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Self-rated intensity of habitual physical activities is positively associated with dopamine $D_{2/3}$ receptor availability and cognition

Ylva Köhncke [a,b,*], Goran Papenberg [a], Lars Jonasson [d,e], Nina Karalija [c,d], Anders Wåhlin [c,d], Alireza Salami [a], Micael Andersson [c,e], Jan E. Axelsson [c,d], Lars Nyberg [c,d,e], Katrine Riklund [c,d], Lars Bäckman [a], Ulman Lindenberger [b,f,g], Martin Lövdén [a]

[a] Aging Research Center, Karolinska Institutet and Stockholm University, S-11330, Stockholm, Sweden
[b] Center for Lifespan Psychology, Max Planck Institute for Human Development, D-14195, Berlin, Germany
[c] Department of Radiation Sciences, Umeå University, S-901 87, Umeå, Sweden
[d] Umeå Center for Functional Brain Imaging, Umeå University, S-901 87, Umeå, Sweden
[e] Department of Integrative Medical Biology, Umeå University, S-901 87, Umeå, Sweden
[f] Max Planck UCL Centre for Computational Psychiatry and Ageing Research, D-14195, Berlin, Germany
[g] European University Institute, I-50014, San Domenico di Fiesole (FI), Italy

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ABSTRACT

Between-person differences in cognitive performance in older age are associated with variations in physical activity. The neurotransmitter dopamine (DA) contributes to cognitive performance, and the DA system deteriorates with advancing age. Animal data and a patient study suggest that physical activity modulates DA receptor availability, but data from healthy humans are lacking. In a cross-sectional study with 178 adults aged 64–68 years, we investigated links among self-reported physical activity, D2/D3 DA receptor ($D_{2/3}$DR) availability, and cognitive performance. $D_{2/3}$DR availability was measured with [^{11}C]raclopride positron emission tomography at rest. We used structural equation modeling to obtain latent factors for processing speed, episodic memory, working memory, physical activity, and $D_{2/3}$DR availability in caudate, putamen, and hippocampus. Physical activity intensity was positively associated with $D_{2/3}$DR availability in caudate, but not putamen and hippocampus. Frequency of physical activity was not related to $D_{2/3}$DR availability. Physical activity intensity was positively related to episodic memory and working memory. $D_{2/3}$DR availability in caudate and hippocampus was positively related to episodic memory. Taken together, our results suggest that striatal DA availability might be a neurochemical correlate of episodic memory that is also associated with physical activity.

1. Introduction

Cognitive performance and its underlying brain structures and functions deteriorate in old age, although there are considerable differences between individuals (Lindenberger, 2014; Nyberg et al., 2012; Rönnlund et al., 2005). These differences may partly be due to lifestyle factors such as physical activity. Positive associations between habitual physical activity and cognitive performance have been observed in numerous observational studies (Bauman et al., 2016; Blondell et al., 2014; Boraxbekk et al., 2016; Memel et al., 2016; Prakash et al., 2015; Sofi et al., 2011; Willey et al., 2016). These findings are substantiated by results from intervention studies that have documented positive effects of exercise on cognitive performance in healthy elderly persons (Ahlskog et al., 2011; Carvalho et al., 2014; Düzel et al., 2016; Jonasson et al., 2016; Liu-Ambrose et al., 2008; Maass et al., 2015; P. J. Smith et al., 2010; Voss et al., 2014; but see Young et al., 2015) as well as in dementia patients (Farina et al., 2014; Groot et al., 2016; Heyn et al., 2004; but see Forbes et al., 2014). Thus, between-person differences in physical activity may partly account for differences in cognitive performance in aging. However, a number of important questions need further exploration, such as the relative importance of intensity and frequency of physical activity and the biological mechanisms that link physical activity to cognition.

Several intervention studies have shown that physical exercise affects the brain's structural integrity, with most evidence obtained for grey-matter volume (Colcombe et al., 2006; Erickson et al., 2011;

* Corresponding author. Center for Lifespan Psychology, Max Planck Institute for Human Development, D-14195, Berlin, Germany.
E-mail address: koehncke@mpib-berlin.mpg.de (Y. Köhncke).

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Kleemeyer et al., 2016; Niemann et al., 2014), and with less evidence for white-matter volume (Colcombe et al., 2006; Erickson et al., 2014; Voelcker-Rehage and Niemann, 2013; Voss et al., 2013). Observational studies suggest that self-reported physical activities are positively related to grey matter volume, most consistently so to frontal (Flöel et al., 2010; McEwen et al., 2015; Rovio et al., 2010; Walhovd et al., 2014) and hippocampal (B. M. Brown et al., 2014; Demirakca et al., 2014; Killgore et al., 2013) volume.

Physical exercise also affects the brain's neurotransmitters, especially monoamines such as DA (Lin and Kuo, 2013). Acute effects of exercise on increased release of DA in striatum have been shown in rodents (Meeusen et al., 1997), but did not replicate in a study on humans (Wang et al., 2000). Also effects of long-term exercise regimes have been reported in rodents; an early study found enhanced [^{3}H]spiperone binding at $D_{2/3}$DR's in striatal post-mortem tissue of rats that had completed a 12 weeks of motorized treadmill training as compared to non-training rats (Gilliam et al., 1984). Furthermore, endurance training increased D_2DR receptor density in striatum of rodents in another study using the same marker and measuring DA levels and metabolites (MacRae et al., 1987). A recent study in rats demonstrated that the beneficial effect of voluntary exercise on learning was disrupted by infusion of a D_2-antagonist into the striatum (Eddy et al., 2014), suggesting D_2 receptor-dependent signalling in striatum as a mediator of exercise-related effects on cognition in these animals. Also, cortical levels of DA are elevated after four weeks of running-wheel exercise in wild-type rats, but not in animal models of Huntington's disease in which the DA system is disrupted (Renoir et al., 2011). Animal studies of Parkinson's disease (PD) have shown that exercise decreases PD symptoms and counteracts the detrimental effects of neurotoxins that are used to induce the disease in the animal models (Gerecke et al., 2010; Mabandla et al., 2004; Tajiri et al., 2010; Yoon et al., 2007). In line with this pattern, a recent exercise intervention study in humans documented increased $D_{2/3}$DR BP_{ND} in abstinent methamphetamine users that completed an 8-week exercise training program ($n = 10$) as compared to a control group ($n = 9$) with the same diagnose residing in the same treatment facility (Robertson et al., 2016). This study suggests that striatal dopaminergic deficits related to methamphetamine addiction might be ameliorated by physical exercise. Epidemiological studies have found associations between physical activity and reduced risk for PD (Xu et al., 2010; Chen et al., 2005; Thacker et al., 2008), suggesting a protective effect of physical activity.

Moreover, because DA is involved in human higher-order cognitive functions, such as episodic memory (Bäckman et al., 2011; Bäckman et al., 2010; Bäckman et al., 2006; Cervenka et al., 2008; Lisman et al., 2011; Nyberg et al., 2016; Shohamy and Adcock, 2010) and working memory (Cools & D'Esposito, 2011; Liggins, 2009; Takahashi, 2013; Takahashi et al., 2008), beneficial effects of physical activity on cognitive performance may be related to the effects of physical activity on DA functioning. In a previous publication using data from the Cognition, Brain, and Aging (COBRA) study, we observed, in a large age-homogeneous sample with 181 participants, that $D_{2/3}$DR availability in caudate nucleus and hippocampus is related to episodic memory performance (Nyberg et al., 2016), extending previous findings from smaller studies with age-heterogeneous samples.

The dose-response patterns regarding intensity, frequency, and duration are not yet sufficiently characterized (Prakash et al., 2015; Young et al., 2015). In observational studies, both frequency and intensity of physical activity have been associated with cognitive performance. Some studies report associations with frequency of light-intensity physical activities (e.g. Johnson et al., 2016; S. Lee et al., 2013), some with mild-to-moderate-intensity activities (e.g. Geda et al., 2010; Makizako et al., 2015), some with frequency of moderate-to-vigorous activities (e.g. B. M. Brown et al., 2012; Kerr et al., 2013). Only few studies examined physical activity intensity independently from frequency and report associations with cognition (Angevaren et al., 2010; Angevaren et al., 2007; B. M. Brown et al., 2012; van Gelder et al., 2004).

Given the involvement of DA in cognition, and the likely presence of positive effects of physical activity on cognitive performance, possibly through enhanced DA integrity, we investigated the correlative triad of physical activity, DA, and cognition in healthy older humans. We assessed $D_{2/3}$ DA receptor ($D_{2/3}$DR) availability with positron-emission tomography (PET) using the radiotracer [^{11}C]raclopride that is typically used for D2-assessment in striatum, but has also been used for hippocampal D2-assessment in the COBRA study (Nyberg et al., 2016). In the present study, we examined on 178 participants of the COBRA study (Nevalainen et al., 2015), whether frequency and intensity of habitual physical activity are associated with episodic memory and with $D_{2/3}$DR availability in caudate, hippocampus, but also putamen. In addition, we examined associations of physical activity to working memory and perceptual speed, even though performance in these domains were not related to $D_{2/3}$DR availability in previous analyses of our data (Nyberg et al., 2016).

2. Methods

The design, recruitment procedure, imaging protocols, cognitive tests, and questionnaires used in the COBRA project have been reported elsewhere (Nevalainen et al., 2015). Here we only describe the methodological details that are directly relevant to the results of the current study. The study was approved by the local Ethical and Radiation Safety Committee of Umeå, Sweden, and all participants provided signed written informed consent before participation.

2.1. Participants

In COBRA, 181 healthy, older individuals (64–68 years; mean: 66.2, standard deviation: 1.2; 81 women) were randomly selected from the population register of Umeå in northern Sweden. Eligible were persons without pathological deviations in brain and cognitive functions, or circumstances that could bias task performance or obstruct imaging sessions (e.g., metal implants). The study participants had a lower prevalence of hypertension than reported for the Swedish population (Carlsson et al., 2008), and normal or slightly higher body-mass index (>30 in 14.4% of the participants). According to nation-wide panels, 60,1% of 55–64 year-old and 58,2% of 65–74 year-old persons report engaging in physical activities comparable with going for a walk for at least 6 h a week (Statistics Statistics-Sweden, 1999). In COBRA, 75,14% reported to engage for at least 6 h a week in physical activity (walking, bicycling, jogging, strength training, sports), thus suggesting that our participants are relatively active (see Table 2).

Data for 3 individuals were excluded. These were persons with imperfect segmentation of magnetic resonance images and PET/MR image coregistration ($n = 2$), as well as deviant brain structure ($n = 1$). Thus, the effective sample included 178 participants (Table 1).

The timing of the assessments was as follows: Participants came to the laboratory on two non-consecutive days (mostly two days in between testing, for $n = 32$ more than 2 days were in-between). At the first day, participants performed a part of the cognitive testing, underwent structural and functional MRI scanning. Between the two days, they filled out a questionnaire on socio-demographic, personality, and lifestyle variables. At the second day of assessment, participants completed cognitive testing, medical anamnesis, testing of physical parameters and finally underwent a PET scan (Nevalainen et al., 2015).

2.2. Physical activity questionnaire

We used an activity questionnaire designed for the purpose of the COBRA study and tailored to life in northern Sweden. This questionnaire included 43 activities, chunked into the categories of intellectual, physical, and social activities. Participants were asked to indicate for how many hours (options: 1–14 h with 1-h increments, or 15 + hrs) they would engage in each of the activities during a typical summer week. Summer was taken as a reference season because the opportunities for

Table 1
Descriptive statistics for the variables of interest in the effective sample (n = 178).

