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Short communication

Decreased dendritic spine density in posterodorsal medial amygdala neurons of proactive coping rats

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ABSTRACT

There are large individual differences in the way animals, including humans, behaviorally and physiologically cope with environmental challenges and opportunities. Rodents with either a proactive or reactive coping style not only differ in their capacity to adapt successfully to environmental conditions, but also have a differential susceptibility to develop stress-related (psycho)pathologies when coping fails. In this study, we explored if there are structural neuronal differences in spine density in brain regions important for the regulation of stress coping styles. For this, the individual coping styles of wild-type Groningen (WTG) rats were determined using their level of offensive aggressiveness assessed in the resident-intruder paradigm. Subsequently, brains from proactive (high-aggressive) and reactive (low-aggressive) rats were Golgi-cox stained for spine quantification. The results reveal that dendritic spine densities in the dorsal hippocampal CA1 region and basolateral amygdala are similar in rats with proactive and reactive coping styles. Interestingly, however, dendritic spine density in the medial amygdala (MeA) is strikingly reduced in the proactive coping rats. This brain region is reported to be strongly involved in rivalry aggression which is the criterion by which the coping styles in our study are dissociated. The possibility that structural differences in spine density in the MeA are involved in other behavioral traits of distinct coping styles needs further investigation.

Distinct behavioral and physiological responses to environmental challenges and opportunities can be observed among individuals across many animal species, which are considered to reflect different coping strategies or animal personalities [1,2]. It has been hypothesized that distinct coping styles may serve as a means to buffer species against fluctuations in environmental conditions via differentiation in the individual phenotypical adaptive capacity to specific environmental demands [1,3]. A study in natural populations of great tits (Parus major) indicated that birds with different coping styles, active or passive, had differential annual survival rates depending on the food availability during the winter [4]. Various terms such as bold or shy, active or passive, and proactive or reactive are used to categorize distinct behavioral coping styles but in general they represent differential behavioral approaches to cope with environmental demands. Henry and Stephens [5] were the first to suggest that differences in offensive aggressiveness might reflect a general differentiation in the way individuals cope or deal generally with environmental challenges. Studies from our laboratory and many others indicated that indeed stable trait-like differences in offensive aggression exist and that they are associated with differences in general behavioral performance under various other stressful conditions [3,6].

These alternative behavioral and physiological response patterns to environmental stressors are represented in animals with aggressive (proactive) and non-aggressive (reactive) behavioral trait characteristics [2]. The individual differences in behavioral and physiological pro- and reactive coping styles likely emerge as a result of functional and/or structural differences in the underlying neurocircuitry that determines coping styles. This basic and evolutionary well-conserved corticolimbic

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circuit is often termed the social decision making network (SDMN) [7], which includes the prefrontal cortex, amygdala, BNST, hippocampus and their afferent and efferent projections. For instance, stimulation of GABAergic and glutamatergic neurons in the medial amygdala is known to promote and inhibit aggression, respectively [8]. In the prefrontal cortex, optogenetic stimulation of excitatory neurons is known to inhibit aggression and suppression of such neurons promotes it [9]. Furthermore, optogenetic activation of medial prefrontal cortex neurons that project to the dorsal raphe caused a rapid and profound shift towards active coping behavior in the forced swim test [10]. This seems in line with several studies revealing that prefrontal cortex dysfunction can lead to either impulsive states with increased tendency to initiate action, a core feature of proactive coping styles [11]. Besides neurochemical differences, structural neuronal differences in the SDMN may also play a role in determining the functional output and hence individual coping style responsivity. Therefore, the current study aimed to assess the possible structural neuronal differences in these key SDMN nodes between proactive and reactive coping style rats.

Adult male Wild-type Groningen (WTG) rats, 4–5 months old (n = 22) were used as experimental subjects. This rat strain originates from rats caught in the wild and were outbred in the laboratory for over 60 generations. Food and water were given *ad libitum*. All animals were housed under regulated lighting conditions (lights on at 22:00 h and off at 10:00 h). All experimental procedures were performed between 11:00 h and 15:00 h. Experimental procedures were approved by the Groningen University Committee on Animal Experiments.

