Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis

Teresa M. Karrer [a],[*],[1], Anika K. Josef [b],[2], Rui Mata [c], Evan D. Morris [d],[e],[f],[g], Gregory R. Samanez-Larkin [a],[h],[*],[3]

[a] Department of Psychology, Yale University, New Haven, CT, USA
[b] Center for Adaptive Rationality, Max Planck Institute for Human Development, Berlin, Germany
[c] Center for Cognitive and Decision Sciences, University of Basel, Basel, Switzerland
[d] Yale PET Center, Yale University, New Haven, CT, USA
[e] Department of Biomedical Engineering, Yale University, New Haven, CT, USA
[f] Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT, USA
[g] Department of Psychiatry, Yale University, New Haven, CT, USA
[h] Center for Cognitive Neuroscience, Duke University, Durham, NC, USA

ARTICLE INFO

ABSTRACT

Many theories of cognitive aging are based on evidence that dopamine (DA) declines with age. Here, we performed a systematic meta-analysis of cross-sectional positron emission tomography and single-photon emission-computed tomography studies on the average effects of age on distinct DA targets (receptors, transporters, or relevant enzymes) in healthy adults (N = 95 studies including 2611 participants). Results revealed significant moderate to large, negative effects of age on DA transporters and receptors. Age had a significantly larger effect on D1- than D2-like receptors. In contrast, there was no significant effect of age on DA synthesis capacity. The average age reductions across the DA system were 3.7%–14.0% per decade. A meta-regression found only DA target as a significant moderator of the age effect. This study precisely quantifies prior claims of reduced DA functionality with age. It also identifies presynaptic mechanisms (spared synthesis capacity and reduced DA transporters) that may partially account for previously unexplained phenomena whereby older adults appear to use dopaminergic resources effectively. Recommendations for future studies including minimum required samples sizes are provided.

© 2017 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Positron emission tomography (PET) and single-photon emission-computed tomography (SPECT) have been used for over 30 years to assess adult age differences in the dopamine (DA) system (Jagust and D'Esposito, 2009; Kessler, 2003). Selective summaries of the literature estimate that the DA system declines at around 5%–10% per decade across adulthood (Bäckman and Farde, 2001; Bäckman et al., 2010; Eppinger et al., 2011; Kaasinen and Rinne, 2002; Li et al., 2009). These qualitative estimates are approximately consistent with nonhuman animal and human postmortem studies (Hoekzema et al., 2010; Ingram et al., 2001; Kish et al., 1995; Madras et al., 1998; Morris et al., 1999). However, there are often overlooked inconsistencies in the size of the age effects across different components of the DA system (e.g., receptor subtypes, transporters, synthesis capacity) and brain regions.

The majority of empirical studies estimate age effects as a linear correlation between age and DA targets (receptors, transporters, or relevant enzymes) in the 2 main destinations of DA pathways: striatum and frontal cortex. The few studies examining D1-like receptors report large, negative age effects in striatal (Bäckman et al., 2011; Suhara et al., 1992) and frontal regions (Ouchi et al., 1999). The majority of studies have focused on D2-like receptors and have reported wide ranging estimates of the age effect from slightly negative to strongly negative effects (Ichise et al., 1998; Inoue et al., 2001; Laulumaa et al., 1993; Maziére et al., 1985; Nadeau et al., 1995). Age effects on striatal DA transporters (DATs)

* Corresponding authors at: Center for Cognitive Neuroscience, Duke University, Box 90999, Durham, NC 27708, USA. Tel.: +1-919-998-6668; fax: +1-919-681-0815.
E-mail addresses: tkarrer@ukaachen.de (T.M. Karrer), g.samanezlarkin@duke.edu (G.R. Samanez-Larkin).
[1] Teresa Karrer is now at RWTH Aachen University, Germany.
[2] Anika Josef is now at VDI/VDE-Innovation + Technik GmbH.
[3] Gregory Samanez-Larkin is now at Duke University, USA.

are also variable ranging from small to large negative effects (Seibyl et al., 1996; Tiihonen et al., 1997). The largest inconsistencies are apparent in studies investigating synthesis capacity. A similar number of studies report positive effects of age (Braskie et al., 2008; Dreher et al., 2008) and negative effects of age (Kumakura et al., 2010; Ota et al., 2006).

Variation in decline between brain regions (Kumakura et al., 2010), gender (Wong et al., 2012), and tracer differences (Wong et al., 1997) have been suggested as potential sources of the inconsistencies in the published literature, but these moderators have not been systematically tested across studies. In the broader literature on structural brain changes some have suggested that there are larger age-related volume declines (Hedden and Gabrieli, 2004) and steeper rates of decline for frontal regions compared with striatal regions (Bäckman et al., 2011; Kumakura et al., 2010; Ota et al., 2006). However, other studies find similar rates of decline in frontal and striatal regions (Raz and Rodrigue, 2006; Raz et al., 2005). Another explanation for the variability of previously reported age effects are low sample sizes and hence, low statistical power. This is likely due to the high monetary cost of molecular imaging and the desire to limit radiation exposure in healthy volunteers for research purposes. Meta-analysis is the ideal tool to comprehensively assess adult age effects across these low-powered individual studies over the past few decades.

In the present study, we conducted a systematic meta-analysis of all previous cross-sectional PET and SPECT studies of adult age effects on different dopaminergic targets (1) D1- and D2-like receptors (hereafter referred to as D1 and D2 receptors); (2) DATs; and (3) DA synthesis capacity. In addition, we used meta-regression to examine potential moderators of the observed inconsistencies between studies (e.g., target, brain region, sex, age range, radionuclide, imaging method). We expected to observe moderate to large negative effects of age on D1 and D2 receptors and DATs (Li et al., 2009). For DA synthesis capacity, we hypothesized a nonsignificant effect of age, since previous findings have been inconsistent, ranging from negative to positive. Given the mixed results in the literature on differential age effects across brain regions and targets, we did not make directional predictions for any of the potential moderators.

2. Methods

2.1. Literature search

The literature search profited from a preexisting corpus of 45 PET and SPECT imaging papers of aging and DA function (from the personal library of GRSL). We used this corpus to identify database search terms that would return these studies in addition to other relevant studies in the literature. We restricted our search to PubMed, the largest biomedical and life science database of journal articles and books. In the PubMed database, each paper is associated with several U.S. National Library of Medicine Medical Subject Heading (MeSH) terms to describe aspects of a paper including methods, participants, main effect, and other important characteristics in a consistent and uniform way (Lipscomp, 2000). The most frequent MeSH terms associated with the papers in the initial study corpus were combined to design a systematic search for additional papers for our meta-analysis. It was determined that the terms "aging OR aged," "tomography, emission-computed," and "humans," as well as the individual DA targets (i.e., D1 receptors, D2 receptors, DAT, synthesis capacity), best described the desired features of the studies we wished to include. Since an initial search with the MeSH term "synthesis capacity" yielded no results, we modified the search terms adding different, specific compounds assessing DA synthesis capacity. In addition, we checked the

references of the included studies for further relevant studies. See Supplementary Methods for full search term list and results of literature search (Supplementary Fig. 1). This exhaustive literature search returned a total of 686 single papers published before 01/03/2017, the date on which we performed the full search. During peer review, a reviewer identified two papers (Cumming et al., 2013; Dagher et al., 2001) that were missed by our search and matched the inclusion criteria that we also included.

Of the papers identified in this keyword search, we included all German or English studies (1) reporting original results, published in a journal accessible through Yale University's library system; (2) reporting data from a cross-sectional sample of healthy, human adults (>18 years) with a minimum age range of 25 years (to obtain age effect estimates from an at least moderate segment of adulthood); and (3) reporting either a linear correlation between age and a DA-relevant tracer kinetic measure from emission-computed tomography during a resting condition or containing sufficient information to calculate this linear correlation (e.g., from data comparing DA-relevant kinetic measures in separate age groups). We excluded studies if (1) the radiotracer used was not specifically selective to DA or only selective to one subtype of a receptor family (e.g., PHNO); or (2) the sample was a subsample of another included study; or (3) primarily consisted of smokers or relatives of Parkinson's patients. Changes in the DA system have been linked with both smoking nicotine (Adermark et al., 2016; Subramaniyan and Dani, 2015) and genes associated with the DA system in Parkinson's patients (Warner and Schapira, 2003).

2.2. Data extraction

For each of the eligible studies, we extracted the age effect for each tracer kinetic measure. The term tracer kinetic measure is used to reference different quantitative measures of system functioning like binding potential, distribution volume ratio (Innis et al., 2007), standardized uptake value ratio, uptake rate constant (Dreher et al., 2008), and effective distribution volume (Sossi et al., 2001). All of these measures provide relevant information about the location and distribution of the radioligand across the brain (Innis et al., 2007; Kaasinen and Rinne, 2002; Kumakura et al., 2005) as estimates of the availability of DA receptors, DATs, and the activity of enzymes contributing to DA synthesis.

