Biomedical research has struggled with individual variation ever since its existence. Clearly, it is not the average population that gets a certain disease, but usually specific individuals under specific environmental conditions. For example, it is well recognized in humans that only a rather small proportion of individuals develop depression/anxiety disorders after stressful life events, become addicted after exposure to drugs of abuse, or express escalated and violent aggression after repeated social conflicts. Likewise, the therapeutic efficacy and/or side-effect profile of pharmacological treatments of these psychopathologies is highly variable between individuals. Hence, the major challenge of contemporary biomedical research is to understand not only this individual disease vulnerability, but also the individual differentiation in response to medication. Biomedical research using animal models starts to recognize this problem as well. During the last decades, preclinical animal research has obtained a wealth of evidence on the way in which the adult phenotype is shaped by the physical and social environment at critical periods during development [151]. Moreover, it becomes increasingly clear that these developmental processes interact with genetic predispositions in a rather complex way [90,119], and the adult phenotype is considered to be the net result of this gene-environment interaction. This complex, rather subtle and poorly understood interaction is one of the main reasons why certain experimental results are often difficult to reproduce in different laboratories [102,149]. The answer to this problem is generally a further reduction of genetic variation by inbreeding and standardizing rearing, housing and experimental conditions. However, even within inbred populations of mice or rats exposed to adverse (stressful) situations, susceptible and unsusceptible subpopulations can be distinguished. The result of more than a century of laboratory animal experimentation is that science can now select their experimental animals out of a list of over 500 officially registered inbred strains of mice and about 250 registered inbred rat strains. In addition, there are numerous outbred strains, unregistered strains and an almost exponentially increasing number of transgenic strains. This has resulted in the peculiar situation where it is virtually impossible to select a given strain of experimental animals on a rational scientific basis, with the exception of transgenic animals. Science is trying to correct this by starting extensive phenotypical characterization of large series of rat and mouse strains [126]. Although it is very useful to start experiments on the basis of an extensive behavioral and neuroendocrine characterization of the strain of experimental animals, the choice may still be rather arbitrary from a biological point of view. It will be argued below that individual variation in nature is not infinite, but seems to be clustered in a limited number of phenotypes or behavioral syndromes. In laboratory animals, it is often unknown how a given strain i.e. genotype and phenotype relates to the biologically functional variation of its wild ancestors living under natural selection pressures. From this point of view, many laboratory animal strains might be considered as laboratory
artifacts having a potential low fitness in nature. This paper will take a rather unconventional approach by considering the biological basis of individual variation as it occurs in nature as an alternative to the use of laboratory animal strains. There is a rapidly growing interest in the biological significance of individual differentiation in behavior and physiology in the science of ecology and evolutionary biology. Individual variation in coping with challenges encountered in the natural habitat determines evolutionary fitness and is considered to be the prerequisite of speciation. Moreover, it may be an important factor in the regulation of populations as well. It seems that evolution has shaped general adaptive response patterns in reaction to everyday challenges in the natural habitat [7,111]. The aim of the present paper is to explore the ultimate biological basis of individual variation in stress reactivity in terms of individual coping styles in animals as they might be observed in nature and to discuss the proximate consequences with respect to neuroendocrine reactivity.

2. Individual variation

Variation between individuals is a well known phenomenon in both human and animal experimentation, often regarded as a nuisance by many researchers rather than a worthy target for investigation. For decades, the dogma in animal experimentation was to reduce individual variation as much as possible in order to obtain statistically significant results with the least number of animals. Due to the 3R doctrine [105], reduction of the number of animals used in an experiment often became a goal in itself. Reducing individual variation by using outbred or inbred strains of laboratory animals and through excessive and rigorous standardization may compromise the general validity and robustness of the experimental results. It may lead to a strong selection bias in the experimental results [148]. Fig. 1 shows an example of this. The frequency distribution of total time spent on offensive aggressive behavior in a standard outbred wistar strain of laboratory rats is compared with the distribution in an outbred strain of wild-derived rats bred in the laboratory, but originating from feral breeding pairs. Despite laboratory breeding of the wild-type rat, this wide distribution is considered to be representative of the individual variation as it might be functional in nature. Clearly, the highly aggressive phenotype is absent in the laboratory strain, most likely due to some (perhaps unintended) artificial-selection for tameness during the century-long domestication process of this wild animal. This is understandable from the point of view of an animal caretaker, but from an experimental point of view this is a scientifically unjustified selection. One may argue that selection bias is inevitable and inherent to the use of animal models, starting with the selection of the animal species followed by the selection of the strain. However, we want to show that the individual variation in behavior and physiology, as it might have a function in nature, can be used experimentally and might be an important standard in the interpretation of experimental results. After all, reducing variation may imply a reduction of the general validity of the experimental results at the same time. Fig. 1 also illustrates the importance of an absolute scale. Obviously, a manipulation that leads to a 4-fold increase in aggressive behavior requires a different biological interpretation when it changes from 2% to 8% of total time than a change from 20% to 80% on the absolute scale. Again, the biology of the species, including the degree of individual variation can be an important reference standard in the interpretation of experimental results.

2.1. Biological significance

In behavioral ecology, individual variation is considered to be a prerequisite for evolution. The general idea is that certain individuals under particular environmental conditions have a higher fitness than others leading to a higher reproduction, better survival, dispersal, etc. Differences in fitness are thought to be the basis of speciation. However, recent studies in feral populations demonstrate that a considerable degree of genetic variation, partly underlying the phenotypic variation, is maintained in the population and might be evolutionary stable [106,110]. Not only has this individual variation been demonstrated to be heritable in many species, but recent computer simulations show that individual differences in responsiveness to the environment could most certainly evolve [146,147]. Apparently, different phenotypes may have a different function in the population ecology of the species. This notion goes back to the original hypothesis by Chitty [27] that genetic variation in aggressive behavior might play an important role in the population dynamics of house mice. Genetic variation for aggression was suggested to be maintained in the population because the extremes in the population have a differential fitness in different population densities or under different environmental conditions. In nature, mouse populations are known to go through phases of growth and decline. Such population cycles may have a period from four to seven years and can be so extreme that the population suddenly collapses at the end of a cycle and becomes extinct [16]. There is still no satisfactory understanding and explanation for the cyclic nature of mammalian populations [83]. Factors such as predation risk, and food availability seem to play a role and the cyclic nature may disappear over time [66,95]. An old hypothesis by Chitty [27] suggests that the cyclic nature of rodent populations might be due to disruptive selection for aggressive behavior in the course of the population cycle. This hypothesis is supported by the early studies of Van Oortmerssen and Busser [57] on feral populations of house mice. Phenotypic characterization of the laboratory bred

