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Higher striatal D2-receptor availability in aerobically fit older adults but non-selective intervention effects after aerobic versus resistance training

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ABSTRACT

There is much evidence that dopamine is vital for cognitive functioning in aging. Here we tested the hypothesis that aerobic exercise and fitness influence dopaminergic neurotransmission in the striatum, and in turn performance on offline working-memory updating tasks. Dopaminergic neurotransmission was measured by positron emission tomography (PET) and the non-displacable binding potential (BP_{ND}) of [^{11}C]raclopride, i.e. dopamine (DA) D2-receptor (D2R) availability. Fifty-four sedentary older adults underwent a six-months exercise intervention, performing either aerobic exercise or stretching, toning, and resistance active control training. At baseline, higher aerobic fitness levels (VO_{2peak}) were associated with higher BP_{ND} in the striatum, providing evidence of a link between an objective measure of aerobic fitness and D2R in older adults. BP_{ND} decreased substantially over the intervention in both groups but the intervention effects were non-selective with respect to exercise group. The decrease was several times larger than any previously estimated annual decline in D2R, potentially due to increased endogenous DA. Working-memory was unrelated to D2R both at baseline and following the intervention. To conclude, we provide partial evidence for a link between physical exercise and DA. Utilizing a PET protocol able to disentangle both D2R and DA levels could shed further light on whether, and how, aerobic exercise impacts the dopaminergic system in older adults.

1. Introduction

The population worldwide is growing increasingly older, with concomitant challenges to preserve brain health and cognitive functions. It has been suggested that dopamine (DA) and changes to DA D2 receptors in the striatum (D2R) is a key factor explaining reduced cognitive functions with increased age (Bäckman et al., 2006; Li et al., 2009). To counteract age-related decline in brain function, it has consistently been shown that exercise may play a key role (Boraxbekk et al., 2016; Colcombe et al., 2004; Stillman et al., 2016). However, the neurocognitive mechanisms explaining why improved fitness positively influences cognition are still not completely identified (Stillman et al., 2016). DA and D2R have been hypothesized to be important factors (Foley and Fleshner, 2008; Lin and Kuo, 2013; Zigmond and Smeyne, 2014), but still quite unexplored in healthy older humans.

Support for a DA hypothesis mainly comes from animal studies. For example, it has been shown that both acute (Hattori et al., 1994; Meeusen et al., 1997), and prolonged (de Castro and Duncan, 1985; Petzinger et al., 2007) periods of running elevates DA concentrations in rodents, the latter potentially reflecting downregulation or internalization of the DA transporter (DAT) (Fisher et al., 2004; Kim et al., 2016). Findings concerning D2R densities are more equivocal. Some studies support increased densities following training (Foley and Fleshner, 2008; Gilliam et al., 1984; MacRae et al., 1987), another study suggested down-regulation of D2R densities (de Castro and Duncan, 1985), and another reported no change in healthy mice but increased D2R in a

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mouse model (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP-mice) of PD (Vučković et al., 2010). As of yet, human studies are sparse, with one study failing to detect release of DA after an acute bout of exercise (Wang et al., 2000). Only two exercise interventions have been conducted. One of these included four PD patients (Fisher et al., 2013) and the other 19 methamphetamine users (Robertson et al., 2015). Both studies showed increased striatal D2R availability following exercise, but suffered from low sample sizes, only including patient groups, and only using 8 weeks of training. In addition, and important for the dopamine hypothesis in healthy older humans, both studies used the high affinity ligand [^{18}F]fallypride, which compared to [^{11}C]raclopride is more sensitive to D2R density (Guo et al., 2010), is less sensitive to endogenous DA release (Slifstein et al., 2010), and also to changes in basal synaptic levels of DA (Cropley et al., 2008).

Here, as the first study in healthy older adults, we wanted to test the hypothesis that improved cognitive functions following greater aerobic fitness is related to altered dopaminergic neurotransmission. Previously (Jonasson et al., 2017b), we showed that aerobic exercise increased performance on a cognitive score composite more so compared with active control training (balance, stretching and resistance circuit training). We also showed that changes in hippocampal volume (Jonasson et al., 2017b) and resting state brain connectivity (Flodin et al., 2017) were significantly related to improved oxygen uptake (VO_{2peak}), but did not differ between exercise groups. Hence, in addition to comparing intervention groups directly, individual variability in improvements of aerobic fitness regardless of exercise training group should also be considered when exploring the neurocognitive mechanisms behind exercise enhanced cognitive function in aging (Duzel et al., 2016; Stillman et al., 2016). We tested the following four hypotheses: (1) based on animal (Foley and Fleshner, 2008; Gilliam et al., 1984; MacRae et al., 1987) and human (Fisher et al., 2013; Robertson et al., 2015) studies, we predicted that VO_{2peak} would be positively associated with BP_{ND} at baseline. (2) based on the observation that the aerobic exercise group exhibited a significantly larger increase in VO_{2peak} compared to the active control group (Jonasson et al., 2017b) we predicted that the aerobic group would show a different pattern of change in BP_{ND}. Potentially, both reduced BP_{ND} due to increased endogenous DA (de Castro and Duncan, 1985; Foley and Fleshner, 2008; Petzinger et al., 2007; Zigmond and Smeyne, 2014), and elevated BP_{ND} due to increased D2R density (Foley and Fleshner, 2008; Gilliam et al., 1984; MacRae et al., 1987; Zigmond and Smeyne, 2014) could be expected. (3) similarly, we predicted that improved VO_{2peak} irrespective of group would influence [^{11}C]raclopride BP_{ND}. (4) based on the known association between DA and working memory, e.g. (Bäckman et al., 2011; Garrett et al., 2015), we predicted that a VO_{2peak}-associated reduction in BP_{ND} would mediate an effect of VO_{2peak} on improved working-memory updating performance (the Letter Memory, n-back, and Keep Track tasks).

2. Materials and methods

2.1. Participants and procedure

A detailed description of the sample and the procedure has been provided elsewhere (Jonasson et al., 2017b). In short, the full sample completing the intervention included a total of 58 participants. Four subjects were excluded in this study due to poor quality of PET registrations. The final sample included 54 participants, 26 in the aerobic group (mean age 68.55 ± 2.63 years, range 63.9–72.5 years, education 13.54 ± 3.56 years, 54% female), and 28 in the active control group (mean age 69.10 ± 2.87 years, range 64.3–77.7 years, education 13.46 ± 4.61 years, 57% female). Aerobic fitness, cognitive testing, magnetic resonance imaging (MRI), and positron emission tomography (PET) assessments were performed on separate days in fixed order. The time between fitness assessment and PET imaging ranged from 1 to 2 weeks, and the participants were not allowed to attend exercise during this time to avoid any acute exercise effects. At follow-up, some PET sessions were postponed 1–2 weeks due to scanner or tracer production malfunction. Affected participants were asked to attend additional exercise sessions in the time between completion of the other parts of the data collection and the postponed PET scan, up until one week before the newly scheduled PET session. The groups did not differ in any variable of interest or demographic characteristics at baseline (all $p > 0.05$). After baseline assessments, participants were randomized into performing supervised aerobic or stretching, toning, and resistance control training, 3 days a week, 30–60min per session, for six months. All participants gave their written informed consent. The regional ethical committee at Umeå University, Sweden, approved this study.

