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Reduced effects of age on dopamine D2 receptor levels in physically active adults

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ABSTRACT

Physical activity has been shown to ameliorate dopaminergic degeneration in non-human animal models. However, the effects of regular physical activity on normal age-related changes in dopamine function in humans are unknown. Here we present cross-sectional data from forty-four healthy human subjects between 23 and 80 years old, showing that typical age-related dopamine D2 receptor loss, assessed with PET [18 F]fallypride, was significantly reduced in physically active adults compared to less active adults.

1. Introduction

Increasing evidence indicates that physical activity has broad benefits for physical health, mental health, and cognitive function across the life span (Kramer and Erickson, 2007). Widespread public health efforts, led by a coalition of national organizations, including the National Institute on Aging and the Center for Disease Control and Prevention, seek to increase physical activity among America's aging population with the intention of, among other stated benefits, sustaining neurotransmitter levels and functional capacity (Sheppard et al., 2003). The dopamine system (Nieoullon, 2002), for which there is extensive evidence of age-related decline in dopamine D1 receptors, D2 receptors (DRD2), and transporters, is strongly implicated in a range of cognitive functions from reward processing to cognitive control (Backman et al., 2006). Thus, any intervention that slows the rate of age-related decline in dopamine functioning should generally promote cognitive health.

Most research examining the causal role of physical activity on dopamine function has been performed in rodents treated with 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), a neurotoxin that kills dopamine neurons. Physical activity prior to MPTP treatment was found to protect mice against MPTP-induced neurotoxicity (Gerecke et al., 2010). After MPTP treatment, physical activity increased the number of dopamine neurons, normalized axonal and dendritic arborization, and increased DRD2 expression (Ahmad et al., 2009; Vuckovic et al., 2010). Physical activity is believed to protect dopamine function by inhibiting inflammation-induced dopaminergic degeneration via suppression of microglial activity or activation of the brain-derived neurotrophic factor signaling pathway (Sung et al., 2012; Wu et al., 2011).

Intriguingly, exercise training was observed to increase striatal DRD2 receptor availability in humans with Parkinson's disease and methamphetamine users (Fisher et al., 2013; Robertson et al., 2016). However, although aging, Parkinson's disease, methamphetamine use and MPTP neurotoxicity all impact dopamine functions, the specificity of their effects on the dopamine system differs significantly. Degeneration associated with Parkinson's disease is much steeper than during normal aging, and dopamine loss in Parkinson's disease is much greater in the putamen than the caudate, whereas in normal aging dopamine loss is approximately equivalent in both striatal structures (Kish et al., 1992; Kumakura et al., 2010). Therefore it remains unknown whether these findings from degenerative and neurotoxic conditions can be extrapolated to disease-free humans.

In a cross-sectional study, we examined whether physical activity is associated with reduced age effects on DRD2 receptors. Forty-four healthy human subjects (27 females) between 23 and 80 years old underwent PET with [18F]fallypride, a high affinity DRD2 ligand (Siessmeier et al., 2005) for the assessment of DRD2 availability, underwent structural MRI to aid coregistration of PET data during data processing, and wore a pedometer for 10 consecutive days to measure

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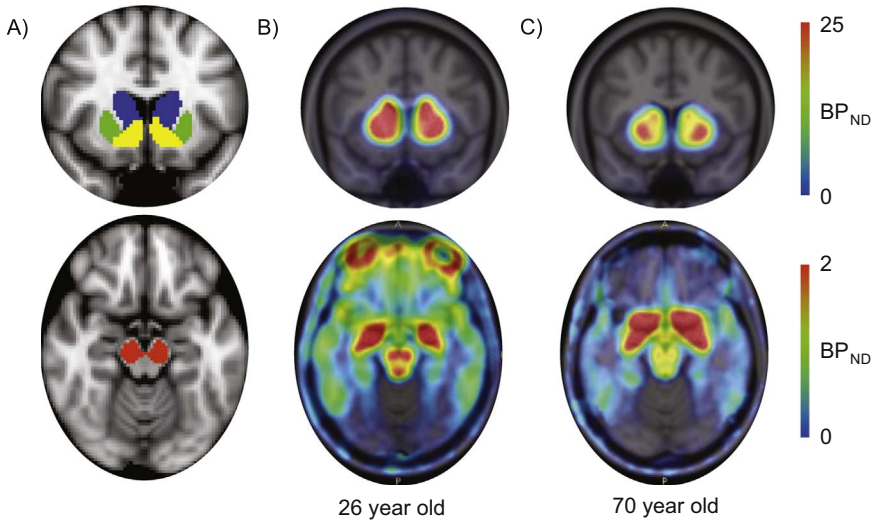

