection index. These robustness traits can include the same physiological, immunological and reproduction traits that are affected as a result of selection for high production efficiency (Rauw et al., 1998). They are often referred to as "functional traits," i.e., traits that are closely related to biological functional ability or fitness, such as longevity, health and fertility. Although these traits are important to all livestock animals, the term is mostly used in dairy cattle production, where they can include structural soundness, udder and teat conformation, frame score, disposition/temperament, body condition score, fertility, calving ease and mothering ability, and adaptability to the environment (Peck, 2006; Egger-Danner et al., 2015). Similar fitness traits related to longevity, health and fertility are described for other livestock species. The Nordic countries (Sweden, Norway, Denmark) in particular have broadened breeding goals to also include fertility and health, which became possible since these countries implemented well-established, national recording systems for health data (Herringstad et al., 2000). Since the mid-1990s also several European and North-American breeding organizations have included fertility and health in their breeding objectives (Oltenacu and Broom, 2010). The International Committee for Animal Recording (ICAR) promotes since 1951 the development and improvement of activities of performance recording and the evaluation of dairy cattle and its Functional Traits Workgroup is in particular involved with recommendations regarding functional traits in dairy cattle. Heritabilities of functional traits and feasibility of inclusion of these traits in the breeding objective has been described in a number of works and several reviews (e.g., Groen et al., 1997; Essl, 1998; Herringstad et al., 2000; Lawrence et al., 2004; Egger-Danner et al., 2015). According to Knap (2009), genetic improvement of robustness traits can improve profitability of production at a similar rate as by improvement of a conventional production trait. In spite of antagonisms between robustness and production performance, a positive genetic trend in both traits can be achieved at the same time when robustness traits are properly included in the breeding goal and selection criteria (Knap, 2009).

In addition, several authors discussed the feasibility of including behavioral traits that are related to animal welfare in the selection criterion. These traits will improve animal welfare and can be expected to lead to improvements in mortality, disease resistance, efficiency, longevity, reproductive performance and carcass wastage as a correlated effect (Turner, 2011). For example, Jones and Hocking (1999) extensively reviewed the feasibility of using selective breeding to improve welfare, describing results of selective breeding studies in which fear, adrenocortical stress responses, social motivation, feather pecking, and growth rate were manipulated in quail and chickens. Star et al. (2008) described including, besides immunological and physiological traits, also behavioral traits in laying hens. Rydhmer and Lundeheim (2008) proposed to include improved piglet survival, stronger legs, a better constitution, improved disease resistance, less aggressive behavior, reduced fear of humans and a great appetite in the breeding programs of pigs. D'Eath et al. (2010) discussed the possibilities of selection for farm animal behavior in livestock species in general, indicating that in many cases, estimated heritabilities are of comparable magnitude to traits already included in the breeding program (0.1 to 0.4) which suggests that selection for behavior would result in a positive selection response. Turner (2011) explored the genetic contribution to harmful social behavior traits using as examples regrouping and poor maternal care in pigs, and oral manipulation of penmates in pigs and laying hens, and concluded that for most traits, improvements in harmful behavior can be made by careful breed choices and selective breeding. Dawkins and Layton (2012) describe the feasibility of breeding for better welfare in broiler chickens, noting that "Broiler chicken welfare is most likely to be improved in practice if animal welfare traits such as good walking ability, good feathering and healthy legs and feet are seen as compatible, rather than in conflict, with other goals such as commercial production." Canario et al. (2013) reviewed the feasibility of including behavioral traits in the selection criteria of cattle, pigs, poultry and fish. They note that animal behavior is a welfare indicator since it relates both to the existence of stressors and to the animal's ability for behavioral adaptation to physical and social environmental stressors. Mormède et al. (2011) proposed to select animals for a higher activity of the stress-related hypothalamic–pituitary–adrenal axis (which releases cortisol or corticosterone) to improve animal robustness and welfare. And finally, Oliveira et al. (2010) proposed assessment of play behavior as a new and promising potential indicator of animal welfare. According to Allen and Bekoff (2005), there are evident emotions associated with play—joy and happiness—that drive animals into it. Indeed, animal play only if they are healthy, safe, well-fed and in a relaxed state, but not if they are under a stressful condition (Burghardt, 2005). According to Held and Špinka (2011), play may signal both the absence of bad welfare and the presence of good welfare, however, it does not consistently reflect favorable environmental conditions. Rauw (2013) investigated the consistency of a behavioral play marker in piglets and proposed investigating the feasibility of using play markers in the selection criterion of livestock species.

The challenge to including behavioral traits in the selection criteria is to define quantifiable traits or proxy measures thereof that can be recorded cost-effectively and reliably on the large number of animals that are necessary for a breeding program (D'Eath et al., 2010; Turner, 2011). In addition, which trait(s) to select for in order to truly improve animal welfare is complicated by the many different conceptions and definitions of animal welfare proposed, defined in terms of, e.g., animal function, the balance of enjoyment or pleasure vs. suffering or pain, preference satisfaction, or natural living (Duncan and Fraser, 1997; Lassen et al., 2006). As Turner (2011) notes, it may be difficult to identify behavior in the recipients vs. the donors (for example of aggression), and it may be challenging to attribute an accurate economic value to behavioral traits. In addition, D'Eath et al. (2010) warn for selecting animals that do no longer show outside signs of negative welfare, but still experience the negative feelings associated with the unwanted behavior, for example in the case of docile animals that are too frightened to move. It may thus be necessary to first further investigate the cognitive processes and emotional experiences underlying the phenotypes (Turner, 2011).

Finally, in addition to production traits, functional traits and behavioral traits, Olesen et al. (2000) discussed the need to define animal breeding goals as an integrated part of sustainable production systems, i.e., based on a holistic, long-term perspective. They stress that higher productivity should not only be balanced with (short-term) improved health, fertility, and feed intake capacity, but also with (long-term) important non-market values of animal traits, such as ethical values of improved animal welfare and possibly also with natural capital and ecosystem services (depletion of fossil energy, degradation of the atmosphere) and social issues. Also Kanis et al. (2005) proposed including "societally important" traits, such as product safety, welfare, and environmental impact, which do not have a clear economic value. They present a retrospective selection-index method to obtain the proper weights for those traits. Olesen et al. (2000) emphasize that animal breeding practices must become part of the pluri- and interdisciplinary, philosophical and ethical debate. Code-EFABAR also follows the principles of sustainable breeding in their Code of Good Practice; the general definition of sustainable farm animal breeding is defined as: "the extent to which animal breeding and reproduction, as managed by professional organizations, contribute to maintenance and good care of animal genetic resources for future generations" (Gamborg and Sandøe, 2005; Code-EFABAR, 2006).

ETHICAL CONSIDERATIONS

Artificial selection was already described by Mago from Carthage in his work "Treatise on Agriculture" several centuries BC in which he recommended choosing oxes that were "young, stocky, sturdy of limb with long horns, darkish and healthy, with a wide and wrinkled forehead, hairy ears and black eyes and chops, the nostrils well-opened and turned back, the neck long and muscular, and dewlap full and descending to the knees, the chest well-developed, broad shoulders, the belly big like that of a cow in calf, the flanks long, the loins broad, the back straight and flat or a little depressed in the middle, the buttocks rounded, the legs thick and straight, the hooves large, the tail long and hairy and the hair on the body thick and short, red-brown in color and very soft to the touch" (Koster, 2015). Selective breeding has been responsible for the domestication of 14 animal species and about 100 plants yielding valuable domesticates (Diamond, 2002). Before the 1940s, breeding objectives were mostly visual with the expectation that form determines performance (Darlow, 1958). Subsequently, breeding industries evolved toward objectives involving performance, such as rapid growth and high milk yield (Harris and Newman, 1994). Breeding value estimation was limited to the data that was available for evaluation. This first included single traits, until models were developed for combining several traits into a selection index by Hazel and Lush (1943), and methods were developed such as those for the estimation of variances and covariances for unbalanced animal data by Henderson (1953) (Philipsson et al., 1994). In dairy cattle, as reviewed by VanRaden (2004), the national index of Swedish dairy cattle included 12 traits in the selection index as early as 1975, including milk production, growth rate, female fertility, stillbirths, ease of milking, temperament, and six conformation traits (Philipsson et al., 1994), but the USDA introduced its first net merit index in 1994, which combined productive life, and somatic cell score with yield traits (VanRaden, 2004). The USDA selection index subsequently included conformation traits in 2000 and cow fertility and calving ease in 2003.

Only recently is selection for production traits under scrutiny for the *consequential* undesirable side effects that this may produce affecting animal welfare (Rollin, 1986), thus leading the British Farm Animal Welfare Council to recommend that new and existing breeding technologies and breeding programs should be evaluated for welfare and ethical issues that may arise as a result (FAWC, 2004). Broadening the breeding objective and including more traits in the selection criteria may alleviate and possibly even prevent such negative side effects, with as the only negative consequence a reduced selection response of production traits. However, genetic modification may also result in an *intrinsic* ethical concern when breeding affects animal integrity. Rollin (1986, 1995) used the Aristotelian concept of the *telos* of an animal to describe animal nature, i.e., the differences "rooted in biological, genetically based, empirically ascertainable, environmentally expressed "blueprints"" giving rise to "the pigness of a pig, the dogness of a dog." Bovenkerk et al. (2002) write: "It implies that the animal is intact or whole, which is an attribute of the animal itself, not just some value we have placed on it." Any artificial genetic modification may be seen as changing the *telos*, however, D'Eath et al. (2010) suggest that animal behavior is much more easily considered to be part of the animal's nature than any other production trait. As to the question of changing the telos by means of changing the genetic make-up, Rollin (1986) writes: "[O]ne cannot argue that because it is wrong to violate the various aspects of a certain animal's *telos* given the *telos*, it is therefore wrong to change the *telos*. This is true only if the change in the *telos* is likely to engender more unhappiness in the animals, given the environment in which they live, than would have accrued to them before" (Rollin, 1986). Indeed, Rollin believes that there is no moral problem if welfare could be *improved* by changing animal natures, even altering animals such that they can be made happier in questionable environments (Rollin, 1995; Bovenkerk et al., 2002). For example, animals bred to have fewer desires or animals with a reduced sentience will be more easily satisfied and consequently have a higher welfare than the population before such selection (D'Eath et al., 2010). In the same way, blind chickens do not show feather pecking or cannibalism, therefore, blind hens may not suffer (Sandøe et al., 1999). Strains that are improved to disguise welfare threatening conditions may discourage the development of higher standards of environmental provisioning (MacArthur Clark et al., 2006). As a consequence, in extreme cases, genetic modification of animals into senseless, emotionless machines that have no desires could be considered a solution to the animal welfare problem.

However, intuitively, a large amount of the human population believes that genetic modification of animals is troubling and morally problematic; as such the public opinion can be expected to influence breeding decisions made by producers that would eventually prevent producing animal machines (Rollin, 1998; Thompson, 2010). As Bovenkerk et al. (2002) note, animal integrity is an intuitive concept, and because it lacks objectivity it is therefore not of practical use since that would entail objective criteria to measure it. However, not different from ethical considerations in humans, the concept of integrity can be used in the ethical discussion on livestock breeding, and in the same way that concepts of human rights based on integrity are formulated into laws, from discussions regarding the ethics of livestock breeding can follow similar agreements and regulations (Bovenkerk et al., 2002). Rauw (2015) suggests that although consumer demand may influence decision making and although consumers may be willing to pay more for products that are produced in more welfare friendly production systems, legislation should really be based on ethics independent of consumer demand and willingness to pay. Similar to the option to buy clothes cheap that are produced unethically versus paying more for clothes that are produced under humane circumstances, we as consumers should not be able to have that option (Rauw, 2015).

The Farm Animal Welfare Council, in its 2012 report, writes: "[In 2004] we were concerned about general trends in breeding, given the commercial pressures on breeders and farmers alike. Today matters are improving: we still have concerns but we are encouraged that many breeding goals now include aspects of animal welfare, e.g., disease resistance." Conclusion 105 of the report reads: "Farm animal breeding companies should be congratulated for the progress made on breeding goals aimed at improving robustness and health and welfare traits.

However, there are still some issues associated with high production levels resulting in poor animal welfare."

The discussion on animal breeding practices has been initiated and is very alive today. This positive trend is part of the sustainable food production movement that aims at feeding 9.15 billion people not just in the near future but also beyond. However, the discussion is taking place in Europe and North America which are home to the largest livestock breeding companies that hold most of the market share (Gura, 2007). These developed countries are projected to account for only part of the increase in meat consumption, whereas more than half of the increase is projected to be accounted for by developing countries in Asia, Latin America, and Africa, countries that still depend heavily on agriculture for their livelihoods (Borlaug and Dowswell, 2005; Thornton, 2010; Appleby and Fuentesfina, 2015). Although the technology and genetic resources are available, this may be of limited use to local farmers when they are threatened by poverty, governmental regulation and intellectual property rights (Borlaug and Dowswell, 2005). In addition, concern for animal welfare and rights is generally stronger in Europe than in Asia (Phillips et al., 2012) and it remains to be seen if European (breeding) companies will apply their animal welfare standards on a global basis, as suggested by Fraser (2008), or whether this may eventually influence breeding decisions in the future when such standards are not required by international food companies and their customers.

SYNTHESIS

Since environmental resources (land, water, and energy) are limited, a 70–100% increase in the projected need for food by 2050 must necessarily come from what is called "sustainable intensification." As Godfray et al. (2010) write: "A threefold challenge now faces the world: Match the rapidly changing demand for food from a larger and more affluent population to its supply; do so in ways that are environmentally and socially sustainable; and ensure that the world's poorest people are no longer hungry." Increasing production limits both in crops and in livestock are inevitably part of satisfying the global food demand in the future. A further increase in livestock yields with continued selection will be facilitated by superior selection methods including genome-wide selection, more sophisticated progeny testing and tracking methods, and a greater predictive power of total genetic merit indices that integrate genomic markers with multiple traits (Hume et al., 2011). However, at the same time, animals in populations that have been selected for high production efficiency are found to be more at risk for behavioral, physiological and immunological problems (Rauw et al., 1998). As a result, in the last few decades, breeding practices have become of ethical concern and consideration of the possible effects on animal welfare are called for (e.g., FAWC, 2012).

The farm animal of the future is described as robust, adapted, and healthy (Mormède et al., 2011). Options for breeding for improved robustness include: (1) estimating breeding values for the environmental sensitivity of the genetic potential for production performance through the use of reaction norms analysis, and (2) direct inclusion of measureable robustness traits in the breeding objective and in the selection index (Knap, 2009). Theories on reaction norms analysis have their basis in genotype by environment interactions that have been described since Lamarck and Darwin. Reaction norms describe phenotypic production values as a function of a gradient of a descriptor of the environment (Knap, 2005). They were first applied in plants, whereas application of reaction norms analysis in livestock production (mostly dairy and beef cattle) is of a much more recent origin. Linear reaction norms are built up of two parts: the level and the slope. A generally observed negative correlation between these parameters suggests that improvement in production yield will result in animals that become more sensitive to changes in the production environment (Kolmodin et al., 2002).

Although livestock selection indexes include multiple, mostly yield-related, traits for several decades, direct inclusion of functional, robustness, traits became more seriously applied since the 90s (Oltenacu and Broom, 2010). Of more recent origin is the consideration of inclusion of behavioral traits (Turner, 2011) and even important non-market values of animal traits, such as ethical values or environmental impact (Olesen et al., 2000). Despite an often antagonistic relationship between robustness and production performance, a positive genetic trend in both traits can be achieved when both are properly included in the breeding goal and selection criteria (Knap, 2009).

According to the Farm Animal Welfare Council, farm animal breeding companies may be congratulated for the progress made so far toward breeding more robust and healthy animals. The discussion and efforts on animal breeding practices is very alive today and will remain to be an important part of the sustainable intensification debate in the future.

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REVIEW
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Go with the flow—biology and genetics of the lactation cycle

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Lactation is a dynamic process, which evolved to meet dietary demands of growing offspring. At the same time, the mother's metabolism changes to meet the high requirements of nutrient supply to the offspring. Through strong artificial selection, the strain of milk production on dairy cows is often associated with impaired health and fertility. This led to the incorporation of functional traits into breeding aims to counteract this negative association. Potentially, distributing the total quantity of milk per lactation cycle more equally over time could reduce the peak of physiological strain and improve health and fertility. During lactation many factors affect the production of milk: food intake; digestion, absorption, and transportation of nutrients; blood glucose levels; activity of cells in the mammary gland, liver, and adipose tissue; synthesis of proteins and fat in the secretory cells; and the metabolic and regulatory pathways that provide fatty acids, amino acids, and carbohydrates. Whilst the endocrine regulation and physiology of the dynamic process of milk production seems to be understood, the genetics that underlie these dynamics are still to be uncovered. Modeling of longitudinal traits and estimating the change in additive genetic variation over time has shown that the genetic contribution to the expression of a trait depends on the considered time-point. Such time-dependent studies could contribute to the discovery of missing heritability. Only very few studies have estimated exact gene and marker effects at different time-points during lactation. The most prominent gene affecting milk yield and milk fat, *DGAT1*, exhibits its main effects after peak production, whilst the *casein* genes have larger effects in early lactation. Understanding the physiological dynamics and elucidating the time-dependent genetic effects behind dynamically expressed traits will contribute to selection decisions to further improve productive and healthy breeding populations.

Keywords: time-dependent, longitudinal, lactation curve, breeding value, genome-wide association, genomic selection, genomic prediction

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Introduction

Lactation is an orchestrated process aimed at providing nutrition and immune protection to the offspring; however, the mother must also retain sufficient resources to ensure her own survival. Thus, the quantity and composition of milk produced is strongly dependent on the developmental stage of the offspring and the maintenance requirements of the mother. As such, milk production is a classic exemplar of a time-dependent dynamic process.

The domestication of animals inevitably led to selective breeding for increased productivity. The uninterrupted increasing global demand for dairy products necessitated a concurrent increase in milk production. Thus, in order to meet market requirements, the dairy sector implemented selective breeding programs which have led to a doubling in the amount of milk produced per cow over the last 50 years, such that total milk production is increasing despite a decline in dairy cattle populations (Food and Agriculture Organization of the United Nations, FAO, 2012[1]). Recently, this has included the implementation advanced breeding programs and the development of tools to utilize genetic and genomic information (Goddard and Hayes, 2007; Seefried et al., 2010). However, increasing the milk production per cow has detrimental effects on animal health and fertility (Ingvartsen et al., 2003; Oltenacu and Broom, 2010). Consequently, breeding goals were adjusted to incorporate health and fertility traits into breeding indices (Osteras et al., 2007; Boichard and Brochard, 2012).

These breeding indices have enabled dairy farmers to breed for milk production and functional traits without requiring knowledge on how these practices impact upon the dynamics of milk production or change the expression of underlying genes. However, the continuous development of genetic and genomic tools, as well as computational capacities, will allow breeders of the future to base their decisions not only on phenotypically observable traits or indirect genetic marker information but also on the direct causative genetic variants.

As with many other complex traits important in livestock production, milk production is influenced by many genetic loci that act directly, interact with each other and/or interact with the environment (Lemay et al., 2009). This makes the study of quantitative traits challenging, especially when time-dependent components are considered. This review details the most important regulators of milk production and their underlying genes in the context of the dynamics of a lactation cycle, and summarizes the efforts made to identify genetic loci affecting the dynamics of milk production during lactation.

Conflict between Production and Functional Traits

The milk production of a cow follows a dynamic curve (**Figure 1A**; Stanton et al., 1992). After an initial rapid increase in milk yield during early lactation, milk yield (as well as protein and fat content) peak around 6 weeks into lactation, after which production slowly decreases until the end of lactation. Dairy cows experience an energy deficiency during early and peak lactation (**Figure 1B**; Collard et al., 2000) due to the high energy requirements for milk production not being met because of physiological limitations which constrain food intake (i.e., bulk capacity; Allen, 1996) and mobilization of bodily energy resources. This energy deficit has been proposed to have detrimental effects on health and fertility which have been reviewed and discussed by Oltenacu and Broom (2010), and negative genetic correlations have been reported between milk production and a variety of functional traits (Zimmermann and Sommer, 1973; Dekkers et al., 1998; Ingvartsen et al., 2003; Muir et al., 2004). However, it has to be noted that total milk yield and the energy balance during early lactation seem to be independent, as correlations have been reported to be very low (Spurlock et al., 2012). Further, the negative impact of lactation on fertility may serve a functional purpose to provide optimal birth spacing for the survival of offspring. Therefore, there may be other endogenous factors yet to be discovered that negatively affect health and fertility traits.

From a nutritionist's point of view it might be necessary to reduce, rather than to increase, peak milk yield in order to decrease the energy deficiency experienced during early and peak lactation, and thereby improve health and fertility traits. However, this is in direct conflict with the desire to increase overall milk production. Therefore, an alternative method of increasing overall milk production might be via increasing production persistency. A better production persistency raises the overall gain per lactation due to an increased persistency affecting the longest part of the lactation (i.e., late lactation; Dekkers et al., 1998; Inchaisri et al., 2011). However, there are some reports indicating that a high persistency may also be antagonistic to the animal's health, and thus also needs to be considered in regards to finding an optimal persistency and lactation duration (Harder et al., 2006; Appuhamy et al., 2009).

Production persistency is most often defined as a lesser decrease in milk production after the peak, i.e., a flatter shape of the lactation curve compared to another animal or the heard average. Such calculations can be based on the difference of peak yield to a 305d measurement, on test-day deviations, or on parameters of lactation curve models (Gengler, 1996). As persistency is negatively correlated to yields, some studies prefer to calculate persistency as a linear regression of test-day deviations on days in milk to achieve a yield independent estimate (Cole and VanRaden, 2006; Cole and Null, 2009). By employing such an estimate, it would enable a breeder to select on milk yield and persistency independently; however, currently only very few breeding companies provide such estimates to their clients.

One problem with persistent production is the requirement to dry-off a cow between lactations. However, if the production system does not require yearly calving, the duration of the lactations can be chosen according to daily yield. Subsequently, with increased lactation duration, the time point of insemination has to be postponed. Assuming that the peak production remains around 6 weeks into the lactation cycle, a later time point for insemination has the added benefit that a new pregnancy begins after the energy deficit caused by the high peak production. Thus, fertility issues potentially arising from an energy deficit will be reduced. Regardless of lactation duration, the general recommendation for days dry is still 45–70 days (Kuhn et al., 2006, 2007; Sawa et al., 2012). The potential implications of increased lactation duration on generation intervals and fewer replacement animals could be counteracted through the utilization of sexed semen to increase the ratio of female calves.

Current methods in animal breeding apply an index of traits weighted according to their economic importance as well as heritability in the breeding goal. Further, phenotypic and genetic correlations between traits within the index are included, on the one hand to increase accuracy on lowly heritable traits, and on the other hand to account for potential negative

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[1] http://faostat.fao.org/site/569/DesktopDefault.aspx?PageID=569#ancor

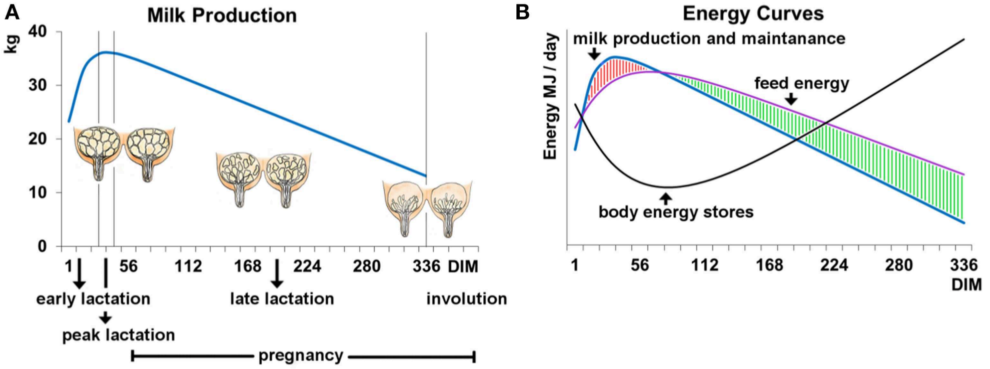

FIGURE 1 | (A) Milk production and **(B)** energy supply and requirements during the lactation cycle of 340 days. **(A)** The curve represents the milk yield per day of lactation and reaches a peak production around lactation days 40–50. Shortly before lactation and until peak production the udder and the alveolar system are highly developed. In later lactation the alveolar system regresses continuously until the end of lactation and into involution. **(B)** The blue curve represents the energy that is needed for milk production and maintenance of vital body functions. The energy needed for milk production is highest when milk production reaches a peak. At the same time the energy taken in through food (purple curve) cannot cover the energy requirements for milk production which leads to a loss in body energy stores (black curve). This imbalance in energy homeostasis changes with the decline of milk production in late lactation.

correlations (Dekkers, 2007).Whilst milk production is still the most important trait in most countries, conformation, udder health, and fertility have been added to balance the negative correlation between a high production and the animal's welfare and longevity (VanRaden, 2004; Miglior et al., 2005). However, the exact impact of such breeding indices on the shape of the lactation curve or the dynamic gene effects remains unknown. In the following section, we look at the physiological interplay that forms the lactation cycle as this is the basis of understanding which genetic factors are ultimately involved.

Physiology of a Dynamic Milk Production

Mammogenesis

The development of the mammary gland is the primary factor affecting milk production. A well-developed mammary gland with many fully differentiated secretory cells, good blood supply, and strong connective tissue will be highly productive over a long time.

The mammary gland forms a rudimentary duct tree during fetal development in response to maternal hormones (Watson and Khaled, 2008). From birth until puberty, mammary gland growth is due to the formation of a fat-pad rather than the development of specialized mammary gland tissue (McNally and Martin, 2011). At puberty the initiation of the estrus cycle, via follicle-stimulating hormones and luteinizing hormone, stimulates the ovaries to synthesize and release estrogen and progesterone. The concurrent elevations in both estrogen and progesterone orchestrate the main growth of the mammary gland during pregnancy by ductal growth and lobular formation which leads to the formation of lobule-alveoli (Hennighausen and Robinson, 2005; Bloise et al., 2010; Koos, 2011). Alveoli are an accumulation of secretory cells grouped around a hollow center, the lumen, where the milk is stored (**Figure 2**). Thus, as pregnancy progresses, the adipose cells of the mammary gland are gradually replaced by specialized mammary gland tissue. Mammary gland growth continues during early lactation until peak lactation, after which the mammary gland shrinks due to the rate of secretory cell loss exceeding the rate of cell division (**Figure 1A**; Capuco and Akers, 1999).

Hormones and growth factors are important in determining how many secretory cells develop, and thus how much milk can be produced in the mammary gland (Watson and Khaled, 2008; McNally and Martin, 2011). By slowing down the process of hormonal stimulation of secretory cell proliferation during late pregnancy and early lactation, and favoring an extended time during which new cells are produced, the peak milk production could be reduced and a better persistency achieved. This may also be achieved by slowing down the rate of cell death which is also regulated through a cascade of hormones and growth factors (Sureshbabu et al., 2011; Watson et al., 2011).

Milk Secretion

A second crucial point for milk production concerns the quantity and quality of the secreted milk. Milk is an emulsion of fat and water containing dissolved carbohydrates, proteins, vitamins, and minerals that all have to be produced in or transported to the mammary gland. During lactation, quantitative milk yield is primarily regulated by lactose within the alveoli. Alveolar lactose influences the osmotic pressure between blood and alveoli and thereby the amount of water drawn into the alveoli (**Figure 2**; Zhao and Keating, 2007). Some of the substances in milk such as minerals, vitamins, or immune-globulins pass the cell membranes directly from the blood into the lumen via transporter proteins (**Figure 2**; Neville and Watters, 1983). The activity of these transporter proteins is increased when milk production starts to enhance the uptake of water into the secretory cells of the mammary gland (**Figure 3**; Zhao and Keating, 2007;

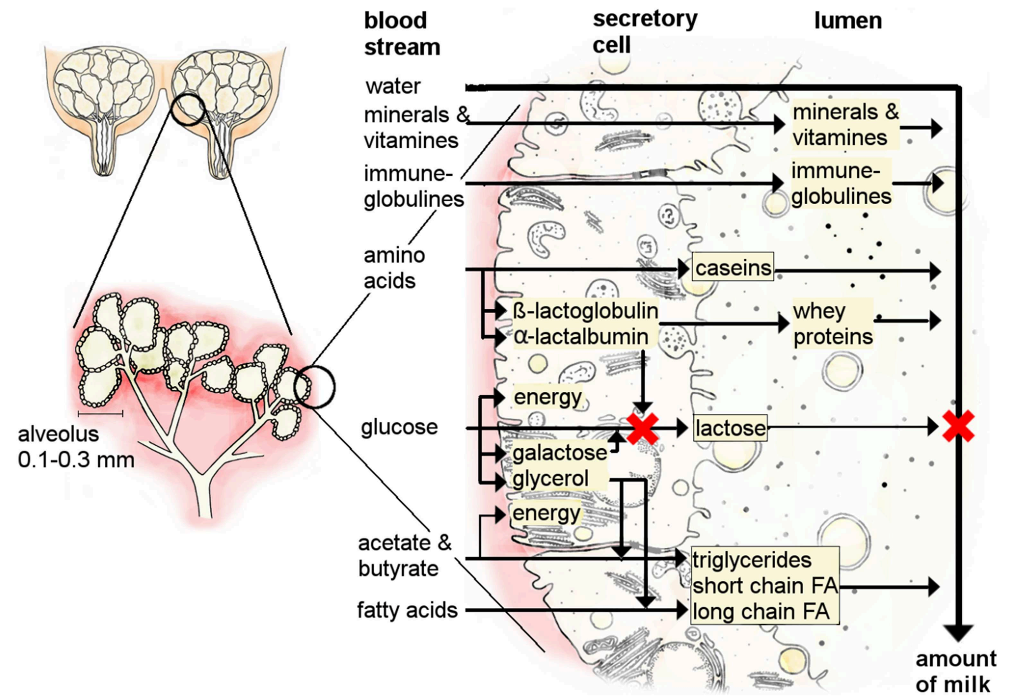

FIGURE 2 | The process of milk secretion in the udder of a cow (partially adapted from Wattiaux, 1996). Milk is secreted in the alveoli system of the mammary gland. Several substances can pass the cell membrane from the blood stream (water, minerals, vitamins, immune-globulins), whilst others need transporters and are produced in the secretory cells (proteins, fat, lactose).

Anantamongkol et al., 2010; Wickramasinghe et al., 2012). Substances such as lactose, proteins and fat have to be synthesized in the secretory cells from components such as glucose, amino acids, triglycerides, or fatty acids that stem from the dietary nutrients or body resources such as adipose tissues or skeletal muscles (**Figures 2**, **3**; Burgoyne and Duncan, 1998; Zhao and Keating, 2007; Bionaz and Loor, 2008b). Lactose is synthesized from blood glucose and galactose (synthesized from glucose) by a lactose synthase enzyme composed of galactosyltransferase and α-lactalbumin in the golgi complex of mammary secretory cells (**Figure 2**). The amount of glucose in the blood is regulated by energy intake, insulin and leptin (**Figure 3**; Li et al., 2010).

