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Voluntary exercise increases striatal dopamine release and improves motor performance in aging mice



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Aging is often accompanied by a decline in mobility across species, which can be improved by aerobic exercise, even in individuals with Parkinson's disease. We showed previously that 30 days of voluntary wheel-running exercise in young male mice leads to enhanced release of the motor-system transmitter, dopamine (DA), in ex vivo corticostriatal slices. Here we tested whether voluntary exercise also increases DA release in aging (12 months old) mice of both sexes, and whether this is associated with improved motor performance. Mice were allowed unlimited access to a rotating (runners) or a locked (controls) wheel for 30 days. Motor behavior was then assessed, and electrically evoked DA release was quantified in slices from these animals using fast-scan cyclic voltammetry. Although daily running distance for females was nearly twice that of males, runners of both sexes showed comparable increases in evoked DA release in dorsolateral striatum and in nucleus accumbens core and shell compared to age- and sex-matched controls. Runners of both sexes showed an increase in locomotion velocity and improved motor coordination. Thus, voluntary exercise boosts striatal DA release and improves motor performance in aging mice, providing new insights into the benefits of exercise in aging humans.

Aging is often accompanied by a decline in mobility and cognition¹. Mobility issues involve physiological changes that include decreased dopamine (DA) transmission that affects motor and sensorimotor pathways^{2–4}. The involvement of DA is unsurprising given the vital roles this transmitter plays in movement, reward, and cognitive function^{5,6}. A key brain center for motor regulation is the striatum, which receives dense DA input from midbrain DA neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA)^{7–9}. Conditions in which DA is depleted, as when the nigrostriatal pathway degenerates progressively in Parkinson's disease (PD), lead to motor impairment including deficits in the initiation, speed, and fluidity of voluntary movement that are hallmarks of PD^{10,11}. Aging alone can be associated with similar deficits, however, and studies of the aging human brain have shown degraded DA signaling that is correlated with slower movement and decreased movement amplitude^{12,13}.

It is well-recognized that aerobic exercise can be beneficial for brain health, including in the aging population^{14–17}. In humans and in animal models, physical activity has been shown to enhance adult hippocampal neurogenesis, synaptic plasticity, and neurotrophin levels that contribute to

improved memory^{17–19}. Physical exercise also provides neuroprotection for brain DA pathways in neurotoxin-based PD models in rodents and improves motor and/or cognitive function in these animal models^{20–29}. Moreover, aerobic exercise has been shown to improve motor activity in human PD patients^{30–33}. Complementing and extending this body of evidence, we recently reported that voluntary exercise leads to an increase in dynamic DA release throughout the striatum of young, healthy male mice and that this requires a neurotrophin, brain-derived neurotrophic factor (BDNF)³⁴. These results suggest that the motor benefits of exercise seen in humans, including those with PD, may involve increased DA release. However, whether amplified DA release in rodents is associated with improved motor performance, and whether these benefits can be extended to the aging brain have not been investigated.

Here, we evaluated the influence of physical exercise on striatal DA release, as well as on mobility and motor coordination in aging (12 months old) male and female mice. Mice were allowed unlimited access to a freely rotating wheel (runners) or a locked wheel (controls) for 30 days. Electrically evoked DA release was quantified using fast-scan cyclic voltammetry

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(FSCV), in the dorsolateral striatum (dlStr) and nucleus accumbens (NAc) core and shell in ex vivo corticostriatal slices from these animals. Given that striatal DA release can be driven by acetylcholine (ACh) released from cholinergic interneurons (ChIs) and acting at nicotinic ACh receptors (nAChRs) on DA axons^{35–41}, we also assessed possible contributions from changes in ACh-dependent regulation of DA release. Behavioral testing was conducted in the same mice used for DA release studies, and included measures of locomotor activity in the open field, time to descend a vertical pole, and grip strength. Daily running activity was monitored for the exercise cohorts, along with weekly assessment of body weight and food consumption for all mice. Consistent with data from our earlier studies in young male mice, voluntary exercise led to increased DA release in striatal slices from aging mice of both sexes. Moreover, this was associated with an increase in the velocity of locomotor activity and improved motor coordination.

Results

Running activity in female and male mice

Voluntary wheel-running activity over 30 days was monitored for singly housed male and female C57Bl6/J mice that were 12 months old at the end of the running period. Data from runners were compared with those from age and sex-matched controls that were singly housed with a locked wheel (Fig. 1A). Mice allowed access to a freely rotating wheel ran primarily during the dark phase, which began at 12:00 Zeitgeber time (Fig. 1B). In these studies, average running activity during the daily dark cycle for females was significantly greater than for males ($F(1,369) = 293.5$, $p < 0.0001$, 2-way ANOVA with repeated measures, $p < 0.0001$ for 12 to 24 h, Sidák's *post hoc* test; females vs. males, $n = 6$ mice per sex) (Fig. 1B). Higher daily running activity in females vs. males was seen from the third day of wheel access and persisted through the rest of the running period; illustrated data show activity through day 26, after which the running period was interrupted intermittently for behavioral testing ($F(1,10) = 46.75$, $p < 0.0001$, 2-way ANOVA with repeated measures; $p < 0.05$ to $p < 0.01$ for days 4–26, Sidák's *post hoc* test; females vs. males, $n = 6$ mice per sex) (Fig. 1C, Supplementary Table 1). Body weight and food consumption were assessed once a week. Initial body weights were ~29 g for females and ~35 g for males. When compared to these initial weights, there was no change in weight for any group. Moreover, there were no differences between runners vs. controls for females or males (female: ($F(1,10) = 0.0251$, $p = 0.8772$; male: ($F(1,10) = 2.532$, $p = 0.1426$ 2-way ANOVA with mixed effects model, $p > 0.05$ at 7, 14, 21 and 28 days Sidák's *post hoc* test, $n = 6$ mice per group) (Fig. 1D, F, Supplementary Table 1). However, maintenance of weight in female runners was associated with increased food consumption after the second week ($F(1,10) = 38.89$, $p < 0.0001$, 2-way ANOVA, mixed effects model, $p < 0.01$ at 14 days, $p < 0.01$ at 21 days and $p < 0.05$ at 28 days, Sidák's *post hoc* test; runners vs. controls, $n = 6$ mice per group) (Fig. 1E). Male runners showed an increase in food consumption only in their third week ($F(1,10) = 2.179$, $p = 0.1707$, 2-way ANOVA, mixed effects, $p < 0.05$ at 21 days, Sidák's *post hoc* test; runners vs. controls, $n = 6$ mice per group) (Fig. 1G, Supplementary Table 1).