Fig. 1. [18F]fallypride BP_{ND} images reflecting DRD2 availability. A) Shown are regions of interest from which we extracted mean BP_{ND} for analyses: caudate (blue), putamen (green), ventral striatum (yellow), and midbrain (red). BP_{ND} image from a 26-year-old subject (B) is juxtaposed with BP_{ND} image from a 70-year-old subject (C) for visual comparison of DRD2 availability at different ages. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the number of steps each subject took per day as an assessment of regular physical activity. Binding potential (BP_{ND}) images, reflecting DRD2 availability, were calculated from PET [18F]fallypride data using the simplified reference tissue model. Striatal (caudate, putamen, ventral striatum / nucleus accumbens) and midbrain regions of interest were defined in standard MNI space using previously published guidelines (Dang et al., 2012a; Mawlawi et al., 2001) and nonlinearly registered to each subject's BP_{ND} image for BP_{ND} extraction (Fig. 1).

2. Materials and methods

2.1. Subjects

Fifty-three healthy volunteers from the Nashville, TN metro area participated in this study. The present report included data from 44 subjects (23 to 80 years old, mean age ± SD: 48 ± 16 years, 27 females) (see the Physical Activity Assessment section for details on the exclusion of 9 subjects from analyses). Exclusion criteria included any history of psychiatric illness on a screening interview (a Structural Interview for Clinical DSM-IV Diagnosis was also available for all subjects and confirmed no history of major Axis I disorders) (First et al., 1997), any history of head trauma, any significant medical condition, or any condition that would interfere with MRI (e.g. inability to fit in the scanner, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, pregnancy, and metallic body inclusions or other contraindicated metal implanted in the body). Subjects with major medical disorders including diabetes and/or abnormalities on screening comprehensive metabolic panel or complete blood count were excluded. Subjects were also excluded if they reported a history of substance abuse, current tobacco use, alcohol consumption greater than 8 ounces of whiskey or equivalent per week, use of psychostimulants (excluding caffeine) more than twice at any time in their life or at all in the past 6 months, or any psychotropic medication in the last 6 months other than occasional use of benzodiazepines for sleep. Any illicit drug use in the last 2 months was grounds for exclusion, even in subjects who did not otherwise meet criteria for substance abuse. Urine drug tests were administered, and subjects testing positive for the presence of amphetamines, cocaine, marijuana, PCP, opiates, benzodiazepines, or barbiturates were excluded. Written informed consent was obtained from all subjects. This study was approved by the Institutional Review Boards at Vanderbilt University and Yale University and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Weight and height were measured by a clinician during each subject's physical exam. Physical activity did not significantly correlate with BMI (r_{42}=−0.22, p=0.146), indicating that individual differences in physical activity did not reflect physical constraint associated with body size.

2.2. Physical activity assessment

Subjects were asked to wear a pedometer (Yamax SW-200 Digi-Walker step pedometer) for 10 consecutive days and instructed to perform physical activity at their regular level while wearing a pedometer. Every day for 10 days, text messages were delivered through ohdontforget.com to each participant at variable times once in the morning, once in the afternoon, and once in the evening, with a link to a mobile web survey asking them to enter the number of steps currently on their pedometers. An average (mean) number of steps taken per day was calculated for each participant. From the pedometer data, six subjects were excluded from analyses for reporting their pedometer count less than 20 times (out of the total 30) over 10 days. Two subjects were excluded for routinely resetting their pedometer to zero. One subject was excluded for having a step-per-day count that was more than three standard deviations from the mean. Thus, data from 44 subjects were included in the analyses.