![Fig. 1. Frequency distribution of offensive aggressive behavior in a sample (N = 77) of adult wistar rats (A) and a sample (N = 315) of adult wild-type rats (B) as measured during ten minutes in the standard resident-intruder paradigm using male wistar intruders of the same age.](image-url)
male offspring (F1) of breeding pairs caught from feral colonies, revealed a bimodal distribution of attack latencies as measured in a standardized resident-intruder paradigm. Subsequent selective breeding for high and low attack latencies resulted within five generations in stable short attack latency (SAL) selection line. After a number of failures due to infertility of the offspring, we managed to obtain a long attack latency (LAL) selection line as well. Embryo transfer, cross-fostering and back-cross experiments show that the phenotypic differentiation in aggressive behavior as observed in the wild has a strong genetic basis that is only marginally influenced by the maternal environment [117]. Several additional data support the general idea that stable genetic variation for aggressive behavior may be a factor in the population dynamics of the wild house mouse. Indeed, analysis of mortality in feral populations reveals a strong increase in dead females, juveniles and pre-weaning juveniles just before the crash of the population [57]. It is tempting to consider the possibility that this is due to high levels of intermale aggression in that phase of the population cycle. During the whole population cycle, animals are migrating from the population. It is suggested that the non-aggressive phenotype is more successful in establishing a new colony than the highly aggressive phenotype. More recently, the ecological significance of genetic variation for aggression was also demonstrated in an extensive field and laboratory study of a passerine bird, the great tit (Parus major) [47]. It was shown that individual variation in exploration of novel trees was stable over time and correlated with a variety of other behavioral characteristics including aggressive behavior [137]. Subsequent selective breeding experiments showed the genetic basis of this differentiation. The fitness of the two phenotypes was studied in individually characterized birds living in a wild population. A differential fitness of the two phenotypes was observed under conditions of high and low food availability [44].

In an extensive review, Sih et al. [110] give several other examples in mammals, birds, fish and insects indicating that phenotypic variation within feral populations can be stable over time and across situations. These behavioral syndromes appear to have a function in the ecology of the species and are somehow maintained within a single natural population. Several studies suggest that the degree in which behavioral syndromes are expressed in nature may depend on the magnitude of selection pressure in feral populations [6,29]. Recent experimental evidence confirms that the degree in which different behavioral characteristics are correlated depend on environmental selection pressure. In an elegant experiment in sticklebacks, it was shown that boldness in terms of the tendency of individual fish to approach a predator became correlated with intra-specific aggression in experimental fish populations only after increasing selection pressure by adding a predator to the population [7,45]. The development of behavioral syndromes was not only due to selection of specific phenotypes by the predator, but also due to phenotypic plasticity. This and other studies support the general view that individual variation in correlated behaviors may have an adaptive function in nature, buffering the species against fluctuations in environmental conditions [100].

2.2. Coping styles

Since the times of the Greek philosophers, scientists have tried to categorize individual variability in behavior and underlying physiology into distinct personalities or temperaments. Currently, the general view is that trait characteristics should be stable over a considerable period of time and should be consistent across situations. Although stable trait characteristics are found in many animal species, there is a lack of consistency and agreement in the literature regarding the terminology used to describe and categorize trait characteristics. Various terms are used to categorize the extremes of the individual variation such as shy versus bold, active versus passive, proactive versus reactive, and hawk versus dove [74,78]. Behavioral ecology has adopted the term behavioral syndrome indicating that trait characteristics should involve suits of correlated behaviors [100,111]. This more neutral term may apply for any set of correlated behaviors that shows consistency over time and across situations. In the biomedical research field the term coping style is commonly used for these individual trait differences.