Proteins and fat are important for qualitative milk yield in terms of organoleptic properties of the milk and downstream industries such as cheese and butter production (Bailey et al., 2005; Bauman et al., 2006). Caseins, α-lactalbumin and β-lactoglobulin represent the main fraction of milk proteins. They are synthesized mainly from amino acids broken down from digested food and transported through the blood stream to the secretory cells (Burgoyne and Duncan, 1998). Milk fat is composed of triglycerides, long- and short-chain fatty acids which are partly synthesized in the liver or in secretory cells of the mammary gland from short-chain dietary lipids that are obtained from the rumen, and partly from mobilized fats from bodily fat depots (**Figure 2**; Bionaz and Loor, 2008b).

Lactation is coupled with changes in the activity of genes in the mammary gland but also in other organs. In the liver, fat and glucose synthesis is highly increased from pregnancy to early lactation to provide fatty acids and blood glucose for milk production (**Figure 3**; Bell and Bauman, 1997; Casey et al., 2009), whereas fat synthesis is decreased in adipose tissue and the expression of transporter genes for the uptake of blood glucose into somatic cells is reduced to ensure that nutrients are available for milk production (Bell and Bauman, 1997; Casey et al., 2009).

In conclusion, to understand the genetics behind a lactation cycle, a number of gene pathways need to be considered. These include genes regulating food intake and blood glucose levels; the digestion, absorption, and transportation of nutrients; the activity of the secretory cells in the mammary gland, liver, and adipose tissue; the synthesis of proteins and fat in the secretory cells; and the pathways which provide triglycerides, fatty and amino acids, transporter proteins, and transcription factors.

Genetics of Milk Production

The establishment of the *Bos taurus* genome assembly (Bovine HapMap et al., 2009), along with proteome and gene expression studies, have made it possible to estimate the number of genes involved in milk production, from mammogenesis to milk secretion. Between 6000 and 19,000 genes distributed across all 29 bovine autosomes and the X-chromosome have been reported to be differentially expressed during the lactation cycle, though not exclusively in the mammary gland (Lemay et al., 2009; Wickramasinghe et al., 2012). Thus, the genes predicted to be involved (directly or indirectly) in the regulation of milk production, account for between 25 and 75% of all predicted cattle genes (*Bos taurus* UMD 3.1-Primary Assembly, Zimin et al., 2009). Most

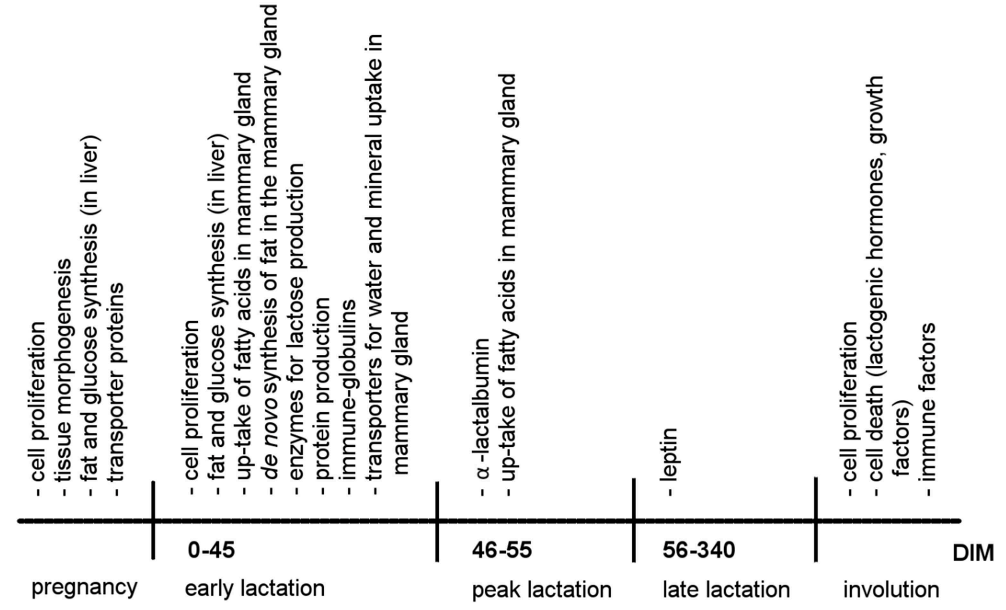

FIGURE 3 | Chronology of gene expression and physiological processes during a lactation cycle. DIM, days in milk.

genes contribute to pathways that directly affect economically important traits such as milk yield and composition. A multitude of genome-wide association studies (GWAS) using high density SNP chip data have previously been conducted to narrow down regions and identify causative genes that affect milk production traits (Cole et al., 2011; Strucken et al., 2012a; Buitenhuis et al., 2014; Raven et al., 2014). Whilst regions and potential genes with effects on milk production traits have been reported for almost all bovine chromosomes, repeatedly occurring genes are located on chromosomes 27, 6, 20, and 14 (Lemay et al., 2009).

Only around a dozen candidate genes have been consistently identified between studies and described more extensively with regards to their association with the main milk production traits (**Table 1**). The pathways through which these genes affect milk production traits depict the variety of processes that have to be considered (**Figure 4**). Genes like the *BDNF*, *FTO*, or *IGF1* impact upon food intake and thus nutrient and energy availability (Mullen et al., 2011; Zielke et al., 2011, 2013; Waters et al., 2012). Other genes such as *GHR*, *PRLR*, or *SPP1* affect growth, proliferation, and apoptosis of cells (Viitala et al., 2006; Khatib et al., 2007; Banos et al., 2008; Lu et al., 2011a; Rahmatalla et al., 2011), whilst *DGAT1* and *AGPAT6* are involved directly in triglyceride synthesis (Winter et al., 2002; Bionaz and Loor, 2008a; Strucken et al., 2010a; He et al., 2011). Of further note are the *casein* genes which encode the major fraction of milk proteins (Velmala et al., 1995). **Figure 4** provides an overview of those candidate genes and the pathways through which they affect milk production traits. To our knowledge, no genes affecting mammogenesis have been directly linked to milk production. Recently, Raven et al. (2014) included traits of the mammary system in a GWAS study which identified five regions on four different chromosomes with significant effects; however, a clear description of the phenotype (the mammary system) was lacking.

Only little is known in regards to time-dependent genetic effects causing a dynamic curve in dairy cattle but the next section summarizes the efforts and results made in this field.

Dynamic Genes in Animal Breeding Systems

Dynamic Association Studies

Whether a single marker for a candidate gene is used or thousands of indirect markers for a GWAS, finding associations between markers and a trait that displays dynamic expression over time can be difficult. The simplest solution may be to estimate associations over various time-points, i.e., treat each measurement as a separate phenotype. Automated milking systems could provide an accurate measurement of milk production for each day of lactation. However, this approach would mean that several hundred phenotypes would have to be analyzed. Further, whilst such measurements would provide daily milk yield, persistency cannot be estimated from a single time point. Ergo, daily measurements should not be treated as separate phenotypes. Therefore, appropriate phenotypic and genetic correlations have to be incorporated or repeated measurement analyses performed. Whilst daily measurements provide a highly accurate description of lactation performance, it might be computationally too time-consuming to be practically applied. Further, milking systems have still not penetrated the entire dairy sector and analyses solely relying on daily measurements would require additional methods to include animals with missing records. Most countries with national evaluation networks record milk production once

TABLE 1 | Major genes involved in milk production.

Gene	Chr.	Position (bp)*	Trait	References
LEPR (leptin receptor)	3	80,071,689–80,147,000	Milk yield Milk fat	Banos et al., 2008
LEP (leptin)	4	93,249,874–93,266,624	Milk yield Milk fat	Banos et al., 2008; Clempson et al., 2011
IGF1 (insulin like growth factor 1)	5	66,532,879–66,604,699	Milk yield Milk fat	Mullen et al., 2011; Waters et al., 2012
ABCG2 (ATP-binding cassette, sub-family G, member 2)	6	37,959,536–38,030,585	Milk protein Milk fat	Cohen-Zinder et al., 2005; Ron et al., 2006
OPN (osteopontin)	6	38,120,578–38,127,541	Milk yield Milk protein Milk fat	Leonard et al., 2005; Khatib et al., 2007
PPARGC1A (peroxisome proliferator-activated receptor gamma, coactivator 1 alpha)	6	44,854,113–44,960,533	Milk yield Milk fat	Khatib et al., 2007
Casein-Cluster (CSN1S1, CSN2, CSN1S2, CSN3)	6	87,141,556–87,392,750	Milk protein	Velmala et al., 1995; Kress et al., 2011
DGAT1(diacylglycerol O-acyltransferase 1)	14	1,795,425–1,804,838	Milk yield Milk fat	Winter et al., 2002; Strucken et al., 2010a
BDNF (brain-derived neurotrophic factor)	15	59,164,519–59,200,908	Milk fat	Zielke et al., 2011
FTO (fat mass and obesity associated)	18	22,118,201–22,541,540	Milk fat Milk protein	Zielke et al., 2013
GHR (growth hormone receptor)	20	31,890,736–32,064,200	Milk yield Milk protein Milk fat	Viitala et al., 2006; Banos et al., 2008; Rahmatalla et al., 2011
PRLR (prolactin receptor)	20	39,073,246–39,137,480	Milk yield Milk protein Milk fat	Bole-Feysot et al., 1998; Viitala et al., 2006; Lu et al., 2011b
PRL (prolactin)	23	35,105,135–35,113,750	Milk yield Milk protein Milk fat	Bole-Feysot et al., 1998
AGPAT6 (1-acylglycerol-3-phosphate O-acyltransferase 6)	27	36,212,352–36,228,987	Milk yield Milk fat	Bionaz and Loor, 2008a; He et al., 2011

Btau_4.6.1.-Primary Assembly.

a month. Assuming the lactation period of a cow lasts for 340 days, one record a month sums up to approximately 11 test-days. Because crucial changes such as peak yield occur roughly 6 weeks into the lactation cycle, one analysis every month could still give a fairly thorough picture of the lactation performance. However, analyzing 50k or 800k markers (the marker number of the most commonly used SNP-chip in dairy cattle at present) for thousands of animals would still take time.

Instead of using the measurements of the actual test-days, fewer parameters can be sufficient to describe an entire lactation. The profile of milk production, and its components, over the course of a single lactation has been described by various mathematical and biological functions (Pollott, 2004; Silvestre et al., 2009). Thus, using these mathematical lactation curve models provides a means of reducing the amount of time-points to a minimum of three curve parameters. These parameters describe the production curve through its properties such as slopes, apex (maximum), and level of production.

Such approaches are known as functional modeling in human genetics where it is mostly applied to map dynamic loci affecting disease traits using growth curves such as cubic splines (Hou et al., 2008; Li et al., 2009; Yang et al., 2009). In livestock research, a similar approach is known as the modeling of longitudinal or dynamic traits (Rodriguez-Zas et al., 2002; Suchocki and Szyda, 2011). In most livestock studies, the change in additive genetic variation over time was analyzed mainly for body weight and milk yield in dairy cattle, sheep, and goats (Lund et al., 2008; Roldan et al., 2008; Forni et al., 2009; Hadjipavlou and Bishop, 2009; Strucken et al., 2011). However, most of these studies used either no marker information or only a few markers on selected chromosomes to conduct their analyses.

The few results of time-dependent association studies in livestock reflect reported dynamic expressions of genes involved in milk production (Bionaz and Loor, 2008a; Verbyla and Verbyla, 2009) or add a time component to known but static effects of candidate genes such as the *DGAT1* gene or the region around the *casein* genes. The described effects of the *DGAT1* gene, with antagonistic impacts on milk yield and fat content, were shown to be detectable only after lactation day 40 (Strucken et al., 2011). This late effect points to a possible utilization of *DGAT1* in changing the persistency of milk production. Markers around the *casein* genes had strongest effects in early lactation (Strucken et al., 2012b), which is confirmed by the higher protein content in colostrum milk. Furthermore, investigations of the genes

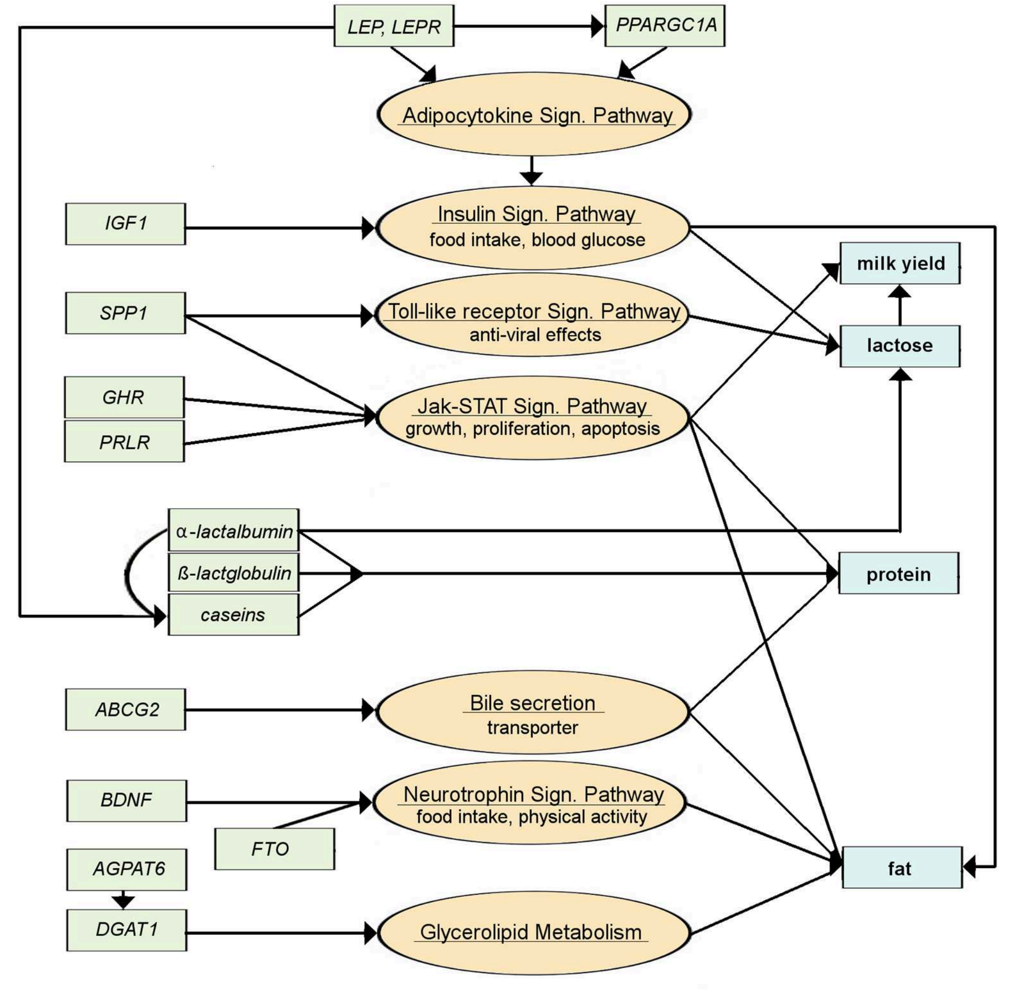

FIGURE 4 | Simplified pathways for major genes involved in milk production. Green boxes are genes, orange circles are the pathways the genes are involved in, blue boxes are the milk production traits that are affected (information is assembled from KEGG Pathway Database, 17.11.2014; http://www.genome.jp/kegg/pathway.html and literature review; for gene names, see **Table 1**).

surrounding trait-associated markers showed that a substantial number of genes with stronger effects in early lactation are involved in immune response and not directly in milk production (Strucken et al., 2012b). Even though those genes have no direct effect on milk production, immune-related genes could influence the productivity of the animal by supporting udder health in a time of high activity (Wheeler et al., 2012; Chaneton et al., 2013) and through effects on food intake (Greer et al., 2008; Laurenson et al., 2011). This adds another group of genes that have to be considered when genetic influences on milk production traits are analyzed.

In general, the highest variation in associated loci were reported for early and late lactation, suggesting that those time periods provide the best opportunity for alteration through breeding schemes. This would also serve the idea of decreasing peak production through a slower increase in early lactation and increase the persistency of production in late lactation. Furthermore, by analyzing marker associations over time, we are more likely to find genetic markers with small effects over the whole lactation but strong effects at a specific time-point as they are not masked by major candidate genes such as *DGAT1*. Thus, time-dependent analyses could aid in detecting the missing genetic variance that explains the observed phenotypic variation.

Finally, differences in genetic effects were not only found for different lactation stages but also between lactations, especially between the first and later lactations (Strucken et al., 2012a). These differences between the first and later lactations are also observed in phenotypic production curves (Schmidt et al., 1988). Even though most cows are in puberty and have reached a sufficient weight and size to support a pregnancy at the age of first mating, first parity cows are still growing and the mammary gland undergoes the required changes to produce milk for the first time (Taylor et al., 2003, 2004). Therefore, this ongoing development during the first parity is most likely the reason for the lower performance compared to later lactations.

Applications

In animal breeding, the ability of an animal to improve a trait in the next generation can be summarized using an estimated breeding value (EBV). The current standard for breeding value estimation is to include the animal's own performance records as well as the records of relatives, assuming that related individuals share a certain amount of genes with each other. In milk production, obviously a bull does not produce milk, and therefore its EBV is entirely dependent on milk production records of female relatives.

Because milk production is routinely recorded once a month in most countries, EBVs are based on these monthly test-day data. To account for the fluctuation of milk yield throughout a lactation, test-day models have been developed through the incorporation of appropriate lactation curve models (Misztal et al., 2000; Schaeffer et al., 2000; Swalve, 2000). Whilst some countries provide separate EBVs for persistency, most production EBVs are averaged over 305 days of lactation or even an average over several lactations. Therefore, the final selection decision is still based on a static value that makes it impossible to tell whether the animal had a high peak production or a good persistency. Though it should be easy for the national breeding evaluation centers to provide breeding values for certain time-periods (estimation equations implement lactation curve model), this would also increase the information output that needs to be handled and might even complicate the decision process about which animal should be used for mating.

One possible solution could be to include the shape of the production curve into the selection index and set a standard curve based on how much milk a cow can produce without inducing an energy deficiency under natural feeding conditions, and how much milk a cow should produce to be still profitable for the farmer. Based on such a standard curve, breeding values could be weighted according to their deviation from the standard curve resulting in a single EBV per animal.

A similar approach could be applied for genomically estimated breeding values (gEBVs) where the information of the genome-wide markers along with the production records of all relatives are included. gEBVs seem to be the way forward as they use the genetic constitution of the animal itself, and thus, what is actually inherited from generation to generation (Goddard and Hayes, 2007; Hayes et al., 2009; Hayes and Goddard, 2010). Nevertheless, gEBVs would require knowledge of either an optimal standard curve or the exact time-dependent genetic effects. Knowing the genetic effect of a marker enables us to simply genotype a selection candidate and sum up its genetic effects to calculate a gEBV, provided that the animals that were used to estimate the genetic effects are closely related to the selection candidate. If the actual causal mutation is known then family relations can be neglected.

Most of the reviewed studies on time-dependent genetic effects, applied a GWAS approach where the effects of each marker were estimated independently from all other markers. However, it is assumed that a quantitative trait such as milk production is shaped through the activity of many genes that might affect and even depend on each other. Thus, marker effects should not be estimated independently of all other markers in a study. A method which includes all markers at the same time has been termed Snp-BLUP, which is an extension of the original BLUP (best linear unbiased prediction) equation used to estimate the EBV of an animal (Goddard, 2009; Koivula et al., 2012).

Information obtained through dynamic GWAS or Snp-BLUP would make it possible to weight each marker according to its effects on the dynamic expression of the trait at different time-points, and thus provide a gEBV that includes the shape of the production curve. With the reducing cost of sequencing, causal genomic variants may be discovered and ultimately used in animal breeding to perform the most accurate selection possible.

Concluding Remarks

Milk production is a dynamic process and factors influencing this process occur as early as the fetal development. Whilst many physiological aspects of a dynamic milk production have been discovered, research on time-dependent genetic effects is still a wide open field. The animal breeding industry considers dynamic milk production by incorporating appropriate lactation curve models into their breeding value estimates to improve accuracy. Further, through an index of traits, breeders attempt to tackle the detrimental effects of a high milk production on other functional traits. However, if we assume that some of the negative issues arising from a high milk production can be overcome by altering the shape of the production curve, the impact of such an index on the actual dynamics of the lactation cycle are poorly understood. Since genetic and genomic tools are constantly developing with whole genome sequencing already being applied, our understanding of genes, their interactions and pathways will improve and direct causative mutations might be the target of future animal breeding programs. Understanding the time-dependent effects of genes and their variants is therefore an important field to study. Finally, whilst the dynamic of milk production is an obvious example, other time-dependent traits such as growth and weight gain, marbling, or onset of puberty could also benefit from a deeper understanding of the underlying dynamic of gene effects.

Author Contributions

EMS conceived of the topic and wrote the manuscript. YCSML and GAB advised and critically revised the manuscript.

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Admixture mapping of tuberculosis and pigmentation-related traits in an African–European hybrid cattle population

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Admixture mapping affords a powerful approach to genetic mapping of complex traits and may be particularly suited to investigation in cattle where many breeds and populations are hybrids of the two divergent ancestral genomes, derived from *Bos taurus* and *Bos indicus.* Here we design a minimal genome wide SNP panel for tracking ancestry in recent hybrids of Holstein–Friesian and local Arsi zebu in a field sample from a region of high bovine tuberculosis (BTB) endemicity in the central Ethiopian highlands. We first demonstrate the utility of this approach by mapping the red coat color phenotype, uncovering a highly significant peak over the *MC1R* gene and a second peak with no previously known candidate gene. Secondly, we exploit the described differential susceptibility to BTB between the ancestral strains to identify a region in which *Bos taurus* ancestry associates, at suggestive significance, with skin test positivity. Interestingly, this association peak contains the toll-like receptor gene cluster on chromosome 6. With this work we have shown the potential of admixture mapping in hybrid domestic animals with divergent ancestral genomes, a recurring condition in domesticated species.

Keywords: *Bos taurus*, *Bos indicus*, SNPs, admixture mapping, *Mycobacterium bovis*

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Introduction

Admixture mapping forms a powerful alternative approach to the ubiquitous genome wide association study design for the discovery of genes that contribute to complex traits. Rather than identifying individual SNP variants that show significant association with phenotype, it seeks to identify segments of chromosome in admixed populations within which ancestry from one parental group diverges from expectation (Smith and O'Brien, 2005).

This approach has several advantages. First, with appropriate trait-population combinations it displays high power. This is manifest most clearly when the ancestral populations to the admixed subjects are divergent in distributions of both genotypes and the targeted phenotypes. Second, although dependent on the generation time-depth since admixture, the SNP density required for a genome wide scan is greatly reduced compared to a typical GWAS experiment, often by over two orders of magnitude. However, a corollary is that genetic mapping resolution is comparatively low. Third, admixture mapping is relatively robust to genetic heterogeneity as a confounder of association (Greenspan et al., 2004; McKeigue, 2005; Winkler et al., 2010).

Although the advantage of admixed subjects for gene detection has been recognized for several decades (Chakraborty and Weiss, 1988), it is only in recent years with high throughput SNP genotyping that the full potential of this design has been realized. The mass human diaspora that proceeded from the age of exploration, e.g., European colonization of the Americas, has resulted in admixed populations of several 100 years establishment that are available for investigation. For example, a genomewide survey of African–American patients with chronic kidney/end stage kidney uncovered convincing evidence that the MHY9 gene is involved in the higher predisposition to the disease conferred by African ancestry (Kopp et al., 2008).

There has been little attention to admixture mapping as an approach in other organisms, despite the potential afforded by the prevalence hybrids of ancestral strains with divergence that exceeds that within humans such as in many domestic animals (Bruford et al., 2003). Domestic cattle offer a particular opportunity. Importantly, there are two major domestic genomes, those of *Bos taurus* and *Bos indicus* that were domesticated from distinct wild populations (Loftus et al., 1994). These genomes are estimated as having diverged 280 Kyr or 56,000 generations ago – about 20 times more generations than calculated in humans since the separation of African and European human ancestors (Murray et al., 2010). This divergence has resulted in marked heritable and important phenotypic differences that should be amenable to gene discovery and also in genomic divergence that facilitates easy genetic identification of chromosome ancestry. Moreover, the two taxa are interfertile and both ancient and recent admixtures are plentiful among world cattle herds, for example within the majority of African livestock (Hanotte et al., 2002). Lastly, cattle are assessed for a range of economically and medically important traits that have importance for both production and potentially assisting in understanding related human biology.

One such trait is bovine tuberculosis (BTB), a chronic respiratory infection caused by *Mycobacterium bovis*. This is an emerging veterinary problem in developing countries and there are several reports that it can also be zoonotic which has serious public health implication (Thoen et al., 2009; Michel et al., 2010; Firdessa et al., 2013; Müller et al., 2013). Ethiopia has the largest cattle herd in Africa, a majority of which is comprised of local zebu breeds but with increasing numbers of imported *Bos taurus* breeds and their hybrids. Susceptibility to BTB has been shown to have a heritable component in European cattle (Brotherstone et al., 2010; Richardson et al., 2014). Also, a comparative analysis of the genetic susceptibility patterns between *Bos taurus* and *Bos indicus* has some suggestion of differential disease risk (Collins-Schramm et al., 2002). Studies in the central highlands of Ethiopia, including regions where BTB is endemic, have shown the prevalence and pathology of the disease significantly skewed toward the *Bos taurus* (Holstein–Friesian) as compared to the local *Bos indicus* (Ethiopian Arsi zebu) cattle (Ameni et al., 2007). Both tuberculosis lesion severity and INF-γ test responses were higher for European *taurus* than zebu cattle (Ameni et al., 2006). BTB related traits have been the subject of both single gene and whole genome association investigations in cattle; SLC11A (NRAMP1) had been previously identified as a susceptibility locus in humans and several bovine studies show significant associations (Bellamy et al., 1998; Barthel et al., 2000; Kadarmideen et al., 2011). Two genome wide SNP array association studies in Holstein–Friesian national herds have given significant results but have, to date, have not been replicated (Finlay et al., 2012; Bermingham et al., 2014).

In this study we develop a low-density genome wide scan for ancestry in cattle and use this to genotype *taurus*-zebu hybrids that are of several generations depth of admixture. Their ancestral populations, Ethiopian Arsi zebu and European Holstein–Friesian, diverge in BTB susceptibility as well as in other phenotypes, including coat color. We first demonstrate the utility of our assay by locating with high significance two loci controlling coat pigmentation differences between these ancestral strains. One of these localization peaks includes the known trait gene MC1R. Secondly, we uncover suggestive evidence for a locus influencing the described divergence in tuberculosis susceptibility between parental strains, as assessed using data from skin testing of herds exposed to known BTB transmission under natural conditions. Interestingly, this peak includes, among other potential causative genes, the toll-like receptor gene cluster on chromosome 6.

The major focus of the project was BTB – the coat color trait was included as an incidental measurement but which nevertheless served as a useful proof of principle of application of the approach in this sample.

Materials and Methods

Sampling and DNA Extraction

Crossbred animals (hybrids) from Ethiopian field herds were used for the admixture mapping the owner of each animal was interviewed and the following information were recorded:, age, sex, physical condition score (Nicholson and Butterworth, 1986), pedigree of the animal, whether artificial insemination was used, a photograph on a side view with a study number, and address of the owner. Information was verified with the field veterinarians. Only hybrid animals with a breed history of at least two generations were included in the study. Similarly if artificial insemination was used (where generally the sire is Holstein–Frisian), the animal was removed from the study group, to prevent the inclusion of animals with less than two generations hybrid history.

This work was carried out as part of a large Wellcome Trustproject (see Acknowledgments) investigating TB in field situations in humans and cattle in Ethiopia. The CIDT test results from this larger work have been published in numerous publications, including four referenced here (Ameni et al., 2006, 2007, 2008, 2010). Ethical approval was obtained from the Institutional Review Board (IRB) of ALIPB and from a specially convened committee of Veterinarians.

A total of 10 ml of whole blood was collected from the jugular vein of 585 hybrid Holstein–Friesian/Ethiopian zebus. DNA was extracted from blood using the Archive Pure^{TM} DNA purification kit (5 PRIME GmbH) at the Armauer Hansen Research Institute (AHRI), Addis Ababa, Ethiopia. DNA concentration of each sample was quantified using the fluorescence method, Qubit^{TM}. A total of 400–700 ng of DNA was used for analysis.

The breeds used to determine which markers were informative (see SNP Mapping Set) were Ethiopian–Arsizebu (40), Boran (8), Holstein–Friesian from the Bovine Hapmap sample collection plus individuals collected in Ireland (56), Hariana (10), Sahiwal (8), Tharparker (7), plus Bovine Hapmap samples from Brahman (20), and Gir (20).

Phenotyping of the Hybrid Population (BTB Case/Control and Coat Pigmentation)

The hybrid animals were classified as "reactor" (case) or "non-reactor" (control) to tuberculosis infection using a single comparative intra dermal tuberculin test (CIDT). The test was performed via skin injection of purified protein derivatives (PPDs) which are crude extracts of *M. bovis* (PPD-B) and *Mycobacterium avium* (PPD-A). 0.1 ml of each PPD-B and PPD-A (2500 IU/ml, Animal Health Veterinary Laboratories Agency, Weybridge, UK) were injected into two different sites on the animal neck. The subject was classified as "reactor" (CIDT positive) if the skin thickness at the PPD-B site was higher than at the PPD-A site by at least 4 mm. In order to increase the sensitivity of the test without affecting the specificity, animals with a PPD-B site thickness greater than 2 mm were classified as "possible reactors" and were also included in the "reactor" group for the analysis. This was based on an extensive study in the Selalle region, Ethiopia (Ameni et al., 2008, 2010). The animals were classified as "non-reactors" if the skin thickness at PPD-B site was below 2 mm. Phenotypic coat color scoring for each sample was assigned using photographs taken in the field and using the scale of Hirooka et al. (2002); each animal was assessed for the presence of red coat color and a binary assignment given.

SNP Mapping Set

Selection of informative markers was carried out by first examining data from the Bovine Hapmap consortium (Gibbs et al., 2009). These markers include a substantial fraction discovered by resequencing a zebu (Brahman) and comparison to the Hereford sequence. SNPs from the Illumina 54001 SNP (Van Tassell et al., 2008) chip data were then added to cover areas of the genome where SNPs from the Hapmap set were missing or did not follow the criteria established. The following criteria were used to choose informative markers from both data sets: absolute allele frequency difference between European *Bos taurus* and *Bos indicus* of 0.6 and above, absolute allele frequency difference between African *Bos taurus* and *Bos indicus* of 0.6 and above and inter marker distance between two consecutive SNPs of on average 3.6 Mb (minimum and maximum distance of 0.1 and 13.9 Mb, respectively, depending on available SNP density) with the aim of even coverage across all autosomes (sex chromosomes were excluded). Furthermore, several additional SNPs from genomic regions of biological importance were added. Genotyping was carried out using the Illumina Golden gate assay and was performed at the Wellcome Trust Centre for Human Genetics, Roosevelt Dr., Oxford, UK.