Variable	Central tendency*	Spread*	Skewness	Kurtosis
Age (years)	66.14	1.21	−0.17	−1.02
Education (years)	13.29	3.51	0.44	0.15
Sex (% female)	44.7			
Physical activity frequency (sum hrs/week)	10.94	7.29	1.09	1.15
- Frequency walking (hrs/week)	5.56	3.67	0.90	0.25
- Frequency cycling (hrs/week)	3.47	3.52	1.60	2.17
- Frequency sports (hrs/week)	1.12	2.85	3.08	9.21
- Frequency strength (hrs/week)	0.47	0.89	1.90	2.91
- Frequency jogging (hrs/week)	0.51	1.35	5.28	40.10
Physical activity intensity (median)	1.25*	1.00*	1.24	0.96
- intensity jogging (rating 1–5)	2.50*	2.00*	0.03	−1.41
- intensity sports (rating 1–5)	2.00*	1.00*	0.74	−0.46
- intensity strength (rating 1–5)	2.00*	2.00*	0.43	−1.00
- intensity walking (rating 1–5)	1.00*	1.00*	1.58	2.02
- intensity cycling (rating 1–5)	1.00*	1.00*	1.53	2.57
EM: word recall	12.94	4.08	0.49	0.17
EM: number-word recall	3.57	2.45	0.93	0.86
EM: object-position recall	12.28	3.70	−0.09	−0.35
WM: letter updating	33.53	7.87	−1.03	0.98
WM: numerical 3-back	78.28	16.42	−0.29	−0.48
WM: spatial updating	13.04	6.17	−0.01	-.28
SPEED: letter comparison	63.44	14.95	0.56	0.06
SPEED: number comparison	71.07	14.22	0.54	0.15
SPEED: figure comparison	29.58	5.32	0.52	−0.23
$D_{2/3}$DR BP_{ND} left caudate	2.03	0.27	−0.56	1.15
$D_{2/3}$DR BP_{ND} right caudate	2.15	0.27	−0.59	0.62
$D_{2/3}$DR BP_{ND} left putamen	3.14	0.26	−0.16	0.25
$D_{2/3}$DR BP_{ND} right putamen	3.20	0.26	−0.33	0.22
$D_{2/3}$DR BP_{ND} left hippocampus	0.18	0.04	−0.43	0.74
$D_{2/3}$DR BP_{ND} right hippocampus	0.17	0.04	−0.25	0.36
$D_{2/3}$DR BP_{ND} left PFC	0.20	0.04	−0.10	−0.26
$D_{2/3}$DR BP_{ND} right PFC	0.21	0.04	−0.02	−0.23

Note. EM: Episodic memory. WM: working memory. SPEED: perceptual speed. $D_{2/3}$DR BP_{ND}: $D_{2/3}$-dopamine receptor binding potential.* If marked with an asterisk, the measure of central tendency is the median and the measure of spread the interquartile range (spanning the most central 50% of the values in the distribution); otherwise, central tendency is the mean and spread is the standard deviation.

Table 2
Count data for ratings of physical activities.

How physically demanding do you experience it is normally for you to do…	n[a)]	Responses (absolute)[b)]				
		Not at all 1	2	3	4	extremely 5
- jogging	38	11	8	12	7	0
- sports	43	18	15	7	3	0
- strength training	46	17	10	12	6	1
- walking	176	114	45	12	5	0
- cycling	153	89	48	12	3	1

Note. a) Number of persons reporting to engage at least 1 h/week in each activity. b) Absolute number of participants choosing this answer category, only counting rating answers from participants who reported to engage at least 1 h/week in the respective activity.

various kinds of activities differ largely across seasons in northern Sweden. For the purpose of the present study, we focused on physical activities (see questionnaire in supplementary material), and in particular on those activities that are purely physical and that individuals are sufficiently engaged in (each of these activities were performed by at least 20% of the participants at least once a week): walking, bicycling, jogging, strength training, and sports. In addition to how often each activity was performed, it was asked how physically demanding it would normally be to perform the activity in question (on a scale from 1 = "not at all" to 5 = "extremely"). The mean self-rated intensity in these activities correlated ($r = 0.50$, $p < .001$) with the vigorous activity score (minutes/week in vigorous activities) from the well-validated International Physical Activity Questionnaire (IPAQ; Craig et al., 2003) in participants from another study (Jonasson et al., 2016) in the same geographical area (n = 62; mean age = 68.7 years, sd = 2.7). This suggests that self-rated intensity in our study largely reflects how vigorously a person engaged in a given activity.

2.3. Cognitive testing

Cognitive abilities (episodic memory, working memory, and perceptual speed) were measured with three tasks each (a verbal, a numerical, and a figural task). Episodic memory ability was assessed with word recall, number-word recall, and object-position recall; working memory was measured with letter-string updating, numerical 3-back, and spatial updating; and perceptual speed was assessed with letter comparison, number comparison, and figure comparison (see Nevalainen et al., 2015, for details). For each task, we computed summary scores across the total number of blocks or trials. These summary scores were then standardized (T score: mean = 50; SD = 10).

2.4. PET imaging

All participants underwent a PET scan (Discovery PET/CT 690; General Electric, WI, US) following an intravenous bolus injection of 250 MBq [^{11}C]raclopride. Before injection, a 5-min low-dose helical CT scan (20 mA, 120 kV, 0.8 s/revolution) was obtained, for the purpose of PET attenuation correction. Following the bolus injection, a 55-min 18-frame dynamic scan was acquired with the participants resting in the scanner. Attenuation- and decay-corrected PET images (47 slices, field of view = 25 cm, 256 × 256-pixel transaxial images, voxel size = 0.977 × 0.977 × 3.27 mm^3) were reconstructed with the iterative algorithm VUE Point HD SharpIR (GE; 6 iterations, 24 subsets, 3.0 mm post filtering; Bettinardi et al., 2011), yielding a full width at half maximum resolution of approximately 3.2 mm (Wallsten et al., 2013). An individually fitted thermoplastic mask was attached to the bed surface to minimize head movements during the PET/CT imaging session.

2.5. Structural MRI

High-resolution anatomical T1-weighted images were acquired by a 3D fast spoiled gradient-echo sequence in a 3T magnetic resonance camera. Images consisted of 176 slices, with thickness = 1 mm. TR = 8.2 ms, TE = 3.2 ms, flip angle = 12°, and field of view = 25 × 25 cm.

2.6. DTI imaging

White-matter microstructure was examined with diffusion tensor imaging (DTI), collected on a 3T Discovery MR750 (General Electrics, WI, US) with a 32-channel head coil. A single-shot, spin-echo-planar T2-weighted sequence was applied, using 3 repetitions and 32 independent directions. The total slice number was 64, with a TR of 8000 ms, a TE of 84.4 ms, a flip angle of 90°, a field of view of 25 × 25 cm, and with $b = 1000$ s/mm2.

2.7. Cerebral blood flow

Blood flow and perfusion were assessed with 3D pseudo-continuous arterial spin labeling with background suppression and a spiral acquisition scheme. Labeling time 1.5 s, post labeling delay time = 1.5 s, field of view = 24 cm, slice thickness = 4 mm, and acquisition resolution = eight arms by 512 data points, with three signal averages. Perfusion maps were calculated to obtain cerebral blood flow in ml/100 g/min. For ROI definition, see volumetric MRI analyses below.

2.8. PET data analyses

PET scans were corrected for head movements, and co-registered to the corresponding MRI image using Statistical Parametric Mapping software (SPM8; Ashburner et al., 2013). $D_{2/3}$DR binding potential to non-displaceable tissue uptake (BP_{ND}) was calculated with Logan analysis (Logan et al., 1996) based on time-activity curves for caudate, putamen, PFC, hippocampus and cerebellum. Grey matter regions were segmented using FreeSurfer and the Desikan-Killiany Atlas (Fischl et al., 2004). For each hemisphere, PFC as a ROI was defined as the mean across the following ROIs in the atlas: superior frontal, lateral orbitofrontal, rostral middle frontal, caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, medial orbitofrontal. Grey matter in cerebellum was used as a reference region due to its negligible $D_{2/3}$DR expression (Camps et al., 1989; Farde et al., 1986; Levey et al., 1993).

2.9. Volumetric MRI analyses

Brain segmentation was performed using FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu; Fischl et al., 2002; Fischl et al., 2004; Han and Fischl, 2007). When necessary, striatal volumes were manually corrected in FreeSurfer's Voxel Edit mode.

2.10. DTI data analysis

The diffusion-weighted data were analyzed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) package (http://www.fmrib.ox.ac.uk/fsl). The full details of DTI data analyses (using the identical imaging parameters but on a different sample) were given elsewhere (Salami et al., 2012). In short, the three-subject-specific diffusion acquisitions were concatenated in time followed by eddy current correction to correct for head motion and eddy current distortions. Accordingly, the b-matrix was reoriented based on the transformation (Leemans and Jones, 2009). We created a binary brain mask with the Brain Extraction Tool (BET; S. M. Smith, 2002) on the first b = 0 and fitted a diffusion tensor with DTIfit (S. M. Smith et al., 2004) to each voxel to yield voxel-wise maps of fractional anisotropy (FA). We then used Tract-Based Spatial Statistics (TBSS; S. M. Smith et al., 2006). FA images were normalized to the most typical subject of the entire sample and then affine-aligned into $1 \times 1 \times 1\ mm^3$ MNI152 standard space. Next, we individually transformed FA images and averaged them to produce a mean FA of the group to produce a group skeleton. The group skeleton was generated by extracting the medial axis of white matter fiber-tracts common to all subjects (the mean FA skeleton was thresholded at 0.2 to exclude voxels containing gray matter or cerebrospinal fluid).

2.11. Statistical analyses

Structural equation modeling (SEM) was used to examine the relations among latent constructs representing physical activity, $D_{2/3}$DR BP_{ND}, and cognitive abilities. The major advantage of using structural equation modeling in this study is that we were able to model the inter-individual variance in each cognitive ability as common variance across tests, setting it apart from test-specific variance and measurement error. We defined one latent factor for each of the three cognitive abilities (working memory, episodic memory, and processing speed) as indicated by the three tests per ability. Similarly, we estimated the variance in $D_{2/3}$DR binding potential in each of the ROIs as common variance across hemispheres, apart from hemisphere-specific variance. That is, the left and right regions of interests were used as indicators of the latent factors for $D_{2/3}$DR BP_{ND} (caudate, putamen, PFC, and hippocampus). Finally, we estimated the common variance across the intensity ratings for walking, bicycling, jogging, strength training, and sports in a latent intensity factor, apart from activity-specific variance in intensity ratings. In so doing, we obtained a latent measure of the tendency to rate physical activities as intense/demanding. Physical activity frequency (the total hrs/week a participant reported to engage in the abovementioned activities) was analyzed as an observed variable. All latent variables and the observed physical activity variable (hrs/week) were included in one model and allowed to covary with one another (Fig. 1). To statistically control for the influence of age, education, and sex, these variables were always included as predictors of all latent variables and physical activity frequency (Table 3).

For the latent physical activity intensity factor, we included only ratings from individuals who performed a given activity at least 1 h/week. The rationale behind this was that the ratings for regular activities would more reliably describe the participants' experience compared to those for irregular/rare activities. Further, activities performed weekly or more often are probably voluntary, so that the ratings of their intensity/demand likely reflect how intensely a person engages in a given activity rather than difficulty in performing the activity. Note that this approach resulted in a large proportion of missing values in the rating data. In the estimation of the structural equation model parameters, we used the WLSMV (weighted least squares with correction for means and variances) estimator in Mplus (Muthén & Muthén, 1998–2015). Missingness in outcome variables that can be predicted by variables in the model is accounted for in this approach (Muthén & Muthén, 1998–2015). Associations between outcome variables are then based on pairwise present data in a second step (Asparouhov and Muthén, 2010). As the intensity ratings for the four activities of interest were positively skewed, due to the fact that several participants rated many of the activities as “not at all demanding” (Table 1), and given that they were on a Likert scale with not more than 5 points, we treated them as ordinal variables and employed the WLSMV estimator in all SEM analyses. This estimator has been suggested as the best estimate in confirmatory factor analysis with ordinal variables as indicators (T. Brown, 2006).