2.2. Aerobic fitness

Details regarding fitness assessments have been described in detail elsewhere (Jonasson et al., 2017b). In short, aerobic fitness was estimated from a standardized graded cycle (Monark 839E, Monark Exercise AB, Sweden) ergometer test performed by an experienced tester at the Sport Science Lab at Umeå School of Sport Sciences. Expired air was measured through a mouthpiece and analysis of O_2 uptake ($VO_2 = O_2$ ml/(kg * min)) was performed. VO_{2peak} was estimated as the highest VO_2 reached before test termination.

2.3. Aerobic training

In the aerobic training group, participants trained in order to increase their VO_{2peak} by walking or jogging on an athletic indoor track, cycling on stationary cycles, or using cross-trainers. The training was supervised by an exercise physiologist and performed in groups, three days a week (30–60 min), for six months. This setup had elements of interval training which could be particularly effective in improving brain function (Duzel et al., 2016). Their heart rate (HR) was monitored while they exercised and their training intensity was increased incrementally, from 40 to 80% of their estimated maximum HR.

2.4. Stretching, toning, and resistance control condition

In the stretching, toning and resistance control condition, participants performed circuit training involving various bodily exercises, 10 per session, two laps, aimed to improve muscle strength, flexibility, and balance without influencing VO_2 to a large extent. They made between 6 and 10 repetitions per exercise and each exercise had various levels of difficulty. The length and frequency of training sessions were the same as for the aerobic training group. Although the active control training was also supervised, HR was not monitored in the control group.

2.5. Cognitive tasks

The three computerized working-memory updating tasks from the original test battery (Jonasson et al., 2017b) were selected due to their reliance on striatum and DA (Bäckman et al., 2011; Garrett et al., 2015; O'Reilly, 2006). A short summary is given here, whereas the full descriptions of the tasks are described elsewhere (Jonasson et al., 2017b). In the Letter Memory task, subjects had to remember the four last letters (A-D) from a stimulus-array (eight blocks, 7–15 items long) where letters were presented one at a time. The dependent measure was percentage correct blocks. In the n-Back task, numbers (1–9) were presented, one number at a time (4 blocks). Subjects had to respond whether a number (1–9) was the same number as the number presented two stimuli back. The dependent measure for both tasks was accuracy (%). In the Keep Track task, subjects were again presented with a stimulus-array (six blocks), but this time had to remember the last presented word belonging to three or four target categories. The dependent measure was the sum of remembered words in completely accurate blocks.

2.6. Positron emission tomography

The Discovery PET/CT 690 (General Electric, WI, US) was used to acquire PET data, and the [^{11}C]raclopride ligand was produced in-house according to Good Manufacturing Practice. A thermoplastic mask (Positocasts Thermoplastic; CIVCO medical solutions; IA, US) was individually fitted to minimize head movements. The same mask was used both at baseline and after the intervention. To provide data for PET attenuation correction, a low-dose helical CT scan (20 mA, 120 kV, 0.8 s/revolution) was performed. Following the CT scan, a PET scan started at the time of an intravenous bolus injection of 250 MBq [11C]raclopride, and a 55-min 18-frame dynamic scan was acquired (9×120 s 3×180 s 3×260 s 3×300 s). Attenuation, scatter, and decay corrected PET images were reconstructed using the SharpIR algorithm, an ordered-subsets maximization algorithm with resolution modelling (Bettinardi et al., 2011), performed with 6 iterations, 24 subsets and 3.0 mm post filtering. The image volume consisted of 47 slices with a 25 cm axial field-of-view, 256x256 matrix, and a voxel size of 0.98x0.98x3.27 mm^3. The Full Width at Half Maximum (FWHM) resolution of this protocol has previously been measured to 3.20 mm (Wallstén et al., 2013).

2.7. MRI acquisition

Structural imaging was performed on a 3T 750 scanner (General Electric, WI, US) equipped with a 32-channel head coil. High-resolution T1-weighted structural images were collected with a 3D fast spoiled gradient echo sequence (180 slices with a 1 mm thickness, TR 8.2 ms, TE 3.2 ms, flip angle 12°, field of view 25×25 cm). Finally, diffusion data was collected with a diffusion tensor imaging (DTI) T2-weighted spin-echo planar sequence (64 slices, TR 8000 ms, TE 84.4 ms, flip angle 90°, field of view 25×25 cm, b 1000 s/mm 2; six B0 images). Images were acquired in two repetitions, with 32 independent directions.

2.8. Preprocessing

Structural T1. SPM12 (Wellcome Department of Imaging Science, Functional Imaging Laboratory, http://www.fil.ion.ucl.ac.uk/spm) Geodesic shooting (Ashburner and Friston, 2011) was used to normalize to create warp fields to the Montreal neurological institute (MNI) template in SPM. A striatum seed used for probabilistic tractography was created by including voxels from putamen, caudate, and nucleus accumbens, segmented with Freesurfer version 5.3 (Fischl et al., 2002).

Diffusion Tensor Imaging. Striatum has a complicated functionality and different parts of striatum are involved in disparate functions such as reward, working-memory and sensorimotor functions, and commonly divided according to function rather than anatomy when specific functions are tested (Egerton et al., 2009). The functional segregation has been shown both anatomically (Haber et al., 2000), by resting-state functional MRI (Gordon et al., 2015) and by the different striatal responses elicited by DA-related drugs (Martinez et al., 2003). For this reason, DTI was used solely to create functionally segmented regions-of-interests (ROI) based on a probabilistic tractography approach described elsewhere (Johansen-Berg et al., 2005; Tziortzi et al., 2014). No DTI metrics were used for any statistical analyses. In short, the DTI-weighted data was preprocessed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library package FSL (http://www.fmrib.ox.ac.uk/fsl). DTI images from the two scans were concatenated and eddy current corrected. We then ran a model estimating crossing fibers within voxels on eddy current corrected and betted volumes (Behrens et al., 2007). Probabilistic tractography was made with individual freesurfer-derived left and right striatum as seeds. Fibers from each seed voxel were tracked until they terminated in either a frontal motor, associative, or limbic cortical target mask (Tziortzi et al., 2014). Each striatal voxel was then assigned to the target having the highest number of terminating fibers. The subject specific results were then normalized to common space by first applying rigid-body parameters from a fractional anisotropy to T1 registration, using *FMRIB's Linear Image Registration Tool* (FLIRT), and then applying non-linear deformation fields from *FMRIB's Nonlinear Image Registration Tool* (FNIRT) from T1 to MNI. Each subject's functionally segmented striatum was then summed for each of the three targets. The sample-specific functional striatum segmentation was finally produced by assigning each voxel to the target function with the highest rate of subjects. All computations were performed on resources provided by the Swedish National Infrastructure for Computing (SNIC) at Umeå University (HPC2N).