For the resident-intruder test, the rats that were used as residents were housed together with an oviduct-ligated female in large observation cages (80 cm x 55 cm x 50 cm) for a week. This facilitates territorial aggressive behavior in rats and also prevents social isolation (Fig. 1A). Offensive aggressive behavior of residential male rats was tested on 4 subsequent days during the dark phase of the light/dark cycle. One hour before testing, female companions were removed from the resident cage. Subsequently, an unfamiliar male intruder rat (4 months old) was introduced for a period of 10 min into the resident's home cage (Fig. 1B). During the first 3 days, attack latency times were scored and during the 4th day full behavioral recordings were made for a period of 10 min after the start of the first clinch attack or, if no attack was made, after placement. At the end of the 10 min interaction, intruder males were removed and residential rats were re-united with their female companion. Behavioral data were analyzed by scoring the behaviors as mentioned in Table 1 using appropriate software, The Observer XT - Noldus. Based upon percentage offensive aggression during day 4, rats were divided in three groups: low aggressive (reactive coping (N = 8): no aggressive behavior)), medium aggressive (N = 6: between 35 and 80 % of time spent on aggressive behavior), and high aggressive (proactive coping (N = 8): >80 % time spent on aggressive behavior).

One day after the 4th confrontation with an intruder male,

Table 1
Behaviors displayed by male residents in the resident-intruder paradigm. Time spent on these behaviors during the 4th interaction is scored in seconds and percentage of time spent on these behaviors during a 10-minute interaction after initiation of the first attack is expressed. Frequency of individual behaviors is also scored.

Behavior	Behavioral code	Description
Aggressive behavior	Attack latency	Time between the first clinch attack by the resident rat
	Lateral threat	Offensive use of lateral movement of the pelvis toward the intruder
	Keep down	Resident rat is at top of intruder rat while intruder rat shows submissive postures
	Clinch	Attacking the intruder rat
	Chase	Running towards the intruder rat
	Upright	Offensive upright postures
Exploratory behavior	Ambulation	Rat explores the surrounding environment and not the intruder rat
	Rearing	Standing on the rear legs and involved in non-social exploration
	Alone inactivity	Resting alone
Social behavior	Anogenital sniffing	Sniffing intruder rat
	Social grooming	Residential rat grooming intruder rat
	Social investigation	Following and playing with the intruder rat

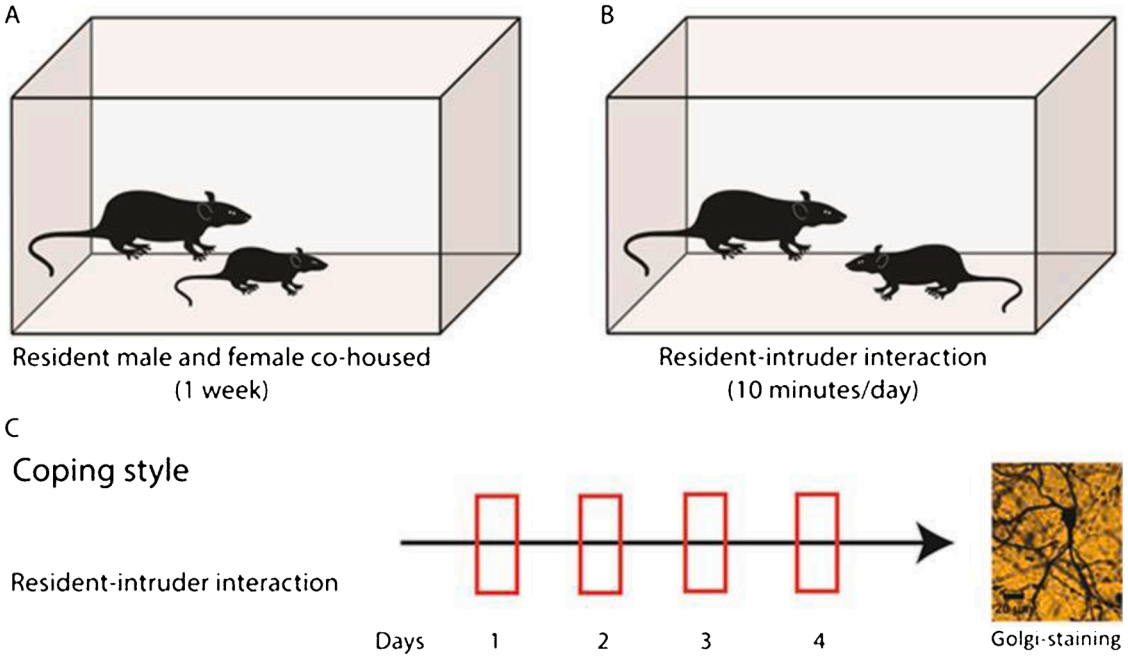

Fig. 1. Experimental design. Schematic depicting the resident-intruder paradigm (A). The resident rat is co-housed with a female partner for a week. B) Resident-intruder interaction for 10 min/day in the home cage of the resident rat. C) Coping style determination protocol, where red open blocks represent each day when resident-intruder interactions were allowed for 4 consecutive days followed by decapitation and Golgi staining.