Model fit was deemed acceptable if RMSEA < 0.05 and CFI > 0.94. To statistically test single parameters in the model, we applied chi-square difference testing using the DIFFTEST-function in Mplus (Muthén & Muthén, 1998–2015). We specified a nested model for each parameter of interest in which we restricted this parameter to zero and tested whether model fit, as indicated by the chi-square (χ^2) value would worsen significantly. If the difference in chi-square ($\Delta\chi^2$) is significant, as indicated by a chi-square test with as many degrees of freedom as parameters are fixed in the nested model, the fixed parameter is considered significant. An alpha level of $p < .05$ was adopted.

3. Results

The three-factor model for cognitive performance with the factors episodic memory, working memory, and processing speed fit the data well (CFI = 0.952; RMSEA = 0.0722; SRMR = 0.042), so that we considered it a suitable representation the covariance structure in the cognitive test results (Fig. 3), despite some heterogeneity in the loadings (Fig. 1). The factor model for $D_{2/3}$DR BP_{ND} in caudate, putamen, PFC, and hippocampus did also fit the data well (CFI = 0.96; RMSEA = 0.093; SRMR = 0.03), with consistently high loadings of indicators (Figs. 1 and 3). The factor model for intensity ratings (analyzed as ordinal variables, fitted with the WLSMV estimator in Mplus) was an acceptable representation of the data (CFI = 0.996; RMSEA = 0.123). For zero-order correlations among the variables see Fig. 3.

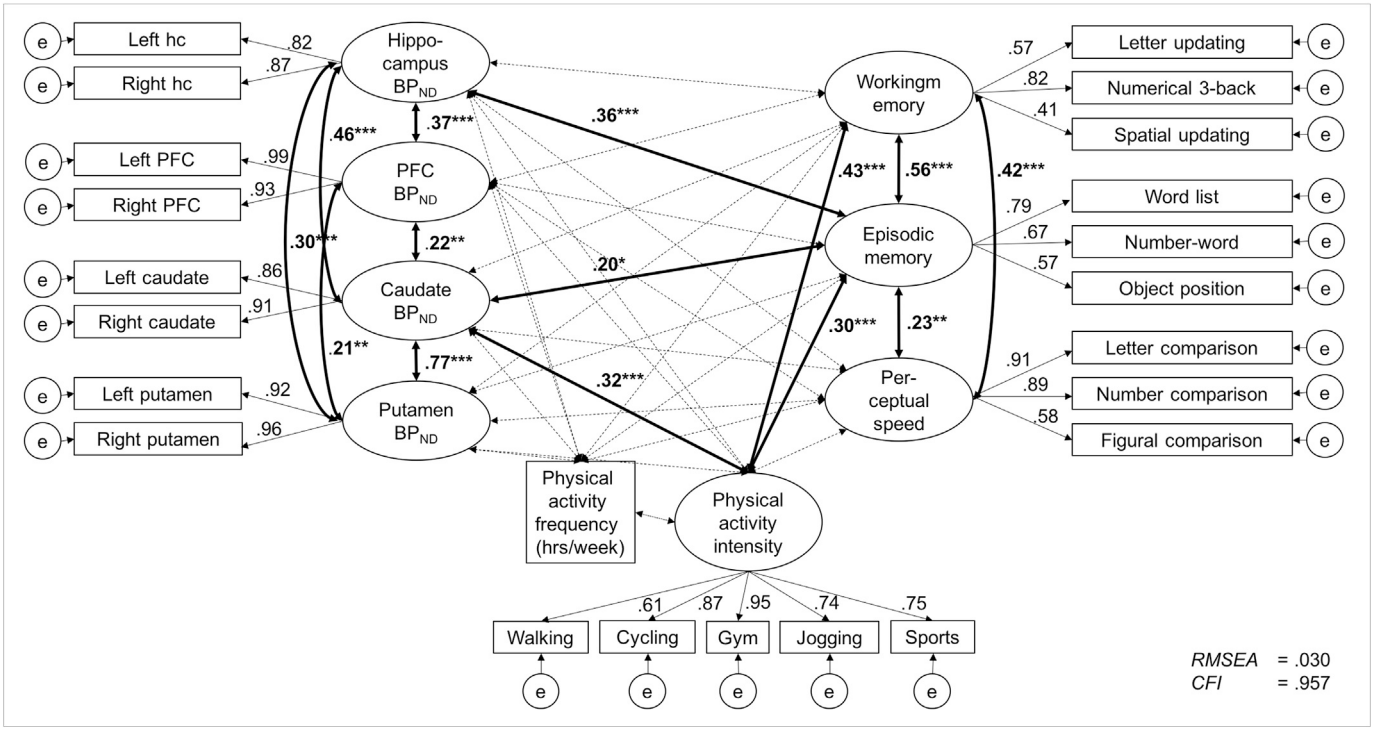

Fig. 1. Structural equation model describing the associations among self-reported frequency and intensity of physical activities, $D_{2/3}$DR BP_{ND} (hippocampus, prefrontal cortex/PFC, caudate, putamen), working memory, episodic memory, and perceptual speed. All latent variables are adjusted for age, sex, and education (covariates in the SEM but not shown here; Table 3). All parameter estimates are standardized. Dashed lines: not significant at $p < .05$; bold lines: significant at $p < .05$. RMSEA: root mean square of approximation. CFI: comparative fit index. * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 3
Unique effects of covariates on variables of interest.

Variable	Age	Education	Sex
Physical activity frequency (sum hrs/week)	1.16*	.22	−2.0
Physical activity intensity (latent factor)	.001	.04	−.12
Episodic memory (latent factor)	−.03	.87***	−3.45**
Working memory (latent factor)	−.09	.41**	2.54*
Speed (latent factor)	−.42	.37	−.48
$D_{2/3}$DR BP_{ND} caudate (latent factor)	−.005	.002	−.09*
$D_{2/3}$DR BP_{ND} putamen (latent factor)	−.02	−.003	−.08*
$D_{2/3}$DR BP_{ND} hippocampus (latent factor)	−.002	<.001	−.01
$D_{2/3}$DR BP_{ND} PFC (latent factor)	<.001	<.001	.001

Note. Non-standardized regression estimates from structural equation model (Fig. 1) with age, education, and sex as predictors. * $p < .05$; ** $p < .01$; *** $p < .001$. Sex is coded 1 for men and 0 for women; positive sex effects indicate higher values for men in the outcome, negative sex effects indicate higher values for women.

Frequency of physical activity as indicated by the sum of hours per week in the five most commonly reported purely physical activities (walking, bicycling, jogging, strength training, or sports) was unrelated to episodic memory, working memory, and speed, as well as to $D_{2/3}$DR BP_{ND} across ROIs ($rs < |0.12|$; $\Delta\chi^2 < 2.65$; $ps > .10$). By contrast, the latent factor for intensity of physical activities was positively associated with episodic memory ($r = 0.30$; $\Delta\chi^2 = 11.05$; $df = 1$; $p < .001$; Fig. 2b) and working memory ($r = 0.43$; $\Delta\chi^2 = 19.26$; $df = 1$; $p < .001$), but not with perceptual speed ($r = -0.01$; $\Delta\chi^2 = 0.009$; $df = 1$; $p = .92$). Intensity of physical activities was also significantly linked to $D_{2/3}$DR BP_{ND} in caudate ($r = 0.32$; $\Delta\chi^2 = 14.56$; $df = 1$; $p < .001$; Fig. 2c), but not in putamen ($r = 0.16$; $\Delta\chi^2 = 3.12$; $df = 1$; $p = .08$) and hippocampus ($r = -0.02$; $\Delta\chi^2 = 0.04$; $df = 1$; $p = .83$). The correlations of intensity of physical activities with caudate $D_{2/3}$DR BP_{ND} on the one hand (r_1) and putamen $D_{2/3}$DR BP_{ND} on the other hand (r_2) did not significantly differ from each other as tested by the change in χ^2 when applying an equality constraint to the correlations in the model ($\Delta r_1 r_2 = 0.16$; $\Delta\chi^2_{(r1=r2)} = 3.10$; $df = 1$; $p = .078$). As reported previously (Nyberg et al., 2016), episodic memory was correlated with $D_{2/3}$DR BP_{ND} in caudate ($r = 0.20$; $\Delta\chi^2 = 4.69$; $df = 1$; $p = .03$; Fig. 2a) and hippocampus ($r = 0.36$; $\Delta\chi^2 = 13.90$; $df = 1$; $p < .001$), but not in putamen ($r = 0.10$; $\Delta\chi^2 = 1.20$; $df = 1$; $p = .27$). Working memory and processing speed were unrelated to $D_{2/3}$DR BP_{ND} in all ROIs ($rs < |0.11|$; $ps > .20$). Expectedly, the three cognitive abilities were related to one another (all $rs > 0.23$; $ps < .01$; Fig. 1), as was $D_{2/3}$DR BP_{ND} in the three ROIs (all $rs > 0.21$; $ps < .01$; Fig. 1). Frequency of physical activities was unrelated to the intensity factor ($r = -0.05$; $\Delta\chi^2 = 0.39$; $df = 1$; $p = .54$).

To check for effects of third variables, we next included a number of potentially confounding variables one-by-one as covariates: frequency of mental activities, frequency of social activities, retirement status, number of grandchildren, time of year (winter/summer), as these variables could potentially influence the accuracy of activity ratings and reported frequency which should all refer to a typical summer week, and might also be associated with cognitive performance. Further, hypertension, and body-mass index (BMI), which also could be related to both physical activity and cognitive performance (for descriptives of these variables, see Table 4, for their associations among each other and with the variables of interest, see Fig. 3). We report any change in r that is greater than 0.02 (arbitrary threshold). Including frequency of social activities in the model slightly attenuated the association between episodic memory and physical activity intensity, but the association remained significant (adjusted model: $r = 0.24$, $\Delta\chi^2 = 7.38$; $df = 1$; $p < .006$). Being retired, number of grandchildren, hypertension (i.e. diastolic blood pressure >90 or systolic blood pressure >140; Chobanian et al., 2003), and BMI did not substantially affect the associations.