Positron Emission Tomography. PET images were processed using the following steps. 1) Movement correction using *FMRIB's Linear Image Registration Tool* (FLIRT). 2) FLIRT was also used to estimate the rigid transformations between the PET and T1 volumes. 3) The Freesurfer segmentation was registered to PET space. 4) The probabilistic tractography derived striatal subdivisions were normalized to native T1 space using the inverse warp created using shoot, and then registered to native PET space. 5) BP_{ND}, i.e. D2R availability, using ROI-based reference Logan graphical analysis with linear regression performed from time 18–55 min (Logan, 2000) with the Freesurfer segmented cerebellum gray matter as reference region. BP_{ND} was calculated for the striatum, for the three functional striatal ROIs derived from probabilistic tractography, and for a control region, the brainstem, also derived from Freesurfer. The brainstem was selected as a control region as it is a large subcortical structure with low binding and for which no changes were expected. This served to control for potential effects induced by the intervention on cerebellum uptake, which could bias longitudinal estimates of BP_{ND}. Considering the heterogeneity of the brainstem and its low binding, individual differences in brainstem BP_{ND} or changes in BP_{ND} should not be interpreted as reflecting true differences in brainstem D2R. BP_{ND} estimates in the left and right hemisphere were averaged for each ROI. To reduce the impact of partial volume effects, PET images were reconstructed with an algorithm using resolution modelling. Although further partial volume corrections (PVC) can improve image data, there are also problems with many PVC methods (Hutton et al., 2013), e.g. sensitivity to registration and/or segmentation errors (Frouin et al., 2002). Furthermore, a homogenous uptake within regions are also assumed by many methods. For the striatum, the observation of a rostro-caudal gradient of [^{11}C]raclopride binding within the striatum (Alakurtti et al., 2013) would violate that assumption. Finally, the differences in the volumes of the striatal ROIs between time points were non-significant and negligible, −1.42 to −1.76%, all $p > 0.05$. We have previously shown with an anthropomorphic brain phantom that a difference in the striatal volume by as much as 10% induces a bias of less than 1% of BP_{ND} (Jonasson et al., 2017a). Considering that an age-homogenous and healthy sample was used no further PVC was applied to the PET data.

2.9. Statistical analyses

All analyses were performed using *R statistics* (https://www.R-project.org/). To analyze the effect of the intervention on BP_{ND}, we performed repeated measures *Analysis of Variance* (ANOVA) with group and time as factors on BP_{ND} in the striatum, and the three functional subdivisions. To analyze the influence of aerobic fitness (VO_{2peak}) on D2R availability (BP_{ND}), partial correlations were performed on baseline BP_{ND} and VO_{2peak}, controlling for ROI volume. Correlations were also performed on the change in VO_{2peak} and BP_{ND}. One subject was excluded from VO_{2peak} analyses due to having a baseline $VO_{2peak} > 3$ SD from the mean. As BP_{ND} between the striatum and its subdivisions were highly correlated at baseline ($r > 0.8$) we did not correct for multiple comparisons at baseline. We considered the correlations between changes in VO_{2peak} and BP_{ND} significant after correcting for three tests ($p < 0.017$). The correlations involving the working memory tasks were considered significant after correcting for nine tests ($p < 0.006$). Finally, we conducted exploratory analyses to test whether the two exercise groups had differential relations between changes in VO_{2peak} and BP_{ND}. This was

done by testing for the difference between the respective groups' correlations with Fisher r-to-z transformations implemented in the psych package (https://CRAN.R-project.org/package=psych).

2.10. Data and code availability statement

All code used to process and analyze the image data as well as the data and code used for statistical analyses will be made available on OSF (https://osf.io/xfnd6/?view_only=ef850eee710f42c3a54f488214277a7e) and if not yet available on OSF, is available upon request from the corresponding author.

3. Results

3.1. The relationship between baseline aerobic fitness and D2R

We first tested the prediction that an objective measure of aerobic fitness ($VO_{2peak} = O_2$ ml/kg*min) estimated with a cycle ergometer test would be positively associated with D2R availability (BP_{ND}) as measured by [11C]raclopride PET and Logan graphical analysis (Logan, 2000) (see Table 1 and Fig. 1). Partial correlations controlling for volume confirmed this hypothesis by showing that VO_{2peak} was significantly and positively associated with BP_{ND} in the striatum, $r(54,1) = 0.283$, $p = 0.040$. The association was significant also after controlling for age, sex, and education, $r(54,4) = 0.282$, $p = 0.047$. To investigate whether the association was general throughout the striatum, or specific to certain parts of the striatum, we repeated the analysis for each striatal functional subdivision, limbic (LST), associative (AST), and sensorimotor (SMST). The association between BP_{ND} and VO_{2peak} was specifically seen in AST, $r(54,1) = 0.302$, $p = 0.028$. This effect was present also after controlling for age, sex, and education, $r(54,4) = 0.322$, $p = 0.023$. BP_{ND} in the LST or the SMST were not associated with VO_{2peak}, $r(54,1) = 0.140$, $p = 0.317$; $r(54,1) = 0.199$, $p = 0.154$ respectively. As a control analysis, the brain stem was added to exclude a general effect on BP_{ND} from potential aerobic-fitness induced differences in e.g. tracer kinetics. Brain stem BP_{ND} was unrelated to VO_{2peak}, $r(54,1) = 0.036$, $p = 0.800$.