experimental rats were decapitated and brains of the 8 least aggressive (reactive copers) and 8 most aggressive rats (proactive copers) were collected and fixed in Golgi Cox fixative to study the underlying neural morphology (Fig. 1C).

After 15 days of incubation at room temperature in the Golgi-cox fixative, 120 μm thick coronal sections were serially collected on gelatin-chrome alum-coated slides using a fixed tissue vibratome (Leica VT 1200S). The color was developed by 5 % sodium carbonate and subsequently the brain sections were dehydrated in grades of alcohol, cleared in xylene and cover-slipped with DPX (Nice Chemicals, India) mountant [12].

Once the slides were ready for analysis, the spine density analysis was done using Neurolucida software (100x, 1.3 numerical aperture; MicroBrightField Inc., Williston, Vermont) attached to an Olympus BX61 microscope. All protrusions along the primary dendrite irrespective of their morphological characteristics were analyzed as spines along an 80 μm stretch [12]. For basolateral amygdala (BLA) and hippocampal CA1 neurons were chosen between bregma −1.92 to –3.12 mm (Paxinos and Watson) and for medial amygdala analysis neurons were chosen between bregma -2.80 and -3.60 mm.

Data provided are expressed as group mean ± standard error of mean (s.e.m). In the morphological analysis 'n' values refer to the number of dendrites on which spines were quantified and capital 'N' refers to the number of animals used. All statistical analyses and plots were made using GraphPad Prism software (GraphPad software Inc., La Jolla, California, USA, version 7.04). Statistical analysis was performed with average values per animal. For the behavior data, one-way ANOVA was used, followed by post-hoc Tukey's test. The total number of dendritic spines were compared with Student unpaired *t* test. For comparison of spine number across 10 μm segments, two-way repeated measures ANOVA was used considering factors: coping styles and distance from the origin from the branch (10–80 μm), followed by post-hoc Sidak's multiple comparisons test. The significance level was set to $p < 0.05$.

Aggressive behavior mentioned in Table 1 was employed to classify rats for either proactive or reactive coping styles. Summation of time spent in each activity categorized them for that respective behavior. Based on the above mentioned criteria we noticed individual variability in offensiveness in WTG rats with three classes of aggression: low, medium and high [13].

Ordinary one-way ANOVA followed by post-hoc Tukey's test revealed that, out of 22 rats, 8 rats showed significantly lower aggressive (reactive copers) behavior [$F(2, 19) = 250.4$; $p < 0.0001$] compared to medium (**** $p < 0.0001$) and high aggressive (proactive copers) rats (**** $p < 0.0001$) (Fig. 2A). The animals showing low aggressive behavior spent significantly more time on exploratory [$F(2, 19) = 21.8$; $p < 0.0001$] and social behaviors [$F(2, 19) = 8.523$; $p = 0.0023$]. This was observed by calculating total percentage of exploratory (low vs high: **** $p < 0.0001$, medium vs high: *** $p < 0.001$) and social behavior (low vs high: ** $p < 0.01$, low vs medium: $p = 0.0530$) displayed by 8 highly aggressive rats which is significantly lower as compared to 6 medium and 8 low aggressive rats (Fig. 2B and C).

Proactive coping style show significantly reduced spine density in the posterodorsal nucleus of the medial amygdala (MeA). Spines were counted in the primary apical dendrite along a stretch of 80 μm length of the dendrite. Results show lower spine density ($t = 4.211$, $p = 0.0010$) in the proactive group (n = 30), compared to reactive (n = 23) animals (Fig. 3E). Upon detailed analysis of spine numbers in steps of 10 μm segments along the length of the dendrite, we found that there was a main effect of coping style [$F(1, 13) = 17.74$; $p = 0.0010$] in a two-way repeated measures ANOVA. Further, post-hoc analysis revealed that this decrease was robust and evident throughout but particularly in the distal dendritic segments (Fig. 3F).