Voluntary exercise increases evoked DA release in aging female and male mice

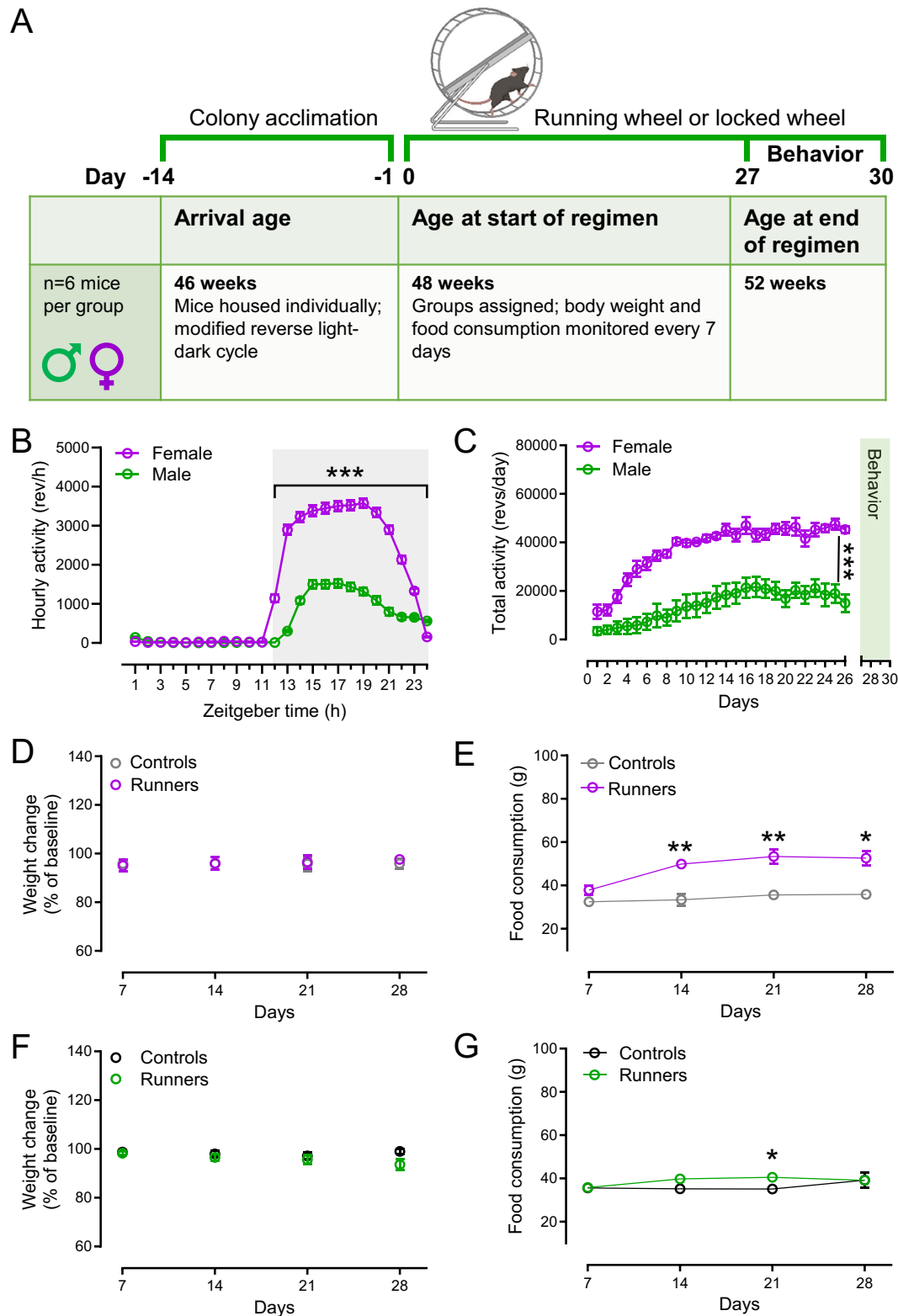
The influence of exercise on dynamic DA release in the striatum was assessed using multiple-site sampling of locally evoked extracellular DA concentration ($[DA]_o$) in dlStr, NAc core, and NAc shell in corticostriatal slices from runners and controls. We found that voluntary exercise led to a significant increase in evoked $[DA]_o$ in each striatal subregion in aging runners of both sexes vs. age and sex-matched controls (Figs. 2 and 3). Notably, these increases were comparable to the exercise-induced increases in striatal DA release reported previously for young (10-week-old) male mice³⁴. In aging females, mean evoked $[DA]_o$ in the dlStr of controls was $0.96 \pm 0.08 \mu\text{M}$ and $1.46 \pm 0.11 \mu\text{M}$ in runners (Fig. 2A, B); in NAc core,

control evoked $[DA]_o$ was $0.58 \pm 0.04 \mu\text{M}$ and $1.15 \pm 0.10 \mu\text{M}$ in runners (Fig. 2C, D); and in NAc shell, control evoked $[DA]_o$ was $0.83 \pm 0.08 \mu\text{M}$ and in runners was 1.24 ± 0.11 (Fig. 2E, F) (dlStr, $p < 0.001$ runners vs. controls, $n = 50$ –59 sites from 6 mice per group, unpaired *U*-test; NAc core, $p < 0.0001$, $n = 40$ –47 sites from 6 mice per group, unpaired *U*-test; NAc shell, $p < 0.01$, $n = 40$ –47 sites from 6 mice per group, unpaired *U*-test). Although less precise, comparing evoked $[DA]_o$ averaged across slices rather than recording sites also showed significant exercise-enhanced DA release in all striatal subregions of female runners vs. controls ($n = 12$ slices per group; Supplementary Fig. 1A–C). Voluntary exercise in female mice was not associated with a change in the maximal rate (V_{max}) for DA uptake in dlStr, but did lead to a significant increase in V_{max} in the NAc core with respect to controls (Fig. 2G) (dlStr, $p = 0.1839$, runners vs. controls, $n = 46$ –53, unpaired *U*-test; NAc core $p < 0.05$, $n = 36$ –40, unpaired *t*-test with Welch's correction).

Despite running significantly less each day than females, aging male runners also showed a significant increase in evoked $[DA]_o$ vs. matched controls (Fig. 3). In aging males, mean evoked $[DA]_o$ in dlStr was $0.99 \pm 0.05 \mu\text{M}$ in controls and $1.40 \pm 0.07 \mu\text{M}$ in runners (Fig. 3A, B); in NAc core, evoked $[DA]_o$ was $0.75 \pm 0.03 \mu\text{M}$ in controls and $1.12 \pm 0.04 \mu\text{M}$ in runners (Fig. 3C, D); and in NAc shell, evoked $[DA]_o$ was $0.57 \pm 0.03 \mu\text{M}$ in controls and 0.91 ± 0.05 in runners (Fig. 3E, F) (dlStr, $p < 0.001$ runners vs. controls, $n = 51$ –50 sites from 6 mice per group, unpaired *t*-test; NAc core, $p < 0.0001$, $n = 56$ –55 sites from 6 mice per group, unpaired *t*-test; NAc shell, $p < 0.0001$, $n = 59$ –58 sites from 6 mice per group, unpaired *t*-test). As seen in females, a significant increase in evoked $[DA]_o$ was seen for each striatal subregion from male runners vs. controls when averaged across slices rather than sites ($n = 12$ slices per group; Supplementary Fig. 1A–C), as seen in females. Analysis of V_{max} in males showed an increase in V_{max} for DA uptake in runners compared to controls in both dlStr and NAc core (Fig. 3G) (dlStr, $p < 0.01$, runners vs. controls $n = 50$ for both; NAc core $p < 0.01$ $n = 54$ –56, unpaired *t*-test). Given that enhanced DA uptake acts to lower $[DA]_o$, these findings indicate that the net effect of voluntary exercise on $[DA]_o$ in both males and females is to enhance DA release.