2.3. PET data acquisition

PET imaging was performed on a GE Discovery STE scanner located at Vanderbilt University Medical Center. The scanner had an axial resolution of 4 mm and in-plane resolution of 4.5–5.5 mm FWHM at the center of the field of view. [18F]fallypride ((S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3[18F]fluoropropyl)-2,3- dimethoxybenzamide) was produced in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures described in US Food and Drug Administration IND 47,245. [18F]fallypride is a substituted benzamide with very high affinity to D2/D3 receptors (Mukherjee et al., 1995). 3D emission acquisition scans were performed following a 5.0 mCi slow bolus injection of [18F]fallypride (specific activity greater than 3000 Ci/mmol). CT scans were collected for attenuation correction prior to each of the three emission scans, which together lasted approximately 3.5 hours, with two 15-minute breaks for subject comfort. PET images were reconstructed with decay correction, attenuation correction, scatter correction, and calibration.

The average time difference between physical activity assessment and PET scanning was less than 2 weeks, with most subjects wearing the pedometer and undergoing PET in the same week.

2.4. MRI data acquisition

Structural MRI scans were performed on a 3 T Phillips Achieva scanner located at the Vanderbilt University Institute for Imaging Science (VUIIS). T1-weighted high-resolution 3D anatomical scans (TR=8.9ms, TE=4.6ms, FOV=256×256, voxel dimensions=1×1×1mm) were obtained for each participant to aid coregistration and spatial normalization of PET images.

2.5. [18F]fallypride binding potential (BP_{ND}) image calculation

Voxelwise D2/D3 binding potential images were calculated using the simplified reference tissue model, which has been shown to provide stable estimates of [18F]fallypride BP_{ND} (Siessmeier et al., 2005). The cerebellum was the reference region because of its relative lack of D2/D3 receptors (Camps et al., 1989). The cerebellar reference region was obtained from an atlas provided by the ANSIR laboratory at Wake Forest University. Limited PET spatial resolution introduces blurring and causes signal to spill onto neighboring regions. Because the cerebellum is located proximal to the substantia nigra and colliculus, which both have DRD2, only the posterior 3⁄4 of the cerebellum was included in the region of interest (ROI) to avoid contamination of [18F]fallypride signal from the midbrain nuclei. The cerebellum ROI also excluded voxels within 5 mm of the overlying cerebral cortex to prevent contamination of cortical signals. The bilateral putamen ROI, drawn according to established guidelines (Mawlawi et al., 2001) on the MNI brain, served as the receptor rich region in the analysis. The cerebellum and putamen ROIs were registered to each subject's T1 image using FSL non-linear registration of the MNI template to individual subject T1. T1 images and their associated cerebellum and putamen ROIs were then coregistered to the mean image of all realigned frames in the PET scan using FSL-FLIRT (http://www.fmrib.ox.ac.uk/fsl/, version 6.00). Emission images from the 3 PET scans were merged temporally into a 4D file. To correct for motion during scanning and misalignment between the 3 PET scans, all PET frames were realigned using SPM8 to the frame acquired 10 min post injection (www.fil.ion.ucl.ac.uk/spm/). Model fitting and BP_{ND} calculation were performed using the PMOD Biomedical Imaging Quantification software (PMOD Technologies, Switzerland). Binding potential images represent the ratio of specifically bound ligand ([18F]fallypride in this study) to its free concentration.

For ROI analyses, mean binding potential in the midbrain and 3 striatal ROIs (caudate, putamen, and ventral striatum / nucleus accumbens) were extracted. The bilateral midbrain and striatal ROIs were drawn in MNI standard space using previously described guidelines (Dang et al., 2012a, b; Mawlawi et al., 2001), registered to PET images using the same transformations for cerebellum registration to PET images, and thresholded at 0.5 after coregistration to ensure high tissue probability.