Genetic Analyses

SNPs with missing genotype data in the cases and/or controls were removed. Poor quality SNPs and samples were filtered and removed using standard quality thresholds (Greenspan et al., 2004). In order to check the homogeneity of the cases and controls (reactor and non-reactor), EIGENSTRAT (Price et al., 2006) was used to verify that the admixed samples clustered in a position intermediate to the parental and outlying populations. For each individual a local and a genome-wide ancestry, indicated by the proportion of European *Bos taurus*, was estimated using ANCESTRYMAP (Greenspan et al., 2004) using a burn-in period of 100 iterations with 200 follow-on iterations. The stability of the result was monitored by increasing the burn-in period and follow-on iterations by a factor of 10. (1000 burn-in and 2000 follow-on iterations).

ANCESTRYMAP calculates individual ancestry estimates averaged across all individuals to identify genomic regions, where there is enhanced ancestry from one of the parental populations indicating the presence of an ancestry-associated gene nearby. For the binomial admixture scan a prior 30 risk model distribution, from 0.1 to 3.0, was tested for the TB admixture analysis. The overall association was calculated by averaging across all the models (Greenspan et al., 2004). The association between phenotypes and ancestry was quantified based on the outputs of two scores from ANCESTRYMAP. The first is a case-only statistic where a locus-specific score, LOD, is calculated as the log 10 of the ratio between the likelihood of the genotype data at the locus under the risk model and the likelihood of the genotype at the locus assuming that the locus is uncorrelated to the phenotype. A locus-specific LOD score >4 is considered as suggestive significance and > 5 as significant. In line with this calculation, ANCESTRYMAP provides an overall account for association scores by taking the averaged likelihood ratio for associations across all loci in the genome and summarizing evidence of a risk locus anywhere in the genome. In this case, a genome wide score >2 is taken as significant and a value >1 as a suggestive significance score (Greenspan et al., 2004). The second statistic used is the case-control score calculated by comparing the locus specific deviations in European ancestry in cases versus controls at each locus across the genome. The score is taken as a Z-score where if there is no phenotype association, the score is expected to normally distribute. The level of locus specific case-control statistical significance is taken as a Z-score >3 which correlates to uncorrected nominal $P < 2 \times 10^{-3}$.

Results

After quality control measures the final set of genome-spaced markers comprised 662 autosomal SNPs. The proxy parental samples for the admixture under examination were East African zebu Arsi and Boran breeds (48 samples), and European *Bos* *taurus* Holstein samples (56). The initial set of 585 Holstein–African zebu hybrid genotypes were reduced to 502 by exclusion of 67 samples with an estimated percentage of either East African zebu or European *Bos taurus* ancestry greater than 0.90 and an additional 16 samples due to low genotype call rates, suspected duplication or because they were closely related. The BTB trait admixture analysis was based on a final set of 341 cases and 161 controls and the coat color calculations featured 76 red and 406 not-red individuals.

Principal component analysis was carried out to ascertain population variation in relation to the parental populations. The plot in **Figure 1** shows the hybrid case-control animals in the center of the plot while the parental populations, the European *Bos taurus* (HOL) and the East African zebu (ETZ and BRN) cluster at alternate sides of the main distribution, as expected. Non-African zebu separate out with the African zebu on eigenvector 1 but form a clearly distinct cluster. The plot also shows that the hybrid animals have dominant zebu ancestry since most of the individuals are concentrated in close proximity to the zebu parental populations. BTB trait cases and controls are labeled separately and no visible sorting of these was evident.

Admixture Mapping for Coat Color

A total of 482 hybrids of *Bos taurus* and *Bos indicus,* of a depth of at least two generations, were used in the first admixture analysis using a binary coat color phenotype. For a single trait variable analysis all the samples were divided into two groups: 76 red, which included animals displaying light-red or red coat color and not-red, the 406 remaining animals. The ANCESTRYMAP analysis was performed using the local Ethiopian zebu (Arsi breed) as one of the ancestral populations. This breed has a variable coat color; animals are mostly dark brown but may also be found with a wide spectrum of black, red, and spotted derivate of colors. The second ancestral population is the European *Bos taurus*, Holstein–Friesian. This breed is majority black and white.

In **Figure 2** the Z and LOD-scores from the ANCESTRYMAP analysis are plotted. The former is based on a comparison of inferred ancestry levels between cases and controls. The latter is a complementary analysis which assesses locus ancestry levels versus those inferred genomewide for each individual. In both analyses the highest positive score centered in a region of chromosome 18 that contains the melanocortin 1 receptor (*MC1R*) gene (**Figure 3**). This gene is known to regulate the level of tyrosinase enzyme production which is responsible for the switch between phaeomelanin (red pigment) and eumelanin (black pigment) production. The dominant *MC1R* gene has been described as associating with black coat color and a recessive allele results in red coat color (Seo et al., 2007). The *Z*-score was a positive value indicating that the ancestral signal originates within East African zebu. The highest negative score achieved marginal significance (z-score = −3.074, LOD = −4.049) in both analyses and was located on chromosome 12. No genes known to be associated

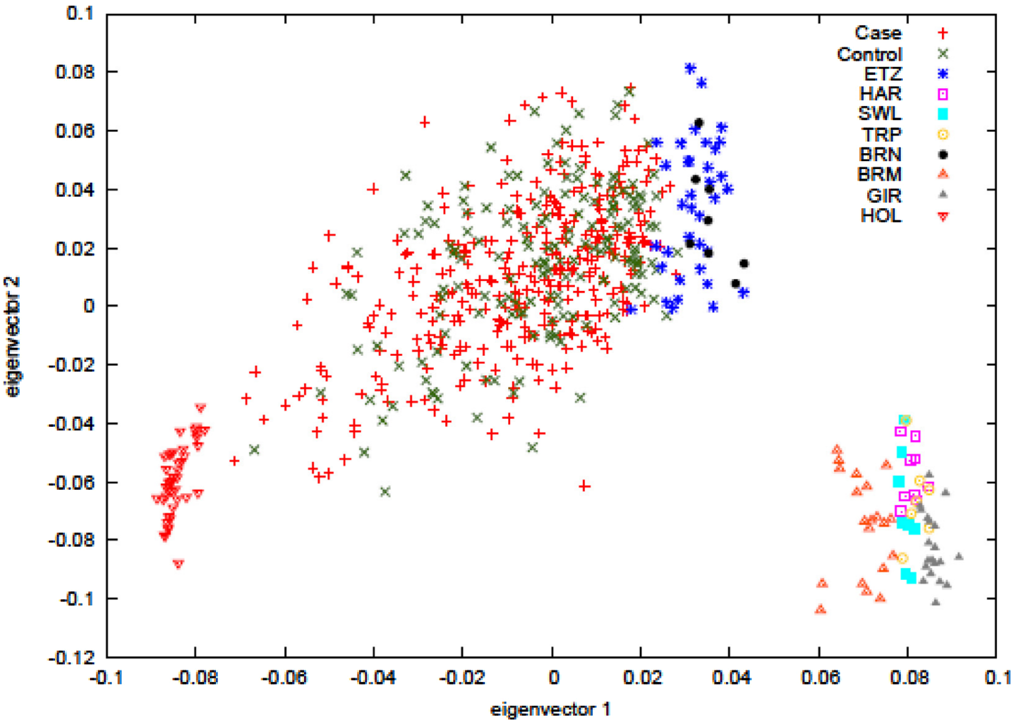

FIGURE 1 | Principal component analysis of hybrids cases (reactors) and hybrids controls (non-reactors). The analysis includes the ancestral populations of European *Bos taurus* (Holstein, HOL), East African zebu (Ethiopian zebu – ETZ and Boran – BRN), and non-African zebu (Hariana – HAR, Sahiwal – SWL, Tharparker – TRP, Brahman – BRM, Gir – GIR).

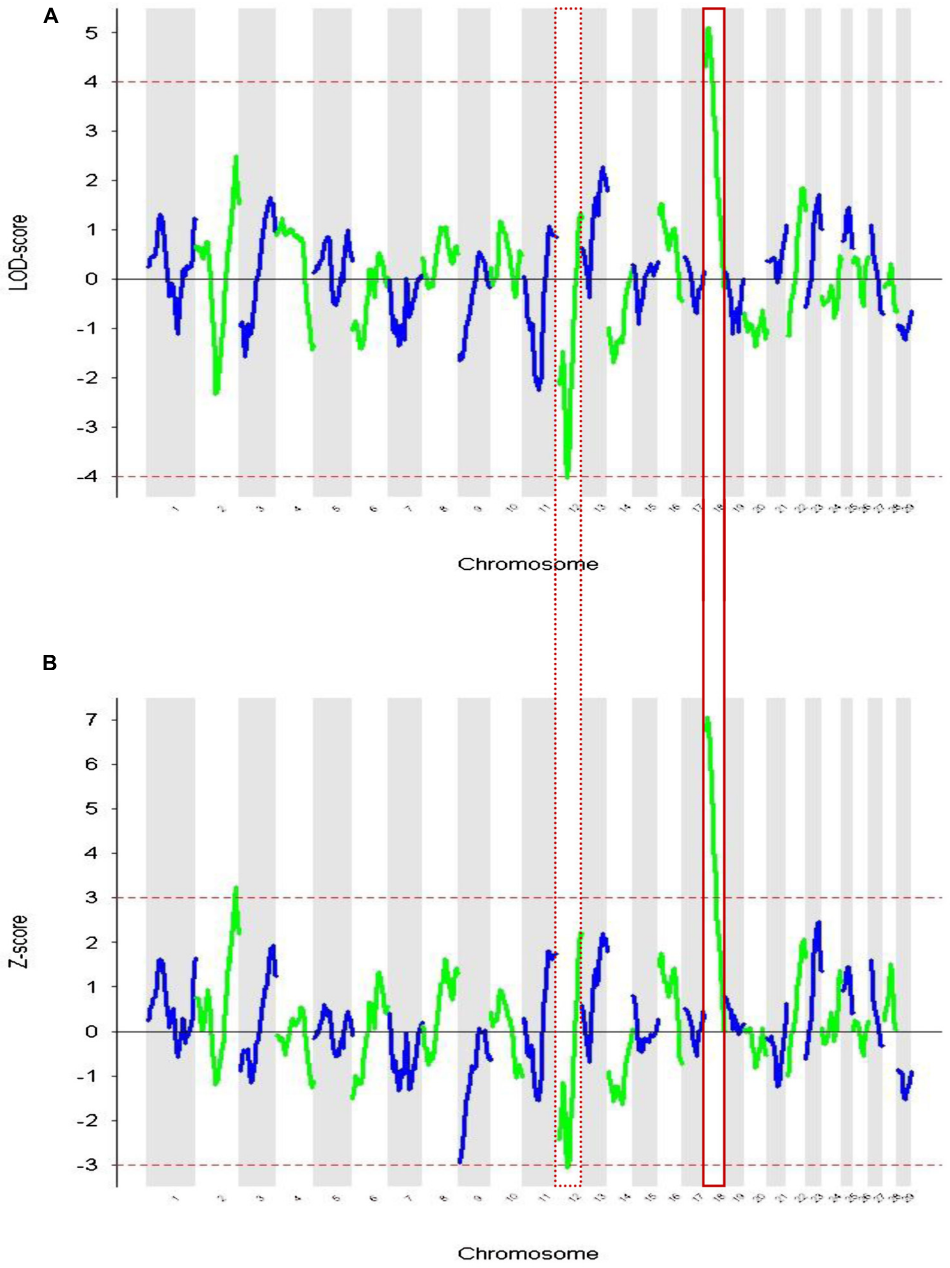

FIGURE 2 | Admixture mapping of coat color phenotype red vs. not-red for each chromosome. (A) Showing LOD score based on differences between local ancestry components vs. genomewide levels. **(B)** Plotting the *Z*-scores derived from case-control comparisons. Chromosome 12 and 18 are highlighted because they show significant values in both analyses.

with coat color phenotypes were identifiable within this peak region.

Genomewide Ancestry Association with Tuberculin Positivity

The association between overall genome ancestry and tuberculin reaction was initially tested; **Figure 3** plots the LOD scores associated with risk models ranging from 0.1 to 3-fold increased risk for European *Bos taurus* (Holstein) ancestry. These values are averaged across the genome and correspond to the increase in risk with addition of one copy of a *Bos taurus* ancestry allele. In effect this model tests the association of genomewide European ancestry with tuberculin reaction. The maximum log-likelihood ratio (LOD) was 4.04 for a risk value of 1.7. The average LOD value over each of the risk models considered was 3.17. This overall risk model analysis gives significant evidence of association between European *Bos taurus* ancestry and tuberculin positivity.

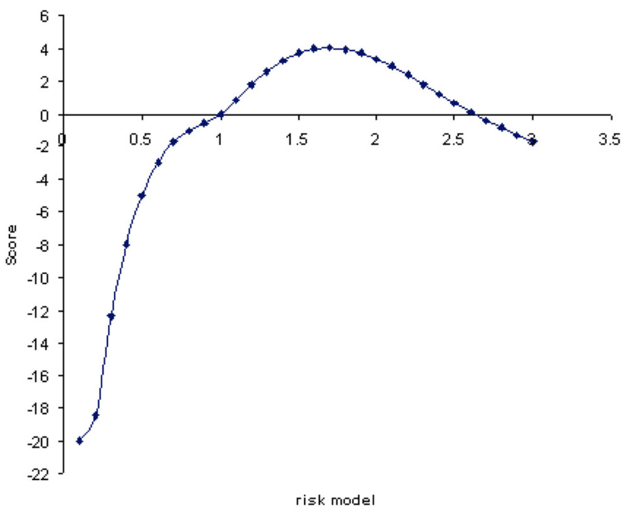

FIGURE 3 | ANCESTRYMAP risk model (*x*-axis) plotted vs. genomewide average LOD scores. The maximum likelihood risk model is 1.7 with a genomewide score LOD of value 4.04 (*y*-axis). The average LOD score for all risk models is 3.17.

Genome Scans for Association with Tuberculin Positivity

As with red coat color, we implemented two approaches in order to search for genome regions associated with TB susceptibility. First, inferred ancestry at each position was compared in 341 CIDT skin test positives (cases) and 161 test negative controls from the hybrid herds, with 48 East African zebu and 56 European Holstein genotypes used as parental reference samples. Second, inferred ancestry at each position was considered versus a genomewide average for case samples without reference to the control genotypes. These are two non-independent approaches of different power and propensity to false discoveries. We consider only signals that appear with both methods.

These admixture mapping scans are plotted for genome position in **Figure 4** with panel A showing LOD scores for the case only analysis and panel B indicating case control comparisons assessed as *Z*-scores. The significance threshold of $Z = 3.0$ and the suggestive significance level of LOD = 4.0 are indicated, respectively. In the case-control comparison, the only significant association found was on chromosome 6 for the marker BTA76573 with a *Z*-score value of 3.11 which corresponds to a nominal $P = 1.8 \times 10^{-3}$ (**Table 1**).

This locus also has a strong suggestive peak signal for the case only analysis with a LOD score of 4.65. The second highest *Z*-score was on chromosome 5 for the marker BTA149284 (*Z*-score = 2.83; $P = 4.6 \times 10^{-3}$); however, here the LOD score for case only analysis was not significant (**Table 1**). Within the case only analysis the highest signal observed was for the marker rs29019760 on chromosome 11 (LOD = 6.87), but the value for the case-control comparison analysis was well below significance (*Z*-score = 1.59; **Table 1**). No other LOD score peaks have corresponding case control *Z*-scores with any support for significance.

The region in chromosome 6 associated with the single locus (BTA76573) that showed support for association in each analysis was examined to list possible candidate genes for association with susceptibility. The Bos_taurus_UMD_3.1.1/bosTau8build of the bovine genome data (UCSC genome browser; http://genome.ucsc.edu/) was used to extract genes from the associated region using a one LOD interval (Lander and Botstein, 1989). The list of genes harbored in the candidate region in chromosome 6 is presented in **Table 2**. The region contains the cluster of toll-like receptor genes *TLR1*, *TLR6*, *TLR10,* and the *RHOH* gene. TLRs are important in bacterial pattern recognition and are known to be cellular receptors that play pivotal roles in host innate immune responses (Ryffel et al., 2005; Khor, 2009). RHOH has a role in the development of T cell lymphocytes via modulation of T cell receptor signaling (Wang et al., 2011).

Discussion

Admixture mapping in humans has had marked success in recent years and displays high power. For example, a sample size of less than 500 was sufficient to effectively scan an African–American population where the differential risk due to ancestry was ~1.6 (Smith et al., 2004). Such a New world admixture has an average time depth of 10–13 generations and requires ~2500 markers for a genomewide screen.

Admixture has been a major theme in bovine genetic research (Bradley et al., 1996; Hanotte et al., 2002; Freeman et al., 2006; Berezhnoy et al., 2009; Gibbs et al., 2009), where the two ancestral genomes result from separate domestications of divergent wild populations in the Near East and Indus Valley regions. The genetic distinction between these bovine genomes greatly exceeds any observed between modern human populations and rather, is more akin to that between *Homo sapiens* and archaic *Homo* species (Canavez et al., 2012). Consequently, the availability of markers with strong parental frequency differential is high, facilitating the identification of ancestral origins of genomic regions. Also, genetic divergence is matched by phenotypic difference as different ecologies, domestic breeding and disease challenge histories have led to important trait differences between *Bos indicus* and *Bos taurus* breeds. The former predominate in arid and tropical regions and the latter in temperate climates. The two genomes have several hybrid zones which range in time depth from those potentially at the dawn of herding in West Asia through those from several 1000 years-old migrations of Asian cattle to Africa to recent deliberate crossbreeding for production (Hanotte et al., 2002; Berezhnoy et al., 2009). In recent decades a common practice has been to improve productivity by crossing exotic European high performance stock with local cattle in many regions, including East Africa.

We sought to exploit the population structure of a 3–4 generations deep admixture of European Holstein and local Arsi zebu cattle from the central highland region of Ethiopia where BTB is prevalent. Recently admixed populations have higher levels of admixture generated linkage disequilibrium compared to ancestral populations (Falush et al., 2003; Halder

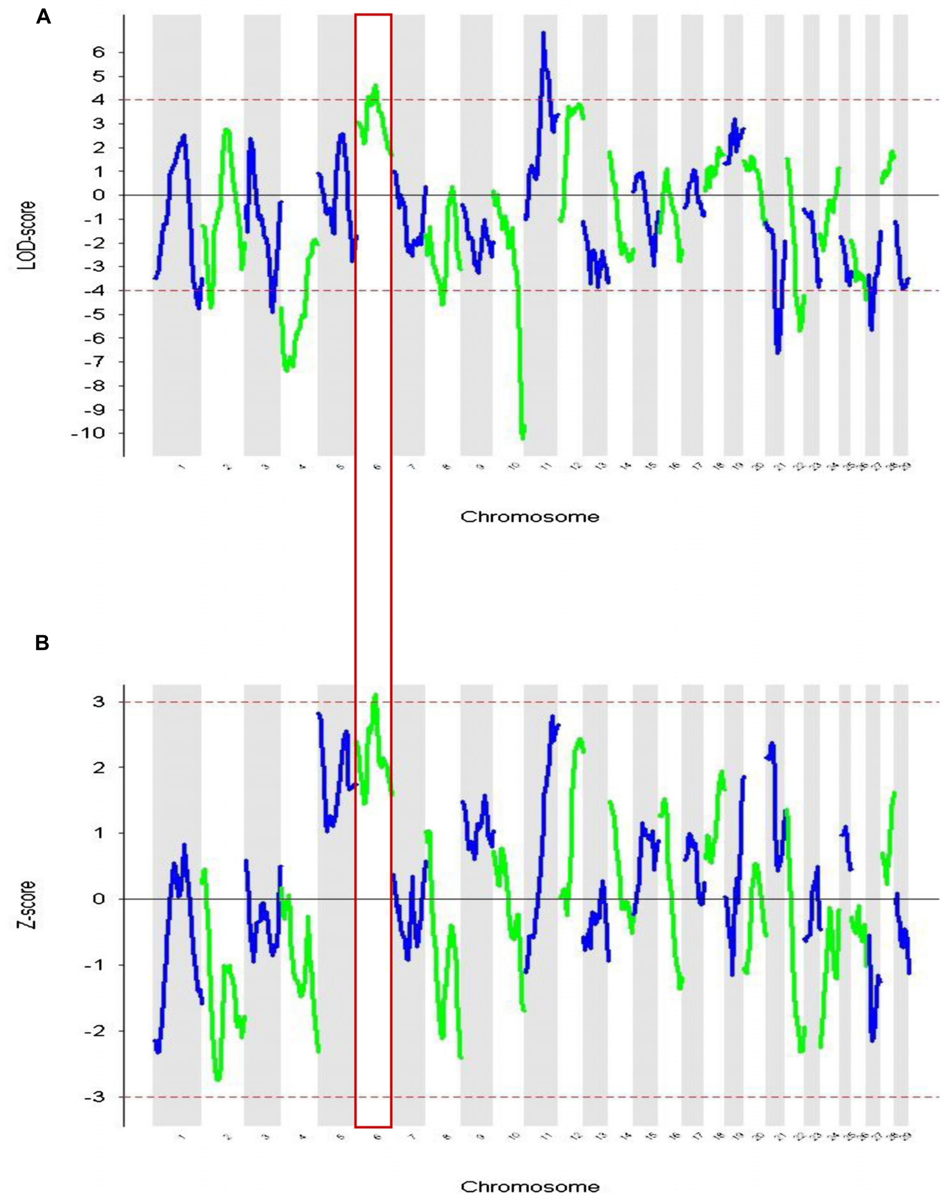

FIGURE 4 | Admixture mapping of cases vs. controls for each chromosome. The association of comparative intra dermal tuberculin test (CIDT) positivity with ancestral origin is shown. **(A)** Cases only analysis (LOD) and **(B)** case-control score (*Z*-score). Chromosome 6 is highlighted and has significant values in both analyses.

TABLE 1 | SNPs showing the strongest genetic background in the tuberculin positivity association analysis.

Chromosome	Marker	Position (bp)	LOD	*Z*-score	OR (95%CI)	*P*-value
5	BTA149284	2436485	0.94	2.83	0.75 (0.49–1.16)	4.6×10^{-3}
6	**BTA76573**	**65162299**	**4.65**	**3.11**	**1.89 (1.23–2.88)**	$\mathbf{1.8 \times 10^{-3}}$
11	rs29019760	64371895	6.87	1.59	2.59 (1.68–3.99)	1.70×10^{-5}
12	BTA152656	35296048	3.77	0.12	1.81 (1.18–2.78)	6.79×10^{-3}
19	BTA133013	35619640	3.23	0.03	1.96 (1.27–3.00)	2.19×10^{-3}

"Marker "is the SNP identification, "Position" is the position of the SNP on the correspondent chromosome, "OR" is the odd ratio at 95% confidence interval. The marker in chromosome 6 is highlighted, being the only one with both LOD and Z-score with significant values.

TABLE 2 | Genes in the one-LOD interval in chromosome 6 with significant LOD and *Z*-score values.

Chromosome	Marker	Position	Upper–lower boundary	LOD	*Z*-score	Genes
6	BTA76573	65162299	53432843–65162299	4.65	3.11	C6H4orf19, RELL1, PGM2, TBC1D1, KLF3, T**LR10, TLR6, TLR1**, TMEM156, WDR19, KLB, RPL9, LIAS, UGDH, SMIM14, UBE2K, **RHOH**, CHRNA9, RBM47, APBB2, UCHL1, LIMCH1, TMEM33, BEND4, SHISA3, ATP8A1, HTATSF1, KCTD8, YIPF7, GUF1, GNPDA2

"Marker" is the SNP, "Position" is the base pair position of the marker, "Upper–lower boundary" is the upper and lower limits of the gene positions associated with the SNP. The genes highlighted are discussed in the text.

and Shriver, 2003; Hoggart et al., 2004) and this, combined with the efficiencies from ancestral divergences allowed us to design a genomewide admixture mapping screen using only 662 highly informative markers with a high ancestral frequency differential and 502 hybrid test subjects.

As a proof of principle we first mapped the red coat color trait, assessed from visual inspection of subject photographs; the red phenotype is absent from the European parental strain and segregates in the local unimproved cattle. This clearly demonstrated utility of the approach, with a strong significant likelihood peak, confirmed in alternate case-control and case only analyses, over the region with the MC1R locus. This gene has been shown to segregate with coat color and is associated with red pigmentation in a number of mammals, including humans. A second peak on chromosome 12 is less strongly supported result and does not correspond to a known pigmentation locus (Hu et al., 2007). Also, chromosomal resolution is low, of the order of several maga base pairs, as would be expected from a shallow generational history of admixture.

Bovine tuberculosis is an emerging veterinary and public health problem in the developing world. Previous studies reported that crossbred animals in the current study area have intermediate level of tuberculosis prevalence and that European cattle (Holstein) were at least two times more susceptible than the local breeds (Ethiopian zebu; Ameni et al., 2007). Using the same subjects we carried out whole genome admixture mapping to search for genomic regions associated susceptibility in hybrid animals using the CIDT test as a binary trait. This skin test is the standard immunodiagnostic procedure used for the identification of BTB infected cattle. An initial analysis established significant evidence for association between CIDT positive reactions and overall genome levels of *Bos taurus* ancestry. A genomewide scan showed several positions that gave significantly trait-associated levels of one or other parental strain ancestry in either the case only or case-control analyses. However, only one peak was replicated in each that centered on marker BTA76573 on chromosome 6 with a regional excess of Holstein ancestry in cases relative to controls and also relative to the genome average.

Interestingly, this chromosome 6 peak harborsa TLR gene cluster of potential importance to *Mycobacterium* infections. The central roles of TLR1, TLR6, TLR10 in innate immunity are well documented (Heldwein and Fenton, 2002; Reiling et al., 2002; Heldwein et al., 2003; Doherty and Arditi, 2004; Korbel et al., 2008; Möller et al., 2010; Liping et al., 2012). They are part of the Toll gene family that is involved in bacterial pattern recognition (pathogen associated molecular patterns, PAMPs) including BTB and initiate the modulation of an innate immune response (Quesniaux et al., 2004; Möller et al., 2010). Mutations have been implied to confer either resistance or increased susceptibility to infectious diseases in humans (e.g., invasive bacterial infections; Coats et al., 2003), human tuberculosis (Selvaraj et al., 2009; Bryc et al., 2010), and malaria (Corr and O'Neill, 2009) specific to the binding spectrum of the TLRs involved (Khor, 2009). Importantly Sun et al., 2012, in a single gene test also found a significant difference between TLR1 allele frequencies between BTB-infected and non-infected Chinese Holstein cattle cohorts (Sun et al., 2012). However, we caution that the mapped interval in our study is wide – a consequence of the recent admixture of the subjects – and contains multiple other genes that could be considered candidates (**Table 2**).

Prior mapping work for BTB susceptibility in cattle has identified association with the SLC11A1 locus (formerly named NRAMP1) including in African cattle, however, this genome region showed no signal of note in this present study (Barthel et al., 2000; Kadarmideen et al., 2011). Additionally, several genome regions identified as candidates in genome wide association studies of BTB traits in British and Irish herds showed no correspondence here (Finlay et al., 2012; Bermingham et al., 2014). These disjunct results may not be surprising given that the present study is designed to detect variants segregating between zebu and European cattle breeds which are likely different to those that segregate within European herds. Also, scans for tuberculosis susceptibility in humans have identified and replicated fewer loci than for other equivalent genome wide studies of infectious diseases; it may be that genetic effects are made up of many segregating polymorphisms which are each of small contribution due to strong and sustained selective pressure by this widespread pathogen (Curtis et al., 2015).

In summary, we have used a genome wide marker set chosen for high allele frequency divergence between the two genomes segregating in modern cattle typed in a hybrid animal sample to conduct admixture mapping on two traits: susceptibility to tuberculosis and coat color pigmentation. Both approaches give significance peaks that correspond with known candidate loci: MC1R for pigmentation and the TLR cluster on chromosome

6 for BTB susceptibility. This work is a first illustration of the potential of this approach in domestic animals which may have wide and efficient applicability given the prevalence of divergent ancestral genomes and their hybrids in the most important domesticates.

Acknowledgments

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fgene.2015.00210/abstract

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Genetic selection for temperament traits in dairy and beef cattle

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Animal temperament can be defined as a response to environmental or social stimuli. There are a number of temperament traits in cattle that contribute to their welfare, including their response to handling or milking, response to challenge such as human approach or intervention at calving, and response to conspecifics. In a number of these areas, the genetic basis of the trait has been studied. Heritabilities have been estimated and in some cases quantitative trait loci (QTL) have been identified. The variation is sometimes considerable and moderate heritabilities have been found for the major handling temperament traits, making them amenable to selection. Studies have also investigated the correlations between temperament and other traits, such as productivity and meat quality. Despite this, there are relatively few examples of temperament traits being used in selection programmes. Most often, animals are screened for aggression or excessive fear during handling or milking, with extreme animals being culled, or EBVs for temperament are estimated, but these traits are not commonly included routinely in selection indices, despite there being economic, welfare and human safety drivers for their. There may be a number of constraints and barriers. For some traits and breeds, there may be difficulties in collecting behavioral data on sufficiently large populations of animals to estimate genetic parameters. Most selection indices require estimates of economic values, and it is often difficult to assign an economic value to a temperament trait. The effects of selection primarily for productivity traits on temperament and welfare are discussed. Future opportunities include automated data collection methods and the wider use of genomic information in selection.

Keywords: temperament, animal welfare, genetic variation, animal personality, genetic correlation

INTRODUCTION

Genetic improvement, including selection between breeds, crossing and within-breed selection, is widely used in farm livestock and has led to dramatic changes in performance in dairy and beef cattle over the last 50 years or so (e.g., Simm, 1998). Historically, most emphasis has been on traits that are most directly associated with profitability, and most easily measured, such as milk yield or body weight. However, selection between or within breeds for a broader set of traits, including health and "fitness" traits, is becoming more widespread as producers realize that productivity can only be maintained or improved with a more holistic view of animal performance. Reproduction, longevity and health traits are used in a number of breeding programmes for dairy and beef cattle, and there is growing interest in behavioral traits associated with animal welfare and ease of management. Temperament traits such as fearfulness or aggressiveness are important to consider as they affect how the animal responds to the husbandry and handling conditions on the farm and during procedures like transport. The aim of this review is to determine what progress has been made in the steps in the chain from trait definition through to the use of these traits in selection, including the recent opportunity for genomic selection. We also review the research that has investigated associations between temperament traits and productivity, health and reproductive traits to determine whether selection for these traits may be altering temperament indirectly.

WHAT IS TEMPERAMENT?

Farmers and others involved with the keeping of cattle and other livestock are well aware that there are differences between individual animals in their behavioral response to alarming or challenging situations. Furthermore, individuals are often consistent in the way they respond when the challenge is repeated. In cattle, the magnitude of response, and the difference between animals are of most importance to humans in situations that involve human interaction, such as where animals are handled, moved or milked. Some animals are calm and docile, while others are distressed and struggle to escape. Animals may also show consistency in their response in other situations, such as response to a new-born calf, and aggression or affiliation toward herd-mates.