In further control analyses, we checked whether the main results hold after adjusting for total intracranial volume (TIV) and grey-matter volume in caudate, putamen, frontal cortex and hippocampus (adjusted for TIV), respectively. Adding regional volumes attenuated the correlations between episodic memory and physical activity intensity (adjusted

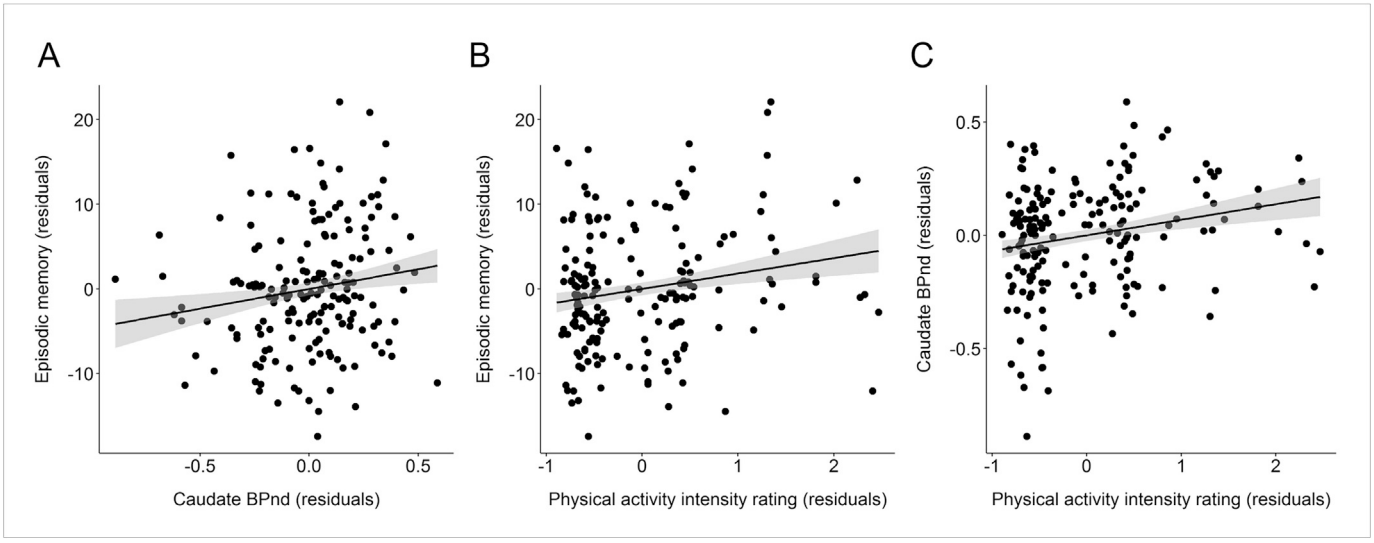

Fig. 2. Scatterplot A illustrates the relationship between mean caudate $D_{2/3}$DR BP_{ND} and a unit-weighted mean episodic memory score. Scatterplots B and C show the associations of median physical activity intensity to (B) episodic memory, and (C) caudate $D_{2/3}$DR BP_{ND}. All variables refer to residuals after regressing out the effects of age, sex, and education. Line: predicted values from linear regression of y on x; grey area: 95% confidence interval based on standard errors of prediction.

model: $r = 0.24$; $\Delta\chi^2 = 6.55$; $df = 1$; $p = .01$), episodic memory and caudate BP_{ND} (adjusted model: $r = 0.18$; $\Delta\chi^2 = 4.89$; $df = 1$; $p = .027$), episodic memory and working memory (adjusted model: $r = 0.53$; $\Delta\chi^2 = 23.47$; $df = 1$; $p < .0001$). Further, the associations of working memory with physical activity intensity was attenuated (adjusted model: $r = 0.35$; $\Delta\chi^2 = 14.43$; $df = 1$; $p = .0001$), and of working memory and hippocampus BP_{ND} (adjusted model: $r = 0.18$; $\Delta\chi^2 = 4.4$; $df = 1$; $p = .0359$). Further, the associations among the regional BP_{ND} values were somewhat weaker (adjusted model: $r_{CAU,PUT} = .75$; $\Delta\chi^2 = 65.78$; $df = 1$; $p < .0001$; $r_{CAU,HC} = 0.43$; $\Delta\chi^2 = 25.61$; $df = 1$; $p < .0001$; $r_{CAU,PFC} = .24$; $\Delta\chi^2 = 12.40$; $df = 1$; $p = .0004$; $r_{HC,PFC} = .42$; $\Delta\chi^2 = 22.34$; $df = 1$; $p < .0001$). To note, none of the associations that previously were significant became non-significant, and none of the previously non-significant associations became significant, at a level of alpha = .05. We did also include cerebral blood flow, because it has previously been related to fitness and to episodic memory (e.g. Maass et al., 2015). We included blood flow in hippocampus, caudate, and putamen, and frontal cortex all at once. Adding these four blood flow variables slightly attenuated the association between physical activity intensity and episodic memory, but the correlation remained significant (adjusted model $r = 0.23$; $\Delta\chi^2 = 7.28$; $df = 1$; $p = .0069$). The association between caudate BP_{ND} and hippocampus BP_{ND} was also slightly attenuated (adjusted model $r = 0.43$; $\Delta\chi^2 = 25.18$; $df = 1$; $p < .0001$), whereas all associations putamen BP_{ND} were slightly strengthened, including the previously non-significant association between putamen BP_{ND} and physical activity intensity (adjusted model $r_{PUT,\ PA\ INT} = .16$; $\Delta\chi^2 = 3.85$; $df = 1$; $p = .0499$; $r_{PUT,\ CAU} = 0.81$; $\Delta\chi^2 = 73.77$; $df = 1$; $p < .0001$; $r_{PUT,\ HC} = 0.36$; $\Delta\chi^2 = 17.74$; $df = 1$; $p = p < .0001$; $r_{PUT,\ PFC} = .23$; $\Delta\chi^2 = 9.42$; $df = 1$; $p = p = .0021$). We also included white-matter microstructure (FA along the entire skeleton), because white-matter microstructure has been related to habitual physical activity (Burzynska et al., 2014; Voss et al., 2013) and to memory (Charlton et al., 2013; Madden et al., 2012) in old age. However, including FA did only slightly strengthen the association between working memory and physical activity intensity (adjusted model $r = 0.46$; $\Delta\chi^2 = 22.22$; $df = 1$; $p < .0001$), and thus not largely alter the results. For zero-order correlations among all control variables and variables of interest, please see Fig. 3.

In summary, the associations of physical activity intensity with episodic memory, working memory, and caudate BP_{ND}, as well as between episodic memory and caudate $D_{2/3}$DR BP_{ND} (Fig. 1) were quite robust against potential confounders.

4. Discussion

In a study with 178 participants in their mid-60s, we observed positive associations among self-reported intensity of physical activity, $D_{2/3}$DR availability in the caudate nucleus, and episodic memory. In line with animal studies showing involvement of $D_{2/3}$DRs in memory consolidation (K. N. Lee and Chirwa, 2015; Manago et al., 2009), we recently reported that $D_{2/3}$DR availability is related to episodic memory in this data set (Nyberg et al., 2016). The association between physical activity and episodic memory is in line with previous studies (e.g. Ferencz et al., 2014; Flöel et al., 2010; Ruscheweyh et al., 2011), as is the association between physical activity intensity and working memory (Erickson et al., 2013; Erickson and Kramer, 2009; Voss et al., 2010). Processing speed was not associated with any of the physical activity measures, although some observational and intervention studies suggest such a link (Chang et al., 2013; Nouchi et al., 2014; P. J. Smith et al., 2010; Willey et al., 2016; but see Young et al., 2015). Most interestingly, we observed an association between reported intensity of habitual physical activity and $D_{2/3}$DR availability. An association between physical activity and dopamine receptor availability has not yet been reported in healthy human participants but is consistent with findings from animal models (Eddy et al., 2014; Gilliam et al., 1984; MacRae et al., 1987) and from an exercise intervention study in methamphetamine users (Robertson et al., 2016).

The finding that physical activity intensity, independently of frequency, was positively related to cognitive performance is in accordance with results from a few other cross-sectional (Angevaren et al., 2007; B. M. Brown et al., 2012) and longitudinal (Angevaren et al., 2010; van Gelder et al., 2004) studies in older adults which separated intensity and frequency of physical activity. In two cross-sectional studies, intensity of physical activity was positively related to cognition (Angevaren et al., 2007; B. M. Brown et al., 2012), and one longitudinal study revealed positive change-change relationships of physical activity intensity to processing speed and fluency in 45-to-75-year old participants over 5 years (Angevaren et al., 2010), another in 70-to-90-year old male participants across a period of 10 years (van Gelder et al., 2004). Thus, the extant literature indicates that individuals with higher cognitive performance performed physical activities with higher intensity (Angevaren et al., 2007; B. M. Brown et al., 2012) and that individuals who dropped less in cognitive performance than others tend to maintain the intensity level of their chosen activities (Angevaren et al., 2010; van Gelder et al.,

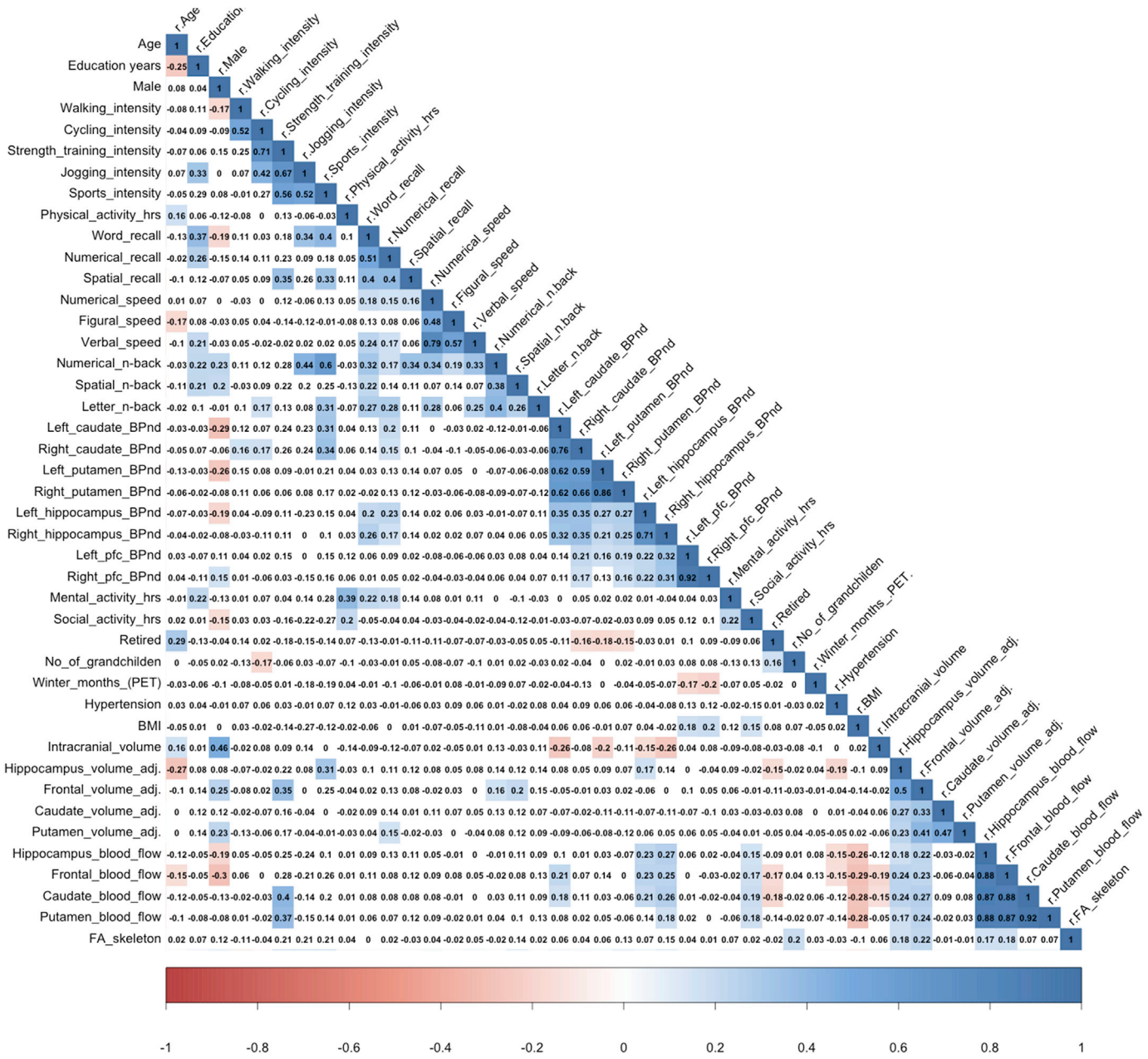

Fig. 3. Zero-order correlations among all control variables and variables of interest. Only correlations that were significant ($p < .05$) are marked with a colored background with the color corresponding to the direction and color saturation to the strength of the correlation.

