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Review

# Individual differences in cardiovascular response to social challenge

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**Abstract**

An important determinant of cardiovascular stress reactivity and morbidity is the individual behavioral strategy of coping with social challenge. This review summarizes the results of a number of studies that we performed in rats, aimed at investigating the relationship between aggression and cardiovascular responsivity under social stress conditions.

We show that rats belonging to the 'aggressive tail' of a population are characterized by a higher sympathetic-adrenomedullary activation during social and non-social stress episodes. Wild-type rats are characterized by a larger sympathetic dominance and a higher susceptibility to cardiac arrhythmias during defeat as compared to Wistars. Cardiovascular habituation takes place when social challenge is an intermittent victory experience, whereas no habituation is observed across repeated defeat episodes. Dominant rats whose social dominance is challenged by the aggression of another subject display long-term alterations of heart rate circadian rhythmicity. Such changes are linked to individual proness to defend social dominance: the more the animal counterattacks the aggressor, the smaller the subsequent rhythm disturbance. These data underline how important it is to carefully consider individual differences in aggression and the context in which aggression is expressed, when studying cardiovascular effects of social interactions.


*Keywords:* Social stress; Aggression; Proactive and reactive; Plasma catecholamines; Sympathetic and parasympathetic nervous system; Heart rate variability; Arrhythmias; Circadian rhythms

**Contents**



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## 1. Introduction

Pathologies affecting the cardiovascular system are relatively frequent among stress related psychosomatic disorders, and have received remarkable attention in the past decades. In particular, social stressors seem to play a significant role in the onset and progression of cardiocirculatory diseases such as hypertension, atherosclerosis and cardiac arrhythmias [1–8].

Social stress factors could be defined as challenging stimuli originating from the interaction with conspecifics. They are present in all mammalian species and are particularly relevant to species with a complex social organization, where they likely provided much of the impetus for the evolution of stress response mechanisms [9]. In many animal species, disputes over resources (territory, food and sexual partners) involve agonistic behaviors with different degrees of aggression, which may result in wounding, exhaustion and sometimes even death. In humans, social stress episodes do not necessarily imply overt aggressive acts; nevertheless, intraspecific interactions involve competitive/hostile behaviors, which represent a severe challenge to physiological and psychological homeostasis. For all these reasons, social stress paradigms are thought to bear a high face validity, and they are being adopted more and more in both human and animal studies aimed at clarifying the mechanisms underlying stress related cardiovascular pathophysiology [10–14].

Human and animal data suggest that an important determinant of cardiovascular stress reactivity and morbidity is the individual behavioral strategy of coping with social challenges [15–18]. In other words, cardiocirculatory pathophysiological consequences seem to depend tightly on what perception an individual has and what behavioral strategy he adopts when dealing with the challenge imposed by another member of the social group.

Henry proposed that there are two innate response patterns, which might explain the differential sensitivity in developing hypertension [2]. One pattern is related to dominance behavior; it is characterized by behavioral arousal, high levels of aggression and territorial control, and is termed the ‘active coping’ response pattern. It is associated with increased cardiac output and redistribution of blood flow to the brain and skeletal muscles, mediated by a robust activation of the sympathetic-adrenomedullary (SAM) system. The other pattern is related to subordination (i.e. defeat or perception of a threat to or loss of control). It is characterized by a generalized behavioral inhibition (‘passive coping’) and a stronger activation of the hypothalamic-pituitary-adrenocortical (HPA) axis [2].