In a series of studies using rats and mice, we have presented experimental evidence that the concept of coping style might explain a considerable proportion of the individual trait like variation in behavior and underlying physiology. Coping styles may be defined as alternative response patterns in reaction to a stressor. The concept is based on the observation that the individual variation in offensive aggressive behavior is stable over time and related to the response pattern in a variety of other challenging conditions. Indeed, the amount of time spent on offensive behavior by male wild-type rats in the resident-intruder paradigm is very stable over time in different individuals [75]. Henry and Stephens [63] were the first to suggest that the individual variation in aggression might be an expression of actively coping with environmental challenges in general. The consistency of aggression as an expression of coping style across situations can be best demonstrated in tests that allow the animal a choice of different response patterns. For example, in the defensive burying paradigm [124] animals are confronted with an electrified probe inserted into their home cage. In response to a brief contact with the shock probe, the animal can either actively bury the probe with the bedding of their cage or show immobility and more passively avoid the electrified probe. Both response patterns can be considered as successful coping, because in neither of the two response patterns the animal will ever touch the probe again. Fig. 2a shows the positive correlation between offensive behavior measured in the resident-intruder paradigm and burying behavior in the defensive burying test. Fig. 2b shows the negative correlation between aggressive behavior and immobility. Similar results were obtained in the SAL and LAL selection lines of mice that were mentioned above [116], and in laboratory rats that were genetically selected for either high or low active shock-avoidance [13]. This demonstrates the consistency of individual variation in behavior across situations, i.e. the aggressive response to an intruder in the home cage predicts an active behavioral response in this non-social burying paradigm. Other examples of this consistency in response pattern to challenging situations can be found in nest building behavior [115], active avoidance behavior [9] and in the forced swim test [135]. The behavioral differentiation observed in wild-type rats and the selection lines of wild house mice are summarized in Table 1. This table supports the view that high levels of offensive aggressive behavior can be considered as an expression of a more general tendency to adopt a proactive coping style. Low levels of offensive aggressive behavior can be considered as a reactive coping style [74]. It is important to notice that the coping style concept implies that animals may react with alternative response patterns. Interestingly, Treit [124] originally described the defensive burying test as an anxiety test. High levels of burying behavior would indicate high levels of anxiety. However, it can just as well be considered as a test for the way in which emotion is expressed behaviorally [38]. The same argument seems to hold for the forced swim test in which floating behavior is frequently interpreted as a behavioral expression of depression. Here too, aggressive males react with active swimming and climbing whereas non-aggressive males show predominantly floating behavior [135]. Hence, in the interpretation of these tests one has to consider not only the magnitude of the behavioral response to a stressor but also the type of behavioral response. One may argue that
the differences in behavior reflect a difference in baseline emotional state. This interpretation is probably incorrect. When animals are tested in the elevated plus-maze in which there is no choice for alternative response patterns, no correlation between aggressiveness and time spent on the open arm is observed [38]. Also, when aggressive animals are placed as intruders within the home-territory of a trained high-aggressive resident (i.e., the defensive aggression test), they tend to (pro-)actively flee from the situation. Low-aggressive intruders, on the other hand, quickly adopt a submissive freezing-like response upon a resident attack. Pro- and reactive coping animals do not differ in general locomotor activity, neither in their diurnal home–cage activity rhythms nor in their exploratory reactivity towards novel environments or objects (although non-aggressive animals tend to have a more thigmotaxic open-field locomotor activity pattern and exploratory behavior in novel environments is more rapidly extinguished in high-aggressive animals). Moreover, no clear differentiation in learning and memory performances is observed in high- and low-aggressive animals as assessed in a variety of cognitive tasks (see Table 1). Overall, it seems that only in those behavioral tests that allow animals to freely choose between two equally adaptive behavioral options, a clear correlation with the aggression trait is observed. In particular, tests that measure aspects of initiative and flexibility seem to be most discriminative between a proactive and a reactive behavioral style to cope with threatening situations.

As demonstrated above in the defensive burying test, confusion may exist whether and to what extent behavioral tasks provide information on coping style or stress reactivity. The idea that stress reactivity and coping style may be independent dimensions was suggested by Steimer et al. [120] on the basis of a behavioral analysis of rats genetically selected for high and low active avoidance behavior. They presented a two-tier model in which stress reactivity is independent of the coping style dimension defined as the way in which emotion is expressed behaviorally. The idea that the quality of the behavioral response may be a dimension that is separate from the magnitude of the response is supported by a more analytical approach of behavioral syndromes in cattle by Van Reenen et al. [129–131]. He measured behavior in a variety of behavioral test paradigms and used principle-component analysis to extract independent factors that might explain the individual variation. Generally, four vectors were found that explain more than 80% of the individual variation. One of these vectors seems to be associated with coping style, and another one with stress reactivity. The terminology used in the literature is source of confusion and considerable debate. In fact, coping styles reflect the quality of the response to a stressor whereas the quantity of the response is expressed as the intensity and duration of behavior and the plasma levels of stress hormones. Hence, we consider the quality and quantity of the stress response as two independent entities.

Fig. 3 gives a graphic representation of such a two-tier model. Considering the four quadrants of this model, one can use different labels for the four extreme characteristics. Many studies use the terms shy and bold. These terms have not been defined very well, but they seem to include both qualitative and quantitative aspects of the differential behavioral response to environmental challenges. In this model, the shy individual is characterized by a high stress reactivity combined with little behavioral initiative (top left quadrant). The bold individuals can be found in the lower right quadrant, i.e. a strong tendency to act combined with low stress reactivity. Animals in the lower left quadrant combine low stress reactivity with reactive coping and might be labeled as docile. The combination between high stress reactivity and a high tendency for proactive coping might be labeled as panicky. Although these terms are rarely used in animal research these types can easily be recognized in any group of animals.

In conclusion, it seems that individuals may show stable, trait like variation on two independent axes, a qualitative coping style axis and a quantitative stress reactivity axis. The model might help in further characterizing genetic selection lines of various species. Depending on the selection criterion, genetic selection lines may show different degrees of variation in these two dimensions. Our data in mice and rats show that selection on the coping style axis, i.e. aggression or attack latency, results in little or no variation on

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**Table 1**

Overview of behavioral differentiation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>High-aggressive</th>
<th>Low-aggressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests for proactivity/assertiveness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attack latency</td>
<td>Short</td>
<td>High</td>
</tr>
<tr>
<td>Defensive burying</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Active shock-avoidance (shuttle box)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Fleeing from dominant aggressor</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Nest-building (mice)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Swimming/struggling forced swim test</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Tests for alertness/flexibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orientation reaction</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Neophobia</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Cue dependency</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Routine formation/perseverance</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>General anxiety tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plus-maze, Light–dark, social exploration, etc.</td>
<td>Low/similar</td>
<td>Similar/high</td>
</tr>
<tr>
<td>Cognition tasks</td>
<td>Similar</td>
<td>Similar</td>
</tr>
</tbody>
</table>

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Fig. 2. Positive correlation between the individual levels of offensive behavior of male wild-type rats measured in the resident-intruder paradigm and burying behavior measured 2 weeks later (A). (B) Depicts the negative correlation with immobility behavior.
the emotionality axis [38]. It is conceivable that genetic selection lines may show a different degree of variation on the two dimensions, depending on the selection criterion used. For example, rats genetically selected for high or low levels of anxiety like behavior (HAB and LAB respectively) vary between 0% and 63% at the emotionality dimension i.e. in anxiety, but differ between 0% and 30% in aggressive behavior as a component of the coping style dimension [132].

