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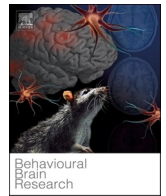
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Repeated victorious and defeat experiences induce similar apical dendritic spine remodeling in CA1 hippocampus of rats

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ABSTRACT

In this study, apical dendritic spine density of neurons in hippocampal, amygdalar and prefrontal cortical areas was compared in rats that were repeatedly winning or losing social conflicts. Territorial male wild-type Groningen (WTG) rats were allowed multiple daily attacks (>20 times) on intruder males in the resident-intruder paradigm. Frequent winning experiences are known to facilitate uncontrolled aggressive behavior reflected in aggressive attacks on anesthetized males which was also observed in the winners in this study. Both winners and losers were socially housed during the experiments; winners with females to stimulate territorial behavior, and losers with two other losing male rats. Twenty-four hours after the last social encounter, brains from experienced residential winners and repeatedly defeated intruder rats were collected and neuronal morphology in selected brain regions was studied via Golgi-Cox staining. Results indicate that spine density in the apical dendrites of the hippocampal CA1 reduced similarly in both winners and losers. In addition, winners showed increased spine densities at the proximal segments (20–30 μm) of the basolateral amygdala neurons and losers tended to show a decreased spine density at the more proximal segments of the infralimbic region of prefrontal cortex neurons. No effect of winning and losing was observed in the medial amygdala. The atrophic effect of repeated defeats in hippocampal and prefrontal regions was anticipated despite the fact that social housing of the repeatedly losing intruder males may have played a protective role. The reduction of hippocampal spine density in the winners seems surprising but supports previous findings in hierarchical dominant males in rat colonies. The dominants showed even greater shrinkage of the apical dendritic arbors of hippocampal CA3 pyramidal neurons compared to the stressed subordinates.

Conspecific conflicts are a ubiquitous aspect of group living in virtually all animals. These conflicts over obtaining and defending territory, resources and social position are resolved by engaging in aggressive behaviors that usually results in a winner and loser of the dispute. Dominant and subordinate profiles quickly emerge after the experience of victory and defeat, respectively, that have major repercussions for an animals' future behavioral and physiological responding. For example, winning a social confrontation is a positive experience that strengthens future aggression and dominance while losing a conflict is an adverse experience that decreases aggressiveness

and increases submissive behavior [1]. These so-called winner and loser effects have been well documented in a wide variety of animal species [1] and are associated with divergent autonomic physiological, neuroendocrine and neurobiological profiles. For example, compared to victorious animals, defeated subjects show longer-lasting increases in hypothalamus-pituitary-adrenocortical (HPA) axis and sympathetic-adrenal activity but considerably inhibited gonadal hormone activity [2,3]. Repeated defeats and/or chronic subjugation lead to reduced appetite, compromised endocrine and immune system activities, disruption of circadian physiological rhythms, and induces

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cardiovascular and metabolic abnormalities, social avoidance/anxiety and anhedonia [2,4]. Along with behavioral and physiological changes, studies have reported functional neuro-adaptations and structural alterations in the brain that are associated with repeated social defeat such as shrinkage of the hippocampal neurons with, on the other hand, amygdalar neurons enlargement [5]. In particular, these long-lasting effects of repeated or chronic social defeat and subjugation have been widely employed as an animal model of social stress in order to study the neurobiological mechanisms of stress-related pathologies [6,7].

Surprisingly, relatively few studies have focused on the neurobiological alterations in repeatedly winning animals and/or have directly compared the neurobiological alterations in winners versus losers of aggressive interactions. Hence, it is unclear whether and to what extent the neurobiological alterations in the individual initiating and winning aggressive confrontations differ from those of the attacked and defeated individual.

Every aggressive encounter elicits a massive activation of the hypothalamic- pituitary- adrenal (HPA) axis in the defeated animals, and high circulating levels of corticosterone [2] which is considered to be involved in structural remodeling of neurons in brain regions like the hippocampus, amygdala and medial prefrontal cortex [8]. As published earlier in a review paper [2], plasma corticosterone (CORT) rises in winners to similar levels as in losers [9]. In combination with activation of the HPA-axis this rewarding aspect of winning may also induce changes in connectivity and plasticity in the same brain regions mentioned above involved in the regulation of emotional and cognitive behavior. Alterations in these brain regions are also associated with aggressive behaviors in humans [10].