Human studies performed by Rosenman and Friedman quite a while ago still represent a significant hallmark on this regard. They defined the ‘type A’ behavioral pattern as associated to a higher proness to develop coronary disease. Type A category includes subjects who are hostile, competitive, achievement oriented. The relative absence of type A characteristics defines ‘type B’, non-coronary-prone behavioral pattern [19–21]. The relationship between type A behavioral pattern and cardiovascular/catecholaminergic responses to experimental conditions designed to induce hostility and competitiveness has been studied also by Glass [22]. Type A subjects showed significantly larger increments of systolic pressure, heart rate and plasma adrenaline as compared to type B counterparts, thus supporting the idea that the style of behavioral coping influences in a significant manner the patterns of physiological responsiveness. Recently, Newton and Bane examined the cardiocirculatory outcome of the exposure to social challenge in man: cardiovascular reactivity (heart rate and arterial pressure changes) was positively correlated with the level of dominance/hostility shown by the opponent in a dyadic interaction [23]. Also studies by Guyll and Contrada confirmed that certain behavioral and trait characteristics go together with specific cardiovascular and neuroendocrine activations in response to stressors [24]. For instance, individuals who are hostile, cynical, with propensity to develop anger and aggression exhibit high cardiovascular reactivity to laboratory stressors [25].

Although these human data are intriguing and rather convincing, a limitation lies in the difficulty to control and standardize for the individual social history preceding laboratory assessment. In addition, the application of social stress stimuli for experimental purposes is obviously bound to ethical limitations. Finally, it is complicated to characterize the role of pathogenic social factors because of the long time span of cardiovascular pathogenesis in humans.

Animal studies properly controlling for social stimuli since weaning allow to partially overcome these limitations.

Experiments on mice and rats have provided further insight in the physiology and pathophysiology of individual differences in stress reactivity. Henry showed that a state of chronic competition (obtained by periodic mixing of males from different colonies) produces blood pressure elevations and cardiovascular pathology in normotensive Long Evans rats [16]. The author suggested that the most effective stimulus for the development of hypertension is, rather than an outright subordination state, a continuing activation of the conflict-based fight/flight response, which results from social instability and the failure of the establishment of a stable dominance hierarchy.

Similar experiments were performed also by the group of Koolhaas. One of these studies showed that male rats with an aggressive coping strategy are characterized by a high sympathetic/adrenomedullary reactivity to social and non-social stimuli [26]. Another study showed that soon after colony aggregation male rats—beforehand classified as highly aggressive—had higher resting blood pressure values. But once hierarchy was established, hypertension was observed in those individuals which continued to exhibit an aggressive coping trait aimed at improving social rank [27].

Koolhaas revised and extended the concept of active/passive coping [18]. The active copers were termed 'proactive' because they are not only characterized by high levels of aggression, dominance and territoriality, but also by a tendency to develop routine-like, rigid, intrinsically driven behaviors. The passive copers were termed 'reactive' and they are not only less aggressive, less territorial and subordinated, but also more flexible and driven by changes in environmental stimuli. In line with the classical differentiation, these two styles of adaptation differ also as far as autonomic/neuroendocrine (re)activity is concerned. Proactive animals are characterized by a higher sympathetic activation and a lower (re)activity of the HPA axis. Reactive animals are parasympathetically driven and have a higher HPA axis (re)activity [18].

The existence of these coping differences in rodents and the fact that they appear as trait characteristics provide a valuable opportunity to explore—in a systematical way—a fundamental issue: to what extent do these trait characteristics influence cardiovascular stress responsivity and pathology?

The present review summarizes the results of a number of studies that we performed in rats, aimed at providing further insight in the relationship between a major feature of behavioral coping—i.e. aggression—and cardiovascular responsivity under social stress conditions. Peripheral sympatho-adrenomedullary activation, sympathovagal balance at the level of the heart, susceptibility to cardiac arrhythmias, and circadian rhythmicity of heart rate were examined in relation to individual differences in aggression and coping with social stressors. The behavioral categorization was based on either the trait characteristic of the animal (i.e. aggressive or non-aggressive on the basis of a beforehand characterization) or the state characteristic (i.e. animals that currently were playing either the role of the dominant or that of the subordinate in short-lasting, binary social confrontations).