Considering the five main trait dimensions in humans (big five), trait characteristics in animals are likely to be multidimensional as well. The research in this area is still relatively young and underdeveloped. In an extensive review of the available animal literature, Reale et al. [100] suggests five trait characteristics, some of which seem to be in line with the two dimensions suggested here. Clearly, the issue needs further experimental support using multidimensional scaling methods of animals tested in a wide range of situations [4]. Moreover, one may argue that the dimensions and the terminology should somehow reflect the individual variation in the proximate causal mechanisms.

2.3. Proximate behavioral considerations

So far, the concept of coping style has been discussed in descriptive terms of behavioral syndromes or sets of correlated behaviors. One may wonder why these behaviors are correlated from a more proximate mechanistic point of view. Characteristic of the proactive coping style is that actions are principally based on predictions. This is in contrast to the reactive coping style in which there is a more direct stimulus–response relationship. This fundamental behavioral difference can be demonstrated in maze experiments showing that proactive and reactive coping styles differ in the degree in which behavior is guided by environmental cues [74]. Animals can be trained to run through a maze for a food reward. Rats and mice can learn such a task easily. When they reached a stable task performance, the reaction to a small change in the maze was studied. In one experiment, a small piece of tape was put on the floor in one of the alleys of the maze, while in another experiment the maze was turned ninety degree with respect to the extra-maze cues. In both experiments, the proactive coping males paid little or no attention to the change; i.e. there was no increase in time to complete the task and no increase in the number of errors made in the maze. Reactive coping males on the other hand started exploring the maze again and hence took much more time to get to the goal box and made more errors in the task. This suggests that the reactive coping style may be much more guided by environmental stimuli, while the proactive coping style seems to develop routines. This fundamental difference in cue dependency between the two coping styles was confirmed in pigs using reversal learning in a T-maze. Proactive coping pigs had far more difficulties in switching from a once learned task to a new one than reactive coping pigs [15]. This difference in behavioral flexibility can be demonstrated in several other situations where the animal has to switch suddenly from a standard situation to a new one. For example, the two coping styles differ strongly in the response to a 12-h shift in light/dark cycle. Proactive coping male mice stay in their original day–night rhythm for a few days after which their rhythm gradually shifts to the new cycle. Reactive coping males on the other hand start to shift their rhythm immediately; they are twice as fast in adapting to the new light–dark cycle as the proactive coping males [8]. Recent experiments in rats and hamsters using operant conditioning paradigms show that this individual differentiation in behavioral flexibility may be related to a differentiation in prefrontal cortex functioning [26,37].

These experiments show that the two coping styles differ more generally in behavioral flexibility. The proactive animal acts primarily on the basis of previous experience, i.e. feed-forward control. The reactive coping animal tends to rely more on the detailed accounts of the environment, i.e. it reacts. This fundamental difference in behavioral control also relates to the adaptive character of the two coping styles. A proactive coping animal may be adapted to stable environmental conditions. The reactive coping style may do better under variable and unpredictable environmental conditions. Indeed, field studies on feral mouse populations indicate that aggressive males are more successful under...
stable colony conditions, whereas non-aggressive males may do better during migration.

3. Neuroendocrinology of adult coping styles

Individual differentiation in behavior has frequently been associated with distinct patterns of both autonomic nervous and endocrine (re)activity. While the majority of studies focus on hormones of the hypothalamic–pituitary–adrenal (HPA) axis, some studies also included the individual difference in and the hypothalamic-pituitary-gonadal axis (HPG) and the balance between the sympathetic and parasympathetic branch of the autonomic nervous system.

3.1. Autonomic nervous system

Social defeat induces a strong release of noradrenalin and adrenalin (Fig. 4). This is consistent with earlier observations that social defeat can be considered as one of the most severe stressors in terms of the magnitude of the physiological stress response [72]. The correlation diagrams in Fig. 4 clearly show that aggressive males respond with the highest increase in both adrenaline and noradrenaline. In the shock-prod burying test the response of plasma catecholamines is on average a fifth of the response to defeat, but noradrenaline is still positively correlated with offensive aggression (Fig. 5). These data support the general view that the aggressive, proactive male is characterized by a high reactivity of the sympathetic nervous system. Baseline levels of adrenaline and noradrenaline are generally similar.

3.2. HPA-axis

Fig. 4 and 5 show that both in the social defeat test and during shock-prod defensive burying plasma corticosterone is not correlated with the individual level of offensive aggressive behavior of wild-type rats measured in the resident-intruder paradigm. This result is in contrast to a number of other studies that suggest that the reactive coping style is associated with both a high baseline activity and a higher stress reactivity of the HPA-axis. In the forced swimming test, LAL males show a higher ACTH and corticosterone response than SAL males [133]. Korte et al. [76] showed that circadian peak values of plasma corticosterone were more than twice as high in non-aggressive (reactive) LAL male house mice as compared to highly aggressive (proactive) SAL males. However, later studies in our lab failed to confirm this finding. Under basal conditions circadian trough values of corticosterone were shown to be higher in SAL males [133,134]. Baseline levels of plasma ACTH were higher in SAL males indicating decreased adrenal cortex sensitivity for ACTH.

The general picture of the relationship between aspects of coping style and HPA-axis activity is rather complicated. In great tits and geese [23,80], the non-aggressive, reactive coping animals show the highest response. However, in the wild-type rats, cynomolgus monkeys [64] and stickle back [7], this association is absent or variable and in trout there is only a weak association between HPA-axis activity and coping style [107].

3.3. HPG-axis

Some early studies in rats and mice demonstrated a positive relationship between intermale aggression and plasma T levels
However, later experiments showed the inconsistency of this relationship [32,51]. Although there are clear indications that testosterone secretion relates to the control of aggression in many species, this mainly holds for aggressive behavior in a reproductive context [58,143,144] and not for trait differences in aggression or coping. It seems that the relatively weak T-aggression relationship explains some of the aggressive displays in particular situations like aggression during the mating season but certainly not in many other situations.