2.6. Statistical analysis

We regressed age on BP_{ND} in the caudate (mean ± SD: 14.22 ± 3.43), putamen (mean ± SD: 23.24 ± 3.50), ventral striatum (mean ± SD: 14.08 ± 2.59), and midbrain (mean ± SD: 1.22 ± 0.23) to confirm that DRD2 availability was lower in older compared to younger age as previously reported (Antonini and Leenders, 1993; Ichise et al., 1998; Rinne et al., 1993). To examine the role of physical activity in the association between age and DRD2 availability, we regressed BP_{ND}, for each of the four ROIs separately, on the interaction between age and physical activity, as measured by average steps taken per day (mean ± SD: 5975 ± 2403), with income as a covariate of non-interest. Observing a significant interaction of age and physical activity on ventral striatal BP_{ND}, we performed a median split of the physical activity data into a less active group and a more active group, and regressed ventral striatal BP_{ND} on age separately for the two groups to characterize the interaction. Additionally, we performed voxelwise regressions in SPM8 to examine the association between age and BP_{ND} (with income as a covariate), separately for the less active group and the more active group, to illustrate the spatial extent of DRD2 loss in these two groups. Voxelwise results were corrected for family wise error and small-volume corrected with a midbrain mask and a striatal mask composed of the caudate, putamen, and ventral striatum ROIs. To quantify the spatial extent of DRD2 loss in each group, we calculated the percent of striatal and midbrain volumes identified by voxelwise analyses as showing significant BP_{ND} decline for the less and more active groups. Additional post-hoc analyses explored potential age effects and interactions with physical activity in cortical regions using FreeSurfer to segment the cortex into grey matter ROIs.

3. Results

To counteract the issue of multiple comparisons with 4 ROIs, we applied Bonferroni correction and utilized a corrected significance threshold of $p < 0.0125$. As expected, we found that age (mean ± SD: 48 ± 16 years) negatively correlated with BP_{ND} in all three regions of the striatum, which has the highest concentration of postsynaptic DRD2 in the brain, as well as in the midbrain, the site of dopamine neurons on which presynaptic DRD2 are located: caudate ($r_{42}=-0.839$, $p < 0.0001$), putamen ($r_{42}=-0.695$, $p < 0.0001$), ventral striatum ($r_{42}=-0.422$, $p=0.004$), and midbrain ($r_{42}=-0.606$, $p < 0.0001$) (Fig. 2). The rate of decline per decade (regression slope with the average BP_{ND} of all subjects in their 20 s as the point of reference) was 10.5% in the caudate, 5.9% in the putamen, 4.9% in the ventral striatum, and 6.3% in the midbrain. Previous studies using PET [18F]fallypride also reported similar rates of decline, ranging from 6% to 13% per decade in the striatum and midbrain (Cumming et al., 2013; Kegeles et al., 2010; Mukherjee et al., 2002). To assess the impact of physical activity on age-related DRD2 loss, we examined the interaction of age and physical activity on BP_{ND}. Physical activity, as indexed with our pedometer-based daily average, was not related to age ($r_{42}=-0.155$, $p=0.317$). As has been shown previously (Ford et al., 1991), physical activity was associated with income ($r_{42}=0.376$, $p=0.012$), so we included income as a covariate of non-interest in all analyses involving physical activity. Age and physical activity significantly interacted to predict BP_{ND} in the ventral striatum ($\beta=3.1\times10^{-5}$, $SE=9.9\times10^{-6}$, $t_{39}=3.085$, $p=0.004$), indicating that the negative correlation between age and ventral striatal BP_{ND} varied across physical activity levels. Without income as a covariate, the interaction of age and physical activity on ventral striatal BP_{ND} was also significant ($\beta=3.55\times10\text{-}5$, $SE=1.1\times10\text{-}5$, $t_{40}=3.365$, $p=0.002$). However, given the established and replicated relation between income and physical activity, we believe that including income as a covariate in our analyses is necessary to isolate the effects of physical activity. To illustrate the nature of this interaction, we performed a median split of the physical activity data (mean ± SD: 5975 ± 2403 steps per day) into a more active group (> 5600 steps per day, mean ± SD: 7807 ± 1870) and a less active group (< 5600 steps per day, mean ± SD: 4143 ± 1139) (Table 1). Age showed a significant inverse association with DRD2 receptor availability in the less active group ($r_{19}=-0.72$, $p < 0.001$). By contrast, there was not a significant effect of age on DRD2 receptor availability in the more active group ($r_{19}=-0.21$, $p=0.368$) (Fig. 3A). Although all individual subject ventral striatal BP_{ND} values were within 3 standard deviations of the mean, the distribution of data points in Fig. 3A suggests that a young subject with very low ventral striatal BP_{ND} in the more active group could be biasing the interaction, potentially inflating the association in this group. We therefore reran the interaction test without this subject, which demonstrated that the

