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Review article

Untangling the neurobiology of coping styles in rodents: Towards neural mechanisms underlying individual differences in disease susceptibility

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ABSTRACT

Considerable individual differences exist in trait-like patterns of behavioral and physiological responses to salient environmental challenges. This individual variation in stress coping styles has an important functional role in terms of health and fitness. Hence, understanding the neural embedding of coping style variation is fundamental for biobehavioral neurosciences in probing individual disease susceptibility. This review outlines individual differences in trait-aggressiveness as an adaptive component of the natural sociobiology of rats and mice, and highlights that these reflect the general style of coping that varies from proactive (aggressive) to reactive (docile). We propose that this qualitative coping style can be disentangled into multiple quantitative behavioral domains, e.g., flexibility/impulse control, emotional reactivity and harm avoidance/reward processing, that each are encoded into selective neural circuitries. Since functioning of all these brain circuitries rely on fine-tuned serotonin signaling, autoinhibitory control mechanisms of serotonergic neuron (re)activity are crucial in orchestrating general coping style. Untangling the precise neuromolecular mechanisms of different coping styles will provide a roadmap for developing better therapeutic strategies of stress-related diseases.

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1. Introduction

Health and disease are generally considered to be influenced by a rather complex interplay between environmental demands and the individual's capacity to deal or cope with these challenges. Throughout life, we are all exposed to stressors ranging from relatively minor daily hassles and worries to severe major life-events and life-threatening traumas. Remarkably, while the majority of

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individuals successfully adapts to these stressors and maintains healthy behavioral and physiological functioning, only a relatively small proportion of individuals develop stress-related illnesses. For example, more than two-thirds of people in the general population experience an uncontrollable traumatic stress event at some point in their lifetime, but only 10–15% develop post-traumatic stress disorder (Kessler et al., 2005; Galea et al., 2005). Similarly, only 20–25% of individuals exposed to stressful events develop major depression (Cohen et al., 2007). Clearly, it is not the average population that gets a certain stress-related disease, but usually susceptible individuals that display particular behavioral and physiological traits under rather specific environmental conditions (Yehuda et al., 2006). Moreover, different types of stress-pathology seem to be associated with distinct behavioral and physiological response patterns.

For ages, researchers have tried to determine the individual vulnerability for stress-related diseases using estimates of individuals' behavioral trait-characteristics, i.e., the temporal and contextual consistency of a behavior that characterize an individual. These attempts date back to the ancient times of Hippocrates who marked out four types of “temperaments”: choleric (hostile/impulsive), sanguine (optimistic/sociable), phlegmatic (calm/thoughtful) and melancholic (depressive/introvert). Each of these temperaments was supposed to reflect a particular behavioral attitude in dealing with everyday problems, and were thought to originate as a consequence of different mixtures of four bodily chemical components e.g., blood, yellow bile, black bile, and phlegm. Half a millennium later, Galenus picked out the melancholicus as being particularly prone to cancer and infectious diseases. Flash-forwarding to the 20th century, the hypothesis that personality influences the development and course of physical illness gained true momentum by the landmark studies of Friedman and Rosenman (1959), demonstrating that people which are hostile, easily angered, competitive, impatient and hard-driving (e.g., type “A” personality) are more prone to cardiovascular, metabolic and autoimmune diseases than their more relaxed type “B” counterparts (Friedman and Rosenman, 1971; Irvine et al., 1982; Dembroski and MacDougall, 1985; Krantz et al., 1989; Ravaja et al., 2000; Trigo et al., 2005; Smith and MacKenzie, 2006; Steptoe and Molloy, 2007; Sirri et al., 2012). In contrast, people with a more avoidant or passive coping style (so-called type “B” or “C” personality) that are characterized by behavioral patterns such as suppression of emotions (primarily anger), denial and avoidance of conflicts, were shown to have a higher risk for infectious diseases and cancer (Baltrusch et al., 1991; Zozulya et al., 2008). Despite ample clinical evidence that personality characteristics are connected to disease susceptibility, plausible neurobiological mechanisms underlying this link have not been clearly revealed yet.

Preclinical research using domesticated laboratory animals has long neglected the issue of individual disease vulnerability mainly because a reduction of individual variation through inbreeding and rigorous standardization has been the common experimental approach. However, even under highly standardized conditions it was clear that animals of the same sex and age within a given strain show consistent individual differences in their behavioral and physiological response patterns (coping style) to environmental demands (Koolhaas et al., 1999). As a matter of fact even in highly inbred laboratory strains, genetically identical subjects may be considerably more or less susceptible to similar experimental manipulations (Krishnan et al., 2007). Rather than viewing individual differences as a limitation or impediment to preclinical research, it should be considered a valid biological factor and focused on in any experimental animal model of human disease. The increasing acknowledgement of the biological significance of individual variation is currently starting a valuable paradigm shift in preclinical behavioral neuroscience studies, e.g., to focus more

on individual phenotypic variations rather than solely on traditional group averages. For example, it appears to be essential to distinguish susceptible from resilient individuals on the basis of predefined behavioral and physiological characteristics (Ebner et al., 2005; Krishnan et al., 2007; Walker et al., 2009; Russo et al., 2012; Schmidt, 2011; Cavigelli et al., 2013; Wood, 2014; Holly and Miczek, 2016). As a matter of fact, clinical research routinely compares select “susceptible” patient groups with “resilient” healthy subject control groups. Hence, for translational validity it seems imperative to adopt this paradigm-shift to focus on and select for particular phenotypic variability.

Although traditionally most of these studies are conducted in the realm of biomedical sciences, there is also a rapidly growing interest of the biological significance of animal personality and/or behavioral and physiological differences among individuals in the science of ecology and evolutionary biology (Sih et al., 2004; Reale et al., 2007; Wolf et al., 2007; Van Oers et al., 2004; Dingemanse and Wolf, 2010). Recent ecological evidence shows that these coping styles should be considered as individual phenotypic adaptations to different environmental conditions. For example, a bird study of the fitness consequences of aggressiveness and/or boldness in the great tit *Parus major* showed that food availability in the field was a major determinant in the differential survival of fast- and slow-exploring animals from year to year (Dingemanse et al., 2004). Consequently, different personality types may ultimately obtain equal overall fitness in terms of gene preservation and will be maintained in the population given frequent alternation of the critical environmental conditions. Basically, resilience and vulnerability becomes a matter of match (adaptation) or mismatch (maladaptation) between expressed personality/coping style and actual or perceived environmental demands (Schmidt, 2011). Obviously, this individual variation in coping with everyday problems encountered in the natural habitat has important evolutionary-fitness consequences and apparently protects the species against fluctuations in their natural environment (Dingemanse et al., 2004; Øverli et al., 2007; Dingemanse and Wolf, 2010; Sih et al., 2004). The basic evolutionary biological concept is that certain individuals under particular environmental conditions have a higher fitness than others leading to a better survival, wider dispersal and higher reproduction. Hence, natural selection favors individuals that contribute most to the gene pool of the population (see Fig. 1). It is tempting to consider this adaptive explanation for the individual variation in animal coping styles as the biological origin of human affect, personality and temperament (Smith and Blumstein, 2008).

In this review, individual differences in trait-aggressiveness are presented as a fundamental and adaptively significant component of the natural sociobiology and ecology of rodents, and used as a starting point in the characterization of the neurobiological causes of stress coping styles in laboratory rats and mice. An important point highlighted in this review is that unraveling and probing this phenotypic variation neurobiologically is fundamental in not only understanding disease susceptibility/resiliency but also in the development of personalized approaches to precision treatments and/or strategies for curbing stress-induced diseases.

2. The sociobiology of feral rodents and individual variation in aggressiveness

Throughout the animal kingdom, aggression is one of the most conspicuous and widespread forms of social behavior that ultimately contributes to reproductive success and survival of individuals. Clearly, aggression is the behavioral weapon of choice for essentially all animals and humans to gain and maintain access to desired resources (food, shelter, mates), defend themselves and their offspring from rivals and predators, and establish and secure

Fig. 1. General framework depicting the biological concept of individual differences in behavior and physiology, its (epi)genetic basis and its ecological and evolutionary significance. Clearly, (epi)genetic variation underlying individual variation in neurobiological, behavioral and physiological functioning is the target of natural selection and/or substrate of evolution. Furthermore, (epi)geno- and phenotypic variation determine individual health, survival and reproductive success thereby influencing dynamics of population densities.

social status/hierarchical relationships. A social hierarchy or rank order develops as a consequence of aggressive and nonaggressive interactions in practically all situations where two or more rodents are housed together. The experience of dominant (winner)-subordinate (loser) relationships are long lastingly retained after a fight and act continuously as a social experiential factor influencing behavior and physiology. Not surprisingly, offensive aggression is one of the most characteristic behavioral traits that, already since the first introduction of laboratory aggression tests, was found to vary considerably among individuals within and between animal strains (Hall and Klein, 1942).

Most neurobehavioral studies of aggressive behavior in laboratory settings are performed in rat and mice species that are highly adaptive in their social behavior both within their natural habitats as well as under captive/restrictive laboratory conditions. In their classic works, Calhoun (1962), Barnett (1975), and Telle (1966) gave a detailed account of the social interactions and ecology of wild brown Norway rats (*Rattus Norvegicus*). Under natural environmental conditions and at low population densities, one adult male rat usually dominates a small group of females and young rats by vigorously marking, patrolling and defending the region (called the territory) around their feeding and underground tunnel and nest sites (burrows) from other male intruders. Outside these territories, neutral areas exist where fighting is minimal and avoidance occurs. In general, a colony comprises a number of territories or breeding demes and neutral areas. In case of an encounter with an intruder, the male displays fierce territorial aggressive behavior causing the intruder to flee. Such dispersive territorial behavior can only persist when invasions of a territory are infrequent. Hence, with increasing population densities, rats and mice become socially more tolerant and cohesive, and adapt to a more despotic social structure, with one male being socially dominant (the *alpha* rat) and prevailing most often over rival or *beta* males and over subordinate and/or outcast *omega* animals in aggressive confrontations. The threats and attacks exerted by dominant individuals are responded to by defensive, evasive and submissive postures in the *beta* and *omega* animals that decrease the probability of being attacked further.

