Chronic Stress Causes Frontostriatal Reorganization and Affects Decision-Making

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Chronic Stress Causes Frontostriatal Reorganization and Affects Decision-Making

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The ability to shift between different behavioral strategies is necessary for appropriate decision-making. Here, we show that chronic stress biases decision-making strategies, affecting the ability of stressed animals to perform actions on the basis of their consequences. Using two different operant tasks, we revealed that, in making choices, rats subjected to chronic stress became insensitive to changes in outcome value and resistant to changes in action-outcome contingency. Furthermore, chronic stress caused opposing structural changes in the associative and sensorimotor corticostriatal circuits underlying these different behavioral strategies, with atrophy of medial prefrontal cortex and the associative striatum and hypertrophy of the sensorimotor striatum. These data suggest that the relative advantage of circuits coursing through sensorimotor striatum observed after chronic stress leads to a bias in behavioral strategies toward habit.

In everyday life, we constantly have to select the appropriate actions to obtain specific outcomes. These actions can be selected on the basis of their consequences (*1*, *2*), e.g., when we press the elevator button to get to the particular floor of our new apartment. This goal-directed behavior is crucial to face the ever-changing environment, but demands an effortful control and monitoring of the response. One way to balance the need for flexibility and efficiency is through automatization of recurring decision processes as a rule or a habit (*3*). Habitual responses no longer need the evaluation of their consequences and can be elicited by particular situations or stimuli (*1*, *2*), e.g., after living for some time in that apartment, we automatically press the button of our home floor when we enter the elevator. The ability to shift between these two types of strategies is necessary for appropriate decision-making (*2*), and in some situations, it may be crucial to be able to inhibit a habit and use a goal-directed strategy, e.g., if we are visiting a new building, we should not press the button for our home floor.

Chronic stress, mainly through the release of corticosteroids, affects executive behavior through sequential structural modulation of brain networks (*4*, *5*). Stress-induced deficits in spatial reference and working memory (*6*) and behavioral flexibility (*7*) are associated with synaptic and/or dendritic reorganization in both the hippocampus (*8*) and the medial prefrontal cortex (mPFC) (*9*). However, the effects of chronic stress on action-selection strategies have not been investigated. Here, we examined whether previous exposure to chronic stress would affect the ability of animals to select the appropriate actions, based on the consequences of their choice. Because associative corticostriatal circuits involving the prelimbic (PL) cortex (*10*) and the dorsomedial striatum (DMS) (*11*) have been implicated in the acquisition and execution of goal-directed actions, whereas sensorimotor circuits, namely, the dorsolateral striatum (DLS) (*12*), are necessary for habit formation, we examined the effects of chronic stress on these brain areas.

In an attempt to mimic the variability of stressors encountered in daily life, adult rats assigned to the stress group were exposed to a well-established stress paradigm (*13*) that combines different stressors in an unpredictable manner to

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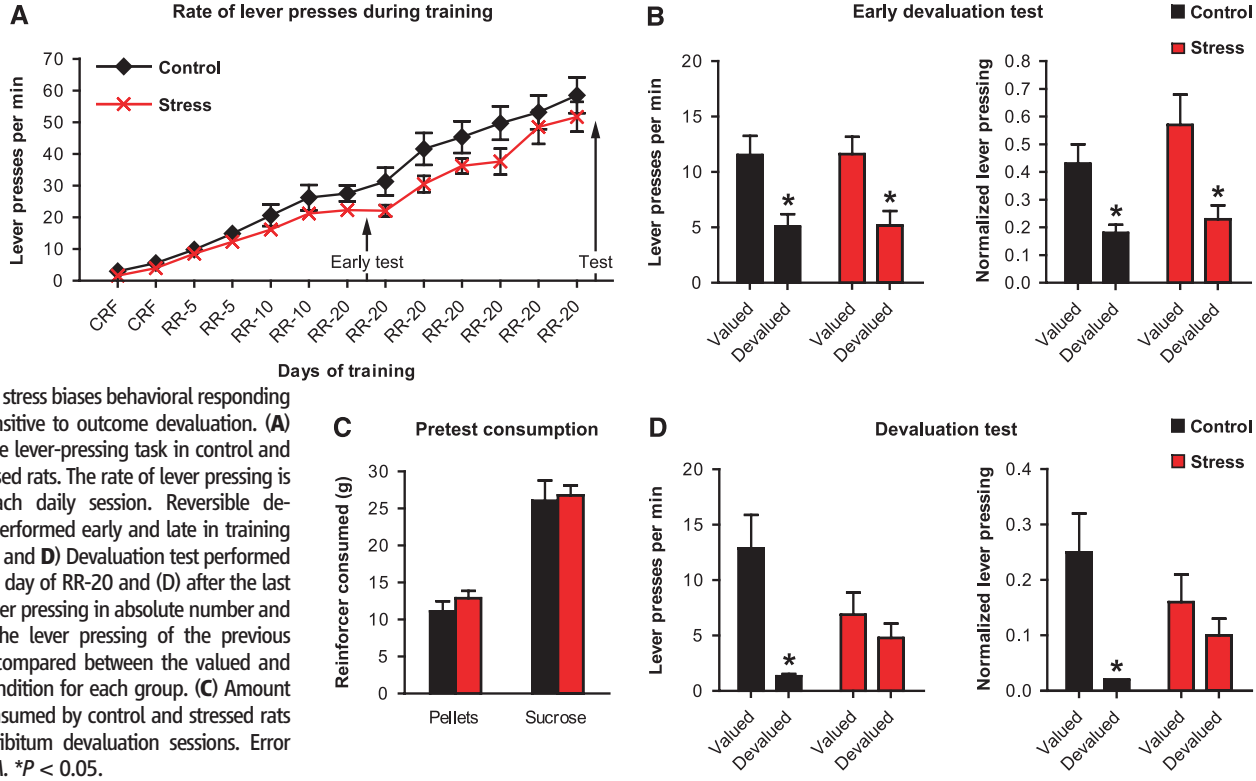