Absence of ACh involvement in exercise-enhanced striatal DA release

Having established that exercise boosts striatal DA release in aging mice of both sexes, we next asked whether the effect involved altered DA release regulation by ACh and nAChR activation. It is well-recognized that activation of nAChRs can trigger striatal DA release^{35–41}, and that this can contribute to DA release enhancement by external regulators, including insulin and leptin^{42–44}. We investigated a role for ACh in exercise-enhanced DA release using a nAChR antagonist, dihydro- β -erythroidine (DH β E; $1 \mu\text{M}$)^{34,35}, to remove the contribution of nAChR activation to evoked DA release. In contrast to the DA-boosting effects of insulin and leptin, the observed exercise-induced enhancement of DA release persisted when nAChRs were antagonized in all but one striatal subregion in one sex, indicating independence from nAChR activation and implying a direct effect of exercise on DA axons (Fig. 4). The exception was in the NAc core of female runners, as discussed further below. In both sexes, whether runners or controls, antagonism of nAChRs by DH β E decreased the amplitude of evoked $[DA]_o$ in regions in which single-pulse stimulation was used to evoke DA release, as previously^{34,35,38}. In the dlStr of females and males, evoked $[DA]_o$ remained significantly higher in runners than controls (Fig. 4A, B) ($p < 0.001$ runners vs. controls, $n = 52$ –42 sites from 6 female mice per group; $n = 60$ sites per group from 6 males per group; unpaired *U*-tests). In NAc core of females, the difference between runners and controls was absent in the presence of DH β E ($p = 0.973$ runners vs. controls, $n = 39$ –38 sites from 6 female mice per group, unpaired *U*-test) (Fig. 4C), whereas higher evoked $[DA]_o$ persisted in the NAc core of male runners ($p < 0.001$ runners vs. controls, $n = 55$ –56 sites per group from 6 male mice per group, unpaired *t*-test) (Fig. 4D). Elevated evoked $[DA]_o$ also persisted in the NAc shell of runners of both sexes (Fig. 4E, F) (females, $p < 0.05$ runners vs. controls, $n = 40$ –45 sites from 6 mice per group, unpaired *U*-test;



males, $p < 0.001$ vs. controls, $n = 60$ – 60 sites from 6 mice per group, unpaired U -test).

Wheel-running exercise improves motor function in aging mice

Our previous studies showed that exercise boosts DA release in young male mice³⁴. Our current results show that voluntary exercise leads to enhanced striatal DA release in aging mice of both sexes, as well. We therefore tested the hypothesis that amplified DA release might contribute to improved

motor performance in aging mice. We tested motor behavior in runners and controls during the last three days of the running period. We first examined locomotor behavior in an open field arena (Fig. 5A, B). The overall distance traveled in the open field across a 60-min test period (females and males combined), was significantly greater for runners than controls ($p < 0.05$, 12 mice per group, unpaired t -test) (Fig. 5C), showing greater velocity of movement in runners over 60 min, with a significant main effect of exercise, although analysis of individual 10-min bins did not reveal a significant

Fig. 1 | Voluntary wheel running. A Timeline for wheel-running protocol. For each study, 12 singly housed mice of a given sex were acclimated to a modified light-dark cycle for two weeks, then randomly assigned to cages with a freely rotating wheel (runners, $n = 6$) or a locked wheel (controls, $n = 6$). Behavioral testing was conducted on days 28 and 29, then on day 30, mice were removed for brain slice studies of evoked DA release using FSCV. Mouse image created in <https://BioRender.com>. B Daily running patterns for each sex, with greatest activity in the dark phase for both sexes (shaded box). Females showed greater activity in revolutions per hour (revs/h) than males ($***p < 0.001$; 2-way ANOVA, Sidák's *post hoc* test, $n = 6$ per sex). C Average total daily running patterns also showed that females showed greater daily

activity (revs/day) than males during the first 27 days that were uninterrupted by behavioral testing ($***p < 0.001$; 2-way ANOVA, Sidák's *post hoc* test, $n = 6$ runners per sex). D, F Change in body weight monitored weekly, with the first day of housing with a wheel taken as baseline (100%). No significant changes in weight were seen in or between any group (female or male runners and controls ($n = 6$ per group; 2-way ANOVA, Dunnett's and Sidák's *post hoc* test). E, G Average food consumption for female and male cohorts assessed weekly ($*p < 0.05$, $**p < 0.001$ female runners vs. female controls, $*p < 0.05$ male runners vs. male controls, $n = 6$ mice per group; 2-way ANOVA, Sidák's *post hoc* test).

exercise group $\times$ time bin interaction ($F(1,22) = 5.191$, $p = 0.0328$ for total exercise; $p > 0.05$ for 10-min bins, $n = 12$ mice per group, 2-way ANOVA, Sidák's *post hoc* test) (Fig. 5D, Supplementary Table 2). The overall time spent moving did not differ between runners and controls ($p = 0.084$, $n = 12$ mice per group, unpaired *t*-test) (Fig. 5E). Monitoring mice in the open field also allowed evaluation of the time each mouse spent in the center vs. perimeter of the arena as a measure of anxiety-like behavior. We found no difference in the time spent in the center of the arena between runners and controls, consistent with a limited anxiety phenotype in healthy aging mice, whether engaged in aerobic exercise or not ($p = 0.347$; 12 mice per group, unpaired *U*-test (Fig. 5F).

We next assessed motor performance in a pole test. Evaluation of time to descend a vertical pole (Fig. 5G) revealed a significantly shorter time to descend the pole in runners compared to controls, indicating a marked improvement in motor coordination in runners ($p < 0.01$; 12 mice per group, unpaired *t*-test) (Fig. 5H). The adhesive tape removal test was used to assess dexterity and fine motor coordination. In contrast to the motor improvements seen in the open field and pole tests, this test showed that although control females were slightly faster to approach the first tape for removal than their male counterparts ($F(1,20) = 13.420$, $p = 0.0015$ for sex $p < 0.05$ for female controls vs. male controls, $n = 6$ mice per group, 2-way ANOVA, Sidák's *post hoc* test), there was little difference between runners and controls, with no effect of exercise on time to first approach in either females or males ($F(1,20) = 0.4855$, $p = 0.4940$ for exercise; $p = 0.9985$ for female controls vs. runners, and $p = 0.9230$ for male controls vs. runners, $n = 6$ mice per group, 2-way ANOVA, Sidák's *post hoc* test) (Supplementary Fig. 2A, Supplementary Table 2) and no significant change in the time to remove the first tape (Supplementary Fig. 2B) or the second tape (Supplementary Fig. 2C) in males and females combined ($p = 0.109$; $p = 0.105$; 12 mice per group, unpaired *t*-test). We also found no difference in forelimb or combined forelimb and hindlimb grip strength between runners and controls (Supplementary Fig. 2D,E) ($p = 0.787$; $p = 0.488$; 12 mice per group, unpaired *t*-test). Overall, these results show that voluntary exercise can counteract the effects of aging to improve motor function without corresponding improvement in fine motor skills or strength.

Discussion

Aging adults experience a decline in mobility involving physiological changes in the brain that include decreased DA transmission which affects motor and sensorimotor pathways^{2,3}. Exercise has long been recognized to benefit human health⁴⁵. Beyond well-recognized benefits for the cardiovascular system^{46,47}, exercise can improve human brain health, with benefits that include improved cognition and memory^{16,48,49}, improved motor function in healthy aging adults and improved motor function in those with PD^{30–32,50}. However, the cellular and circuit mechanisms involved in the beneficial effects of exercise are not yet well understood. Our previous studies in young male mice showed that 30 days of voluntary wheel-running exercise boosts evoked striatal DA release³⁴. Notably, in that study, we found that exercise-enhanced DA release persists in the dlStr and NAc core after 7 days of rest (Bastoli et al. 2022). This indicates that the increase in evoked [DA]_o is not from the act of running per se but rather is an enduring

consequence of exercise. Here we report that aerobic exercise can also enhance striatal DA release in aging males and in females. Moreover, we found that this is associated with improved motor performance, including increased locomotor speed and improved coordination.

