Differential regional decline in dopamine receptor availability across adulthood: Linear and nonlinear effects of age

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Data: Pictures, scatterplots, and statistics for each ROI are available in an interactive app online at http://13.58.222.229:3838/agebp/. Data and code used in the manuscript can be viewed and downloaded from https://osf.io/h67k4/.

Abstract

Theories of adult brain development, based on neuropsychological test results and structural neuroimaging, suggest differential rates of age-related change in function across cortical and subcortical sub-regions. However, it remains unclear if these trends also extend to the aging dopamine system. Here we examined cross-sectional adult age differences in estimates of D2-like receptor binding potential across several cortical and subcortical brain regions using PET imaging and the radiotracer [18F]fallypride in two samples of healthy human adults (combined *N*=132). After accounting for regional differences in overall radioligand binding, estimated percent declines in receptor binding potential by decade (linear effects) were highest in most temporal and frontal cortical regions (~6–16% per decade), moderate in parahippocampal gyrus, pregenual frontal cortex, fusiform gyrus, caudate, putamen, thalamus, and amygdala (~3–5%), and weakest in subcallosal frontal cortex, ventral striatum, pallidum, and hippocampus (~0–2%). Some regions showed linear effects of age while many (e.g., temporal cortex, putamen) showed curvilinear effects such that binding potential declined from young adulthood to middle age and then was relatively stable until old age. Overall, these data indicate that the rate and pattern of decline in D2 receptor availability is regionally heterogeneous. However, the differences across regions were challenging to organize within existing theories of brain development and did not show the same pattern of regional change that has been observed in gray matter volume, white matter integrity, or cognitive performance. This variation suggests that existing theories of adult brain development may need to be modified to better account for the spatial dynamics of dopaminergic system aging.

Introduction

One of the most prominent theories of adult brain development is the dopamine hypothesis of aging (Bäckman & Farde, 2001; Bäckman et al., 2000; Bäckman, Lindenberger, Li, & Nyberg, 2010; Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Li, Lindenberger, Nyberg, Heekeren, & Bäckman, 2009). In its strongest form, this hypothesis posits that age-related changes in cognition are due primarily to well-documented losses of dopaminergic function with age. However, many cognitive functions that also are posited to rely on dopaminergic circuits, particularly motivational cognitive functions (Carstensen, 2006; Carstensen & Mikels, 2005; Charles, Mather, & Carstensen, 2003; Lang & Carstensen, 2002; Mather, 2006), appear to be preserved with age. To reconcile these disparate theories and results, either motivational functions do not depend on the dopamine system in older age or there may be regional differences in the decline of the dopaminergic system. An example of the latter account would be that regions supporting preserved cognitive function show relatively preserved dopaminergic function, while regions supporting cognitive functions showing declines would have steeper dopaminergic loss. Thus, clarifying the degree to which regions are, and are not, demonstrating dopaminergic signaling decline with age could help elucidate why various dopamine-dependent cognitive functions differentially change with age.

Studies of neurocognitive function, as well as gray matter and white matter structure, have identified differential decline in cognitive aging. Some theories of adult brain development suggest that compared to other brain regions, the frontal lobes show steeper age-related decline. These theories include the frontal lobe hypothesis of cognitive aging (West, 1996, 2000) and the anterior-posterior gradient described in studies of both gray matter volume (e.g. (Raz & Rodrigue, 2006)) and white matter integrity (e.g. (Sullivan & Pfefferbaum, 2006)). Recent work, however, has suggested a more nuanced view of adult development and aging. For instance, cognitive functions that are thought to be independent of the frontal lobes also display significant age-related decline (Greenwood, 2000; Rubin, 1999) while tasks that are assumed to be frontal-dependent can be impaired with caudate or putamen lesions (Rubin, 1999). Further, several studies have showed that a monotonic decrease in white matter integrity extends well beyond the frontal lobes (Bennett, Madden, Vaidya, Howard, & Howard, 2010; Davis et al., 2009).

These qualifiers led to revised theories of adult brain development, which suggest that relative to medial brain regions, lateral regions undergo greater age-related decline. For example,

the dorsolateral prefrontal theory of cognitive aging suggests that compared to ventromedial-dependent tasks, greater age-related differences are found in dorsolateral-dependent tasks (MacPherson, Phillips, & Della Sala, 2002). Similarly, the "last-in, first-out" or retrogenesis hypothesis of aging (Davis et al., 2009; Fjell et al., 2009; Raz, 2000) suggest regions which mature later in development and evolution are the first to display age-related vulnerability to decline, while phylogenetically older areas of the brain are preserved. This theory is supported by studies showing age-related gray matter decreases in the association cortices in middle age (McGinnis, Brickhouse, Pascual, & Dickerson, 2011), medial temporal lobes in early-old age (Fjell et al., 2013; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Raz et al., 2005; Yang et al., 2016), and primary sensory cortices later in late-old age (Yang et al., 2016). Additionally, some studies have shown that in healthy aging, the hippocampus is best fit by a quadratic model because it is relatively preserved until relatively late in the adult life span (Fjell et al., 2014; Fjell et al., 2013). Thus, theories of adult brain development, supported by neuropsychological and structural neuroimaging evidence, suggest differential rates of age-related change across cortical and subcortical sub-regions.