In the brain, T is aromatized to estradiol acting on estrogen receptors and via 5-α reductase reduced to di-hydro-testosterone acting on androgen receptors. These enzymes and receptors are known to be causally involved in aggression [112,123]. However, a recent study in song sparrows shows that the involvement of the androgen receptor in aggression is restricted to the breeding season [118]. There is some evidence in mice that individual variation in aromatase [33] and in the estrogen 2 receptors in distinct brain areas might explain individual variation in aggression [122].
To what extent the involvement of HPG system in aggressive behavior may be generalized to other behavioral expressions of coping style is unknown.

3.4. Discussion

Little is known about the exact causal relationship between the differential behavioral and neuroendocrine characteristics. However, based on the outcome of several studies performed in our lab and with the exception of the HPG-axis, we consider it likely that the differential neuroendocrine characteristics are mainly a consequence rather than the cause of the behavioral differentiation. This is supported by the magnitude of the corticosterone response observed in male wild-type rats during winning of a social interaction (Fig. 6). In this situation there is a significant positive correlation between the individual level of aggressive behavior as an independent trait characteristic and the corticosterone response. Apparently, HPA-axis reactivity is not a trait characteristic. Correlations with coping style that are situational dependent should be considered as the consequence of the differential appraisal of the environmental challenge. Walker et al. [138] came to a similar conclusion in a study of the corticosterone response during social defeat. A similar type of reasoning may hold for the correlation between coping style and sympathetic activation. Sympathetic nervous activity in general and plasma noradrenaline in particular is considered to be a direct reflection of the metabolic and cardiovascular demands required for physical activity. Because of the fact that proactive coping is characterized by an active response to environmental challenges, it is no surprise to find a positive correlation between proactive coping and sympathetic reactivity.

4. Neuroendocrine factors in the development of coping styles

The adult individual difference in behavioral coping styles and the accompanying differences in neuroendocrine and physiological (re)activity are the result of a complex interaction between genetic background and environmental modulation. There are two periods in the life history during which hormones have a clear organizational action in neural structures that might be involved in the regulation of coping behavior: the perinatal period and puberty. The organizational role of pre- and postnatal variation in neuroendocrine (re)activity on the brain and its relationship to adult coping behavior has been extensively studied. More recently, interest is increasing in the question to what extent environmental and neuroendocrine factors during adolescence and puberty may alter brain circuitry and in this way contribute to differences in adult coping style.

4.1. HPG-axis during perinatal development

The organizational role of neuroendocrinology in the ontogeny of coping styles has been addressed in several studies. Hormones of the hypothalamic–pituitary–gonadal (HPG) axis and in particular testosterone (T) received a substantial amount of attention in this respect. Studies in SAL and LAL mice in our laboratory indicated that perinatally circulating T levels [33] and T secreting capacity of the testis [42] and brain aromatase activity [33] were strikingly different in aggressive and non-aggressive mice. The results indicated that the circulating T peaks earlier in LAL than in SAL mice. In LAL males T surges prenatally at embryonic day 17–18. At this stage plasma testosterone is still low in SAL males. Neonatally, at postnatal day 1, T has decreased to low levels in LAL males but peaks in SAL males together with brain aromatase activity. The peak activity of this enzyme in brain areas of LAL mice occurs also on postnatal day 1 but is much lower compared to SAL males. Neonatal T surges are known to be involved in the permanent organization of brain circuitry resulting in higher responsiveness to T facilitating aggression in adulthood in both male and female animals [17]. This modulatory role of T on adult behavior is very elegantly demonstrated in avian studies on the role of maternal androgens and estrogens that are transferred via egg yolk to the embryos (see [22,59]). Experimentally increasing T concentration in the yolk of eggs of Japanese quails can induce a shift towards a more proactive coping style of hatchlings irrespective of sex [35]. The described effects of maternal steroids on behavior and physiology of the chick are mainly short-lasting. A recent study provides indications, however, that they can also permanently shape the phenotype of the offspring [50]. In this study aggressive and sexual displays were enhanced one year after a single androgen injection in Black-headed gull eggs. Although androgens apparently facilitate adult aggressive behavior, modulation of neonatal T fails to alter coping styles in SAL and LAL males. Cross-fostering experiments and embryo transfer with SAL and LAL male house mice further support the suggestion that maternal environmental influences are minimal in changing coping styles [117].

The ontogenetic differences in gonadal steroid related mechanisms within the perinatal time frame may be related to a differential organization of the testosterone dependent vasopressin (AVP) system. The density of AVP neurons in the bed nucleus of the stria terminalis and its projections to the lateral septum is much higher in adult LAL mice [32]. A study in wild-type Groningen rats confirmed this finding, showing a much denser AVP innervation of the lateral septum in non-aggressive animals [51]. The role of a differential central nervous AVP regulation regarding coping style will be discussed in detail in the next chapter.

4.2. HPA-axis during perinatal development

There are numerous studies performed on effects of perinatal stress, maternal care and in specific of corticosterone on adult physiology and behavior in various animal models and even in humans [56,88,90]. All these studies focus mainly on changes on the emotionality axis in the two-tier model described previously. Virtually no studies exist that aimed at the specific effects of perinatal stress or corticosterone on behaviors on the coping style axis. Concerning the postnatal period, many studies have clearly demonstrated the powerful effects of early life stressors and/or maternal care on the expression of adult endocrine, autonomic and behavioral responses to stressors. In general, increased behavioral stress responsiveness (anxiety and depressive-like behavioral reactivity) and neuroendocrine stress reactivity (increased HPA reactivity) are observed in adult animals that have experienced adverse early life experiences like maternal deprivation or neglect [90,98]. For example, studies by Menard and Hakvoort [92] have shown that adult rats that received high levels of maternal licking and grooming in infancy display dramatic reductions in shock-prod burying and aggression relative to offspring of low licking and grooming mothers. The concurrent decrease in immobility indicates that differences in maternal care have little effect on coping style of the offspring but rather alters behaviors on the emotionality axis [46]. Although circulating glucocorticoid levels in lactating mothers have been assigned an important role in the induction of these programming effects [24,25,101] a recent study of Menard and Hakvoort [92] failed to confirm this hormonal role. A study of Meerlo et al. [91] showed that offspring of mothers receiving corticosterone in drinking water during the weaning period were less aggressive in the resident-intruder test and also responded with increased immobility and decreased prod-directed activity in the shock-prod defensive burying test as compared to control treated rats. This study indicates that neonatal increases in corticosterone levels may in fact facilitate the development of adult reac-
tive coping styles. It is obvious that more research is needed to elu-
cidate whether and how differences in neonatal corticosterone lev-
eels or other neuroendocrine factors can affect the central nervous
system circuits involved in the selection and generation of proac-
tive and reactive coping responses. However, ontogenetic studies
employing embryo transfer, cross-fostering and cross-breeding
experiments do clearly suggest that individual differences in coping
styles are already detectable early in life and may have a strong
genetic basis [82,99,117,142].

