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# Early-life stress diminishes the increase in neurogenesis after exercise in adult female mice

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## Abstract

Exposure to early-life stress (ES) has long-lasting consequences for later cognition and hippocampal plasticity, including adult hippocampal neurogenesis (AHN), i.e., the generation of new neurons from stem/progenitor cells in the adult hippocampal dentate gyrus. We had previously demonstrated a sex-specific vulnerability to ES exposure; female mice exposed to ES from P2-P9 exhibited only very mild cognitive changes and no reductions in AHN as adult, whereas ES-exposed male mice showed impaired cognition closely associated with reductions in AHN. Given the apparent resilience of AHN to ES in females, we here questioned whether ES has also altered the capacity to respond to positive stimuli for neurogenesis. We therefore investigated whether exercise, known for its strong pro-neurogenic effects, can still stimulate AHN in adult female mice that had been earlier exposed to ES. We confirm a strong pro-neurogenic effect of exercise in the dorsal hippocampus of 8-month-old control female mice, but this positive neurogenic response is less apparent in female ES mice. These data provide novel insights in the lasting consequences of ES on hippocampal plasticity in females and also indicate that ES might lastingly reduce the responsiveness of the hippocampal stem cell pool, to exercise, in female mice.

**KEYWORDS**
dentate gyrus, doublecortin, Ki67, running, sex-specific

## 1 | INTRODUCTION

Exposure to early-life stress (ES) lastingly affects brain structure and function. ES has e.g., been associated with later hippocampal volume reductions and cognitive impairments (Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014; Nemeroff, 2016; Teicher, Anderson, & Polcari, 2012). Interestingly, vulnerability to ES appears to be sex-specific and human and rodent female offspring seem often resilient to ES (Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010; Loi et al., 2017; Oomen et al., 2009).

One form of hippocampal plasticity consistently affected by ES in male rodents, is adult hippocampal neurogenesis (AHN) (Korosi et al., 2011; Lajud & Torner, 2015; Loi, Koricka, Lucassen, & Joels, 2014). Neuronal progenitors in the dentate gyrus (DG) undergo proliferation, migrate into the granular cell layer and eventually differentiate into functional neurons. These adult-generated neurons have been implicated in various hippocampus-dependent cognitive functions (Clark et al., 2012; Oomen, Bekinschtein, Kent, Saksida, & Bussey, 2014) and their level is strongly regulated by various factors (Lucassen et al., 2015; Schoenfeld & Gould, 2012), including stress (Schoenfeld & Gould, 2012), circulating sex hormones (Pawluski et al., 2009), and physical exercise (Duzel, van Praag, & Sendtner, 2016).

Previously we have shown that, whereas male mice exposed to chronic ES exhibited a reduced survival of adult-born neurons, associated with learning and memory impairments, female mice, exposed to the same ES, did not show such changes in AHN and exhibited less prominent cognitive deficits (Naninck et al., 2015). In male rodents, exercise has been able to rescue various measures of neuroplasticity that were altered by different types of adverse early-life events (Maniam & Morris, 2010, Naylor et al., 2008, Lajud & Torner, 2015). Despite the apparent resilience of female mice to ES, it is unknown whether the neurogenic capacity to respond to a positive stimulus is also affected in this sex. We hypothesize that in female mice, ES occurring during a period of ongoing hippocampal development, may lastingly program the stem cells or the neurogenic niche. Because exercise has strong pro-neurogenic effects, we here studied whether prolonged exercise can still stimulate AHN in female ES-exposed mice during late adulthood.

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## 2 | MATERIALS AND METHODS

All animal procedures were performed as previously described in (Naninck et al., 2015). In short, a total of 9 litters with six C57Bl/6J mouse pups each, including both males and females were bred in house. At postnatal day (P) 2, litters were randomly assigned to the control (CTL) or ES condition, consisting of exposure to the limited nesting/bedding-material model from P2–9. At P21, animals were weaned and housed in groups of the same sex with 2–3 animals/cage. At 8 months of age, female mice were moved to a larger cage (type III, Technilab-BMI, Someren, the Netherlands) and housed with 2–3 animals/cage to avoid isolation stress (Leasure & Decker, 2009; Stranahan, Khalil, & Gould, 2006). For six weeks (P237-P280) the cages were equipped with either a functional or a locked running wheel