This observed consistency of response within the animal, and the variation shown between individual animals or groups of animals, has historically been given a number of different labels, depending on whether the user is from a psychological, farm livestock or behavioral ecology background. In human psychology, it is known as personality, while in behavioral ecology the term "behavioral syndrome" is used to describe differences in clustering of traits between animal populations. In animal husbandry settings, the term "temperament" is largely used. In cattle, temperament is often described as an animal's response to handling or forced movement by humans (Tulloh, 1961; Burrow, 1997). This definition appears to have come from the terminology that farmers use to describe the way their cattle behave during handling (e.g., Hassall, 1974, a paper from a beef producer). It is also similar to the term "disposition" used in North America (Beef Improvement Federation Guidelines, 2010). This human-focussed definition of temperament has been used broadly across the cattle sector, particularly in beef cattle. A number of authors have used the term "temperament" with a situation "specifier" to describe the context (e.g., Brown, 1974 uses the term "maternal protective temperament"). Thus the term "handling temperament" can be used to differentiate the response from other contexts. The use of terms such as "maternal temperament" and "aggressive temperament" or simply a descriptor term such as "aggressiveness" and "sociability" are found in studies that consider consistency in the animal's response in contexts other than handling (Brown, 1974; Kilgour and Dalton, 1984; Reale et al., 2007; Gutierrez-Gil et al., 2008; Gibbons et al., 2009a, 2010).

WHY IS TEMPERAMENT IMPORTANT?

The temperament traits that have received most attention are generally those that have adverse production, welfare or human safety consequences. The foremost of these is handling temperament, and the impacts of poor temperament on farm management efficiency and animals has been a key driver for many studies (e.g., Burrow, 1997; Barrozo et al., 2012). A beef animal that responds to confinement in a chute, weigh crush or handling race by struggling violently and trying to escape is at a higher risk of injury to itself, human handlers and other animals than an animal that responds calmly (Voisinet et al., 1997a). This type of animal is also more likely to make the process of handling a group of animals for weighing or drafting much slower and less efficient. A number of studies have shown that handling temperament is also linked to growth, feeding efficiency and meat quality in beef cattle. Understanding the extent of this association has driven a great deal of research that will be discussed below. For dairy cattle, a calm response to the milking procedure is important both to maximize the efficiency of the milking process and to minimize the residual milk volume. Docility in dairy cattle at milking and during handling is a trait that has been under selection informally and formally for generations, so extreme responses are rare. However, the problems created by an animal that is not easy to handle and milk mean that "dairy temperament" (which is measured as strength of response to the milking procedure) has been investigated and is still part of many dairy breeding programmes worldwide (Interbull:www.interbull.org/ib/geforms).

There are other temperament traits that have received less attention in the literature, but are important from an animal welfare or human safety standpoint. Maternal aggressiveness, where a dam shows defensive aggressiveness toward any human or animal attempting to interfere with her calf, is a trait that clearly had evolutionary advantages for wild animals, and still does in some extensive production environments. However, when this aggression is directed at stockworkers or members of the public entering grazing fields, it clearly becomes much more problematic (Turner et al., 2013). Other traits that are important for welfare include resource-based aggression, where an animal shows aggression toward another when in competition for a resource such as feed or water, and social motivation or sociability, which is the willingness to be in close proximity to group-mates.

TRAIT DEFINITION AND MEASUREMENT

Given the potential adverse effects of excitable temperament on human safety and handling efficiency, the use of selective breeding to improve temperament is important. A number of steps must be taken to enable selection to take place (**Figure 1**). Firstly, the trait (in this case a behavior or response) must be defined, which typically includes a definition of the context in which it is important. The next step is to devise a measurement system so that the trait can be assessed in a rapid, quantifiable and reliable way by non-scientists, and then to validate it against other measures of the trait if possible, so that the chosen measure accurately characterizes the response. This measure can then be used in a number of ways. It can be used as a "screening" tool, such as when individual animals with poor scores for a temperament trait are culled or not considered for breeding, or the measure can be used as part of a genetic improvement programme. This section will investigate the progress with regards to trait definition and measurement.

HANDLING—BEEF CATTLE

Fearful or excitable responses may be expressed by animals in many novel or challenging contexts, such as during interactions with other animals or when entering a new field or pen, but it is largely during handling that this characteristic becomes a problem. A fearful response to handling manifests itself in a variety of ways. Animals may struggle, show agitated movements, attempt to escape, vocalize, show increased respiration rates, defaecate, show changes in their ear, head and tail positions and facial expressions and be more or less motivated to move away from the handling area or handler. The challenge is to find a scale or measure that adequately represents these varied responses. In beef cattle, there are some very well established assessments: flight speed or flight time, chute (known as a crush in Australasia/Europe) score and the docility score. These have sometimes been grouped into restrained and non-restrained categories (Burrow, 1997). Restrained tests are primarily those assessing the response to restraint in a handling chute, confinement in a pen or raceway, or alternatively measuring the response to that confinement by assessing the flight time or speed to move away from the place of confinement. Unrestrained tests are those in which the animal is not confined, but the animal's response to being approached, moved or handled is scored. These unrestrained tests are also characterized by more directly measuring the response to proximity to a human, whereas the restrained tests may measure the response to physical restraint as well as the proximity to humans. The main tests are described below.

Flight speed/time

The flight speed or flight time assessment was originally used by Burrow et al. (1988) and has been widely used by groups in

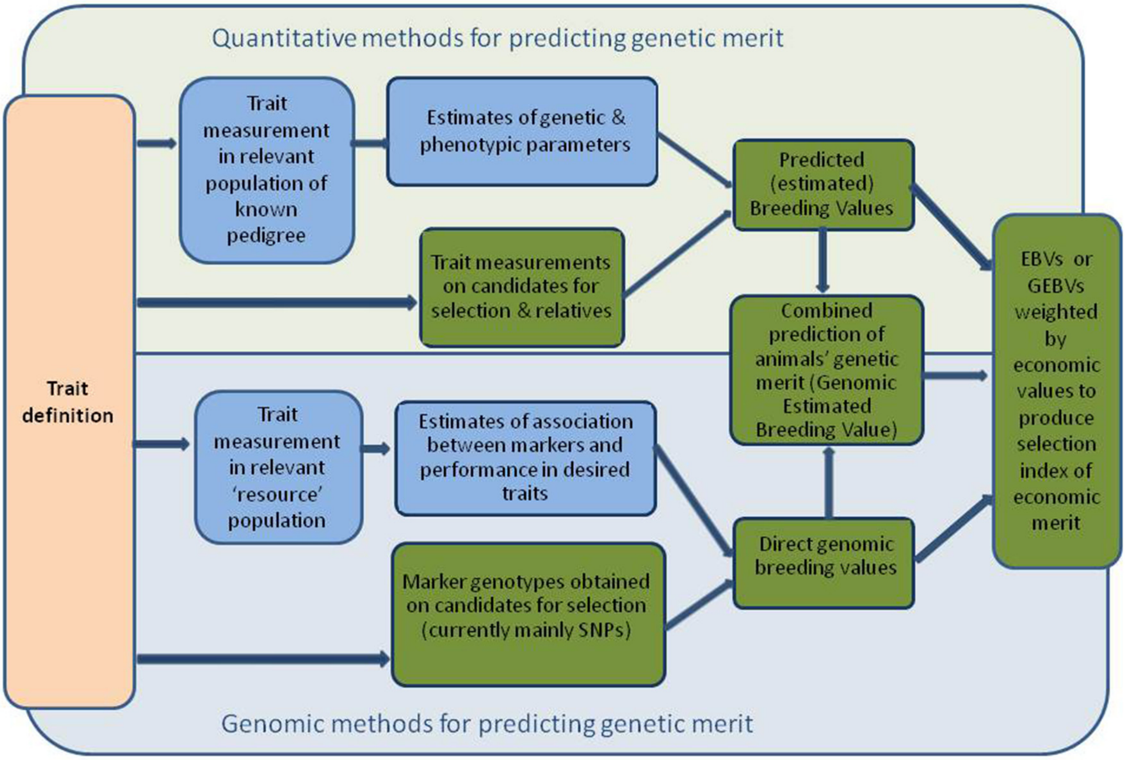

FIGURE 1 | Diagram showing sequence of process from trait definition to estimation of breeding values or genomic breeding values, and ultimately to GEBVs. Blue fill indicates that these are processes required at the initiation of a breeding programme and are updated periodically. Green fill indicates routine processes on each cohort of candidate animals for selection.

Australia and elsewhere. The assessment typically takes place as part of a routine weighing or handling procedure, where the animal is held in a handling system, such as a race or chute. Once the procedure is complete, the animal is released from the chute. The time it takes to cover a set distance along a raceway is calculated. This distance is typically short to capture the immediate response to release (e.g., 1.7 m: Burrow and Dillon, 1997; Cafe et al., 2011b; 1.83 m: Curley et al., 2006a). This can be presented as a velocity (e.g., "exit velocity"; Curley et al., 2006a) or as a "flight time" for a set distance (e.g., Fell et al., 1999).

Chute test

The chute test assesses the strength of response to confinement, whilst the animal is inside the chute. It is made on a categorical scale (typically 1–5), with qualitative or descriptive definitions given to states of increasing agitation, from no response, docile or calm through to vigorous, wild or violent response (e.g., Tulloh, 1961; Hearnshaw et al., 1979; Grandin, 1993). Similar categorical scoring systems have been used to quantify the response to confinement in handling races or pens (e.g., Fordyce et al., 1985).

Docility test

The main type of unrestrained test is a "docility test" in which the animal is separated from its group mates and moved to another pen. After a short period, the handler tries to drive the animal to a corner of this pen and hold it there for a predetermined period of time without physical aids. The responses to all parts of the test are integrated into a single score, but scores for the component parts can also be analyzed (Boivin et al., 1994; Le Neindre et al., 1995).

Some authors also score response to human approach in a pen on a categorical scale (e.g., King et al., 2006). Similar to this is an assessment of flight distance, which is the distance at which an animal starts to move away from an approaching human (Fisher et al., 2001). This is similar to the approach/avoidance distance assessments used in dairy cattle (Waiblinger et al., 2003; Gibbons et al., 2009b).

Animal responses to each of these measures of temperament have been shown to be repeatable over time (e.g., Hearnshaw and Morris, 1984; Grandin, 1993; Burrow and Dillon, 1997; Gibbons et al., 2009b; Turner et al., 2011). It is of interest to understand whether these different tests measure the same underlying trait. A number of studies have found a significant relationship between the measures. In beef cattle, flight speed and chute test score have been found to be significantly moderately correlated (e.g., Fell et al., 1999; Olmos and Turner, 2008; Hoppe et al., 2010; Cafe et al., 2011b) and positive correlations between chute score and flight speed, and chute score and docility have also been shown (Turner et al., 2011). Grignard et al. (2001) found a significant relationship between the docility test and the chute test in Limousin cattle, with and without a human present in front of the chute. Additionally, Curley et al. (2006b) found a moderate relationship between chute scores and response to confinement in a pen. These relationships are not found universally; others have reported weaker correlations (Burrow and Corbet, 2000), or variations in strength of the correlations between breeds (Cafe et al., 2011b). Overall, this would suggest that these tests are assessing similar if not identical underlying traits.

HANDLING AND MILKING—DAIRY CATTLE

Typically, milking temperament is seen as the response to the whole milking procedure, and is mostly scored by the farmer or milking staff. A categorical scale based on descriptive definitions of different levels of response to the milking and handling procedures are often used, with scores from 1–5 or 1–9 typically representing poor to good milking temperament. Temperament scores are often combined with other assessments such as milking speed to derive a "workability" trait. Milking temperament data are collated by herd improvement or milk recording organizations in many countries (www.interbull.org). A number of researchers have used more objective assessments such as an assessment of the number of steps, kicks or flinches the cow makes in response to the milking procedure (e.g., Willis, 1983; Breuer et al., 2000). In experimental situations, human approach or flight distance tests have been used with dairy cattle (e.g., Waiblinger et al., 2003; Gibbons et al., 2009b), and shown to have good within-animal repeatability. The tests involve scoring the response of the animal as the experimenter moves toward her. Gibbons et al. (2011) found that approach distance was related to flight speed, but not chute score, in dairy heifers.

OTHER TRAITS

Other temperament traits such as sociability, intra-specific aggression and response to novelty and social separation have been assessed in beef and dairy cattle, and maternal behavior in beef cattle. Maternal behavior, or maternal aggressiveness is a human safety as well as a calf survival issue, particularly in farming systems in which humans come in close contact with cows and calves (Turner et al., 2013). Improvement of animal welfare is the main driver for assessing many of the other traits, as well as the desire to understand the relationship between the specific handling tests and the wider personality of the animal (Kilgour et al., 2006). It is thought that animals that are not excessively fearful of novel objects or isolation from other animals will cope better with modern intensive or semi-intensive farming systems than more reactive animals (Kilgour et al., 2006; Gibbons et al., 2009b). Similarly, it has been hypothesized that an animal with high social motivation will integrate and cope better with group housing than low sociability animals, and that animals showing low aggression will suffer less stress and have less negative impact on other animals (Gibbons et al., 2009a, 2010). Methods to quantify these characteristics have involved assessing the response of animals to novel objects, social isolation or to a competitive situation. A number of studies have shown moderate to high repeatabilities of scores for individual animals, indicating that they can be classed as temperament traits (e.g., novelty: Kilgour et al., 2006; Gibbons et al., 2009b, 2010; aggression: Gibbons et al., 2009a; MacKay et al., 2013).

In terms of trait definition, it would appear that there are some very good definitions for a number of temperament traits, particularly for beef handling and dairy cow milking temperament. These traits have established measurement protocols and measurement scales. There are other traits that have received less attention, but which show good repeatability.

GENETIC VARIATION BETWEEN AND WITHIN BREEDS

Once a trait has been defined and a reliable measurement system created, the degree of genetic variation within and between breeds must be determined, if genetic improvement is to be made. Genetic variation can be exploited in one of three ways currently—selection between breeds (or breed substitution—replacing one breed with another, superior breed), crossbreeding (crossing different breeds to create animals with intermediate performance to the parent breeds, or to produce animals with attributes of both parental breeds, or to exploit heterosis or "hybrid vigor"—the boost in performance often seen in crosses, over and above that expected from the mean performance of the parent breeds), or selection within breeds. Whether crossbreeding leads to significant heterosis effects on temperament traits such as handling ease has not been studied, but warrants investigation (Burrow, 1997). A fourth option, direct genetic modification, is also available, but this is largely confined to experimental use rather than commercial practice at the moment. This may change as techniques such as "gene editing" used in human gene therapy begin to be applied to allow targeted changes in livestock (Lilico et al., 2013).

BREED DIFFERENCES

The choice of breed or strain by producers is influenced by temperament, but choice is often based on subjective information. Differences in performance of breeds managed in the same environment provide more objective evidence that a trait is under genetic control. Substitution of one breed by another is a rapid way to effect genetic change. Information on the differences between breeds and their crosses is also a prerequisite for the design of optimal crossbreeding schemes. Stark differences in handling ease between the relatively docile *Bos taurus* and relatively flighty *Bos indicus* cattle are well known (Hearnshaw et al., 1979; Becker and Lobato, 1997; Voisinet et al., 1997a; Buchenauer, 1999; Burrow, 2001). Large differences between individual breeds of *Bos taurus* cattle have also been demonstrated, although individual reports often conflict (e.g., Hearnshaw and Morris, 1984; Gauly et al., 2001; Boissy et al., 2005; Hoppe et al., 2010). There are also reported differences between the dairy breeds in their milking temperament (Sewalem et al., 2010). In many cases, these reported differences are most likely to be due to differences in the way in which cattle from the different breeds were raised and their level of exposure to humans. However, in those studies in which the rearing environment was standardized, breed differences have still been found, indicating that the response of cattle to handling by humans is, at least at the level of the breed, under some genetic control. Other than the distinction between *Bos indicus* and *Bos taurus*, studies in which different breeds have been reared and handled together in a standardized manner are not numerous enough to allow a "league table" of breed temperament to be created at present.

GENETIC VARIATION WITHIN BREEDS

Having identified the optimal breeds or crosses for a given production system, there are opportunities for further genetic improvement via selection of the best parents within the chosen breed, or within each of the breeds making up the chosen crossbreed. Objective within-breed selection usually requires knowledge of the traits affecting profitability (breeding goal traits) and their relative economic values, potential proxy traits on which to base selection (selection criteria) if breeding goal traits can not be measured directly (e.g., if they are expressed late in life, can only be measured *post-mortem* or are time-consuming and costly to measure), and estimates of the genetic and phenotypic variances and covariances among these traits.

Typically, estimates of heritability (the ratio of additive genetic variation to total phenotypic variation) are required to establish the degree to which the traits of interest are under genetic control, and hence the scope for changing them by selection (the variation in the trait concerned is also important here). Accurate estimates of heritability require measures of the trait of interest, as well as pedigree information, on many animals. Heritability estimates alone are sufficient to produce simple (univariate) predicted or estimated breeding values (EBVs) which are predictions of the genetic merit of candidates for individual traits of interest. Most modern breeding programmes use more sophisticated statistical techniques (based on "best linear unbiased prediction") to produce multivariate EBVs (a suite of EBVs for traits of interest, that takes into account relationships among animals, and associations among traits). This requires estimates of phenotypic and genetic variances and covariances among all traits (these are also required to derive regressions or correlations usually used to quantify associations among traits). Often multivariate EBVs are weighted and combined in a selection index, producing a single score identifying animals with the highest predicted genetic merit for overall economic performance. This requires estimates of the economic value of all traits that contribute to the overall breeding goal. **Figure 1** illustrates the steps involved in prediction of conventional breeding values.

Heritability estimates for temperament traits

The extent of current knowledge on the heritability of temperament is reviewed in the section below. A large number of studies have estimated heritability for the three major handling traits in beef cattle and also for milking temperament in dairy cattle (**Tables 1–4**). A smaller number of studies have also investigated the heritability of other temperament traits (**Table 5**). There are also a number of previous reviews on the genetics of behavior (Burrow, 1997; Buchenauer, 1999; Wiener, in press).

Handling—beef cattle. For the handling temperament traits, there is a wide range of heritabilities, from low to moderate, indicating that some genetic progress can be made in selective breeding programs for these traits (See **Tables 1–3** for heritability estimates for beef cattle for chute tests, flight speed and docility tests, respectively). However, variation among estimates is sometimes high. The unweighted mean and range of heritabilities (irrespective of the models used) for the three traits are in the same range [chute scores/response to restraint: 0.24 (0.03–0.67); flight speed: 0.36 (0.05–0.7), and docility: 0.26 (0.0–0.61)]. Burrow (1997) concluded that despite the different types of methodologies involved, the estimates of heritability were similar (0.36 for non-restrained and 0.23 for restrained tests). Some of the difference in estimates may be explained by sampling bias alone. However, it is also likely that the variability in estimates for temperament traits given the same name is partly due to differences in measuring protocols or recording method, or to breed differences. Heritability estimates do vary between breeds, and are generally higher for *Bos indicus* breeds and crosses than for *Bos taurus* breeds. *Bos taurus* breeds of British and continental European origin have been bred for longer, in less extensive conditions, with a higher level of human contact than *Bos indicus* breeds. This history may have produced animals that are genetically less predisposed to fear humans and restraint, and which show less genetic variation in response to handling. There appears to be little maternal genetic effect on measures of offspring temperament (maternal heritabilities for flight time: 0–0.03; Prayaga and Henshall, 2005; chute test score: 0.01 to 0.05 for the different models used; Beckman et al., 2007).

Some methodological differences may also explain the variation among estimates of heritability. In most cases, objective measures have higher heritabilities than more subjective scores (e.g., Burrow and Corbet, 2000; Benhajali et al., 2010). As expected, repeated measures result in higher heritabilities than a single measure (Burrow and Corbet, 2000). It is also apparent that heritability estimates decline with age at scoring. This may be due to habituation to the handling situation, which means that animals which show notable differences in temperament from group-mates when young gravitate toward the calmer end of the spectrum as they age, probably reducing both the genetic and phenotypic variation in the population. A reduction in phenotypic variation may also be expected through repeated testing of animals in a short period of time, as repeated handling reduces response intensity [as has been shown for flight speed (Burrow and Corbet, 2000; King et al., 2006)]. The influence of familiarity with humans on responsiveness is also shown by the effect of rearing intensity, whereby animals reared indoors are typically more docile than those reared under range conditions (Boivin et al., 1994). There may also be sex effects, with some finding that bulls are more excitable that cows (Burrow et al., 1988), but other studies have shown heifers to be more excitable than bulls (Voisinet et al., 1997a; Hoppe et al., 2010) or no difference (e.g., Cafe et al., 2010).

Handling—dairy cattle. There is also a range of heritabilities for milking temperament in dairy cattle from low to moderate with an unweighted mean of 0.19 (range 0.07–0.53) (**Table 4**). The larger number of records used in these studies ought to reduce measurement error, but compared to the heritabilities for beef cattle handling temperament measures, those for dairy cattle are

Table 1 | Heritability estimates for the chute test in beef cattle.

References	Breed and sample size	Age at test	Confinement context and score	Heritability ± *SE*
Shrode and Hammack, 1971	Hereford (58) Angus (114)	Yearling	Squeeze chute (1–**5**)	0.40 ± 0.30
Sato, 1981	Japanese Black/Shorthorn ($n = 200$)	Calves to adult	Weigh scale (1–**4**)	0.45 $P < 0.05$
Fordyce et al., 1982	Bos indicus cross and Hereford-Shorthorn cross ($n \sim 957$)	9–10 or 21–22 months	Movement in crush (1–**7**) Audible respiration in a crush (1–**4**) Movement in race (1–**7**) Audible respiration in a race (1–**4**) Movement in a headbail (1–**7**)	0.25 ± 0.20 0.20 ± 0.16 0.17 ± 0.21 0.57 ± 0.22 0.67 ± 0.26
Hearnshaw and Morris, 1984	Bos taurus Bos indicus-sired	8 months	Chute (0–**5**)	0.03 ± 0.28 0.46 ± 0.37
Fordyce et al., 1996	Bos indicus crosses ($n = 485$; $n = 312$ for 12 months)	Weaning 12 months 24 months	Handling/confinement in a race (1–**13.5**)	0.14 ± 0.11 0.12 ± 0.11 0.08 ± 0.10
Burrow and Corbet, 2000	Bos indicus cross ($n = 851$)	12–36 months	Weigh crate (1–**5**)	0.30
Schmutz et al., 2001	Bos Taurus (130)	6–12 months	Weight scale "Habituation" (difference between two repeats of test)	0.36 0.46
Beckman et al., 2007	Limousin (21,932)	Weaning	Chute (1–**6**)	0.34 ± 0.01
Benhajali et al., 2009	Limousin (1,271)	8 months	Chute score (1–**5)** No. of rush movements (1–**6**) Total no. movements (1–**6**)	0.18 ± 0.07–0.09 0.23 ± 0.07–0.09 0.29 ± 0.07–0.09
Kadel et al., 2006	2358 Bos indicus (Brahman, Santa Gertrudis, Belmont Red)	8 months 19 months	Chute score (1–**15**)	0.19 ± 0.02 0.15 ± 0.03
Benhajali et al., 2010	Limousin (2,141)	5 and 7 months	Weigh crate TW: no. of movements CTW: categorical score of TW RW: no. rush movements CRW: categorical score of RW	 5 months: 0.14 ± 0.09 7 months: 0.31 ± 0.10 5 months: 0.16 ± 0.08 7 months: 0.29 ± 0.10 5 months: 0.11 ± 0.07 7 months: 0.28 ± 0.09 5 months: 0.11 ± 0.07 7 months: 0.23 ± 0.09
Hoppe et al., 2010	German Angus (706) Charolais (556) Hereford (697) Limousin (424) German Simmental (667)	5–11 months	Chute score (1–**5**)	0.15 ± 0.06 0.17 ± 0.07 0.33 ± 0.10 0.11 ± 0.08 0.18 ± 0.07
Barrozo et al., 2012	Nellore (37,692)	Long yearlings (12+ months)	Corralled and human presence (1–**4**)	0.18 ± 0.02

The context refers to the location or situation in which the confinement or restraint was recorded. Sample size is shown in parentheses with breed. The scale used to measure the temperament trait is shown with the most excitable/nervous score shown in bold.

typically lower. This may be due to the fact that individual farmers score their own dairy cows, and there may be lower inter-observer reliability than among trained assessors (the norm for beef cattle). Alternatively, there may be inherently low variation in dairy cattle temperament.

Other traits. The studies of aggression and dominance with an adequate sample size appear to show that these traits have a low heritability (**Table 5**). However, for maternal traits, there is a range of heritability from low to moderate. This variation may reflect the quality of the trait definition, but

Table 2 | Heritability estimates for flight speed (m/s) and flight time (s*100).

References	Breed and sample size	Age at test	Measure	Heritability ± *SE*
Burrow et al., 1988	Bos indicus derived (561)	Weaning (42 sires)	Flight speed (m/s)	0.54 ± 0.16
		18 m (38 sires)		0.26 ± 0.13
Burrow and Corbet, 2000	Zebu-derived *n* = 851 (Duckponds popn)	12 months 2–4×	Flight speed score (rating: slow to fast)	0.08
			Flight speed	0.35
	Zebu-derived *N* = 1277 (Belmont popn)	Weaning	Flight speed score	0.39
		12 months		0.33
		18 months		0.29
Burrow, 2001	Zebu-derived (Belmont Red) (1871)	Weaning, 12 and 18 months	Flight speed	0.44 direct 0.05 maternal effects
Johnston et al., 2003	Tropically adapted (Brahman, Belmont Red and Santa Gertrudis) (7622)	Post-weaning	Flight time	0.31 ± 0.03–0.06
Prayaga and Henshall, 2005	European and Zebu breeds (2555)	*N* = ∼2555	Flight time	0.20 ± 0.03 (direct)
Kadel et al., 2006	Bos indicus: Brahman, Santa Gertrudis and Belmont Red (3594)	8 months	Flight time	0.30 ± 0.02
		19 months		0.34 ± 0.03
Nkrumah et al., 2007	Bos taurus: Angus/Charolais/beef hybrid (302)	8 months	Flight speed	0.49 ± 0.18
Rolfe et al., 2011	Bos taurus (Hereford, Angus others) (1141)	Finishing phase	Flight speed	0.34 ± 0.11
Hoppe et al., 2010	German Angus (706)	5–11 months	Flight speed score (1–4: walk to jump out of chute)	0.20 ± 0.08
	Charolais (556)			0.25 ± 0.10
	Hereford (697)			0.36 ± 0.06
	Limousin (424)			0.11 ± 0.07
	German Simmental (667)			0.28 ± 0.07

High flight speeds and low flight times indicate animals with excitable temperaments.

does suggest that selective breeding could improve maternal temperament.

A review of studies estimating heritability of temperament traits suggest that handling temperament traits have moderately high heritabilities that should allow them to be included in multi-trait selection programmes. Recent work on a larger scale and across different breeds has confirmed and extended earlier work by Burrow (1997). The estimates are similar to the heritability of some of the productivity traits which are primary targets for selection in the cattle sector [e.g., milk yield: 0.25 (Emanuelson et al., 1988); 0.27 (Woolliams, 1989)]. The variation in the heritability estimates is high in some cases, but may be due to variation between observers or the type of protocol used, which could be overcome with training of assessors and the creation of precise protocols.

RELATIONSHIP BETWEEN TEMPERAMENT TRAITS AND OTHER TRAITS

In this section, the relationship between temperament traits, and productivity, health and fitness traits are reviewed. Some studies have investigated the mechanisms underlying these correlations. (See also Supplementary Material Tables A1–A7 for a list of papers and results).

Beef cattle

Temperament, bodyweight, and growth. Correlations between response to handling and weights at key ages (birth, weaning, yearling, and final weights) have been investigated. Generally, genetic and phenotypic correlations with temperament traits are low for weights from birth to one year of age, with high variation among estimates (e.g., Burrow, 2001; Prayaga and Henshall, 2005; Phocas et al., 2006). However, in a study with large numbers of animals, Sant'Anna et al. (2012) found unfavorable genetic and phenotypic relationships between weaning weight and flight speed in *Bos indicus* (Nellore) cattle, showing that animals with fast speeds had lower weights. Similarly, in a large study with *Bos taurus* cattle, Reinhardt et al. (2009) found that animals showing more excitable temperament scores in a chute test were phenotypically more likely to have a lower bodyweight on entry to a feedlot. Beyond the yearling stage, a number of studies with smaller numbers of cattle have shown phenotypic correlations between calm temperament and higher slaughter weights in both *Bos indicus* and *Bos taurus* breeds (chute score: Reinhardt et al., 2009; Cafe et al., 2011b; flight speed: Cafe et al., 2011b). However, a number of authors report contrasting relationships or different results in different animal populations within the same study (Burrow and

Table 3 | Heritability estimates for docility and flight distance.

References	Breed and sample size	Age at test	Measure	Heritability ± *SE*
Le Neindre et al., 1995	Limousin heifers (904)	10 months	Docility score Docility criterion (categorical score of docility test)	0.22 0.18
Gauly et al., 2001			Elements of Docility test (illustrative traits shown) and categorical score	
	German Angus (249)	8 months (×2)	Range across elements	0.0–0.61 ± 0.17
			Time taken for separation from penmates (PH) (s)	Test 1: 0.03 ± 0.05 Test 2: 0.02 ± 0.05
			Docility score test 1 (1–5: calm-very excited)	Pre-handling: 0.13± 0.11 Handling: 0.61± 0.17
			Docility score test 2	Pre-handling: 0.11 ± 0.07 Handling: 0.18 ± 0.07
	Simmental (206)	8 months (×2)	Range across elements	0.0–0.59 ± 0.41
			Time taken for separation from penmates (s)	Test 1: 0.16 ± 0.07 Test 2: 0.38 ± 0.22
			Docility score test 1 (1–5: calm-very excited)	Pre-handling: 0.17± 0.12 Handling: 0.55 ± 0.15
			Docility score test 2	Pre-handling: 0.35 ± 0.21 Handling: 0.52 ± 0.20
Phocas et al., 2006	Limousin heifers (2781; 102 sires)	10–14 months	Docility test	0.18 ± 0.01
Fordyce et al., 1996	Bos inducus crosses (485) 12 months: (312)	Weaning 12 months 24 months	Flight distance	0.40 ± 0.15 0.32 ± 0.14 0.70 ± 0.23
Benhajali et al., 2009	Limousin (1,271; 65 sires)	8 months	Flight distance: Response to human approach (1–6: come near-charge)	0.17 ± 0.07–0.09

Sample size shown in parentheses in column with breed.

Dillon, 1997; Burrow, 2001; Prayaga and Henshall, 2005). It is not clear why these studies had different results. They were based on a population of *Bos indicus* × *Bos taurus* cross-breds, in contrast to the other studies which used Bos taurus or Bos indicus breeds, but the differences may also be due to the specific test conditions. Some studies also report higher correlations with one measure over another (e.g., chute score higher than flight speed: Turner et al., 2011) but others find similar results for different measures (e.g., Hoppe et al., 2010; Cafe et al., 2011b). This suggests that interactions between breed and local contexts affect estimates.