2004). Note, however, that our intensity measure deviates from the measures used in most other studies. We did not assign intensity values to each activity, but focused rather on the subjective intensity of activities in which participants engaged in at least 1 h a week. The subjective intensity ratings were combined across activities in a latent score to reflect the general tendency of a person to engage more or less vigorously in his or her physical activities. In a different study, the mean score of these intensity ratings was strongly related to the vigorous activity score from the validated IPAQ questionnaire (Craig et al., 2003). An advantage of subjective measures is that they take inter-individual differences in predispositions into account. Imagine two persons who both walk 3 h per week and cycle 1 h per week (same frequency values). Whereas one person is physically fit and walks briskly and cycles fast, the other person is less fit and walks and cycles rather slowly. Still, in their subjective intensity ratings, they both might rate the activities as somewhat demanding, because both individuals engage in them in a way that challenges them to some degree. The fitter person is then challenged at a more intense level of activity and the less fit person at a less intense level. Thus, subjective intensity is likely confounded with physical fitness or capacity, but does also likely reflect the degree to which an individual physically challenges him- or herself. Note that more direct measures of physical activity intensity are often also measured in relation to a person's capacity (e.g. heart rate in percent of maximum heart rate), to take individual differences in capacity into account.

We did not find any association between frequency of physical activity and cognition, although such a link has been reported in other observational studies (Ahlskog et al., 2011; Bauman et al., 2011; Blondell et al., 2014; Prakash et al., 2015; Sofi et al., 2011). Likewise, we did not observe an association between physical activity frequency and $D_{2/3}$DR availability (Lin and Kuo, 2013). This may be due to the quite high frequency with which our participants engaged in some of the activities, such as walking and cycling. For instance, 87,7% of the participants

Table 4
Descriptive statistics for all covariates used in robustness analyses.

	N	Mean	SD	Median	Skewness	Kurtosis
Mental activity hrs/w	176	34.05	15.02	31.50	0.64	0.40
Social activity hrs/w	176	31.70	14.90	29.00	0.92	0.71
Retired	178	72%	–	–	–	–
No. of grandchildren	178	2.69	2.36	2.00	0.78	0.20
Winter months (PET)	178	34%	–	–	–	–
Hypertension	178	51%	–	–	–	–
BMI	177	26.09	3.47	25.35	0.59	0.03
Intracranial volume	177	1 534 666	267 508	1 480 264	1.40	2.34
Hc volume corr. [1]	175	7744	822	7793	−0.49	0.53
Frontal volume corr. [1]	176	163 929	16 117	165 291	−0.31	0.16
Caudate volume corr. [1]	177	7309	962	7173	0.63	0.71
Putamen vol. corr. [1]	177	8827	1023	8746	0.25	0.19
Hc blood flow [2]	177	79.15	14.33	78.57	0.57	0.62
Frontal blood flow [2]	177	946.19	206.69	938.61	0.48	0.19
Caudate blood flow [2]	177	72.56	11.44	71.18	0.26	−0.28
Putamen blood flow [2]	177	88.43	14.00	87.19	0.57	0.67
FA skeleton	175	0.47	0.02	0.48	−0.42	0.37

Note. Hc: hippocampus. PET: positron emission tomography. BMI: body mass index. [1] vol are reported in mm^3 and statistically adjusted for intracranial volume. Summary scores for each structure are the sum of mm^3 across both hemispheres. [2]Blood flow is reported in ml blood/100g tissue/min. FA: fractional anisotropy.

cycled at least 1 h/week. Umeå is a town where people often walk for errands and cycle for transportation purposes. Thus, inter-individual differences in physical activities might mainly lie in the intensity with which people engage in their activities, not in the frequency. That is, it is not whether or not, but rather the way in which people are physically active that matters in this sample from a northern Swedish population. Note also that our participants are just at retirement age, and thus, many of them have the time and physical fitness necessary for a physically active lifestyle. Therefore, variance in frequency might characterize differences in physical activity less than variance in intensity in this population.

Not only episodic memory, but also working memory was related to the intensity of physical activity. However, working memory showed no association with D2/3DR availability in the present sample (Nyberg et al., 2016). A latent class analysis on the same data (Lövdén et al., 2017) set out to identify clusters of participants in an unsupervised way based on their performance in episodic memory, working memory, processing speed, D2/3 receptor binding potential in striatum, hippocampus, and cortex. This analysis resulted in 3 classes. The largest class was characterized by relatively high values in all variables, the second largest class by low values in all variables. Thus, across these two classes of participants, working memory (and episodic memory and processing speed) was positively related to D2/3 receptor binding potential across regions. However, the third subclass of participants ($n = 40$) was characterized by high binding potential and poor cognitive performance, especially poor working memory performance. Interestingly, on a range of covariates, this third class differed from the other two in education (lower) and BMI (higher) and it differed from first class in the intensity ratings for physical activities (lower) (Lövdén et al., 2017). Thus, the latent class analysis suggested complex non-linear associations between D2/3DR availability and working memory, and suggested that the sample might be heterogeneous in the interrelations of physical activity, cognition, and D2/3DR availability.

The question of whether physical activity increases $D_{2/3}$DR availability or whether higher $D_{2/3}$DR availability leads to more intense physical activity remains unanswered. Mechanisms for both directions of causal influence have been proposed. When it comes to effects of physical activity on DA functioning, animal studies have documented that exercise alleviates or reverses the effects of experimentally induced DA deficiency or depletion by preserving DA neurons in striatum and substantia nigra through increased expression of $D_{2/3}$DR (e.g. Fisher et al., 2004; Vuckovic et al., 2010) and down-regulation of DA transporter proteins (Fisher et al., 2004; Petzinger et al., 2007), by expression of mitochondrial biogenesis and enzymatic antioxidant defenses (Aguiar et al., 2016), and by increasing dendritic spine density and arborisation (Toy et al., 2014, for review see Petzinger et al., 2013). Others have suggested a pathway via calcium-level regulation (Sutoo and Akiyama, 2003). According to this view, physical exercise induces acidity in the blood, on which parathyroid calcium metabolic hormones act to increase calcium levels in the blood, using calcium stored in the bones. Calcium may then be transported to the brain and enhance DA synthesis through a calmodulin-dependent system, which in turn normalizes disrupted DA-dependent brain functions in animal models of epilepsy and hypertension (Sutoo and Akiyama, 2003). Moreover, DA is involved in a number of mechanisms of cognition-related brain plasticity, such as synaptic plasticity and expression of neurotrophins, which may be enhanced by physical activity. Regarding synaptic plasticity, DA is involved in both long-term depression (Chen et al., 1996) and long-term potentiation (Frey et al., 1990; Lisman et al., 2011) in C1 neurons in hippocampus, which fits with the association between hippocampus $D_{2/3}$DR availability and episodic memory (Nyberg et al., 2016), but since hippocampus D2/3DR availability was not directly related to physical activity in the present study, this link might be less related to physical activity.

The link between $D_{2/3}$DR availability and physical activity intensity may also reflect the fact that persons with higher dopamine system integrity are prone to engage in physical activity with higher intensity. DA is crucial for motivational processes and movement initiation (see Schultz, 2007, for review). Rodents that are selectively bred for higher levels of wheel-running behaviour also show higher concentrations of DA and stronger exercise-induced elevations of DA in the nucleus accumbens than their more sedentary counterparts (Mathes et al., 2010). Mice given a $D_{2/3}$DR antagonist lose their natural preference of wheel-running over sucrose consumption (Correa et al., 2016). D_2DR knockdown mice, fed with obesity-inducing diet and placed in an enriched environment, engaged less in voluntary exercise, spent less energy, and gained more weight than their wild-type counterparts with the same diet and environment (Beeler et al., 2016). This suggests that the ability to express D_2DR enabled the wild-type mice to take advantage of the enriched environment by engaging in physical activity. Another study demonstrated that obese mice had lower $D_{2/3}$DR binding of [^{3}H]spiperone in striatum than their lean counterparts, and that the obese mice moved less than the lean mice and showed disrupted movement-related firing patterns in striatum (Friend et al., 2016). In an animal motivation model, high tonic DA levels in nucleus accumbens lead to more vigorous responding, akin to intensity (Niv et al., 2007), and a similar effect of striatal DA has been suggested also in humans (Jonasson et al., 2014). In humans, a polymorphism in the $D_{2/3}$DR gene has been related to levels of habitual physical activity in women (Simonen et al., 2003), suggesting that genetically determined individual differences in $D_{2/3}$DR expression

might result in differences in physical activity engagement. Taken together, these examples suggest that inter-individual differences in $D_{2/3}$DR availability could explain inter-individual differences in physical activity engagement, including differences in how vigorously individuals engage in physical activity.

Longitudinal studies or large-scale interventions in humans are needed to answer questions as to whether DA functioning is a cause of physical activity, an effect thereof, or both. Further, the dose-response relationship between physical activity (intensity or frequency) and cognitive performance needs further exploration (Prakash et al., 2015). Another caution to keep in mind is that [^{11}C]raclopride can be displaced by endogenous DA at its target receptors (Ginovart, 2005; Ross and Jackson, 1989; Seeman et al., 1989). Consequently, binding potential, or $D_{2/3}$DR availability, not only reflects receptor density and affinity, but is also affected by endogenous DA levels. Further, it has been argued that D2/3DR-specific raclopride binding is only interpretable in striatum. The absolute values for binding potential in hippocampus and PFC that we observed were indeed smaller than those in striatum. Nevertheless, they were reliably above zero, which means that there was more binding in hippocampus and PFC than in the reference region cerebellum. Note that the standard deviations around the mean BPND values in hippocampus and PFC are relatively small, so that the means differ from zero by 4.25–5.25 standard deviations (Table 1). That is, we measure these relatively low values with high precision. In addition, the inter-individual differences in these variables do show sensible associations with other variables, which indicates that there are not merely noise or measurement error. Not only the reported associations in the present article, but also the associations found between hippocampal BPND and episodic memory (Nyberg et al., 2016), and, in large subgroups of participants, with associations with working memory and functional and structural connectivity (Lövdén et al., 2017; Salami et al., 2018) support this view. Of course, high precision or low variance does not safeguard against bias. However, as similar mean differences between striatum and cortex/hippocampus were found in human post-mortem Bmax data (Hall et al., 1994), it seems reasonable to assume that the relatively low BP values in hippocampus and PFC reflect relatively low D2/3DR density. Competitive assay experiments comparing striatal and neocortical tissue in rhesus monkeys (Lidow et al., 1989) have documented, for both striatal and extrastriatal regions, that raclopride is a potent and selective D2/3 ligand, which can be displaced from its binding sites by D2/3-selective drugs.

Whether the effect is totally attributable to binding at postsynaptic D2/3DR's is unclear, as raclopride also binds to presynaptic autoreceptors on dopaminergic neurons. Autoreceptors play an important regulatory role in DA signalling, with consequences for locomotion and reinforcement-driven behaviour (Ford, 2014). Certainly, whether we partly measure presynaptic binding may have implications for the possible interpretation of the mechanisms involved, such as synaptic plasticity, about which we now can only speculate. For example, a rodent study suggests that pre-synaptic D2DRs are crucial for long-term depression and involved in long-term potentiation (Rocchetti et al., 2015). However, there are considerably fewer presynaptic than post-synaptic D2 receptors (Ford, 2014) and thus binding potential should mainly reflect binding to post-synaptic D2/3 receptors. Another limitation of these data is that physical activity frequency and intensity measures are based on self-reports, which can be subject to recall bias and social desirability.