Although overt aggressive displays may initially be necessary to obtain a dominance-subordinate relationship, once established, a stable hierarchy suppresses further physical aggressive conflicts and unwanted or serious fights among the group members. Basically, stable dominant-subordinate hierarchies require cer-

tain behavior patterns from their members: dominants' approach, threat and aggressive display towards inferiors, subordinates' anxiety towards and avoidance from superiors; elation on winning conflicts and going up in social rank and depression on losing contests and going down. Because of the great survival advantage to the group that a well-functioning hierarchy provides, these behavior patterns have been strongly selected for during evolution. Equilibrium is reached when the advantage they provided is balanced by the disadvantage of excesses of such behavior. Hence, the cluster of "depression"-like symptoms associated with losing social status (defeat and subordination) like reduced sociability, sex and appetite, inactivity and increased submissiveness may well be interpreted as an evolutionary adaptation rather than a disease (Price, 1967; Nesse, 2000; Hendrie and Pickels, 2009). Basically, it is tempting to speculate that these behavioral manifestations are interpreted as signs or symptoms of mental disease state in the human realm only.

When environmental conditions such as weather, food supplies, nesting opportunities, infectious and predatory pressures are favorable, wild rats and mice crowd together in colonies that rapidly increase and eventually may number many hundreds. Nevertheless, life in the colony is not easy. In particular when no escape from the behavioral consequences of rising population density is possible, colonies may crash periodically due to increasing and intense social conflict in spite of conducive environmental conditions. It is very well known that populations of many small rodent species undergo marked fluctuations with a periodicity of 3–7 years (see Fig. 2A). The causes of these cycles have interested ecologists for nearly a century (Elton, 1942; Christian, 1950), and an old hypothesis by Chitty (1967) suggests that the cyclic nature of rodent populations might be due to disruptive selection for aggressive behavior in the course of the population cycle. Aggressive individuals might be at a selective advantage as the population increases in settled demes and under stable environmental conditions. This hypothesis is strongly supported by the early studies of Van Oortmerssen and Busser (1989) and Van Zegeren (1980) on outdoor semi-natural populations of house mice consisting of both males and females. Phenotypic characterization of individuals caught from these feral outside colonies, revealed a bimodal distribution of attack latencies as measured in a standardized resident-intruder paradigm. Interestingly, these distribution patterns shift from a relative high abundance of low-aggressive ani-

Fig. 2. Change in population density of a feral population of house mice in large outdoor enclosure (A), and the relative frequency distribution of Attack latency times (ALT) as indicator of aggressiveness in different groups sampled during the increase, peak and pre-crash phases of the population cycle. Mortality of adult, juvenile and preweanling house mice during the various phases of the population cycle (B). Adapted from [Van Oortmerssen and Bakker \(1981\)](#) and [Van Zegeren \(1980\)](#).

mals to a high abundance of high-aggressive individuals over the initial growing phase of the population cycle towards the pre-crash phase, respectively (Fig. 2B). This indeed seems to indicate that in established and growing colonies, a selection for aggressiveness can occur. Furthermore, it supports the view that aggressive and non-aggressive phenotypes have a differential fitness depending on the phase of the population cycle ([Van Oortmerssen and Busser, 1989](#)).

Subsequent artificial and selective breeding for high- and low-attack latencies resulted within five generations already in a stable short attack latency (aggressive SAL) selection line ([Van Oortmerssen and Bakker, 1981](#)). Embryo transfer, cross-fostering and back-cross experiments showed that the phenotypic differentiation in aggressive behavior as observed in the wild has indeed a strong genetic basis that is only marginally influenced by the early maternal rearing environment ([Sluyter et al., 1995](#); [Benus](#)

and Rondigs 1997). Generally, heritability estimates for aggressive behavioral traits in both animals and humans range between 35 and 60%, indicating that a substantial genetic component is responsible for this innate behavioral trait. Despite a decade of hunting for the responsible genes employing a variety of molecular genetic techniques, no clear picture of the candidate genes or gene-networks underlying trait aggressiveness is unequivocally established yet (Vassos et al., 2013; Maxson and Canastar, 2003; Anholt and Mackay, 2012; Malki et al., 2014, 2016). Similarly, genome-wide association studies (GWAS) have largely failed to identify common genetic variants that underpin aggressive behavior (Fernandez-Castillo and Cormand, 2016).

Several additional datasets support the general idea that stable genetic variation for aggressive behavior may be an important factor in the population dynamics of the wild house mouse. While non-aggressive mice seem to fare better as colonizers in establishing novel territories or under rapidly changing environmental conditions, aggressive mice do better in settled stable demes and growing colonies (Van Oortmerssen and Busser, 1989). Moreover, analysis of mortality in these feral populations reveals a strong increase in dead females, juveniles and pre-weanling juveniles just before the crash of the population (see Fig. 2).

It is tempting to consider the possibility that this is due to high levels of inter-male aggression in that phase of the population cycle, i.e., development of hyper-aggressiveness within social groups could then be the direct cause of the population decline. Substantial increased infant and juvenile mortality due to social behavior pathology (i.e., termed “behavioral sink”) was already observed in Calhoun’s populations of enclosed wild Norway rats, and were considered the ultimate limiting population growth factor (Calhoun, 1962).

Indeed, increasing social conflicts and frequent hyper-aggressive behavior among individuals in social unstable groups of laboratory and feral rats not only increases the risk of direct fatal injuries due to fighting, but particularly induces considerable social tension, stress and/or chronic subordination that physiologically compromises the cardiovascular, metabolic and immune systems, diverts energy from reproductive activities and foraging, disrupts circadian and physiological rhythms, places prolonged demands on endocrine functions resulting in gonadal atrophy and adrenal hypertrophy, and ultimately may negatively affect health/fitness and shorten lifespan (Fleshner et al., 1989; Blanchard et al., 1985; Stefanski, 2001; Koolhaas and Van Oortmerssen, 1988). Not surprisingly, social instability, defeat and/or chronic subordination in rats, mice and other animals are increasingly employed as ecologically-valid social stress models in fundamental laboratory research of the mechanisms underlying stress-related pathologies (e.g., cardiovascular, metabolic and immunological diseases as well as mood, anxiety, substance use and personality disorders) in humans. Importantly however, considerable individual differences seem to occur as to the behavioral, physiological and pathological repercussions of these social stress conditions that can be linked to individual trait-like differences in behavioral coping styles and/or personality (Meerlo et al., 1999; Berton et al., 2012; Walker et al., 2009; Wood et al., 2010; Kinn Rød et al., 2014).

3. Individual differences in aggression as an important indicator of distinct coping styles

Given the general despotic territorial and/or gregarious hierarchical social structure of feral rodents, much of the preclinical aggression research is conducted in territorial/dominant male resident rats/mice confronting an unfamiliar intruder conspecific. This so-called resident-intruder paradigm allows the spontaneous and natural expression of both offensive aggression and defensive

Fig. 3. Frequency distribution of offensive resident-intruder aggression in a population of unselected feral Wild-Type Groningen rats (A) and in standard Wistar laboratory rats (B). The two rat strains differ considerably in the number of animals that will show aggressive behavior at all; note that the highly aggressive phenotype is absent in the domesticated rat strain. Note also that in the feral rodent populations, animals with an extreme high or low aggressive behavioral phenotype do not only coexist but are also encountered at a much higher rate than expected by chance, i.e., a bi- or tri-modally distributed pattern. This is in sharp contrast with the usually encountered normal distribution patterns for most behavioral phenotypes in laboratory animals. (See De Boer et al., 2003 for more details).

behavior in laboratory rodents (Koolhaas et al., 2013). In general, much higher levels and wider-ranges of spontaneous intraspecific territorial aggression are encountered in feral or semi-natural populations of rats and mice as compared to their laboratory bred conspecifics (see Fig. 3, and de Boer and Koolhaas, 2003 for a comprehensive review of the aggressive characteristics of the WTG rat strain). These individual levels of aggressiveness seem to be rather stable over time (Fig. 4A) and can be considered an individual trait-like behavioral characteristic.

In addition, in our search for possible differences and commonalities between behaviors expressed in different contexts, we correlated this broad individual variation in offensive aggression with behavioral performances expressed in a wide variety of non-social stress-related contexts. Basically the incentive for these studies was derived from Jim Henry, one of the founders of stress research in a more naturalistic social setting. Henry, together with Stephens (Henry and Stephens, 1977), was the first to recognize the importance of the social environment as a main source of stress and to suggest that the individual variation in aggressiveness might more generally be an expression of the way in which individuals deal or cope with a variety of challenging conditions. In this view, aggression is just a means of actively controlling the social environment. A more timid, passive response may indicate a conformation to the actual social environment. Extensive research both with genetic selection lines of feral house mice for high and low

Fig. 4. Stability of individual variation in aggressiveness of male wildtype rats over time (A; temporal consistency) and between different contexts (B). In the latter graph the individual levels of aggressiveness are positively correlated with the levels of shock-prod burying behavior as assessed one week later. Fig. 4B adapted from Koolhaas et al. (2010). R = Pearson's correlation coefficient.

levels of aggression (Van Oortmerssen and Bakker, 1981) and with the unselected wild-derived outbred strain of WTG rats (De Boer et al., 2003), largely confirmed and substantiated the brilliant original ideas of Henry (Benus et al., 1991a,b; Koolhaas et al., 1999, 2007, 2010; De Boer et al., 2003, 2015). In an extensive series of studies, some of them outlined below, we have presented persuasive empirical evidence that the concept of coping style explains a considerable proportion of the individual trait-like variation in behavior and underlying physiology of rats and mice.