3.2. Group differences in D2R

The aerobic exercise group improved their VO_{2peak} (Table 1) compared to the active control group, $F(1,52) = 6.25$, $p = 0.016$. The prediction of a significant group (aerobic exercise vs. active controls) difference with respect to changes in BP_{ND} following the intervention was not confirmed. Repeated-measures ANOVA revealed a significant effect of time on BP_{ND} in the striatum, $F(1,52) = 16.85$, $p < 0.001$, but no interaction $F(1,52) = 0.09$, $p = 0.77$. The same pattern was observed in the LST, $F(1,52) = 9.58$, $p = 0.003$, interaction $F(1,52) = 0.07$, $p = 0.80$, AST, $F(1,52) = 5.81$, $p = 0.019$, interaction $F(1,52) = 0.21$, $p = 0.65$, and SMST, $F(1,52) = 10.98$, $p = 0.002$, interaction $F(1,52) = 0.32$, $p = 0.58$. BP_{ND} in the brainstem, our control region, did not change over time, $F(1,52) = 0.001$, $p = 0.98$, and there was no interaction $F(1,52) = 0.275$, $p = 0.60$. Both groups exhibited a significant reduction in BP_{ND} in the striatum after six months of exercise, 1.82% for the aerobic, and 2.11% for the active control (see Table 1 for means and paired t-tests). Notably, this reduction is several times greater than the predicted annual decline in D2R density in older adults where estimates range from 0.2% to 0.8% (Seeman et al., 1987; Volkow et al., 1996). A recent meta-analysis estimated the annual rate of decline to 0.8% (Karrer et al., 2017). Adjusting for the time between the two PET scans led to an estimated annual rate of decline of 3.03% for the aerobic group and 3.55% for the control group.

Table 1
Summary of the non-displaceable binding potential (BP_{ND}) of [^{11}C]raclopride, cognition, and aerobic fitness (VO_{2peak}) at baseline and after six months for the aerobic exercise and stretching, toning, and resistance active control group (M±SD).

	Aerobic n = 26			Active Control n = 28		
	Baseline	6-months	Paired *t*-test	Baseline	6-months	Paired *t*-test
BP_{ND}						
Striatum	2.53 ± .33	2.49 ± .36	**$t(25) = -2.24$, $p = .03$**	2.53 ± .29	2.48 ± .27	**$t(27) = -3.95$, $p < 0.01$**
LST	2.21 ± .32	2.14 ± .36	**$t(25) = -2.90$, $p < 0.01$**	2.18 ± .38	2.12 ± .34	$t(27) = -1.78$, $p = 0.09$
AST	2.29 ± .45	2.25 ± .42	$t(25) = -1.19$, $p = 0.24$	2.29 ± .33	2.22 ± .30	**$t(27) = -2.36$, $p = .03$**
SMST	3.01 ± .40	2.96 ± .41	$t(25) = -1.60$, $p = 0.12$	3.02 ± .32	2.95 ± .33	**$t(27) = -3.48$, $p < 0.01$**
Brainstem	0.16 ± .04	0.16 ± .04	$t(25) = 0.46$, $p = 0.65$	0.16 ± .04	0.16 ± .04	$t(27) = -0.30$, $p = 0.76$
Cognition						
Letter Memory (%)	26.9 ± 18.3	22.1 ± 19.5	$t(25) = -1.21$, $p = 0.24$	28.6 ± 22.8	28.2 ± 16.8	$t(26) = -0.34$, $p = 0.74$
2-Back (%)	67.8 ± 20.9	75.0 ± 18.3	**$t(25) = 2.69$, $p = .01$**	72.4 ± 20.8	75.2 ± 21.8	$t(25) = 1.03$, $p = 0.31$
Keep Track (No.)	13.4 ± 2.6	13.4 ± 2.1	$t(25) = 0.09$, $p = 0.93$	12.9 ± 3.4	12.8 ± 3.6	$t(27) = -0.21$, $p = 0.83$
Cognitive Score (z)	−0.02 ± .45	0.25 ± .51	**$t(25) = 6.02$, $p < 0.01$**	0.02 ± .62	0.08 ± .69	**$t(27) = 3.12$, $p < 0.01$**
Aerobic fitness						
VO_{2peak}	21.46 ± 4.22	27.63 ± 5.44	**$t(25) = 8.28$, $p < 0.01$**	19.71 ± 3.16	23.38 ± 5.08	**$t(27) = 5.45$, $p < 0.01$**
Additional						
BMI	25.90 ± 3.27	25.46 ± 3.08	**$t(25) = 3.36$, $p < 0.01$**	26.36 ± 2.91	26.45 ± 2.81	$t(27) = -0.61$, $p = 0.55$
Attendance (%)		85.42 ± 9.53			81.99 ± 10.48	$t(51.98) = 1.26$, $p = .21$[a]

Note. LST = limbic striatum, AST = associative striatum, SMST = sensorimotor striatum, $VO_{2peak} = O_2$/ml/(kg * min), BP_{ND} = non-displaceable binding potential of [^{11}C]raclopride using Logan graphical analysis. BP_{ND} was averaged across hemispheres. [a]Welch's *t*-test for comparing group differences in exercise attendance.