In summary, this study is the first to demonstrate an association between physical activity and $D_{2/3}$DR availability in a large sample of participants. We observed that subjective intensity of physical activity was related to $D_{2/3}$DR availability in the caudate nucleus and to episodic memory performance, which in turn was related to $D_{2/3}$DR availability in the same striatal subregion. Considering the extant literature, we conclude that $D_{2/3}$DR in the caudate nucleus is a potentially important player in accounting for the influence of physical activity on episodic memory, or that DA activity in the caudate is involved in motivation to engage in physical activity, which might in turn benefit cognition. Both causal pathways seem plausible and not mutually exclusive.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.07.036.

References

Aguiar, A.S., Duzzioni, M., Remor, A.P., Tristao, F.S.M., Matheus, F.C., Raisman-Vozari, R., Prediger, R.D., 2016. Moderate-intensity physical exercise protects against experimental 6-hydroxydopamine-induced hemiparkinsonism through Nrf2-antioxidant response element pathway. Neurochem. Res. 41 (1–2), 64–72. https://doi.org/10.1007/s11064-015-1709-8.

Ahlskog, J.E., Geda, Y.E., Graff-Radford, N.R., Petersen, R.C., 2011. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin. Proc. 86 (9), 876–884. https://doi.org/10.4065/mcp.2011.0252.

Angevaren, M., Vanhees, L., Wendel-Vos, W., Verhaar, H.J., Aufdemkampe, G., Aleman, A., Verschuren, W.M., 2007. Intensity, but not duration, of physical activities is related to cognitive function. Eur. J. Cardiovasc. Prev. Rehabil. 14 (6), 825–830. https://doi.org/10.1097/HJR.0b013e3282ef995b.

Angevaren, M., Vanhees, L., Nooyens, A.C., Wendel-Vos, C.G., Verschuren, W.M., 2010. Physical activity and 5-year cognitive decline in the Doetinchem cohort study. Ann. Epidemiol. 20 (6), 473–479. https://doi.org/10.1016/j.annepidem.2010.03.007.

Ashburner, J., Barnes, G., Chen, C.-C., Daunizeau, J., Flandin, G., Friston, K.J., Phillips, C., 2013. SPM8 Manual. Institute of Neurology, University College London. Wellcome Trust Centre for Neuroimaging, London.

Asparouhov, T., Muthén, B.O., 2010. Weighted Least Squares Estimation with Missing Data. Mplus Notes.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: current status and future prospects. Neurosci. Biobehav. Rev. 30 (6), 791–807. https://doi.org/10.1016/J.Neubiorev.2006.06.005.

Bäckman, L., Lindenberger, U., Li, S.-C., Nyberg, L., 2010. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci. Biobehav. Rev. 34 (5), 670–677. https://doi.org/10.1016/j.neubiorev.2009.12.008.

Bäckman, L., Karlsson, S., Karlsson, P., Fischer, H., Brehmer, Y., Rieckmann, A., Nyberg, L., 2011. Dopamine D 1 receptors and age differences in brain activation during working memory. Neurobiol. Aging 32 (10), 1849–1856. https://doi.org/10.1016/j.neurobiolaging.2009.10.018.

Bauman, A., Ainsworth, B.E., Sallis, J.F., Hagstromer, M., Craig, C.L., Bull, F.C., Grp, I.P.S., 2011. The descriptive epidemiology of sitting. A 20-country comparison using the International Physical Activity Questionnaire (IPAQ). Am. J. Prev. Med. 41 (2), 228–235. https://doi.org/10.1016/j.amepre.2011.05.003.

Bauman, A., Merom, D., Bull, F.C., Buchner, D.M., Singh, M.A.F., 2016. Updating the evidence for physical activity: summative reviews of the epidemiological evidence, prevalence, and interventions to promote "Active Aging". Gerontol. 56, S268–S280. https://doi.org/10.1093/geront/gnw031.

Beeler, J.A., Faust, R.P., Turkson, S., Ye, H.G., Zhuang, X.X., 2016. Low dopamine D2 receptor increases vulnerability to obesity via reduced physical activity, not increased appetitive motivation. Biol. Psychiatr. 79 (11), 887–897. https://doi.org/10.1016/j.biopsych.2015.07.009.

Bettinardi, V., Presotto, L., Rapisarda, E., Picchio, M., Gianolli, L., Gilardi, M.C., 2011. Physical performance of the new hybrid PET/CT Discovery-690. Med. Phys. 38 (10), 5394–5411. https://doi.org/10.1118/1.3635220.

Blondell, S.J., Hammersley-Mather, R., Veerman, J.L., 2014. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC Publ. Health 14. https://doi.org/10.1186/1471-2458-14-510.

Boraxbekk, C.J., Salami, A., Wahlin, A., Nyberg, L., 2016. Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional

connectivity of the posterior default-mode network-A multimodal approach. Neuroimage 131, 133–141. https://doi.org/10.1016/j.neuroimage.2015.12.010.
Brown, T., 2006. Confirmatory Factor Analysis for Applied Research. Guilford, New York.
Brown, B.M., Peiffer, J.J., Sohrabi, H.R., Mondal, A., Gupta, V.B., Rainey-Smith, S.R., Grp, A.R., 2012. Intense physical activity is associated with cognitive performance in the elderly. Transl. Psychiatry 2. https://doi.org/10.1038/tp.2012.118.
Brown, B.M., Bourgeat, P., Peiffer, J.J., Burnham, S., Laws, S.M., Rainey-Smith, S.R., Grp, A.R., 2014. Influence of BDNF Val66Met on the relationship between physical activity and brain volume. Neurology 83 (15), 1345–1352.
Burzynska, A.Z., Chaddock-Heyman, L., Voss, M.W., Wong, C.N., Gothe, N.P., Olson, E.A., Cooke, G.E., 2014. Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. PLoS One 9 (9), e107413.
Camps, M., Cortes, R., Gueye, B., Probst, A., Palacios, J.M., 1989. Dopamine receptors in human brain: autoradiographic distribution of D2 sites. Neuroscience 28 (2), 275–290. https://doi.org/10.1016/0306-4522(89)90179-6.
Carlsson, A.C., Wandell, P.E., de Faire, U., Hellenius, M.L., 2008. Prevalence of hypertension in immigrants and Swedish-born individuals, a cross-sectional study of 60-year-old men and women in Sweden. J. Hypertens. 26 (12), 2295–2302. https://doi.org/10.1097/HJH.0b013e32831391c3.
Carvalho, A., Rea, I.M., Parimon, T., Cusack, B.J., 2014. Physical activity and cognitive function in individuals over 60 years of age: a systematic review. Clin. Interv. Aging 9, 661–682. https://doi.org/10.2147/cia.s55520.
Cervenka, S., Backman, L., Cselenyi, Z., Halldin, C., Farde, L., 2008. Associations between dopamine D2-receptor binding and cognitive performance indicate functional compartmentalization of the human striatum. Neuroimage 40 (3), 1287–1295. https://doi.org/10.1016/j.neuroimage.2007.12.063.
Chang, M., Saczynski, J.S., Snaedal, J., Bjornsson, S., Einarsson, B., Garcia, M., Jonsson, P.V., 2013. Midlife physical activity preserves lower extremity function in older adults: age gene/environment susceptibility–Reykjavik study. J. Am. Geriatr. Soc. 61 (2), 237–242. https://doi.org/10.1111/jgs.12077.
Charlton, R.A., Barrick, T.R., Markus, H.S., Morris, R.G., 2013. Verbal working and long-term episodic memory associations with white matter microstructure in normal aging investigated using tract-based spatial statistics. Psychol. Aging 28 (3), 768.
Chen, Z.X., Ito, K.I., Fujii, S., Miura, M., Furuse, H., Sasaki, H., Miyakawa, H., 1996. Roles of dopamine receptors in long-term depression: enhancement via D1 receptors and inhibition via D2 receptors. Recept. Channel 4 (1), 1–8.
Chen, H., Zhang, S.M., Schwarzschild, M.A., Hernan, M.A., Ascherio, A., 2005. Physical activity and the risk of Parkinson disease. Neurology 64 (4), 664–669.
Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Wright, J.T., 2003. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 42 (6), 1206–1252.
Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., Kramer, A.F., 2006. Aerobic exercise training increases brain volume in aging humans. J. Gerontol. Biol. Med. Sci. 61 (11), 1166–1170.
Cools, R., D'Esposito, M., 2011. Inverted-U–shaped dopamine actions on human working memory and cognitive control. Biol. Psychiatr. 69 (12), e113–e125.
Correa, M., Pardo, M., Bayarri, P., Lopez-Cruz, L., San Miguel, N., Valverde, O., Salamone, J.D., 2016. Choosing voluntary exercise over sucrose consumption depends upon dopamine transmission: effects of haloperidol in wild type and adenosine A(2A)KO mice. Psychopharmacology 233 (3), 393–404. https://doi.org/10.1007/s00213-015-4127-3.
Craig, C.L., Marshall, A.L., Sjostrom, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Oja, P., 2003. International physical activity questionnaire: 12-country reliability and validity. Med. Sci. Sports Exerc. 35 (8), 1381–1395. https://doi.org/10.1249/01.mss.0000078924.61453.fb.
Demirakca, T., Brusniak, W., Tunc-Skarka, N., Wolf, I., Meier, S., Matthaus, F., Diener, C., 2014. Does body shaping influence brain shape? Habitual physical activity is linked to brain morphology independent of age. World J. Biol. Psychiatr. 15 (5), 387–396. https://doi.org/10.3109/15622975.2013.803600.
Düzel, E., van Praag, H., Sendtner, M., 2016. Can physical exercise in old age improve memory and hippocampal function? Brain 139, 662–673. https://doi.org/10.1093/brain/awv407.
Eddy, M.C., Stansfield, K.J., Green, J.T., 2014. Voluntary exercise improves performance of a discrimination task through effects on the striatal dopamine system. Learn. Mem. 21 (7), 334–337. https://doi.org/10.1101/lm.034462.114.
Erickson, K.I., Kramer, A.F., 2009. Aerobic exercise effects on cognitive and neural plasticity in older adults. Br. J. Sports Med. 43 (1), 22–24. https://doi.org/10.1136/bjsm.2008.052498.
Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. U.S.A. 108 (7), 3017–3022. https://doi.org/10.1073/pnas.1015950108.
Erickson, K.I., Banducci, S.E., Weinstein, A.M., MacDonald, A.W., Ferrell, R.E., Halder, I., Manuck, S.B., 2013. The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance. Psychol. Sci. 24 (9), 1770–1779. https://doi.org/10.1177/0956797613480367.
Erickson, K.I., Leckie, R.L., Weinstein, A.M., 2014. Physical activity, fitness, and gray matter volume. Neurobiol. Aging 35, S20–S28. https://doi.org/10.1016/j.neurobiolaging.2014.03.034.
Farde, L., Hall, H., Ehrin, E., Sedvall, G., 1986. Quantitative analysis of D2 dopamine receptor binding in the living human brain by PET. Science 231 (4735), 258–261. https://doi.org/10.1126/science.2867601.
Farina, N., Rusted, J., Tabet, N., 2014. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. Int. Psychogeriatr. 26 (1), 9–18. https://doi.org/10.1017/s1041610213001385.
Ferencz, B., Laukka, E.J., Welmer, A.-K., Kalpouzos, G., Angleman, S., Keller, L., Bäckman, L., 2014. The benefits of staying active in old age: physical activity counteracts the negative influence of PICALM, BIN1, and CLU risk alleles on episodic memory functioning. Psychol. Aging 29 (2), 440.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Klaveness, S., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33 (3), 341–355.
Fischl, B., Salat, D.H., van der Kouwe, A.J., Makris, N., Segonne, F., Quinn, B.T., Dale, A.M., 2004. Sequence-independent segmentation of magnetic resonance images. Neuroimage 23 (Suppl. 1), S69–S84. https://doi.org/10.1016/j.neuroimage.2004.07.016.
Fisher, B.E., Petzinger, G.M., Nixon, K., Hogg, E., Bremmer, S., Meshul, C.K., Jakowec, M.W., 2004. Exercise-induced behavioral recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- lesioned mouse basal ganglia. J. Neurosci. Res. 77 (3), 378–390. https://doi.org/10.1002/jnr.20162.
Flöel, A., Ruscheweyh, R., Kruger, K., Willemer, C., Winter, B., Volker, K., Knecht, S., 2010. Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage 49 (3), 2756–2763. https://doi.org/10.1016/j.neuroimage.2009.10.043.
Forbes, D., Thiessen, E.J., Blake, C.M., Forbes, S.S., Forbes, S., 2014. Exercise programs for people with dementia. Sao Paulo Med. J. 132 (3), 195–196. https://doi.org/10.1590/1516-3180.20141323t2.
Ford, C.P., 2014. The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. Neuroscience 282, 13–22.
Frey, U., Schroeder, H., Matthies, H., 1990. Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. Brain Res. 522 (1), 69–75. https://doi.org/10.1016/0006-8993(90)91578-5.
Friend, D.M., Devarakonda, K., O'Neal, T.J., Skirzewski, M., Papazoglou, I., Kaplan, A.R., Kravitz, A.V., 2016. Basal ganglia dysfunction contributes to physical inactivity in obesity. Cell Metabol. https://doi.org/10.1016/j.cmet.2016.12.001.
Geda, Y.E., Roberts, R.O., Knopman, D.S., Christianson, T.J., Pankratz, V.S., Ivnik, R.J., Rocca, W.A., 2010. Physical exercise, aging, and mild cognitive impairment: a population-based study. Arch. Neurol. 67 (1), 80–86. https://doi.org/10.1001/archneurol.2009.297.
Gerecke, K.M., Jiao, Y., Pani, A., Pagala, V., Smeyne, R.J., 2010. Exercise protects against MPTP-induced neurotoxicity in mice. Brain Res. 1341, 72–83. https://doi.org/10.1016/j.brainres.2010.01.053.
Gilliam, P.E., Spirduso, W.W., Martin, T.P., Walters, T.J., Wilcox, R.E., Farrar, R.P., 1984. The effects of exercise training on [3H]-spiperone binding in rat striatum. Pharmacol. Biochem. Behav. 20 (6), 863–867. https://doi.org/10.1016/0091-3057(84)90008-X.
Ginovart, N., 2005. Imaging the dopamine system with in vivo [11C] raclopride displacement studies: understanding the true mechanism. Mol. Imag. Biol. 7 (1), 45–52.
Groot, C., Hooghiemstra, A.M., Raijmakers, P., van Berckel, B.N.M., Scheltens, P., Scherder, E.J.A., Ossenkoppele, R., 2016. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. Ageing Res. Rev. 25, 13–23. https://doi.org/10.1016/j.arr.2015.11.005.
Hall, H., Sedvall, G., Magnusson, O., Kopp, J., Halldin, C., Farde, L., 1994. Distribution of D1-and D2-Dopamine Receptors, and Dopamine And Its Metabolites In The Human Brain.
Han, X., Fischl, B., 2007. Atlas renormalization for improved brain MR image segmentation across scanner platforms. IEEE Trans. Med. Imag. 26 (4), 479–486. https://doi.org/10.1109/tmi.2007.893282.
Heyn, P., Abreu, B.C., Ottenbacher, K.J., 2004. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch. Phys. Med. Rehabil. 85 (10), 1694–1704. https://doi.org/10.1016/j.apmr.2004.03.019.
Johnson, L.G., Butson, M.L., Polman, R.C., Raj, I.S., Borkoles, E., Scott, D., Jones, G., 2016. Light physical activity is positively associated with cognitive performance in older community dwelling adults. J. Sci. Med. Sport 19 (11), 877–882. https://doi.org/10.1016/j.jsams.2016.02.002.
Jonasson, L.S., Axelsson, J., Riklund, K., Braver, T.S., Ogren, M., Backman, L., Nyberg, L., 2014. Dopamine release in nucleus accumbens during rewarded task switching measured by C-11 raclopride. Neuroimage 99, 357–364. https://doi.org/10.1016/j.neuroimage.2014.05.047.
Jonasson, L.S., Nyberg, L., Kramer, A., Lundquist, A., Riklund, K., Boraxbekk, C.J., 2016. Aerobic exercise intervention, cognitive performance, and brain structure: results from the Physical Influences on Brain in Aging (PHIBRA) study. Front. Aging Neurosci. 8 (336) https://doi.org/10.3389/fnagi.2016.00336.
Kerr, J., Marshall, S.J., Patterson, R.E., Marinac, C.R., Natarajan, L., Rosenberg, D., Crist, K., 2013. Objectively measured physical activity is related to cognitive function in older adults. J. Am. Geriatr. Soc. 61 (11), 1927–1931. https://doi.org/10.1111/jgs.12524.
Killgore, W.D.S., Olson, E.A., Weber, M., 2013. Physical exercise habits correlate with gray matter volume of the hippocampus in healthy adult humans. Sci. Rep. 3 https://doi.org/10.1038/srep03457.
Kleemeyer, M.M., Kühn, S., Prindle, J., Bodammer, N.C., Brechtel, L., Garthe, A., Lindenberger, U., 2016. Changes in fitness are associated with changes in hippocampal microstructure and hippocampal volume among older adults. Neuroimage 131, 155–161. https://doi.org/10.1016/j.neuroimage.2015.11.026.
Lee, K.N., Chirwa, S., 2015. Blocking dopaminergic signaling soon after learning impairs memory consolidation in Guinea pigs. PLoS One 10 (8). https://doi.org/10.1371/journal.pone.0135578.
Lee, S., Yuki, A., Nishita, Y., Tange, C., Kim, H., Kozakai, R., Shimokata, H., 2013. Relationship between light-intensity physical activity and cognitive function in a community-dwelling elderly population. An 8-year longitudinal study. J. Am. Geriatr. Soc. 61 (3), 452–453. https://doi.org/10.1111/jgs.12119.