Hence, a major objective of our study was to investigate if structural changes occur in repeatedly winning rats and how these changes relate to changes observed in the opponents that constantly were the losers in these confrontations. Since agonistic interactions can be stressful for any individual, our particular interest were regions involved in the brain involved in regulating emotional and cognitive behavior such as the hippocampus, amygdala and infralimbic (IL) cortex of the mPFC as they play an important role in regulating the stress response [11].

Studies of the neural circuitry underlying behavioral consequences of winning or losing focus mainly on signaling pathways [12,13] whereas structural neuronal remodeling receives relatively little attention. Thus, the current study is designed to fill in the gap in knowledge in understanding the underlying neurological structural correlates of

repeated experience of winning and losing.

Adult male Wild-type Groningen (WTG) rats, 5–6 months old at the start of the experiments (440 ± 6 g), were used as experimental subjects. Food and water were given *ad libitum*. All animals were housed under a 12 – 12 -h light regimen (lights on at 22:00 h). All experimental procedures were performed in the active circadian phase of the rats between 11:00 h and 15:00 h and approved by the Groningen University Committee on Animal Experiments.

For the resident-intruder test, 24 residential males were housed in pairs with an oviduct-ligated companion female in observation cages (80cm × 55cm x 50 cm) for a week. This facilitates territorial aggressive behavior in rats and also prevents social isolation (Fig. 1A). One hour before testing, female rat partners were removed from the resident cage. Subsequently, an unfamiliar male intruder rat from the same WTG strain (5 months old at the start of the experiments) was introduced into the resident's home cage (Fig. 1B). After the first 4 days we proceeded with the 12 most aggressive residential males that were confronted daily with 12 randomly selected intruder males. Losing intruder males were shifted daily to another resident and in the rotation residents were confronted 2–3 times with the same intruder (see Table 1 in the supplementary data). Intruder rats were taken out of the residential cage after a clinch attack was launched by the resident and residential rats were reunited with their female companion. Since the clinch attack was launched on average after 134 ± 10 s, intruder rats were for 2–3 min in the cage of the winning residents. Intruder rats were housed together with two other intruder males. Although we realize that social housing buffers the negative impact of social stress [14], this was done to avoid differences in structural remodeling between winners and losers because of social isolation.

Table 1

Effects of winning and losing on total dendritic spine density on the first 80 μ m stretch of the apical dendrites of the hippocampal (CA1) brain region. Control (C), Winner (W) and Loser (L).

Brain regions	Groups	no. of dendrites (n)	Mean \pm s.e.m	Comparison between groups	p value
CA1	Control	32	86.63 ± 1.283	C vs W	0.0047
	Winner	29	78.15 ± 2.036	C vs L	0.0023
	Loser	33	77.34 ± 1.305	W vs L	0.9310

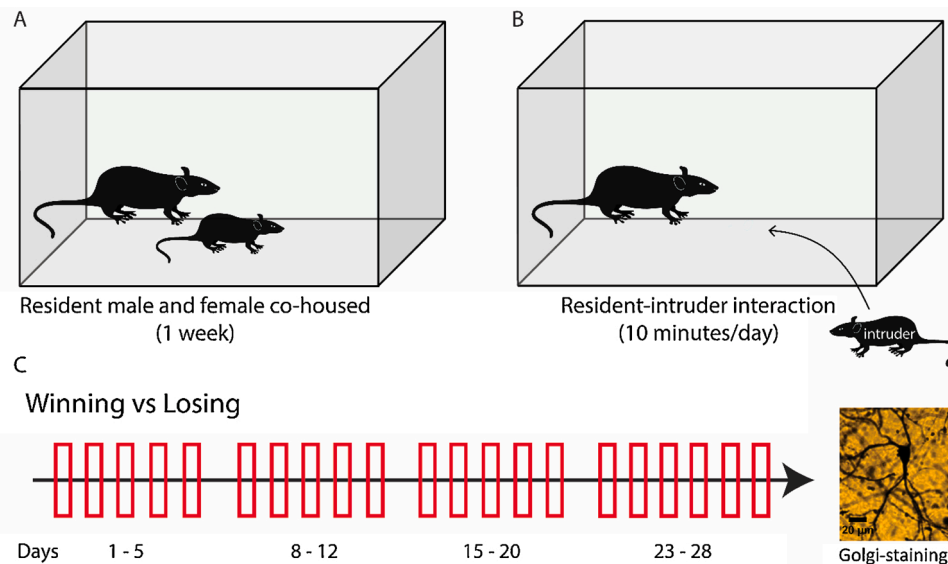


Fig. 1. Experimental design. A) Schematic depicting the resident-intruder paradigm. The resident rat is co-housed with a female partner for a week. B) Resident-intruder interaction for 10 min/day in the home cage of the resident rat. C) Experimental scheme followed consisting of more than 20 resident-intruder interactions over 5 weeks of duration.