The relationship of handling temperament with growth rate, rather than weight at a certain age, has also been investigated. Growth rate or daily gain are likely to be more accurate assessments, as they obviously take into account variation in initial bodyweight. Growth rates have also been shown to have unfavorable phenotypic relationships with temperament, indicating that cattle with excitable temperaments grow more slowly (*Bos indicus*: Voisinet et al., 1997a; Petherick et al., 2002; Cafe et al., 2011b; Sant'Anna et al., 2012; *Bos taurus*: Voisinet et al., 1997a; Fell et al., 1999; Müller and von Keyserlingk, 2006; Reinhardt et al., 2009; Turner et al., 2011). Estimations of genetic correlations often have large standard errors, but also show generally that more excitable animals tend to have slower growth (Hoppe et al., 2010; Sant'Anna et al., 2012). Phenotypic measures of feed efficiency also show a similar relationship, with lower efficiencies associated with high flight speed (Petherick et al., 2002; Cafe et al., 2011b). However, residual feed intake (RFI), studies have shown a low but negative genetic and phenotypic correlation of temperament with RFI values or no correlation with flight speed (Nkrumah et al., 2007; Elzo et al., 2009; Rolfe et al., 2011), with low (efficient) RFI scores associated with higher flight speeds. The correlations are low, indicating that the traits can be considered independent.

There is a similar picture for carcass weights. Excitable temperament, as measured objectively or subjectively by speed of movement from a chute, is genetically and phenotypically associated with lower carcass weights in both *Bos indicus* and *Bos taurus* animals but the relationship may not be present in all cohorts or breeds of animals (flight speed: Burrow and Dillon, 1997; Nkrumah et al., 2007; Cafe et al., 2011b; response to release from chute: Reinhardt et al., 2009). An unfavorable genetic correlation between temperament and carcass weight has also been reported, although the standard errors are large (Nkrumah et al., 2007).

Overall the data strongly suggests that animal growth and efficiency is unfavorably associated with behaviors in which the underlying trait is fearfulness of humans and/or of confinement. This may be because a fearful personality trait affects the animal in many situations that reduce its ability to eat sufficient feed, or that it responds more strongly to fear-inducing events than

Table 4 | Heritability estimates for dairy cattle milking temperament.

References	Breed and sample size	Measure*	Heritability ± *SE*
Dickson et al., 1970	Holstein (1017)	Milking temperament (1–**4; quiet to restless**)	0.47
Wickham, 1979	Friesian (~6300)	Milking temperament (occasionally to often unsatisfactory)	0.11 – 0.12
	Jersey (~7800)		0.09 – 0.11
Sharma and Khanna, 1980	Dairy crossbreds (319)	Milking temperament (1–**4; quiet to restless**)	0.19
Lawstuen et al., 1988	Holstein (12,646)	Milking temperament (**1**–50: excitable-docile)	0.12 ± 0.02
Visscher and Goddard, 1995	Holstein Friesian (14,596)	Milking temperament (1–**5** good to poor)	0.22 ± 0.03
	Jersey (4695)		0.25 ± 0.06
Cue et al., 1996	Holstein (59,623)	Adaptability (how soon the animal settles into milking routine after calving: **1**–9: slowly to quickly)	0.111 ± 0.015
		Shed temperament: temperament of the animal during milking: **1**–9 vicious to placid)	0.137 ± 0.015
	Jersey (45,396)	Adaptability	0.179 ± 0.015
		Shed temperament	0.172 ± 0.015
	Ayrshire (6,599)	Adaptability	0.357 ± 0.06
		Shed temperament	0.333 ± 0.06
Schrooten et al., 2000	Holstein Friesian (656 bulls)	Milking temperament (1–9; direction not stated)	0.15
Pryce et al., 2000	Holstein Friesian (44,672)	Milking temperament (**1**–9: nervous-quiet)	0.07 ± 0.001
Hiendleder et al., 2003	Holstein (16 grandsires; mean sons: 54.5)	Milking temperament (1–9; direction not stated)	0.07
Sewalem et al., 2011	Holstein (1,940,092)	Milking temperament (**1**–5; nervous-calm)	0.13 ± 0.014

All animals were scored as adults.

**For milking temperament, figure in bold indicates score for most "restless/excitable/nervous" behavior.*

Table 5 | Estimates of heritability for traits other than handling.

DOMINANCE/AGGRESSION				
Beilharz et al., 1966	Holstein (105) + Guernsey (8)	Adult	Dominance	0.40
Dickson et al., 1970	Holstein (1017)	Adult	Dominance	0.0
Phocas et al., 2006	Limousin (2781)	Youngstock	Maternal temperament	0.06 ± 0.02
Sartori and Mantovani, 2010	Valdostana (5981)	Adult	Fighting ability (winning):All fights	0.078
			Best result of each year	0.098
MATERNAL TEMPERAMENT				
Brown, 1974	Hereford (162)	Adult	Maternal temperament score	0.32
	Angus (266)			0.17
Morris et al., 1994	Bos taurus (2121; 486 sires)	Adult	Maternal temperament	0.09 ± 0.03
Phocas et al., 2006	Limousin (1502)	Youngstock	Maternal temperament	0.36 ± 0.06

calmer animals, thereby reducing the energy available for growth (Petherick et al., 2002). Alternatively, the adverse response to handling may be long-lasting and reduce growth overall (MacKay et al., 2013). The genetic correlations are not strong, however, which suggests that selection for growth, final weight or efficiency will not have a dramatic impact on temperament. The general picture that poor temperament reduces productivity suggests that improvement of temperament will have a positive impact on animal welfare as well as farm profitability.

Temperament and reproduction. A number of studies have assessed the relationship between male and female reproductive characteristics and handling temperament traits. Scrotal circumference is often used as a measure of male and female reproductive performance. Low and negative genetic and phenotypic relationships with temperament have been reported suggesting that excitable animals have low scrotal circumference (response to corral/human presence: Barrozo et al., 2012; flight speed: Burrow, 2001; Sant'Anna et al., 2012). For females, Phocas et al. (2006) found significant genetic correlations showing that docile heifers had a lower age at puberty and higher fertility than less docile heifers, but other measures of fertility and reproductive function were not associated with temperament. A weak favorable genetic correlation between docility and maternal behavior was also found by Phocas et al. (2006), indicating that more docile animals had better maternal behavior, but this relationship was not confirmed by Turner et al. (2013) studying a wider range of maternal behavior traits. Other associations between temperament and reproductive traits are poorly studied but appear to be weak and variable in their direction. Burrow et al. (1988) found that calm cows were more likely to show behavioral signs of estrus in the presence of a human observer than excitable cows. Turner et al. (2013) found that cows which respond calmly to pre-calving handling produce slightly heavier calves that grow faster to weaning. It must be concluded however, that the weak relationships suggest either that the traits are largely independent, or that selection for reproductive traits is likely to have favorable but small effects on temperament.

Temperament and stress physiology. The physiological basis for the effect of temperament on productivity has been investigated in a number of studies. Differences in baseline levels of cortisol have been shown, with excitable animals having higher levels than calm animals (Fell et al., 1999; Curley et al., 2006b; King et al., 2006; Cafe et al., 2011a). Curley et al. (2008) looked at the response in detail and showed that despite having higher baseline levels, the excitable animals showed a blunted adrenal response to challenge compared to calm animals, indicating an elevated basal adrenal function that is often associated with chronic stress. Similarly, excitable animals have higher levels of epinephrine (a hormone associated with the sympathomedullary system) in baseline measures and following challenge such as transportation (Curley et al., 2006b; Burdick et al., 2011). These findings provide an explanation for the possible relationship between temperament and health discussed below.

Carcass traits and meat quality. In the *post-mortem* period in a normal animal, stored body energy in the form of glycogen is converted into lactate, which reduces muscle pH. Low lactate levels (and higher pH) are associated with tough meat (Maltin et al., 2003). As stress leads to a reduction in the levels of glycogen in muscle, it can reduce the levels available for conversion to lactate, thus affecting meat quality. This is particularly important in the pre-slaughter period when animals are transported and handled (King et al., 2006), events which excitable animals respond to adversely, as discussed above. Thus, the potential relationship between temperament and meat quality has important implications for animal welfare and farmer profit if payment based on meat eating quality becomes more widespread. A number of studies have shown a relationship between temperament and meat quality. The meat from excitable animals has higher shear force indicating lower tenderness than calmer animals as assessed by flight speed, chute test score and a combination of the two (Voisinet et al., 1997b; Reverter et al., 2003; Kadel et al., 2006; King et al., 2006; Cafe et al., 2011b; Hall et al., 2011). This relationship appears to be stronger at the genetic than the phenotypic level (Reverter et al., 2003; Kadel et al., 2006). A high carcass ultimate pH is also associated with poor temperament (Petherick et al., 2002; King et al., 2006) as is cooking loss (Kadel et al., 2006). However, there appears to be no phenotypic association between meat quality and temperament in frequently handled *Bos taurus* animals (Turner et al., 2011). The relationship between stress, pH and meat tenderness is not straight-forward, as the effects of acute and chronic stress on muscle physiology depend on a number of other factors such as post-mortem meat processing practices (King et al., 2006), which may explain some of the phenotypic variation.

Temperament and health. Chronic stress is known to have an immunosuppressive effect. However, there is only limited evidence that temperament is associated with clinical health parameters. For example, Fell et al. (1999) found that calm animals are less likely to be hospitalized in feedlots than excitable animals, and Reinhardt et al. (2009) showed that mortality rates were higher in excitable than calm steers. However, Burrow (2001), Prayaga (2003), and Prayaga and Henshall (2005) did not find significant relationships between temperament and counts of ticks or flies and fecal egg counts. Reinhardt et al. (2009) did not find any effect of temperament on number of respiratory treatments required or on incidence of lung lesions at slaughter. There is more evidence of a link between temperament and health at the level of immune function. A number of researchers have investigated a possible link between higher cortisol levels shown in animals with excitable temperaments and possible suppression of immune function. It has been reported that the innate immune system of calm animals shows more resistance to microbial invasion after a stressful challenge (transportation) (Hulbert et al., 2011). In contrast, calm beef steer calves had lower IgM levels than excitable calves (Fell et al., 1999; Burdick et al., 2009), but heifer calves showed the reverse pattern (Burdick et al., 2009). It is normally expected that higher immunoglobulin levels in young animals is beneficial in mounting a response to disease challenge.

Dairy cattle

Less work has been done on correlations between temperament and other traits in dairy cattle (See Supplementary Material Table B1). Research suggests that animals showing calm temperaments have better yields (Drugociu et al., 1977; Lawstuen et al., 1988; Breuer et al., 2000) and faster milking speed (Lawstuen et al., 1988; Sewalem et al., 2011). There is a positive relationship between temperament and survival in the herd, such that calmer cows are less likely to be culled (Haile-Mariam et al., 2004; Sewalem et al., 2010). There are also positive effects on health, with better resistance to mastitis, lower udder edema and better general health from animals with calmer temperaments (Lawstuen et al., 1988). However, there are conflicting reports on the relationship between temperament and somatic cell count (Fulwider et al., 2007; Sewalem et al., 2011). A strong genetic correlation between ease of calving and calm temperament was shown by Lawstuen et al. (1988) (0.48 ± 0.18), but in general, low phenotypic correlations have been reported for calving ease as well as other fertility traits, with high standard errors for the estimates reported (Lawstuen et al., 1988; Haile-Mariam et al., 2004; Sewalem et al., 2011).

CONSEQUENCES OF SELECTION FOR PRODUCTION ON TEMPERAMENT

It would appear the inclusion of temperament in selection indices for both beef and dairy would have benefits for productivity and also animal welfare although many of the phenotypic associations between temperament and economic traits require further investigation at the genetic level. In beef cattle, calmer animals grow faster and have better feed conversion rates. Meat quality is better in calmer animals, and there may be benefits in terms of health and reproduction. In dairy cattle, milk production and milking speed is higher in calmer animals. Survival is higher in calmer animals, perhaps because farmers are more liable to cull animals that are difficult to milk. The health and fertility benefits are less clear in dairy animals.

In beef cattle, the low genetic correlations between productivity and temperament traits suggest that while selection for efficiency and growth would improve temperament, the correlated response to selection will be low. However, this also implies that current selection goals focussed on productivity alone will result in only a slow improvement in temperament. This may justify placing selection pressure on temperament itself in order to achieve more significant genetic progress in behavior and welfare which may be especially desirable for *Bos indicus* animals (Sant'Anna et al., 2012). Inclusion of temperament into a selection index would result in a reduction in selection pressure on other economically important productivity traits, and the implications of this would need to be quantified and considered.

MOLECULAR APPROACHES: QTLs AND GWAS

Over the last 30 years there has been a great deal of work worldwide to investigate the molecular genetic basis of a wide range of traits of interest in livestock production. This has included studies intended to detect quantitative trait loci (QTL), which are loci explaining a portion of the variation in traits of interest, as well as work to develop increasingly dense genome maps for farm livestock, and studies investigating associations between molecular genetic markers and traits of interest.

QTLs which influence behavioral traits have been found in a number of breeds (**Table 6**). Studies have shown significant or indicative QTL for a number of behavioral traits. Chromosomes 1, 8, 9, 16, and 29 are implicated across studies, although QTLs affecting behavior have been found on other chromosomes as well. Glenske et al. (2011) found an association between a candidate gene DRD4 on chromosome 29 and performance in the docility test. DRD4 is a dopamine receptor gene involved in curiosity and novelty seeking in mammals (Rubenstein et al., 1997). A database containing information on behavioral QTLs can be found at www.animalgenome.org/cgi-bin/QTLDB/index.

However, while there are a few traits of interest in livestock that are largely determined by genotype at a single locus or a few loci, there are many more traits of interest that appear to be polygenic in nature, and influenced by many, often hundreds, of loci (Hayes et al., 2009). Moreover, there are often rather few genes that have a large effect on these polygenic traits, and many more that individually have a small effect.

Increasingly dense genome maps are available for livestock with tens or hundreds of thousands of single nucleotide polymorphisms (SNPs) measured throughout the genome. These, coupled with automated platforms for genotyping on so-called SNP "chips," allow genome-wide association studies (GWAS) to be done relating markers to traits of interest, including temperament traits. In beef cattle, a study of temperament and meat quality in Nellore-Angus beef cattle found an association between response to social separation in a pen and a gene regulating sodium ion transport, indicating a difference in nervous system responsiveness (Hulsman Hanna et al., 2014). Additionally, a study in Brown Swiss cattle identified regions with high influence on temperament and aggression on chromosomes 4, 8, and 14 (Kramer et al., 2014). As mathematical techniques are developed that will allow evaluations across breeds and as costs of genotyping fall, more studies that include the assessment of temperament traits are likely.

The availability of dense genome maps and rapid, increasingly affordable genotyping has altered the paradigm for application of molecular genetics in livestock breeding, for many traits of interest. Rather than relying on genotypes at a few loci to predict genetic merit, predictions are increasingly based on information from tens or hundreds of thousands of SNPs throughout the genome. The prediction of genetic merit itself relies on GWAS in a "reference population" of animals—large populations of relevant animals that have both molecular genetic and phenotypic information available. GWAS followed by genomic selection is thought to be a particularly useful approach to improving traits that are difficult, expensive or time-consuming to measure, such as temperament traits. Once the trait has been measured in the reference population, candidates for selection from other similar populations need only be genotyped to predict their genetic merit for temperament (though associations need to be re-estimated periodically). Direct genomic breeding values (dGEBVs) can be predicted from molecular genetic information alone, but increasingly these are combined with EBVs derived from phenotypic records on candidates for selection and their relatives, to enhance accuracy. **Figure 1** illustrates the steps involved in prediction of genomic and conventional breeding values.

Both the dairy and beef industries are already using, or moving toward the use of, genomic estimated breeding values (GEBVs). Until recently, much of the genomic research has focussed on productivity traits, meat quality and reproductive traits (see Hayes et al., 2009; and Garrick, 2011 for reviews). This may be because the number of animals with phenotypes required is very large. The need to do the analysis on each breed individually, and the costs of phenotyping and genotyping relative to the perceived benefit of assessing temperament traits are likely to be (at least short term) constraints on the use of this technique. However, many phenotypes can be assessed in each study, allowing temperament to be assessed alongside traits seen to be more economically important.

THE USE OF TEMPERAMENT TRAITS IN SELECTION PROGRAMMES

From the research reviewed above, it would appear that many of the building blocks for selection indexes that include temperament traits exist: the traits can be defined and measured, heritability estimates are available from studies on large numbers of animals in which the traits are carefully measured, and these are similar to heritabilities of many other traits currently under selection. Genetic correlations for a number of temperament traits with productivity measures have been estimated. There is not always consensus across the studies, but some of the larger studies provide strong evidence of favorable genetic correlations.

Table 6 | Studies identifying QTLs affecting behavior.

References	Breed	Test	Chromosome	Position	Flanking markers
Spelman et al., 1999	Holstein Friesian and Jersey	Milking temperament (1–9: vicious-placid)	4		TGLA215
Schmutz et al., 2001	Beef cattle	"Temperament" (movement on a weigh scale in a race)	1	14	BMS574
			5	29	RM103
			9	44	ILSTS013
			11	57	ILSTS036
			14	19	RM180
				35	ILSTS008
			15	12	ADCY2
		"Habituation" (difference in response to two repeats of above test)	1	14	BMS574
			5	29	RM103
			9	44	ILSTS013
			11	57	ILSTS036
			15	12	ADCY2
Hiendleder et al., 2003	Holstein	Milking temperament (1–9)	5*	136	
			18*	105	
			29*	20	
			XY*	0	
Wegenhoft, 2005	Brahmanx Angus Mendelian model	Disposition (1–5: calm to crazy)	1*	37	DIK70-PIT17B7
			4	46	TEXAN17-LAMB1
			8	0	BMS1864-BM3419
			9	72	BM6436-BM4208
			16	79	INRA013-BMS462
			18*	43	BL1016-BM8151
Boldt, 2008	Popn 1: Brahman/Nellore × Angus Parent of origin model	Disposition (1–5: calm to crazy)	8	3 cM	BMS1864-CTSB
			8	2 cM	BMS1864-CTSB
	Popn 2: Angus × Nellore Mendelian model	Aggressiveness (toward humans when held in a raceway: 1–9 non-aggressive – extremely aggressive)	3	45 cM	BM7225-ILSTS64
			6*	1 cM	CSSM22-CSSM34
			12	20 cM	BMS2252-RM094
			29*	21 cM	BMC3224-BMS764
		Flightiness (1–9: quiet to flighty)	12*	22 cM	BMS2252-RM094
		Overall disposition (weaning)	12*	22 cM	BMS2252-RM094
		Overall disposition (yearling)	26*	33 cM	IDVGA59-HEL11
		Overall disposition (calving)	16*	70 cM	INRA48-BM3509
Esmailizadeh et al., 2008	Limousin × Jersey	Docility	2	5.6 cM	–
Gutierrez-Gil et al., 2008	Charolais × Holstein	Flight from feeder (distance moved when approached at feeder)	20*	64 cM	DIK15-BM5004
			25*	30	BM737-INRA222
			29	65	DIK94-MNB101
		Flight from feeder in repeated test	28*	0	BP23
			29*	66	DIK94-MNB101
		Sociality (locomotion in response to social separation)	16	0	BM121
		Habituation of above trait	6*	3	DIK5076-BM1329
			8*	115	DIK75-CSSM47
			9*	69	BM888-CSRM60
			19	40	BMS2142-CSSM65
			21*	65	HEL10-TGLA337
		Standing alert (response to social separation)	16	87	HUJ625-DIK4011

(Continued)

Table 6 | Continued

References	Breed	Test	Chromosome	Position	Flanking markers
		Standing alert in repeated test	19*	72	CSSM65-ETH3
		Habituation of above trait in repeated test	1*	0	BM6438
			4	69	MAF50-DIK26
			11*	44	ILSTS100-IDVGA3
		Vocalization response to social separation	7*	41	RM6-BM1853
			16	49	ETH11-BM719
			18	21	IDVGA31-ABS13
		Vocalization in repeated test	9*	31	BM2504-UWCA9
			19*	72	CSSM65-ETH3
			25	33	BM737-INRA222
			26*	6	ABS12-HEL11
		Habituation of above trait in repeated test	1*	142	BNS4044
			4	68	MAF50-DIK26
			7*	93	ILSTS006-INRA53
			10*	43	BMS528-TGLA378
			29	31	RM44-MNB166
Glenske et al., 2010	German Simmental and German Angus	Weighing test (response to being weighed)	1	8	Allele 169 of BMS1928 (German Simmental) Allele 153 BMS574 (German Angus)
		Restraint (docility test)	1	15	Allele 153 BMS574 (German Simmental)
Glenske et al., 2011	German Angus	Temperament—response to entering a weigh scale	29	15.3	ILSTS081

Significance at "suggestive" level ($p < 0.05$ chromosome-wide). Loci without superscripts are significant ($P < 0.01$ at chromosome-wise level or genome-wide).

However, temperament is not often included in breeding indexes. In dairy cattle breeding, EBVs for milking temperament are available as stand-alone EBVs, or information on bulls is available in sub-index scores for "workability" that includes milking speed for some countries. The situation for beef cattle is similar. Although the correlation between handling temperament and growth and meat quality suggest that including temperament in a selection index would be beneficial from a profit and welfare point of view, it is not currently used. Animals may be excluded based on their raw score. Stand-alone EBVs are available (such as flight time for some *Bos indicus* breeds in Australia and North America, and docility scores for British and European breeds in some countries), but the trait is not currently included in a selection index (Johnston, personal communication).

CONSTRAINTS AND BARRIERS

There are a number of possible technical and producer motivational reasons why temperament traits are not incorporated into selection indexes. A major technical barrier to the use of temperament traits in selection indexes is the need for economic values to allow the trait to be weighted in a selection index. However, it should be possible to derive an economic weight for temperament from the effects that it has on meat quality and growth in beef cattle and the additional labor costs incurred from an animal that is difficult to handle or a cow that is slow or difficult to milk. This has indeed been done for *Bos taurus* cattle by a team in the US (Busby et al., 2006), but other estimates of economic values are lacking. Another issue is the lack of complete information on genetic and phenotypic correlations of temperament with all the parameters that could be used in selection indexes. For some breeds in some countries, correlations between productivity, meat quality, some fertility traits and temperament have been investigated, but by no means all. New traits are also being incorporated into selection indexes, such as calving ease, and the correlation of this trait with temperament must be determine before both traits can be included. Herd or industry scale and level of organization at the national level may also be important. The pattern of uptake suggests that in regions or countries where a breed is numerous and the breed society or governmental body is well-organized enough to provide support for the recording and evaluation of temperament traits, handling temperament traits may be evaluated. It may be that addition of temperament to an existing selection index has little impact on the overall response, but it should be examined.

Producer motivational factors are also involved. It is clear that temperament is generally poorer in *Bos indicus* breeds than *Bos taurus* animals, which may explain the greater motivation to assess temperament in *Bos indicus* animals. In some *Bos taurus* breeds, the perception of the breed as being flighty or difficult to handle appears to motivate the breed society to make genetic evaluations on temperament measures such as docility, to improve the trait and improve the popular image of the breed. Additionally, as the response to handling can be modified by repeated handling and habituation to the proximity of humans, the farming system used in any country or region will influence the necessity or motivation of producers to use genetic selection mechanisms to deal with temperament issues. On smaller farms, which are typical of much of Europe, animals arguably experience a higher level of human contact during pasture rotations or seasonal housing than the larger extensive rangeland or feedlot systems more typical of Australia and America. Extreme responses to handling may decline as repeated exposure allows the animal to habituate to human proximity and the handling process. Thus, husbandry conditions may reduce the necessity to use genetic selection to improve temperament. There is also the perception amongst some European producers that some degree of reactivity in animals is desirable, as it promotes survival and competitiveness. Clearly, farm extension and advisory work is needed to inform producers of the negative effects of poor temperament on productivity and profitability.

THE FUTURE: MOVING FORWARD AND OVERCOMING CONSTRAINTS

As it appears important for welfare and economic reasons to improve handling temperament, we need to facilitate the use of these traits in selection indexes. Research has shown that it is possible to clearly define and accurately record these traits. An increased understanding of the biological basis of these traits will also improve progress. Across the globe, several breed societies and countries have developed EBVs based on farmer-recorded assessments of temperament in dairy cattle and different types of temperament tests in beef cattle. In beef cattle, the lack of a single measure of temperament in beef cattle may impede progress. In the dairy sector in particular, standardization of recording—initially for milk-related traits, and latterly for a much wider set of traits—has helped to underpin improvement in these traits (along with the widespread use of artificial insemination, well-designed breeding programmes usually based on progeny testing, and development of statistical techniques to improve the prediction of genetic merit of animals within and across countries).

Genomic selection may provide an important opportunity for increased use of temperament traits, as increasingly, the prediction of the genetic merit of farm animals will include molecular genetic information. As the cost of genotyping falls, and the predictive power of the information increases, the rate-limiting step to application is likely to be the lack of high-quality records of traits of interest, or phenotypes, both to investigate associations between genotypes and traits of importance in the first place, or to allow ranking of candidates for selection. Temperament traits would therefore need to be measured in comprehensively recorded reference populations, and the correlations between these traits and all others estimated. Within the foreseeable future, GEBVs could also be based on complete DNA sequence information, at least for potentially influential animals.

We should also look to the inclusion of temperament traits other than the response to handling. The correlations between tests measuring response to handling and responses in other contexts can be low. Therefore, selection on the basis of chute test or flight speed may have little impact on traits which are contextually different, such as intra-specific aggressiveness, sociability and maternal defensiveness (e.g., Turner et al., 2013). This review suggests little work has been done on personality traits other than handling temperament, and yet selection for maternal ability and appropriate levels of aggression and sociability and flexibility may be important in terms of animal health and welfare, and also in terms of farm efficiency. Achieving improvements in the latter traits will require the development of automated methods for their measurement. This may come from technologies such as the use of automatic measurement of eye-white (Core et al., 2009), thermal imaging of body areas that show alteration due to stressful events or from other methods, or the use of data collected from activity monitors used to detect oestrus that can be used to characterize personality traits (MacKay et al., 2013). Automatic methods for assessment of meat quality in abattoirs will provide further incentives to improve temperament in beef cattle.

However, even when more efficient methods of phenotyping behavior and other correlated traits are developed, implementation of selection will continue to require that the industry recognizes the need for temperament traits to be used in breeding programs. The case for inclusion seems clearest for handling temperament in beef and dairy, but other traits require more research. Understanding the value of selection for temperament traits will be facilitated by continued effort to clarify and quantify the full range of economic and welfare implications of poor temperament. The primary focus of selection pressure primarily on "output" traits such as carcass weight or milk yield will most likely change in future, as new traits such as RFI are likely to be included in selection goals, particularly in beef, but possibly also in dairy cattle, responding to the need to reduce greenhouse gas emissions from agriculture or the economic necessity for improved feed use efficiency. Animal behavior, particularly behavioral responses to stress, has been hypothesized to be a determinant of feed use efficiency (Richardson and Herd, 2004). In reality, there is a paucity of information on how temperament correlates with feed use efficiency and the information available is contradictory (Petherick et al., 2002; Nkrumah et al., 2007; Elzo et al., 2009; Cafe et al., 2011b; Rolfe et al., 2011). Therefore, it has yet to be established whether improving feed use efficiency will bring with it improvements in temperament, but the low correlations shown in this review suggest that progress will be slow. Changes in some biological systems in response to improvements in feed use efficiency, such as a down-regulation of the rate of endogenous protein turnover, could compromise the animals' ability to respond to stress (Baldwin et al., 1980) leading to changes in behavior and implications for welfare. Given the global interest in improving feed use efficiency in cattle, there is therefore a need to understand the role of temperament as a driver of efficiency and, conversely, how changing feed use efficiency may impact on welfare through other routes.

As handling temperament and other behavioral traits clearly have economic value and animals that respond poorly to handling, and in other situations, suffer negative emotional and physical experiences, resulting in reduced welfare, it is clearly important to improve temperament. Genetic improvement will be important as well as investment in appropriate housing and handling systems. Genetic improvement may become more important against a background of increased herd size, intensification of beef and dairy enterprises and reduced availability of labor. Increased automation and advances in genomic techniques that allow identification of genetically superior animals once the markers have been located in training populations will contribute and quantitative methods will also continue to be important.

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SUPPLEMENTARY MATERIAL

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The prospects of selection for social genetic effects to improve welfare and productivity in livestock

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Social interactions between individuals living in a group can have both positive and negative effects on welfare, productivity, and health of these individuals. Negative effects of social interactions in livestock are easier to observe than positive effects. For example, laying hens may develop feather pecking, which can cause mortality due to cannibalism, and pigs may develop tail biting or excessive aggression. Several studies have shown that social interactions affect the genetic variation in a trait. Genetic improvement of socially-affected traits, however, has proven to be difficult until relatively recently. The use of classical selection methods, like individual selection, may result in selection responses opposite to expected, because these methods neglect the effect of an individual on its group mates (social genetic effects). It has become clear that improvement of socially-affected traits requires selection methods that take into account not only the direct effect of an individual on its own phenotype but also the social genetic effects, also known as indirect genetic effects, of an individual on the phenotypes of its group mates. Here, we review the theoretical and empirical work on social genetic effects, with a focus on livestock. First, we present the theory of social genetic effects. Subsequently, we evaluate the evidence for social genetic effects in livestock and other species, by reviewing estimates of genetic parameters for direct and social genetic effects. Then we describe the results of different selection experiments. Finally, we discuss issues concerning the implementation of social genetic effects in livestock breeding programs. This review demonstrates that selection for socially-affected traits, using methods that target both the direct and social genetic effects, is a promising, but sometimes difficult to use in practice, tool to simultaneously improve production and welfare in livestock.

Keywords: genetic selection, social genetic effects, welfare, laying hens, pigs

INTRODUCTION

Social interactions among individuals can have large effects on their phenotypes, both in domestic and natural populations. Such interactions affect the outcome of evolutionary processes and of domestic breeding programs (e.g., Hamilton, 1964; Griffing, 1967, 1977; Frank, 1998; Denison et al., 2003; Muir, 2005; Rodenburg et al., 2010; Bijma, 2011a). Social interactions can have both positive and negative effects on welfare, productivity, and health of livestock. Cooperation and mothering behavior are examples of positive social interactions, whereas competition and aggression are examples of negative social interactions.

There are more examples of negative than of positive social interactions in livestock. Domestic laying hens, for example, can develop feather pecking and cannibalism, which may result in mortality (Allen and Perry, 1975; Blokhuis and Arkes, 1984; Savory, 1995; Craig and Muir, 1996; Kjaer and Sørensen, 1997; Rodenburg et al., 2013). Domestic pigs may show injurious behaviors such as tail biting (Schrøder-Petersen and Simonsen, 2001; Zupan et al., 2012). Using classical selection methods, such as mass selection or selection on estimated breeding values, animal breeders have successfully improved many traits of agricultural importance. Typical examples are growth rate in broilers and pigs and egg number in laying hens (Hill, 2008). Genetic selection can also be used to improve traits affected by social interactions (in this review we will refer to these traits as socially-affected traits) and, thereby, reduce the negative effects of social interactions in livestock. With classical selection methods, however, improvement of socially-affected traits has been proven to be difficult (Wade, 1976, 1977; Goodnight, 1985; Craig and Muir, 1996; Muir and Cheng, 2004). Those selection methods target only the direct effect of an individual's genotype on its own phenotype and neglect the social effect of an individual on the phenotype of other individuals (Griffing, 1967). The use of classical selection methods for socially-affected traits has sometimes resulted in responses in the opposite direction (Wade, 1976, 1977; Craig and Muir, 1996; Muir, 2005). This can occur because the best individuals in the classical setting may have negative genetic effects on other individuals. For example, laying hens that have good genes for survival could also be more likely to show high levels of aggressive and competitive behavior. The use of such hens as parents for the next generation reduces survival of their group mates and potentially of the entire population (Muir and Cheng, 2004).