The consistency of trait-aggressiveness as a behavioral expression of general stress 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 (de Boer and Koolhaas, 2003; Boersma et al., 2011; Gracueva et al., 2011) animals are confronted with an electrified prod inserted into their home cage. In response to a self-initiated brief contact with the shock prod, the animal can either actively bury the prod with the available bedding of their cage or show withdrawal/immobility and more passively avoid the electrified prod. Both response pat-

terns can be considered as successful coping, because in neither of the two response patterns the animal will ever touch the prod again. Fig. 4B depicts the positive correlation between offensive aggressive behavior measured in the resident-intruder paradigm and active burying behavior in the defensive shock-prod test.

Interestingly, the defensive burying test is originally described as an anxiety test (Treit, 1989), and high levels of burying behavior would indicate high levels of anxiety. However, when animals are tested in other well-validated anxiety tests like the elevated plus-maze or the light-dark test, no clear correlations between aggressiveness and anxiety-like indices were found (Fig. 5B; de Boer and Koolhaas, 2003; Hogg et al., 2000; Veenema et al., 2003; Boersma et al., 2011). Hence, the individual level of defensive burying in the shock-prod test can be regarded as an expression of an individual's tendency for using an initiative (i.e., proactive) coping style, whereas the level of immobility/freezing behavior is an expression of its passive/reactive coping tendencies (de Boer and Koolhaas, 2003). Accordingly, we interpret the defensive shock-prod burying as a test for the way in which emotional responding is expressed behaviorally, i.e., a coping style test. The same argument seems to hold for the Porsolt's forced swim test (FST) where rodents are placed in a cylinder filled with water from which it is not possible to escape. In this test, animals exhibit periods of passive floating interspersed with epochs of active escape (swimming and climbing) behaviors. The immobile floating behavior is frequently interpreted as a behavioral expression of "despair" or "depression" as this behavior is decreased by antidepressants (Cryan et al., 2005) and increased by prior stressor experience (Willner, 2005). However, the passive behavior should be interpreted as a highly adaptive strategy for conserving energy and does not reflect depression (see also Molendijk and de Kloet, 2015 for a recent comprehensive review of refuting the FST as a depression test). Thus, animals can select or decide to adopt an active or passive behavioral response to this challenging situation depending upon their innate or acquired strategy of coping. Indeed, our studies demonstrated that aggressive male mice and rats react with active swimming and climbing whereas non-aggressive mice (Veenema et al., 2005) and WTG rats (Fig. 5C) show predominantly passive floating behavior.

Other examples of this consistency in response patterns to challenging situations can be found in active shock-avoidance behavior in a shuttle box (Benus et al., 1989; Coppens et al., 2012), nest building behavior in mice (Sluyter et al., 1995), or defensive behavior towards a dominant (Benus et al., 1991b). In the latter situation, when aggressive animals are placed as intruders within the home-territory of a trained high-aggressive resident, they tend to (pro)actively flee from the situation. Low-aggressive intruders quickly adopt a submissive freezing-like response upon a resident's attack. Not surprisingly then, aggressive individuals usually acquire and maintain the (sub)dominant positions in a social hierarchy of colony housing situations, while the low-aggressive animals tend to hold the subordinate ranks (Fokkema et al., 1995).

On the other hand, high- and low-aggressive animals do not consistently differ in general locomotor activity, neither in their diurnal home-cage rhythms nor in their exploratory reactivity towards novel environments, objects or engaged conspecifics (Fig. 5A; De Boer et al., 2003; Boersma et al., 2011). However, nonaggressive animals tend to have a more thigmotaxic open-field activity pattern, indicative of a more cautious strategy to explore novel environments. Moreover, no differentiation in learning and memory performances are observed between high- and low-aggressive animals as assessed in a variety of cognitive tasks, like for example the Morris water maze (Everts and Koolhaas, 1999), 8-arm radial maze, Y-maze, Rabinowich-Rosvold maze (Benus et al., 1990) and operant conditioning paradigms (Coppens et al., 2014). Finally, even though considerable individual differences in neophobia, alcohol

Fig. 5. Relationship between aggressiveness (expressed as mean attack latency time) of individual WTG male rats as measured in the resident intruder test and behavioral performance in the social exploration test (A), elevated plus-maze test (B), Porsolt's forced swim test (C) and sudden silence orientation-reaction test (D). Adapted from [De Boer et al. \(2003\)](#). All R's are Pearson's correlation coefficients.

Table 1

Summary of the behavioral differences between high-aggressive and low-aggressive male rats and mice. The various tests are grouped according to a particular behavioral control function/domain.

Measure	High-aggressive	Low-aggressive	References
Tests for proactivity			
Attack latency	Short	High	Van Oortmerssen and Bakker (1981)
Defensive burying	High	Low	De Boer et al. (2003)
Reaction to dominant aggressor	Fleeing/resist	Freeze/submit	Benus et al. (1991a,b)
Active shock-avoidance (shuttle)	High	Low	Benus et al. (1989)
Nest building (mice)	High	Low	Sluyter et al. (1995)
Swimming/struggling FST	High	Low	Veenema et al. (2005)
Tests for behavioral flexibility/impulse control			
Orientation reaction	Low	High	De Boer et al. (2003)
Adaptation day/night reversal	Low	High	Benus et al. (1987)
Routine formation/perseverance	High	Low	Benus et al. (1990)
Reversal learning tasks	Poor	Good	Benus et al. (1990)
Impulsive responding	High/similar	Similar/low	Coppens et al. (2014)
Efficiency Variable Interval conditioning tasks	Low	High	Coppens et al. (2014)
General emotional reactivity tests			
Plus-maze, Light-dark,	Similar	Similar	De Boer et al. (2003)
Open field	Similar	Similar	Boersma et al. (2011)
Morris-maze, radial maze,	Similar	Similar	Everts and Koolhaas (1999)
Operant FR conditioning tasks	Similar	Similar	Benus et al. (1990) , Coppens et al. (2014)
Reward processing/harm avoidance tests			
Neophobia	Low/similar	Similar/high	De Boer et al. (2003)
Novelty-seeking	High/similar	Similar/low	Fig. 5
Alcohol preference	High/similar	Low/similar	Hensbroek et al. (1996)

preference, exploration of novel objects and enclosed conspecifics (Fig. 5A; Table 1) are observed in WTG rats, these generally do not or only poorly correlate with their levels of aggressiveness. However, excessive aggressive SAL mice do demonstrate a higher preference for alcohol in a two-bottle test than the non-aggressive LAL mice (Hensbroek et al., 1996).

Overall, it can be concluded that the way in which an individual deals with an intruder in its home territory predicts the way in which they express their behavioral response tendencies in entirely different contexts. This convincingly supports our view that overt aggression is part of a larger set of behavioral characteristics that make up the proactive coping strategy (De Boer et al., 2015). Furthermore, it is important to emphasize that the differentiation in coping strategies may not be expressed equally clear in all challenging situations. In particular, behavioral tests that truly allow animals to freely choose between two potentially equal adaptive behavioral options, and that measure aspects of initiative behavior or action tendency, seem to be very discriminative between a proactive and a passive/reactive behavioral coping strategy. In addition, context generality has also been demonstrated in the correlations between aggression and a range of general behavioral control functions that an animal recruits to directly respond and adjust its behavior to environmental stimuli, i.e., behavioral flexibility, impulse control, emotional reactivity and reward processing.

4. Behavioral flexibility, impulse control, emotional reactivity and reward processing: towards a multidimensional perspective of coping styles

Although behavioral flexibility is a rather ill-defined construct (sometimes termed behavioral plasticity or behavioral reaction norm in the evolutionary ecology field), it basically reflects the degree to which behavior is guided by stimuli or cues from the environment. Behavioral flexibility is thought to aid colonization success by facilitating a rapid response to new conditions, thus enabling population establishment and persistence (Pigliucci, 2001). A wide range of studies suggests that (re)actions of the proactive coping style are principally based on rather rigid and internally organized (i.e., ‘brain-engrained’) predictions/expectancies of the actual environment. This is in contrast to the reactive style of coping where behavior is more guided by environmental stimuli, i.e. there is a more direct stimulus-response relationship. This particular phenomenon has been demonstrated in a broad range of experimental paradigms of varying complexity. One of the first clues that proactive, aggressive animals are less sensitive to environmental changes than reactive, low-aggressive individuals came from a rather simple experimental paradigm that assesses animals’ orientation reaction (immobile/freezing behavior) to a sudden silence (i.e., switching off a 70 dB background white noise Fig. 5D; see for description and validation of this test Koolhaas et al., 1990).

Furthermore, this particular phenomenon can also be demonstrated by the way in which aggressive and nonaggressive animals react to small changes in an otherwise stable environment. Rats or mice can easily be trained to run a maze for a food reward. After reaching a stable task performance, the reaction to a small change in the maze is studied. In one experiment on mice, 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 degrees with respect to the extra-maze cues. In both experiments, the aggressive 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. Nonaggressive 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

(Benus et al., 1990). This clearly suggests that the reactive coping style may be much more guided by environmental stimuli, while the proactive coping style seems to rely on routines.