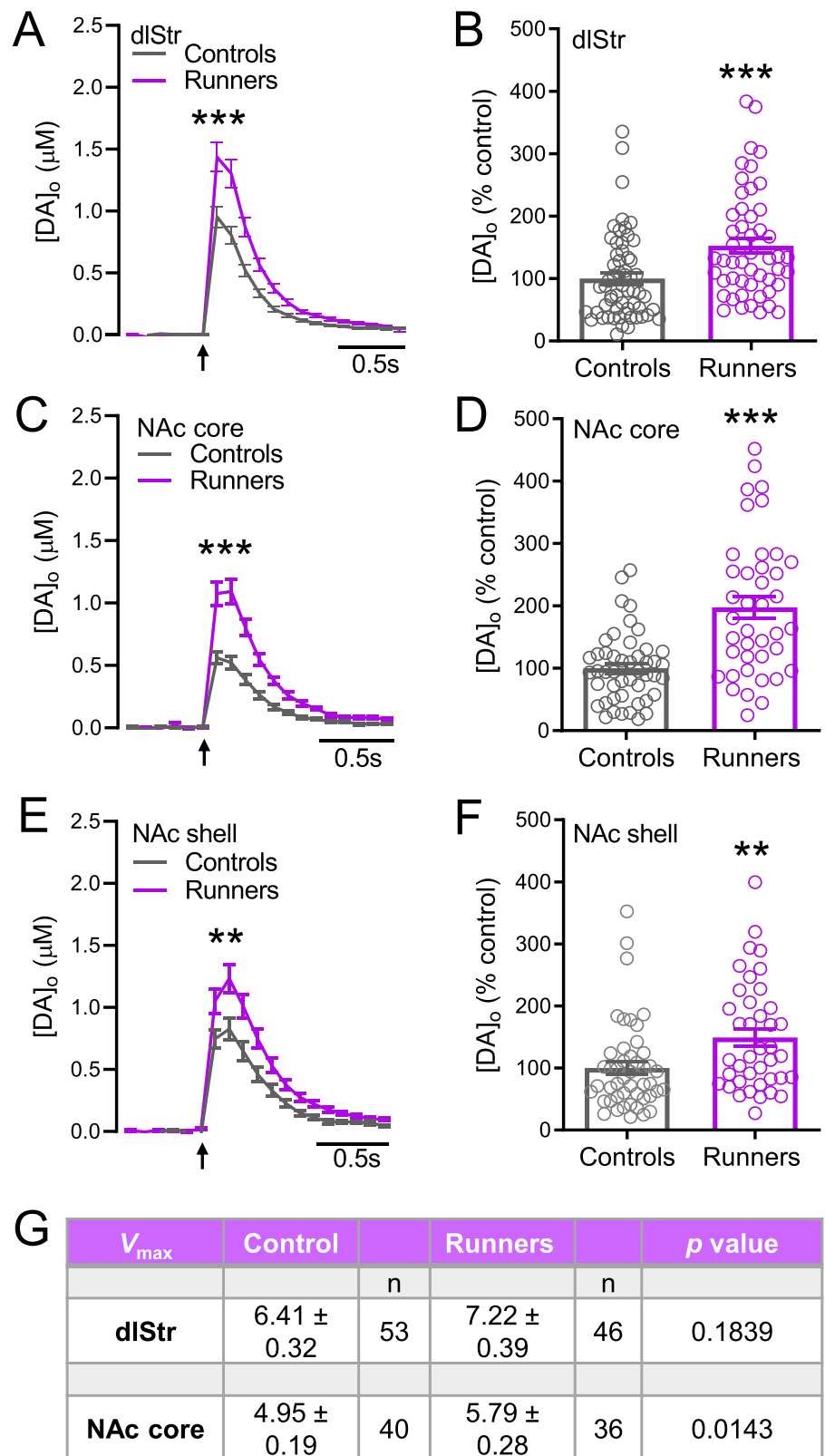
Voluntary exercise increased evoked DA release in all striatal subregions in both sexes. Interestingly, female mice ran more than twice the daily distance of age-matched males, consistent with previous studies showing greater activity in females^{51,52}. Nevertheless, there was enhanced evoked DA release in both sexes, with comparable increases seen in males and females (Figs. 2 and 3), and comparable behavioral improvements, as well. Given the far greater activity of females vs. males, this implies that a threshold level of activity was met in both sexes to produce benefits.

Previous studies have established that female mice and rats run faster and farther than males, particularly at younger ages^{52–55}. However, it has been suggested sex differences in running behavior decline with aging. For example, Bartling and colleagues found that although female mice exhibit more running activity than males when young, this difference diminishes by 9 months with continued access to the running wheel⁵⁶. Our data, however, show that sex differences in running activity are clearly evident in older mice when running wheels are available for 30 days rather than throughout the aging process. It is relevant to note that there are also strain differences in the propensity to run⁵³ that might contribute: Bartling et al. (2016) examined C57Bl/6N and the present study examined C57Bl/6J. Higher wheel-running activity in females than males remains incompletely explained. Implicated factors include circulating sex hormones and estrogen receptors^{54,55}, although contributions from these would be expected to diminish by 12 months of age in C57Bl/6J females⁵⁷. Other previously reported sex differences include respiratory capacity, food intake and energy metabolism^{58,59}, each of which could impact running activity⁶⁰. In our study, female runners showed increased food consumption over the 30-day running period without weight gain, whereas no other group, including male runners, showed such marked changes in either consumption or weight. Although this observation in females might suggest a change in physiological processes governing food intake and energy metabolism with exercise, it may simply reflect normal, homeostatic balancing of energy intake and expenditure.

It is well-established that striatal DA release can be driven by ACh acting at nAChRs on DA axons^{35–41}. To test a role for cholinergic involvement in the influence of exercise on evoked [DA]_o, we compared absolute evoked [DA]_o in striatal slices from runners and controls in the presence of the nAChR antagonist, DH β E. Consistent with our results from young male mice³⁴, we found that exercise-induced enhancement of evoked [DA]_o was independent of cholinergic involvement with persistence of higher DA release in runners vs. controls even with nAChR antagonism. This demonstrates a cell-autonomous effect of voluntary exercise on evoked increases in [DA]_o in both sexes. Moreover, we show that this reflects enhanced axonal DA release rather than decreased DAT-mediated uptake. Indeed, our V_{max} analysis revealed slight but significant increases in striatal DA uptake that would slightly temper the dominance of exercise-enhanced DA release to evoked [DA]_o.

The mechanism by which exercise enhances DA release is not yet established, although we do know from our previous work in young males that this requires BDNF and is absent in mice that have

Fig. 2 | Increased evoked $[DA]_o$ in striatal slices from female mice, after 30 d of voluntary wheel running. **A, C, E** Averaged evoked increases in $[DA]_o$ with SEM in dStr and NAc core (single-pulse stimulation) and NAc shell (5 pulses, 100 Hz) in ex vivo slices from female runners and controls. Arrows indicate time of stimulation. **B, D, F** Data summary for evoked $[DA]_o$ in each region for runners vs. controls, normalized to mean peak $[DA]_o$ for each region in controls. **A–F** $n = 40–59$ sites/region, 2 slices/mouse, 6 mice/group; $**p < 0.01$, $***p < 0.001$; unpaired U -tests. **G** V_{max} values derived for evoked striatal DA release using a fixed K_m of $0.9 \mu M$ in control female mice and in female runners. Data are means $\pm$ SEM and were analyzed using a U -test for dStr and an unpaired t -test with Welch's correction for NAc core ($*p < 0.05$; vs. control); data with a goodness of fit $R^2 < 0.90$ were excluded.