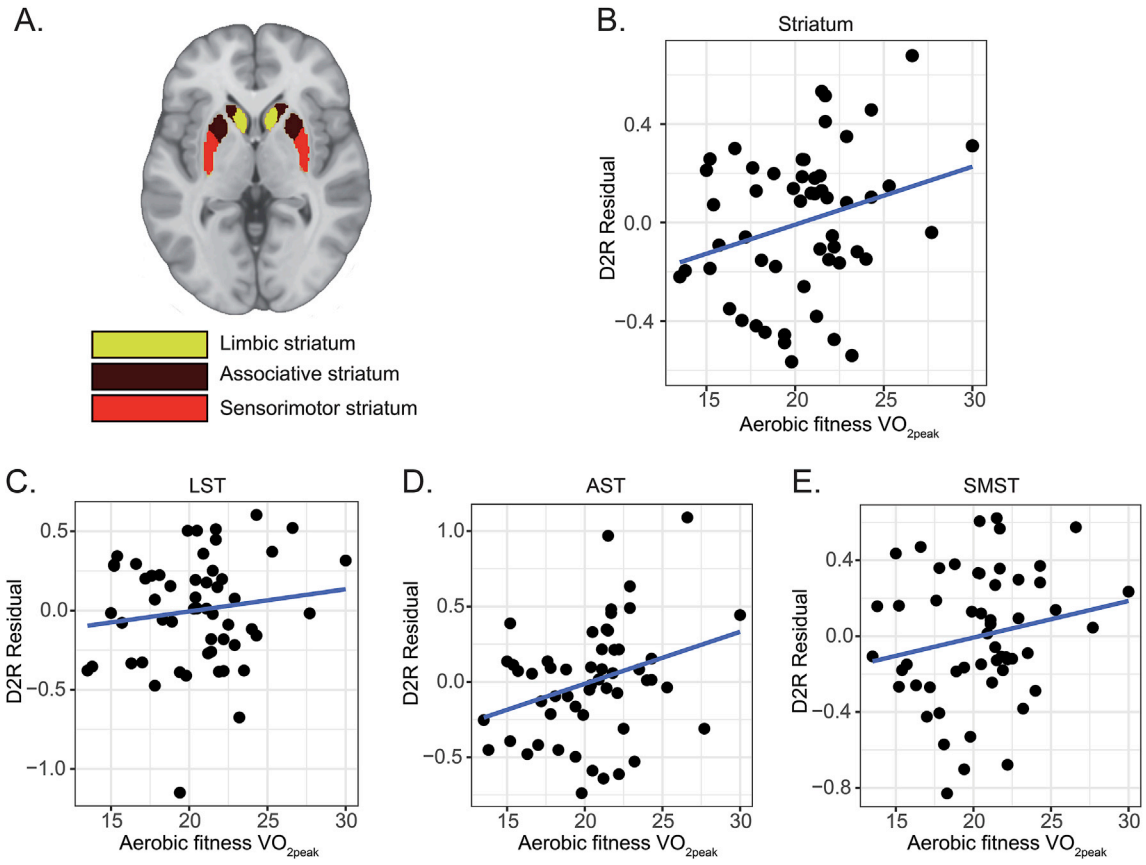

Fig. 1. Aerobic fitness is significantly associated with [^{11}C]raclopride BP_{ND} in the striatum in older individuals. (A) Functional subdivision of the striatum into limbic (LST), associative (AST) and sensorimotor striatum (SMST) from diffusion tensor imaging based probabilistic tractography (Tziortzi et al., 2014). The residual (controlling for the volume of the structure, age, sex, and education) BP_{ND} estimated with [^{11}C]raclopride positron emission tomography (PET) is depicted along the y-axis (D2R Residual), and aerobic fitness ($VO_{2peak} = O_2$/ml/(kg * min)) is depicted along the x-axis for the (B) striatum averaged across hemispheres, (C) limbic striatum, (D) associative striatum, and (E) sensorimotor striatum.

Assuming that this decrease is not due to other factors impacting D2 expression, this suggests that reduced BP_{ND} is due partly to increased DA rather than solely decreased D2R density. However, if DA has increased, it is likely that part of the reduction in BP_{ND} can also be accounted for by internalization of D2R (Laruelle, 2000) considering [^{11}C]raclopride's lower affinity to internalized compared to surface D2R. In other words, one should be cautious in trying to infer the amount of the tentative DA increases from changes in BP_{ND}. What is more, although the reduction of BP_{ND} was large, some individuals actually increased BP_{ND} over time (Fig. 2), raising the possibility that individual differences in e.g. genotype, may trigger different responses to the exercise regimen (discussed under the "*Aging, dopamine, and cognition*" subsection).

3.3. Relationship between changes in aerobic fitness and D2R

Next, we investigated the prediction that changes in aerobic fitness would increase DA (de Castro and Duncan, 1985; Foley and Fleshner, 2008; Meeusen et al., 1997), which would be translated into a reduction

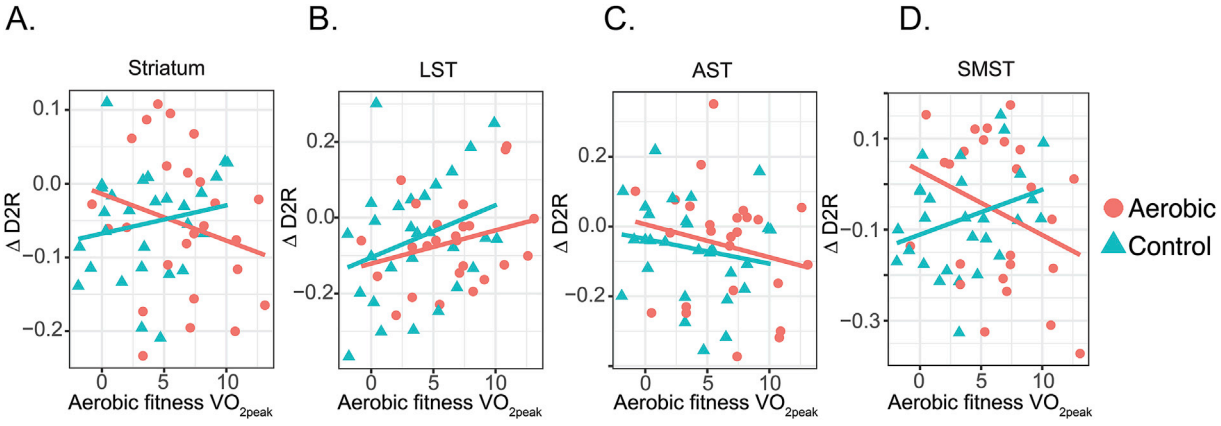

Fig. 2. Post-intervention changes in aerobic fitness and [^{11}C]raclopride BP_{ND} in the striatum. The change in BP_{ND} estimated with [^{11}C]raclopride is depicted along the y-axis (ΔD2R), and aerobic fitness (VO_{2peak} = O2/ml/(kg * min)) is depicted along the x-axis for the (A) striatum, (B) limbic striatum (LST), (C) associative striatum (AST), and (D) sensorimotor striatum (SMST) averaged across hemispheres.

in BP_{ND}. We examined the relationship in the entire striatum as well as in the sub-divisions for each group respectively (Fig. 2). Although the direction of effects was generally negative in the aerobic group, the change in VO_{2peak} did not show any significant relationship to change in BP_{ND}: Striatum, $r(23) = -0.23$, $p = 0.26$, LST, $r(23) = 0.28$, $p = 0.18$, AST, $r(23) = -0.20$, $p = 0.33$, and SMST, $r(23) = -0.31$, $p = 0.13$. In the active control group the correlations were generally positive, but also non-significant: Striatum, $r(26) = 0.19$, $p = 0.33$, LST, $r(26) = 0.30$, $p = 0.12$, AST, $r(26) = -0.18$, $p = 0.36$, and SMST, $r(26) = 0.31$, $p = 0.11$. Controlling for age, sex, education, and the change in volume between time points did not alter the overall pattern of relationships. Only the correlation between changes in aerobic fitness and SMST for the active control group showed a significant positive association after controlling for age, sex, education, and change in volume, $r(28,4) = 0.52$, $p = 0.009$ ($p = 0.072$ adjusted for eight tests). Additional exploratory analyses were performed to test whether the effect of aerobic fitness on BP_{ND} differed depending on exercise group. To that end, we used the Fisher r-to-z transformation to test for differences between correlations. The groups experienced a different pattern with regards to changes in VO2peak and BP_{ND} specifically in the SMST, $z = -2.19$, $p = 0.029$, where the aerobic group showed a negative relation and the active control group a positive relation. This effect became even more evident when controlling for, age, sex, education, and the change in volume between time points $z = -3.23$, $p = 0.001$ ($p = 0.005$ adjusted for four tests).