Besides maze tests, operant-conditioning tasks are recently more often employed to test for behavioral flexibility and/or cue dependency. In these tasks, animals are trained to perform an operant (usually to press a lever, turn a wheel or poke their snout in a hole) to trigger a reinforcement (usually a food reward). Operant conditioning paradigms allow precise experimental control of the stimuli that the animals can respond to, and of the responses they make (contingency control). Hence, a more refined analysis of the various behavioral control mechanisms that determine behavioral flexibility is possible. These include impulsive responding or behavioral inhibition and response perseveration. We recently performed several studies aimed at documenting the relationship between aggressiveness, behavioral flexibility and response inhibition using different contingency schedules of lever-pressing for food reinforcement within animals’ home cage (Coppens et al., 2014). While no significant individual differences and/or correlations with aggression were found during simple fixed-ratio schedules of reinforcement, individual performances differed widely when employing an unpredictable variable interval (VI-15 s) schedule of food reinforcement. These profound individual differences in the number of lever presses were positively correlated with individual levels of aggressiveness (Fig. 6). Even though the outcome in terms of obtained rewards is similar for all animals, high-aggressive animals do not inhibit their behavior and press the lever excessively (and thus very inefficiently) whereas the low-aggressive subjects pay more attention to the environment (delivery of a food pellet) and adapt their lever-pressing most efficiently to the situational contingency.

Although these results on variable interval schedules of reinforcement are explained in terms of behavioral flexibility and/or cue dependency, they could also be considered as a reflection of impulsivity and/or lack of behavioral inhibition. Impulsivity has emerged as a key behavioral construct in various psychiatry research fields, defined by the tendency for premature, poorly planned and unduly risky actions (Evenden, 1999; De Wit, 2009). In order to assess impulse control function specifically in experimental studies, differential reinforcement of low-rate responding (DRL) paradigms are employed that measures the ability of an animal to refrain from responding for a set time period. In a DRL-60 s paradigm, rats only receive a reward following lever press if the lever press was preceded by 60 s of no lever pressing. Hence, we recently demonstrated that individual WTG rats profoundly vary in this particular behavioral feature that was only weakly correlated with their individual level of aggressiveness or VI-15 performance. Only well-trained and excessively aggressive (i.e., violent-like) subjects showed significantly more impulsive-like behavior in this task compared to normal aggressive animals (Fig. 7; Coppens et al., 2014). Basically similar results have been found in hamsters where highly aggressive hamsters perform impulsively compared to low-aggressive hamsters in a two lever delay-discounting paradigm. These high-aggressive hamsters were more likely to press a lever for an immediate but small gratification, whereas low-aggressive animals showed a preference for a delayed but larger reward (Cervantes and Delville, 2007, 2009). Comparable results were also obtained in a genetic model of coping styles; the Roman high (RHA)- and Roman low (RLA) avoidance rats. These animals were genetically selected for their avoidance performance in an active (shuttle-box) shock avoidance paradigm. Extensive studies show that the RLA animals are also less aggressive in social interaction and resident-intruder paradigms, and are more efficient in a delayed reinforcement task than RHA rats (Zeier et al., 1978).

These experiments indicate that different aspects of behavioral flexibility and/or impulse control seem to be associated with the

Fig. 6. Relationship between individual level of aggressiveness in WTG rats and the number of lever presses on a Variable Interval (VI) 15 s schedule of food reinforcement (middle panel). The upper and bottom panels show tracings of the cumulative lever-pressing records from an high-aggressive animal and low-aggressive animal, respectively. Each response moves the line upwards and reinforcement is indicated by a downward flick. VI-15 responses are reinforced at variable intervals averaging 15 s (range 2–32 s). Data from Coppens et al. (2014).

High “Violent-like “aggressive

Low-aggressive

Fig. 7. The distribution of the latencies of lever presses in the DRL-60 task of a low-aggressive WTG rat (bottom panel) and an excessively high-aggressive animal (upper panel). Values are presented for latencies binned in 6 s intervals. The dotted line represents the minimum response latency (60 s) that is rewarded. See text for more information. Data from Coppens et al. (2014).

individual level of aggressiveness, suggesting that these general executive behavioral functions can be considered as rather fundamental components of coping styles. Notably, it may explain the consistency of individual behaviors across different contexts. Although a discrete, one-dimensional approach of individual variation characterized the early stages of animal coping style and personality research, contemporary views consider individual variation as being composed of several, more or less independent, trait characteristics (Steimer and Driscoll, 2003; Koolhaas et al., 2007; Coppens et al., 2010). A two-dimensional model of coping styles has been advocated as a simplified model of personality in animals where a coping style axis reflects how an animal responds to a challenge (qualitative dimension) and an emotional reactivity axis reflects how strongly it responds (quantitative dimension). These dimensions were originally determined using principal component analyses of the variation in behavior between individuals tested in various conditions (Van Reenen et al., 2005). In human personality research, this analytical strategy has resulted in four (Cloninger's model of temperamental traits e.g., novelty seeking, harm avoidance, reward dependence, and persistence) or five independent dimensions or axis at which individuals may vary (e.g., the big five: neuroticism, extraversion, agreeableness, conscientiousness, and openness) (Cloninger, 1994; Digman, 1997; Goldberg, 1990).

Based on the presence or lack of correlations between different behavioral control functions or domains outlined above, we updated our two-tier model into a three-dimensional model where the different axes reflect distinct behavioral domains that possibly may allow for a better delineation of the neural circuits and brain chemicals that drive them as outlined in the next section (Fig. 8). Basically, the main axis of this model represents the behavioral executive control functions flexibility and inhibition ranging from rigid, cue-independent and impulsive-like to rather flexible, cautious and open to external cues. This executive control or flexibility/impulsivity axis shows strong similarity with the openness dimension of the big-five model of human personality and the persistence component of Cloninger's Temperament and Character Inventory (TCI) model.

The second axis of the proposed model represents emotional arousal (degree of vigilance or activation), which basically indicates how strong an animal reacts to an environmental threat. This more quantitative dimension can be largely independent from the flexibility and impulsivity dimension and seems to be reflected more in behavioral responding in fear/anxiety-inducing behavioral tests, complemented by autonomic physiological measures of vital signs and circulating levels of stress hormones (see De Boer et al., 2003 and Koolhaas et al., 2010 for reviews of the neuroendocrinology of coping styles). For example, aggressive, proactive coping males are generally characterized by a high reactivity of the sympathetic nervous system, the adrenal medulla and the hypothalamic-pituitary-gonadal axis whereas low-aggressive males show a higher reactivity of the pituitary-adrenocortical axis and the parasympathetic branch of the autonomic nervous system (Koolhaas et al., 2010; Sgoifo et al., 2014). Even though many studies have considered these autonomic/neuroendocrine systems as part of a common somatic component of coping styles, it is unlikely that phasic state-like responses determine the type of behavioral response to a challenge. For example, it is important to notice that both the sympathetic-adrenomedullary (SAM) system and the hypothalamic pituitary adrenocortical (HPA) axis have a crucially important function in the physiological (metabolic and/or cardiovascular) support of behavior or physical exertion. Therefore, it is very likely that the magnitude of the physiological responses like heart rate, blood pressure and core body temperature, may be a direct consequence of differences in the physical activity associated with the expressed coping strategy. Consequently, the frequently

observed associations between coping styles and neuroendocrine stress reactivity, in particular the SAM system, (Table 2) may be secondary to the individual differences in the expressed behavioral activity. This emotional arousal axis shows some similarity with the harm-avoidance component of Cloninger's temperament and character inventory (TCI) model.

The third axis of the model may possibly be associated with a reward/punishment processing behavioral domain. Basically, acquiring reward and avoiding punishment lie at the heart of all behavioral responses to salient stimuli and situations. Approach and avoidance behaviors appear to be the primary reactions to novel, rewarding, and dangerous stimuli, respectively. In a wide range of animal species large individual differences in approach and avoidance behaviors have been observed, based on direction of the action toward positive (e.g., rewarding) stimuli and away from negative (e.g., dangerous) situations, in neophobia, novelty-seeking, or on exploratory or withdrawal behaviors (Table 1). In both animals and humans, it is well known that individuals that demonstrate high novelty-seeking behavior also show enhanced behavioral responsivity and/or sensitization to psychostimulant drugs (Volkow et al., 1993; Tournier et al., 2013), and hence an increased risk for developing addiction. For example, our artificially-selected high-aggressive SAL mice drink more alcohol than low-aggressive LAL mice in a two-bottle, free choice paradigm (Hensbroek et al., 1996), and are also more behaviorally sensitive to psychostimulants (Benus et al., 1991a). However in our unselected outbred WTG rats, no clear correlations between aggressiveness and alcohol preference or psychostimulant sensitivity have been observed (unpublished results; Wallinga et al., 2009). Compared to low-aggressive animals, high-aggressive WTG rats also do not work harder for food reward in operant conditioning procedures (Coppens et al., 2014), or preferentially escalate their normal aggressive behavior into violent-like forms of aggressiveness upon repetitive rewarding winning experiences (De Boer et al., 2009). However, in view of considerable individual differences in the abovementioned reward-related behavioral indices but lack of clear correlation with aggressiveness, it seems warranted to conclude that reward/punishment processing may be considered a separate behavioral domain of coping style. Obviously, this dimension is comparable with the reward dependence temperamental trait of Cloninger's TCI model in humans.