Fig. 1. Chronic stress biases behavioral responding to become insensitive to outcome devaluation. (**A**) Acquisition of the lever-pressing task in control and chronically stressed rats. The rate of lever pressing is depicted for each daily session. Reversible devaluation tests performed early and late in training are indicated. (**B** and **D**) Devaluation test performed (B) after the first day of RR-20 and (D) after the last training day. Lever pressing in absolute number and normalized to the lever pressing of the previous training day is compared between the valued and the devalued condition for each group. (**C**) Amount of reinforcer consumed by control and stressed rats during the ad libitum devaluation sessions. Error bars denote SEM. *$P < 0.05$.

avoid the resilient effect of behavioral control over stressors (*14*). Twenty-one days of stress exposure decreased body-weight gain (fig. S1A), reduced the thymus/body-weight ratio (fig. S1B), and resulted in persistently raised serum corticosterone levels (fig. S1C), when compared with attributes of handled controls. After stress exposure, we tested whether chronic stress affected the ability of animals to perform actions, based on the consequences of their behavior, using two different instrumental tasks.

We first examined whether previous exposure to chronic stress affected the ability of animals to perform actions based on the expected value of predicted outcomes (*1*, *15*). Rats ($n = 8$ per group) were trained to press a lever for a particular outcome (pellets or sucrose, counterbalanced) under a random ratio schedule that was previously shown to bias for goal-directed behavior (*3*, *15*, *16*). Training started with 2 days of continuous reinforcement (CRF) and progressed under increasing random ratio (RR) schedules of reinforcement to RR-20 (on average one reinforcer every 20 lever presses). Both groups increased lever pressing across training days ($F_{12,168} = 95.489$, $P < 0.001$), and there was no interaction with ($F_{12,3} = 1.089$, $P = 0.372$) or main effect of ($F_{1,14} = 3.094$, $P = 0.100$) stress treatment (Fig. 1A). To evaluate whether animals could learn to press for the specific outcome delivered contingent on lever pressing, we performed an early devaluation test after the first day of RR-20 (Fig. 1B). Both stressed animals and controls significantly reduced their responses after the outcome they pressed for during training was devalued by sensory-specific satiety (devalued condition), when compared with the situation when a different outcome was devalued (valued condition) (*13*) (lever presses per min: control, $t_7 = 3.197$, $P = 0.015$; stress, $t_7 = 2.931$, $P = 0.022$; normalized lever pressing: control, $t_7 = 3.106$, $P = 0.017$; stress, $t_7 = 2.694$, $P = 0.031$). With increased training and in accordance with previous studies (*3*, *15*, *16*), the actions of control animals became highly sensitive to sensory-specific satiety [(Fig. 1D) lever presses per min: $t_7 = 3.672$, $P = 0.008$; normalized lever pressing: $t_7 = 3.042$, $P = 0.019$]. In contrast, the actions of stressed animals became insensitive to the expected value of the outcome, as indicated by the lack of a devaluation effect [(Fig. 1D) lever presses per min: $t_7 = 0.984$, $P = 0.358$; normalized lever pressing: $t_7 = 1.095$, $P = 0.310$]. It is noteworthy that the early devaluation test demonstrates that this insensitivity did not arise from an inability of the stressed animals to learn the relation between the action and the outcome or from changes in motivation, food valuation, or hedonics (*17*), but rather because stressed animals rapidly shift to a habitual strategy as training progresses. The amount of reinforcer consumed during the ad libitum devaluation sessions was similar in stressed and control animals [(Fig. 1C) pellets: $t_{14} = -1.072$, $P = 0.302$; sucrose: $t_{14} = -0.252$, $P = 0.805$].