Pearson's correlation coefficients, r, between age and the PET or SPECT kinetic measure used to assess neurotransmission were obtained (1) directly from a report of r in the study; (2) estimated from the age and kinetic measure for each subject provided in a table or from the extracted data of a digitized graph using Source Forge's Plot Digitizer (Huwaldt, 2001); or (3) converted from reported group values of young and old adults, which were first transformed into Cohen's d. In each paper, we extracted the correlation between age and the kinetic measure from 3 regions of interest: midbrain, striatum (consisting of caudate, putamen, and ventral striatum or nucleus accumbens), and frontal cortex (consisting of frontal gyri, anterior cingulate, and anterior insula). If the correlation coefficient was provided separately for males and females or only for subregions instead of the whole region, these values were averaged equally in weight using Fisher's z-transform. This has been shown to introduce less estimation bias than a direct averaging of correlation coefficients (Silver and Dunlap, 1987). If a study reported r for several different kinetic measures, we extracted the measure which was recommended as the most accurate by the authors or the most commonly used one across studies. In addition, we extracted the following variables as possible moderators of the age effect: (1) DA target; (2) brain region; (3) age range in sample; (4) female percentage in sample; (5) imaging method; (6) year of introduction of scanner model;

(7) effective resolution of the imaging data; (8) radionuclide; and (9) reference region of the kinetic measure.

Among the total of 688 papers, a final pool of 95 studies with 2611 individual participants were considered in the current meta-analyses to assess adult age differences in the DA system (cf. Supplementary Methods for a full reference list). Of the 95 included studies, 64 studies used PET and 31 studies used SPECT imaging. The average sample consisted of 27 participants with 38% women on average. The average age range was 25–75 years (cf. Supplementary Table 1 for additional characteristics of the included studies).

2.3. Data analysis

Statistical analyses were carried out in R version 3.2.2 with RStudio (R Core Team, 2013; R Studio Team, 2015) using the metafor package (Viechtbauer, 2010). Because the correlation coefficient r is bound and non-normally distributed, we Fisher's z-transformed r before running the meta-analysis models to stabilize the variances of the estimates (Viechtbauer, 2010). We applied separate random-effects (REs) meta-analyses for each target to obtain summary correlation coefficients over the included estimates weighted by their sample sizes. In contrast to fixed-effect models, which assume that one true effect underlies all effect sizes and differences in the effect sizes are only due to random sampling variance (Borenstein et al., 2009), we expected RE models to be more appropriate for our data: The underlying true effect varies between the studies since they are not comparable in many variables (e.g., age range, female percentage, or method used). This variation is assumed to be random, so that the summary effect size can be estimated (Borenstein et al., 2009). Nevertheless, we checked for consistency of the results of both models.

To specify the regional age effects, we calculated the summary r for each target split into regions of interest. If two or more correlation coefficients from the same sample were included in one analysis (e.g., r for several brain regions in the same target), we used a multivariate RE model to allow for correlated sampling errors and/or true effects. All mentioned statistical models were fitted by Restricted Maximum Likelihood estimation.

Although the correlation coefficient provides a standardized measure of the size of the age effect, we also wanted to assess age differences in the DA targets across years or decades of life. This corresponds to an unstandardized regression slope, which was less often reported in the studies. To quantify differences per decade, we calculated a sample-size–weighted average for each target. For this, we used reported percent differences per year or computed a consistent measure (unstandardized regression slope of age on kinetic measure divided by the range of kinetic measure) for each study.

We supplemented our analyses by examining the nonlinearity of age effects in different DA targets. For this, we used the ages and kinetic measures that were available for individual participants provided either in a table or from the extracted data of a digitized graph. Due to different scales, we z-standardized the kinetic measure within each study to make them comparable between studies. We then merged the standardized raw data for each of the 4 DA targets over frontal and striatal regions (since the age effect did not significantly differ between regions in our analyses; see Results). We fitted linear, quadratic, and exponential models and calculated the corresponding slopes, the coefficient of determination, R^2, as well as the adjusted R^2 for each DA target separately.

Q-statistics and I^2 are widely used measures of the amount of heterogeneity in the effect sizes (Borenstein et al., 2009). To identify moderators that might account for potential heterogeneity in effect sizes between studies, we integrated potential moderator variables in a multivariate mixed-effects meta-regression across all effect sizes, controlling for the fact that some effect sizes stemmed from the same sample. Continuous variables were centered before entering them in the model for easier interpretation and the other variables were categorized (see Supplementary Methods and Supplementary Table 2). Note that the continuous variable "effective resolution of imaging data" had to be categorized into 3 groups, since the study corpus did not provide more detailed information.

2.4. Publicly available data and code

The data file and analysis code are publicly available on OSF (https://osf.io/6uf82/).

3. Results

3.1. Meta-analysis models

Funnel plots were created to examine potential publication biases. Funnel plots depicting the distribution of effect sizes and corresponding standard error (SE) for each target across all studies in the 4 examined DA targets are displayed in Supplementary Fig. 2. Studies with small sample size—corresponding to a large SE—and an effect size close to zero were rare, whereas studies with large sample size were spread approximately symmetrically around the mean effect size. The applied rank correlation tests for funnel plot asymmetry did not indicate any publication bias in the study selection ($p_{D1} = 0.80$; $p_{D2} = 0.27$; $p_{DAT} = 0.49$; $p_{SC} = 0.94$).

The RE meta-analysis models revealed significant moderate to large, negative mean correlations between age and striatal and frontal cortical DA receptors ($r_{D1} = -0.77$; $r_{D2} = -0.56$) and striatal DATs ($r = -0.68$; Figs. 1–3 and Table 1). In contrast, there was a nonsignificant effect of age on DA synthesis capacity ($r = -0.06$) across the striatum, frontal cortex, and midbrain (Fig. 4 and Table 1). Fig. 5 illustrates differences in summary effect sizes across the DA system comparing their 95% confidence intervals (CIs). The negative age effect was significantly larger for D1 than for D2 receptors. The age effect on synthesis capacity was significantly smaller than the age effects on the other targets. Univariate RE models as well as fixed-effect models yielded comparable results. Largely overlapping CIs suggested that the age effects within each DA target were comparable across midbrain, striatal, and frontal regions (Table 1). Likewise, an analysis of striatal subregions did not find any differences in age effects between the putamen and caudate (Supplementary Table 3).

The majority of the studies ($N = 83$) contained enough data to quantify the percentage differences in kinetic measure per decade, which was also sample-size weighted. The observed decline in the kinetic measure over all DA targets was 8.3% per decade ranging from 3.7% in synthesis capacity to 14.0% in D1 receptors (Table 2).

3.2. Nonlinear analysis of individual subject data

In exploratory analyses, we fit linear, quadratic, and exponential models to the individual subject data from 75 studies (Fig. 6; Supplementary Table 4). The linear model of age explained a significant amount of variance in D1 (Adj. $R^2 = 46.0\%$, $p < 0.001$) and D2 receptors (Adj. $R^2 = 24.9\%$, $p < 0.001$) and DATs (Adj. $R^2 = 38.6\%$, $p < 0.001$). In these 3 DA targets, the quadratic and exponential effects of age explained approximately similar amounts of variance as the linear fits according to adjusted R^2 which accounts for model complexity. Although age did not account for much variance in DA synthesis capacity in any of the models, the quadratic function (Adj. $R^2 = 5.4\%$) explained more variance than the linear (Adj. $R^2 = 1.8\%$) and the exponential function (Adj. $R^2 = 1.0\%$).
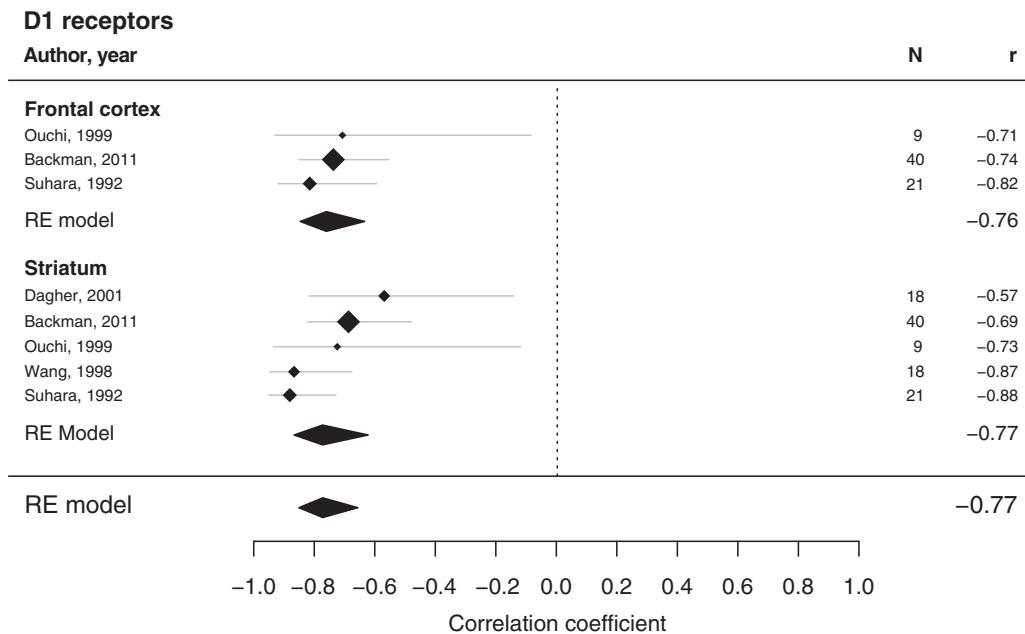
Fig. 1. Forest plot for studies describing adult age differences in D1-like receptors (multivariate REM with 5 studies and 106 individual participants). The position of the diamond on the x-axis indicates the effect size (Pearson's correlation coefficient) between age and kinetic measure for each study, and its size corresponds to the weight each study had in the analysis. The gray bars indicate the 95% CI of the effect size. The polygons summarize the sample size–weighted effect (also for subregions) with its width representing the 95% CI. Abbreviation: CI, confidence interval.