Clearly, the multi-dimensional approach of unraveling coping styles needs much more elaborate experimental testing and empirical support. However, the fact that individual variation in behavior can be reduced to variation in a limited number of more or less independent dimensions is particularly important from a neurobiological and evolutionary perspective. It is reasonable to suggest that variance in these dimensions reflect variability in the underlying causal mechanisms. From the point of view of behavioral neuroscience, it is reasonable to suggest that behaviors are correlated because they share the same neurobiological and/or molecular genetic mechanisms (Bell, 2007). Basically, the latter functions as the fundamental evolutionary building blocks of stress coping styles. This line of reasoning implies that the dimensions used to describe individual variation in behavior should reflect variation in the main proximate causal mechanisms controlling the distinct behavioral domains. In other words, the dimensions of coping styles should preferably reflect individual variation in the pattern or level of activity of the underlying causal neural mechanisms.

5. The neurobiological basis of coping styles

It is generally accepted that individual differences in behavioral and physiological coping style emerge as a consequence of an underlying variability in the activation of a basic and evolu-

Fig. 8. Three-dimensional model for separating coping style into 3 different behavioral domains. The x-axis reflects the degree of executive control functions flexibility and impulsivity; this behavioral dimension can be linked to the functioning of prefrontal-cortex regions. The Y-axis indicates the intensity of emotional reactivity or arousal, and seems to be embedded in the reactivity of the amygdala-hypothalamic-periaqueductal gray-locus coeruleus brain network. The Z-axis depicts the level of reward sensitivity that seems to be processed by the ventral tegmental-nucleus accumbens pathway. The two arrows indicate where proactive and reactive coping styles are expressed in this three-dimensional space.

Table 2

Summary of the neuroendocrine, autonomic physiological and neurobiological differences between high-aggressive and low-aggressive male rats and mice.

Measure	High-aggressive	Low-aggressive	References
Neuroendocrine markers			
HPA-axis (re)activity (ACTH/CS)	Low/similar	Similar/high	Korte et al. (1996)
Neurosympathetic reactivity (NA)	High	Low	Carnevali et al. (2013)
Adrenomedullary reactivity (A)	High	Low	Fokkema et al. (1995)
HPG-axis (re)activity(testosterone)	High	Low	De Boer et al. (2003)
Autonomic physiological indices Neurosympathetic markers			
Tachyarrhythmia incidence	High	Low	Carnevali et al. (2013)
Hypertensive stress responsivity	High	Low	Fokkema et al. (1995)
Respiratory rate	High	Low	Carnevali et al. (2014)
Parasympathetic markers			
Bradycardia orientation reaction	Low	High	Carnevali et al. (2013)
Heart Rate Variability	Low	High	Sgoifo et al. (2014)
Neurobiological parameters			
AVP activity	High	Low	Everts and Koolhaas (1999)
OXT activity	Low	High	Calcagnoli et al. (2014a,b)
Hippocampal mossy fibers	Small	Large	Sluyter et al. (1994)
Hippocampal neurogenesis	Low	High	Veenema et al. (2004)
Striatal dopamine	High	Low	Benus et al. (1991a,b)
Brain tissue 5-HT levels	Low/similar	Similar/high	Van der Vegt et al. (2003)
5-HTT functionality	Low	High	Natarajan (2010)
5-HT _{1A} receptor mRNA & binding	High	Low	Korte et al. (1996)
5-HT _{1A} autoreceptor sensitivity	High	Low	Caramaschi et al. (2007)
5-HT _{1A} heteroreceptor sensitivity	Low/similar	Similar/high	De Boer et al. (2015)
5-HT _{1B} receptor sensitivity	High	Low	De Boer and Koolhaas (2005)
5-HT _{2A/C} receptor sensitivity	Similar	Similar	Visser et al. (2015)

tionary well-conserved corticolimbic neural circuitry (also termed social decision-making network; O'Connell and Hofmann, 2012) that includes the prefrontal cortex, amygdala, bed nucleus of the stria terminalis, hypothalamus, hippocampus, septum and their common input/output projection nodes (thalamus, sensorimotor cortices, dorsal and ventral striatum, periaqueductal gray, ventral tegmental area, locus coeruleus, raphe nuclei), as depicted in Fig. 9. Although this neural circuitry is mapped relatively well in terms of brain (sub)nuclei and its interconnections (see De Boer et al., 2015 for recent review), it still remains a challenging task to decipher how the activity of distinct sets of neurons or nodes within this basic mesocorticolimbic circuitry give rise to different levels of

aggressive behavior and/or other behavioral expressions of general coping style.

Obviously, the functional properties of this basic circuitry are constantly determined by a dynamic interplay of various neurochemicals. Undisputedly, among the neurochemical systems that are considered key signaling molecules in this neural network are the monoamines serotonin (5-HT), dopamine (DA) and noradrenaline (NA), and the neuropeptides corticotropin-releasing factor (CRF), oxytocin (OXT) and arginine-vasopressin (AVP) (De Boer and Koolhaas, 2003; Coppens et al., 2010; De Boer et al., 2015).

As outlined in the previous section, the presence of context generality implies that certain components of the causal neu-

Fig. 9. Overview of the main brain structures and their connections involved in aggressive behavior and/or general coping styles, and their serotonergic input from the dorsal raphe (A) and dopaminergic input from the ventral tegmental area (B).

Abbreviations: AMYG: amygdala, cp: caudate putamen, DRN: dorsal raphe nucleus, HAA: hypothalamic attack area, hpc: hippocampus, LS: lateral septum, MRN: medial raphe nucleus, NAcc: nucleus accumbens, ob: olfactory bulb, PAG: periaqueductal gray, PFC: prefrontal cortex, pit: pituitary, SNR: substantia nigra, thal: thalamus, VP: ventral pallidum, VTA: ventral tegmental area.

robiological mechanism of offensive aggression are shared with the causal neurobiological mechanisms of other behaviors and/or behavioral control functions that together determine coping style. Hence, it is interesting to decipher to what extent this highly-conserved social decision neural network has an overlap with the neuronal circuitries that subserve other behaviors/behavioral domains expressed in different contexts, and its associated physiological output. In other words, the question is whether context generality can be considered as the activation of different dedicated brain (sub)regions or distinct neurons within these regions of the same basic brain circuitry. One possibility is that two intermingled but distinct subpopulations of neurons in the same region have the same modulating function for different behaviors (i.e., qualitative distinction). Alternatively, the same population of neurons might affect different behaviors through different levels or degree of neuromodulation (i.e., quantitative difference).

On the basis of minimal empirical data as to the behavioral activation and inhibition effects of several lesion and stimulation experiments, Henry and Stephens already provocatively linked distinct brain regions to the two divergent coping styles. In their original scheme, the amygdala was associated with the proactive “fight/flight” reaction pattern and the hippocampus–septum with the “conservation-withdrawal” (reactive non-aggressive) coping response (Henry and Stephens, 1977). This original idea subsequently evolved, based on several rather crude brain lesion and stimulation experiments, in the view that distinct but parallel

and highly interacting neuroanatomical circuits underlie the initiation and execution of active/aggressive and passive/immobile coping strategies (Henry and Stephens, 1977; Davidson et al., 2000; Bandler et al., 2000; Keay and Bandler, 2001).

Obviously, this picture is too simple and with the subsequent advances in neuroanatomical tracing, lesion, stimulation and imaging techniques, a considerably more complex and refined neuronal circuitry emerged. In particular studies of the last two decades using immediate-early gene protein (e.g., Fos, Jun, Zenk, etc.) expression mapping, have revealed the individual neurons in the entire brain that become activated or inhibited during the expression of different behavioral coping-style reactions (Haller et al., 2006; Clinton et al., 2011; Kerman et al., 2011). For example, in the resident-intruder paradigm proactive high-aggressive resident mice in comparison to reactive low-aggressive resident mice show an increased number of Fos-positive neurons in the central and medial amygdala, anterior bed nucleus of the stria terminalis, ventrolateral hypothalamus, nucleus accumbens shell, orbitofrontal cortex (OFC), lateral/ventrolateral periaqueductal gray and dorsal raphe, while in the medial prefrontal cortex (mPFC), lateral septum and dorsolateral periaqueductal gray a reversed pattern was seen (Veening et al., 2005; Haller et al., 2006). Employing selectively-bred high responder Sprague-Dawley rats (bHR) that are hyperactive and vigorously explore novel environments, exhibit elevated impulsivity and aggression and enhanced psychostimulant self-administration compared to low responder rats (bLR),

Clinton et al. (2011). High and low responder rats demonstrated divergent patterns of c-fos mRNA expression and 5-HT_{1A} receptor mRNA in lateral septum, multiple hypothalamic nuclei, hippocampus and some cortical areas following an aggressive encounter (Clinton et al., 2011; Kerman et al., 2011).

Although much less well scrutinized, divergent behavioral reaction patterns in either the defensive shock-prod burying paradigm (Menard et al., 2004) or the forced swim test (Choi et al., 2013; Duncan et al., 1996) seem to be associated with different numbers of c-Fos immunoreactive cells in several of the social behavior decision-making network nodes as outlined before. Hence, the available neuroanatomical data based on neuronal activation mapping so far clearly support the view that a quantitatively different number or set of activated neurons within several brain regions that are part of a qualitatively similar neural circuitry underlie the initiation and execution of proactive/aggressive and reactive/non-aggressive coping strategies. However, the extent to which similar or different sets of neurons within these brain regions are involved in the distinct behavior patterns remains a challenging issue for future functional mapping and manipulation studies.