4.3. Neuroendocrine factors during puberty

Puberty is marked by profound behavioral and neuroendocrine
changes. The activation of the HPG-axis leads to maturation of
reproductive behaviors [108]. Also the HPA-axis sensitivity [103] and
the sensitivity of brain areas to corticosterone [86] is appar-
etly higher during puberty than in adulthood. The hormonal changes
during puberty are clearly involved in organizing the adoles-
cent brain and play a role in individual differences in adult
behavior [113]. The organization effects of hormones during pub-
erity are not restricted to sexual behavior, but extend to a variety
of social behaviors like agnostic and anxiety-related behaviors
[108,113]. No studies up till now focus on the role of neuroendo-
crine maturation during puberty on adult coping style.

5. Neurobiology

It is commonly accepted that the behavioral, neuroendocrine
and autonomic physiological (re)activity is the ultimate output of
a complex organization of the brain at the level of the structural
and functional activity in various neuronal networks, neurotrans-
mitter systems and the molecular processes of signal transduction
in neurons. Hence, animals with different coping styles can also be
expected to show consistent differences in the putative neurobi-
ological characteristics that underlie the respective behavioral and
physiological coping responses. Indeed, the past 30 years have wit-
nessed an explosion of research in the discipline of affective neuro-
science. This has provided evidence that stress coping behaviors
and its associated physiological output are subserved by a basic
circuitry of emotional limbic brain areas including prefrontal cor-
tex, nucleus accumbens, amygdala, BNST, septum, hippocampus
and hypothalamus and their common output projection nodes. A
schematic presentation of this circuitry is presented in Fig. 7A.

The entire functioning of this network is tightly controlled by the
brainstem ascending monoaminergic inputs [36]. A much harder
to resolve but intriguingly fundamental question is whether differ-
ent brain regions or distinct neurons within these brain regions
underlie the two different coping styles, or are both coping styles
a function of the same basic brain circuitry? In other words, one
possibility is that two intermingled but distinct subpopulations
of neurons in the same region mediate proactive and reactive cop-
ing patterns (i.e., qualitative distinction). Alternatively, the same
population of neurons mediates both proactive and reactive coping
styles through different levels or degree of neuromodulation (i.e.,
quantitative difference).

Based upon the behavioral activation and inhibition effects of
several global regional brain lesion and stimulation experiments,
Henry and Stephens [63] provocatively linked distinct brain re-
gions to the two divergent coping styles. In their original scheme,
the amygdala was associated with the active fight/flight reaction
pattern and the hippocampus–septum with the reactive non-
aggressive coping response [63]. Obviously, this picture is too sim-
ple and with the subsequent advances in neuro-anatomical tracing,
lesion, stimulation and imaging techniques, a more complex and
refined neuronal coping circuitry emerged. In particular the recent
studies using immediate-early gene proteins (e.g., Fos, Jun, Zenk,
etc.) expression mapping, have revealed the individual neurons
in the various emotional brain regions that become activated dur-
ing the expression of different coping-style reactions [2,3,6,71,93,132,136]. For example, in the resident-intruder para-
digm proactive fighting residents in comparison to reactive non-
fighting residents show an increased number of Fos-positive neu-
rons in central amygdala, anterior bed nucleus of the stria termi-
nalis, ventrolateral hypothalamus, nucleus accumbens shell,
orbital frontal cortex, lateral/ventrolateral periaqueductal gray
and dorsal raphe, while in the lateral septum and dorsolateral peri-
aqueductal gray a reversed pattern was seen [60,128,132]. The
available neuro-anatomical data so far clearly support the view
that a quantitatively different number of activated neurons within
several brain regions that are part of a qualitatively similar neural
network underlie the initiation and execution of proactive/aggressive
and reactive coping style. However, the extent to which similar or
different sets of neurons within these brain regions are involved in
the distinct coping styles remains a challenging issue for future
functional neuro-anatomical studies.

The functional activity of this neural network, and thereby the
tendency to cope either proactively or reactively with environmen-
tal challenges, is determined by a wide variety of molecular sub-
strates (i.e., neurotransmitters, hormones, cytokines and their
respective metabolic enzymes, receptors and intraneuronal signal-
ing molecules). Indeed, several studies in our wild-type rats and
artificially selected SAL and LAL mice show a widespread central
nervous differentiation between proactive and reactive coping
styles, for example at the level of the peptidergic innervation and
modulation of the central nucleus of the amygdala [104], the vaso-
pressinergic neurons in the bed nucleus of the stria terminalis and
its innervation of the lateral septum [30,51] and the suprachias-
matic nucleus [20], the auto-inhibitory control of serotonin neuro-
transmission [21,77,127], the hippocampal mossy fiber system
[114], and striatal dopaminergic mechanisms [10]. They may be
considered as a suite of correlated neurobiological trait character-
istics, which in concert may determine the tendency to cope either
proactively or reactively with environmental challenges. With the
exception of mainly serotonin and vasopressin (see Fig. 7), the
causal involvement of these neurobiological substrates in the indivi-
dual differentiation in coping style is still far from clear.