Hippocampus and basolateral amygdala did not show any differences in spine densities in the proactive and reactive group. Spine density analysis was also carried out in pyramidal neurons of BLA and the stratum radiatum of hippocampal CA1 region. Spines were counted in the primary dendrite along the 80 μm length of the dendrite. Different coping styles did not affect the overall density of dendritic spines in the BLA ($t = 0.1578$, $p = 0.8771$; Fig. 3C) and CA1 region of hippocampus ($t = 1.074$, $p = 0.3022$; Fig. 3A). Unpaired *t*-test showed that there was no difference between the reactive (BLA: n = 48; CA1: n = 40) and proactive (BLA: n = 45; CA1: n = 37) group. Segmental analysis did not reveal any effect of coping styles [BLA: $F(1, 13) = 0.08508$; $p = 0.7751$; CA1: $F(1, 13) = 3.122$; $p = 0.1007$], although there was a main effect of distance along the dendrite in both BLA [$F(7, 91) = 3.141$; $p = 0.0051$] and CA1 region of hippocampus [$F(1, 13) = 5.259$; $p < 0.0001$]. There was no interaction of the main factors in either BLA or CA1 dendritic spines.

The behavioral results of this experiment confirm the well-known phenotypic distribution of individual levels of aggressiveness in WTG rats [13]. Clearly, some animals showed a reactive, non-aggressive phenotype while others exhibited proactive, high-aggressive behavior. Analysis of dendritic spine density revealed no change in both basolateral amygdala and CA1 hippocampus between proactive and reactive coping rats. These brain regions are known to be sensitive to modulation by stressful events and exhibit contrasting patterns of structural plasticity in response to social and non-social stressors [12]. If spine morphology is causally involved in behavior, the similarity in spine density in these two brain regions between the two coping styles

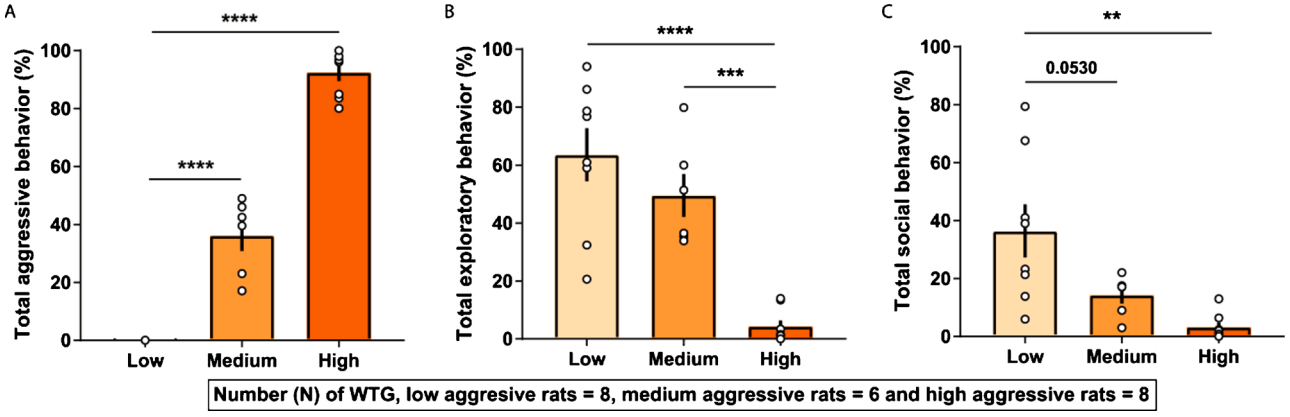

Fig. 2. WTG rats exhibit distinct behaviors during resident-intruder interactions. A) Aggressive behavior displayed by rats characterized by clinch attack, threat, chasing, offensive upright and keep down behavior. B) Exploratory behavior combined with ambulation, rearing and immobility by the rats. C) Non-aggressive social behaviors shown by rats consisted of anogenital sniffing, social grooming and investigation. Open circles represent individual data points. Asterisks indicate significant differences (** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, post-hoc Tukey's multiple comparisons test). Error bars expressed as mean ± s.e.m.