The functional activity of this entire “coping style decision neural network”, and thereby the selection of the appropriate behavioral response to environmental challenges and opportunities, is determined by a wide variety of molecular substrates (i.e., neurotransmitters, hormones, cytokines and their respective metabolic enzymes, receptors and intraneuronal signaling molecules). Indeed, several studies in our WTG rats and SAL and LAL mice have shown a widespread central nervous differentiation between the high- and low-aggressive extremes. Examples are observed at the level of the oxytocinergic modulation of the central nucleus of the amygdala (Calcagnoli et al., 2015), the vasopressinergic neurons in the bed nucleus of the stria terminalis and its innervation (density) of the lateral septum (Koolhaas et al., 1998) and the suprachiasmatic nucleus (Bult et al., 1992), the auto-inhibitory control of serotonin neurotransmission (De Boer et al., 2009), and striatal dopaminergic mechanisms (Benus et al., 1991a). Hence, these may be considered as a suite of correlated neurobiological trait characteristics, which in concert may determine the appropriate behavioral and physiological response to environmental challenges. However, the precise functional role these neurochemicals have within the different neural circuits in the generation of a particular behavior and/or their behavioral specificity is still far from clear. Moreover, with the notable exception of dorsal raphe serotonin, the causal involvement of these neurobiological substrates in context generality and/or in the different behavioral domains of coping styles requires further experimental evidence.

Nevertheless, it is tempting to speculate that the expressed behavioral and physiological coping response is the ultimate functional output of several distinct but highly interconnected microcircuitries or nodes within the general social decision network are coupled to the specific behavioral domains (e.g., flexibility/impulsivity, emotional reactivity and reward processing) as outlined above in the multidimensional model of coping styles (Fig. 9).

6. Prefrontal cortex and impulse control/behavioral flexibility

Several of the tasks used to measure impulse control and/or behavioral flexibility in rodents are derived from tests of prefrontal cortex functioning. In general, the prefrontal cortex (PFC) has been associated with aggressive behavior (De Bruin et al., 1983; Raine et al., 2000; Blair, 2004; Siever, 2008; Takahashi et al., 2014), dominance (Wang et al., 2011) and various aspects of behavioral flexibility such as impulsive action and impulsive choice

(Dalley et al., 2011), ever since the famous industrial accident that destroyed Phineas Gage PFC some 160 years ago. After a tamping iron exploded up through Gage's skull, Gage recovered physically well but his personality was permanently altered by damage to his left frontal lobe. As a result of Gage's misfortune, the frontal lobes were identified as the seat of the personality (Macmillan and Lena, 2010). Similarly in birds, the nidopallium, which is considered the avian homologue of the mammalian prefrontal cortex, has an important function in choice behavior and optimal foraging (Matsushima et al., 2008). In mammals, the PFC can be divided into several sub-regions, each with a somewhat different function in the executive control of behavior. Lesions or inactivation of the orbital PFC in rats and mice induced an increase in impulsive behavior as measured by a reduced performance in a delayed reinforcement task and a preference for smaller and more immediate reward (Mobini et al., 2002). Similarly, dysfunction of this region impairs the ability of individuals to flexibly adapt behavior to changing stimulus-reward contingencies (i.e., reversal learning) (Boulougouris et al., 2007; Bissonette and Roesch, 2015; Barlow et al., 2015). Lesions or inactivation of the medial PFC also causes an escalation of aggressiveness, while selectively activating mPFC neurons suppresses aggressive behavior (Takahashi et al., 2014) and social interest (Yizhar et al., 2011). Furthermore, enhancement of the glutamatergic AMPA current in the mPFC caused an increase of social rank while inhibition caused a reduction of dominance status (Wang et al., 2011). Hence, it thus seems very likely that the executive control behavioral domain (i.e., behavioral flexibility and impulse control) in the dimensional model is closely associated with prefrontal cortex functioning. The PFC represents a key node in both the extended amygdala-hypothalamus-periaqueductal gray emotional arousal pathway and the ventral tegmental area-nucleus accumbens reward processing circuit outlined below.

The prefrontal cortex receives a dense innervation from the evolutionary ancient neurotransmitter system serotonin (5-HT) originating in the dorsal raphe nucleus (DRN, see Fig. 9A). Throughout the animal kingdom, 5-HT is involved in the regulation of aggression (Kravitz and Huber, 2003; Miczek et al., 2004) and seems to have an evolutionary well-conserved function in behavioral flexibility as well (Kravitz and Huber, 2003; Evers et al., 2007). The serotonergic input of the prefrontal cortex plays an important role in the individual variation in both aggression and/or behavioral flexibility/impulsivity. Low levels of serotonin in the PFC have been associated with escalated aggression, impulsive behavior and impaired flexibility at the level of the PFC (Van Erp and Miczek, 2000; De Boer et al., 2003; Winstanley et al., 2004; Caramaschi et al., 2007; Miczek et al., 2004; Barlow et al., 2015).

Several studies show that proactive and reactive coping rats and mice differ in the serotonergic input to the prefrontal cortex. Rats with extensive experience of aggressive behavior have profoundly lower levels and/or release of 5-HT in the PFC (Van Erp and Miczek, 2000; De Boer et al., 2003; Ferrari et al., 2003; Caramaschi et al., 2007; Miczek et al., 2007). Similarly, aggressive mice strains have significantly lower levels of 5-HT and its metabolite 5-HIAA in the prefrontal cortex (Caramaschi et al., 2007).

A decrease in serotonergic function has also been implicated in impulsive action in various paradigms of impulsivity in both humans and rodents (Roberts, 2011; Fletcher, 1995; Harrison et al., 1997; Crean et al., 2002; Homberg et al., 2007). In the five-choice serial reaction time task (5-CSRTT), a task that has been developed to test for the inhibitory control of behavior, 5-HT depletion has been found to increase premature responding (Harrison et al., 1997). In addition, administration of the 5-HT releasing agent *d*-fenfluramine has been shown to decrease premature responding in the 5-CSRTT (Carli and Samanin, 1992). The role of serotonin in behavioral inhibition is confirmed by the behavioral disinhibition induced by 5-HT lesions of the raphe nuclei in rats using a

selective neurotoxin (Fletcher, 1995). In the serotonin transporter (SERT) knockout rats, a continuously enhanced level of prefrontal cortex serotonin is associated with reduced aggression as measured in a resident-intruder paradigm. SERT knockout rats also show improved inhibitory control in a five-choice serial reaction task (5-CSRTT), but unchanged behavioral flexibility investigated in a reversal-learning task (Homborg et al., 2007). Control of impulsive choice and action (behavioral inhibition) seems to be mediated by the medial PFC, because a delay-discounting paradigm enhances 5-HT efflux in the medial PFC but not in the orbital PFC (Winstanley et al., 2004). Very recently, one managed to control the activity of dorsal raphe serotonin neurons optogenetically and demonstrated in a behavioral delayed reward task that transiently triggering the firing of 5-HT neurons enhanced patience for future rewards, i.e., suppression of impulsivity, a typical characteristic aspect of the reactive/passive coping style (Miyazaki et al., 2014; Fonseca et al., 2015).

Taken together, brain serotonin seems to be causally involved in both aggressiveness and behavioral flexibility/impulse control. Individual variation in the serotonergic input to the medial PFC may explain the correlated individual variation in the flexibility/impulse control dimension. This is consistent with the hamster studies in an operant conditioning paradigm by Cervantes and colleagues mentioned before in which aggressive hamsters had less 5-HT innervation of the PFC and were more impulsive than their non-aggressive counterparts (Cervantes and Delville, 2007, 2009).

Next, one may wonder about the specific neuromolecular mechanisms that control dorsal raphe 5-HT neural activity to the PFC. We have found that the broad individual differences in offensive aggressiveness in WTG rats are strongly associated with pronounced functional differences in 5-HT_{1A} and 5-HT_{1B} receptor properties: compared to low aggressive animals, high aggressive animals are characterized by enhanced somatodendritic 5-HT_{1A} and terminal 5-HT_{1B} autoreceptor activity (Caramaschi et al., 2007; Van der Vegt et al., 2001; De Boer et al., 2015). Similarly, in SAL mice the presynaptic 5-HT_{1A} auto- and post-synaptic 5-HT_{1A} hetero-receptors are more sensitive than in LAL mice (Korte et al., 1996; Van der Vegt et al., 2001; Feldker et al., 2002; Veenema et al., 2005; Caramaschi et al., 2007). Analysis of the dose–response relationship for various behavioral (i.e., anti-aggressive, appetite-enhancing) and physiological (suppression of stress-induced hyperthermia, attenuation of 5-HT release), effects of the 5-HT_{1A} autoreceptor agonist S-15535 revealed a 15-fold difference in sensitivity between high- and low-aggressive male rats, i.e. indicating that the high-aggressive males have a far more sensitive 5-HT_{1A} auto-receptor mediated inhibition of 5-HT neuronal activity. Similarly, using the specific 5-HT_{1B} receptor agonist CP-94253 had an almost 20-fold stronger anti-aggressive potency in high- compared to low-aggressive rats. This strongly enhanced tonic inhibitory control of the serotonergic neuron in aggressive males may explain the negative correlation between baseline levels of 5-HT and 5-HIAA and escalated aggression found in many species. Furthermore, to signify the causality of this correlation, 5-HT_{1A} autoreceptor sensitivity increased or decreased upon enhancing (by repeated victory experiences) or attenuating (by repeated defeat experiences) aggressiveness, respectively (unpublished data). Moreover, recent molecular genetic studies by Gross and colleagues have convincingly shown that transgenic mice with conditional (at adult age) overexpression of somatodendritic 5-HT_{1A} autoceptors demonstrate chronically suppressed 5-HT neural firing and PFC 5-HT levels that were associated with a heightened aggressive behavioral phenotype (Audero et al., 2013). These data persuasively confirm the causal role of tonic 5-HT activity, likely in the PFC, in setting thresholds for aggressiveness and presumably the behavioral

Fig. 10. Qualitatively opposite behavioral (pro- or anti-aggressive) effects of various serotonergic drugs after their chronic administration in low-trait and high-trait aggressive WTG rats. MDMA-data and experimental procedures from Wallinga et al. (2009).

inflexibility and impulsivity characteristics of the proactive coping style.