3.4. The relationship between changes in BP_{ND} and working-memory updating performance.

We next tested the prediction that aerobic fitness-induced changes in the D2R system would be related to improved working-memory updating. Considering the updating function of striatum (Dahlin et al., 2008; O'Reilly, 2006), and its sensitivity to DA (Bäckman et al., 2011; Cools and D'Esposito, 2011; Garrett et al., 2015) we expected that an increase in DA, shown by reduced $BP_{ND,}$ would be related to improved working-memory updating performance. Conversely, none of the groups displayed any significant correlations between changes in BP_{ND} and performance in either of the three updating tasks. The trend was generally negative for Letter memory, the most difficult task, in the aerobic group: Striatum, $r(24) = -0.28$, $p = 0.17$, LST, $r(24) = -0.05$, $p = 0.80$, AST, $r(24) = -0.31$, $p = 0.12$, and SMST, $r(24) = -0.06$, $p = 0.77$ whereas the pattern was more mixed in the active control group: Striatum, $r(25) = 0.11$, $p = 0.60$, LST, $r(25) = 0.13$, $p = 0.52$, AST, $r(25) = -0.11$, $p = 0.58$, and SMST, $r(25) = -0.01$, $p = 0.98$. Changes in 2-back performance was unrelated to BP_{ND} in the aerobic group: Striatum, $r(24) = 0.02$, $p = 0.91$, LST, $r(24) = -0.13$, $p = 0.51$, AST, $r(24) = 0.10$, $p = 0.61$, and SMST, -0.07, $p = 0.73$, and for the active control group: Striatum, $r(24) = -0.25$, $p = 0.20$, LST, $r(24) = 0.16$, $p = 0.44$, AST, $r(24) = -0.27$, $p = 0.18$, and SMST, $r(24) = -0.25$, $p = 0.22$. For the keep track task, the aerobic group showed a generally positive pattern: Striatum, $r(24) = 0.32$, $p = 0.12$, LST, $r(24) = 0.08$, $p = 0.69$, AST, $r(24) = 0.28$, $p = 0.17$, SMST, $r(24) = 0.25$, $p = 0.22$, but not the active control group: Striatum, $r(26) = 0.05$, $p = 0.78$, LST, $r(26) = 0.07$, $p = 0.73$, AST, $r(26) = -0.15$, $p = 0.46$, SMST, $r(26) = 0.10$, $p = 0.63$. As there were no significant associations between BP_{ND}, VO_{2peak}, and working-memory updating performance we do not report any planned mediation models.

4. Discussion

In a sample of healthy older adults, we studied the influence of aerobic fitness (VO_{2peak}) and 6-months supervised exercise on D2R availability (BP_{ND}) in the striatum using PET and [11C]raclopride. We made four predictions: (1) that VO_{2peak} would be associated with higher BP_{ND} at baseline; (2) that a group by time interaction would differentiate aerobic from active control training with respect to changes in BP_{ND}; (3) that increased VO_{2peak} would be associated with reduced BP_{ND}; (4) that reduced BP_{ND} would mediate improved working memory performance following improved VO_{2peak}. The results partially confirmed our hypotheses. Specifically, we observed that older adults with higher VO_{2peak} at baseline had higher striatal BP_{ND}. The intervention, however, did not result in a difference in BP_{ND} between groups, improvements in VO_{2peak} did not predict changes in BP_{ND}, and BP_{ND} did not predict improvements in working-memory updating. Hence, based on the results of this study, there is limited evidence suggesting that performing aerobic exercise at an old age influences striatal D2R and its related updating function. Nonetheless, the reduction of [^{11}C]raclopride BP_{ND} was several times greater than any pre-existing estimation of annual rate of decline, suggesting that DA may have increased. However, the intervention effects were non-selective after aerobic exercise versus stretching, toning, and resistance exercise. Below, we provide a thorough discussion of the results, and lack of effects thereof, particularly in light of the methodology used, and providing suggestions for future projects aiming to study the fitness-dopamine-cognition hypothesis.

4.1. Aerobic fitness and [^{11}C]raclopride BP_{ND}

4.1.1. Baseline relationships

In this study, we observed associations between VO_{2peak} on the dopaminergic system in striatum at baseline but not across the six months intervention. At baseline, VO_{2peak} and BP_{ND} were positively related, suggesting that being aerobically fit may preserve a dopaminergic system otherwise prone to age-related decline (Seeman et al., 1987; Volkow et al., 1998). Two recent cross-sectional studies support the notion that physical activity in aging may preserve the striatal dopaminergic system (Dang et al., 2017; Köhncke et al., 2018). With an objective measure of aerobic fitness, $VO2_{peak}$, our results suggest that the aerobic component could be important for explaining the relationship previously observed between physical activity and striatal D2R. Other research in animals have implicated that aerobic exercise may have several positive and neuroprotective effects on the dopaminergic system in striatum that could influence D2R over time. For instance, the action of brain derived neurotrophic factor (BDNF) stimulated by exercise may protect against inflammation-induced loss of DA neurons (Wu et al., 2011). Moreover, aerobic exercise could induce hypoxia in the brain, thereby altering the transcription of Hypoxia Inducible Factors (HIF) in the dopaminergic neurons located in substantia nigra (SN) pars compacta (Smeyne et al., 2015). These alterations may protect against later oxidative stress and promote cell survival. Preservation of midbrain dopaminergic neurons may thus promote striatal D2R system integrity due to the dopaminergic input originating from midbrain cells (Haber et al., 2000), and could be important in explaining the positive association between VO_{2peak} and BP_{ND} observed in the striatum at baseline. However, the lack of longitudinal effects warrants caution in interpreting the observed association.

4.1.2. Intervention effects

Our prediction of a specific impact of aerobic exercise and fitness on BP_{ND} relative to stretching, toning and resistance training was not confirmed. Performing aerobic exercise compared to active control training did not have a differential effect on BP_{ND} in any striatal region. These results are in line with a previous study with this cohort, not finding any effects of the intervention or improved aerobic fitness on striatal resting-state connectivity (Flodin et al., 2017). Nevertheless, BP_{ND} decreased substantially in striatum for both groups over the six months training period (Table 1). This reduction was several times greater than would be expected from normal age-related decline in D2R over six months, where annual estimates range from 0.2% to 0.8% (Seeman et al., 1987; Volkow et al., 1996), and a recent meta-analysis has estimated the rate to be 0.8% (Karrer et al., 2017). Given the known inverse relations between DA levels and [^{11}C]raclopride binding (Hietala et al., 1999; Verhoeff et al., 2002), this raises the possibility that the large reduction observed on BP_{ND} could be due to increased DA. Considering extant animal work, increases in striatal DA concentrations have been