3.3. Meta-regression model

We used Q-statistics to test the null hypothesis that all the studies are based on the same true effect by comparing the observed between-study variation to the variance within the single studies (Borenstein et al., 2009). Significant Q-statistics in the meta-analysis of D2 receptors ($Q = 117.6$; $p < 0.0001$), DATs ($Q = 73.4$; $p < 0.001$), and synthesis capacity ($Q = 88.9$; $p < 0.0001$) suggested that the studies do not share a common true effect size. However, the nonsignificant Q-statistics in D1 receptors ($Q = 7.8$; $p = 0.352$) are not valid evidence for a common true effect within the studies, since this could be also due to the low number of D1 studies ($N = 8$). The I^2 measure also takes into account the expected heterogeneity of the studies (random sampling variance of the effect sizes) and hence, provides the proportion of true heterogeneity in the observed between-studies variance (Borenstein et al., 2009). This proportion was 10.1% in D1 receptors, 56.4% in DATs, 56.6% in D2 receptors, and 80.9% in DA synthesis capacity.

To determine the source of the observed heterogeneity, we added potential moderators in a multivariate mixed-effects meta-regression over all correlation coefficients. Supplementary Table 5 presents the results of the meta-regression including 77 of the original 112 correlation coefficients, since studies lacking sufficient moderator information were omitted from the moderator analysis. The model estimated coefficients for centered continuous variables and single factor levels in contrast to their reference level as well as their corresponding SE and 95% CI. To examine each factor as a whole, we tested the null hypothesis that the coefficients of all factor levels are equal to zero simultaneously. This revealed DA target as the only significant moderator ($p < 0.001$) with increasingly negative age effects for DA synthesis capacity, D2 receptors, DAT, and then D1 receptors. Post-hoc tests assessing differences between single factor levels found a significantly smaller age effect for DA synthesis capacity compared with all other targets ($p < 0.001$, significant on a Bonferroni corrected level of $\alpha = 0.017$). The other tested variables did not influence the age effect, but a

significant test for residual heterogeneity indicated that other unknown moderators might account for variability in the age effect. To increase the size of included studies and therefore power, we also calculated separate meta-regressions for each individual moderator variable separately. Still, no measure significantly explained the variance in age effects besides DA target.

4. Discussion

We found significant moderate to large, negative age effects on striatal DATs and striatal and frontal cortical DA receptors. However, DA synthesis capacity was not significantly correlated with age. The observed age difference per decade in the kinetic measures over all the targets ranged between 3.7% and 14.0% and was approximately consistent with estimates of dopaminergic decline of 5%–10% per decade in prior reviews (Kaasinen and Rinne, 2002; Li et al., 2009). Critically, here we provide the first differentiated and precise quantification of age effects across distinct DA targets and brain regions. The evidence for declines in receptors and transporters and potential preservation of synthesis capacity challenges existing theories based on global declines in DA function with age (Braver and Barch, 2002; Li et al., 2001; Nieuwenhuis et al., 2002).

The large negative effects of age on D1 and D2 receptors reveals limitations in the function of the dopaminergic system with age, since transmission of the dopaminergic signal is limited through a smaller number of postsynaptic DA receptors. However, the combination of large losses in DATs and the lack of age effects on DA synthesis capacity might together partially compensate for fewer DA receptors at older ages. The observed reduction of DATs should lead to a lower reuptake rate of DA into the presynaptic neuron. Hence, DA may remain active in the synaptic cleft for a prolonged time interval and may be able to modulate signal transmission for a lengthier period of time in older age. In fact, others have suggested that upregulated DA synthesis capacity might act as a compensation mechanism for reduced DA receptors (Braskie et al., 2008). If we can assume retained DA synthesis capacity may also be
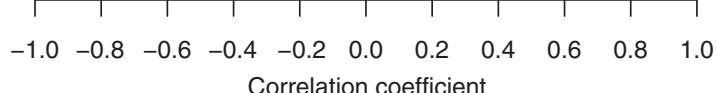
D2 receptors

Author, year	N	r
Frontal cortex		
Wang, 1996	42	−0.39
Maziere, 1985	13	−0.41
Wong, 1984	44	−0.54
Kaasinen, 2002	37	−0.70
Kaasinen, 2000	24	−0.73
Mukherjee, 2002	6	−0.84
Inoue, 2001	27	−0.88
RE model		−0.66
Striatum		
Laulumaa, 1993	8	0.72
Nadeau, 1995	12	0.05
Crawley, 1986	13	−0.02
Blin, 1989	28	−0.05
Vernaleken, 2007	21	−0.17
Lappin, 2009	10	−0.20
Pirker, 1997	14	−0.20
vanRoyen, 1993	21	−0.22
Reeves, 2005	30	−0.23
Kim, 2011	24	−0.31
Chen, 2005	62	−0.32
Cumming, 2013	50	−0.33
Chabriat, 1992	14	−0.38
Staedt, 1996	10	−0.41
Oyanagi, 2002	8	−0.43
Nakajima, 2015	70	−0.45
Kuwabara, 2012	47	−0.46
Wong, 1997	24	−0.50
Pohjalainen, 1998	54	−0.52
Hierholzer, 1992	8	−0.52
Volkow, 2000	37	−0.55
Wang, 1996	42	−0.55
Ichise, 1993	22	−0.58
Tomer, 2008	19	−0.58
Antonini, 1993	32	−0.59
Rinne, 1993	21	−0.62
Volkow, 1996 (PR)*	20	−0.62
Maziere, 1985	13	−0.65
Dang, 2016	130	−0.66
Wong, 1984	44	−0.67
Asanuma, 2005	13	−0.69
Larisch, 1998	18	−0.70
Volkow, 1996 (PR)*	24	−0.71
Kufferle, 1996	8	−0.73
Baron, 1986	17	−0.74
Wienhard, 1990	6	−0.75
Brucke, 1995	21	−0.77
Ichise, 1998	40	−0.78
Eisensehr, 2003	7	−0.79
Ishibashi, 2009	16	−0.79
Eisenstein, 2012	14	−0.80
Backman, 2000	11	−0.82
Leenders, 1993	5	−0.84
Mukherjee, 2002	6	−0.90
Iyo, 1993	11	−0.94
RE model		−0.54
RE model		−0.56

Correlation coefficient

−1.0 −0.8 −0.6 −0.4 −0.2 0.0 0.2 0.4 0.6 0.8 1.0

Fig. 2. Forest plot for studies describing adult age differences in D2 receptors (multivariate REM with 47 studies and 1213 single participants). The position of the diamond on the x-axis indicates the effect size (Pearson's correlation coefficient) between age and kinetic measure for each study, and its size corresponds to the weight each study had in the analysis. The gray bars indicate the 95% CI of the effect size. The polygons summarize the sample size–weighted effect (also for subregions) with its width representing the 95% CI. Abbreviation: CI, confidence interval.