Given the striking similarities of different 5-HT_{1A} receptor agonists as to their anti-aggressive and suppression of shock producing properties, it may be feasible to conclude that 5-HT_{1A} receptor agonists, likely via their 5-HT_{1A} autoreceptor-mediated inhibition of 5-HT activity, generally reduce different expressions of proactive coping behavior. Considering the individual variation in the behavioral effects of 5-HT_{1A} 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 animal shows a decrease in escape and an increase in immobility behavior. In other words, activation of the 5-HT_{1A} auto-receptor leads to a reduction of the preferred behavioral reaction in this test, and to an increase in the alternative behavioral response rather than to a general reduction in anxiety (Veenema et al., 2005). If the serotonergic system is related to coping style rather than the emotional reactivity, one might indeed expect opposite dose response relations in the extremes of the variation. If serotonin was associated more with the emotional reactivity, 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 pharmacological dose-response relations in the extremes of the population (Fig. 10).

Additional more direct support for a general role of 5-HT neuronal activity to shift appraisal and responding to challenging situations along a proactive approach–passive/reactive avoidance behavioral axis, comes from several classical neuropharmacological studies demonstrating that the selection of active or passive coping strategies can 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 (Valentino et al., 2009; Wood, 2014; Wood and Bhatnagar, 2015). This concept is supported by findings that these qualitatively different functional consequences of CRF are mediated via a distinct expression level and/or cellular distribution of CRF1 and CRF2 receptors in the dorsal raphe, with CRF1-mediated inhibition and CRF2-mediated excitation of the dorsal raphe 5-HT

system facilitating proactive and reactive/passive coping strategies, respectively (Amat et al., 2004; Hammack et al., 2002).

7. Mesolimbic dopamine system and reward processing

The drive to seek and experience reward (e.g., motivational incentive) is profoundly conserved across species and, in mammals, involves interactions between subcortical dopaminergic systems and limbic structures. This mesocorticolimbic dopamine system has its cell bodies in the ventral tegmental area (VTA) and innervates not only the nucleus accumbens (Nacc), but also several other nodes of the social decision-making neural network including the prefrontal cortex (Fig. 8B). For over 40 years, this circuit is extensively studied for its involvement in natural reward processing, motivation and the development of drug addiction (Kelley and Berridge, 2002). Several studies show that individual variation in coping with environmental challenges is related to differences at the level of this mesolimbic dopamine system. For example, proactive coping RHA rats compared to reactive coping RLA rats have attenuated dopamine D₂-autoreceptor expression and functioning in VTA and Nacc (Tournier et al., 2013). This lower D₂R-mediated autoinhibitory control of DA neurons results in enhanced DA tone and in a specific pattern of DA signaling that may subserve the enhanced novelty-seeking behavior and augmented behavioral and neurochemical responses to acute administration of psychostimulants (Steimer et al., 1997; Giorgi et al., 2007) in RHA rats. Furthermore, it may explain the enhanced susceptibility of RHA rats to develop addiction-related behaviors as extensive research in humans, monkeys and rodents has shown that increased vulnerability to drug addiction correlates with reduced availability of striatal D₂ receptors (Zald et al., 2008; Bello et al., 2011; Morgan et al., 2002; Volkow et al., 2002). Finally, rats deemed socially dominant showed enhanced novelty reactivity but were neither more impulsive nor anxious compared with subordinate rats. Dominant rats additionally maintained higher rates of cocaine self-administration but showed no differences in the acquisition, extinction and reinstatement of this behaviour. D₂/3 binding was elevated in the nucleus accumbens shell and dorsal striatum of dominant rats when compared to subordinate rats, and was accompanied by elevated DAT and reduced dopamine content in the nucleus accumbens shell (Jupp et al., 2016).

Numerous studies in a wide variety of animal species have convincingly demonstrated that in addition to securing access to resources, the most intriguing consequence of winning an aggressive conflict is the self-reinforcing effect of this type of behavior. Actually, individuals seek out the opportunity to fight and engaging in aggressive behavior appears to be a source of pleasure. The most convincing evidence that successful aggression seems rewarding to animals is that the opportunity to engage in aggressive behavior can reinforce operant responding, i.e., animals are willing to work (e.g., bar pressing, nose poking) for aggression as a source of reward and satisfaction (see Miczek et al., 2004 for review). Not surprisingly, just like other events that function as positive reinforcers such as food, drugs or sex, the mesocorticolimbic dopamine system is associated with the incentive salience of the rewarding properties of winning fights. Nucleus accumbens (Nacc) dopamine is strongly released during (anticipation of) aggressive episodes (Ferrari et al., 2003) and pharmacological antagonism of dopamine D₁/D₂ receptors in the Nacc diminishes the seeking of the opportunity to fight (Couppez and Kennedy, 2008). In addition, direct optogenetic activation of ventral tegmental area (VTA) dopamine neurons increases aggression (Yu et al., 2014), proving that dopamine function and aggression are causally linked. However, to what extent these types of manipulations selec-

tively affect the rewarding/motivational components of aggressive behavior or modulate other behavioral control functions linked to general coping style is not clear yet. With regard to the argument of the present paper, these data support the view that individual differences in reward processing and/or sensitivity resulting from different functioning in the underlying mesocorticolimbic dopamine system is an important behavioral domain of coping styles.

8. Amygdala-hypothalamus-periaqueductal pathway and emotional reactivity

For more than a century after the original discoveries that temporal lobe and hypothalamic structures govern emotional behaviors (Brown and Schaefer, 1888; Goltz, 1884; Bard, 1928; Hess and Bruegger, 1943), increasingly sophisticated brain mapping and manipulation experiments have led to the identification of key loci controlling fear, rage, anxiety and/or several other “emotional” behavioral reactions. This includes the canonical amygdala complex, the bed nucleus of the stria terminalis (BNST), the ventral hippocampus (vHPC) and septal area, the hypothalamus and their projections to the periaqueductal gray (PAG) and ventral medulla (Calhoun and Tyne, 2015). One of the first studies to investigate the amygdala in terms of social behavior (Rosvold et al., 1954) found that proactive, high-ranking monkeys with surgical lesions of the amygdala lost their status in the dominance hierarchy and became extremely submissive. Indeed a major determinant of whether environmental stimuli are interpreted as threatening occurs in the amygdala that receives sensory information of virtual all modalities from the thalamus and sensory cortices. The amygdala is generally believed to be a rapid processing station where the level of salience is imparted to a given stimulus (LeDoux, 2003). This valued information is then relayed via the stria terminalis to the medial hypothalamus that in turn can initiate fight, flight and other defensive behavioral responses as well activate the pituitary neuroendocrine axes. In addition both the amygdala and hypothalamus relay information to specific parts of the PAG for further integration and coordination with the autonomic and other physiological motor centers in the brainstem to support the somatic “fight or flight” responses (e.g., increase in blood pressure, respiratory rate etc.). Moreover, the amygdaloid complex has widespread reciprocal connectivity with virtually all other cortical and limbic nodes of the social decision-making network, including the prefrontal cortex and the dorsal and ventral striatum. In particular the prefrontal cortex exerts a tonic inhibitory control over amygdala functioning via pathways to intercalated GABAergic neurons (Barbas et al., 2003).

The amygdaloid complex not only receives a dense innervation of noradrenergic fibers from the pontine nucleus locus coeruleus, it also provides an important source of corticotropin releasing factor (CRF) from the central amygdala that mediates LC activation (Retson and Van Bockstaele, 2013). The locus coeruleus-noradrenaline (LC-NA) system is a major brain stress response system, and activation of this LC-NA system is important in maintaining general arousal and vigilance (Van Bockstaele and Aston-Jones, 1995). In addition, LC activation via its inhibitory influence on parasympathetic neurons and excitatory action on sympathetic neurons, results in increased peripheral catecholamine release with consequent rises in heart rate and blood pressure (Wang et al., 2014). Interestingly, recent research mapped out evidence of distinct excitatory CRF and inhibitory enkephalin regulation of LC afferents in passive versus active coping rats (Reyes et al., 2015; Wood and Valentino, this issue).

Besides their important peripheral neuroendocrine/physiological functions as hypophyseal-released hormones,

the evolutionary highly conserved hypothalamic neuropeptides CRF, arginine vasopressin (AVP) and oxytocin (OXT) are also implicated in inter-neuronal communication within this amygdala-hypothalamus-PAG/LC emotional arousal pathway (Meyer-Lindenberg et al., 2011). While brain CRF and AVP are generally known to increase anxiety-like behaviors, stress and arousal, OXT on the other hand has the opposite effects and facilitates anxiety-reduction and affiliation (Heinrichs et al., 2009; Insel et al., 1998). Existing data from the pioneering work of the late Bohus and de Wied (1998) already convincingly demonstrated opposite “ying-yang” roles for AVP and OXT in fear learning processes. More recent studies in wild-type rats, Roman high- and low-avoidance rats, artificially-selected SAL and LAL house mice and high-aggressive prairie voles and low-aggressive meadow voles have demonstrated that non-aggressive males are characterized by a far more extensive vasopressinergic immunoreactive network and/or a higher AVP content and AVP-IR density in the extended amygdala (i.e., BNST, MeCeA, LS) than high-aggressive males (Everts and Koolhaas 1999; Aubry et al., 1995; Compaan et al., 1993).