Although it seems unlikely that the results obtained in the test above were due to differences in hedonics or value processing, we used a different task to confirm whether animals previously exposed to chronic stress really had impairments performing actions on the basis of the consequences of their behavior. We therefore investigated whether the behavior of chronically stressed animals would depend on the contingency between getting the outcome and the previous execution of the action (*1*, *18*). We trained a separate group of rats ($n = 15$ per group) in a task in which one action (pressing the left lever) would lead to a particular outcome (i.e., pellets), and another action (pressing the right lever) would lead to a different outcome (i.e., sucrose). Every day animals had two training sessions, one for each action-outcome pair (counterbalanced). Both groups increased lever pressing as training progressed across days under increasing ratio schedules of reinforcement (pellets: $F_{11,308} = 138.213$, $P < 0.001$; sucrose: $F_{11,308} = 88.578$, $P < 0.001$), and there was no interaction with stress (pellets: $F_{11,18} = 0.419$, $P = 0.947$; sucrose: $F_{11,18} = 0.831$, $P = 0.609$), or main effect of stress (pellets: $F_{1,28} = 2.742$, $P = 0.109$; sucrose: $F_{1,28} = 0.781$, $P = 0.384$) on acquisition (Fig. 2A). Similar to the previous task, both controls and stressed animals were able to learn the action-outcome relation as shown by their clear preference toward the valued lever in an early devaluation test after the first day of RR-20 (lever presses per min: control valued, 15.73 ± 2.24; devalued, 4.88 ± 0.95; $t_{14} = 4.150$, $P = 0.001$; stress valued, 11.19 ± 1.40; devalued, 5.33 ± 0.77; $t_{14} = 4.262$, $P = 0.001$; normalized lever pressing: control valued, 0.41 ± 0.04; devalued, 0.14 ± 0.03; $t_{14} = 5.167$, $P < 0.001$; stress valued, 0.34 ± 0.04; devalued, 0.18 ± 0.03; $t_{14} = 4.133$, $P = 0.001$; results are means ± SEM). After the last day of acquisition, we tested whether stressed animals were performing actions because they were necessary to obtain the outcome or not. For each animal, we degraded the contingency between one of the actions and the respective outcome (degraded condition: to get this outcome, the animals no longer needed to press the lever), but not between the other action-outcome pair (non-degraded: to obtain this outcome, the animals needed to press the lever) (*13*). After 2 days of forced-choice degradation training in which