5.1. Serotonin

Variability in central serotonin (5-hydroxytryptamine; 5-HT) function is associated with individual differences in affect, temper-
ament and personality. For more than 40 years now, this phyloge-
etically ancient and anatomically well conserved 5-HT system has
been postulated to be essential in the control of aggressive and
impulsive behavioral traits in many animal species, ranging from
invertebrates like fruit flies, crickets and lobsters [81] to verte-
brates like lizards [121], fish [97], birds [70], rodents [94] and pri-
mates including humans [64,87]. In most animal species, high
levels and/or inappropriate forms of aggressive behavior are gener-
ally associated with low levels of brain 5-HT and its metabolite 5-
HIAA. This is confirmed in some recent studies in feral mice and
rats from our laboratory see [41] for review.

In view of the two-tier model presented above, one may wonder
how serotonin relates to the two dimensions of the model. Numer-
ous studies over the past two decades have convincingly shown
that pharmacological compounds that activate 5-HT\textsubscript{1A} or 5-HT\textsubscript{1B}
receptor subtypes, potently suppress the display of aggressive
behavior in various animal species ranging from invertebrates, fish,
rodents, guinea pigs to primates, including man [39]. Despite this
overwhelming evidence, it is still a matter of debate which brain
area is the most important site of action of these compounds. A
A schematic presentation of a serotonergic neuron and its connections and receptors is given in Fig. 7B. The 5-HT_{1A} and the 5-HT_{1B} receptor are not only found post-synaptically, they have also an important function in the negative feedback control of the 5-HT neuron itself. The 5-HT_{1B} receptor is present pre-synaptically at the 5-HT axon terminals, where it inhibits 5-HT release. The 5-HT_{1A} receptor located on the soma and dendrites of the serotonergic neuron at the level of the raphe nuclei acts as an inhibitory auto-receptor reducing the firing of the 5-HT neuron. Hence, at the presynaptic level these agonists reduce 5-HT signaling, whereas at the level of the postsynaptic receptors, they mimic the effects of an enhanced 5-HT signaling. A proper interpretation of the role of serotonin in aggression therefore depends on the predominant site of action of these 5-HT receptor agonists. Using the compound S-
15535, which is a selective, full agonist of the somatodendritic 5-HT1A autoreceptor and a partial (ant)agonist of the postsynaptic 5-HT1A receptor sites, De Boer [39] showed a potent and behavioral selective reduction in aggressive behavior as well. This means that the aggression reducing effect of 5-HT1A agonists is most likely due to their action on the auto-receptors. Analysis of the dose–response relationship of 5-HT1A agonists revealed a 15-fold difference between high- and low-aggressive male rats, i.e. the high-aggressive males have a far more sensitive 5-HT1A autoreceptor mediated inhibition. Similarly, using the specific 5-HT1B receptor agonist CP-94253 an almost 20-fold difference in its anti-aggressive potency was observed between high- and low-aggressive rats. This strongly enhanced tonic inhibitory control of the serotonergic neuron in the aggressive males may explain the negative correlation between baseline levels of 5-HT and 5-HIAA and aggression found in many species [39].

In view of the intricate and causal involvement of serotonin in aggressive behavior and the strong individual differentiation in auto-receptor feedback control in relation to aggression as a trait characteristic, one may wonder whether serotonin is more generally involved in coping style. Indeed, 5-HT1A and 5-HT1B receptor agonists also reduce swimming behavior in the Porsolt forced swim test [34] and burying behavior in the defensive burying test [3,38]. So far, these and similar data have been interpreted in terms of emotionality, anxiety or depression. However, one cannot exclude the possibility that serotonin is related to the coping style axis rather than the emotionality axis. Considering the individual variation in the behavioral effects of 5-HT1A receptor agonists in the forced swim test, there is a clear qualitative difference in the way the extremes of the variation react to these compounds. The reactive coping males show a reduction of immobility and an increase in escape attempts, whereas the proactive coping males show a decrease in escape and an increase in immobility behavior. In other words, activation of the 5-HT1A autoreceptor leads to a reduction of the preferred behavioral response in this test, and to an increase in the alternative behavioral response rather than to a general reduction in anxiety [135]. It is tempting to interpret this in terms of the two-tier model as presented in Fig. 3. If the serotonergic system is related to the coping style axis rather than the stress reactivity axis, one might indeed expect opposite dose response relations in the extremes of the variation. If serotonin was associated with the stress reactivity axis, one would have expected a decrease in immobility and swimming/escape at the two ends of the distribution respectively, without an increase in the alternative response. Preliminary data from our laboratory using the resident-intruder test in rats indeed show opposite dose response relations in the extremes of the population.

Recently, Valentino and coworkers have proposed that the selection of active or passive coping strategies can also be mediated via bimodal effects of the stress-related neuropeptide CRF in inhibiting or enhancing the functional outflow of the dorsal raphe 5-HT system targeting limbic and associated structures [125]. They support this novel concept by their own and other findings that these qualitatively different functional consequences of CRF are mediated via a distinct expression level or cellular distribution of CRF1 and CRF2 receptors [139]. CRF1-mediated inhibition and CRF2-mediated excitation of the dorsal raphe 5-HT system facilitates active and passive coping strategies, respectively [61,89].

5.2. Vasopressin and oxytocin

Besides their important peripheral physiological functions as neurohypophysial released hormones, the neuropeptides arginine vasopressin (AVP) and oxytocin (OXT) are also implicated in inter-neuronal communication within various areas of the brain to modulate emotional and social behavioral and physiological responding [65]. While AVP is generally known to increase anxiety like behaviors, stress and aggressiveness, OXT on the other hand has the opposite effects and facilitates social attachment, care and affiliation [62,68]. Existing data from the pioneering work of the late Bohus and de Wied [14,79] already convincingly demonstrated opposite roles for AVP and OXT in fear learning processes. More recent studies in wild-type rats, Roman high- and low-avoidance rats and artificially selected SAL and LAL house mice have demonstrated that non-aggressive males are characterized by a far more extensive vasopressinergic network and a higher vasopressin content in several brain regions than high-aggressive males [1,19,31,51]. Interestingly, these differences in density of lateral septum AVP fibers within males turn out to be as large as the differences between the sexes. Males are characterized by a considerably higher density of lateral septum AVP fibers than females. Since low storage levels of neuropeptide (and hence low AVP-immunoreactivity and peptide content) may well be linked to enhanced or stimulated release patterns [84,85], this suggests that high-aggressive animals exhibit higher levels of release when compared to their non-aggressive counterparts. Although far less intensely scrutinized, the closely related “affiliative” neuropeptide oxytocin does not appear to be differently expressed between aggressive and non-aggressive animals [40].