At first glance, selection for improved social behaviors should ideally be based on behavioral observations. In laying hens, for example, number of bouts of feather pecking was used to select against feather pecking behavior. After three generations, feather pecking was significantly decreased (Kjaer et al., 2001). Unfortunately, collecting behavioral observations is very time consuming, making breeding based on behavioral observations not feasible in practice. Moreover, individual behavior may depend not only on the genotype of the individual expressing the behavior, but also on the genotype of its social partners. Cannibalism in laying hens, for example, depends both on a genetic effect due to the actor (the pecker), and a genetic effect originating from the victim (Ellen et al., 2008). Simply selecting against pecking behavior using behavioral observations will disregard the genetic variation originating from the victim, and therefore yield a suboptimal response. Thus, breeding based on behavioral observations both requires an unrealistic effort with respect to data collection, and disregards part of the genetic variation. Breeders, therefore, need better solutions.

A solution feasible in practice may come from statistical methods that take into account both the direct genetic effect of an individual on its own phenotype and the social genetic effect of an individual on the phenotype of its group mates [also known as associative effect or Indirect Genetic Effect (IGE)]. Such methods allow us to estimate both the breeding value for the direct effect and the breeding value for the social effect, without the need for behavioral observations. For mortality due to cannibalism in laying hens, for example, the direct effect corresponds to the victim effect, whereas the social effect corresponds to the pecker effect (Ellen et al., 2008; Peeters et al., 2012). The advantage of such methods is that they capture the total genetic variation underlying the trait (Bijma, 2011b; see below).

Here, we review the theoretical and empirical work on social genetic effects, with a focus on livestock. First, we present the theory of social genetic effects. Subsequently, we evaluate the evidence for social genetic effects in livestock and other species, by reviewing estimates of genetic parameters for direct and social genetic effects. Then we describe the results of different selection experiments. Finally, we discuss issues concerning the implementation of social genetic effects in livestock breeding programs.

THEORETICAL BACKGROUND

Models of socially-affected traits have been developed within two frameworks (McGlothlin and Brodie, 2009; Bijma, 2014). In the so-called trait-based framework (Moore et al., 1997; Wolf et al., 1998), the social effect of a focal individual on trait values of other individuals is modeled as a function of specific traits of the focal individual. Hence, trait-based models describe the social effect as a function of observable traits and explicitly model the mechanism underlying the social effect. Trait-based models of social effects are an extension of maternal-effect models of Falconer (1965) and Kirkpatrick and Lande (1989). In the variance-component framework, in contrast, the traits causing the social effects are not specified. Instead, the social effect is added to the model as an additional random genetic effect (Griffing, 1967, 1977, 1981), similar to the maternal-genetic effects models of Willham (1963), and its variance is estimated based on family relationships in the data. Trait-based models may be of greater biological interest as they provide insight in the traits underlying the social effects, whereas variance-component models are empirically more powerful because they can be applied without knowledge of those traits. For livestock genetic improvement, the variance-component models are more relevant, because the traits underlying the social effects are usually unknown and recording of a wide range of traits on individuals is difficult. The following, therefore, considers only variance-component models.

MODEL

In the classical quantitative genetic model (Fisher, 1918), the phenotype of an individual is the sum of its breeding value and a residual non-heritable effect ($P = A + E$). With social interactions, the model needs to be extended to incorporate social effects. When social interactions occur within a group consisting of n individuals, the phenotype of individual i may be modeled as the sum of its own direct effect, and the sum of the social effects of each of its $n - 1$ group mates. Both the direct and social effect can be partitioned into an additive genetic and a non-heritable (residual) component (Griffing, 1967),

$$P_i = A_{D,i} + E_{D,i} + \sum_{j \neq i}^{n-1} \left(A_{S,j} + E_{S,j}\right) \tag{1}$$

where $A_{D,i}$ is the direct breeding value (DBV; see **Table 1** for notation) of individual i, $E_{D,i}$ is the corresponding non-heritable direct effect, $A_{S,j}$ the social breeding value (SBV) of group member j, and $E_{S,j}$ the corresponding non-heritable social effect. This model applies to each of the n group members. Note that DBV and SBV are distinct breeding values. For example, when the trait of interest is survival, the DBV refers to the heritable effect of an individual on its own survival, whereas the SBV refers to the heritable effect of an individual on survival of its group mates, which may, for example, relate to aggression. So the DBV is comparable to the "classical" breeding value (Lynch and Walsh, 1998), whereas the SBV is a generalization of a breeding value for a maternal effect (Willham, 1963).

In populations consisting of groups of n members, each individual expresses its DBV once in its own phenotype and its SBV

Table 1 | Notation key.

Symbol	Meaning
P_i	Observed trait value for individual i
j, n	Group mate of individual i, Group size
$A_{D,i}$, $A_{S,i}$	Direct genetic effect of i, social genetic effect of i
$E_{D,i}$, $E_{S,i}$	Direct non-genetic effect of i, social non-genetic effect of i
DBV, SBV	Direct breeding value, social breeding value
TBV$_i$	Total breeding value of i: $TBV_i = A_{D,i} + (n-1)\,A_{S,i}$
$\sigma^2_{A_D}$, $\sigma^2_{A_S}$	Direct genetic variance, social genetic variance
$\sigma_{A_{DS}}$, r_A	Covariance and correlation between direct and social genetic effects
σ^2_{TBV}, T^2	Total heritable variance, relative heritable variance
σ^2_P	Phenotypic variance
$\sigma_P, \ \sigma_{\overline{P}_{grp}} \sigma_{\overline{P}_{rel}}$	Standard deviation among phenotypic values of individuals, among average phenotypic values of groups, and among average phenotypic values of relatives in family groups
σ^2_{SC}	Variance of the selection criterion
ΔG	Selection response in observed trait value per generation
SC$_i$	Selection criterion
$\iota, \ \rho$	Selection intensity, accuracy of selection
r	Relatedness between selection candidates and its relatives
r_{rel}	Relatedness between group members
g	Degree of between-group selection
τ	Intraclass correlation among relatives adjusted for interactions
η^2	Analogy of heritability: $\sigma^2_{TBV}/\sigma^2_{TPV}$

$n-1$ times, once in the phenotypes of each of its $n-1$ group mates. The total heritable impact of a single individual's genes on the mean trait value of the population is, therefore, given by the individual's total breeding value (TBV; Moore et al., 1997; Muir, 2005; Bijma et al., 2007b),

$$TBV_i = A_{D,i} + (n-1)\,A_{S,i} \tag{2}$$

Note that, in contrast to the phenotype (Equation 1), the TBV in Equation 2 is entirely a heritable property of individual i itself. It is a generalization of the classical breeding value, and is the heritable component relevant for response to selection in socially-affected traits (Bijma, 2011b). The total heritable variance available for response to selection equals the variance in TBVs among individuals (Griffing, 1977; Bijma et al., 2007a),

$$\sigma^2_{TBV} = \sigma^2_{A_D} + 2\,(n-1)\,\sigma_{A_{DS}} + (n-1)^2\sigma^2_{A_S} \tag{3}$$

where $\sigma^2_{A_D}$ is the direct genetic variance, $\sigma^2_{A_S}$ is the social genetic variance, and $\sigma_{A_{DS}}$ is the covariance between DBVs and SBVs of individuals. The direct-social genetic covariance indicates the relationship between the direct and social effects expressed by an individual. For example, if individuals that show cannibalistic behavior have on average better survival themselves, then the direct-social genetic covariance is negative. The magnitude of social effects may depend on group size, and for most traits it is probably smaller in larger groups. This is relevant for the estimation of social effects from data with varying group size, and also for the relationship of total heritable variance and response to selection with group size. The dependency of social effects on group size can be modeled as a dilution effect (Arango et al., 2005; Bijma, 2010b). For details see Bijma (2010b).

Analogous to ordinary heritability, the total heritable variance can be expressed relative to the phenotypic variance (Bergsma et al., 2008),

$$T^2 = \frac{\sigma^2_{TBV}}{\sigma^2_P} \tag{4}$$

A comparison between T^2 and classical heritability reveals the impact of social interactions on the heritable variation that determines the potential of the population to respond to selection.

SELECTION RESPONSE

The classical expression for response to selection is the product of the intensity of selection, ι, the accuracy of selection, ρ, and the additive genetic standard deviation, σ_A; $\Delta G = \iota\rho\sigma_A$. This expression can be generalized to encompass socially-affected traits (Griffing, 1977; Ellen et al., 2007; Wade et al., 2010),

$$\triangle G = \iota\rho_{TBV}\sigma_{TBV}. \tag{5}$$

The σ_{TBV} is the square root of total heritable variance (Equation 3) and ρ_{TBV} is the accuracy which is the correlation between the selection criterion and the total breeding value in the selection candidates (Bijma, 2011a). The accuracy is the key parameter measuring the quality of a selection criterion. The following shows that relatedness between interacting individuals is the most important factor determining the accuracy for socially-affected traits.

ACCURACY OF SELECTION

Below we describe five different selection methods that can be applied to improve socially-affected traits; individual selection, group selection, multilevel selection, selection based on relatives, and selection on estimated breeding values. With the first three methods, selection candidates need to be kept in groups, whereas with the last two methods selection candidates can be kept individually and can be selected based on information from group-housed relatives. For each of the five selection methods, we present expressions for accuracy of selection. Derivations are given in Griffing (1977), Ellen et al. (2007), Bijma and Wade (2008), Wade et al. (2010), and Bijma (2011a). **Table 2** summarizes the selection methods, the selection criteria, and the accuracies.

Individual selection (IS)

With individual or mass selection, group-housed selection candidates with the best phenotypes are selected as parents of the next generation. Thus, the selection criterion is the individual trait value, $SC_i = P_i$ (Wade et al., 2010). Accuracy of individual

Table 2 | Selection criterion and accuracies of the different selection methods.

Selection method[a]	Selection criterion	Accuracy[b]
IS	P_i	$\left\{r\sigma^2_{TBV} + (1-r)\left[\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}}\right]\right\}/\sigma_P\sigma_{TBV}$
GS	$\overline{P}_{grp}$	$[(n-1)\,r+1]\,\sigma_{TBV}/n\sigma_{\overline{P}_{grp}}$
MS	$P_i + g\cdot\sum_{n-1}P_j$	$\dfrac{[g+r+(n-2)\,gr]\,\sigma^2_{TBV} + (1-g)\,(1-r)\left[\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}}\right]}{\sigma_{TBV}\sigma_{SC}}$
SR	$\overline{P}_{rel_i} = 1/mn\sum_{l=1}^{m}\sum_{j=1}^{n}P_{j,l}$	$r_{rel}\eta/\sqrt{\tau+(1-\tau)/mn}$ where $\eta = \sigma_{TBV}/\sigma_{TPV}$, $\tau = r\eta^2$
EBV	$\widehat{a}_i$	$\approx \rho_{MME}\left[\dfrac{\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}}}{\sigma_{A_D}\sigma_{TBV}}\right]$

[a] *IS is individual selection; GS is group selection; MS is multilevel selection; SR is selection based on relatives; EBV is selection on estimated breeding values ignoring social genetic effects;* [b] *r denotes relatedness between group members; n = number of group members; mn = number of relatives in m groups;* r_{rel} *= relatedness between the candidate and its relatives;* $\sigma^2_{TBV} = \sigma^2_{A_D} + 2\,(n-1)\,\sigma_{A_{DS}} + (n-1)^2\sigma^2_{A_S}$; $\sigma^2_P = \sigma^2_{A_D} + \sigma^2_{E_D} + (n-1)\left(\sigma^2_{A_S} + \sigma^2_{E_S}\right) + r\left[2\,(n-1)\,\sigma_{A_{DS}} + (n-1)\,(n-2)\,\sigma^2_{A_S}\right]$; $\sigma^2_{\overline{P}_{grp}} = \left\{\sigma^2_P + 2\,(n-1)\,Cov\,(P_i, P_j) + (n-1)\left[\sigma^2_P + (n-2)\,Cov\,(P_i, P_j)\right]\right\}/n^2$ *(Ellen et al., 2007);* $\sigma^2_{SC} = \sigma^2_P + 2gCov\left(P, \overline{P}_{grp}\right) + g^2\sigma^2_{\overline{P}_{grp}}$ *(Bijma and Wade, 2008; Wade et al., 2010);* $\sigma^2_{TPV} = \sigma^2_{P_D} + 2\,(n-1)\,\sigma_{P_{DS}} + (n-1)^2\sigma^2_{P_S}$.

selection equals (Wade et al., 2010)

$$\rho_{TBV,IS} = \frac{r\sigma^2_{TBV} + (1-r)\left[\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}}\right]}{\sigma_{TBV}\sigma_P} \tag{6}$$

In the numerator of this expression, the first term is always positive, whereas the second term can take negative values when the direct-social genetic covariance is sufficiently negative. When group members are unrelated ($r = 0$), accuracy depends only on the second term in the numerator, and can thus be negative when direct and social genetic effects are negatively correlated (Griffing, 1967, 1977). This theoretical prediction agrees with empirical observations (Wade, 1976; Craig, 1982; Goodnight, 1985; Agrawal et al., 2001; Muir, 2005; Muir et al., 2013). In *Tribolium*, for example, it was found that individual selection for increased population size gave a decrease in population size in the next generation (Wade, 1976). Muir (2005), Muir et al. (2013) showed in quail selected for 6-week body weight in groups of 16, that individual selection in unrelated groups resulted in a slight decline. With unrelated group members, therefore, individual or mass selection is inadequate to improve socially-affected traits. With fully related group members ($r = 1$, i.e., clones), accuracy is always positive so that response is in the same direction as selection. However, usually a limited relatedness suffices to guarantee positive accuracy (Wade et al., 2010).

Group selection (GS)

With group selection, groups with the highest average phenotypic value are selected to become parents of the next generation (Muir, 1996). Thus, the selection criterion is the group average, $SC_i = \overline{P}_{grp}$. Accuracy of group selection equals (Ellen et al., 2007)

$$\rho_{TBV,GS} = \frac{[(n-1)\,r+1]\,\sigma_{TBV}}{n\sigma_{\overline{P}_{grp}}} \tag{7}$$

where $\sigma_{\overline{P}_{grp}}$ denotes the standard deviation in the average phenotype of group members. In equation 7, both the numerator and denominator are positive, which results in a positive accuracy and a positive response to selection. Thus, group selection prevents negative response to selection. Group selection is, however, only efficient when group members are sufficiently related (Bijma, 2011a). As shown by Muir (1996), group selection can result in rapid short-term responses. However, when groups are composed of relatives, selection between groups will result in between-family selection, which increases rates of inbreeding (Muir et al., 2013). Hence, this selection method should be combined with selection algorithms that restrict the rate of inbreeding, such as optimal contribution selection (Meuwissen, 1997).

Multilevel selection (MS)

With multilevel selection, selection is based on a linear combination of the phenotypes of the individual and the phenotype of its group mates, $SC_i = P_i + g\cdot\sum_{n-1}P_j$, where g is the degree of group selection ($g = 0$ corresponds to individual selection, whereas $g = 1$ corresponds to group selection) (Griffing, 1977; Bijma et al., 2007b; Muir et al., 2013). The accuracy of multilevel selection equals (Wade et al., 2010)

$$\rho_{TBV,MS} = \frac{\begin{gathered}\left\{\left[g+r+(n-2)\,gr\right]\sigma^2_{TBV} + \right.\\ \left.\left(1-g\right)(1-r)\left[\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}}\right]\right\}\end{gathered}}{\sigma_{TBV}\sigma_{SC}} \tag{8}$$

where σ^2_{SC} is the variance of the selection criterion. Equation 8 shows that both multilevel selection ($g > 0$) and relatedness between group mates ($r > 0$) create a positive accuracy, so that response to selection is positive. Without multilevel selection ($g = 0$), Equation 8 reduces to Equation 6.

Selection based on relatives (SR)

The above three selection methods have considered selection candidates kept in groups. Keeping selection candidates in groups, however, may be undesirable because it may interfere with collection of individual trait values, such as egg number in laying hens. To improve socially-affected traits when selection candidates are kept individually, information of relatives kept in family groups can be used (Ellen et al., 2007). In such schemes, individually housed selection candidates are selected based on the performance of sib or offspring groups, $SC_i = \overline{P}_{rel,i}$ (Ellen et al., 2007). Keeping relatives in family groups guarantees that both direct and social effects are captured in the selection criterion, even when social effects are ignored in the breeding value estimation (e.g., because genetic parameters are unknown). When relatives are kept in m groups of n individuals each, the accuracy of selection based on relatives (Ellen et al., 2007) equals

$$\rho_{TBV,SR} = \frac{r_{rel}\eta}{\sqrt{\tau + (1-\tau)/mn}}, \qquad (9)$$

in which $\tau = r\eta^2$, being the intraclass correlation between relatives; $\eta = \sigma_{TBV}/\sigma_{TPV}$ is an analogy of the square root of heritability; and mn is the number of relatives for each selection candidate (m is number of groups with n relatives each). Ellen et al. (2007) showed that using full sib groups (either full sibs of the selection candidate, or full-sib offspring of the selection candidate) gave the highest accuracies, and thus the highest expected responses to selection. Particularly when relatives are sibs of the selection candidates, restriction of the rate of inbreeding requires attention.

Selection on estimated breeding values (EBV)

For the above selection methods, knowledge of genetic parameters is not needed. When genetic parameters of a trait are known, however, the use of BLUP (Best Linear Unbiased Prediction) to estimate breeding values is to be preferred, because it utilizes information of all relatives and corrects for systematic environmental effects, such as herd-year-season effects (Henderson, 1975). Often genetic parameters for ordinary (direct) breeding values will be known, but parameters for the social effects may not be known. In that case, BLUP may be implemented ignoring social genetic effects. In the following, therefore, we will first consider selection on BLUP-EBV when social effects are ignored, and subsequently consider the case where social effects are included in the model.

Ignoring social genetic effects (EDBV). In this case, breeding values are predicted using the classical mixed animal model

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Za} + \mathbf{e}, \qquad (10)$$

where $\mathbf{y}$ is the vector of observations, $\mathbf{b}$ is a vector of fixed effects with incidence matrix $\mathbf{X}$, $\mathbf{a}$ is a vector of breeding values with incidence matrix $\mathbf{Z}$ linking phenotypes of individuals to their own breeding value, and $\mathbf{e}$ is a vector of residuals. Subsequently, animals are selected on their estimated breeding value, $SC_i = \hat{a}_i$. When group members are unrelated, the approximate accuracy of the classical BLUP approach equals (Bijma, 2011a)

$$\rho_{TBV,BLUP}\,(r=0) \approx \hat{\rho}_{MME}\left[\frac{\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}}}{\sigma_{A_D}\sigma_{TBV}}\right], \qquad (11)$$

where $\widehat{\rho}_{MME}$ is the ordinary accuracy calculated from the MME, and the term in square brackets is the correlation between an individual's DBV and its TBV. This second term is required because the model predicts the DBV, whereas accuracy of interest is the correlation between EBV and TBV. Thus, using selection for classical BLUP-EBVs with unrelated group members can result in a negative accuracy [when $\sigma^2_{A_D} + (n-1)\,\sigma_{A_{DS}} < 0$], just as with individual selection (Equation 6). When groups are composed of families, however, the EBV resulting from Equation 10 is an estimate of TBV of the individuals; not of their DBV (Bijma, 2011a; Peeters et al., 2013). Hence, in that case the accuracy will always be positive, and $\rho_{TBV,BLUP,fam} \approx \widehat{\rho}_{MME}$. This theoretical expectation was confirmed in a selection experiment with quail, where selection for classical BLUP-EBVs with family groups yielded positive response, whereas selection for classical BLUP-EBVs with random groups yielded negative response (Muir et al., 2013).

Including social genetic effects. When genetic parameters are known for both direct and social genetic effects, breeding values can be estimated using a direct-indirect effects model (Muir and Schinckel, 2002; Muir, 2005; Muir et al., 2013),

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Z}_D\,\mathbf{a}_D + \mathbf{Z}_S\,\mathbf{a}_S + \mathbf{Vg} + \mathbf{e} \qquad (12)$$

where $\mathbf{y}$ is the vector for observations, $\mathbf{b}$ is a vector of fixed effects with incidence matrix $\mathbf{X}$, $\mathbf{a}_D$ is a vector of direct breeding values with incidence matrix $\mathbf{Z}_D$ linking phenotypes of individuals to their own direct breeding value, $\mathbf{a}_S$ is a vector of social breeding values with incidence matrix $\mathbf{Z}_S$ linking phenotypes of individuals to the social breeding values of their group mates, $\mathbf{g}$ is a vector of non-genetic random group effects with incidence matrix $\mathbf{V}$ (Bergsma et al., 2008), and $\mathbf{e}$ is a vector of residuals. The covariance structure of the genetic terms is $var\begin{bmatrix}\mathbf{a}_D \\ \mathbf{a}_S\end{bmatrix} = \mathbf{C} \bigotimes \mathbf{A}$, where $\mathbf{C} = \begin{bmatrix}\sigma^2_{A_D} & \sigma_{A_{DS}} \\ \sigma_{A_{DS}} & \sigma^2_{A_S}\end{bmatrix}$, $\mathbf{A}$ is a matrix of relatedness coefficients between individuals, and $\bigotimes$ denotes the Kronecker product of matrices. This model yields estimates of direct and social breeding values, which can be combined into an estimate of the total breeding value, $\hat{a}_{TBV,i} = \hat{a}_{D,i} + (n-1)\,\hat{a}_{S,i}$, which is the selection criterion; $SC_i = \hat{a}_{TBV,i}$.

When genetic parameters are known, breeding values can be estimated from the mixed model in Equation 12 irrespective of relatedness among group members. Muir et al. (2010, 2013), however, showed that relatedness within a group resulted in substantially higher accuracy, and that using related group members contributed more to accuracy than distinguishing between direct and social effects in the mixed model (i.e., the use of Equation 12 rather than 10).

Predicted responses

To illustrate the results of the different selection methods, we calculated predicted response to selection for survival time in laying hens showing cannibalism. For this trait, accurate genetic parameters have been published, both for purebred (Ellen et al., 2008) and crossbred populations (Peeters et al., 2012). Estimated genetic parameters are shown in Table S1. Predicted responses were calculated from Equation 5, using a selection intensity of unity ($\iota = 1$). For the accuracy, equations presented in **Table 2** were used. For the calculation of accuracy, different group compositions were used. Group members were either unrelated ($r = 0$), half sibs ($r = 0.25$), or full sibs ($r = 0.5$). For selection based on relatives, the relationship between selection candidates and relatives kept in groups was either half sibs ($r_{rel} = 0.25$) or full sibs ($r_{rel} = 0.5$). **Table 3** shows the predicted responses. No values are given for selection on BLUP-EBVs, since these will depend on details of the population (e.g., distant relatives) that are not considered here.

In purebred laying hens, the covariance between DBV and SBV was positive. Therefore, for all selection methods, predicted response for survival time was positive, ranging from 8.8 through 30.4 days (**Table 3**). In crossbred laying hens, the covariance between DBV and SBV was moderately to strongly negative. Therefore, for individual selection response to selection was negative (−8.1 days), when selection candidates were kept with unrelated group mates and zero when selection candidates were kept with half sibs. This result implies that, for those group compositions, responses to BLUP-selection using Equation 10 will also be negative and around zero (compare Equations 11 and 6). For both purebreds and crossbreds, with a single group of related individuals, group selection resulted in the largest predicted response to selection. With ten groups of related individuals, selection based on relatives resulted in the largest predicted response to selection. For both purebred and crossbreds, and for all selection methods, using groups of full sibs resulted in the largest predicted response to selection. Note that, when accurate estimates of genetic parameters are available, selection on estimated total breeding values from Equation 12 is always equally good or better than any other selection method applied to the same population structure (Muir et al., 2013).

In conclusion, highest accuracies and responses to selection for socially-affected traits will be obtained using a population structure where individuals are kept in family groups.

Table 3 | Predicted response for survival time in purebred and crossbred laying hens using individual selection, group selection, and selection based on relatives.

Selection method[a]	m[b]	$\Delta G_{predicted}$ Purebred			$\Delta G_{predicted}$ Crossbred		
		Unrelated	HS	FS	Unrelated	HS	FS
IS	1	9.7	12.6	15.5	−8.1	0.0	8.1
GS	1	9.6	16.1	22.1	10.5	17.5	24.1
SR	1		8.8	16.7		9.3	18.0
	10		19.1	30.4		21.5	35.0

*[a]IS is individual selection; GS is group selection; SR is selection based on relatives. [b]m is number of groups per selection candidate. Response were predicted using $\Delta G = \iota\rho\sigma_{TBV}$, where $\iota = 1$. For each selection method, ρ was based on the Equations presented in **Table 2**. To predict ρ and σ_{TBV}, genetic parameters for survival time were used (Ellen et al., 2008; Peeters et al., 2012) as shown in Table S1.*

EMPIRICAL EVIDENCE OF SOCIAL GENETIC EFFECTS

ESTIMATED GENETIC PARAMETERS

Several studies have estimated genetic parameters for socially-affected traits. **Table 4** gives an overview of the estimated heritabilities (h^2) from a classical model, estimated total heritable variance relative to the phenotypic variance (T^2) from a direct-indirect effects model, and the estimated genetic correlations between direct breeding values and social breeding values (r_A).

In most populations, total heritable variance was greater than the ordinary additive genetic variance ($T^2 > h^2$). In two populations of trees, however, a strongly negative direct-social genetic correlation was found, causing total heritable variance to be smaller than additive genetic variance (Brotherstone et al., 2011; Costa e Silva et al., 2013). In those cases, there is strong heritable competition, and social interactions may decrease total heritable variation to zero (Costa e Silva et al., 2013). Moreover, for some traits competition is necessarily complete, so that there cannot be a response to selection. For example, in dyadic fighting contests, where the trait of interest is winning vs. loosing (1–0), a change in population mean is impossible since each contest has precisely one winner and one loser. Social effects models properly account for this by fitting a direct-indirect correlation of -1 and a total heritable variance of zero (Wilson et al., 2011; Sartori and Mantovani, 2013).

Table 4 shows that for most traits, social interactions had a substantial effect on the total heritable variation, explaining 6% through 98% of T^2. For example, for survival time in laying hens showing cannibalism, social interactions explain 33% through 87% of the total heritable variation in survival time (Ellen et al., 2008; Peeters et al., 2012). The classical animal model suggests a genetic standard deviation of 27–44 days, whereas the direct-social effects model yields a standard deviation of the total breeding value of 50–65 days. In those cases, response to selection can be increased by taking into account social effects in the selection strategy.

There appears to be no systematic pattern in the direct-social genetic correlation (r_A). For example, for bite mark score in mink r_A was strongly positive, meaning that an individual that bites more (social effect) also attract more bites (direct effect) and *vice versa* (Alemu et al., 2014b). At first glance, biting in mink may seem similar to pecking in laying hens. Peeters et al. (2012) found a strongly negative r_A for survival time in crossbred laying hens, indicating that individuals that live longer are more likely to be cannibalistic, i.e., lives longer at the expense of others. This is precisely opposite to the situation in mink. In quail, Muir (2005) also found a strong negative r_A for growth indicating that birds that grew the fastest reduced the growth of other birds in the group due to strong negative social interactions.

SELECTION EXPERIMENTS

Evidence of social genetic effects may also be obtained from selection experiments aiming to utilize such effects to generate response to selection. One of the first empirical studies used group selection for increased or decreased population size in randomly formed groups of flour beetles (Wade, 1976, 1977). In both directions, group selection was effective, even though groups were composed at random, whereas individual selection was not effective. Goodnight (1985) compared individual and group selection for leaf area in *Arabidopsis*. Leaf area responded to group selection, but not to individual selection. These results suggest the presence of social genetic effects ($\sigma^2_{A_S} > 0$), together with a negative direct-social genetic correlation.

Table 4 | Overview of genetic parameters using a classical model and a direct-indirect effects model.

Species	Trait	Classical model	Direct-indirect effects model	
		h^2	T^2	r_A
CATTLE (*BOS TAURUS*)				
	Feed lot growth rate[1]	0.06	2.01	0.69
	Social dominance[2]	0.12	0.01	−0.98
COD (*GADUS MORHUA*)[3]				
	Change in condition factor	0.13	0.22	−0.08 (n.s.)
	Dorsal fin erosion	0.01–0.83	0.48–1.29	0.30–0.78 (n.s.)
	Caudal fin erosion	0.06	0.43	0.21 (n.s.)
	Body weight	0.24–0.34	0.41–0.43	0.05–0.31 (n.s.)
DEER MICE (*PEROMYSCUS MANICULATUS*)[4]				
	Rearing rate	0.10	0.61	0.79
	Reciprocal latency to fight	0.05	0.56	0.86
FOREST TREE (*EUCALYPTYS GLOBULUS*)[5]				
	Diameter at breast height	0.34–0.42	0.05–0.08	∼ −0.9
	Mycrospaerella leaf disease	0.41	0.67	0.8
LAYING HENS (*GALLUS GALLUS*)				
	Survival time, purebred[6]	0.07–0.10	0.15–0.19	−0.31 to 0.18 (n.s.)
	Plumage condition, purebred[7]	0.02–0.10	0.10–0.54	−0.38 to 0.16 (n.s.)
	Survival time, crossbred[8]	0.05–0.06	0.17–0.26	−0.83 to -0.37
	Early egg performance, crossbred[9]	NE	0.50–0.55	NE
MINK (*NEOVISON VISON*)[10]				
	Total bite mark score	0.23	0.61	0.90
MUSSEL CULTURES (*MYTILUS GALLOPROVINCIALIS*)[11]				
	Length	0.17	0.21	−0.09 (n.s.)
	Area	0.17	0.27	−0.30(n.s.)
NILE TILAPIA (*OREOCHROMIS NILOTICUS*)[12]				
	Harvest weight	0.31	0.32	−0.38
PIGS (*SUS SCROFA*)				
	Growth rate fattening[13]	0.20	0.59	0.24
	Growth rate fattening[14]	0.13	0.23	−0.02 (n.s.)
	Final body weight[15]	0.39	0.47	0.07 (n.s.)
	Back fat depth[15]	0.45	0.55	0.08 (n.s.)
	Muscle area[15]	0.29	0.31	−0.63 (n.s.)
	Growth suckling piglets[16]	0.07	0.15	−0.27 (n.s.)
	Androstenone[17]	0.61	0.75	0.24 (n.s.)
	(Net) Daily gain[18]	0.22–0.24	0.32–0.34	0.01
	Feed intake[18]	0.19	0.35	0.05
RED DEER (*CERVUS ELAPHUS*)[19]				
	Social dominance	0.10	0.03	−0.91
SITKA SPRUCE (*PICEA SITCHENSIS*)[20]				
	Diameter			−0.93
QUAIL (*COTURNIX COTURNIX JAPONICA*)[21]				
	Body weight	0.16	1.35	−0.24

[1] Van Vleck et al., 2007, first 28 days of growth period; [2] Sartori and Mantovani, 2013; [3] Nielsen et al., 2014; [4] Wilson et al., 2009; [5] Costa e Silva et al., 2013; [6] Ellen et al., 2008; [7] Brinker et al., 2014; [8] Peeters et al., 2012; [9] Peeters et al., 2014; [10] Alemu et al., 2014b; [11] Brichette et al., 2001; [12] Khaw et al., 2014; [13] Chen et al., 2008; [14] Canario et al., 2010, d = 1; [15] Hsu et al., 2010; [16] Bouwman et al., 2010, model 4; [17] Duijvesteijn et al., 2012; [18] Bergsma et al., 2013; [19] Wilson et al., 2011; [20] Brotherstone et al., 2011; [21] Muir et al., 2013; NE is not estimable; n.s. is not significant.