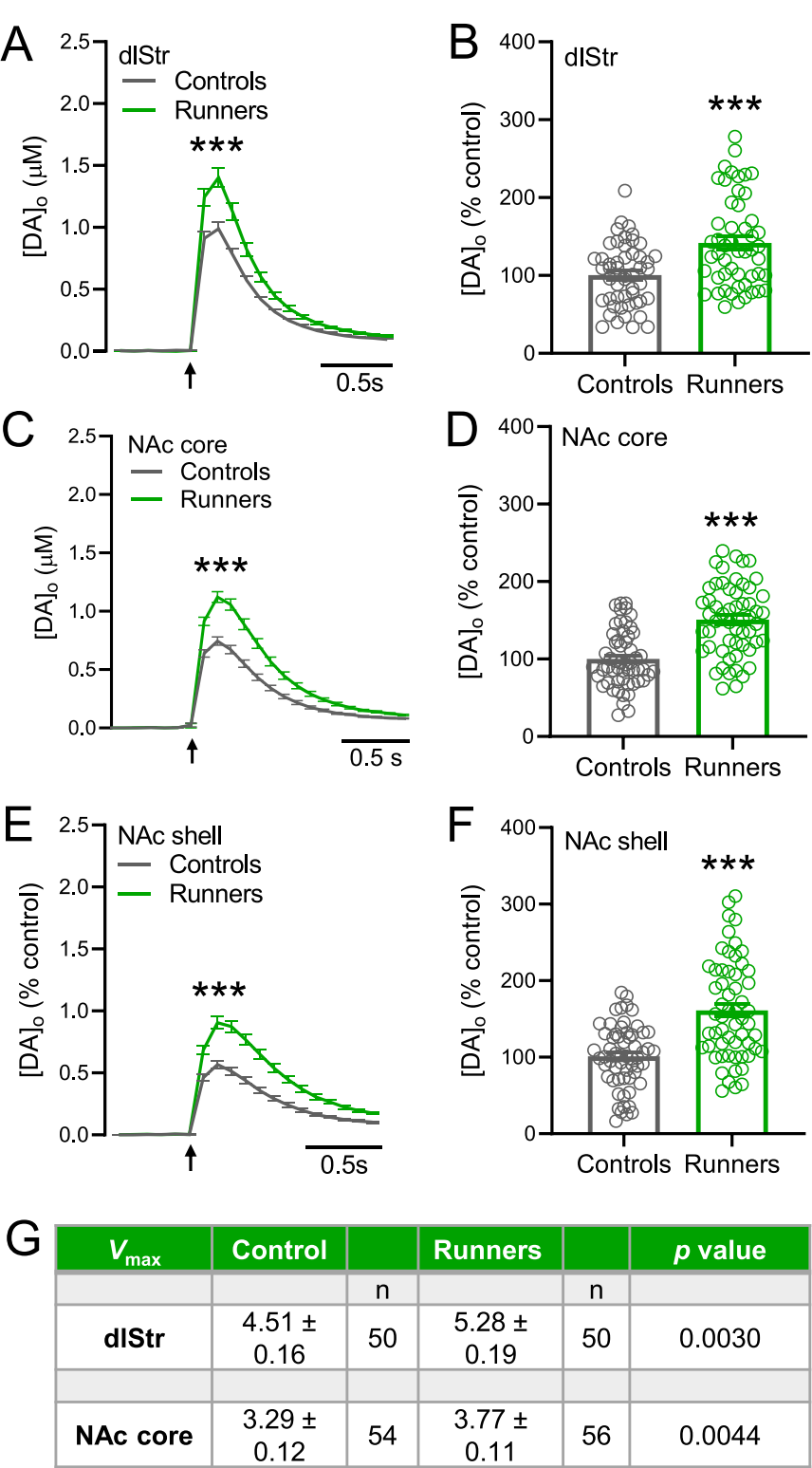


heterozygous BDNF deletion ($BDNF^{+/-}$)³⁴. The main target of BDNF in the brain is the tropomyosin receptor kinase B (TrkB) receptor^{61–63}. We find that TrkB agonist application in slices increases evoked $[DA]_o$ throughout the striatum, implying that BDNF elevation is not only necessary, but also sufficient for DA release amplification³⁴. These data are in line with earlier work showing that exogenous BDNF enhances

$[^3H]DA$ overflow from rat striatal tissue^{64,65} and increases evoked $[DA]_o$ in slices from $BDNF^{+/-}$ mice⁶⁶. Notably, BDNF levels in SNc and striatum fall in PD^{67–69}, and neuroprotective effects of exercise after MPTP⁷⁰, are lost in $BDNF^{+/-}$ mice^{70,71}.

Our investigations of the effect of exercise on DA release were initially motivated by increasing evidence of motor improvement in PD patients

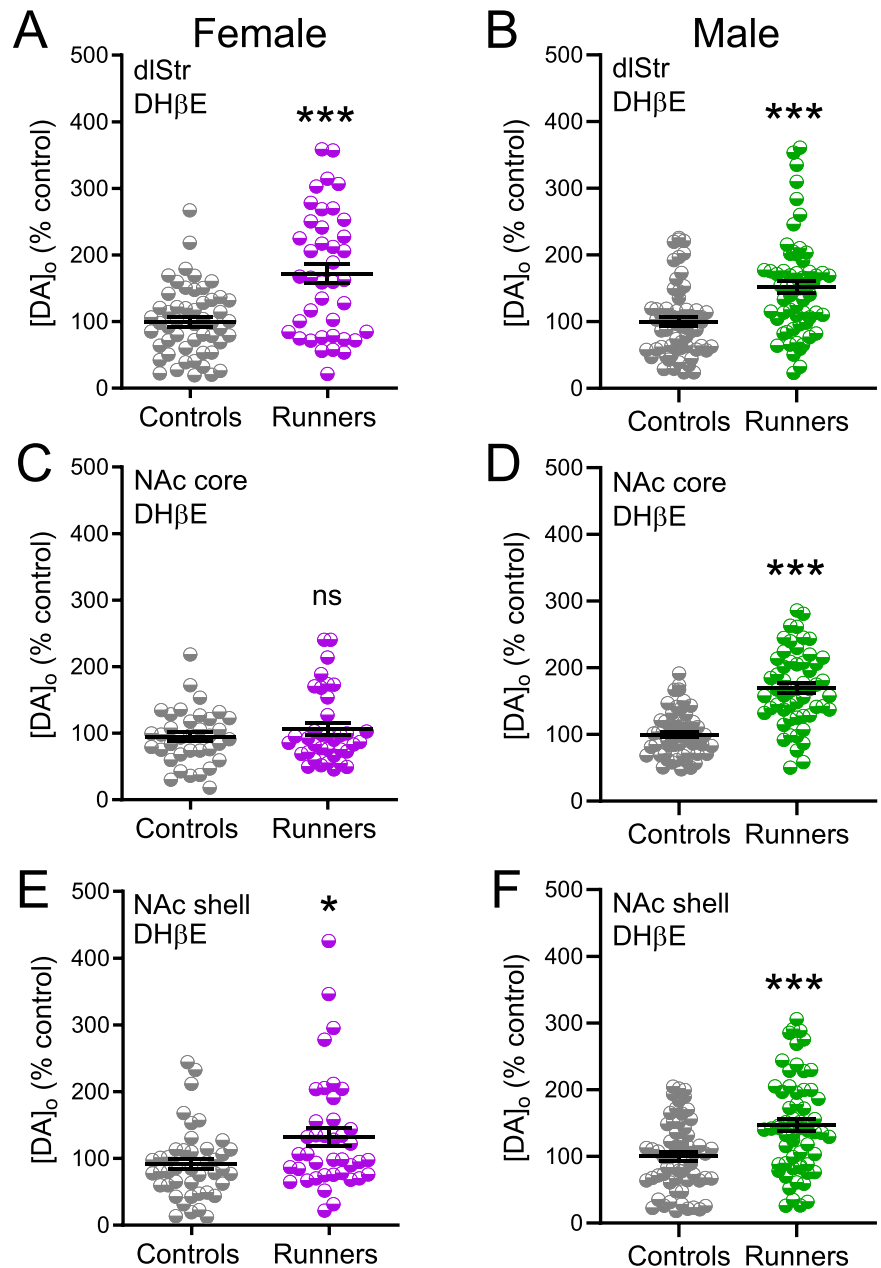
Fig. 3 | Increased evoked [DA]_o in striatal slices from male mice after 30 d of voluntary wheel running. **A, C, E** Averaged evoked increases in [DA]_o with SEM in dStr, NAc core (single-pulse stimulation) and NAc shell (5 pulse, 100 Hz) in ex vivo slices from male runners and controls. Arrows indicate time of stimulation. **B, D, F** Data summary for evoked [DA]_o in each region for runners vs. controls, normalized to mean peak [DA]_o for each region in controls. **A–F** *n* = 50–59 sites/region, 2 slices/mouse, 6 mice/group; ****p* < 0.001; unpaired *t*-tests. **G** *V*_{max} values derived for evoked striatal DA release using a fixed *K*_m of 0.9 μM in control male mice and in male runners. Data are means ± SEM and were analyzed using an unpaired *t*-test for each region (***p* < 0.01 vs. control); data with a goodness of fit *R*² < 0.90 were excluded.