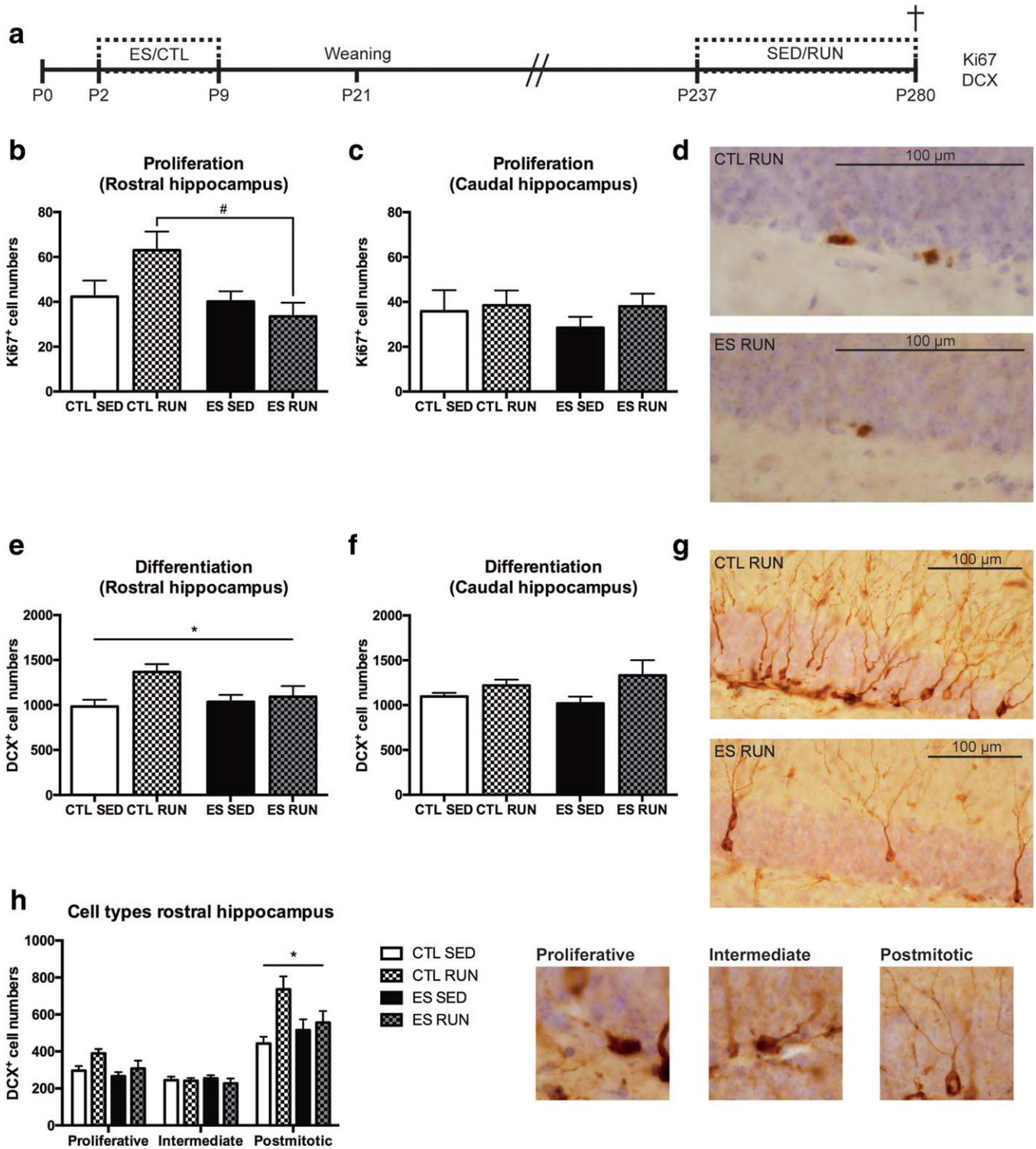


FIGURE 1.

(160 mm diameter, Ferplast, Italy) to control for cage enrichment (see Figure 1a) (Dostes et al., 2016). For the experiments described here, a total of 23 females was used (CTL-RUN $N = 6$ (from 3 litters), ES-RUN $N = 6$ (from 2 litters), CTL-SED $N = 4$ (from 2 litters), ES-SED $N = 7$ (from 4 litters)). The relatively low power of some of the experimental groups calls for caution when interpreting the data from this study. Engagement in exercise was monitored and confirmed daily by the researcher (30 minute observations/day for 6 weeks). No differences were observed in the engagement in exercise between control and ES-exposed animals. At the end of the running period (P280) animals were sacrificed. Estrous cycle stage at P280 was determined by vaginal smear cytology (Caligioni, 2009). All experimental procedures were conducted under Dutch national law and EU directives and approved by the animal welfare committee of the University of Amsterdam.