observed in healthy rodents following prolonged periods of exercise (de Castro and Duncan, 1985; Foley and Fleshner, 2008; Petzinger et al., 2007), potentially due to downregulation of nigral D2-autoreceptors (Foley and Fleshner, 2008), internalization of DAT (Fisher et al., 2004; Foley and Fleshner, 2008; Kim et al., 2016), and a mechanism where calcium released from bone tissue reaches the brain via the blood and activates calcium/calmodulin dependent dopamine synthesis (Sutoo and Akiyama, 2003). Synaptic levels of DA are not only moderated by synthesis and release of DA, but also from reuptake by the DA transporter (DAT). In the rat, although basal levels of DA did not increase from chronic exercise, there was a blunted release of DA following an amphetamine challenge (Marques et al., 2008). Conversely, DA levels remained at higher levels over time, suggesting reduced reuptake of DA from chronic exercise. Hence, the large reduction in BP_{ND} observed after the intervention in the present study is potentially due to fewer receptors available for [^{11}C]raclopride binding because of elevated levels of endogenous DA. Importantly, as 1–2 weeks passed between the last exercise session and the PET scan in the present study, increased DA levels from an acute bout of exercise are unlikely to explain the reduction in BP_{ND}. Increases in DA from an acute bout of exercise are transient and in the order of hours rather than days (Hattori et al., 1994), and the only [^{11}C]raclopride study performed on human subjects did not find an effect on binding 5–10 min after vigorous running (Wang et al., 2000).

Our finding a large reduction in BP_{ND} is in contrast to two previous exercise interventions in metamphetamine abusers and PD patients showing increased [^{18}F]fallypride D2R availability in striatum following mixed and aerobic exercise respectively (Fisher et al., 2013; Robertson et al., 2015). Hence, it seems less likely that the large reduction observed on BP_{ND} is due to downregulation of D2R, although this has been observed in young mice after exercise (de Castro and Duncan, 1985). Several differences between the studies should be highlighted however. A general point is that we studied a healthy sample of elderly rather than populations with known dopaminergic deficits. In the first study, Parkinson's Disease (PD) patients ($n = 4$), were randomized to 8 weeks of treadmill training, or to no-contact (passive) controls (Fisher et al., 2013). Petzinger and colleagues previously found that healthy mice and PD mice differ with respect to striatal DA concentrations following exercise, where only healthy mice increased dopamine levels (Petzinger et al., 2007; Vučković et al., 2010). This may be important considering that [^{11}C]raclopride is more sensitive to endogenous levels of DA compared to the high-affinity ligand [^{18}F]fallypride (Cropley et al., 2008; Ginovart et al., 1997; Slifstein et al., 2010; Verhoeff et al., 2002). This issue was also recognized by (Vučković et al., 2010) to justify the use of [18F]fallypride to image D2R density. Of interest in that particular study, MPTP lesioned mice, but not saline treated mice, exhibited increased D2R densities after running exercise. Hence, there may be important differences in the dopaminergic response to exercise in PD and normal aging that involve both D2R density and endogenous DA. In the second study, metamphetamine abusers ($n = 19$) were randomized to receive 8 weeks of combined cardiovascular and resistance training, or to educational control (Robertson et al., 2015). Of note, resistance training was part of their exercise regimen, rather than part of the control training as in the present study. If resistance exercise also influences the dopaminergic system, this could possibly explain why we found substantially reduced BP_{ND} in both groups. Future projects studying aerobic exercise specifically could include a non-physical exercise control group to avoid concealment of true effects by having experimental and control exercise protocols with potentially overlapping effects (Garcia et al., 2012; Niemann et al., 2014; Voelcker-Rehage et al., 2011). Moreover, the dose-response relationship between aerobic exercise/fitness and D2R/DA is not known, and our active control group improved their aerobic fitness over six months, potentially enough to influence the dopaminergic system.

Even though aerobic exercise and non-aerobic physical exercise may have partly overlapping effects on striatal DA, there may also be specific effects for each form of training. On that note, our exploratory analyses showed that the relation between changes in VO_{2peak} and BP_{ND} in SMST displayed a different pattern for the two groups. Improvements in VO_{2peak} decreased BP_{ND} in the aerobic group, but increased BP_{ND} in the active control group. In other words, improvements in VO_{2peak} could potentially give rise to different patterns of plasticity in aerobic exercisers and stretching, toning, and resistance exercisers (reviewed by Voelcker-Rehage and Niemann, 2013). For instance, whereas hippocampal volume is increased both by coordination training and aerobic training (Niemann et al., 2014), the two exercise types displayed diverging patterns of blood-oxygenation-dependent (BOLD) changes during Flanker Task performance after a 12 month intervention (Voelcker-Rehage et al., 2011). In the latter study, compared to a relaxation control group, the two exercise groups displayed a similar pattern of change in e.g., middle frontal gyrus and cingulate cortices, whereas the cardiovascular group specifically displayed decreased activation in e.g. medial frontal gyrus and parts of the left anterior cingulate cortex, and finally, the coordination group specifically displayed increased activation in e.g., inferior frontal gyrus and caudate. Other evidence suggesting that the specific plastic response to different forms of physical exercise can be found in the rodent literature. One study investigated the differential effect of aerobic and acrobatic exercise on the expression of plasticity related resources in motor cortex, striatum, and cerebellum (Garcia et al., 2012). Whereas aerobic exercise induced widespread increases of proteins involved in neurotransmitter release and vesicular function across motor regions, acrobatic exercise increased structural protein expression. The latter was suggested to depend on the more specific and complex processing requirements of acrobatics (Garcia et al., 2012). Given the above, of the different striatal regions one could expect to see a difference in SMST particularly, as this is the striatal region involved in motor control. To speculate in relation to Garcia et al. (2012), a possible scenario in SMST is that VO_{2peak} primarily increased DA in aerobic exercisers, i.e. increases in proteins related to neurotransmitter levels, whereas the added motor complexity of exercises performed by the active control group, involving novel motor skills, could have increased SMST D2R, i.e. structural protein expression. The analyses involving SMST were exploratory in nature and the conclusions we offer should be considered tentative until the findings have been replicated.