In our study, 12 residential WTG male rats were confronted 22 times with 12 intruder males. Residential males were always the agonistic offenders in these confrontations. In a number of cases residents laterally threatened intruders without actually launching a clinch attack (intruder males were left in these cases for 600 s in the cage (see Table 1; supplementary data). In these situations, loser rats usually responded with a freezing response. Experimental winner and loser rats won or lost conflicts between 20–22 times. This facilitated aggressive behavior in a number of the residents. In order to select the most aggressive rats we also tested aggressive behavior in a novel cage and the amount of aggression directed against an anesthetized male WTG male rat (0.6 mL sodium pentobarbital 4%, intraperitoneal). Selected winners (n, animal = 6) all rapidly attacked intruders in their home cage (134 ± 10 s) and attacked opponents in a novel cage within 5 min. They also all attacked anesthetized rats multiple times in their home cage within 3 min (mean # bite attacks per resident 5.3 ± 0.8). A day after the last interaction, the selected winners were sacrificed via rapid decapitation together with 6 loser animals that underwent the most defeats and all showed strong freezing behavior during the confrontations and clear submissive postures. Also 6 control rats (housed 3/cage) were sacrificed. These rats were left undisturbed and were not subjected to any resident-intruder tests. Subsequently, brains were removed and immersed in Golgi-Cox fixative for 15 days to study the underlying neural morphology (Fig. 1C). Later, coronal sections (120 μ m) were serially collected on gelatin-chrome alum-coated slides using a 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 mountant (Nice Chemicals, India).

Once the sections were ready for analysis, the spine density analysis was done using Neurolucida software (100x, 1.3 numerical aperture) from MicroBrightField Inc., Williston, Vermont, attached to an Olympus BX61 microscope. The apical dendrites of pyramidal neurons from CA1 region of the hippocampus, infralimbic region (layer 2/3) of the medial prefrontal cortex (mPFC), basolateral region and posterodorsal region of the medial nucleus (MePD) of the amygdala located within bregma -2.40 to -3.96 mm, 3.7 to 2.7 mm, -1.92 to -2.64 mm and -2.4 to -3.4 mm respectively were selected for analysis. Both acute stress (unpublished data) and chronic stress studies [15] from our laboratory have shown that immobilization stress leads to decreased spinogenesis only in the infralimbic cortex. In these studies, the prelimbic cortex do not show stress induced effects. Hence, in this study infralimbic cortex was chosen for analysis. All protrusions along the primary dendrite, irrespective of their morphological characteristics, were analyzed as spines on the first 80 μ m of the apical dendrite using Neurolucida software.

The pyramidal neurons have a stereotypic morphology by the presence of apical and basal dendritic trees. While basal dendrites branch diffusely before terminating, the apical dendrites are known to extend their branches to over long distance from soma. Particularly in Golgi Cox studies these long extensions are beneficial in analyzing spines over 80 μ m length since in Golgi studies on structural dendritic remodeling due to stress the morphological alterations were majorly found on dendrites of the apical tree. For instance, the remarkable dendritic atrophy occurred in the apical dendrites of the CA3 region of the hippocampal pyramidal neurons after 21 days of chronic restraint stress [16]. Similarly, the prefrontal cortex showed a dendritic atrophy of the apical dendrites in response to stress [17–19]. Though the functional significance between apical and basal dendrites are not always completely understood, the apical dendrites play a role in synaptic integration where voltage-gated channels are abundant in the apical dendrites of most pyramidal neurons. These channels in apical dendrites are potentially important in the dendritic spikes that may lead to axonal action potentials and subsequently to altered stress-relating neuronal functioning [20].