associated with the potential for at least partially spared DA release, this—together with reduced DATs—might imply a potentially retained dopaminergic functionality with age. This combined mechanism might account for previously unexplained phenomena whereby older adults appear to use dopaminergic resources effectively, especially in socio-emotional and affective tasks (Samanez-Larkin and Knutson, 2015). A number of studies have shown that age differences in cognitive function are minimized or eliminated when using stimuli that are more personally salient (goal-relevant) and presumably more motivating (e.g., Charles et al., 2003; Gorlick and Maddox, 2015; Mather and Carstensen, 2003; Mikels et al., 2005). There is currently not a neurobiologically
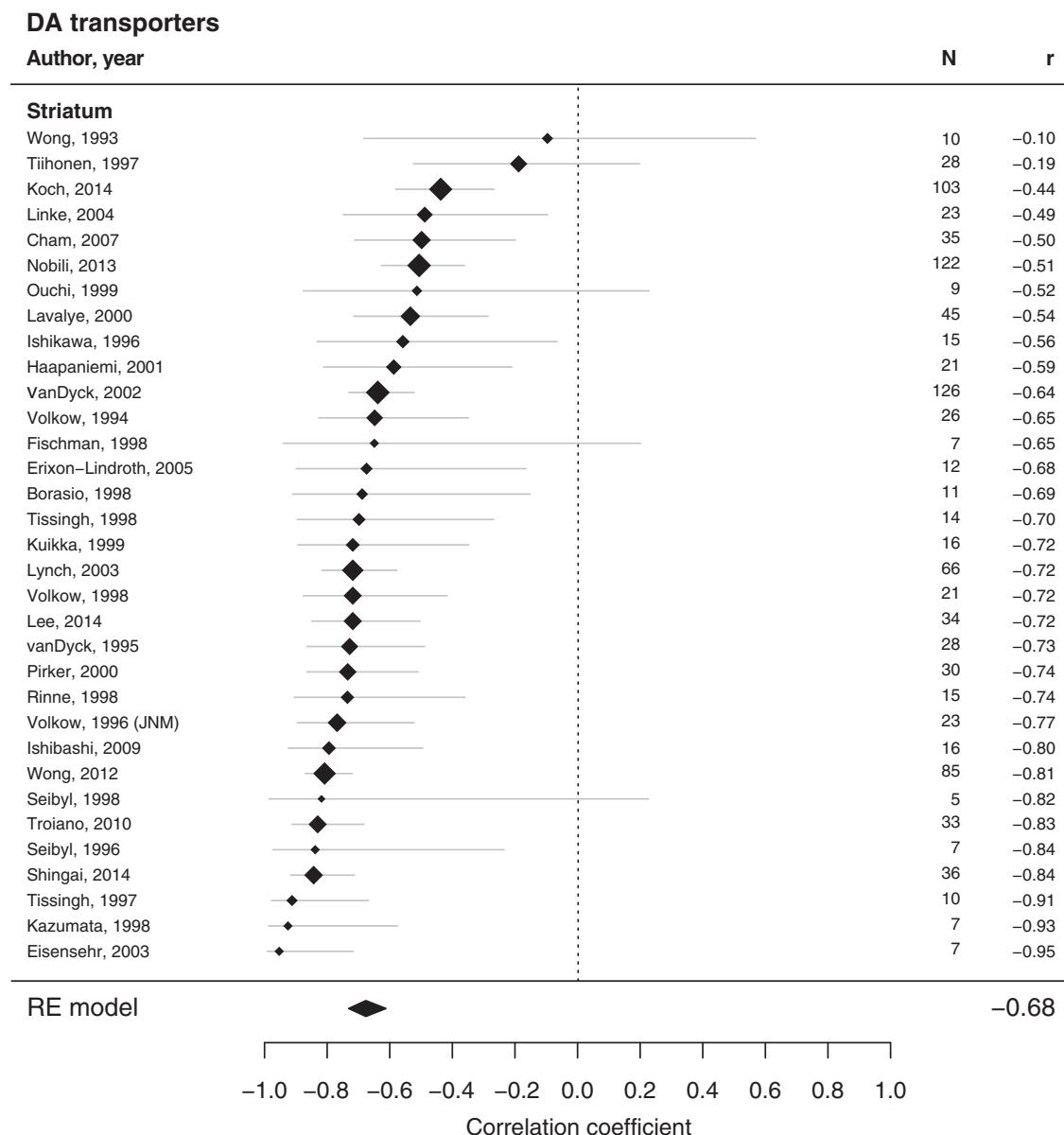
DA transporters

Author, year		N	r
Striatum			
Wong, 1993		10	−0.10
Tiihonen, 1997		28	−0.19
Koch, 2014		103	−0.44
Linke, 2004		23	−0.49
Cham, 2007		35	−0.50
Nobili, 2013		122	−0.51
Ouchi, 1999		9	−0.52
Lavalye, 2000		45	−0.54
Ishikawa, 1996		15	−0.56
Haapaniemi, 2001		21	−0.59
VanDyck, 2002		126	−0.64
Volkow, 1994		26	−0.65
Fischman, 1998		7	−0.65
Erixon–Lindroth, 2005		12	−0.68
Borasio, 1998		11	−0.69
Tissingh, 1998		14	−0.70
Kuikka, 1999		16	−0.72
Lynch, 2003		66	−0.72
Volkow, 1998		21	−0.72
Lee, 2014		34	−0.72
vanDyck, 1995		28	−0.73
Pirker, 2000		30	−0.74
Rinne, 1998		15	−0.74
Volkow, 1996 (JNM)		23	−0.77
Ishibashi, 2009		16	−0.80
Wong, 2012		85	−0.81
Seibyl, 1998		5	−0.82
Troiano, 2010		33	−0.83
Seibyl, 1996		7	−0.84
Shingai, 2014		36	−0.84
Tissingh, 1997		10	−0.91
Kazumata, 1998		7	−0.93
Eisensehr, 2003		7	−0.95
RE model			**−0.68**

Correlation coefficient

Fig. 3. Forest plot for studies describing adult age differences in DA transporter (univariate REM with 33 studies and 1046 single participants). The position of the diamond on the x-axis indicates the effect size (Pearson's correlation coefficient) between age and kinetic measure for each study, and its size corresponds to the weight each study had in the analysis. The gray bars indicate the 95% CI of the effect size. The polygons summarize the sample size−weighted effect (also for subregions) with its width representing the 95% CI. Abbreviation: CI, confidence interval.

based theoretical account of these findings in part because cognitive aging theories assume global decline of DA functionality.

In highly motivating situations, older adults might be able to enhance DA function through these compensatory mechanisms to achieve higher cognitive performance. However, studies have also revealed that spared or even upregulated synthesis capacity in older age can be associated with worse cognition (Braskie et al., 2008), perhaps because this measure is providing an indirect measure of losses elsewhere in the DA system.

It should be emphasized that there was great heterogeneity in age effects on synthesis capacity as indicated in the large CI of the summary effect (95% CI = [−0.33; 0.22]). Although the point estimate suggests the lack of an effect, age effect sizes ranged from negative to positive. Some of this variance may be due to differences between studies in tracers and the estimated kinetic measures (Braskie et al., 2008; Kumakura and Cumming, 2009). Both studies using the tracer FMT reported positive age effects, but the majority of the studies used FDOPA and reported both positive and negative effects. Some have argued that FMT provides a purer measure of DA synthesis since measurement of FDOPA signal is more affected by postrelease metabolism (Braskie et al., 2008), so the true age effect may in fact be positive. A limitation of this meta-analytic study is that we were underpowered to precisely examine how different tracers or kinetic measures (e.g., BP, Ki, DVR, SUV) impacted the results for an individual target (see Supplementary Discussion).

Importantly, the synthesis capacity tracers only measure aspects of conversion of DOPA to DA. Downstream DA release depends on packaging into vesicles and trafficking (Walker and Rodda, 2011). Very few studies provide information about age effects on vesicular storage (Bohnen et al., 2006; Frey et al., 1996; Lin et al., 2013), and there is no tracer to measure trafficking, per se. Some of these vesicular processes may decline with age even if synthesis does not (Kumakura et al., 2005, 2010). Potential age differences in these

Table 1
Results of meta-analyses for age effects on DA D1-like receptors, D2-like receptors, transporters (DAT), and synthesis capacity (SC)

Target	r	95% CI	# Studies	# Participants
D1	−0.77	[−0.85, −0.66]	5	106
Frontal cortex	−0.76	[−0.85, −0.64]	4	70
Striatum	−0.77	[−0.85, −0.62]	5	106
D2	−0.56	[−0.63, −0.49]	47	1213
Frontal cortex	−0.66	[−0.79, −0.48]	7	193
Striatum	−0.54	[−0.63, −0.49]	44	1125
DAT				
Striatum	−0.68	[−0.73, −0.61]	33	1046
DA SC	−0.06	[−0.33, 0.22]	13	278
Midbrain	−0.20	[−0.48, 0.13]	3	70
Frontal cortex	−0.57	[−0.73, −0.34]	3	64
Striatum	−0.06	[−0.36, 0.24]	12	257

mechanisms and the lack of data on age differences in DA release (e.g., using dual-scan protocols with administration of methylphenidate or amphetamine) are important qualifiers to the view raised above that spared synthesis may facilitate spared DA release in some contexts in old age. Further studies are needed to examine if spared DA synthesis capacity is associated with spared DA release and if spared DA release in combination with reduced DATs acts as a compensatory mechanism for cognition in older age. These potential age-related compensatory mechanisms may require

qualification of claims of global declines in the DA system, which are the foundation of many theories of cognitive aging (Braver and Barch, 2002; Li et al., 2001; Nieuwenhuis et al., 2002).