4.1.3. Aging, dopamine, and cognition

It has been suggested that with increasing age, the dopaminergic system deteriorates, thereby causing reduced cognitive ability (Bäckman et al., 2006; Li et al., 2009), and higher levels of DA is generally considered beneficial for working memory in older adults (Bäckman et al., 2006; Cools and D'Esposito, 2011; Garrett et al., 2015). The binding of DA to striatal D2R serves to destabilize information held in prefrontal cortex to accommodate the updating of new information in working memory (O'Reilly, 2006). Hence, an increase in striatal DA should in theory improve performance on such a task (Cools and D'Esposito, 2011; Garrett et al., 2015), especially in individuals with lower levels of DA (Van Holstein et al., 2011), as can be expected in older adults. Conversely, we found no association between changes in updating task performance and BP_{ND} and thus failed to provide direct evidence that increasing physical activity in old age is a factor positively influencing the functionality of the striatal DA system. One of the tasks used, Letter Memory, is an updating task known to induce robust DA release in AST (Bäckman et al., 2011). We did observe a negative pattern between improved Letter Memory performance and BP_{ND} in AST but this effect was not significant. Others have however, provided indirect support for a fitness-dopamine-cognition link, showing the greatest benefits on executive task performance from overall physical fitness levels in older adults with a catechol-O-methyl transferase (COMT) polymorphism leading to lower levels of prefrontal DA (Voelcker-Rehage et al., 2015). Unfortunately, no genetic data was collected in the present sample, but future well-powered studies could investigate several candidate genes known to influence striatal DA. It is conceivable that individual differences also in the profile of striatal DA-related genes could impact an individual's

response to a physical exercise intervention. One hypothesis is that individuals predisposed to exhibit lower levels of striatal DA would benefit more from physical exercise, akin to the interacting effect of COMT on the fitness-cognition link observed previously (Voelcker-Rehage et al., 2015). In line with this, one study on adolescents observed that carriers of the A allele of a DAT1/SLC6A3 polymorphism, predisposed to more active reuptake of DA, benefitted more than T carriers on a shifting task after an acute bout of exercise (Berse et al., 2015). In the present study it would also have been interesting to study genes known to influence [^{11}C] raclopride binding affinity (Hirvonen et al., 2009) and the relationship between [^{11}C]raclopride binding and cognition, e.g. C957T (Karalija et al., 2019).

4.1.4. Limitations

Considering previous work in relation to our analyses, a plausible explanation is that aerobic exercise could influence both D2R densities and endogenous concentrations of DA in striatum (Foley and Fleshner, 2008; Zigmond and Smeyne, 2014). A number of factors limits our ability to draw any firm conclusions however. The most critical limitation is the use of [^{11}C]raclopride to measure D2R availability, due to its sensitivity to endogenous levels of DA (Verhoeff et al., 2002). In the scenario described above it is possible that an exercise-induced increase in D2R (Fisher et al., 2013; Foley and Fleshner, 2008; Gilliam et al., 1984; MacRae et al., 1987; Robertson et al., 2015) is masked by increased DA (de Castro and Duncan, 1985; Foley and Fleshner, 2008; Meeusen et al., 1997; Petzinger et al., 2007), resulting in a null effect on BP_{ND}, or even resulting in a decrease in BP_{ND} despite constant D2R densities. On that note, a rather short period of time elapsed between scans, and receptor densities should not decrease by more than a fraction of a percentage from aging alone (Karrer et al., 2017; Seeman et al., 1987; Volkow et al., 1996), suggesting that our measurement of BP_{ND} was indeed influenced by DA. Our inability to draw firm conclusions is a clear limitation with the PET methodology used here, as multiple scans would be required to measure both receptor density and affinity in the same individual (Doudet and Holden, 2003; Hirvonen et al., 2009; Martinez et al., 2009).

A second limitation concerns the potential link between D2R and cognition. A recent study with a large sample of older adults ($n = 181$) failed to find an association between [^{11}C]raclopride BP_{ND} and working-memory updating performance (Nyberg et al., 2016), questioning the sensitivity of the D2R availability measure for capturing individual differences in working-memory updating function. Moreover, there was no direct linear relationship between improved VO_{2peak} and working-memory updating performance in this sample of older adults (Jonasson et al., 2017b), and could for example be due to an insensitivity of the tasks, whereby a larger sample size would be required. However, the actual relationships between aerobic fitness and specific cognitive functions are not well known, and often display low to moderate effect sizes (Angevaren et al., 2008; Colcombe and Kramer, 2003; Kramer and Colcombe, 2018; Young et al., 2015). Another limitation, discussed in detail elsewhere (Jonasson et al., 2017b), derives from the fact that our active control group also improved their aerobic fitness considerably, rendering group comparisons less interpretable. This is particularly true because it is unclear how large improvements in fitness are necessary to produce a certain plastic response or at what level of fitness such responses levels off (Etnier et al., 2006). One reason that could explain why the control group participants also improved their VO_{2peak} in the present study is that their behaviors related to physical activity changed during the intervention. Umeå is a small city with a population of around 100 000. Many control group participants reported that they had started to walk or cycle to the training facility for example. Furthermore, considering the potential differences between exercise types, measures of motor fitness not available in the present sample, and many other similar samples, could provide important insights. In addition, there is a general lack of knowledge related to how aerobic exercise and fitness interacts with other activities. Increases in plastic resources arising from aerobic exercise and/or improved aerobic fitness could lead to different effects on brain circuitry depending on the processing demands of other activities pertinent to an individual during the intervention. This would be akin to the added effect of environmental enrichment on aerobic exercise-induced hippocampal neurogenesis (Fabel et al., 2009; Kempermann, 2008). Furthermore, longer interventions, ~1 year, may be required to detect exercise-induced changes in brain function and cognitive performance not visible after six months (Voss et al., 2010). Finally, additional post-intervention scans could shed light on how long exercise effects on DA persist, which is still largely unknown.

5. Conclusion

To conclude, we tested the hypothesis that DA-dependent cognitive functioning is improved in healthy older adults due to benefits on striatal DA function following aerobic exercise. Partial support was provided for the claim that being aerobically fit at an older age may be a factor protecting the striatal D2R system, finding higher baseline BP_{ND} as a function of VO_{2peak}. Conversely, no group differences in BP_{ND} following the six months intervention was observed, and changes in aerobic fitness were unrelated to changes in BP_{ND}. However, aerobic exercise and fitness could have complex effects on both D2R density and levels of endogenous DA. With the PET protocol utilized we are unable to disentangle any such effects, as density and DA have opposite effects on BP_{ND}. We can only speculate that both groups exhibited increased endogenous striatal DA over the intervention period, resulting in a reduction in BP_{ND} several times greater than any existing longitudinal estimates of decline in D2R density. To more comprehensively test the fitness-dopamine-cognition hypothesis in human adults, a critical step will be to utilize a PET protocol providing estimates of both DA receptor density and endogenous DA levels.

6. Author contributions

C-J.B., L.N., K.R, A.K conceived of the study. C-J.B., L.N., K.R., A.K., and L.S.J. designed the project. L.S.J. and J.A. performed the analyses. L.S.J., C-J.B., and L.N. wrote the manuscript. All authors reviewed the manuscript for content.

7. Competing financial interests

The authors declare no competing financial interests.

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