Muir et al. (Craig and Muir, 1996; Muir, 1996) used group selection to improve survival and egg number of laying hens in multiple-bird cages. In their study, each sire family was housed as a group in nine-bird cages, and selected or rejected based on the performance of the group. The group-selected line kept in multiple-bird cages was compared with an unselected control line kept in single-bird cages. Mortality in the selected line decreased from 68% in generation 2–8.8% in generation 6. In generation 6, the mortality of the selected line was similar to that of the unselected control kept in single-bird cages (Muir, 1996). This rapid short-term response suggests a substantial social genetic variance in mortality. In the seventh generation, the selected line was compared with a control and a commercial line all kept in multiple bird cages. Hens of the selected line had a significantly better plumage condition than hens of the control and commercial line, whereas there was no significant difference in body weight (Craig and Muir, 1996).

In another experiment, Muir (2005) selected for TBV among individuals kept in groups of 16 members to improve 43-day body weight in Japanese quail. Individuals of the first two generations were used to estimate genetic parameters. In subsequent generations, parents were selected either on TBV (C-BLUP) or on direct EBVs only (D-BLUP; Muir, 2005). After 6 generations, C-BLUP resulted in a significant improvement of body weight, whereas D-BLUP resulted in a non-significant decrease in body weight. Furthermore, selection using C-BLUP resulted in a slight decrease in mortality, whereas D-BLUP resulted in an increase in mortality. These results suggest presence of social genetic effects and a negative direct-social genetic correlation.

Later on, Muir et al. (2013) used multi-level selection on classical BLUP-EBVs to improve 43-day body weight in Japanese quail. They compared two experimental set ups; individuals were either kept in family groups or in groups with unrelated individuals. After 18 mini generations (MG; five MG is one generation), responses were positive with family groups, resulting in a regression coefficient of 1.30 g/MG, whereas responses were much smaller with unrelated groups (regression coefficient of 0.13 g/MG). Furthermore, a significant difference in mortality was found, yielding the lowest mortality in family groups (6.6 vs. 8.5% in unrelated groups). Again, results indicate presence of social genetic effects, and agree with the theoretically expected effect of relatedness on response to selection (see above).

Ellen et al. (2013, in prep) investigated the potential to select against mortality due to cannibalism in laying hens, within the ordinary commercial operations of a laying breeding company, where selection candidates are kept individually. In total, six generations were selected. In each generation, individually housed selection candidates were selected based on survival time of relatives kept in family groups. Relatives had intact beaks and were kept with 4 or 5 sibs in traditional battery cages under commercial circumstances. **Figure 1** gives an overview of the selection design. For generations 1, 5, and 6, selection candidates were selected in two directions, high (HIGH) and low (LOW) survival. Remaining selection candidates were used to breed a control group (CONT). For generation 2 through 4, selection candidates were selected only to breed HIGH, and there was no CONT present. Because hens of the six generations were kept at different locations (**Figure 1**), it was not possible to compare hens of HIGH across generations. **Table 5** shows the expected and realized responses. Because information on survival becomes available late in life, in ordinary commercial operation individuals had to be mated when information on survival was very limited, resulting in a low selection intensity and expected responses (Ellen et al., 2014). In generation 1, 5, and 6, the realized difference in survival days between HIGH and LOW ranged from 26 to 29 days. Difference in survival days between HIGH and CONT was 13 and 19 days in generation 1 and 6, respectively, whereas the difference was −12 days in generation 5. On average, these realized differences agree with the theoretical expectation. These results show that selection against mortality due to cannibalism is feasible under ordinary commercial circumstances, but also that it is difficult to achieve high intensities of selection. Moreover, they illustrate that mortality due to cannibalism is very sensitive to changes in the environment (e.g., stocking density, light intensity, climate).

Selection also changed the physiology and behavior of birds. In generation 2, hens of HIGH showed less fear-related behavior than hens from the founder line (Bolhuis et al., 2009). This was confirmed both in young (before cannibalism develops) and in adult birds using sibs of generation 4 (Rodenburg et al., 2009a,b; Nordquist et al., 2011; de Haas et al., 2012). In generation 2, hens of HIGH had higher whole-blood serotonin concentrations and a lower platelet serotonin uptake velocity than hens of the founder line, indicating differences in functional activity of the serotonergic system (Bolhuis et al., 2009). Again, results were confirmed in sibs of generation 4. Moreover, HIGH hens of generation 4 showed dopaminergic and noradrenergic changes in two brain areas, the arcopallium (Kops et al., 2013) and the nidopallium caudolaterale (Nordquist et al., 2013). These results are in line with the proposed role of serotonergic and dopaminergic activity in feather pecking behavior (Van Hierden et al., 2004). Furthermore, sibs of generation 4 showed a reduced stress response to manual restraint and less comb and toe lesions, indicating lower levels of aggression and cannibalism (Rodenburg et al., 2009a).

Camerlink et al. (2013) investigated the effect of one generation of selection on diverging social breeding values for growth rate in pigs. In commercial pigs, behaviors such as aggressive attacks, tail biting and other injurious oral manipulation of group mates, may profoundly affect welfare and productivity. In their selection experiment, dams and sires with the most extreme (HIGH and LOW) EBVs for social genetic effects for growth during the finishing phase were selected to create the next generation, while DBVs were kept the same for both populations. In the offspring, the estimated contrast for social genetic effects was 14 g ADG (Camerlink et al., 2013, 2014b). After weaning, offspring were housed in pens of six unrelated individuals. Surprisingly, both populations did not differ in growth during the finishing phase, which could be due to the relatively small contrast in EBVs. Camerlink et al. (2014a) suggested, however, that this unexpected result might also be due to the fact that measures were taken to limit harmful behavior to an acceptable level to safeguard the welfare of the experimental animals, which may have reduced the effects of this harmful behavior on growth rate (Camerlink et al., 2012). Even though there was no effect on growth rate, systematic differences in behavior were found between both groups. HIGH pigs showed less unilateral biting and less ear biting (Camerlink et al., 2014b). They also had a lower usage of jute sacks, and inflicted less tail damage, whereas no effects on general activity were found (Camerlink et al., 2014b).

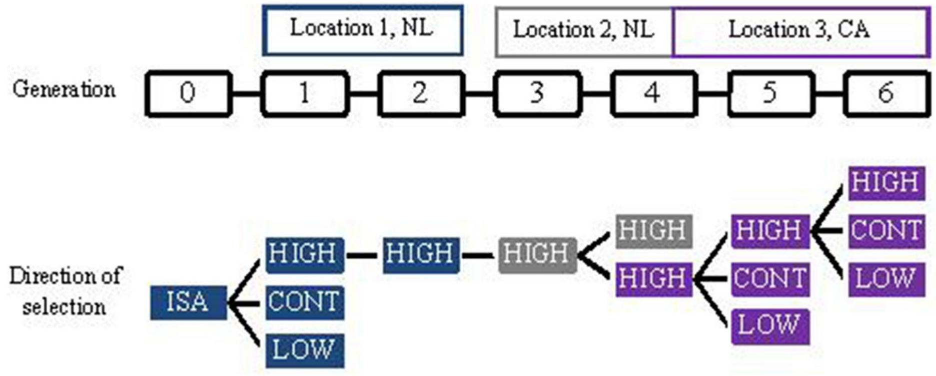

FIGURE 1 | Design of the selection experiment.

Table 5 | Expected and realized responses for survival time in laying hens using selection based on relatives.

Location	Generation	ι^1	$\rho_{TBV,SR}{}^2$	$\Delta G_{expected}{}^3$ (days)	$\Delta G_{realized}$ (days)	
					HIGH vs. CONT	CONT vs. LOW
1	1	0.14	0.3	1.7	13	16
	2	0.09	0.3	1.3		
2	3	0.52	0.2	3.5		
	4	0.21	0.3	1.9		
3	4	0.25	0.3	4.0		
	5	0.32	0.3	5.0	−12	40
	6	0.32	0.3	2.8	19	7

$^a\iota = S_P/\sigma_P$; $^b\rho_{TBV,SR} = r_{rel}\eta/\sqrt{\tau + (1-\tau)/mn}$, where $\eta = \sigma_{TBV}/\sigma_{TPV}$, $\tau = r\sigma^2_{TBV}/\sigma^2_{TPV}$, and $m = 1$; $^c\Delta G_{expected} = \iota\rho_{TBV,SR}\sigma_{TBV}$, where ι and ρ refer to parents.

Moreover, HIGH pigs showed less aggression at reunion with familiar group mates after a 24-h regrouping test in which they were confronted with unfamiliar conspecifics (Camerlink et al., 2013), which is likely related to differences in stress-sensitivity rather than aggressiveness *per se*, as no differences in aggression during mixing or in body lesion scores were found. In line with this, these HIGH pigs tended to respond less fearfully and stressed to novel and challenging situations (Reimert et al., 2014a), already during the piglet stage (Reimert et al., 2013) and they had lower leukocyte, lymphocyte and haptoglobin concentrations than LOW pigs (Reimert et al., 2014b). These behavioral and physiological data indicate that selection on high SBV for growth can result in pigs that show less harmful biting behavior, such as tail biting, and are possibly less fearful and better capable of handling stressful situations (Camerlink et al., 2013; Reimert et al., 2014a,b).

APPLICATION

Livestock are nowadays more frequently kept in (larger) groups, resulting in an increase in social interactions between individuals. Moreover, treatments to limit the consequences of adverse social interactions, such as beak trimming in poultry and tail docking in pigs, will probably be banned in the future (at least in EU countries), so that the negative effects of social interactions will likely increase unless action is taken to avoid that. Actions are needed to prevent or diminish the negative effects of social interactions. In this review, we have shown that many traits show genetic variation in social effects. Moreover, we have reviewed selection methods for socially-affected traits, showing that methods exist that utilize the social genetic variation for genetic improvement. Thus, the genetic variation and selection tools required for genetic improvement of socially-affected traits are available, indicating that genetic solutions are feasible in principle. Nevertheless, successful application in commercial breeding programs faces a number of challenges, some of which we review below.

ACCURACY OF EBVs

For commercial livestock breeding, it is most important to estimate accurate breeding values. When the objective is to separately estimate direct and social breeding values, rather than only the total breeding value, genetic parameters for direct and social effects are required. Genetic parameters for direct and social effects cannot be estimated when group members are equally related (i.e., all full sibs or half sibs). The optimal design for estimating direct and social genetic parameters has groups composed of two families. Moreover, the number of groups, rather than the number of individuals, is the key parameter determining accuracy of the estimated variance components. Bijma (2010a) showed that ~250–500 groups are needed.

The optimal group-composition for estimating direct and social genetic parameters differs from the optimal group-composition for estimating the TBV and maximizing response to selection. Accuracies of estimated TBVs are maximized when using groups composed of families (Griffing, 1976; Ellen et al., 2007; Muir et al., 2013). However, direct and social genetic parameters cannot be estimated from such designs (Bijma, 2010a). Groups composed of two families probably also yield good accuracy of estimated TBVs, certainly better than groups composed at random, but this has not been investigated thoroughly.

When interest is merely in the TBV, rather than in separate breeding values for direct and social effects, there appears to be less conflict between estimation of genetic parameters and breeding values. In this case, groups consisting of complete families can be used to estimate both the total additive genetic variance and TBVs of selection candidates. This can be achieved by fitting a classical animal model ignoring social genetic effects, as the additive genetic variance and EBVs from this model will refer to the TBV (Peeters et al., 2013, 2014). However, this will only work well if groups indeed consist of complete families.

In commercial pig production, the number of groups is often limited, and separate rooms within a barn often consist of a limited number of groups. This design makes it challenging to estimate accurate genetic parameters and breeding values for direct and social effects, and validation is difficult (Duijvesteijn, 2014). Group composition is not always recorded accurately in pig production. This will affect both the EBV of the individual of interest, and the EBVs of its group mates, and may lead to exclusion of entire groups. Moreover, group composition often changes over time because individuals are regrouped to create homogeneous groups, so as to avoid penalties when delivering pigs to the slaughter house. This creates serious problems for the breeding value estimation. For example, it is unclear which individuals to include as social partners in the model, and how to weigh those individuals. In principle, one could weigh social effects of group mates on the focal individual by the time both individuals spent together in the group. However, regrouping of individuals is often not at random, but based on individual traits that are partly genetic. Hence, simply weighing the social incidence matrix by the time both individuals spent together may therefore bias the breeding value estimation (personal observations in simulated data). Hence, when pig breeders aim to improve social genetic effects, regrouping should be avoided in breeding herds.

Other livestock species, such as dairy cattle and broilers, are regularly kept in one large group per farm. In this design, it is not (yet) possible to estimate genetic parameters for direct and social effects (see also paragraph about social genetic effects in large groups). This occurs because direct and social genetic parameters are not statistically identifiable when fitting a fixed effect for the farm (Cantet and Cappa, 2008). Consequently, it is unknown whether social interactions are important in dairy cattle and broilers.

In laying hens, small groups of sibs are used to evaluate roosters (so-called recurrent tests). Though direct and social genetic parameters cannot be estimated from this design, the design is ideal for the estimation of TBVs and probably also for the estimation of total genetic variance (Peeters et al., 2013, 2014). Hence, ordinary recurrent tests in laying hen breeding programs implicitly includes the social effects in the EBVs in an optimum manner, even though they are not explicitly modeled.

When the data contain repeated observations, presence of permanent environmental effects may complicate the estimation of genetic parameters and breeding values for social effect. In beef cattle, for example, permanent environmental effects may cause overestimation of breeding values for maternal effect when information on paternal additive genetic relationships is limited. To our knowledge, the impact of permanent environmental effects on the genetic analysis of socially-affected traits has not been investigated.

PUREBRED vs. CROSSBRED POPULATIONS

In commercial pig and poultry farming, crossbred populations are used. So far, selection experiments to improve socially-affected traits in laying hens and pigs have focused on purebred populations. Efficient improvement of socially-affected traits in crossbred populations based on data from purebred populations requires a purebred-crossbred genetic correlation (r_{pc}) close to one. When r_{pc} is small to moderate, crossbred information is needed. So far, however, r_{pc} for socially-affected traits is unknown. Results in laying hens suggest that socially-affected traits in crossbreds may differ considerably from those in purebreds. Peeters et al. (2012) found that average survival time in crossbreds was much lower than in purebreds, while social genetic effects were much larger in crossbreds. Furthermore, they found a direct genetic correlation between both crosses of almost 1, but a social genetic correlation of only 0.41. When the social genetic correlation between both lines is only 0.41, it is mathematically impossible that both purebred-crossbred social genetic correlations are near one. Thus, results of Peeters et al. (2012) suggest that r_{pc} is lower for social effects than for direct effects, indicating a greater need for crossbred data when selecting for socially-affected traits. In principle, one could estimate r_{pc} to decide on the need for crossbred information. However, unless data are available already, the amount of data required to accurately estimate r_{pc} is not very different from the amount required to select based on crossbred information, particularly when using genomic selection (Bijma and Bastiaansen, in press). Hence, it is probably better to start breeding for crossbred performance immediately, and estimate r_{pc} once sufficient data has been collected.

ENVIRONMENT

As with any trait, expression of socially-affected traits will depend on the environment, and genotype-by-environment (GxE) interaction may occur. Whether GxE-interactions are greater for socially-affected traits than for other traits is unknown at present. Cannibalism in laying hens is very sensitive to environmental conditions. Ellen et al. (in preparation), for example, found a 20% difference in survival when birds of the same generation were kept at two different locations. Whether such large differences imply substantial GxE-interaction is unclear. GxE-interaction due to differences between purebred and crossbred environments would reduce r_{pc}, but this can be resolved by selection based on crossbred information. GxE-interaction between different commercial environments, however, would reduce additive genetic variance expressed in the overall environment, restricting response to selection irrespective of the data used for selection.

The expression of social interactions might also depend on early life experiences. In laying hens, incubation and rearing conditions substantially affect feather pecking and cannibalism (reviewed in van de Weerd and Elson, 2006; Rodenburg et al., 2008). Ellen et al. (in preparation) found an 18% difference in survival between different batches of hens kept in the same environment. These batches were hatched at different weeks. In pigs, early isolation changed behavioral, neuroendocrine, and immune regulation, which can have negative consequences for health and welfare later in life (Kanitz et al., 2004). Therefore, to improve socially-affected traits, it is important to also consider early life experience.

Within a group, however, there can be different social interactions. Individuals tend to behave different toward strangers than to familiar (sibs or reared in the same group) individuals, also known as kin recognition (Hamilton, 1964). When groups consist of both sibs and random individuals, genetic parameter estimation using the direct-indirect effects model as shown in Bijma et al. (2007a) can result in biased estimates of social genetic effects and can yield suboptimal response to selection (Alemu et al., 2014a). Both in pigs and fish it was found that kin recognition explained a substantial part of the phenotypic variation, after correcting for group and family effects (Duijvesteijn, 2014; Khaw et al., 2014). However, when social genetic effects differ between kin and non-kin, it is not (yet) possible to estimate those genetic parameters (Alemu et al., 2014a). Further studies are needed to disentangle the social genetic effect for kin and non-kin.

SOCIAL GENETIC EFFECTS IN LARGE GROUPS

So far, estimation of genetic parameters and selection experiments focused on relatively small group sizes. Small group sizes have been used for several reasons. For estimation of genetic parameters, small groups are preferred (1) because in small groups it is a reasonable assumption that all group members interact with each other; and (2) because accurate estimation of social genetic parameters requires data on many groups (Bijma, 2010a). For estimation of breeding values and selection, small groups have been used (1) to have related individuals in a group (either full sibs or half sibs); (2) to have at least one group of relatives per family. Both lead to increased accuracy of the selection method. When groups are large, it is unclear which individuals interact with each other, and the number of groups will be small resulting in inaccurate breeding values. So far, no experiments or analysis have been done to improve socially-affected traits in large groups.

We see two opportunities to genetically improve socially-affected traits in large groups. First, selection decisions can be based on breeding values estimated from data on small groups. This approach will be successful only when the correlation between total breeding values in small *vs.* large groups is reasonably close to one. Whether that is the case is an empirical question. In laying hens, for example, feather pecking and mortality due to cannibalism are more problematic in larger groups (e.g., Nicol et al., 1999; Bilčik and Keeling, 2000; Lay et al., 2011). Furthermore, spreading of social interactions due to social learning might be more pronounced in larger groups, but larger groups may also show greater social tolerance (Turner et al., 2001; Zimmerman et al., 2006). Second, one can attempt to estimate genetic parameters and breeding values from data on large groups, or even a single group. This requires that the individuals that interact with each other are identified. In a forest, for example, social genetic effects can be estimated by using the inverse of the distance between two trees in the incidence matrix for social effects (Muir, 2005). When the location of individuals in large groups can be traced sufficiently precise, for example with sensor technology, similar approaches may be feasible in livestock. Such systems are not available at present, but the basic technology exists.

FUTURE DIRECTIONS

In this part, we will describe some future developments, which also hold promise for social genetic effects models.

GENOMIC SELECTION

Genomic selection is currently being implemented in livestock breeding. Genomic selection has the greatest impact for traits that are: difficult to measure, cannot be measured on the selection candidates, are measured late in life, or have low heritability (Meuwissen et al., 2001; Muir, 2007). Improvement of socially-affected traits using genomic selection would be promising for a number of these reasons (Muir et al., 2014). For mortality due to cannibalism in laying hens, genomic selection would solve the problem of low intensities of selection that occurs in traditional schemes because information becomes available late in life (see **Table 5**). On the one hand, genomic selection methods could be extended to explicitly include social genetic effects; i.e., to estimate both direct and social genomic EBVs. For this purpose, the additive genetic relationship matrix (see below Equation 12) could be replaced with a genomic relationship matrix, an approach known as “Genomic BLUP” (Strandén and Garrick, 2009), or with a relationship matrix combining pedigree and genomic data, known as the H-matrix (Legarra et al., 2009). The use of genomic information may help to solve identifiability issues, since pairs of full sibs no longer all have the same relationship. A challenge will be to design a reference population that can be used for genomic selection of socially-affected traits. However, so far it is unknown what the optimal design of the reference population is (i.e., group structure, number of groups, relatedness within a group). An alternative is to use family groups and estimate total genomic breeding values. For example, in recurrent tests in laying hens where crossbred offspring are kept in sire-family groups, genotyping the fathers and fitting an ordinary genomic selection model would yield genomic estimates of total breeding values, rather than direct breeding values. A similar approach could be used for tail-biting in pigs, where crossbred offspring could be kept in full-sib groups.

SOCIAL GENETIC EFFECTS AND DISEASES

In this review, social interactions have implicitly been interpreted as behavioral interactions. However, also infectious disease traits, represent socially-affected traits. The disease status of an individual is affected both by the individual’s susceptibility to the disease (direct effect) and by the infectivity of its social partners (social effect; Lipschutz-Powell et al., 2012). Classical genetic analyses of disease data focused on individual susceptibility (Lipschutz-Powell et al., 2012). Recently, researchers started to model infectious diseases using social genetic effects models. Anche et al. (2014) showed that the individual’s breeding value for R_0 (R_0 determines risk and severity of infectious diseases) is a function of its own allele frequency for susceptibility and infectivity and of the population average susceptibility and infectivity. Again, relatedness between interacting individuals is an important component, resulting in increased response in R_0. This work, therefore, suggests that breeders can considerably increase response to selection in infectious disease traits by collecting disease data from family groups. This is the case even when there is no genetic variation in infectivity, since also genetic variation in susceptibility generates social genetic effects (see Anche et al., 2014, for details). Empirical studies are needed to confirm theoretical expectations. These approaches could also lead to novel insights applicable in the field of breeding animals for group housing.

CONCLUSION

Social interactions are important for livestock genetic improvement. Applying a selection method that targets both direct and social effects will be a key factor to improve welfare and productivity of livestock simultaneously. There is growing evidence that methods are effective for animals kept in small groups. Challenges are in the application in commercial livestock breeding programs, for example in populations consisting of large groups.

AUTHOR CONTRIBUTIONS

Esther D. Ellen wrote and prepared the manuscript for submission. T. Bas Rodenburg, J. Elizabeth Bolhuis, Egbert F. Knol, and Gerard A. A. Albers were involved in the discussion of the manuscript and reviewed the manuscript. T. Bas Rodenburg, J. Elizabeth Bolhuis, Irene Camerlink, Naomi Duijvesteijn, William M. Muir, and Piter Bijma wrote and reviewed the manuscript. Katrijn Peeters, Inonge Reimert, Ewa Sell-Kubiak, Johan A. M. van Arendonk, and Jeroen Visscher reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fgene.2014.00377/abstract

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Methods to address poultry robustness and welfare issues through breeding and associated ethical considerations

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As consumers and society in general become more aware of ethical and moral dilemmas associated with intensive rearing systems, pressure is put on the animal and poultry industries to adopt alternative forms of housing. This presents challenges especially regarding managing competitive social interactions between animals. However, selective breeding programs are rapidly advancing, enhanced by both genomics and new quantitative genetic theory that offer potential solutions by improving adaptation of the bird to existing and proposed production environments. The outcomes of adaptation could lead to improvement of animal welfare by increasing fitness of the animal for the given environments, which might lead to increased contentment and decreased distress of birds in those systems. Genomic selection, based on dense genetic markers, will allow for more rapid improvement of traits that are expensive or difficult to measure, or have a low heritability, such as pecking, cannibalism, robustness, mortality, leg score, bone strength, disease resistance, and thus has the potential to address many poultry welfare concerns. Recently selection programs to include social effects, known as associative or indirect genetic effects (IGEs), have received much attention. Group, kin, multi-level, and multi-trait selection including IGEs have all been shown to be highly effective in reducing mortality while increasing productivity of poultry layers and reduce or eliminate the need for beak trimming. Multi-level selection was shown to increases robustness as indicated by the greater ability of birds to cope with stressors. Kin selection has been shown to be easy to implement and improve both productivity and animal well-being. Management practices and rearing conditions employed for domestic animal production will continue to change based on ethical and scientific results. However, the animal breeding tools necessary to provide an animal that is best adapted to these changing conditions are readily available and should be used, which will ultimately lead to the best possible outcomes for all impacted.

Keywords: genomic selection, multi-level selection, kin selection, ethics, behavior, animal welfare, indirect genetic effects, robustness

INTRODUCTION

Consumers and society in general are becoming more aware of ethical and moral dilemmas associated with confined rearing systems (Swanson, 2007; Croney et al., 2012). Simultaneously, industry personnel are concerned about competitive social interactions that are inherent to less confined rearing production systems (Swanson, 1995; Rodenburg et al., 2008; Lay et al., 2011). Such interactions can result in injuries, stress, and mortalities. Unfortunately, there is also a concern that selection for increased productivity contributes to these welfare issues (Oltenacu, 2009; Rodenburg et al., 2010; Muir and Cheng, 2013). These concerns have brought about mandated or consumer driven changes in the way poultry and livestock can be managed (Croney and Millman, 2007; Croney, 2010) and raised issues for sustainability of the industry (Mench et al., 2011; Swanson et al., 2011). These mandates can limit selection programs in the interest of well-being or robustness of the animal (Blokhuis et al., 2007; Michel et al., 2007; Sorensen and Fraser, 2010). However, selective breeding programs are rapidly advancing, enhanced by both genomics and new quantitative genetic theory. The objective of this review is to examine the potential for new breeding programs to address these concerns.

BEHAVIOR AND MANAGEMENT

Laying hens were domesticated several 1000 years ago. Early domesticated chickens lived in a small group in backyards, scratching and foraging food from the ground, performing heritable behaviors such as dust-bathing and pre-laying nesting, and returning to settle in the evening. Over the past several decades, the management and production systems for laying hens have undergone dramatic changes, with many groundbreaking scientific discoveries and technological advances, such as intense animal breeding programmers and mass-produced housing facilities. Farming practices were shifted from backyard farming to the modern intensified and specialized industries such as the poultry industry. See Eitan and Soller (2012) for review.

Several housing systems for laying hens have been developed in the modern egg industry: cage systems (conventional cage, furnished/enriched cage, and colony cage) and non-cage (alternative) systems (single tiered/floor housing, multi-tiered/aviaries with or without integrated nest boxes, and outdoor/free-range; LayWel, 2004a). The conventional (battery) cage system is the most common commercial housing facility for laying hens in the United States and in most non-EU countries. Typically, 5–9 hens, provided 412–438 cm^2/hen, are housed together. The advantages of a conventional cage system, compared to other housing systems, in hen welfare are (1) a stable social hierarchy associated with the small group size; (2) low mortality; (3) low risk of damaging feather pecking and outbreaks of cannibalism; (4) cleaner eggs with low levels of parasitism; (5) improved bird health with low levels of infection, bumble foot, keel bone damage (deformation and fractures), and aerial pollution; (6) low risk of predation; (7) easy management and care; and (8) high economic efficiency. However, there is considerable morphological, physiological, and behavioral evidence demonstrating that the use of battery cages increases stress reactions in hens and decreases quality of life due to an overcrowded and barren environment. The main disadvantages are (1) discomfort and abnormal behavior resulting from limited space for hens to perform heritable behaviors such as dust-bathing, roosting, and pre-laying nesting; (2) decreased bone quality (osteoporosis) with high susceptibility of fractures on depopulation; and (3) increased body injury from feather pecking and cannibalism, resulting from insufficient space to escape from dominants (LayWel, 2004a,b; Savory, 2004; Lay et al., 2011; Sumner et al., 2011). Given these problems, there is growing pressure from animal welfare and consumer groups advocating a global ban of battery cage systems in the poultry industry. Similar lobbing by organizations within Europe led to a ban on battery cages as of 2012 and only furnished cages and non-cage systems are allowed (CEC, 1999). Poultry producers and scientists are in a prime position to develop hen-friendly housing systems that minimize stress and safeguard welfare while maintaining the favorable characteristics previously found in cage-based production system.

Various furnished (also called enriched) cage systems have been developed to meet the hen's behavioral repertoire including: large group cages housing 60 or more hens; medium group cages for 15–30 hens; and small group cages for up to 15 hens (LayWel, 2004a). Furnished cages attempt to provide enrichment to hens while still taking advantage of the benefits of a small group size. The cages are equipped with perches, dust baths, and nesting areas allowing for the hens to meet "the needs for their natural behaviors," such as nesting, roosting, and scratching (Appleby, 1998; Newberry, 1999; Cordiner and Savory, 2001; Appleby et al., 2002). Previous studies have shown that birds housed in furnished cages also experience improved well-being due to reduced fear, aggression, and feather pecking, and increasing bone mineral density (Newberry, 1995; Vits et al., 2005). Although furnished cage system seem to be a possible way to improve hen welfare, high mortality and feather pecking and cannibalism can occur, particularly with non-beak trimmed hens; additionally, bumble foot and keel bone damage can result from roosting (Vits et al., 2005; Sandiland et al., 2009).

Several non-cage (alternative) systems have also been developed for hens to express more of their behavioral repertoires, especially foraging, dust-bathing, and nesting; with freedom to display wing-flapping and flying. The most popular are single tiered/floor housing; multi-tiered/aviaries with or without integrated nest boxes; and outdoor/free range system. These housing systems are becoming more commonplace, especially in European countries. The main disadvantages of non-cage systems, compared to cage systems, are: (1) unstable hierarchy associated with the large flock group size; (2) high levels of mortality resulting from high risks of feather pecking and cannibalism; (3) high risk of hens sustaining fractures associated with collision damage with perches, nest-boxes, and other structures; (4) increased risk of smothering; (5) increased risk of disease and parasites due to contact with droppings, infective agents, and wild birds; (6) increased risk from predation; and (7) reduced egg production due to high mortality and poor bird welfare, especially in subordinate hens which may have limited access to feed, water, and other provided structures (nest-boxes and range) due to aggressive encounters and resource guarding by dominant hens (LayWel, 2004b; Lay et al., 2011). Further studies are needed to investigate optimal housing designs to improve access to food and water such that welfare of subordiante birds is imporoved, such as dividers, distribution, and means for alternative access.

Each housing system has itself advantages and disadvantages for the welfare of laying hens realtive to the five freedoms (Shimmura et al., 2010, 2011; Huneau-Salaun et al., 2011; Lay et al., 2011; Mench et al., 2011; Tuyttens et al., 2011). Its influences are hen strain-, age-, and facility-dependent. Furnished cage systems and non-cage (alternative) systems are developed for hens to express their nature behaviors. However, there is a high risk of reduced stability of hen social hierarchies and poorer welfare on a flock basis in all systems, i.e., a large group size with high risk of feather pecking and cannibalism. Feather pecking and cannibalism are significant contributors to mortality rates chickens with untrimmed beaks. Beak trimming is a common practice to prevent feather pecking and cannibalism. However, beak trimming causes tissue damage, exposing billions of chickens to pain (acute, chronic, or both) annually. Beak trimming is not an acceptable intervention to prevent feather pecking and mortalities but genetic selection may provide opportunities to reduce the need for beak trimming.