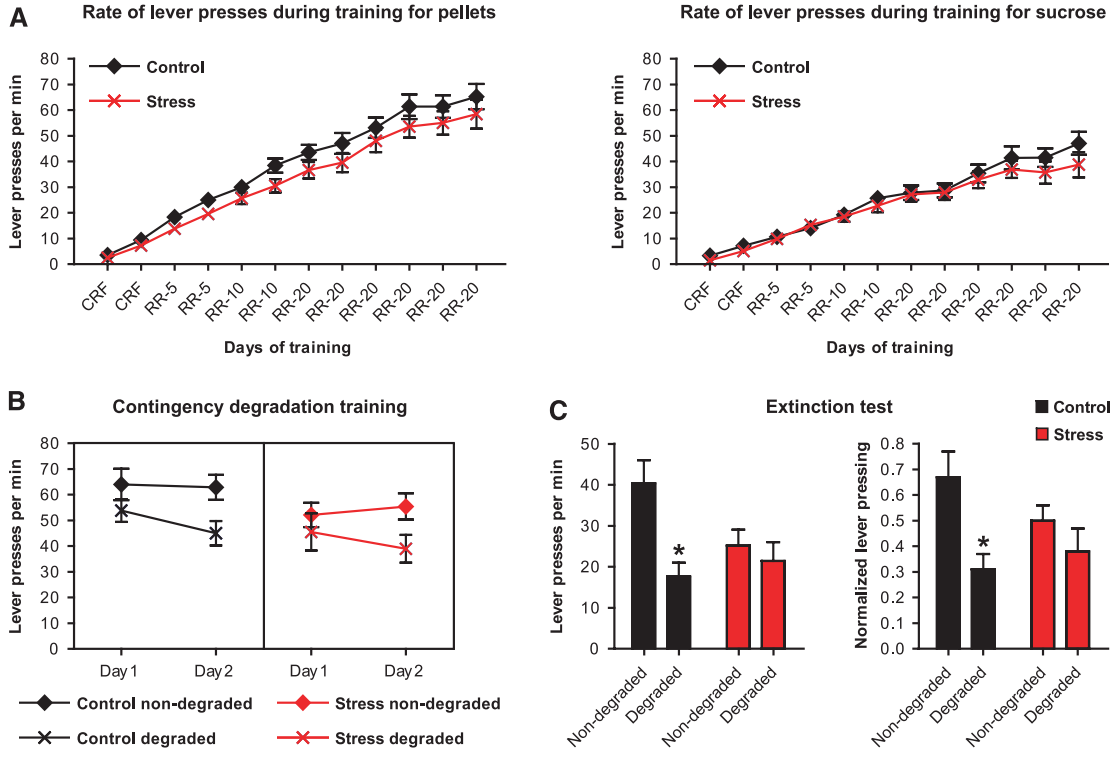

Fig. 2. Chronic stress predisposes choices to be insensitive to changes in action-outcome contingency. (**A**) Acquisition of the lever-pressing task in control and chronically stressed rats. The rate of lever pressing is depicted for each daily session for pellets and for sucrose. (**B**) Performance for each group during forced-choice sessions in which one instrumental outcome continued to be obtained in a RR-20 schedule (non-degraded) and the other outcome was delivered noncontiguously or freely (degraded). (**C**) Critical choice test between the lever for which the action-outcome contingency was preserved and the lever that had the contingency degraded. Lever pressing in absolute numbers and normalized to the lever pressing of the last acquisition training day is compared between levers for each group. Error bars denote SEM. *$P < 0.05$.

both groups changed their behavior [(Fig. 2B) degradation effect: control, $F_{1,28}$ = 4.342, P = 0.046; stress, $F_{1,28}$ = 2.189, P = 0.150; training × degradation interaction: control, $F_{1,28}$ = 2.396, P = 0.133; stress, $F_{1,28}$ = 5.580, P = 0.025], animals were given a free-choice test between the degraded and non-degraded lever, in extinction [to avoid the confounding effects of consumption and reinforcement (*11*)] (Fig. 2C). Control animals significantly reduced their responses on the degraded lever compared with the non-degraded (lever presses per min: t_{14} = 2.552, P = 0.023; normalized lever pressing: t_{14} = 2.645, P = 0.019). However, stressed animals pressed both levers similarly (lever presses per min: t_{14} = 0.808, P = 0.433; normalized lever pressing: t_{14} = 1.330, P = 0.205), which indicated that they failed to choose the action that was necessary to obtain the outcome and that their behavior was habitual.

These data indicate that previous exposure to chronic stress biases decision-making and pre-