The mean correlation with age differed significantly between D1 and D2 receptors in striatum and frontal cortex. These findings may imply a stronger age-related decline in the maintenance compared with the updating function of working memory (Seamans and Yang, 2004). However, Braver and Barch (2002) have proposed the opposite effect although their theory is based more on phasic and tonic DA changes than specific receptor subtypes. Another possibility is that this differential decline explains age differences across different forms of memory. The findings are consistent with evidence that working memory and cognitive control might decline faster with age than episodic memory (Erixon-Lindroth et al., 2005), which have been associated with D1 receptor−mediated processes (Liggins, 2009) and D2 receptor−mediated processes (Nyberg et al., 2016), respectively. Future studies should examine the cognitive consequences of differential decline across receptor subtypes. A weakness of the present meta-analysis is that we did not include cognitive measures given the lack of consistency in use of measures across studies. Only 10 out of 95 studies reported associations with measures of cognitive functions, and they spanned several domains such as cognitive control (Lappin et al., 2009), episodic memory (Bäckman et al., 2000), or working memory (Bäckman et al., 2011).
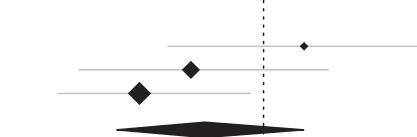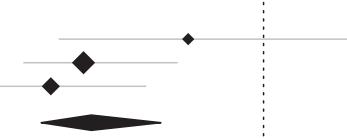

Fig. 4. Forest plot for studies describing adult age differences in DA synthesis capacity (multivariate REM with 13 studies and 278 single participants). The position of the diamond on the x-axis indicates the effect size (Pearson's correlation coefficient) between age and kinetic measure for each study, and its size corresponds to the weight each study had in the analysis. The gray bars indicate the 95% CI of the effect size. The polygons summarize the sample size−weighted effect (also for subregions) with its width representing the 95% CI. Abbreviation: CI, confidence interval.
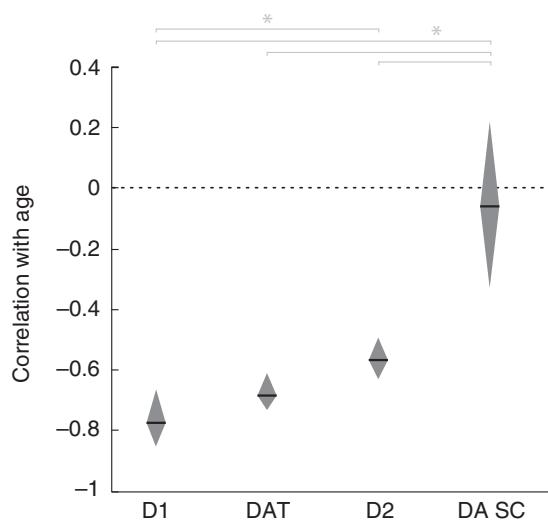
Fig. 5. Comparison of average correlations with age (horizontal line within polygon) as well as 95% CIs (polygon height) for DA D1-like receptors, transporters (DAT), D2-like receptors, and synthesis capacity (SC). Dotted line indicates age effect of zero. *Significant differences at $p < 0.01$ (Cumming, 2009).

The meta-regression analysis revealed DA target as the only significant moderator of the age effect. This supports the results from separate meta-analysis models in each target. Yet, we were not able to explain the observed heterogeneity with other potential moderators (e.g., brain regions, gender, age range, or nuclear imaging characteristics). These variables did not significantly moderate the age effects which is inconsistent with prior evidence from individual studies showing less steep decline in women (Pohjalainen et al., 1998; Wong et al., 1984) and steeper declines in frontal than in striatal regions (Bäckman et al., 2011; Kumakura et al., 2010; Ota et al., 2006). However, the results of the meta-regression should be interpreted with caution. Critically, comparisons between targets and regions are somewhat confounded given differential receptor subtype and transporter expression between frontal cortex and striatum. We also used some categorical moderators (like imaging method, reference region of the tracer kinetic measure, or resolution group of the scanner), which may have lacked sensitivity. In addition, several studies were lacking moderator information, so the meta-regressions likely suffered from a lack of power (cf. Supplementary Discussion for additional limitations and suggestions for variables and methodological details to include in future studies to facilitate meta-analyses).

A limitation of the current results is that they are based exclusively on cross-sectional data. Although the term "age-related decline" is frequently used in this literature, few studies have provided limited longitudinal data from healthy control groups (e.g., Colloby et al., 2005; Jakobson Mo et al., 2013). The estimates of age differences per year or decade reported in the literature and here are based on the assumption that age effects in cross-sectional studies are representative of developmental rather than cohort effects, which has not yet been verified with longitudinal data. This is a major limitation of the present study as well as nearly all of the previous molecular imaging literature. In fact, studies of brain volume find some evidence that longitudinal age effects are even stronger than would be predicted by cross-sectional data (Raz et al., 2003). However, a relatively large longitudinal study is currently being conducted which will provide more causal evidence for age-related effects (Nevalainen et al., 2015).

Another limitation is that our regions of analysis were quite large (i.e., frontal cortex, striatum). Given the previously reported differential age-related atrophy rates within subregions of frontal cortex and striatum (Raz et al., 2005, 2010), and differential connectivity and function (Alexander and Crutcher, 1990; Alexander et al., 1986; Haber and Knutson, 2009) of ventral versus dorsal frontostriatal regions, a comprehensive subanalysis could have provided more specific implications for age differences in DA-mediated cognitive function. Some studies provided data from subregions within frontal cortex or striatum but these data were not reported consistently across studies. We were able to separately analyze age effects in the caudate and putamen within the striatum (Supplementary Table 3), but there was no evidence for differential effects of age between these structures. Given the anatomical ascending connectivity of frontostriatal regions, it would be ideal if future studies reported more functionally relevant ventromedial to dorsolateral frontostriatal subregions (Kish et al., 1992; Kumakura et al., 2010).

All meta-analytic effects reported here are based on linear effects of age. Most studies assume age effects to be linear, but some studies have reported quadratic or exponential effects (Kim et al., 2011; van Dyck et al., 2002) in line with the evidence that decline in many biological systems is more exponential than linear (Crevecoeur, 2001). Previous studies of age-related change in brain volume also reveal many nonlinear age effects (Fjell et al., 2009; Raz et al., 2005, 2010). Our exploratory analyses yielded some suggestive evidence for quadratic and exponential age effects in D1 and D2 receptors and DATs with steeper declines in earlier adulthood. We found that DA synthesis capacity is fit best by a quadratic rather than a linear function. This could partially account for inconsistencies between prior studies that only compare younger and older adults, although it should be noted that even the best fitting exponential function revealed that very little variance in synthesis capacity is explained by age. Although these assessments of the nonlinearity of effects are potentially interesting, the combination of individual subject data across studies—even after standardization within study—should be interpreted with caution. As scientists become more open about data sharing of single-subject data, future analyses will be able to better characterize these nonlinear effects of age.