who exercise. A variety of exercise programs have been shown to increase the health-related quality of life (HRQOL) status of individuals with PD³². Improvements have been reported in motor and also non-motor symptoms of PD^{25,32,72–83}. In rodent toxin models of PD, exercise has been shown not only to improve motor outcome, but also to slow DA neuron loss^{20–29,70,84,85}. Consistent with evidence for neuroprotection is the role identified for neurotrophic factors, including BDNF, as key players in the benefits of exercise^{14,34,71,86–90}.

The studies in aging mice reported here represent a key step in understanding a role for exercise-enhanced DA release in motor improvements in PD. Aging is frequently associated with a decline in mobility, as well as cognition^{2–4}. To assess the impact of exercise on mobility and other aspects of movement, we conducted several distinct motor-related behavioral tests on runners and controls. Consistent with the observed increase in DA release, we found that 30 days of exercise increased the average velocity of locomotor activity in the open field. Runner mice also

Fig. 4 | Evoked $[DA]_o$ in striatal slices from female and male runners and controls in the presence of a nAChR antagonist. Data summary for dlStr, NAc core, and NAc shell from female (A, C, E; fuchsia) and male (B, D, F; green) runners and controls. Data are normalized to mean peak evoked $[DA]_o$ in controls for each region in DH β E (1 μ M) (n = 38–60 sites/region, 2 slices/mouse, 6 mice/group; ns not significant, * p < 0.05, *** p < 0.001; unpaired U - or t -tests).



descended a vertical pole roughly twice as fast as controls. Thus, exercise improved mobility and coordination in runners compared to control mice. In contrast, dexterity, fine motor coordination and strength were unaffected in the same cohorts of mice. The lack of change in grip strength is informative, as it suggests that the observed increase in locomotor speed is not simply a consequence of increased muscle strength from the month of wheel-running exercise. This pattern of motor benefits is strikingly similar to that seen in PD patients who have exercise therapy vs. no intervention or placebo, who show improvement in gait outcomes, including speed, and also in balance^{31,91}.

The critical role of DA in restoring motor function is clearly demonstrated in the efficacy of L-DOPA, the primary treatment for PD, which is a DA precursor molecule that helps boost DA levels and function in humans and in rodent models of PD^{41,92}. However, L-DOPA does not slow disease progression and eventually leads to debilitating DOPA-induced dyskinesia^{92–95}. Consequently, the development of new directions for PD treatment and age-dependent motor decline in general is critical. Previous studies have found that in aging mice, long-intensity or mild-intensity physical exercise programs can improve cognitive functions and synaptic

plasticity^{96–98}, but short-term exercise programs using a treadmill do not⁹⁹. These findings point to the importance of developing appropriate exercise programs to obtain improvements in motor and cognitive functions in the human population, whether for healthy aging or as adjunct therapy for PD or other disorders^{48,78,83,100}. Current evidence implicates loss of DA as a contributing factor to aberrant plasticity underlying motor dysfunction in PD^{29,50,101,102} with reversal of this following DA replacement¹⁰³. Given these results, as well as the established role of DA in striatal circuitry and plasticity^{104,105}, our findings implicate exercise-enhanced endogenous DA release as a contributing factor in motor improvements seen with exercise, not only in mice, but also in aging humans.

Methods

Animal handling

Studies were conducted using male and female C57Bl/6J mice, 46–52 weeks of age, obtained from The Jackson Laboratory (JAX stock No. 000664). Animal procedures were in accordance with the National Institutes of Health guidelines and approved by the New York University Grossman School of Medicine Animal Care and Use Committee.