Leemans, A., Jones, D.K., 2009. The B-Matrix must Be rotated when correcting for subject motion in DTI data. Magn. Reson. Med. 61 (6), 1336–1349. https://doi.org/10.1002/mrm.21890.

Levey, A.I., Hersch, S.M., Rye, D.B., Sunahara, R.K., Niznik, H.B., Kitt, C.A., Ciliax, B.J., 1993. Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. Proc. Natl. Acad. Sci. U.S.A. 90 (19), 8861–8865.

Lidow, M.S., Goldman-Rakic, P.S., Rakic, P., Innis, R.B., 1989. Dopamine D2 receptors in the cerebral cortex: distribution and pharmacological characterization with [3h] Raclopride. Proc. Natl. Acad. Sci. 1–5.

Liggins, J.T., 2009. The roles of dopamine D1 and D2 receptors in working memory function. Msurj 4 (1), 39–45.

Lin, T.W., Kuo, Y.M., 2013. Exercise benefits brain function: the monoamine connection. Brain Sci. 3 (1), 39–53. https://doi.org/10.3390/brainsci3010039.

Lindenberger, U., 2014. Human cognitive aging: corriger la fortune? Science 346 (6209), 572–578.

Lisman, J., Grace, A.A., Düzel, E., 2011. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. Trends Neurosci. 34 (10), 536–547. https://doi.org/10.1016/j.tins.2011.07.006.

Liu-Ambrose, T., Donaldson, M.G., Ahamed, Y., Graf, P., Cook, W.L., Close, J., Khan, K.M., 2008. Otago home-based strength and balance retraining improves executive functioning in older fallers: a randomized controlled trial. J. Am. Geriatr. Soc. 56 (10), 1821–1830. https://doi.org/10.1111/j.1532-5415.2008.01931.x.

Logan, J., Fowler, J.S., Volkow, N.D., Wang, G.J., Ding, Y.S., Alexoff, D.L., 1996. Distribution volume ratios without blood sampling from graphical analysis of PET data. J. Cerebr. Blood Flow Metabol. 16 (5), 834–840.

Lövdén, M., Karalija, N., Andersson, M., Wåhlin, A., Jan, A., Köhncke, Y., Lindenberger, U., 2017. Latent-profile analysis reveals behavioral and brain correlates of dopamine-cognition associations. Cerebr. Cortex 1–14. https://doi.org/10.1093/cercor/bhx253.

Maass, A., Duzel, S., Goerke, M., Becke, A., Sobieray, U., Neumann, K., Duzel, E., 2015. Vascular hippocampal plasticity after aerobic exercise in older adults. Mol. Psychiatr. 20 (5), 585–593. https://doi.org/10.1038/mp.2014.114.

Mabandla, M., Kellaway, L., Gibson, A.S., Russell, V.A., 2004. Voluntary running provides neuroprotection in rats after 6-hydroxydopamine injection into the medial forebrain bundle. Metab. Brain Dis. 19 (1–2), 43–50. https://doi.org/10.1023/B:MEBR.0000027416.13070.c3.

MacRae, P.G., Spirduso, W.W., Walters, T.J., Farrar, R.P., Wilcox, R.E., 1987. Endurance training effects on striatal D2-dopamine receptor binding and striatal dopamine metabolites in presenescent older rats. Psychopharmacology 92 (2), 236–240.

Madden, D.J., Bennett, I.J., Burzynska, A.Z., Potter, G.G., Chen, N.-K., Song, A.W., 2012. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1822 (3), 386–400. https://doi.org/10.1016/j.bbadis.2011.08.003.

Makizako, H., Liu-Ambrose, T., Shimada, H., Doi, T., Park, H., Tsutsumimoto, K., Suzuki, T., 2015. Moderate-intensity physical activity, hippocampal volume, and memory in older adults with mild cognitive impairment. J. Gerontol. Biol. Med. Sci. 70 (4), 480–486. https://doi.org/10.1093/gerona/glu136.

Manago, F., Castellano, C., Oliverio, A., Mele, A., De Leonibus, E., 2009. Role of dopamine receptors subtypes, D1-like and D2-like, within the nucleus accumbens subregions, core and shell, on memory consolidation in the one-trial inhibitory avoidance task. Learn. Mem. 16 (1), 46–52. https://doi.org/10.1101/lm.1177509.

Mathes, W.F., Nehrenberg, D.L., Gordon, R., Hua, K.J., Garland, T., Pomp, D., 2010. Dopaminergic dysregulation in mice selectively bred for excessive exercise or obesity. Behav. Brain Res. 210 (2), 155–163. https://doi.org/10.1016/j.bbr.2010.02.016.

McEwen, S.C., Hardy, A., Ellingson, B.M., Jarrahi, B., Sandhu, N., Subotnik, K.L., Nuechterlein, K.H., 2015. Prefrontal and hippocampal brain volume deficits: role of low physical activity on brain plasticity in first-episode schizophrenia patients. J. Int. Neuropsychol. Soc. 21 (10), 868–879. https://doi.org/10.1017/s1355617715000983.

Meeusen, R., Smolders, I., Saare, S., DeMeirleir, K., Keizer, H., Serneels, M., Michotte, Y., 1997. Endurance training effects on neurotransmitter release in rat striatum: an in vivo microdialysis study. Acta Physiol. Scand. 159 (4), 335–341. https://doi.org/10.1046/j.1365-201X.1997.00118.x.