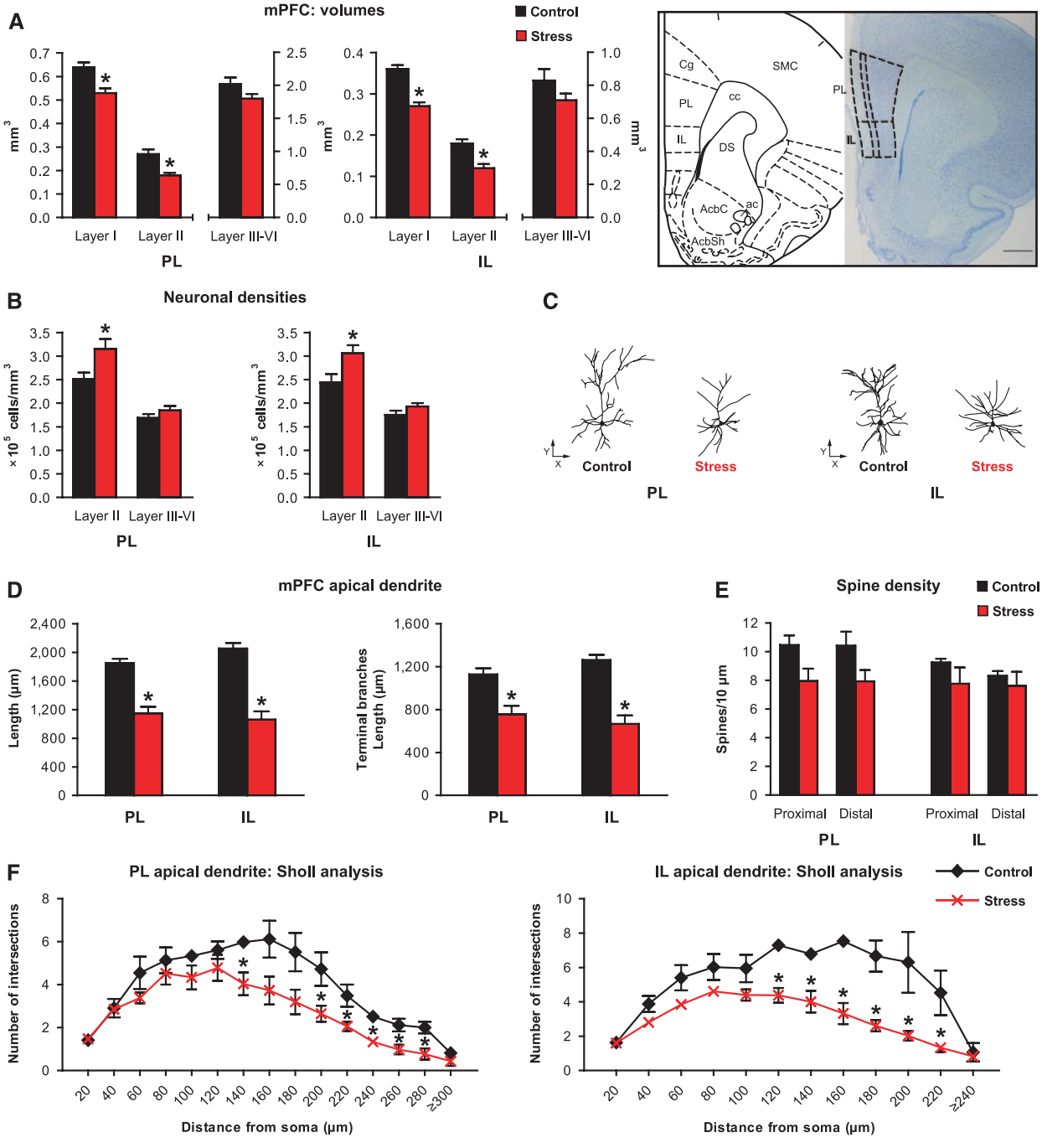

Fig. 3. Chronic stress results in selective atrophy within the external layers of both PL and IL mPFC subregions. Several structural measurements of control and chronically stressed rats are compared. (**A** and **B**) Stereological estimations of (A) volumes and (B) neuronal densities. (A, right) Outlining between regions and layers is represented; diagram was adapted from (*31*) and corresponding brain slice stained with Giemsa (2.20 mm from bregma). Cg, cingulate cortex; SMC, sensorimotor cortices; cc, corpus callosum; DS, dorsal striatum; AcbC, core, and AcbSh, shell, of nucleus accumbens; ac, anterior commissure. Scale bar, 800 µm. (**C** to **F**) Morphometric analysis in 3D of Golgi-stained pyramidal neurons of superficial layers (II/III). (C) Computer-assisted reconstructions of representative neurons depicted in the XY orthogonal plane. (D) Length, (E) spine density, and (F) differential rearrangement of apical dendrites. Error bars denote SEM. *P < 0.05.