The scatterplots also suggest that between-subject variance relative to the mean may slightly increase with age. This has implications for the design of future PET/SPECT studies suggesting that statistical power may be lower in older adult groups. To address this issue in the functional neuroimaging literature, others have suggested that studies comparing younger and older groups should include a larger number of older adults (Samanez-Larkin and D'Esposito, 2008). This may be necessary for PET/SPECT studies as well. Additional recommendations for future studies are provided in the Supplementary Materials.
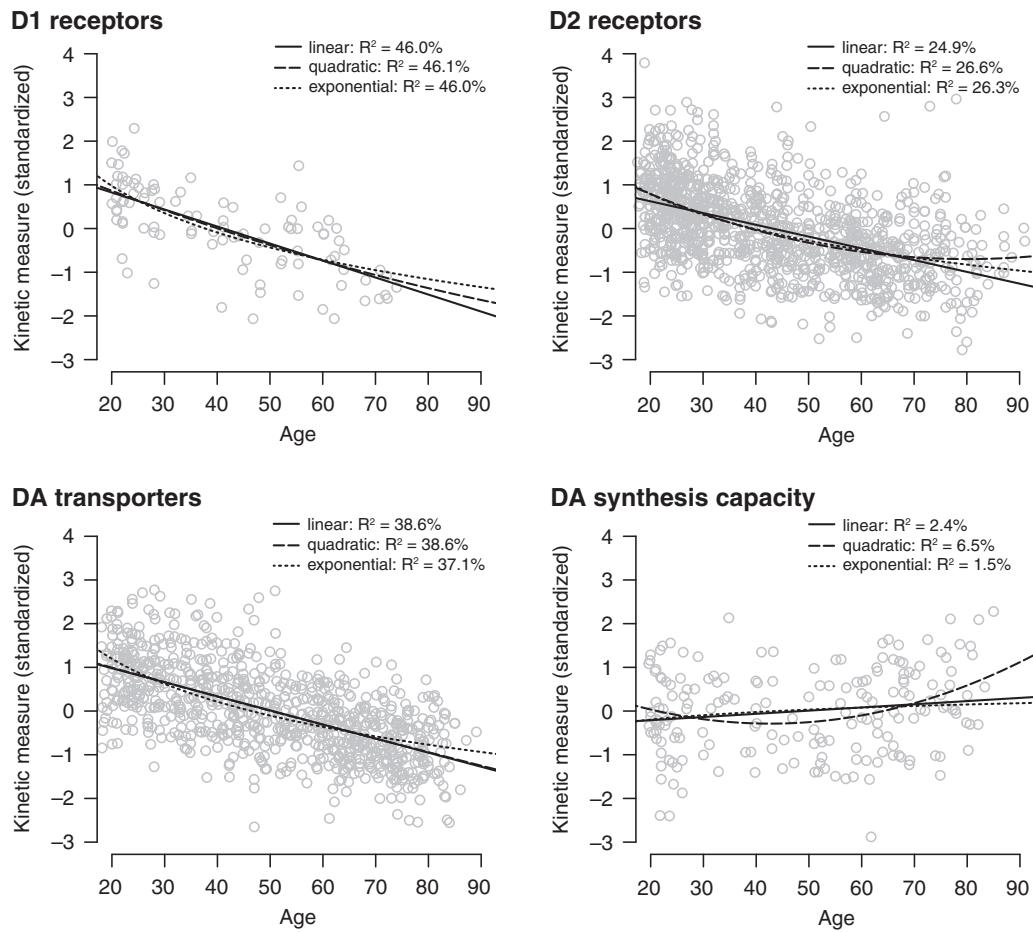
Table 2
Percentage differences in DA D1-like receptors, D2-like receptors, transporters (DAT), and synthesis capacity (SC) per decade of adulthood

Target	Differences per decade in %	# Studies	# Participants
D1	−14.0	5	106
Frontal cortex	−14.1	3	70
Striatum	−12.9	5	106
D2	−8.2	42	1067
Frontal cortex	−9.3	7	193
Striatum	−8.0	39	979
DAT			
Striatum	−8.9	29	897
DA SC	−3.7	10	222
Midbrain	−9.3	1	28
Frontal cortex	−10.8	2	49
Striatum	−1.4	10	222
DA overall	−8.3	83	2236

Fig. 6. Scatterplots depicting the relationship between age and kinetic measure (z-standardized within study) for D1-and D2-like receptors, DA transporters (DAT), and DA synthesis capacity (SC). A linear, a quadratic, and an exponential function were fit to the data.

General limitations of meta-analyses include the dependency on the quality of included studies as well as potential bias due to lower publication rates of nonsignificant results. Examination of funnel plots (Supplementary Fig. 2) did not reveal obvious publication bias. Despite these general limitations, it should be noted that meta-analysis is a particularly useful tool for PET/SPECT imaging studies of the DA system, which typically contain very few participants per study. The low sample sizes (median N = 21) of the studies analyzed here—likely either due to monetary costs of nuclear imaging methods or the fact that the majority of the studies did not focus on a healthy sample but rather used it as a control group—led to widespread low statistical power within most of the included studies. Many studies had fewer than 15 participants and the vast majority of studies had fewer than 30 participants. This may not be surprising given that radiochemistry, imaging, and medical personnel costs are typically about $3000—$4000 per subject per scan. The average power over all included studies was only 65.4%, with 53.6% of the studies with statistical power below the usually recommended 80% minimum. An additional benefit of meta-analysis is that the weighted summarized effects can be used for sample size calculations for adequately powered future studies.

Using the point estimates from our significant meta-analytic results, the minimum sample sizes required to detect a linear effect of age are relatively small (D1 N = 8, D2 N = 19, DAT N = 12). It is important to note that the average age effects on which these estimates are based may be overestimated given that very few studies controlled for partial volume effects (see Supplementary

Discussion). Almost none of the studies in the literature controlled for age-related atrophy, so the reported age effects are a combination of specific DA differences and nonspecific age differences in brain volume (Morris et al., 1999). Thus, if the true effect sizes are smaller than estimated here, more participants may be needed to detect simple effects of age for specific DA targets.

After over 30 years of research and 95 published studies, it seems unlikely that a researcher would be interested only in testing the age effect for a specific target. Future studies will be focused more likely on correlations between DA targets and cognitive performance (for which we unfortunately were not able to provide average effect sizes) or interactions between age and other variables (e.g., age by target, age by brain region). For a linear regression model with 3 predictors (age main effect, other main effect, interaction term), the minimum required sample size is much larger to detect a medium-sized effect (e.g., for $f^2 = 0.15$, N = 76 which would likely cost well over $250,000 for data collection alone). Making comparisons across targets was relatively simple with meta-analysis, but in a single study (e.g., interaction analysis of differential age slopes) many participants would be exposed to higher levels of radiation. This highlights the benefit of quantitative meta-analysis to enhance statistical power and minimize human subject risk. Given the common small sample sizes in human PET imaging studies, meta-analysis will remain an essential tool for verifying and quantifying age effects across the adult life span.

At a time when many are raising concerns about the reliability and reproducibility of individual neuroimaging studies

(Poldrack et al., 2017), the present results provide an example of how significant advances can be made from the systematic aggregation of incremental findings. The evidence for differential age effects across the human DA system would require extremely high monetary costs and increased radiation exposure in human research participants to comprehensively and reliably assess in a single study. Although it has been well established that DA receptors and transporters decline with age, the evidence for the lack of an age effect on synthesis capacity is highly novel, a significant advance in neuroscience, and would have been difficult to reveal without meta-analysis.

Disclosure statement

The authors have no actual or potential conflicts of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2017.05.006.

References

Adermark, L., Morud, J., Lotfi, A., Danielsson, K., Ulenius, L., Söderpalm, B., Ericson, M., 2016. Temporal rewiring of striatal circuits initiated by nicotine. Neuropsychopharmacology 41, 3051–3059.

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Bäckman, L., Farde, L., 2001. Dopamine and cognitive functioning: brain imaging findings in Huntington's disease and normal aging. Scand. J. Psychol. 42, 287–296.

Bäckman, L., Ginovart, N., Dixon, R.A., Wahlin, T.-B.R., Wahlin, A., Halldin, C., Farde, L., 2000. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am. J. Psychiatry 157, 635–637.

Bäckman, L., Karlsson, S., Fischer, H., Karlsson, P., Brehmer, Y., Rieckmann, A., MacDonald, S.W.S., Farde, L., Nyberg, L., 2011. Dopamine D$_1$ receptors and age differences in brain activation during working memory. Neurobiol. Aging 32, 1849–1856.

Bäckman, L., Lindenberger, U., Li, S., Nyberg, L., 2010. Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci. Biobehav. Rev. 34, 670–677.

Bohnen, N.I., Albin, R.L., Koeppe, R.A., Wernette, K.A., Kilbourn, M.R., Minoshima, S., Frey, K.A., 2006. Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson disease. J. Cereb. Blood Flow Metab. 26, 1198–1212.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Introduction to Meta-Analysis. John Wiley & Sons Ltd, Chichester, West Sussex, UK.

Braskie, M.N., Wilcox, C.E., Landau, S.M., O'Neil, J.P., Baker, S.L., Madison, C.M., Kluth, J.T., Jagust, W.J., 2008. Relationship of striatal dopamine synthesis capacity to age and cognition. J. Neurosci. 28, 14320–14328.