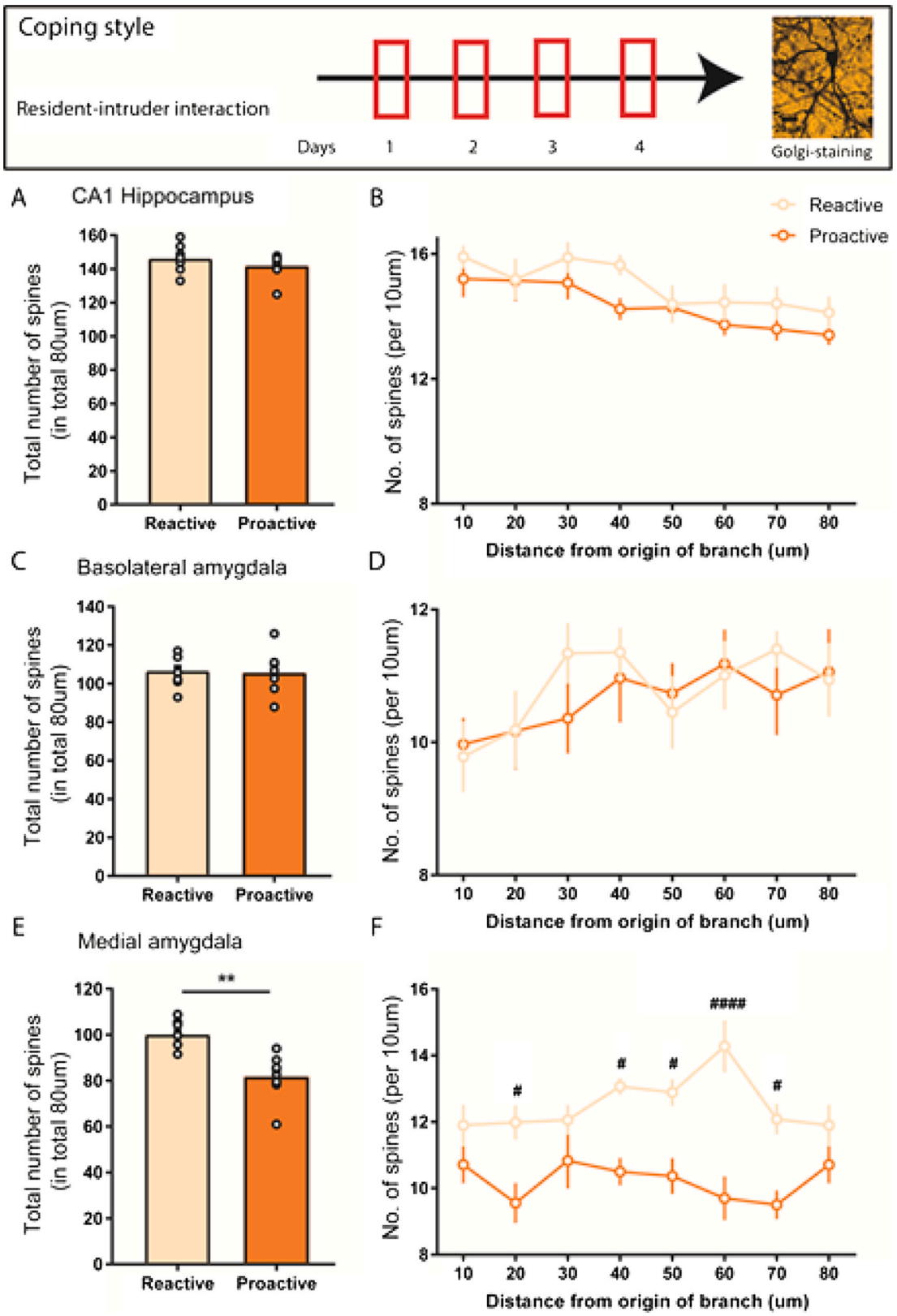

Fig. 3. Trait aggression decreases spine density in posterodorsal medial amygdala in proactive animals compared to reactive. (A, C, E) Mean values for spine-density (calculated as the average number of spines per 80 μm of primary branches) for proactive (N = 7) and reactive (N = 8) animals. Open circles represent individual data points. (B, D, F) Segmental analysis of mean numbers of spines in each successive 10 μm segment of the 80 μm primary dendrite as a function of the distance of that segment from the origin of the main shaft. Asterisks and hashtags indicate significant differences (** $p < 0.01$, Student's unpaired *t* test; # $p < 0.05$, #### $p < 0.0001$, post-hoc Sidak's multiple comparisons test). Error bars expressed as mean ± s.e.m.

suggests that there are no indications that baseline structural neuronal differences in the hippocampal CA1 and BLA underlie trait-like differences in stress vulnerability. There was, however, a strikingly lower spine density in the posterodorsal nucleus of the MeA observed in proactive coping rats. This nucleus is strongly involved in the regulation of social behaviors such as rivalry aggression [14] and sexual behavior [15, 16]. Correlation data between different behaviors from all the animals and spine density analysis in CA1, BLA and MePD regions displayed mainly significant correlations for all the behaviors with spines in the MePD region (supplementary Fig. 1). In addition, a positive correlation was also observed between social behavior and CA1 hippocampus spine density (supplementary Fig. 1).