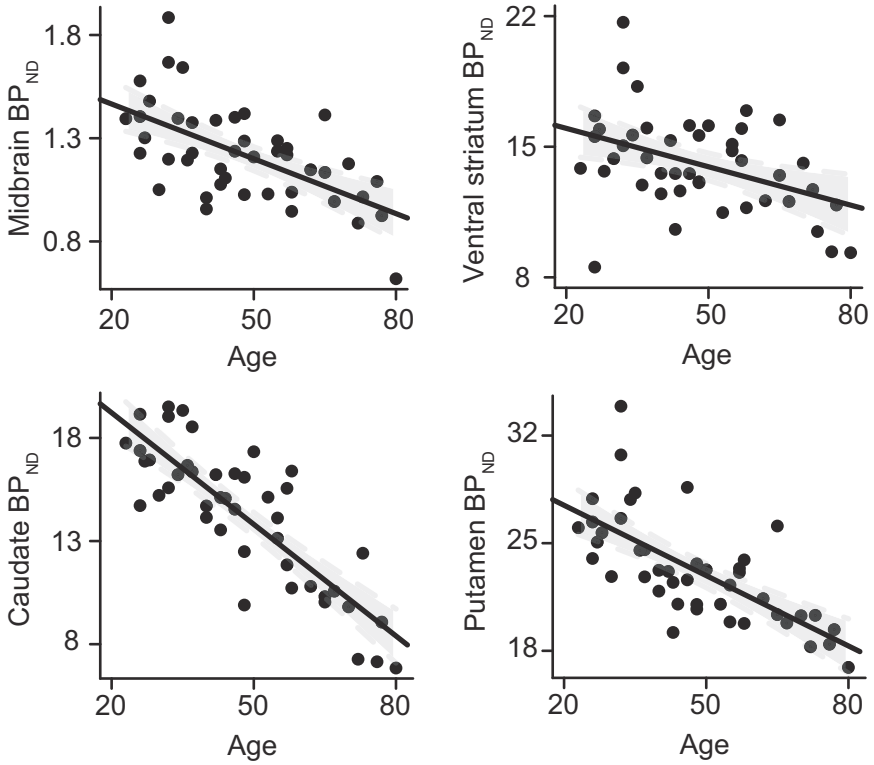

Fig. 2. DRD2 availability across adulthood. Age negatively correlated with BP_{ND} in the midbrain (r_{42}= −0.606, p < 0.0001), the ventral striatum (r_{42}= −0.422, p = 0.004), the caudate (r_{42}= −0.839, p < 0.0001), and the putamen (r_{42}= −0.695, p < 0.0001).

Table 1
Characteristics of participants.

	Less active group	More active group	p-value
Age	51.2 ± 18.0	44.2 ± 13.2	0.151
Sex	13F / 9M	14F / 8M	0.764
Household income	$60 K - $69 K	$80 K – 89 K	0.058
Physical activity (steps/day)	4143 ± 1139	7807 ± 1870	< 0.001
Ventral striatal BP_{ND}	14.5 ± 3.0	13.7 ± 2.0	0.293
Caudate BP_{ND}	14.0 ± 3.9	14.4 ± 2.9	0.713
Putamen BP_{ND}	23.3 ± 4.2	23.2 ± 2.8	0.936
Midbrain BP_{ND}	1.2 ± 0.3	1.2 ± 0.2	0.785

interaction of age and physical activity on ventral striatal BP_{ND} remained significant ($\beta=2.2\times10^{-5}$, $SE=1.1\times10^{-5}$, $t_{38}=2.132$, p=0.040). The interaction of age and physical activity did not significantly predict BP_{ND} in the caudate ($\beta=5.24\times10^{-6}$, $SE=9.64\times10^{-6}$, $t_{39}=0.543$, p=0.590), putamen ($\beta=1.59\times10^{-5}$, $SE=1.28\times10^{-5}$, $t_{39}=1.242$, p=0.222), or midbrain ($\beta=1.22\times10^{-6}$, $SE=9.17\times10^{-7}$, $t_{39}=1.326$, p=0.193).