GENETIC SELECTION AND IMPACTS ON WELL-BEING

"Should we change housing to better accommodate the animal or change the animal to accommodate the housing" is a rather old question facing new changes especially concerning welfare of laying hens housed in modern intensive production systems (Cheng, 2007). Recent research findings have indicated that an animal's welfare is dependent on its genetic characteristics, environmental factors, and genetic–environmental interactions, i.e., an animal has the ability to adapt to its environment and the environment leads to behavioral and physiological plasticity in the animal. The outcomes of adaptation could lead to improvement of animal welfare by increasing fitness of the animal for the given environments, which might lead to increased contentment in those systems. Genetic selection for phenotypic characteristics associated with specific physiological or behavioral displays, including domestic behavior, has become a major tool to improve animal production and welfare. Studies have evidenced that animal productivity and welfare can be improved at the same time through genetic selection (Muir, 1996; Cheng and Muir, 2005; Cheng, 2010a). Genetic improvements of farm animals, with the discovery of genomic sequences, may speed up breeding programs and has the potential to be used very successfully in selecting laying hens with high production efficiency and optimal welfare, resulting from resistance to stress, disease or both. Primary among new selection methods are (1) multi-level and multi-trait selection directed at improving associative effects and (2) genomic selection (GS).

SELECTION PROGRAMS TO IMPROVE ASSOCIATIVE EFFECTS

In production environments social interactions are ubiquitous and unavoidable, except by housing animals individually, which is neither practical nor desirable as isolation is itself a stressor. Associative effects are social impacts of one animal on the performance of another (Muir and Schinckel, 2002). Such impacts can be positive, such as with mutualism where stress is abated by companionship, or antagonistic, such as with pecking and cannibalism. When such behaviors are inherited, the environmental effect on the target animal is a genetic effect in the associated animal. These inherited social effects were first defined as associative effects (Griffing, 1968, 1977) and later as indirect genetic effects (IGEs; Agrawal et al., 2001; Bijma and Wade, 2008). There are three methods to improve associative effects, i.e., either reduce negative or increase positive IGEs: (1) direct selection to reduce aggressiveness, such as pecking (Kuo et al., 1991; Kjaer and Sorensen, 1997; Kjaer et al., 2001), (2) multi-level selection (Bijma and Wade, 2008; Wade et al., 2010a; Muir et al., 2013), and (3) multi-trait selection where the direct and associative effects of each animal are estimated and directly selected for in an index (Muir and Schinckel, 2002; Muir, 2005; Bijma et al., 2007a,b).

Multilevel selection

Multilevel selection theory focuses on merit relative to levels of organization, i.e., groups and within group. This concept was originally developed in the context of non-interacting genotypes, i.e., no social effects (Lush, 1947, 1971). The issue was how much weight to place on the family means as opposed to individuals within family. Lush developed an optimal index for weighting the independent sources of variation which was purely a function of heritability. As the heritability decreases the weight on the family mean increases to average out environmental effects. At the opposite extreme, with high heritability, most of the weight is placed on individual merit because there are no (or minor) environmental effects to average out. In this regard, housing was a side issue, animals housed individually were treated the same as animals housed in groups. In the next 20 years Henderson and Quaas (1976) and Henderson (1984a,b) developed mixed models and BLUP which replaced the Lush index as it always produces the optimal weights on individual vs. family means assuming individual performances are independent, i.e., no social effects.

Griffing (1967, 1977) extended Lush's concept to include interacting genotypes, including social effects. With interacting genotypes it was necessary to define a new trait; that trait was the social effect of one animal on another and was called the associative effect, in contrast to genes that have effects on the animal's own performance, which were called direct effects. The associative effect is an IGE of one animal on another and later termed IGE's (Wolf et al., 1998; Agrawal et al., 2001). Griffing showed that if the direct and IGE effects are negatively correlated, then individual selection would be antagonistic to selection goals and actually increase negative social interactions, i.e., a gene increases performance of the individual, but has negative impacts on the trait to others in the group. In this situation Griffing recommended "group selection" where groups consist of related individuals, i.e., families. Theoretically, group selection always improves group adaptations regardless of the sign of the genetic correlation. Group selection is an extreme form of multi-level selection where all the weight is placed on the family mean.

Group selection has been shown to be highly effective in improving productivity while also improving animal well-being (Craig and Muir, 1996a,b; Muir, 1996; Cheng et al., 2001a,b, 2002, 2003; Cheng and Muir, 2005; Bolhuis et al., 2009; Rodenburg et al., 2010; Wade et al., 2010b; Nordquist et al., 2011; Kops et al., 2013; Nicol et al., 2013). Muir (1996) was the first to apply group selection in domesticated animals. In that experiment, a sample of the commercial Dekalb Delta X layer line (Dekalb Poultry Reserch, Dekalb Ill) was obtained. A random bred line from the same stock was maintained as a control (C). The group selected chicken we termed the Kinder Gentler Bird (KGB). Craig and Muir (1996a,b) and Muir (1996) showed that annual percentage mortality of the group selected line in multiple-bird cages without beak trimming decreased from 68 to 8.8% in five generations while eggs per hen housed increased from 91 to 237. Mortality in group housed birds at the termination of the experiment was no different than that in single bird cages demonstrating that mortality due to competitive interactions had been greatly reduced or eliminated. **Figure 1** clearly demonstrates improvement in feathering and survival associated with reduced pecking and negative social interactions in group selected birds (KGB) (**Figure 1A**) as opposed to individual selection (DXL) (**Figures 1B,C**). Physiological indicators showed that group selection caused changes in behavior, stress physiology, and immunology (Cheng et al., 2001a,b; Cheng and Muir, 2004). Interestingly, group selection also had impacts on robustness, a trait not associated with social interactions. In multiple-hen cages the KGB had an increased resistance to heat exposure, as indicated by lower mortality, when compared to the control and commercial lines (Hester et al., 1996) indicating the group selected KGB birds had an overall greater ability to cope with stressors.

The data also supported the conclusion that individual selection in non-social environments can worsen animal well-being and performance in social environments (Craig and Muir, 1996a,b). In that experiment a second sample of the Dekalb line was taken 20 years after the first. The Dekalb line had continued under commercial development and was selected based on productivity in single bird cages using essentially a Lush (1947) "optional" index, and later updated to traditional animal model BLUP (Harris and Newman, 1994). The new sample of the Dekalb Delta was designated (X). These two Dekalb lines (X and C) were compared to each other and the KGB for production and mortality in both

FIGURE 1 | KGB (A) and DXL (B,C) chickens after 12 months of housing in 12 bird colony cages.

single and 12 bird colony cages. Housing was at 17 weeks of age, and without beak trimming. Results showed that in single-bird cages, in terms of eggs per hen housed, eggs per hen per day, egg weight and egg mass, all were significantly greater for X than for the KGB line, which in turn was greater than C. However, in 12-bird cages the reverse was seen, with the KGB line superior to X and C for eggs per hen housed, egg mass, and eggs per hen per day. The most remarkable difference was for mortality. The X line experienced 89% mortality at 58 weeks of age as compared to the group selected KGB line with 20% and C at 54%. Clearly continued individual selection of X, as compared to its original performance (C), caused further deterioration of well-being in social situations. In contrast, group selection almost eliminated the problem. It should be noted that the experiments were conducted without beak trimming and with full light such that the full extent of the behavior could manifest itself. In commercial production environments, birds are beak trimmed and lights dimmed to control cannibalism due to pecking.

A less extreme form of multi-level selection is sometimes called kin selection, but the literature is inconsistent in this regard (Wade et al., 2010a). This form of selection is based on performance of the individual where animals are housed in family groups. Because individual performance is affected by all of the individuals in the group, if those individuals are related, the performance of the individual automatically includes its own associative effect. Thus individual selection in kin group should improve both direct and IGE effects. This theory was tested by Muir et al. (2013). In that experiment, Japanese quail (*Coturnix japonica*) were used as a model. The quail were housed in 16 bird colony cages and selected for increased 43 days weight. A positive control was also utilized in which identical selection procedures and models were used (animal model BLUP). The only difference in selection methods was the way in which quail were allocated to cages. The control was allocated at random whereas kin were allocated by half-sib family.

The results showed that responses to selection for increased 43 days weight using kin selection were an order of magnitude greater than for the control. Response of the control was not significantly different from zero. Overall mortality due to fighting and cannibalism for Kin and Random grouping was respectively 6.6 and 8.5%, the difference was highly significant. Mortality was a correlated trait responding as an IGE, as expected with multi-level selection. Thus multilevel selection in kin groups was effective in reducing detrimental social interactions while improving productivity.

Multi-trait selection

Neither group selection nor kin selection as practiced above is optimal. The optimal multi-level selection program is dependent on correctly weighting the family vs. individual merit. These weights are dependent on a number of factors, including, the genetic variances for direct and IGE effects, the correlation between them, the group size, and the degree of relationship within groups (Griffing, 1977; Bijma et al., 2007a,b; Bijma and Wade, 2008; Bijma, 2010b). An alternative is multi-trait selection. Muir and Schinckel (2002), Muir (2005), and Bijma et al. (2007a,b) extended the theoretical results of Griffing (1977) to a multi-trait mixed model such that the direct and IGE effects, and their (co)variances, could be estimated. In a companion to the Muir et al. (2013) experiment with quail, Muir and Schinckel (2002) and Muir (2005) had also performed optimal two-trait selection for direct and IGE effects, the optimal being one times the direct effect and n-1 times the associative, and randomly assigned to cages, the same as the control (C).

Although the selection program was effective, and much more so than the control, the two-trait approach did not achieve the theoretical gains expected and was most likely due to errors in the genetic (co)variances, and as with any multi-trait selection program, selection induces changes in the genetic parameters, making construction of an optimal index problematic. Estimation of the genetic parameters for direct and associative effects requires moderately large data sets of groups of a small numbers of families (Bijma, 2010a). Moreover, the use of an optimal index requires recording of individual phenotypes within group, which may be difficult for egg production. Nevertheless, the optimal breeding program, even with the two-trait, is to rear animals in kin groups. In this way accuracy of selection for total breeding value is maximized (Ellen et al., 2007).

Implications of selection for associative effects on breeding programs and management

Because feather pecking can be effectively addressed by group selection, the need for beak trimming as a management practice is greatly reduced or eliminated. Also group selection increases robustness as indicated by the overall greater ability to cope with stressors suggesting that group selection is an effective method to increase robustness which should impact management. In terms of sustainability of domestication breeding programs, kin selection is easy to implement, does not require multi-trait estimates of genetic parameters and is thus robust to parameter estimation errors (Grundy et al., 1994), and is expected to improve both productivity and animal well-being similar to group selection, but with somewhat lower levels of inbreeding because families are not the unit of selection as with group selection. On the other hand, kin selection, and two-trait selection require assessment of productivity on an individual level which can be problematic for layers where group housing often makes individual records difficult except with trap nesting.

Because associative effects are improved with multi-level selection, it might be possible to increase stocking density, increase light levels, use larger groups in floor pens, and with increase in robustness, production animals may not be as sensitive to environmental stressors and disease. However, ethical concerns also limit those choices. Just because the animal can now cope better with more intensive agriculture environments should not be used as justification to allow extreme conditions. Ethical consideration need to be considered. Two other issues that need to be further researched are (1) GxE interactions, i.e., will selection to improve social effects in one environment, such as battery cages, improve social effects in another, such as floor pens. And (2) Cross breeding programs. Commercial production is often on crosses between lines, while selection is within line. In the case of hybrids, is heterosis for social effects positive? Some preliminary observational data in a commercial floor pen setting with the KGB birds suggests that social effects were also improved in large floor pens. Further testing of the KGB (C. Danchin, personal communication, October 12, 1998) showed that when the KGB was crossed to a commercial pure bred layer, mortality and aggression was more like the commercial bird than the KGB, suggesting that heterosis for social effects is for individual and not group performance. This result would imply that if crossbreds are used, that selection must be for crossbred social effects, or that both lines need to be group selected for improved social effects.

TRAITS OF SELECTION AND SELECTION METHODS

Direct selection against traits associated with unwanted behaviors, is effective but requires measuring behavior on 100–1000s of animals to implement and raises practical implementation issues (D'Eath et al., 2010). More easily measured proxy traits can be used if shown to be highly related to the behavioral trait. However, direct selection on either behavior or physiological objectives should be viewed with caution. The intended results may not be as expected. For example, Webster and Hurnik (1991) showed that traits associated with non-aggression, such as sitting and resting, were negatively correlated with productivity. Furthermore, the link between behavior and stress is misinterpreted. For example, Duncan (1979) showed that a flighty strain of birds which exhibited avoidance and panic behavior following stimulation returned to a normal heart beat sooner than a line of more docile birds, implying that docile birds may be too frightened to move. Similar problems can occur if selection is directed at the physiological responses to stress. Gross and Siegel (1985) were successful in selecting lines of birds for high and low plasma corticosterone in response to social strife but further testing (Siegel, 1993) showed that the birds did not differ in their corticosterone response to a non-social stressor. Thus, direct selection on specific behavior traits may not lead to improved animal welfare overall.

Selection response may be enhanced by GS. GS is a relatively new selection method based on genome wide predicted breeding values (GEBVs), which was first proposed by Meuwissen et al. (2001). This selection method coincides with the new single nucleotide polymorphism (SNP) technology which is high throughput, accurate, and relatively inexpensive. The concept of GS is to estimate effects of all markers simultaneously in a random effects mixed model. GS requires dense markers spaced across the genome (equal spacing being optimal without prior knowledge of QTL positions), thereby taking advantage of all available genetic variation in population wide linkage disequilibrium (LD) with those markers. Many different evolutions of GS has since evolved based on alternative assumptions and methods to estimate effects (Fernando et al., 2007; Calus et al., 2008; Aguilar et al., 2010, 2011b; Calus, 2010; Hayes and Goddard, 2010; Calus and Veerkamp, 2011; Habier et al., 2011, 2013; Meuwissen et al., 2011, 2013; VanRaden et al., 2011; Christensen et al., 2012; Garrick et al., 2014). GS has the potential to change the structure of genetic improvement schemes. For example, there are a number of traits that cannot be directly recorded on the selection candidates, e.g., performance under crossbreeding conditions, laying performance in males, slaughter quality, disease resistance, and social interaction traits. Moreover, with traditional BLUP evaluation of breeding values based on sib information, such as egg production and disease resistance, phenotypic BLUP cannot differentiate among full sibs, while this is theoretically possible with GS (Goddard et al., 2010; Garrick, 2011; Daetwyler et al., 2012; Goddard, 2012; Calus et al., 2013; Chen et al., 2013). GS also provides the opportunity to select for such traits at a younger age, i.e., genotyping and selection can occur at hatching.

The potential of GS was demonstrated by Muir (2007) using simulations based on associations with single SNPs. Relatively, GS more than doubled the accuracy of selection for a trait of low heritability (0.72 vs. 0.32). These results suggest that with adequate numbers of phenotypes and sufficiently dense SNP chip, response with GS can exceed traditional BLUP, but especially for traits of low heritability. This results because for traits of high heritability, additional information from genomics, or other sources, cannot improve accuracy. In practice GS may not increase the accuracy of selection for a number of reasons, including: (1)The density of the SNP chip is not adequate; (2) LD structure of the species is not favorable, with large LD blocks SNP effects are confounded; (3) Number of samples in the training population is low (Goddard et al., 2010). For low heritability traits, more phenotypic data is needed to train the model than with high, thus there is a trade off in terms of time and resources; And (4) the proportion of the genetic variation that is additive is small. A trait with low heritability can result because the trait has high non-additive genetic variation rather than high environmental variation. In which case neither progeny testing or GS can increase the accuracy of selection, unless some cross breeding program is considered. As a result, the success of GS is likely to vary greatly depending on the trait, species, SNP chip, and amount of phenotypic data collected.

There are several other limitations of GS, including additional cost (Tribout et al., 2012, 2013; Abell et al., 2014) and the need to control inbreeding (Goddard et al., 2010). Sonesson et al. (2012) concluded that to control inbreeding, "it is necessary to account for it on the same basis as what is used to estimate breeding values, i.e., pedigree-based inbreeding control with traditional pedigree-based BLUP estimated breeding values and genome-based inbreeding control with genome-based estimated breeding values." Simulation studies have also shown that if inbreeding rates are constrained for optimal contributions of breeding animals, that improvements of GS would be significantly reduced (Lillehammer et al., 2011; Bouquet and Juga, 2013). Finally several simulations have shown that the accuracy of GS rapidly declines rapidly after selection starts (Muir, 2007; Sonesson and Meuwissen, 2009; Bastiaansen et al., 2012) necessitating the continued collection of phenotypes to update the models.

Genomic selection is currently undergoing testing in many species (Legarra et al., 2008; Hayes et al., 2009a,b; VanRaden et al., 2009; Chen et al., 2011, 2013; de Roos et al., 2011; Wolc et al., 2011; Duchemin et al., 2012; Gao et al., 2012; Su et al., 2012; Azevedo et al., 2013; Bolormaa et al., 2013; Carillier et al., 2013; Colombani et al, 2013; Ding et al., 2013; Lillehammer et al., 2013; Badke et al., 2014; Baloche et al., 2014; Boddhireddy et al., 2014; Nordbø et al., 2014) with mixed results. Differences in methods to implemnent GS, SNP density, species, LD, traits of selection, and number of traits selected make comparisons difficult. Also, most studies compare accuracy based on a single generation of data, few studies reported actual multi-generation selection results and even fewer studies have directly comparted GS to phenotypic BLUP in a multigenerationl selection experiment. A noteable exception was a commercial test by a layer breeding company (Hendrix Genetics) using a 60 K SNP chip (Heidaritabar et al., 2014). Traditional BLUP and GS selection methods were compared side by side in three different lines of egg-laying chicken. For all lines, the responses for GS over BLUP were between 21 and 62% depending on line. However, the greatest impact of GS was annual rate of progress is due to shorter generation intervals. With traditional BLUP 2 years were required per generation of selection. With GS, selection is possible at the hatch, with breeding occurring 20 weeks later, or two generations per year. Thus on an annualized basis, the rate of progress was increased a minimum of 400% and with the increase in accuracy factored in, the rate of improvement is between 500 and 600%. The economic impact of which is large considering that one pure line breeder is multiplied in 550,000 commercial birds. However, with the increased turn over of generations, the rate of inbreeding per unit of time increases, which will limit future progress (Robertson, 1960; Hill, 1985), ability to meet changing objectives or challenges (Muir et al., 2008) and negatively affect fitness and animal wellbeing (AWB) (Meuwissen and Woolliams, 1994; Hedrick and Kalinowski, 2000; Goddard, 2009).

Selection programs, limitations, ethical considerations, and animal well-being

Animal well-being traits are often expensive or difficult to measure, or have a low heritability, such as pecking (Kjaer and Hocking, 2004; Buitenhuis and Kjaer, 2008), cannibalism (Kjaer and Hocking, 2004), robustness (de Jong and Bijma, 2002; Kanis et al., 2004; Mulder et al., 2009), mortality, leg score, bone strength (Hocking, 2010), disease resistance (Cheng et al., 2008; Cheng, 2010b), and pulmonary hypertension in broilers (Emmerson, 1997; Julian, 1998; Hocking, 2010). These traits may respond more rapidly to GS provided the economics, LD structure, and genetic architecture are favorable as discussed previously. However, GS cannot overcome issues that are inherent with collecting phenotypes, i.e., accuracies of recording and trait definitions. Phonemics and the accurate definition of traits and how to measure them may be the next challenge for breeders (Houle et al., 2010).

As an example, Mark and Sandoe (2010) discussed potential impacts of GS on dairy cattle breeding for the welfare of dairy cows. They note that in the past, some emphasis has been placed on rather poorly defined measures of traits relevant to cow welfare, including calving ease score and 'clinical disease or not' but such selection has not been sufficient to overcome these issues given the current unfavorable genetic trends for metabolic, reproductive, claw and leg diseases in dairy cattle. The authors expressed concern that GS may facilitate breeding schemes that reduce generation intervals and carry higher risks of unwanted side-effects on animal welfare. They advocate a need for measuring traits related to animal welfare and include selection pressure on those traits, either through GS or traditional breeding.

Similarly, in poultry, animal well-being traits are generally poorly defined and rarely measured. In broilers, production traits, such as growth, may need to be de-emphasized due to possible conflicts with robustness (Rauw et al., 1998; Knap, 2005, 2012). Robustness is the ability to combine a high production potential with resilience to stressors, allowing for unproblematic expression of a high production potential in a wide variety of environmental conditions (Knap, 2005, 2012). Robustness may be reduced when production-related processes demand so many resources that coping and immune responses are compromised (Knap, 2005, 2012). Other traits related to AWB need to be collected to at least ensure AWB is not being compromised as a result of the traits being selected.

All of these concerns emphasis the need to relate traits of selection, and the selection program itself, to animal well-being. As detailed previously, selection on behavior traits may not improve AWB and selection on production traits may compromise AWB, emphasizing the need for a comprehensive breeding program where traits are well-defined, recorded, and combined with a breeding program/objective that directly includes AWB. The only breeding programs that ensures that AWB will improve while at the same time improves production traits are multi-level selection and multi-trait selection where one of the traits includes IGEs. Multi-level selection emphasizes productivity of the group, not the individual, while multi-trait selection including IGEs is an alternative method to achieve the same goal. Both of these programs can include possible enhancement from GS. GS can be combined with multi-level selection and multi-trait IGE selection to IGEs and animal well-being. The methodology is strait forward using the single step method (Legarra et al., 2009; Aguilar et al., 2010, 2011a; Chen et al., 2011; Christensen et al., 2012; Legarra and Ducrocq, 2012). With the single step method of GS, the genomic information is integrated into the pedigree relationship matrix. For BLUP evaluation, either in a multi-level evaluation setting, or in a multi-trait evaluation including IGEs, the augmented relationship matrix is used directly in the mixed model equations to derive BLUP estimates of either direct effects or IGEs. In this way, GS can increase the response in production traits while at the same time improve AWB through improved social effects measured as IGEs.

A major citicism of modern food animal production is the failure to adequately consider the ethical implications of current and proposed pratices, including genetic selection of animals. Although the criteria and methods used for selection are often well-described relative to their scientific implications, the broader ethical issues that are embedded tend to be poorly addressed. All of these areas must be well-understood to ensure that sound decisions are made. It is well-established that although science can help to gage the risks of decisions, science cannot decide what level of risk is acceptable to all whom are impacted (Mench, 2003). The latter question falls squarely in the realm of ethics (Croney et al., 2012).

The criteria for trait selection must be scrutinized. Those giving due consideration to the impacts of selection on animals must consider to what extent the selection of certain traits at the expense of others is in the subject animals' best interests. For example, as noted previously, selecting animals that fit the environments in which they are kept may appear to resolve ethical concerns in regard to keep them in environments that do not fully meet their welfare needs. Following that logic, given that laying hens cannot perform certain key behaviors such as dust-bathing and nestbuilding in many commercial operations and that this compromises their well-being, it might seem reasonable to consider selecting for birds that do not (apparently need to) express such behaviors. However, while this may resolve one scientific concern, it may raise others and accompanying ethical concerns. For example, lack of expression of a behavior is not de facto evidence of lack of motivation to do so. Motivation to perform dust-bathing behavior may still exist although the actual performance of or threshold for stimulating the behavior may be altered. Further, even if the question of motivation can be resolved, behaviors such as dust-bathing serve a functional purpose (control of ectoparasites) that can be impaired by altering expression of that behavior. Consequently, selecting for reduced or eliminated dust-bathing may make economic sense (eliminating the need to provide dust baths to hens and loss of energy expended in dust-bathing) and may appear at first glance to resolve a public concern. However, it is certainly not in the best interest of the hen who still must cope with parasites, but now has one less means by which to do so.

Moreover, the idea that dust-bathing is a fundamental component of hen ethology and that attempting to eliminate it (or similar behaviors) may negatively impact the telos (Rollin, 1995) or integrity of the species must be considered (Thompson, 2008) Although the concept of species integrity is in itself somewhat contentious (Sandøe and Holtug, 1998), here, the previous discussion of robustness becomes especially relevant. Determining which selection methods are 'good' or 'best' will depend in large part on their capacity to simultaneously attend to hens' health and well-being as a function of the environments in which they are intended to be kept, while also addressing concerns related to species integrity (Star et al., 2008). The extent to which genetic integrity and animal welfare can be balanced should therefore be factored into selective breeding methods and decisions (Sandoe et al., 1999).

Given growing public concerns about intensification of animal agriculture (Swanson, 2007; Croney et al., 2012), especially relative to negative implications for animal welfare, attempting to select animals to fit increasingly more challenging or restrictive environments is likely to elicit public criticism. To avoid worsening existing problems, it is imperative that those with the authority to make breeding decisions focus not just on immediate concerns and a few traits of economic importance. Long-term impacts relating to various aspects of animal health and well-being must be appropriately considered. As is the case for all aspects of animal production, the selection methods used for layer hen production should be subject to ethical assessment as well as scientific scrutiny to ensure the best possible outcomes for all impacted.

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Examples of overlooking common sense solutions: the domestication gene and selection against mortality

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A commentary on

Multilevel selection 1. Quantitative genetics of inheritance and response to selection
by Bijma, P., Muir, W. M., and Arendonk, J. A. M. (2007a). Genetics 175, 277–288. doi: 10.1534/genetics.106.062711

Multilevel selection 2. Estimating the genetic parameters determining inheritance and response to selection
by Bijma, P., Muir, W. M., Ellen, E. D., Wolf, J. B., and Arendonk, J. A. M. (2007b). Genetics 175, 289–299. doi: 10.1534/genetics.106.062729

Whole-genome resequencing reveals loci under selection during chicken domestication
by Rubin, C. -J., Zody, M. C., Eriksson, J., Meadows, J. R. S., Sherwood, E., Webster, M. T., et al. (2010). Nature 464, 587–591. doi: 10.1038/nature08832

Today the developments in genetics are exciting. Perhaps this explains why geneticists sometimes seem to overlook common sense solutions. One example of this is the selection experiment done by Bijma et al. (2007a,b). These authors developed a sophisticated statistical method of group selection against mortality in hens randomly placed together. One may safely assume that this mortality is due to cannibalism as a result of severe feather pecking. However, they seemed to overlook the possibility that severe feather pecking is no normal behavior performed by all individuals. As a result their selection seemed not very efficient. It is often assumed that layers selected for production traits show severe feather pecking because more aggressive hens have more opportunities to obtain food. Sufficient food is necessary for a good production. Therefore, aggressive hens are supposed to have a higher fitness during the selection for production traits resulting in an undesirable correlated selection response for this trait. However, aggression does not explain why in other strains selected for production traits severe feather pecking is almost absent. It does also not explain why in species not selected for production traits severe feather pecking occurs frequently under husbandry conditions. For instance, game pheasants, partridges, ostriches and in the wild ancestor of our domestic fowl: the bankiva (*Gallus gallus*; Van Rooijen, 2010a). Severe feather pecking differs from aggressive pecking in several respects, for instance, aggressive pecks are always aimed at the head, whereas severe feather pecks are aimed at other body parts (Savory, 1995). Unlike aggressive pecking, severe feather pecking is not performed by all individuals but it is a deviant behavior performed by particular individuals (Keeling, 1994). The aim of selection under commercial conditions must be to select against these individuals (Van Rooijen, 2010b).

Another example of overlooking a common sense solution is the experiment performed by Rubin et al. (2010). To reveal loci under selection during domestication, these authors resequenced the whole genome of groups of domestic poultry and that of bankiva jungle fowl. These authors found that essentially all individuals of domesticated fowl carry a TSHR allele (the locus for the thyroid stimulating hormone receptor). The TSHR-gene plays a role in the photoperiod control of reproduction, i.e. it explains why domestic hens lay eggs almost the year round. In bankiva zoo populations this allele was only found at intermediate frequency. Therefore, these authors concluded that TSHR may be a domestication locus in chicken. They assumed that the presence of this deviant TSHR-gene in bankiva zoo populations was due to hybridization with domestic chicken. Apparently they overlooked the possibility that this gene could originate from the Ceylon jungle fowl (*Gallus lafayetti*), otherwise they had incorporated this fowl in their study. There is a good reason to consider this possibility. During the breeding season, to attract females, the male bankiva is less camouflaged than the female. Outside the breeding season the plumage of the bankiva cock is more hen-like (eclipse plumage). The domestic cock does not possess such an eclipse plumage and is able to reproduce the year round. Probably, the TSHR-gene plays also a role in the photoperiod control of the male eclipse plumage, i.e., it probably explains why domestic males have a similar plumage the year round. Also the Ceylon male does not possess an eclipse plumage. The Ceylon male and female seem able to reproduce the year round (this is confirmed by fancy fowl keepers) and, thus, oviposition and male sexual behavior seem hardly controlled by photoperiod. The explanation may be that Ceylon fowl lives on Sri Lanka (formerly Ceylon), where from May to August the Yala monsoon brings rain to the south western half of the island, and from October to January the Maha monsoon to the North and East (Cummings et al., 2006). Therefore the relation between day length and the most suitable period for reproduction is not straightforward for the Ceylon jungle fowl population on Sri Lanka. This suggests that the Ceylon jungle fowl carry the deviant TSHR-locus. Probably, the domestic chicken has a multiple origin (Nishibori et al., 2005). For instance, the gene for the yellow skin descents from the Sonnerats jungle fowl (*Gallus sonneratii*) (Eriksson et al., 2008. Therefore one may question whether the TSHR-locus does not descend from Ceylon jungle fowl and thus is much older than domestication. The suggestion that the TSHR-locus is a domestication locus seems premature, due to a focus on the genetic method.

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Response to commentary on "Examples of overlooking common sense solutions: the domestication gene and selection against mortality"

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A commentary on

Examples of overlooking common sense solutions: the domestication gene and selection against mortality
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In a commentary in Frontiers, Van Rooijen (2014) states: "Today the developments in genetics are exciting. Perhaps this explains why geneticists sometimes seem to overlook common sense solutions. One example of this is the selection experiment done by Bijma et al. (2007a,b). ……As a result their selection seemed not very efficient." In those two papers, however, we do not report a selection experiment. The first paper presents general quantitative genetic theory, showing how interactions among individuals alter heritable variation in traits, and how this can affect response to selection. The second paper presents general methodology to estimate the quantitative genetic parameters for such traits, and illustrates this methodology using a population of laying hens showing high mortality due to pecking behavior. Neither of those papers report results of a selection experiment.

For the specific case of feather pecking, Van Rooijen suggests that the methodology would rest on the assumption that feather pecking results from aggression. This is not true. The strength of the methodology is that it captures the full heritable variance in the trait, irrespective of the underlying mechanism. Hence, for mortality due to pecking, the method captures both the actor component originating from the individual performing the pecking behavior and the victim component, as well as their covariance. These components are identified statistically from the covariances between trait values of relatives and their social partners, without any assumption on the underlying mechanisms. The method produces optimal breeding values, given the genetic parameters. Results of selection experiments based on the theory, presented in other papers (Muir, 1996; Muir et al., 2013; Ellen et al., 2014), confirm the efficiency of the proposed methodology.

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