## 2. General methods

### *2.1. Social challenge: single or intermittent agonistic episodes*

The classical resident-intruder test was used as an experimental paradigm to induce intraspecific/intrasexual aggression, that is based on the establishment of a territory by a male and its defense against an unfamiliar male intruder. The intruder was introduced for a brief period of time (either 15 or 30 min) to the home cage of an aggressive male, the former being attacked and submitted by the latter [28]. In the experiments hereby described, this paradigm was used either as a single episode or as a series of intermittent episodes of the same type, taking place once daily on alternated days (intermittent homotypic stressor) [29].

### *2.2. Cannulation/blood sampling technique and ECG recording via radiotelemetry*

Blood samples were obtained using a cannulation/sampling technique originally described by Steffens [30]. Rats were provided with a Silastic heart cannula through the right jugular vein, with one end reaching the entrance of the right atrium and the other one externalized on top of the skull. ECGs were recorded by means of a radiotelemetry system consisting of a chronically implanted miniature transmitter and a platform receiver placed under the experimental cage [31]. Both recording techniques allow reliable measurements from freely-behaving animals, in baseline and challenging conditions [32]. For the sake of reducing as much as possible interference with the animal behavior and physiology, each individual rat was provided with only one of the two measuring means, i.e. either the transmitter or the jugular cannula.

### *2.3. Indirect measurements of the autonomic input to the heart: plasma catecholamines, heart rate variability and cardiac arrhythmias*

The major neuroendocrine mediator of cardiovascular arousal in response to (social) stressors is the sympathetic-adrenomedullary (SAM) system, whereas the parasympathetic system has as a conservation role, counter balancing the effects produced by the sympathetic branch [33].

In the experiments further described, plasma levels of catecholamines (i.e. noradrenaline and adrenaline, determined via high-performance liquid chromatography and electrochemical detection) were used as a marker of

the influence of the SAM system on the heart function. In view of the discrete nature of efferent sympathetic innervation, this measurement can only partially represent cardiac sympathetic control. However, a number of studies showed reasonable agreement between nerve firing and venous levels of catecholamines and between hemodynamic functions and noradrenaline/adrenaline plasma concentrations [34].

ECG analysis was performed by means of a software package developed in our lab ('XRRECG') [29] for quantification of time-domain indexes of heart rate variability [35]. The following parameters were quantified: (i) the mean R–R interval duration (RR, ms), (ii) the standard deviation of RR ($SD_{RR}$, ms), and (iii) the root mean square of successive R–R interval differences (r-MSSD, ms). $SD_{RR}$ estimates overall heart rate variability and therefore includes the contribution to heart rate variations of both components of the autonomic nervous system; it measures the state of the balance between the activities of the sympathetic branch (low-frequency variations) and the parasympathetic branch (high-frequency variations). The r-MSSD focuses on high-frequency, short-term variations of R–R interval, which are due to the activity of the parasympathetic nervous system [32,36,37]. Generally speaking, increased sympathetic and/or decreased parasympathetic tone (i.e. shift of sympathovagal balance towards sympathetic dominance) are reflected in decreased values of variability indexes, while decreased sympathetic and/or increased vagal nervous system activity (i.e. shift of the balance towards parasympathetic prevalence) are reflected in increased values of heart rate variability parameters [35]. Finally, the incidence of the most common cardiac tachyarrhythmias in normal rats, namely ventricular and supraventricular premature beats, was quantified as number of events via offline, visual inspection. In this species, the susceptibility to cardiac arrhythmias represents a useful marker of autonomic balance at the level of the heart. In fact, previous studies showed that there is a significant, positive correlation between the degree of sympathetic dominance and the amount of ventricular ectopic beats [5,32]. In other words, higher levels of sympathetic prevalence are typically associated with larger occurrence of ventricular premature beats during an acute social challenge.

## 3. Study 1. Plasma catecholaminergic response to stressors in highly aggressive and non-aggressive rats

This first study provided evidence supporting the hypothesis that more aggressive animals have a higher sympathetic-adrenomedullary activation than less aggressive counterparts, when facing an acute challenge [26].