In addition to the magnitude difference in age-related DRD2 loss between the less active group and the more active group, we performed voxelwise analyses, with family-wise error correction, correlating age with BP_{ND} separately for the less active and more active groups to illustrate the spatial extent of DRD2 loss in these two groups. This analysis complements the above ROI analysis by emphasizing the spatial breadth of observable age effects on DRD2 receptor availability as opposed to the magnitude of the age effects within the entire a priori anatomically defined region. We normalized each subject's BP_{ND} image to standard MNI space using FSL's nonlinear registration tool and performed a voxelwise regression in SPM with age as the dependent variable predicting [18F]fallypride BP_{ND}. We found that the age effects on DRD2 receptor availability were more spatially extensive in the less active group than the more active group throughout the striatum and in the midbrain. In the more active group, age effects on DRD2 receptor availability reached statistical significance in 11% of the striatum (ventral striatum, caudate, putamen) and 6% of the midbrain. By contrast, in the less active group, significant age effects on DRD2 levels covered 27% of the striatum and 36% of the midbrain (Fig. 3B).

We focused on the striatum because it has the highest concentration of DRD2 in the brain, and the midbrain because that is where most forebrain-projecting dopamine neurons (and somatodendritic DRD2 autoreceptors) are located. Previous studies have also reported age-related effects on DRD2 in cortical areas (Kaasinen et al., 2000). For additional exploratory, post-hoc analyses we used FreeSurfer to segment the cortex into 72 cortical grey matter ROIs, of which 23 have mean BP_{ND} statistically higher than 0.5, a typical cutoff point for classifying data relative to noise in dopamine D2 receptor BP_{ND} images. To reduce the number of potential comparisons, we combined the cortical ROIs to create masks of the left (8 ROIs) and right (7 ROIs) temporal cortex, left (3 ROIs) and right (3 ROIs) frontal cortex, and left (1 ROI) and right (1 ROI) insula, and extracted mean BP_{ND} from these six brain regions. Except left insula BP_{ND}, BP_{ND} in the other 5 regions showed significant negative effects of age: left temporal (r_{42}=−0.54, p < 0.001), right temporal (r_{42}=−0.56, p < 0.001), left frontal (r_{42}=−0.47, p=0.001), right frontal (r_{42}=−0.48, p=0.001), left insula (r_{42}=−0.12, p=0.440), and right insula (r_{42}=−0.32, p=0.034). However, physical activity did not significantly interact with age to predict BP_{ND} in any of the 6 cortical regions (all p > 0.3). Voxelwise analyses similarly did not identify cortical areas showing significant physical activity by age interaction on BP_{ND}.

Pohjalainen et al. (1998) previously reported a non-significant but suggestive effect of sex differences on age differences in DRD2. We did not find any significant interaction of age and sex on striatal or midbrain BP_{ND} (all p > 0.15), or any significant 3-way interaction of age, sex, and physical activity on BP_{ND} (all p > 0.35).

Given previous reports of volume reductions with age (Fjell et al., 2009; Salat et al., 2004), we performed additional post-hoc analyses using FSL-FIRST to segment and determine the volume of the 3 striatal components for each subject. There were indeed significant negative