Immunocytochemistry on perfusion-fixed brain sections was performed to identify proliferating ($Ki67^+$) cells and newborn neurons (Doublecortin, $DCX^+$ cells) in the hippocampus according to previously described methods (Naninck et al., 2015). Antibodies used were: polyclonal rabbit-anti-Ki67 (Novocastra NCL-L-Ki67_MM1, 1:20.000), goat anti-rabbit biotinylated secondary antibody (Vector Laboratories, 1:500), polyclonal goat-anti-DCX (SantaCruz Biotechnology sc-8066; 1:800) and donkey-anti-goat biotinylated secondary antibody (Jackson Laboratories, 1:500). All $Ki67^+$and $DCX^+$ immune-reactive cell counts were performed manually by means of a modified stereological procedure, using a 20x objective (200x magnification), as described in detail in (Naninck et al., 2015). Immuno-reactive cells were counted in the subgranular zone of the dentate gyrus and cell numbers are expressed unilaterally. For each hippocampus, eight coronal, 40 μm thick sections were stereologically sampled along the rostro-caudal axis (corresponding with Bregma: −1.34, −1.70, −2.06, −2.46, −2.92, −3.16, −3.52, −3.80). A distinction was made between the rostral DG (i.e., the first four sections, (Vivar, Peterson, & van Praag, 2016)) versus caudal DG (the last four sections, (Vivar et al., 2016)), and the supra- versus infrapyramidal blade. Morphological subtypes of $DCX^+$ cells (i.e., proliferative, intermediate, or post mitotic stage) were analyzed as described before (Oomen et al., 2010).

Data were analyzed using SPSS 24.0 (IBM software) and Graphpad Prism 5 (Graphpad software). To compare body weight gain (BWG) between CTL and ES animals, independent t-tests were used. To compare all four groups, we used mixed models with fixed factors: condition (CTL vs. ES) and exercise (RUN vs SED). The number of newborn cells in the left and the right hippocampus were analyzed separately for each animal and nested under the factor "animal" (Aarts, Verhage, Veenvliet, Dolan, & van der Sluis, 2014). Random factors "animal," "litter" and/or "estrous cycle stage" were included only when a factor significantly influenced the outcome variable. For the final Ki67 analysis, none of the random factors were included, while for DCX-data, the effect of the factor "animal" was significant (likelihood ratio = 9.935 $p = .001$) and therefore included in the model. Post-hoc analyses were performed using LSD multiple comparison tests when appropriate.

## 3 | RESULTS AND DISCUSSION

We confirm that ES-exposure induced physiological signs of chronic ES in the pups, including a reduced body weight gain from P2-P9 (CTL: $3.49 \pm 0.11$, ES: $2.76 \pm 0.16$, independent $t$-test $t(21)=3.58$, $p = .002$*) (Naninck et al., 2015). Bodyweight was no longer different from weaning (P21) onwards (bodyweight at P21: $9.69 \pm 0.19$ grams in CTL vs. $9.61 \pm 0.51$ grams in ES, independent $t$-test $t(21)=0.153$, $p = .88$).

We questioned whether ES affected neurogenic capacity in response to physical exercise and compared AHN in various anatomical and functional subregions of the dentate gyrus (i.e., rostral and caudal) between all four experimental groups. The number of proliferating ($Ki67^+$) cells was reduced by ES in the *rostral* hippocampus ($F_{condition}(1,40) = 5.103$ $p = .03$*; $F_{running}(1,40) = 0.999$ $p = .32$; $F_{interaction}$ $(1,40) = 3.789$ $p = .058$, trend, Figure 1b). Because of the strong trend in the interaction, we performed exploratory *posthoc* testing to further study the relationships between condition and running. This revealed that there was no significant difference between CTL-SED and ES-SED (LSD, $p = .28$) under basal conditions, while after running, the number of $Ki67^+$ cells was higher in the CTL-RUN females compared to ES-RUN (LSD, $p = .04$*) suggesting that ES might reduce the