Memel, M., Bourassa, K., Woolverton, C., Sbarra, D.A., 2016. Body mass and physical activity uniquely predict change in cognition for aging adults. Ann. Behav. Med. 50 (3), 397–408. https://doi.org/10.1007/s12160-015-9768-2.

Muthén, L.K., Muthén, B.O., 1998-2015. Mplus User's Guide, 7 ed. Muthén & Muthén, Los Angeles CA.

Nevalainen, N., Riklund, K., Andersson, M., Axelsson, J., Ogren, M., Lovden, M., Nyberg, L., 2015. COBRA: a prospective multimodal imaging study of dopamine, brain structure and function, and cognition. Brain Res. 1612, 83–103. https://doi.org/10.1016/j.brainres.2014.09.010.

Niemann, C., Godde, B., Voelcker-Rehage, C., 2014. Not only cardiovascular, but also coordinative exercise increases hippocampal volume in older adults. Front. Aging Neurosci. 6.

Niv, Y., Daw, N.D., Joel, D., Dayan, P., 2007. Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology 191 (3), 507–520. https://doi.org/10.1007/s00213-006-0502-4.

Nouchi, R., Taki, Y., Takeuchi, H., Sekiguchi, A., Hashizume, H., Nozawa, T., Kawashima, R., 2014. Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: evidence from a randomized controlled trial. Age 36 (2), 787–799. https://doi.org/10.1007/s11357-013-9588-x.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. Trends Cognit. Sci. 16 (5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005.

Nyberg, L., Karalija, N., Salami, A., Andersson, M., Wahlin, A., Kaboovand, N., Backman, L., 2016. Dopamine D2 receptor availability is linked to hippocampal-caudate functional connectivity and episodic memory. Proc. Natl. Acad. Sci. U.S.A. 113 (28), 7918–7923. https://doi.org/10.1073/pnas.1606309113.

Petzinger, G.M., Walsh, J.P., Akopian, G., Hogg, E., Abernathy, A., Arevalo, P., Jakowec, M.W., 2007. Effects of treadmill exercise on dopaminergic transmission in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse model of basal ganglia injury. J. Neurosci. 27 (20), 5291–5300. https://doi.org/10.1523/jneurosci.1069-07.2007.

Petzinger, G.M., Fisher, B.E., McEwen, S., Beeler, J.A., Walsh, J.P., Jakowec, M.W., 2013. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol. 12 (7), 716–726.

Prakash, R.S., Voss, M.W., Erickson, K.I., Kramer, A.F., 2015. Physical activity and cognitive vitality. In: Fiske, S.T. (Ed.), Annual Review of Psychology, Vol 66, vol 66, 769-+.

Renoir, T., Chevarin, C., Lanfumey, L., Hannan, A.J., 2011. Effect of enhanced voluntary physical exercise on brain levels of monoamines in Huntington disease mice. PLoS Curr 3. https://doi.org/10.1371/currents.RRN1281. Rrn1281.

Robertson, C.L., Ishibashi, K., Chudzynski, J., Mooney, L.J., Rawson, R.A., Dolezal, B.A., London, E.D., 2016. Effect of exercise training on striatal dopamine D2/D3 receptors in methamphetamine users during behavioral treatment. Neuropsychopharmacology 41 (6), 1629–1636. https://doi.org/10.1038/npp.2015.331.

Rocchetti, J., Isingrini, E., Dal Bo, G., Sagheby, S., Menegaux, A., Tronche, F., Giros, B., 2015. Presynaptic D2 dopamine receptors control long-term depression expression and memory processes in the temporal Hippocampus. Biol. Psychiatr. 77 (6), 513–525. https://doi.org/10.1016/j.biopsych.2014.03.013.

Rönnlund, M., Nyberg, L., Bäckman, L., Nilsson, L.G., 2005. Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. Psychol. Aging 20 (1), 3–18. https://doi.org/10.1037/0882-7974.20.1.3.

Ross, S.B., Jackson, D.M., 1989. Kinetic properties of the accumulation of H3-raclopride in the mouse brain invivo. N. Schmied. Arch. Pharmacol. 340 (1), 6–12.

Rovio, S., Spulber, G., Nieminen, L.J., Niskanen, E., Winblad, B., Tuomilehto, J., Kivipelto, M., 2010. The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol. Aging 31 (11), 1927–1936.

Ruscheweyh, R., Willemer, C., Kruger, K., Duning, T., Warnecke, T., Sommer, J., Floel, A., 2011. Physical activity and memory functions: an interventional study. Neurobiol. Aging 32 (7), 1304–1319. https://doi.org/10.1016/j.neurobiolaging.2009.08.001.

Salami, A., Eriksson, J., Nilsson, L.-G., Nyberg, L., 2012. Age-related white matter microstructural differences partly mediate age-related decline in processing speed but not cognition. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1822 (3), 408–415. https://doi.org/10.1016/j.bbadis.2011.09.001.

Salami, A., Rieckmann, A., Karalija, N., Avelar-Pereira, B., Andersson, M., Wåhlin, A., et al., 2018. Neurocognitive profiles of older adults with working-memory dysfunction. Cerebr. Cortex 131, 567–15. http://doi.org/10.1093/cercor/bhy062.

Schultz, W., 2007. Multiple Dopamine Functions at Different Time Courses *Annual Review of Neuroscience*, vol 30, pp. 259–288.

Seeman, P., Guan, H.C., Niznik, H.B., 1989. Endogenous dopamine lowers the dopamine D2 receptor density as measured by [3H] raclopride: implications for positron emission tomography of the human brain. Synapse 3 (1), 96–97.

Shohamy, D., Adcock, R.A., 2010. Dopamine and adaptive memory. Trends Cognit. Sci. 14 (10), 464–472. https://doi.org/10.1016/j.tics.2010.08.002.

Simonen, R.L., Rankinen, T., Perusse, L., Leon, A.S., Skinner, J.S., Wilmore, J.H., Bouchard, C., 2003. A dopamine D2 receptor gene polymorphism and physical activity in two family studies. Physiol. Behav. 78 (4–5), 751–757. https://doi.org/10.1016/s0031-9384(03)00084-2.

Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155. https://doi.org/10.1002/hbm.10062.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23, S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Behrens, T.E.J., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31 (4), 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Sherwood, A., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. 72 (3), 239–252.

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G.F., Casini, A., Macchi, C., 2011. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J. Intern. Med. 269 (1), 107–117. https://doi.org/10.1111/j.1365-2796.2010.02281.x.

Statistics-Sweden, 1999. Undersökning Av Levnadsförhållanden (ULF).

Sutoo, D., Akiyama, K., 2003. Regulation of brain function by exercise. Neurobiol. Dis. 13 (1), 1–14. https://doi.org/10.1016/s0969-9961(03)00030-5.

Tajiri, N., Yasuhara, T., Shingo, T., Kondo, A., Yuan, W.J., Kadota, T., Date, I., 2010. Exercise exerts neuroprotective effects on Parkinson's disease model of rats. Brain Res. 1310, 200–207. https://doi.org/10.1016/j.brainres.2009.10.075.

Takahashi, H., 2013. PET neuroimaging of extrastriatal dopamine receptors and prefrontal cortex functions. J. Physiol. Paris 107 (6), 503–509. https://doi.org/10.1016/j.jphysparis.2013.07.001.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., Suhara, T., 2008. Differential contributions of prefrontal and hippocampal dopamine D1 and D2

receptors in human cognitive functions. J. Neurosci. 28 (46), 12032–12038. https://doi.org/10.1523/jneurosci.3446-08.2008.

Thacker, E.L., Chen, H., Patel, A.V., McCullough, M.L., Calle, E.E., Thun, M.J., et al., 2008. Recreational physical activity and risk of Parkinson's disease. Movement Disorders 23 (1), 69–74. https://doi.org/10.1002/mds.21772.

Toy, W.A., Petzinger, G.M., Leyshon, B.J., Akopian, G.K., Walsh, J.P., Hoffman, M.V., Jakowec, M.W., 2014. Treadmill exercise reverses dendritic spine loss in direct and indirect striatal medium spiny neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. Neurobiol. Dis. 63, 201–209. https://doi.org/10.1016/j.nbd.2013.11.017.

van Gelder, B.M., Tijhuis, M.A.R., Kalmijn, S., Giampaoli, S., Nissinen, A., Kromhout, D., 2004. Physical activity in relation to cognitive decline in elderly men - the FINE Study. Neurology 63 (12), 2316–2321.

Voelcker-Rehage, C., Niemann, C., 2013. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci. Biobehav. Rev. 37 (9), 2268–2295. https://doi.org/10.1016/j.neubiorev.2013.01.028.

Voss, M.W., Prakash, R.S., Erickson, K.I., Basak, C., Chaddock, L., Kim, J.S., White, S.M., 2010. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front. Aging Neurosci. 2, 32.

Voss, M.W., Heo, S., Prakash, R.S., Erickson, K.I., Alves, H., Chaddock, L., Kramer, A.F., 2013. The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: results of a one-year exercise intervention. Hum. Brain Mapp. 34 (11), 2972–2985. https://doi.org/10.1002/hbm.22119.

Voss, M.W., Carr, L.J., Clark, R., Weng, T., 2014. Revenge of the "sit" II: does lifestyle impact neuronal and cognitive health through distinct mechanisms associated with sedentary behavior and physical activity? Ment. Health Phys. Activ. 7 (1), 9–24. https://doi.org/10.1016/j.mhpa.2014.01.001.

Vuckovic, M.G., Li, Q.Z., Fisher, B., Nacca, A., Leahy, R.M., Walsh, J.P., Petzinger, G.M., 2010. Exercise elevates dopamine D2 receptor in a mouse model of Parkinson's disease: in vivo imaging with F-18 fallypride. Mov. Disord. 25 (16), 2777–2784. https://doi.org/10.1002/mds.23407.

Walhovd, K.B., Storsve, A.B., Westlye, L.T., Drevon, C.A., Fjell, A.M., 2014. Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. Neurobiol. Aging 35 (5), 1055–1064. https://doi.org/10.1016/j.neurobiolaging.2013.11.011.

Wallsten, E., Axelsson, J., Sundstrom, T., Riklund, K., Larsson, A., 2013. Subcentimeter tumor lesion delineation for high-resolution 18F-FDG PET images: optimizing correction for partial-volume effects. J. Nucl. Med. Technol. 41 (2), 85–91. https://doi.org/10.2967/jnmt.112.117234.

Wang, G.-J., Volkow, N.D., Fowler, J.S., Franceschi, D., Logan, J., Pappas, N.R., Netusil, N., 2000. PET studies of the effects of aerobic exercise on human striatal dopamine release. J. Nucl. Med. 41 (8), 1352–1356.

Willey, J.Z., Gardener, H., Caunca, M.R., Moon, Y.P., Dong, C.H., Cheung, Y.K., Wright, C.B., 2016. Leisure-time physical activity associates with cognitive decline: the northern manhattan study. Neurology 86 (20), 1897–1903. https://doi.org/10.1212/wnl.0000000000002582.

Xu, Q., Park, Y., Huang, X., Hollenbeck, A., Blair, A., Schatzkin, A., Chen, H., 2010. Physical activities and future risk of Parkinson disease. Neurology 75, 341–348.

Yoon, M.C., Shin, M.S., Kim, T.S., Kim, B.K., Ko, I.G., Sung, Y.H., Kim, C.J., 2007. Treadmill exercise suppresses nigrostriatal dopaminergic neuronal loss in 6-hydroxydopamine-induced Parkinson's rats. Neurosci. Lett. 423 (1), 12–17. https://doi.org/10.1016/j.neulet.2007.06.031.

Young, J., Angevaren, M., Rusted, J., Tabet, N., 2015. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst. Rev. 4 https://doi.org/10.1002/14651858.CD005381.pub4.