Plasma noradrenaline (NA) and adrenaline (A) responses to social and non-social stressors were studied in adult male members of a strain of wild type rats (Wild Type Groningen, WTG) widely differing in their level of aggression. Individual aggressiveness was preliminarily established by measuring the latency time to attack a male intruder in a standard resident-intruder test (ALT, in seconds, average of four trials). Animals were then provided with a jugular vein cannula that enabled blood sampling before, during and after stress exposure. Implanted rats were randomly assigned to three experimental treatments: social stress (defeat experience, $n=19$) [38], non-social stress (presentation of a shock prod, $n=16$) [39], and control (animals undisturbed in their home cages, $n=7$). At the behavioral level, a significant correlation was found between ALT and the amount of time spent in burying the probe (cumulative time, in seconds): the more aggressive the animal, the higher the amount of active, burying behavior. This indicated that the individual level of aggressive behavior is somewhat predictive of the behavior of an animal in the shock prod burying test and confirmed the idea that aggressive males generally adopt an active behavioral coping strategy in a challenging situation. At the physiological level, this study showed that experiencing social defeat has a much stronger effect on plasma NA and A concentrations than shock prod presentation. Noteworthy, a significant negative correlation was found between aggression scores and the values of the area under the response time curve for NA and A, in both social and non-social stress situations. In other words, the higher the degree of trait aggression, the higher the catecholaminergic reactivity to social and non-social stressors [26].

It is worth mentioning that this behavioral/neuroendocrine association was not found when the level of aggressiveness was correlated with catecholamine concentrations in resting conditions. This suggests that individual behavioral/neuroendocrine differentiation might not be evident when animal physiology (in this case, sympathoadrenomedullary function) is studied out of a challenging context (i.e. baseline conditions).

Altogether, these findings in an unselected strain of wild-type rats confirmed that an aggressive/proactive strategy of coping with stressors is associated with a high sympathetic-adrenomedullary activation and support the concept of individual differentiation in coping styles as a coherent set of behavioral and neuroendocrine characteristics [18].

## 4. Study 2. Cardiac autonomic balance, arrhythmias and plasma noradrenaline levels during social challenge in two rat strains

This second experiment indicated that rats belonging to a wild type strain react to a brief social challenge (defeat) with a higher sympathetic activation, a lower parasympathetic (protective) antagonism, and a higher incidence of ventricular arrhythmias than laboratory (Wistar) counterparts [40].

Cardiac sympathovagal balance, arrhythmia susceptibility and plasma noradrenaline concentrations were

investigated in adult male rats belonging to two rat strains, Wistar ($n=24$) and WTG ($n=24$). Rats were provided either with a jugular vein cannula for blood sampling ($n=8$ per group) or with a radiotelemetry system for electrocardiographic recordings ($n=16$ per group) in freely behaving animals. All individuals were exposed to an acute (15 min duration) social challenge (as obtained via the resident-intruder test), in which they were attacked and subordinated by a trained, aggressive fighter (social defeat). Average R–R interval and heart rate variability measures ($SD_{RR}$ and r-MSSD), as well as plasma noradrenaline concentrations indicated that rats of both strains were significantly activated during and just after the social test. However, WTG rats were characterized by a higher sympathetic tone, a larger sympathetic responsiveness, and a lower parasympathetic antagonism to sympathetic activation during defeat. In the post-test phase (15 min duration), not only were heart rate variability measures still significantly lower in wild-type compared with Wistar rats, but they again indicated a qualitatively different pattern of autonomic response. In Wistar rats, heart rate variability measures were significantly ($SD_{RR}$) or almost significantly (r-MSSD) enhanced in this phase compared with baseline, whereas they were still significantly lowered (r-MSSD) or back to baseline ($SD_{RR}$) in wild-type rats. In other words, while Wistar rats show a remarkable vagal recruitment in the period of time just after stress exposure, wild-type counterparts only show a poor parasympathetic rebound after sympathetic stimulation. Such differences in stress-induced autonomic responsiveness were coupled with a 3-fold higher incidence of arrhythmias (ventricular premature beats) in WTG as compared to Wistar rats [40]. This association between lower heart rate variability and higher susceptibility to ventricular tachyarrhythmias is in accordance with the view of a 'protective role' against cardiac electrical instability exerted by the parasympathetic nervous system [33,41].