Data provided are expressed as group mean \pm s.e.m. In the morphological analysis “n” values refer to the number of dendrites on

which spines were quantified and “n, animal” 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). The total number of dendritic spines was compared with one-way ANOVA, followed by Tukey’s test for *post-hoc* analysis. The comparison of spine number across 10 μ m segments, two-way repeated measures (RM) ANOVA was used with factors treatment (control, winner and loser) and distance from the origin from the branch (10–80 μ m), followed by *post-hoc* Tukey’s multiple comparisons test. The significance level was set to $p < 0.05$.

Compared to controls, frequent winning and losing rats show similar reductions in dendritic spine density in the hippocampal CA1 brain region. One-way ANOVA revealed significant decreases in spine density in the CA1 region [F (2, 15) = 10.6, $p = 0.0013$; Fig. 2A]. Further, *post-hoc* Tukey’s test confirmed significant reduction in spine density in both the winner ($p = 0.0047$; $n = 29$) as well as the loser ($p = 0.0023$; $n = 33$) group when compared to the control ($n = 32$). For segmental analysis in the CA1 region, Two-way RM ANOVA showed significant effects of both factors, treatment [F (2, 15) = 10.6, $p = 0.0013$] as well as distance of dendritic segments from the origin of the dendrite [F (7, 105) = 15.07, $p < 0.0001$], with the interaction between the two [F (14, 105) = 1.904, $p = 0.0339$]. Specifically, Tukey’s test followed by RM two-way ANOVA showed decrease in spines mainly at the distal segments (50 μ m–80 μ m) of the dendrites (Fig. 2B). However, in the BLA region, main effect of distance [F (7, 105) = 3.444, $p = 0.0023$] and interaction [F (14, 105) = 1.935, $p = 0.0305$] of the both factors was seen and not of the treatment factor [F (2, 15) = 2.169, $p = 0.1488$]. Unlike CA1 region, neurons in the BLA region showed increase in spinogenesis at the proximal segments of the dendrites, 20 μ m and 30 μ m (Fig. 2E), in winners ($n = 34$; control: $n = 34$) but no overall increase in spines was observed [F (215) = 2.272, $p = 0.1374$; Fig. 2D]. Whereas, frequent loser ($n = 34$) WTG rats showed no overall change in dendritic spine density or with segmental dendritic analysis (Fig. 2D–E). The detailed statistical analyses of the entire spine density data can be found in the Table 1 and supplementary table 2.

In the MePD region of the amygdala [F (215) = 0.2546, $p = 0.7785$; control: $n = 18$, winner: $n = 28$, loser: $n = 22$; Fig. 2G] and IL of the mPFC [F (215) = 2.325, $p = 0.1319$; control: $n = 27$, winner: $n = 23$, loser: $n = 24$; Fig. 2J], both the winner and the loser groups showed no change in the total spine density upon one-way ANOVA. Segmental analysis revealed only a significant effect of distance in both the regions [MePD: F (7, 105) = 5.442, $p < 0.0001$; IL: F (7, 105) = 2.683, $p = 0.0135$] but no effect of stress [MePD: F (2, 15) = 0.2546, $p = 0.7785$; IL: F (2, 15) = 2.325, $p = 0.1319$] or interaction [MePD: F (14, 105) = 0.7150, $p = 0.7150$; IL: F (14, 105) = 1.312, $p = 0.2126$] between the two factors (Fig. 2H and K).

The current research aimed at exploring neurological structural correlates underlying repeated experience of winning and losing. Surprisingly, results from our study show that winning animals have reduced spine density in the CA1 pyramidal neurons, similar to losing rats. However, the basolateral amygdala showed an increased spinogenesis in the proximal end of the dendrites in the winning rats. The structural phenotypes in the winning rats are similar to studies related to stress exposure where amygdala elicit spinogenesis and hippocampus induce reduction in spines which in turn regulates emotional and cognitive behavior [21]. This similarity actually might suggest that winners too may experience the physical conflicts with the intruders as stressful which is surprising considering the eagerness with which the residents attack the intruder males.

Plasma corticosterone (CORT) rises in winners to similar levels as during highly aversive challenges [2]. From other studies, it is known that an increase in circulating CORT level plays an important role in structural remodeling in various brain regions [11,22]. Although the majority of findings focus on chronic elevations in CORT, acute increase in CORT can also cause lasting opposite effects on dendritic arborization with different temporal dynamics in the prefrontal cortex and BLA [23].