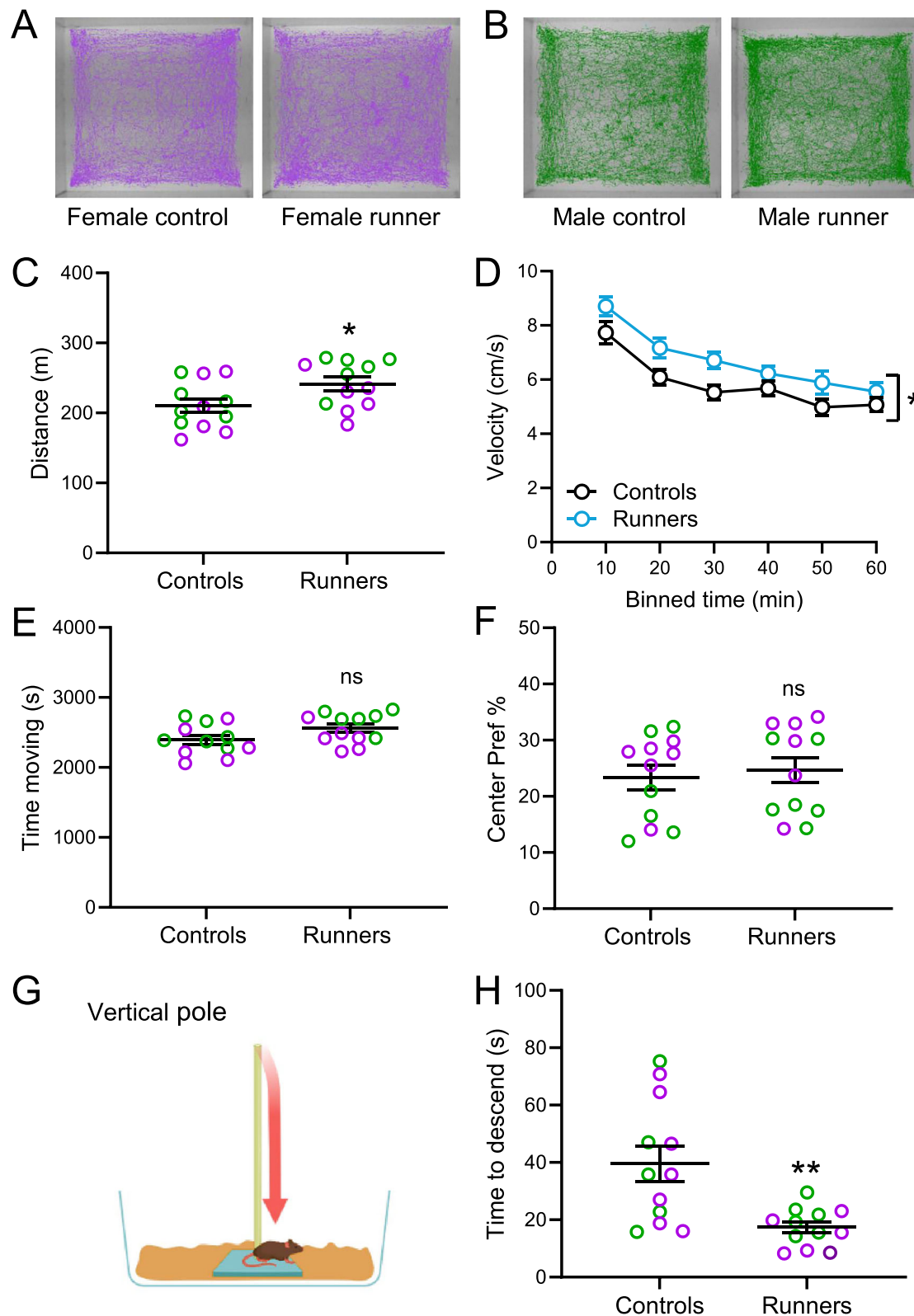


Fig. 5 | Increased motor speed and improved motor coordination in runners vs. controls. **A, B** Example of locomotor behavior in the open field for a female control and female runner and a male control and male runner recorded over 1 h. **C** Distance traveled for runners vs. controls (pooled data from both sexes, females in fuchsia, males in green) (* $p < 0.05$ runners vs. controls, $n = 12$ mice/group; unpaired t -tests). **D** Movement velocity (pooled data from both sexes) averaged in 10-min bins (runners vs. controls, $n = 12$ mice/group; 2-way ANOVA RM, Sidák's *post hoc* test).

E Time spent moving over 60 min for runners and controls (pooled data from both sexes; female in fuchsia, male in green) (ns not significant; $n = 12$ mice/group; unpaired t -tests). **F** Time spent in the center of the open field over 60 min of observation for runners and controls (pooled data from both sexes; female in fuchsia, male in green) ($n = 12$ mice/group; unpaired U -tests). **G** Pole test diagram. **H** Time to descend pole for runners and controls (pooled data from both sexes; female in fuchsia, male in green) (** $p < 0.01$, $n = 12$ mice/group; unpaired t -tests).

Housing and voluntary wheel-running exercise

For the wheel-running paradigm, mice were 46 weeks old upon arrival, and 52 weeks old at the end of the study. Cohorts of 12 male or 12 female mice were examined. Immediately after arrival, mice were housed individually in a modified 12 h reverse light/dark cycle, with lights off from 10:00 a.m. to 10:00 p.m. local time, with *ad libitum* access to food and water. After 14 d of acclimation to the light/dark cycle (Fig. 1A), mice were randomly assigned at staggered intervals to either runner (freely rotating wheel) or control (locked wheel) groups and given unlimited, voluntary access to the wheel and to food and water for 30 d, as in previous studies^{34,87,106} (Fig. 1A). All behavioral testing and striatal slice recording of evoked DA release was conducted in the early hours of the dark phase when mice are most active (e.g., Fig. 1B).

Custom vertical running wheels (11.5 cm diameter, 5.8 cm width), developed by the NYU Langone Rodent Behavior Core, were utilized within universal InnoVive home caging, as previously³⁴. The wheels were wire mesh, mounted on a 3D-printed suspension with low-torque double-shielded ball bearings. Rotational events were detected using a 5 mm neodymium magnet attached to the wheel paired with a calibrated Hall effect sensor (A3144) mounted to the suspension. Data acquisition was managed using Arduinos programmed with custom code (by ACM) to ensure precise and high-speed measurement of rotation events, which allowed monitoring of running activity (indicated by number of wheel revolutions) across the light-dark cycle. Body weight and food consumption were assessed for each subject at the beginning of each study, then once weekly thereafter. Mice were housed continuously with wheels in their home cages, except when they were removed briefly for weekly weighing or for motor behavior testing on days 27–30 (Fig. 1A).

Dopamine recording using FSCV

Procedures for preparing *ex vivo* brain slices were as described previously^{34,38,44,107}. Each animal was deeply anesthetized with isoflurane then the brain removed and placed into ice-cold HEPES-buffered artificial cerebrospinal fluid (aCSF)^{34,35} containing the following (in mM): 120 NaCl, 20 NaHCO₃, 10 glucose, 6.7 HEPES acid, 5 KCl, 3.3 HEPES sodium salt, 2 CaCl₂, and 2 MgSO₄, equilibrated with 95% O₂/5% CO₂. Coronal corticostriatal slices (300 μ m thickness) were cut in this solution using a Leica VT1200S vibrating blade microtome (Leica Microsystems). For studies of evoked DA release, slices were maintained in HEPES-buffered aCSF at room temperature for 1 h before transfer to the recording chamber. For recording, slices were maintained at 32°C and superfused with recording aCSF at a flow rate of 1.5 mL/min controlled by a peristaltic pump (Gilson). The recording aCSF had the following composition (in mM): 124 NaCl, 3.7 KCl, 26 NaHCO₃, 2.4 CaCl₂, 1.3 MgSO₄, 1.3 KH₂PO₄, and 10 glucose, equilibrated with 95% O₂/5% CO₂. Slices were allowed to acclimate to this environment for 30 min before recording was initiated^{34,35,38,44}. Increases in extracellular DA concentration ([DA]_o) were evoked by local electrical stimulation using a concentric stimulating electrode. Evoked increases in [DA]_o were quantified using 7- μ m diameter carbon-fiber microelectrodes made in-house¹⁰⁷ with a Millar voltammeter that generated a triangular FSCV waveform, −700 mV to +1300 mV then back to −700 mV vs. Ag/AgCl at a scan rate of 800 V/s, and recorded the resulting DA oxidation and reduction currents. Sampling frequency was 10 Hz; electrodes were out-of-circuit between scans to minimize DA adsorption¹⁰⁷. Scans were initiated immediately after the electrode was placed in the superfusing aCSF and were repeated continuously under the control of a Master-8 timing circuit (AMPI). Data were collected using a Digidata 1550B controlled by AxoScope 10.7 software (Molecular Devices). A single stimulus pulse (100-ms duration, 0.4-mA amplitude) was sufficient to evoke DA release in the dlStr and NAc core, whereas a train of five pulses at 100 Hz was required to elicit reliable release in the NAc shell^{34,42,44}. All electrodes were calibrated with a standard concentration of DA in aCSF in the recording chamber immediately after the last tissue measurement to indicate absolute evoked [DA]_o¹⁰⁷. The influence of exercise on DA release was assessed by comparing evoked [DA]_o between runners and controls. Two slices were examined from each animal, and evoked [DA]_o was recorded from 3–5 sites in the dlStr, in the NAc core, and

in the NAc shell in each of these. This multiple-site sampling protocol is used to minimize sampling bias that can occur because site-to-site variability in the amplitude of evoked [DA]_o in a given region can exceed average differences between slices^{34,38,42–44,108–110}. Initial sampling of evoked [DA]_o in two slices was completed in 20–30 min. Immediately afterward, superfusion with aCSF was either continued or the medium changed to aCSF plus a nAChR antagonist DH β E (1 μ M) for 20 min, then recording of evoked release was repeated to test the possible involvement of cholinergic regulation of DA release via nAChRs^{34,42–44}.