There is abundant experimental evidence for the suggestion of a causal function of vasopressin in proactive aggressive behavior. Micro-infusion of AVP into the cerebral ventricles [145] or within the anterior ventrolateral hypothalamus, BNST or lateral septum [43,52,54,68,73] facilitates offensive aggression in hamsters and rats. In addition, there is a positive correlation of CSF concentrations of vasopressin with life history of general aggression as well as aggression towards individuals [28]. Furthermore, mutant mice with the vasopressin receptor V1a gene, deleted showed virtually no offensive aggressive behavior anymore [140,150], although their defensive aggressiveness remained intact [141]. In addition, offensive aggression is not changed in vasopressin receptor V1a gene knock-out mice [141]. Consistent with this, systemic as well as intra-hypothalamic administration of AVP V1A receptor antagonists effectively block offensive aggressive behavior in male hamsters [12,43,55,53]. We recently replicated this potent anti-aggressive effect of the non-peptidergic AVP V1a selective receptor antagonist SSR149415 in our wild-type rats (Fig. 8). These findings strongly suggest that increased vasopressinergic activity in discrete brain regions that are strongly linked to stress-coping regulation is associated with increased levels of aggressiveness and, perhaps in general, proactive coping styles. On the other hand, increased oxytocinergic activity in these very same neural structures may be implicated more in reactive/passive coping. Therefore, it can be hypothesized that an endogenous balance between vasopressin and oxytocin signaling within (components of) this neural circuit may gate the expression of either proactive or reactive/passive responses to stressors.

One key brain area that importantly controls behavioral and autonomic stress-coping responses, and where vasopressin and oxytocin modulate neuronal activity in opposite ways, is the central nucleus of the amygdala (CeA) [67] Stressful stimuli increase the levels of both peptides in the extracellular space of the CeA, possibly due to the release from local synaptic terminals [84]. Furthermore, a recent study in rats showed that stress-induced activation of oxytocinergic system in the CeA is implicated in generating some of the passive/reactive stress-coping style characteristics [49]. Individual variations in concentrations of these peptides and/or expression of their receptors within the CeA may thus provide a neuro-physiological mechanism for the selection and expression of a distinct coping style.

Clearly, the two hypotheses that the two distinct modes of coping are causally associated with distinct neurobiological substrates
Indeed, several studies show that the concept of discrete coping there is a certain degree of clustering of individual characteristics. number of phenotypes. An across species comparison suggests that in nature, is not infinite; nature seems to accept only a limited the individual variation in behavior and physiology, as observed the species in question (see de Boer et al. (1998), for methodological details). \(^{(p < 0.05)}\).

6. Concluding remarks and future perspectives

Contemporary animal research is characterized by a strong tendency to reduce variation. This has attenuated the search for principles underlyng genotypic variation and phenotypic plasticity for a long time. Although this has changed during the last decades with studies on gene-environment interactions, there is still a lack of a conceptual framework for individual variation and its function, causes and consequences. This paper has argued that such a framework should be based on a thorough understanding of the role of individual variation in the evolutionary biology and ecology of the species in question (see Fig. 9). It is important to notice that the individual variation in behavior and physiology, as observed in nature, is not infinite; nature seems to accept only a limited number of phenotypes. An across species comparison suggests that there is a certain degree of clustering of individual characteristics. Indeed, several studies show that the concept of discrete coping styles may hold for quite a number of species \(^{[100]}\). Moreover, genetic selection for one behavioral or physiological characteristic usually leads to co-selection of all other characteristics of a given phenotype as well. For example, genetic selection for proactive behavior in response to a cold environment (nest building) leads to higher levels of aggression in a social environment. Conversely, genetic selection for aggression leads to a co-selection of nest building \(^{[117]}\). It is intriguing that genetic selection for one aspect of proactive coping such as active avoidance behavior \(^{[48]}\), sympa-thetic reactivity \(^{[11]}\), anxiety \(^{[132]}\) and neonatal ultrasonic vocal-ization \(^{[18]}\) seems to result in a nearly complete proactive phenotype, irrespective of the exact selection criterion.

With respect to the neuroendocrine differentiation, one has to consider the possibility that this individual variation is a conse-quence of behavioral differentiation and its related differentiation in metabolic demands and cardiovascular requirements, rather than causal trait characteristic. It seems plausible that a trait-like neuroendocrine differentiation may develop with increasing selec-tion pressure (or continuing artificial genetic selection), that will consequently become a constraint in phenotypic plasticity. In the model presented in Fig. 3, coping style is considered as a qualita-tive dimension that is independent from the quantity of the stress response. Considering stress reactivity as a dimension separate from the type of stress response might explain some of the inconsis-tencies observed in the wide variety of genetic selection lines of laboratory animals. Although these selection lines are generally developed to study the genetic basis of stress reactivity, they may differ in the selection criterion. Some selection lines have been selected exclusively on the coping style dimension, whereas others have been selected on the stress reactivity dimension or a mixture between the two. Multidimensional models and better concepts of individual variation may help in a better phenotypic characterization required for a scientifically solid rationale for the selection of a certain strain from the vast amount of laboratory animal strains.

We would argue that the individual variation in behavior and physiology as it occurs in nature should: (1) serve an important function in nature that (2) can and should be wisely used experimentally in the laboratory and (3) might be an important standard to obtain biologically more meaningful and robust results that (4) better translate to the clinical situation. In particular for scientific questions related to stress vulnerability, it is crucial to avoid selection bias in the early stages of the research. The choice for a certain phenotype for more detailed mechanistic research should ideally be based on a screening of the full spectrum of natural individual variation.

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