disposes animals to more readily shift between goal-directed and habitual behavioral strategies as training progresses, similar to the effects observed after manipulations of the associative (*10*, *11*) or sensorimotor (*12*, *16*) corticostriatal circuits (*19*–*21*). Therefore, in a separate cohort of animals ($n = 5$ per group, submitted to chronic stress or handling but not submitted to instrumental training), we investigated the effects of chronic stress on the structure of cortical and striatal circuits known to be required for goal-directed actions and habits. Within the mPFC, the PL and infralimbic (IL) subregions have been implicated in instrumental behavior (*10*, *19*). Volumetric estimations showed a selective atrophy of external cortical layers in both mPFC subregions of stressed animals [(Fig. 3A) PL: layer I, $t_8 = 4.066$, $P = 0.004$; layer II, $t_8 = 3.697$, $P = 0.006$; layer III-VI, $t_8 = 1.725$, $P = 0.123$; IL: layer I, $t_8 = 6.225$, $P < 0.001$; layer II, $t_8 = 4.743$, $P = 0.001$; layer III-VI, $t_8 = 1.411$, $P = 0.196$]. Consistently, we observed an increase in neuronal density in these layers in the same animals [(Fig. 3B) PL: layer II, $t_8 = -2.602$, $P = 0.032$; layer III-VI, $t_8 = -1.383$, $P = 0.204$; IL: layer II, $t_8 = -2.488$, $P = 0.038$; layer III-VI, $t_8 = -1.688$, $P = 0.130$]. Three-dimensional (3D) morphometric analysis of dendritic arbors of layer II/III pyramidal cells in the mPFC indicated that these changes in volume and density could be ascribed to dendritic atrophy (PL: $t_8 = 6.457$, $P < 0.001$; IL: $t_8 = 7.021$, $P < 0.001$), particularly in terminal branches (PL: $t_8 = 3.851$, $P = 0.005$; IL: $t_8 = 6.389$, $P < 0.001$) of the apical tree (Fig. 3, C and D). These effects suggest a loss of neuronal connectivity that does not seem to result from spine loss [(Fig. 3E) PL: proximal, $t_8 = 2.290$, $P = 0.051$; distal, $t_8 = 1.960$, $P = 0.086$; IL: proximal, $t_8 = 1.270$, $P = 0.240$; distal, $t_8 = 0.669$, $P = 0.522$] or maturation (fig. S2A), but rather to an impoverished arborization confined to distal portions [(Fig. 3F) PL: stress effect, $F_{1,8} = 12.150$, $P = 0.008$; post hoc 140, 200 to 280 μm, $P < 0.05$; IL: stress effect, $F_{1,8} = 17.117$, $P = 0.003$; post hoc 120 to 220 μm, $P < 0.05$] of the apical tree. No consequences were observed in basal dendrites (fig. S3). Note that this atrophy was not generalized to all the regions of the frontal cortex. The orbitofrontal cortex (OFC), which is also a target of stress (*22*) and has been implicated in decision-making (*23*), showed a different pattern of change, with the most medial portions (medial orbital, MO) showing no alteration, whereas the most lateral regions (lateral orbital, LO) displayed a clear structural hypertrophy (fig. S4). In addition, no differences were found in the motor and somatosensory cortices (fig. S5).

We next examined the effects of chronic stress on the projection areas of these cortices into the dorsal striatum (DS), which has been previously implicated in controlling goal-directed and habitual strategies. We investigated more specifically the DMS, which receives input from the PL cortex (*24*) and has been implicated in goal-directed