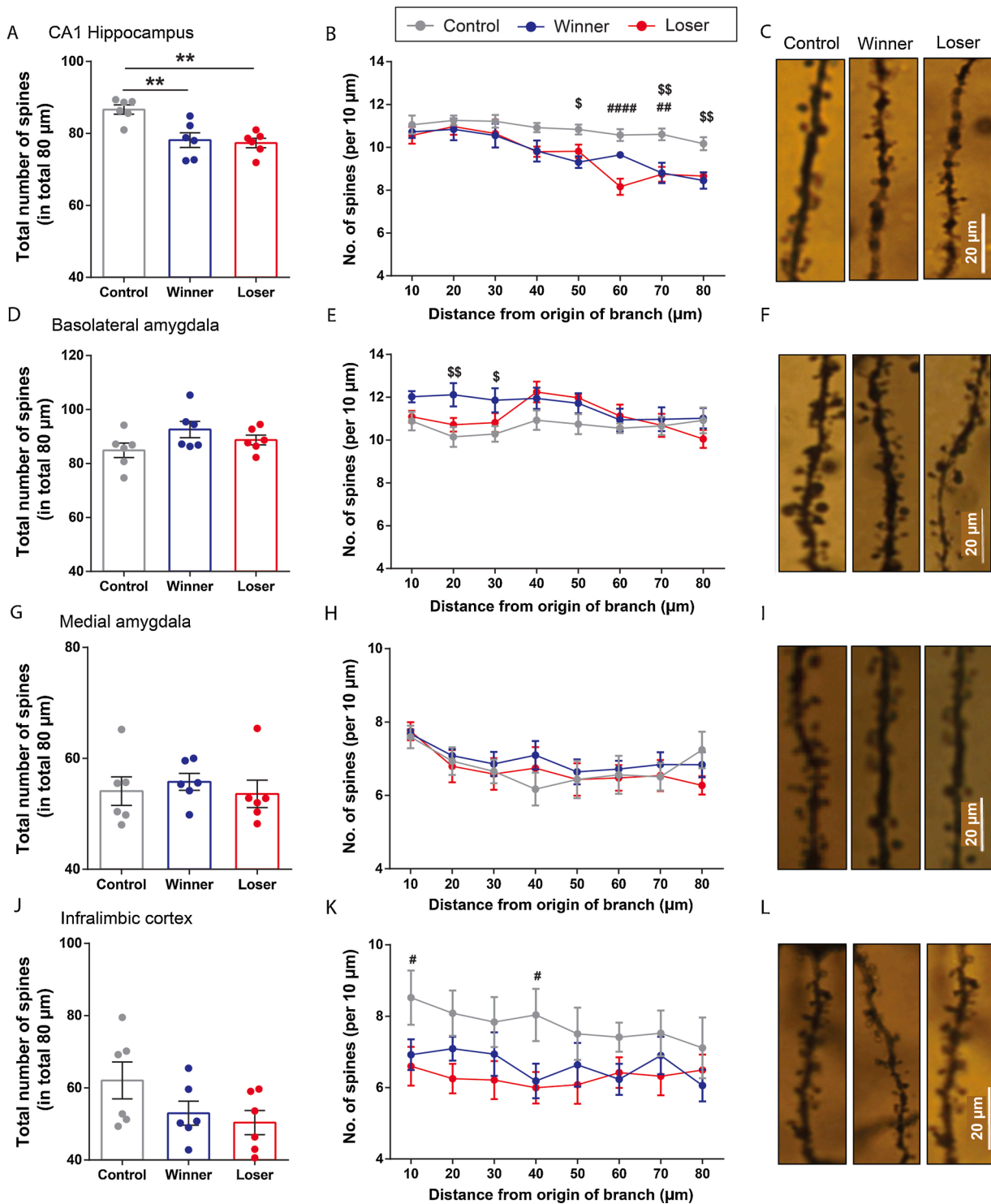


Fig. 2. Mean values for spine-density (calculated as the average number of spines per 80 μm of primary branches) for control (n, animal = 6), winners (n, animal = 6) and losers (n, animal = 6) in hippocampal CA1 (A), basolateral amygdala (D), medial posterodorsal amygdala (G) and infralimbic cortex (J). Closed grey colored circles represent individual data points of the control group while blue and red closed circles represent data points of winner and loser group of rats respectively. In 2B, E, H, and K, segmental analysis of mean numbers of spines is shown for these respective brain regions for 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. (C, F, I, L) Photomicrographs of representative segments of primary dendritic branches from neurons in controls (left), winners (middle) and losers (right) (scale bar, 20 μm). Asterisks indicate significant differences in column plots (***p* < 0.01 level, One-way ANOVA). Hashtags and dollars indicate significant differences between control vs loser and control vs winner groups respectively in line plots (\$*p* < 0.05, \$\$*p* < 0.01, #*p* < 0.05, ##*p* < 0.01, ####*p* < 0.0001 level, *post-hoc* Tukey's multiple comparisons test). Error bars expressed as mean ± s.e.m.