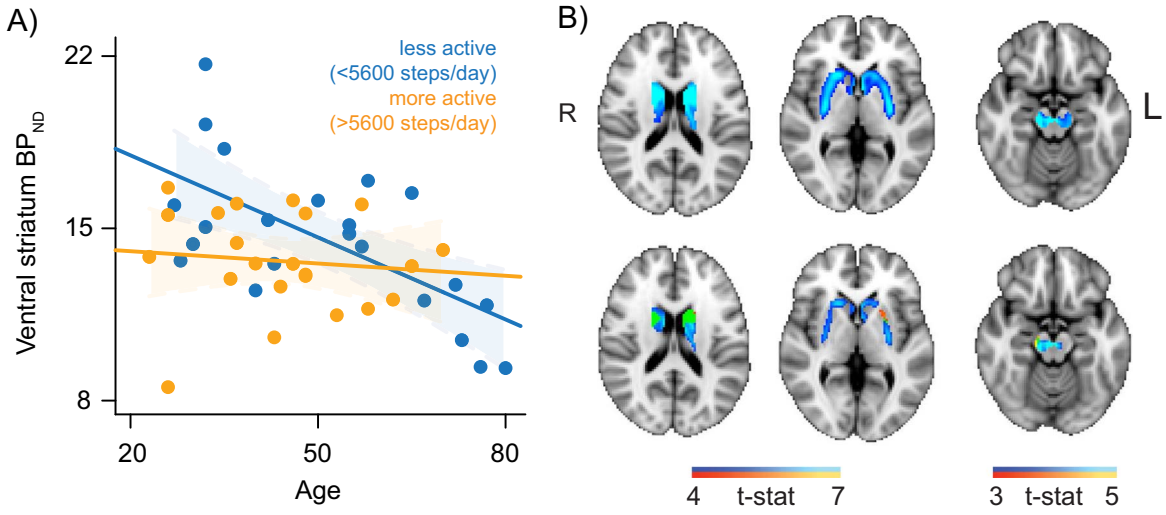

Fig. 3. DRD2 availability across adulthood by physical activity levels. A) Age and physical activity significantly interacted to predict BP_{ND} in the ventral striatum (t_{39}=3.085, p=0.004). There was no significant DRD2 loss with age in the more active group (r_{19}= −0.21, p= 0.368), but in the less active group, DRD2 availability was significantly lower at older compared to younger ages (r_{19}= −0.72, p < 0.001). B) Voxelwise analyses across all subjects examined the spatial extent of DRD2 loss in the striatum and midbrain (top). Age-related DRD2 loss was observed in 27% of the striatum and 36% of the midbrain in the less active half of the sample (blue) and 11% of the striatum and 6% of the midbrain in the more active half of the sample (orange); overlapping areas are shown in green (bottom). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

effects of age on ventral striatal (r_{42}=−0.46, p=0.002), caudate (r_{42}=−0.35, p=0.018), and putamen (r_{42}=−0.53, p < 0.001) volumes, but there were no significant age by physical activity interactions on striatal volume (all p > 0.25). The interaction of age and physical activity on ventral striatal BP_{ND} remained significant (and appeared slightly stronger) with the inclusion of ventral striatal grey matter volume in the model (β=3.35×10^{-5}, SE=9.8×10^{-6}, t_{38}=3.407, p=0.002), suggesting that the role of physical activity in age-related effects on DRD2 availability was not attributable to lesser grey matter atrophy. The interaction of age and physical activity on caudate and putamen BP_{ND} remained non-significant after controlling for caudate and putamen volumes, respectively (both p > 0.2).

4. Discussion

These results provide *in vivo* evidence supporting a positive association between regular physical activity and postsynaptic DRD2 availability in healthy disease-free human adults. Consistent with previous literature, postsynaptic DRD2 availability was negatively associated with age (Rinne et al., 1993). Using the high affinity radiotracer [18F]fallypride, we extended these findings, showing that there is also significant loss of presynaptic DRD2 in the midbrain, which may reflect either age-related decline in the number of dopamine neurons (as previously observed in postmortem human brains (Fearnley and Lees, 1991)) and/or the expression of autoreceptors on those neurons. PET studies using the DRD3-preferential tracer [11 C]-(+)-PHNO have not observed age-dependent decline in midbrain BP_{ND} (Matuskey et al., 2016; Nakajima et al., 2015), potentially suggesting that the age-related [18F]fallypride BP_{ND} decline at least partially reflects autoreceptor loss with age rather than neuronal loss, which would have presumably been similarly detected by [11 C]-(+)-PHNO.