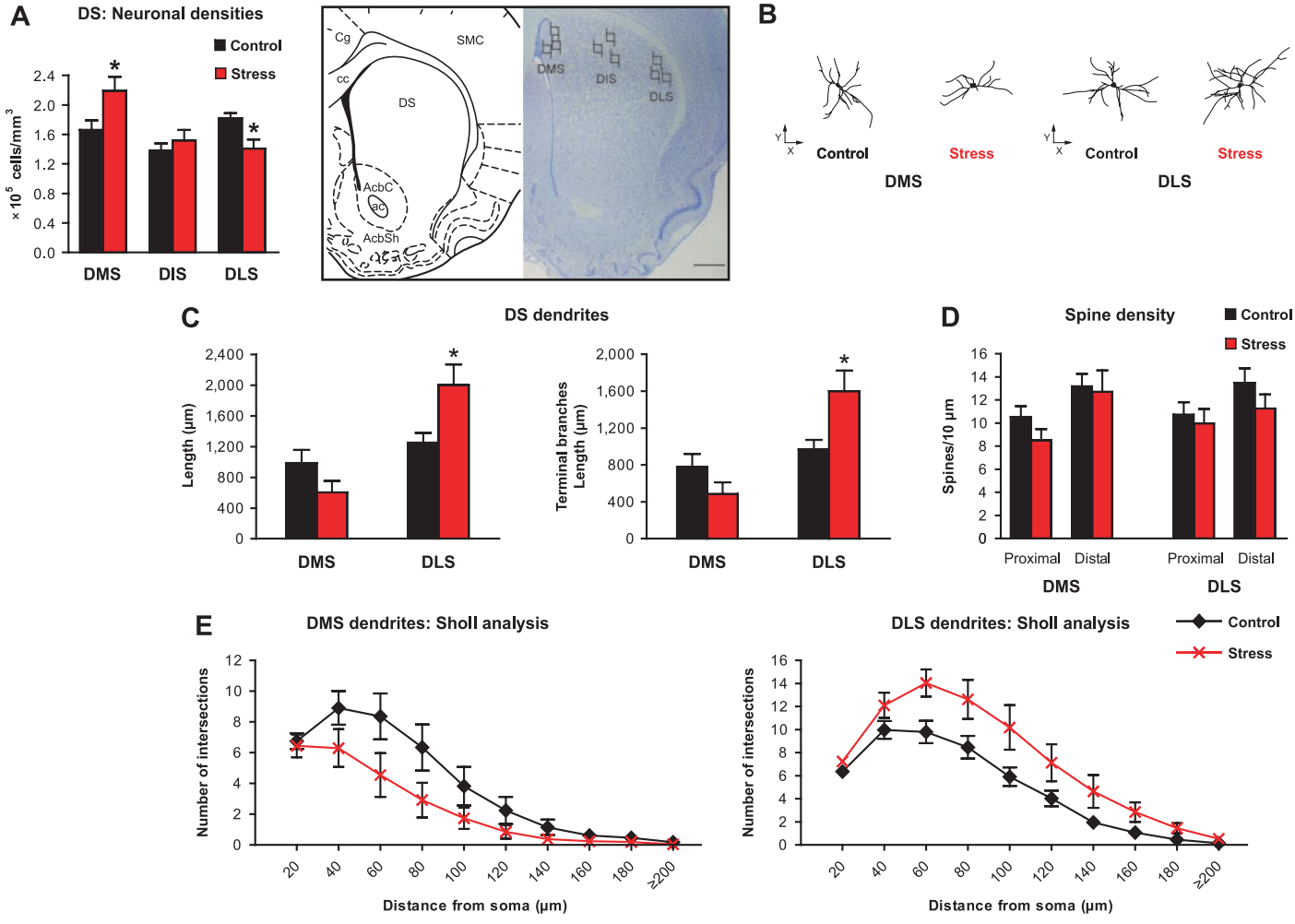

Fig. 4. Chronic stress induces opposing modulating effects in DMS and DLS networks. Several structural measurements of control and chronically stressed rats are compared. (**A**) (Left) Stereological estimation of neuronal densities. (Right) Sampling of the DMS, DIS, and DLS regions is illustrated; diagram was adapted from (*31*) and corresponding brain slice stained with Giemsa (1.00 mm from bregma). Abbreviations are as in Fig. 3. Scale bar, 800 μm. (**B** to **E**) Morphometric analysis in 3D of Golgi-stained MSNs [sampling following the same approach as for neuronal densities; for illustration, see (A)]. (B) Computer-assisted reconstructions of representative neurons depicted in the XY orthogonal plane. (C) Length, (D) spine density, and (E) differential rearrangement of dendrites. Error bars denote SEM. *$P < 0.05$.

actions (*11*), and the DLS or sensorimotor striatum, which is critical for habit formation (*12*) and receives input from the sensorimotor cortices (*24*) and, more laterally, from the LO cortex (*25*). Given the lack of precise anatomical landmarks delimiting these subregions in the DS, which could bias volumetric measures, we measured neuronal densities within the areas previously shown to be important for goal-directed and habitual behavior (Fig. 4A) (*11*–*13*) and found opposing effects of chronic stress in DMS and DLS. Neuronal density decreased in the DLS ($t_8 = 2.970$, $P = 0.018$) and increased in the DMS ($t_8 = -2.343$, $P = 0.047$) (Fig. 4A); these findings indicate atrophy of DMS and hypertrophy of DLS after stress exposure. These differences were not the result of generalized changes in the DS, because no differences in neuronal density were found in the intermediate area between medial and lateral regions (DIS: $t_8 = -0.802$, $P = 0.446$). To determine whether these changes in density were due to changes in dendritic arborization, we performed a 3D morphometric analysis of the medium spiny neurons (MSNs) within the same conservative limits for these DS subregions (Fig. 4, B, C, and E). We found a significant increase in dendritic arbors of DLS neurons [(Fig. 4C) length, $t_8 = -2.527$, $P = 0.035$; terminal branches length, $t_8 = -2.563$, $P = 0.033$; (Fig. 4E) $F_{1,8} = 5.016$, $P = 0.055$] and a nonsignificant trend toward a reduction in the dendrites in DMS neurons [(Fig. 4C) length, $t_8 = 1.682$, $P = 0.131$; terminal branches length, $t_8 = 1.550$, $P = 0.160$; (Fig. 4E) $F_{1,8} = 2.820$, $P = 0.132$] of stressed animals. No significant effects of stress were observed in spine density [(Fig. 4D) DMS: proximal, $t_8 = 1.504$, $P = 0.171$; distal, $t_8 = 0.221$, $P = 0.831$; DLS: proximal, $t_8 = 0.451$, $P = 0.664$; distal, $t_8 = 1.267$, $P = 0.241$] or morphology (fig. S2B). Taken together, the neuronal density and dendritic measures suggest a bidirectional modulation of neuronal connectivity in the DS expressed by a global hypertrophy of the DLS and shrinkage of the DMS.