Braver, T.S., Barch, D.M., 2002. A theory of cognitive control, aging cognition, and neuromodulation. Neurosci. Biobehav. Rev. 26, 809–817.

Charles, S.T., Mather, M., Carstensen, L.L., 2003. Aging and emotional memory: the forgettable nature of negative images for older adults. J. Exp. Psychol. 132, 310–324.

Colloby, S.J., Williams, E.D., Burn, D.J., Lloyd, J.J., McKeith, I.G., O'Brien, J.T., 2005. Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using ^{123}I-FP-CIT SPECT. Eur. J. Nucl. Med. Mol. Imaging 32, 1176–1185.

Crevecoeur, G.U., 2001. A system approach modelling of the three-stage non-linear kinetics in biological ageing. Mech. Ageing Dev. 122, 271–290.

Cumming, G., 2009. Inference by eye: reading the overlap of independent confidence intervals. Stat. Med. 28, 205–220.

Cumming, P., Xiong, G., La Fougère, C., Rominger, A., Bartenstein, P., Buchholz, H.G., Piel, M., Rösch, F., Gründer, G., Vernaleken, I., 2013. Surrogate markers for cerebral blood flow correlate with [18F]-fallypride binding potential at dopamine D$_{2/3}$ receptors in human striatum. Synapse 67, 199–203.

Dagher, A., Bleicher, C., Aston, J.A., Gunn, R.N., Clarke, P.B., Cumming, P., 2001. Reduced dopamine D1 receptor binding in the ventral striatum of cigarette smokers. Synapse 42, 48–53.

Dreher, J.-C., Meyer-Lindenberg, A., Kohn, P., Berman, K.F., 2008. Age-related changes in midbrain dopaminergic regulation of the human reward system. Proc. Natl. Acad. Sci. U. S. A. 105, 15106–15111.

Eppinger, E., Hämmerer, D., Li, S.-C., 2011. Neuromodulation of reward-based learning and decision making in human aging. Ann. N. Y. Acad. Sci. 1235, 1–17.

Erixon-Lindroth, N., Farde, L., Robins Wahlin, T.-B., Sovago, J., Halldin, C., Bäckman, L., 2005. The role of the striatal dopamine transporter in cognitive aging. Psychiatry Res. Neuroimaging 138, 1–12.

Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. J. Neurosci. 29, 15223–15231.

Frey, K.A., Koeppe, R.A., Kilbourn, M.R., Vander Borght, T.M., Albin, R.L., Gilman, S., Kuhl, D.E., 1996. Presynaptic monoaminergic vesicles in Parkinson's disease and normal aging. Ann. Neurol. 40, 873–884.

Gorlick, M.A., Maddox, W.T., 2015. Social incentives improve deliberative but not procedural learning in older adults. Front. Psychol. 6, 1–12.

Haber, S.N., Knutson, B., 2009. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26.

Hedden, T., Gabrieli, J.D.E., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nat. Rev. Neurosci. 5, 87–96.

Hoekzema, E., Herance, R., Rojas, S., Pareto, D., Abad, S., Jiménez, X., Figueiras, F.P., Popota, F., Ruiz, A., Torrent, E., Fernandez-Soriano, F.J., Rocha, M., Rovira, M., Victor, V.M., Gispert, J.D., 2010. The effects of aging on dopaminergic neurotransmission: a microPET study of [11C]-raclopride binding in the aged rodent brain. Neuroscience 171, 1283–1286.

Huwaldt, J.A., 2001. Plot Digitizer (Version 2.6.6). Available at: http://plotdigitizer.sourceforge.net. Accessed March 29, 2017.

Ichise, M., Ballinger, J.R., Tanaka, F., Moscovitch, M., St George-Hyslop, P.H., Raphael, D., Freedman, M., 1998. Age-related changes in D$_2$ receptor binding with iodine-123-iodobenzofuran SPECT. J. Nucl. Med. 39, 1511–1518.

Ingram, D.K., Chefer, S., Matochik, J., Moscrip, T.D., Weed, J., Roth, G.S., London, E.D., Lane, M.A., 2001. Aging and caloric restriction in nonhuman primates—behavioral and in vivo brain imaging studies. Heal. Aging Funct. Longev 928, 316–326.

Innis, R.B., Cunningham, V.J., Delforge, J., Fujita, M., Gjedde, A., Gunn, R.N., Holden, J., Houle, S., Huang, S.-C., Ichise, M., Iida, H., Ito, H., Kimura, Y., Koeppe, R.A., Knudsen, G.M., Knuuti, J., Lammertsma, A.A., Laruelle, M., Logan, J., Maguire, R.P., Mintun, M.A., Morris, E.D., Wong, D.F., Parsey, R., Price, J.C., Slifstein, M., Sossi, V., Suhara, T., Votaw, J.R., Wong, D.F., Carson, R.E., 2007. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J. Cereb. Blood Flow Metab. 27, 1533–1539.

Inoue, M., Suhara, T., Sudo, Y., Okubo, Y., Yasuno, F., Kishimoto, T., Yoshikawa, K., Tanada, S., 2001. Age-related reduction of extrastriatal dopamine D$_2$ receptor measured by PET. Life Sci. 69, 1079–1084.

Jagust, W.J., D'Esposito, M., 2009. Imaging the Aging Brain. Oxford University Press.

Jakobson Mo, S., Linder, J., Forsgren, L., Holmberg, H., Larsson, A., Riklund, K., 2013. Pre- and postsynaptic dopamine SPECT in idiopathic parkinsonian diseases: a follow-up study. Biomed. Res. Int. 2013, 1–14.

Kaasinen, V., Rinne, J.O., 2002. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. Neurosci. Biobehav. Rev. 26, 785–793.

Kessler, R.M., 2003. Imaging methods for evaluating brain function in man. Neurobiol. Aging 24 (Suppl 1), S21–S35.

Kim, J.-H., Son, Y.-D., Kim, H.-K., Lee, S.-Y., Cho, S.-E., Kim, Y.-B., Cho, Z.-H., 2011. Effects of age on dopamine D$_2$ receptor availability in striatal subdivisions: a high-resolution positron emission tomography study. Eur. Neuropsychopharmacol. 21, 885–891.

Kish, S.J., Shannak, K., Rajput, A., Deck, J.H.N., Hornykiewicz, O., 1992. Aging produces a specific pattern of striatal dopamine loss: implications for the etiology of idiopathic Parkinson's disease. J. Neurochem. 58, 642–648.

Kish, S.J., Zhong, X.H., Hornykiewicz, O., Haycock, J.W., 1995. Striatal 3,4-dihydroxyphenylalanine decarboxylase in aging: disparity between postmortem and positron emission tomography studies? Ann. Neurol. 38, 260–264.

Kumakura, Y., Cumming, P., 2009. PET studies of cerebral levodopa metabolism: a review of clinical findings and modeling approaches. Neurosci. 15, 635–650.

Kumakura, Y., Vernaleken, I., Buchholz, H.G., Borghammer, P., Danielsen, E., Gründer, G., Heinz, A., Bartenstein, P., Cumming, P., 2010. Age-dependent decline of steady state dopamine storage capacity of human brain: an FDOPA PET study. Neurobiol. Aging 31, 447–463.

Kumakura, Y., Vernaleken, I., Gründer, G., Bartenstein, P., Gjedde, A., Cumming, P., 2005. PET studies of net blood-brain clearance of FDOPA to human brain: age-dependent decline of [18F]fluorodopamine storage capacity. J. Cereb. Blood Flow Metab. 25, 807–819.

Lappin, J.M., Reeves, S.J., Mehta, M.A., Egerton, A., Coulson, M., Grasby, P.M., 2009. Dopamine release in the human striatum: motor and cognitive tasks revisited. J. Cereb. Blood Flow Metab. 29, 554—564.

Laulumaa, V., Kuikka, J.T., Soininen, H., 1993. Imaging of D2 dopamine receptors of patients with Parkinson's disease using single photon emission computed tomography and iodobenzamide 1 123. Arch. Neurol. 50, 2—4.

Li, S., Lindenberger, U., Sikström, S., 2001. Aging cognition: from neuromodulation to representation. Trends Cogn. Sci. 5, 479—486.

Li, S.-C., Lindenberger, U., Nyberg, L., Heekeren, H.R., Bäckman, L., 2009. Dopaminergic modulation of cognition in human aging. In: Imaging the Aging Brain. Oxford University Press, New York, NY, pp. 71—91.

Liggins, J.T.P., 2009. The roles of dopamine D1 and D2 receptors in working memory function. Mcgill Sci. Undergrad. Res. J. 4, 39—45.