The differences in spine density in this brain region might explain existing differences in these behaviors in proactive and reactive copers. Trait-like characteristics in WTG rats were determined by measuring offensive aggressive behaviors during the four agonistic interactions in the resident-intruder paradigm. These differences in offensive aggressive behavior are possibly caused by the structural differences in the MeA. The same holds for differences in sexual behavior in pro- and reactive coping rats with proactive males reaching more rapidly ejaculation than reactive males (unpublished data, J.D.A. Olivier, Neurobiology, GELIFES, University of Groningen). However, differences in spine morphology or density may also be the consequence of behavioral experience [17]. To what extent the actual experiences in aggressive as well as sexual behavior prior to and during the resident-intruder testing are contributing to the observed structural differences is not known. It is possible that animals with different coping styles perceive these experiences differently and that these perceived differences play a role in state-induced structural remodeling. Modulatory factors like oxytocin [15], sex-steroids [18] or AVP [19] may play an important role in these coping style related structural differences. It is known that environmental stimuli may lead to changes in dendritic spine density and morphology. For instance, chronic restraint stress induces a reduction in spine density in medium spiny stellate neurons of the MeA which is mediated by tissue plasminogen activator (tPA) [20]. tPA is mainly released into the extracellular space in the MeA during stress as a resultant of activation of corticotropin-releasing factor (CRF) receptor [21]. This might be due to a substantial projection from the MeA to the paraventricular nucleus, the apex of the HPA axis [22]. Hence, stimulation of MeA triggers activation of HPA axis [23]. Along with this, arginine-vasopressin (AVP) in the medial amygdala is also known to be involved in the modulatory role of this structure in stress-related behaviors suggesting the role of MeA in stress coping [19,24]. Further experiments to corroborate the current findings and to provide a causal relationship between coping style and dendritic spine density could include the study and local manipulation of the modulatory factors mentioned above but also of growth factors like BDNF, and intracellular ratio's between cofilin and p-cofilin involved in altering actin filaments necessary for structural plasticity including cAMP, PDE4 and PKA. Furthermore, studying regional differences between coping styles in glutamatergic (AMPA and NMDA) and steroid receptors (GR/MR) and manipulation of these are interesting to reflect on the causal relationship between molecular pathways involved in structural differences and coping styles.

The experience of social challenges is particularly relevant since coping styles are actually not only based upon differences in aggressive behavior but they represent distinctly different behavioral and physiological response patterns in reaction to a wide range of challenges. In a proactive coping style, animals are also impulsive in decision-making and score high in frustration tests [3]. In general, proactive copers try to actively control the environment. In doing this, they rely on routine-like behaviors that include relatively little flexibility. Reactive coping animals, on the other hand, have a tendency for behavioral inhibition in order to respond to the demands of the environment [25]. They will be more guided by specific environmental stimuli asking for much more behavioral flexibility. Differential degrees of flexibility may explain why aggressive males are more successful under stable conditions, whereas non-aggressive males do better in a variable or unpredictable environment. Apparently these differences in behavioral flexibility are not represented in baseline dendritic spine structure in the BLA and CA1 regions studied. This suggests that baseline dendritic structure in these brain regions do not contribute to coping style differences. However, depending on the nature of the environmental challenge, the neuronal structure in these brain regions might be affected differently matching the differential capacity to adapt between coping styles which may subsequently lead to individual differences in stress vulnerability. The difference found in the structure of the MeA corresponds with the observed behavioral differences in the two coping styles.

CRediT authorship contribution statement

Shobha Anilkumar: Formal analysis, Investigation, Writing - original draft, Visualization. **Deepika Patel:** Formal analysis, Investigation, Writing - original draft, Visualization. **Sietse F. de Boer:** Writing - review & editing, Conceptualization. **Sumantra Chattarji:** Writing - review & editing, Conceptualization, Supervision. **Bauke Buwalda:** Writing - review & editing, Conceptualization, Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bbr.2020.112940.

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