Strikingly, the effect of age on DRD2 availability, specifically in the ventral striatum, varied across physical activity levels. The less active half of the sample showed the expected significant negative effect of age on ventral striatal DRD2 receptor availability, whereas there were only modest non-significant age effects on ventral striatal DRD2 levels in the more active half of the sample. These results are consistent with rodent data showing a neuroprotective effect of physical activity on dopamine neurons in the ventral tegmental area, which projects to the ventral striatum (Ahmad et al., 2009). In addition to a difference in the magnitude of age effects in the ventral striatum, we found that compared to the more active group, age effects on DRD2 levels in the less active group were more than twice as spatially extensive in the striatum and the midbrain. These observations suggest that physical activity, although potentially beneficial in multiple components of the dopamine system, may be particularly impactful in the ventral striatum. The reason why physical activity might be more associated with ventral striatal relative to dorsal striatal dopamine receptors is unclear, but is consistent with a wealth of studies showing functional differences between the dorsal and ventral striatum. The ventral striatum is associated with reward processing and motivated cognitive processes, whereas the dorsal striatum is more associated with non-reward-related processes like attention shifting and working memory (Cools et al., 2001, 2003). The ventral and dorsal striatum are also differentially affected by pathology; in Parkinson's disease, dopamine depletion begins in the dorsal striatum and later progresses to the ventral striatum (Agid et al., 1993; Kish et al., 1988). Slightly lower rates of decline in dopamine levels have also been suggested in the ventral striatum relative to dorsal striatal regions in normal aging (Kumakura et al., 2010). The findings raise the possibility that physical activity may be particularly impactful with functions involving the ventral striatum, such as reinforcement learning and value-based decision making which have been shown to decline with age in some contexts (Samanez-Larkin and Knutson, 2015). We note that past analyses of DRD2 declines with aging have focused on the magnitude of BP_{ND} changes within a region. Our results suggest that consideration of spatial extent in addition to magnitude difference may provide additional information about changes in the dopamine system.

An obvious limitation of this study is its cross-sectional design, which cannot directly speak to the causality of the present findings. Although several studies have shown causal links for short-term activity interventions and DRD2 receptors in animals, humans with Parkinson's Disease, and human methamphetamine users (Fisher et al., 2013; Robertson et al., 2016; Vuckovic et al., 2010), our data do not directly show that physical activity causally ameliorates DRD2 loss in normal aging. It may be that individuals with higher DRD2 in the ventral striatum, an area associated with reward functions, are more motivated to be physically active as they age. There is a paucity of longitudinal studies performed with PET dopamine tracers and none have addressed physical activity. Future studies employing a longitudinal design or utilizing an experimental manipulation of regular physical activity over a sustained time scale will be necessary to

determine if physical activity causally reduces the impact of normal aging on DRD2 loss.

It is of note that to qualify for this study, participants had to have no major medical problems. At older ages fewer potential participants are likely to meet such criteria so there is a potential bias when selecting healthy subjects in the older age groups. This problem is not unique to this study, but may nevertheless influence findings from any study with strict exclusion criteria. It is also notable that physical activity, at least as indexed with our pedometer measure, was not related to age (r_{42}=−0.155, p=0.317) in our sample, but the extent to which it provides an index of physical activity over prior years is uncertain. Although we did not collect physiological measures of fitness (e.g., basal metabolic rate, VO2max, resting heart rate, glucose tolerance test), there is some evidence that daily step counts via pedometers are at least moderately correlated with direct physiological measures (Cao et al., 2009). Nevertheless, it would be ideal for future studies to collect direct physiological measures.

We additionally note that although [18F]fallypride binding potential is generally interpreted as representing DRD2 availability (especially given the high affinity of [18F]fallypride for DRD2), lower [18F] fallypride binding potential is also influenced by endogenous dopamine levels (with higher dopamine causing lower BP_{ND}) because [18F] fallypride competes with endogenous dopamine for DRD2. An additional caveat is warranted that among the younger half of our subjects, there was a small non-significant difference (t_{21}=1.93, p=0.067, 95% CI for d=[−.06, 1.66]), suggesting that more active subjects may have had slightly lower ventral striatal DRD2 availability than less active subjects. Although the difference was not significant, the small potentially suggestive effect raises the possibility that there may be more complicated relations between physical activity and dopamine at different stages of adult development. Future studies are needed to examine relations between physical activity and dopamine in early adulthood to examine the role of physical activity in dopamine function beyond the context of age-related dopamine decline.

In conclusion, the present data suggest an interaction between physical activity and aging on DRD2 receptors in the ventral striatum. If physical activity were indeed shown to ameliorate age-related declines in dopamine functioning, this would have major implications for behavioral interventions in both normal aging and in neurological disorders such as Parkinson's disease that are associated with declines in dopamine functioning.

Conflict of interest

none.

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