Lin, K.-J., Weng, Y.-H., Hsieh, C.-J., Lin, W.-Y., Wey, S.-P., Kung, M.-P., Yen, T.-C., Lu, C.-S., Hsiao, I.-T., 2013. Brain imaging of vesicular monoamine transporter type 2 in healthy aging subjects by ^{18}F-FP-(+)-DTBZ PET. PLoS One 8, 1—7.

Lipscomp, C.E., 2000. Medical Subject Headings (MeSH). Bull. Med. Libr. Assoc. 88, 265—266.

Madras, B.K., Meltzer, P.C., Liang, A.Y., Elmaleh, D.R., Babich, J., Fischman, A.J., 1998. Altropane, a SPECT or PET imaging probe for dopamine neurons: I. transporter binding in primate brain. Synapse 29, 93—104.

Mather, M., Carstensen, L.L., 2003. Aging and attentional biases for emotional faces. Psychol. Sci. 14, 409—415.

Maziére, B., Loch'h, C., Baron, J.-C., Sgouropoulos, P., Duquesnoy, N., D'Antona, R., Cambon, H., 1985. In vivo quantitative imaging of dopamine receptors in human brain using positron emission tomography and [^{76}Br]Bromospiperone. Eur. J. Pharmacol. 114, 267—272.

Mikels, J.A., Larkin, G.R., Reuter-Lorenz, P.A., Carstensen, L.L., 2005. Divergent trajectories in the aging mind: changes in working memory for affective versus visual information with age. Psychol. Aging 20, 542—553.

Morris, E.D., Chefer, S.I., Lane, M.A., Muzic, R.F., Wong, D.F., Dannals, R.F., Matochik, J.A., Bonab, A.A., Villemagne, V.L., Grant, S.J., Ingram, D.K., Roth, G.S., London, E.D., 1999. Loss of D$_2$ receptor binding with age in rhesus monkeys: importance of correction for differences in striatal size. J. Cereb. Blood Flow Metab. 19, 218—229.

Nadeau, S.E., Couch, M.W., Devane, C.L., Shukia, S.S., 1995. Regional analysis of D2 dopamine receptors in Parkinson's disease using SPECT and Iodine-123-Iodobenzamide. J. Nucl. Med. 36, 384—393.

Nevalainen, N., Riklund, K., Andersson, M., Axelsson, J., Ögren, M., Lövdén, M., Lindenberger, U., Bäckman, L., Nyberg, L., 2015. COBRA: a prospective multimodal imaging study of dopamine, brain structure and function, and cognition. Brain Res. 1612, 83—103.

Nieuwenhuis, S., Ridderinkhof, K.R., Talsma, D., Coles, M.G.H., Holroyd, C.B., Kok, A., van der Molen, M.W., 2002. A computational account of altered error processing in older age: dopamine and the error-related negativity. Cogn. Affect. Behav. Neurosci. 2, 19—36.

Nyberg, L., Karalija, N., Salami, A., Andersson, M., Wåhlin, A., Kaboovand, N., Köhncke, Y., Axelsson, J., Rieckmann, A., Papenberg, G., Garrett, D.D., Riklund, K., Lövdén, M., Lindenberger, U., Bäckman, L., 2016. Dopamine D2 receptor availability is linked to hippocampal—caudate functional connectivity and episodic memory. Proc. Natl. Acad. Sci. 113, 7918—7923.

Ota, M., Yasuno, F., Ito, H., Seki, C., Nozaki, S., Asada, T., Suhara, T., 2006. Age-related decline of dopamine synthesis in the living human brain measured by positron emission tomography with L-[β-^{11}C]DOPA. Life Sci. 79, 730—736.

Ouchi, Y., Kanno, T., Okada, H., Yoshikawa, E., Futatsubashi, M., Nobezawa, S., Torizuka, T., Sakamoto, M., 1999. Presynaptic and postsynaptic dopaminergic binding densities in the nigrostriatal and mesocortical systems in early Parkinson's disease: a double-tracer positron emission tomography study. Ann. Neurol. 46, 723—731.

Pohjalainen, T., Rinne, J.O., Någren, K., Syvälahti, E., Hietala, J., 1998. Sex differences in the striatal dopamine D$_2$ receptor binding characteristics in vivo. Am. J. Psychiatry 155, 768—773.

Poldrack, R.A., Baker, C.I., Durnez, J., Gorgolewski, K.J., Matthews, P.M., Munafò, M.R., Nichols, T.E., Poline, J.-B., Vul, E., Yarkoni, T., 2017. Scanning the horizon: towards transparent and reproducible neuroimaging research. Nat. Rev. Neurosci. 18, 115—126.

R Core Team, 2013. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. Retrieved from. http://www.R-project.org/.

R Studio Team, 2015. RStudio: Integrated Development for R. RStudio, Inc, Boston, MA. Retrieved from. http://www.rstudio.com/.

Raz, N., Ghisletta, P., Rodrigue, K.M., Kennedy, K.M., Lindenberger, U., 2010. Trajectories of brain aging in middle-aged and older adults: regional and individual differences. Neuroimage 51, 501—511.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676—1689.

Raz, N., Rodrigue, K.M., 2006. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci. Biobehav. Rev. 30, 730—748.

Raz, N., Rodrigue, K.M., Kennedy, K.M., Head, D., Gunning-Dixon, F., Acker, J.D., 2003. Differential aging of the human striatum: longitudinal evidence. Am. J. Neuroradiol 24, 1849—1856.

Samanez-Larkin, G.R., D'Esposito, M., 2008. Group comparisons: imaging the aging brain. Soc. Cogn. Affect. Neurosci. 3, 290—297.

Samanez-Larkin, G.R., Knutson, B., 2015. Decision making in the ageing brain: changes in affective and motivational circuits. Nat. Rev. Neurosci. 16, 278—289.

Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 74, 1—57.

Seibyl, J.P., Laruelle, M., Van Dyck, C.H., Wallace, E., Baldwin, R.M., Zoghbi, S., Zea-ponce, Y., Neumeyer, J.L., Charney, D.S., Hoffer, P.B., Innis, R.B., 1996. Reproducibility of iodine-123-β-CIT SPECT brain measurement of dopamine transporters. J. Nucl. Med. 37, 222—228.

Silver, N.C., Dunlap, W.P., 1987. Averaging correlation coefficients: should Fisher's z transformation be used? J. Appl. Psychol. 72, 146—148.

Sossi, V., Doudet, D.J., Holden, J.E., 2001. A reversible tracer analysis approach to the study of effective dopamine turnover. J. Cereb. Blood Flow Metab. 21, 469—476.

Subramaniyan, M., Dani, J.A., 2015. Dopaminergic and cholinergic learning mechanisms in nicotine addiction. Ann. N. Y. Acad. Sci. 1349, 46—63.

Suhara, T., Nakayama, K., Inoue, O., Fukuda, H., Shimizu, M., Mori, A., Tateno, Y., 1992. D1 dopamine receptor binding in mood disorders measured by positron emission tomography. Psychopharmacology (Berl) 106, 14—18.

Tiihonen, J., Kuikka, J., Bergström, K., Lepola, U., Koponen, H., Leinonen, E., 1997. Dopamine reuptake site densities in patients with social phobia. Am. J. Psychiatry 154, 239—242.

van Dyck, C.H., Seibyl, J.P., Malison, R.T., Laruelle, M., Wallace, E., Zoghbi, S.S., Zea-Ponce, Y., Baldwin, R.M., Charney, D.S., Hoffer, P.B., 2002. Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. Am. J. Psychiatry 10, 36—43.

Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw. 36, 1—48.

Walker, Z., Rodda, J., 2011. Dopaminergic imaging: clinical utility now and in the future. Int. Psychogeriatrics 23, 32—40.

Warner, T.T., Schapira, A.H.V., 2003. Genetic and environmental factors in the cause of Parkinson's disease. Ann. Neurol. 53, 61—70.

Wong, D., Wagner, H., Dannals, R., Links, J., Frost, J., Ravert, H., Wilson, A., Rosenbaum, A., Gjedde, A., Douglass, K., Et, A., 1984. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 226, 1393—1396.

Wong, D.F., Young, D., Wilson, P.D., Meltzer, C.C., Gjedde, A., 1997. Quantification of neuroreceptors in the living human brain: III. D$_2$-like dopamine receptors: theory, validation, and changes during normal aging. J. Cereb. Blood Flow Metab. 17, 316—330.

Wong, K.K., Müller, M.L.T.M., Kuwabara, H., Studenski, S.A., Bohnen, N.I., 2012. Gender differences in nigrostriatal dopaminergic innervation are present at young-to-middle but not at older age in normal adults. J. Clin. Neurosci. 19, 183—184.