The present results show a divergent structural reorganization of corticostriatal circuits after chronic stress, with atrophy of the associative corticostriatal circuits and hypertrophy of the circuits coursing through the sensorimotor striatum. This frontostriatal reorganization is accompanied by a shift toward habitual strategies, affecting the ability of stressed animals to perform actions based on their consequences. These data are consistent with previous studies showing that lesions of the PL cortex (*10*) and the DMS (*11*) can bias behavior to be more habitual, whereas inactivation of the DLS (*12*) can render the behavior of habitual animals goal-directed again, which suggest that competing corticostriatal circuits underlie the ability of animals to switch between these two modes of responding (*1*). Our results, using a natural model, indicate that the relative advantage of the sensorimotor network after chronic stress biases behavioral strategies toward habit and offer further insight into how chronic stress can lead to dysfunctional decision-making.

In addition to the role of the PL cortex (*10*), DMS (*11*), and DLS (*12*), the role of other brain regions affected by chronic stress in the behavioral bias herein described should be further investigated. For example, we did not observe changes in the sensorimotor cortices projecting to DLS but did find that the LO cortex, which also projects to the more lateral parts of the dorsal striatum (*25*), presents a clear hypertrophy. [The MO that projects to more medial striatal areas (*25*) does not.] Therefore, the role of the different subregions of the OFC in instrumental conditioning should be further explored, especially because although the atrophy of the PL cortex could contribute to the observed effects, the atrophy of IL cortex does not easily explain the bias toward habitual strategies, because lesions of this region have been shown to impair habit formation (*19*). Another possibility is that changes in the sensorimotor striatum relative to the associative striatum without parallel changes in the projecting cortices are sufficient to readily shift the behavioral strategies as training progresses. This is an interesting possibility given that more ventral striatal areas like the nucleus accumbens seem to have a more prominent role in appetitive Pavlovian responses than in control of instrumental behavior (*26*, *27*). Furthermore, a potential role of thalamic inputs to the sensorimotor striatum in mediating habitual strategies should not be discarded. Finally, the effects of chronic stress on the hippocampus (*8*) and amygdala (*28*) cannot easily explain the behavioral bias observed, because the early devaluation tests revealed that chronically stressed animals can learn action-outcome relations, and their behavior becomes biased as training progresses.

Optimization of decision-making processes confers an important advantage in response to a constantly changing environment. The ability to select the appropriate actions on the basis of their consequences and on our needs at the time of the decision allows us to respond in an efficient way to changing situations. However, the continuous control and attention that this process demands can result in an unnecessary expenditure of resources and can be inefficient in many situations. For instance, when behavior is repeated regularly for extensive periods without major changes in outcome value or contingency, or under uncertain situations where we cannot manipulate the probability of obtaining an outcome, general rules and habits can be advantageous (*3*). Thus, the more rapid shift to habits after chronic stress could be a coping mechanism to improve performance of well-trained behaviors, while increasing the bioavailability to acquire and process new information, which seems essential for adaptation to complex environments (*4*, *5*). However, when objectives need to be re-updated in order to make the most appropriate choice, the inability of stressed subjects to shift from habitual strategies to goal-directed behavior might be highly detrimental. Such impairment might be of relevance to understand the high comorbidity between stress-related disorders and addictive behavior or compulsivity (*29*, *30*), but certainly has a broader impact spanning activities from everyday life decisions to economics.

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Supporting Online Material

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Materials and Methods
Figs. S1 to S5
References

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