**FIGURE 1** Early-life stress diminishes the increase in neurogenesis after exercise in adult female mice. (a) Experimental design. (b) The number of proliferating (Ki67+) cells in the rostral hippocampus was reduced by ES (two-way ANOVA, main effect of condition $F1,40 = 5.103$ $p = .03$, no effect of running $F1,40 = 0.999$ $p = .32$, trend towards interaction effect $F1,40 = 3.789$ $p = .058$). The effect of condition was mainly attributable to the difference between the running wheel exposed CTL and ES females, as exploratory post hoc testing revealed no differences in proliferating (Ki67+) cells between CTL-SED and ES-SED animals (post hoc comparison, LSD, $p = .28$), but showed a significant lower number of proliferating (Ki67+) cells in ES-RUN females compared to CTL-RUN females (post hoc comparison, LSD, $p = .04$). (c) In the caudal hippocampus, no differences in the number of proliferating (Ki67+) cells were observed (two-way ANOVA no effect of condition: $F1,40 = 0.358$ $p = .55$, no effect of running: $F1,40 = 0.865$ $p = .36$, no interaction effect: $F1,40 = 0.273$ $p = .60$) (d) Representative images of a nuclear Ki67 immunostaining, indicating proliferating cells in a CTL-RUN animal (upper panel), versus a ES-RUN animal (lower panel). (e) The number of differentiating, immature neurons (DCX+ cells) in the rostral hippocampus is increased by running (main effect of running $F1,23 = 4.236$ $p = .05$, no effect of condition $F1,23 = 0.082$ $p = .78$, no interaction effect $F1,23 = 1.775$ $p = .20$). (f) In the caudal hippocampus, no differences in the number of DCX+ cells were observed (two-way ANOVA, no effect of condition: $F1,23 = 0.125$ $p = .73$, no effect of running: $F1,23 = 0.315$ $p = .58$, no interaction effect: $F1,23 = 0.414$ $p = .53$). (g) Representative image of a cytoplasmic DCX immunostaining, indicating newborn immature neurons in a CTL-RUN animal (upper panel), versus a ES-RUN animal (lower panel). (h) Voluntary wheel running particularly increases the number of postmitotic DCX+ cells in the rostral hippocampus (two-way ANOVA, main effect of running $F1,23 = 5.758$ $p = 0.03$, no effect of condition $F1.23 = 0.370$ $p = .55$, no interaction effect $F1.23 = 2.447$ $p = .13$). * = Main effect of running, # = significant post hoc comparison [Color figure can be viewed at wileyonlinelibrary.com]

neurogenic response to physical exercise. In the *caudal* hippocampus, there were no significant differences among the groups ($F_{condition}$ (1,40) = 0.358 $p$ = .55; $F_{running}$ (1,40) = 0.865 $p$ = .36; $F_{interaction}$(1,40) = 0.273 $p$ = .60, Figure 1c).

Running increased the number of young ($DCX^+$) neurons in the *rostral*, but not caudal hippocampus. In the rostral hippocampus, $DCX^+$ cell numbers were significantly increased after exercise ($F_{running}$(1,23) = 4.236 $p$ = .05*, Figure 1e), without a main effect of condition ($F_{condition}$(1,23) = 0.082 $p$ = .78, $F_{interaction}$(1,23) = 1.775 $p$ = .20, Figure 1e). Even though no significant interaction was observed in this study, it is interesting to note that DCX expression is modulated by ES and running in a similar fashion as Ki67+: Rostral-hippocampal $DCX^+$ cells are 39.0% higher in CTL-RUN females compared to CTL-SED females, while there is only a minor (5.4%) increase between ES-SED and ES-RUN females. In the caudal hippocampus, no differences were observed ($F_{condition}$(1,23) = 0.125 $p$ = .73, $F_{running}$ (1,23) = 0.315 $p$ = .58, $F_{interaction}$(1,23) = 0.414 $p$ = .53, Figure 1f). For neither Ki67 nor DCX were differences observed between the supra- and infra-pyramidal blade.

Interestingly, detailed analyses of the three different morphological types of $DCX^+$ cells (i.e., proliferative, intermediate and post-mitotic) (Figure 1h) revealed that exercise particularly enhanced the number of postmitotic $DCX^+$ cells in the rostral hippocampus (mixed model analysis for postmitotic cells $F_{running}$(1,23) = 5.758 $p$ = .03*, $F_{condition}$(1,23) = 0.370 $p$ = .55, $F_{interaction}$(1,23) = 2.447 $p$ = .131). Exercise increased the number of postmitotic neurons by 66.2% in CTL-RUN vs CTL-SED females and only by 7.9% in ES-RUN vs ES-SED females (Figure 1h). Thus, suggesting that exercise selectively enhanced $DCX^+$ cell numbers in control mice, but that previous exposure to ES diminished this pro-neurogenic effect.