Determination of $V_{\max}$ from evoked [DA]_o transients in striatal slices

To evaluate voluntary exercise-induced changes in DAT-mediated DA uptake, the initial portion of the falling phase of single pulse evoked [DA]_o curves was fitted to the Michaelis-Menten equation to extract $V_{\max}$ (maximal uptake rate)¹⁰⁸. K_m (which is inversely related to the affinity of the DAT for DA) was fixed at 0.9 μ M^{43,108,111}. We evaluated $V_{\max}$ for dlStr and NAc core, but not for NAc shell because five-pulse stimulation rather than a single pulse was used in that region. Data with a goodness of fit $R^2 > 0.90$ were included in the $V_{\max}$ analysis.

Open field testing

Tests were conducted using an open-topped 40x40x40 cm acrylic arena with white walls and floor located in the center of the testing room. For testing, a mouse was removed from its home cage and placed in the center of the open field arena and allowed to explore freely for 60 minutes. The open field sessions were video recorded from above. Each animal's movements were subsequently tracked, and movement patterns were analyzed using Noldus Ethovision XT 11.5. For analysis, each mouse was tracked based on three body landmarks (nose point, body centroid and tail), with the floor of the arena divided into two different zones: a central zone (defined as the area equivalent to 4 inner squares resulting from dividing the arena in 16 10x10 cm squares) and a border zone (10 cm from each of the walls) consisting of four sides and four corners. The outcome measures included the distance moved (m); mean velocity (cm/s); time spent moving (s); movement defined as change in coordinates of the center point of the mouse for >2 consecutive seconds; and frequency of entry, distance traveled and time spent within specific zones. Extracted measures were analyzed as the average across the entire 60-min period, as well as more granularly using consecutive 10-min bins.

Vertical pole test

To assess motor coordination, a mouse was placed facing upwards at the top of a vertically-oriented, rough-surface plain steel rod (60 cm long and 1.2 cm in diameter), with the base of the pole placed in the center of the animal's home cage. Each mouse was initially given two training trials to learn to turn and descend the pole back into the home cage. Each mouse was subsequently assessed across a video-recorded, 4-trial session; trials were limited to 120 s with a minimum interval of 15 min between trials. The time required to turn to orient downward and the total time to descend the pole were recorded. The mean and median scores across the 4 trials for each measure were used for analysis.

Adhesive tape removal

For this test, a mouse was placed into an empty chamber of the same dimensions as its home cage and tested for adhesive tape removal from the forepaws to provide an index of possible changes in sensorimotor behavior. Small adhesive tape strips (0.3 cm x 0.4 cm) were applied on the forepaws of each animal at the same time so that they covered the hairless part of the paws. The time taken to make first contact with the tape, the paw used (left or right), the number of attempts, and the latency to remove the tape(s) were recorded. If the mouse did not contact or remove the tape(s) within 120 s, the trial was ended and the tape removed by the experimenter. Each mouse was given three adhesive tape removal trials, with a minimum interval of 15 mins between trials, and the results for each mouse averaged.

Grip strength

Muscle/grip strength was assessed as the maximal horizontal force generated by the subject while grasping a 6 × 10 cm stainless steel grid platform connected to a sensitive force sensor (Bioseb)^{112,113}. Two different grip strength indices were collected: forelimb only and combined forelimb and hindlimbs (all-limb). For the assessment of forelimb only grip strength, each mouse was removed from its home cage then given six testing trials with an inter-trial interval of 10–20 s. On each trial, the mouse was gently lowered onto the grid platform allowing only its forepaws to clasp onto the central top-half portion of the grid. Once both paws were grasping the grid, the mouse was pulled swiftly yet steadily away by the base of its tail which was held between the experimenter's thumb and forefinger. Mice were pulled with the torso in a horizontal position until the grip was released from the grid. All-limb grip strength trials to assess the coordinated contribution of forelimbs and hindlimbs were performed similarly except that all four paws of the mouse were placed centrally on the grid and the torso of the mouse kept parallel to the grid during pulling. A 40-min interval was given between forelimb and all-limb measurements. The maximum force achieved for each trial was recorded as the peak tension (g) at the time the grasp was released for each trial. For all assessments, the truncated means of six consecutive trials (highest and lowest scores removed) were taken as the index of grip strength. Body weight was determined after grip strength testing was complete to evaluate for possible co-variability with performance.

Statistics

All data are given as means ± SEM. Statistical analyses were conducted using Prism 10.4 (GraphPad Software, Inc.). For running activity, body weight measures, and food consumption, n = number of mice. Data were analyzed using 2-way ANOVA with repeated measures or with a mixed effects model using sex or exercise as between-subjects factor and timepoint as within-subjects factor (Supplementary Table 1). Significant interactions were decomposed with Sidák's multiple comparisons *post hoc* test. For FSCV data, n = number of recording sites from multiple-site sampling for each cohort of runners or controls. For each data set, normality was determined using D'Agostino-Pearson test (α = 0.05 for normality), and equal variance was assessed using F-tests. The influence of exercise on evoked [DA]_o and $V_{\max}$ in a given brain region and given sex was assessed using an unpaired Student's *t*-test (parametric) with or without Welch's correction, or Mann-Whitney *U*-test (nonparametric) as appropriate for the data. Velocity in the open field by time bin was analyzed by 2-way ANOVA with repeated measures and Sidák's multiple comparison *post hoc* test (Supplementary Table 2). Data for all other parameters in the open field, as well as other motor performance tests were analyzed using 2-way ANOVA with sex and exercise as between-subject factors and Sidák's multiple comparisons of selected pairs *post hoc* test. When data analysis did not show sex differences between controls or runners, data for both sexes were combined and unpaired Student's *t*-tests were used (Supplementary Table 2). It should be noted that in some cases, the general 2-way ANOVA indicated a sex difference, but no significant differences were seen between relevant pairs in *post hoc* comparisons (see Supplementary Table 2). Differences were considered significant when p < 0.05.

Data availability

All data used in this study are available upon request to the corresponding author.

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Author contributions

G.B., M.M., J.C.A., and M.E.R. designed the studies. G.B., M.M., and J.C.A. collected and analyzed DA release data. J.C.P. conducted analyses to determine $V_{\max}$ from DA concentration profiles. A.C.M. and B.G.-L. designed and conducted behavioral experiments and evaluated data from these. G.B. and J.C.P. conducted statistical analyses of all data. G.B., M.E.R. and J.C.P. drafted the manuscript, with editing and input from the other authors who approved the submission.

Competing interests

The authors declare no competing interests.

Additional information

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