The comparison between these two rat strains might represent a useful experimental model for studying in more detail the cellular/molecular mechanisms responsible for individual differences in the vulnerability to arrhythmias, in subjects exposed to stressful situations.

## 5. Study 3. Habituation to social challenge: role of controllability

This third study showed that habituation of cardiac autonomic responsiveness to an intermittent social challenge takes place only when the animal can exert a reasonable degree of control over the stressor [29].

A number of previous studies indicated that the intermittent exposure to the same stressor can lead to a gradual decline in physiological, neuroendocrine and behavioral stress responses (habituation) [42–44]. We investigated possible habituation processes of cardiac autonomic responsiveness and susceptibility to cardiac arrhythmias in male WTG rats exposed to either intermittent social victory (VIC) or defeat (DEF). More specifically, VIC animals ($n=12$) received an unfamiliar male intruder into their home cage, that they vigorously attacked and finally submitted. On the contrary, DEF animals ($n=12$) were introduced to the home cage of a highly aggressive unfamiliar male, by which they were attacked and submitted. Victory and defeat tests were repeated 10 times on alternate days, each time using a different opponent. Electrocardiograms were recorded via radiotelemetry and cardiac sympathovagal balance was evaluated via time-domain parameters of heart rate variability. During the 1st social challenge, the values of these parameters were significantly lower in DEF as compared to VIC rats in the second part of the test period (from 6 to 15 min), suggesting a more pronounced sympathetic dominance in the former group of animals. This finding is consistent with published data documenting a much higher catecholaminergic activation during defeat than during victory. Plasma noradrenaline and adrenaline levels, determined just at the end of the conflict, have been shown to be significantly larger in rats losing a combat as compared to rats winning a fight [45]. Accordingly, the occurrence of ventricular and supraventricular premature beats was higher in DEF rats. A clear habituation profile of cardiac autonomic responsivity was observed across repeated exposure to victory, both in terms of sympathovagal balance and susceptibility to cardiac tachyarrhythmias, whereas no habituation was found in repeatedly defeated animals [29]. A possible explanation of this result relies on the different degree of controllability characterizing the two social challenge situations. In fact, an animal playing the role of the dominant in its own territory can exert much more control over the agonistic episode than an animal forced to play the role of the subordinate in an unknown environment. The level of controllability by defeated animals was likely reduced also by the fact that they were exposed each time to a different aggressive dominant and in a different experimental cage.

## 6. Study 4. Long term heart rate changes as a consequence of loss of social status

In this last study, we collected data suggesting that the sudden loss of a previously achieved state of dominance may produce long-lasting consequences on the circadian rhythmicity of heart rate, body temperature and physical activity [46].

Experimental animals consisted of WTG male rats ($n=12$), which became dominants by winning 10 consecutive agonistic encounters with unfamiliar intruders. Finally, they were introduced to the cage of an aggressive conspecific for 30 min and an intense fight took place. The effects on daily rhythms of heart rate, body temperature, and physical activity thereafter were