To summarize our findings, prolonged voluntary exercise in eight-month old female mice (i) increases AHN selectively in the rostral hippocampus, and (ii) previous ES-exposure seems to reduce this exercise-induced neurogenic response. Our data further indicate that exercise in late adulthood has a survival promoting effect, specifically for the post-mitotic $DCX^+$ cells, an effect that is less pronounced for proliferation. The reason for the modest effect of running on the number of proliferating cells might be explained by the fact that control mice were exposed to a locked running wheel, a form of cage enrichment which alone can already increase proliferation (Dostes et al., 2016). In addition, our paradigm of 6 weeks of running might have contributed as well, as effects of exercise on cell proliferation typically peak at 3–10 days after running onset and return to baseline after 32 days of running (Kronenberg et al., 2006; Naylor, Persson, Eriksson, Jonsdottir, & Thorlin, 2005). In contrast, in line with our observations, the number of $DCX^+$ cells is stably increased when longer exercise periods are involved (Kronenberg et al., 2006). Finally, we housed our animals together to prevent isolation stress, which could also have interfered with the stimulatory effect of running on AHN (Leasure & Decker, 2009; Stranahan et al., 2006).

Our findings also highlight regional differences in the neurogenic response to voluntary exercise with a pronounced increase found in $DCX^+$ numbers in the rostral/dorsal but not caudal/ventral hippocampus. This is consistent with previous studies showing similar rostral-specific changes in AHN upon running. Three weeks of voluntary exercise e.g., increased DCX numbers in young (8-week old) C57Bl/6 female mice to a greater extent in the rostral then in the caudal hippocampus (Bolz, Heigele, & Bischofberger, 2015), while retroviral- and BrdU-based approaches in male mice also revealed selective increases after exercise in the dorsal hippocampus (Vivar et al., 2016). These AHN effects of exercise mainly in the dorsal hippocampus suggest that exercise may preferentially benefit spatial aspects of cognition (Wu & Hen, 2014). The mechanisms underlying these topographical differences remain unclear, but differences in input, mossy cell activity and GABAergic or glutamatergic cells density likely contribute.

Up to date, little was known as to how ES exposure affects the later neurogenic response to a positive stimulus in female mice. As mentioned above, our study has a relatively low power, which calls for caution in its interpretation. Despite this limitation, our data are the first to suggest that the running-induced increase in newborn cells in the rostral hippocampus, as occurs in control animals, is less pronounced in ES animals. Intriguingly, while AHN in female mice appeared to be resilient to the negative effects of ES (Naninck et al., 2015, Loi et al., 2017), this indicates that ES-exposed females might also be less responsive to a potent positive stimulus for AHN. This concept of ES-induced unresponsiveness at the level of this structural plasticity has been suggested before (Korosi et al., 2011) and is in line with previous studies showing that learning in prenatally stressed rats could not upregulate AHN (Lemaire, Koehl, Le Moal, & Abrous, 2000). The reasons why later exercise fails to stimulate AHN in ES-exposed females remain elusive, but as the dentate gyrus still undergoes active development from P2-P9 (Navarro-Quiroga, Hernandez-Valdes, Lin, & Naegele, 2006), a substantial proportion of the developmentally born granule cells have likely been migratory and/or dividing during the period of ES, and may thus have been particularly sensitive to programming effects induced by the elevated stress hormone levels, that could have altered neurogenic properties, e.g., through epigenetic modifications (Singh-Taylor et al., 2017).

Various (growth) factors have been implicated in the pro-neurogenic effects of exercise, including catepsin B (Moon et al., 2016), BDNF (Marlatt, Potter, Lucassen, & van Praag, 2012), cytokines and various neurotransmitters, a.o. (Bolijn & Lucassen, 2015). Hence, to explain the current results, it will be interesting to study in the future whether ES differentially affects the induction of these factors by exercise. Another candidate is an altered programming of the hypothalamic-pituitary-adrenal-axis by ES. Running reduces stress (Kannangara et al., 2011) and ES-exposed male rats subjected to exercise display e.g., a lower corticosterone response (Maniam & Morris, 2010), but whether such effects also apply to female mice awaits future study.

## 4 | CONCLUSION

In conclusion, while seemingly resilient to the negative effects of ES, AHN in adult female ES mice is less responsive to the positive stimulus of exercise at a later age, suggesting that ES could induce lasting effects on the responsiveness and properties of the hippocampal stem

cell pool in females. These data underscore the importance of studies that assess the sex-dependent vulnerability to ES, and highlight that further research is needed to better understand the mechanisms that underlie the programming of stem cell properties, and of hippocampal plasticity in general, by ES.

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