Although there are similarities in structural dendritic remodeling between winners and losers, the behavioral consequences of the experience of repeated winning or losing conflicts are quite different. The repeatedly defeated intruder males showed strong behavioral immobility to placement in the resident's cage indicating a fear response, whereas the repeatedly winning rats showed a very rapid attack response and no behavioral indicators of stress or fear. Despite the similarity in acute CORT response of winners and losers during the conflict, Koolhaas et al. [2] clearly showed that the recovery of the stress response is much faster in winners than in losers. Perceived control over the stressor is considered pivotal in this faster recovery. Considering the different behavioral consequences of these repeated social challenges in winners and losers, it is important to realize that similar structural remodeling can occur in the CA1 of both winners and losers and that this apparently can go hand in hand with different functional consequences. This is particularly relevant since hippocampal atrophy of dendritic structures has been related in general with failure to adapt to stressors.

The experience of repeated winning may have induced behavioral alterations in the selected winners. Aggressiveness increased in these rats and they all attacked opponents in a novel cage within 5 min and rapidly attacked an anesthetized male rat in their home cage. It is possible that the remodeling that occurs in the winners can also be related to this change in aggressive behavior. A striking similarity was reported in dominant males living in a mixed-sex social colony in a so-called Visible Burrow System. These dominant males showed a very robust atrophy of apical dendrites in the hippocampal CA3 that was even stronger than that observed in subordinate males [24]. This was an unexpected and surprising result since the subordinate males, particularly in a social colony, show behavioral and physiological indicators of exposure to chronic social stress. Many of the male dominants also show high amounts of offensive aggressiveness [25]. Previous studies have indicated an important role of mPFC in the regulation of aggression [26]. Unexpectedly, we did not see a significant decrease in the dendritic spines in the repeated winner group. This could be attributed to the relatively small number of rats in the group and spread in the data.

Despite the frequent activation of HPA axis in the losing rats, they did not display the anticipated amygdalar structural phenotype, i.e. increase in spinogenesis. In order to make a proper comparison between winners and losers, we housed the defeated rats socially after each interaction with the winners. Otherwise the experience of social isolation in only one part of the experimental rats might have played a large role in observed differences in dendritic remodeling. This social housing, however, likely had a buffering effect of the social stress exposure. Studies show that social interaction can moderate or buffer the effects of stressors [14,27]. Specifically, social buffering can suppress fear-associated activation of the amygdala in male rats [28]. On the other hand, behavioral observation showed a very strong freezing response in the intruder rats, immediately after placement in the residential home cage, indicative of context-dependent fear response.

Our study provides puzzling similarities in the dendritic structural alterations in winners and losers of a conflict. Along with the amygdala, the nucleus accumbens (NAc) is also involved in the regulation of emotion and reward pathways such as winning [29]. Winning a social fight for the winners is rewarding but also enhances their aggression [30]. The NAc has been implicated in controlling aggression-related reward via meso-limbic-dopaminergic circuits [31]. In addition, aggression self-administration and seeking in mice induces higher Fos expression in the NAc shell than in the core region [32]. Apart from aggression, NAc has also been involved in stress related behavioral dysfunction. For instance, anhedonia and other depression related symptoms are correlated with reduced NAc volume and responses to rewards in depressed patients. However, in animal studies, chronic stress induces increased spine density in the medium spiny neurons located in the shell of NAc region [33]. Hence, further mechanistic insights might be gained by studying the nucleus accumbens, specifically in the shell region, in winners and losers of social conflicts.

Author statement

The authors state that the animal experiments comply with the ARRIVE guidelines and are carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments. The sex of animals is indicated in the manuscript.

CRediT authorship contribution statement

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

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.2021.113243>.

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