Impaired brain OXT-ergic signaling has been firmly implicated in several human neuropsychiatric disorders characterized by social deficits, impulsivity and excessive aggression (Lee et al., 2009). Hence, research in the past decade has revolved around elucidating the precise role of OXT on social and impulsive aggressive behaviors in rodents and many other animal species. Our ethopharmacological studies in WTG rats have clearly shown that both acute and chronic enhancement of brain OXTergic function, using intraventricular (Calcagnoli et al., 2014a,b), intracerebral, and even intranasal administration routes (Calcagnoli et al., 2015), produced marked anti-aggressive effects that are dose-dependent, behavior- and receptor-selective and long-lasting. Interestingly, these behavioral changes are strongly moderated by the individual's basal level of aggressiveness, strongly suggesting an inverse relationship between trait-like aggressiveness and endogenous brain OXTergic signaling. Indeed, in-situ hybridization and receptor autoradiography revealed a significantly lower OXT mRNA expression in the paraventricular nucleus, but not in the supraoptic nucleus, of excessively aggressive/violent rats as compared to both low and medium-high normal aggressive ones (Calcagnoli et al., 2014a). These findings strongly support the hypothesis that variations in the structural and functional properties of brain oxytocinergic circuits may give rise to individual differences in aggressiveness and/or proactive coping with conflict.

The findings outlined above strongly suggest that increased vasopressinergic activity in discrete brain regions that are 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 selective nodes of this neural circuit may gate the expression of either proactive or reactive/passive responses to stressors. One key brain area that is implicated in 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) (Stoop et al., 2015). Stressful stimuli increase the levels of both peptides in the extracellular space of the CeA, possibly due to the release from local synaptic terminals (Landgraf and Neumann, 2004). 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 (Ebner et al., 2005; Neumann and Landgraf, 2012). 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 or neuronal networks (qualitative difference) or different levels or degree of neuromodulation within and across (some of) the nodes of one and the same neuronal network (i.e., quantitative difference) needs careful further exploration, preferably employing the naturally occurring individual variation within a species in tests that allow a differential expression of coping style.

9. Coping styles and disease susceptibility

From a biomedical point of view, the concept of distinct coping strategies implies that differently coping animals may have a differential capacity to adapt successfully to the same environmental conditions. Negative health consequences may arise if an animal cannot cope with the stressor or needs very demanding coping efforts, i.e., a mismatch (maladaptation) between expressed coping style and actual environmental demands. In view of the differential autonomic/endocrine reactivity and neurobiological makeup, one may expect different types of stress pathology to develop under conditions in which a particular coping strategy fails and/or under conditions of very-demanding and sustained coping efforts. Although there are only a limited number of rodent studies performed concerning true pathology development in relation to the type of coping strategy, there are several indications that the two coping strategies differ in susceptibility to develop cardiovascular pathology, gastro-intestinal and infectious diseases (Table 3 and see Koolhaas et al., 1999; Kavelaars et al., 1998; Sgoifo et al., 2014; Carnevali et al., 2013; for more detailed information). In addition to a different vulnerability for somatic diseases, distinct coping styles may also demonstrate a different proneness to develop behavioural disorders like antisocial violent-like aggressiveness (De Boer et al., 2009), stereotypies (Dantzer et al., 1988; De Boer et al., 1990), substance use disorders (LeMoal, 2015), metabolic disorders (Boersma et al., 2011), anxiety, depression and PTSD (Buwalda et al., 2005; Bertoni et al., 2012).

Concerning the enhanced risk for cardiovascular dysfunctions (e.g., cardiac arrhythmias, sudden cardiac death, hypertension) in proactively coping animals that are socially stressed and/or lose their social status, a number of studies have demonstrated that a feasible pathophysiological mechanistic link appears to be the stress-induced augmentation of the diminished cardiac sympatho-vagal autonomic balance (enhanced sympathetic and/or reduced vagal tone) that characterizes these proactive animals (Table 2). In an attempt to elucidate the neurobiological mechanisms underlying these social stress-induced autonomic imbalances, it is very likely that diminished serotonergic signalling at 5-HT_{1A} (auto)receptors is playing a key role. For example, it has been shown that chronic genetic lack of 5-HT_{1A} receptors appears to increase the risk of fatal cardiac events in mice when exposed to chronic psychosocial stress (Carnevali et al., 2012). In addition, mice with excessive 5-HT inhibition due to conditional overexpression of 5-HT_{1A} autoreceptors exhibit sporadic autonomic dysregulation and sudden cardiac death (Audero et al., 2008). Furthermore, 5-HT_{1A} receptor agonists have potent bradycardiac, hypotensive and anti-arrhythmogenic effects (Nalivaiko and Sgoifo, 2009). Given the serotonergic alterations, particularly 5-HT_{1A} receptor functionality, in proactively aggressive WTG rats as outlined above, it is tempting to speculate that these play also a crucial role in their enhanced stress-induced vulnerability for autonomic physiological dysfunctions.

Besides different disease vulnerability, animals differing in general coping style may also differently react to pharma-

Table 3

Summary of differential stress-disease susceptibility between proactive (high-aggressive) and passive/reactive (low-aggressive) coping male rats and mice.

Pathology	High-aggressive	Low-aggressive	References
Somatic diseases			
Autoimmune EAE disease	High	Low	Kavelaars et al. (1998)
Tachyarrhythmia	High	Low	Sgoifo et al. (2014)
Hypertension	High	Low	Fokkema et al. (1995)
Bradyarrhythmia	Low	High	Koolhaas et al. (1999)
Obesity/metabolic syndrome	High	Low	Boersma et al. (2011)
Gastric ulceration	High	Low	Murison et al. (1992)
Behavioral disorders			
Violent-like aggressiveness	High	Low	De Boer et al. (2009)
Anxiety/PTSD	Low	High	Buwalda et al. (2005)
Social phobia	Low	High	De Boer et al. (2003)
Substance use disorder	High	Low	Hensbroek et al. (1996), Dantzer et al. (1988)
Stereotypies/Compulsivity	High	Low	De Boer et al. (1990)

cotherapeutic treatments. Evidence for this comes from some of our recent psychopharmacological studies investigating the effects of acute or chronic administration of several serotonergic compounds. Both acute administration of the 5-HT_{1A} receptor agonist WAY100635 as well as chronic administration of 5-HT_{1A} receptor agonists (S-15535 and alnespirone), the SSRI antidepressant compound fluoxetine or the serotonin releasing agent MDMA effectively reduced aggressive behavior in high-aggressive animals but induced, sometimes even to high levels, aggressiveness in low-aggressive individuals (Fig. 10; Wallinga et al., 2009; de Boer et al., in preparation). Although still in its infancy at the experimental level, it is suggested that individual differences in therapeutic responsiveness to drugs may be strongly associated with type of personality or expressed coping style.

10. Concluding remarks

The present paper advocates that individual differences in trait-aggressiveness reflect general stress coping styles that are a fundamental and adaptively significant component of the natural sociobiology of rodents. These basic individual differences can be exploited experimentally in the laboratory in order to understand the causes and consequences of aggression and general coping strategies to deal with stressors. We have provided arguments that coping styles can be classified in a three-dimensional space according to their level of behavioral flexibility and/or impulse control, emotional reactivity and reward sensitivity. These fundamental behavioral control functions can be translated into phylogenetically-conserved neural circuitries that are highly interconnected and together form the so-called “stress coping decision-making network”. In particular, the medial prefrontal cortex is a key node of this neuronal network to provide important direct “top-down” regulation of behavioral flexibility, impulse control and/or planning of behavior in time. In addition, the PFC also executes prime control over the “emotional” amygdala circuitry and the “reward-processing” VTA-NAcc network (Arnsten and Rubia, 2012). Distinct regions of the PFC are believed to regulate this spectrum of behavioral functions and emerging opto- and chemico-genetic neuronal manipulation studies are expected in the near future to provide a more detailed understanding of the precise population of PFC neurons in each of these functions. Recent evidence demonstrated that naturally occurring differences in PFC functioning (intrinsic neuronal firing rate and reactivity) underlie individual differences in stress susceptibility (Kumar et al., 2014).

The same promise holds for the elusive dorsal raphe nucleus-serotonergic system that is implicated in virtually all of the above-mentioned neural circuits and its putative behavioral control functions. This neurotransmitter system typically has a general modulating role in the control of behavior and physiology. Variabil-

ity in global brain 5-HT activity seems to be associated more with individual differences in general coping style or personality than a specific behavior. Indeed, its main neurophysiological function seems to be gating of sensory input and motor output (Hurley et al., 2004; Dugue et al., 2014). Low levels of 5-HT cause an organism to reduce on external input in favor of more intrinsically generated behavior. The frequently observed negative correlation between prefrontal serotonin and low cue dependency of highly aggressive and proactive rats and mice is consistent with this view.

Finally, studies aimed at understanding individual stress (disease) vulnerability show that the behavioral flexible, passive/reactive coping animal shows the strongest stress-induced changes at the level of behavior, neuroendocrinology and neurobiology. Although many of these changes have often been interpreted as signs of stress-induced pathology, these alterations might just as well reflect the behavioral and physiological underpinnings of successful individual adaptation. This line of reasoning suggests that high behavioral flexibility characterizing passive/reactive coping styles is associated with a high capacity to adapt to novel and changing environments. Hence, it allows a better answer to the fundamental question of the adaptive or maladaptive nature of the changes observed. Basically, untangling the precise neural circuitries and molecular mechanisms of different coping styles is essential for a better comprehension of the etiology of stress-related (psycho) pathologies, and hence provides a roadmap for future therapeutic development.

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