measured by means of radiotelemetry. In some rats, the confrontation caused a significant reduction in the amplitude of the daily rhythm of all parameters that lasted up to 3 weeks, whereas other subjects showed only minor chronobiological consequences. The degree of alteration in rhythm amplitude did not correlate with the number of attacks received from the cage owner, in accordance with previous studies [47]. On the contrary, rhythm changes were negatively correlated with the aggression of the experimental rats themselves: the more the subjects counterattacked the cage owner, the smaller the subsequent reduction in the rhythm amplitude. In addition, there was a clear correlation with the time spent exploring the unfamiliar territory of the aggressive opponent: rats that spent more time on exploration during the intruder test had a larger rhythm amplitude thereafter. These data suggest that the long-term consequences of a social conflict in dominant rats do not depend on the physical intensity of the fight in terms of aggression received, rather on how the subjects deal with it. The more they resist and respond to the aggression of the territory owner with counter aggression, the smaller the subsequent chronobiological disturbances. One might assume that rats that exhibited subordination postures and hardly ever counterattacked during the conflict experienced defeat and loss of social status, whereas rats that frequently counterattacked and hardly showed any submissive behavior did not experience defeat. Indeed, several of the experimental subjects were facing a situation that was clearly dominated by the aggressive territory owner; on the contrary, for some of the rats that resisted and fought back, it was difficult to establish whether they were subordinated or not. In a few cases the experimental rat even seemed to dominate the social confrontation [46]. Thus, the interpretation that links individual differences in long-term chronobiological stress consequences to individual proness to defend previously gained social dominance sounds reasonable. As such, these data support the idea that the experience of loss of social status is an important determinant of the long-lasting physiological consequences of intrasexual competition. It does not necessarily follow that the observed changes in physiological rhythms reflect a maladaptive, pathological state. Nonetheless, it can be hypothesized that circadian rhythm disturbances make an individual more vulnerable to sensitization-like processes, i.e. prone to exaggerated responses when exposed to further stress episodes.

## 7. Conclusions

The thread of this series of studies was to relate individual differences in cardiovascular stress responsiveness with different levels of aggressive behavioral coping in wild-type rats. Individual differences in aggression were established via different approaches: (i) beforehand determined trait characteristics, i.e. belonging to one of the two tails of the aggressiveness distribution within a population (non-aggressive and highly aggressive animals); (ii) strain differences, i.e. wild-type vs laboratory (Wistar) rats; (iii) current role in a dyadic interaction, i.e. winner or loser during a fight; (iv) proness to defend previously gained social dominance.

The set of data reviewed above allows us to draw a few interesting conclusions. Individuals belonging to the 'aggressive tail' of a population are characterized by a higher plasma catecholaminergic responsiveness during defeat stress as compared to subjects belonging to the 'non-aggressive tail', although these two behavioral types do not differ between each other for sympathetic-adrenomedullary activity in resting conditions.

Wild-type rats are characterized by a higher cardiac sympathetic drive in baseline conditions as compared to Wistar counterparts; most importantly, they show a larger sympathetic reactivity and a lower parasympathetic antagonism during social defeat, that goes together with a much higher susceptibility to cardiac arrhythmias.

Being the winner or loser during a social competition implies a different cardiac autonomic recruitment. Defeated animals exhibit a larger shift of sympathovagal balance toward sympathetic dominance and higher vulnerability to ventricular premature beats. This differential impact on cardiac electrophysiology is tentatively explained by calling on different degrees of controllability over the social context. In addition, rats show cardiovascular habituation when facing a repeated victory experience, i.e. the shift toward sympathetic dominance and the susceptibility to ventricular arrhythmias gradually fade across exposures. On the contrary, animals fail to habituate when the social stressor is an intermittent defeat experience.

Dominant rats whose social dominance is challenged by the aggression of another aggressive subject display long-term reductions in the amplitude of heart rate circadian rhythm. However, the degree of such chronobiological alteration is tightly linked to individual proness to defend previously gained social dominance: the more the animal counterattacks the aggressor, the smaller the subsequent reduction in the rhythm amplitude.

Altogether, these data underline how important is to carefully consider individual differences in trait and state aggression and the context in which aggression is expressed, when studying acute and long-term cardiovascular effects of social interactions.

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