Given these differential rates of age-related change in brain structure and cognitive function, it is possible that there are also differential rates of age-related change in dopaminergic function across cortical and subcortical regions. The vast majority of studies examining the correlations between age and dopamine have reported linear declines in non-displaceable binding potential (BP_{ND}) in D2-like receptors in striatal regions (e.g. (Bäckman & Farde, 2001; Inoue et al., 2001)), with only a handful of studies examining BP_{ND} in frontal regions (e.g. (Kaasinen et al., 2000; Ouchi et al., 1999)). Specifically, studies of D2-like receptor BP_{ND} report wide-ranging age-related effects, ranging from slightly negative (Kim et al., 2011) to strongly negative (Bäckman et al., 2000). A recent meta-analysis shows strongly negative linear effects of adult age on D2-like receptors in both frontal (r = –.66) and striatal (r =–.54) regions (Karrer, Josef, Mata, Morris, & Samanez-Larkin, 2017). In exploratory analyses, this meta-analysis also showed that linear and quadratic effects of age fit the data equally well. Only a few individual studies have examined nonlinear effects of age and these studies reported concave-down quadratic effects of age on dopamine transporters (Mozley et al., 1996; van Dyck et al., 2002). However, non-linear effects have not yet been systematically investigated in individual studies of D2-like receptors.

In part because of the limited ability for D2 radiotracers (with varying affinities) to capture receptor availability in both receptor dense (striatum) and sparse (frontal cortex) areas in the same scan session and the relatively low spatial resolution of many PET scanners, the vast majority of prior studies of age differences in the dopamine system have used large regions of interest (ROIs) spanning the whole frontal lobe or striatum. Few studies have examined the potential differences between sub-regions within these relatively large structures. Further, these prior studies did not use partial volume correction, which given the differential rates of age-related gray matter atrophy, could impact BP_{ND} levels.

Thus, in the present study we examined regional age differences in dopamine BP_{ND} across adulthood in cortical and subcortical sub-regions. We examined partial volume corrected (PVC) dopamine BP_{ND} of D2-like receptors in two cross-sectional, adult life-span studies. Using [^{18}F]Fallypride, which provides broad coverage throughout both cortical and subcortical regions (Slifstein et al., 2004), allowed us to explore regional age differences in the dopamine system across the brain. Study 1 (N = 84) included participants continuously sampled across the adult life span and Study 2 (N = 48) included a group design with younger adults and older middle-aged adults. On the basis of theories of adult brain development described above, we hypothesized that BP_{ND} in most regions would show strong, negative effects of age, with steeper declines in lateral and frontal regions than in medial and posterior regions. There is also some limited evidence for linear declines in dopaminergic function with age in the hippocampus (Kaasinen et al., 2000; Stemmelin, Lazarus, Cassel, Kelche, & Cassel, 2000). However, based on anatomical studies, we hypothesized that BP_{ND} in the hippocampus would display preservation across most of adulthood with accelerated decline in old age.

Methods

Both data sets (Study 1 and Study 2) were collected as part of large-scale multimodal neuroimaging projects focused on decision making. Subsets of the Study 1 behavioral (Seaman et al., 2016), fMRI (Seaman et al., 2018) and PET (Dang et al., 2017; Dang et al., 2016; Smith et al., 2017) data were previously included in other publications. Specifically, age effects on D2-like BP_{ND} in a subset of Study 1 participants were reported or noted in three previous publications (Dang et al., 2017; Dang et al., 2016; Smith et al., 2017). However, these were limited to non-PVC striatal ROIs (Dang et al., 2017; Dang et al., 2016) or very large cortical

ROIs (i.e., frontal cortex, parietal cortex) that averaged across all gyri within a lobe (Smith et al., 2017). Here we focus on *regional* age differences in partial-volume corrected D2-like receptor BP_{ND} across the adult life span using the full sample from Study 1 (not previously reported) and a new study (Study 2).

Participants. For both studies, volunteers were recruited from the Nashville community for a multiday, multimodal neuroimaging study of decision making using the Vanderbilt School of Medicine subject database of healthy adults, Research Match (www.researchmatch.org), and a combination of newspaper, radio, and local TV advertisements. All participants were mentally and physically healthy; exclusion criteria included a history of psychiatric illness, head trauma, any significant medical condition, pregnancy, substance abuse, or any condition that would interfere with MRI (e.g. claustrophobia or metal implants). For Study 1, of the 92 adult volunteers recruited, a total of 84 participants (M= 49.43, Range = 22 to 83 years old) completed both MRI and PET scans. For Study 2, of the 73 volunteers recruited, 48 participants (M = 41.40, Range = 20 – 65 years old) completed MRI and baseline PET scans. Study 2 participants additionally completed a second [18F]fallypride PET scan after taking oral d-amphetamine to measure dopamine release, and a third PET scan using [18F]FE-PE2I to measure dopamine transporter availability. The dopamine release and transporter data are not included here. All participants gave written informed consent and were compensated $350 for Study 1 and $370-675 depending on (1) task performance, (2) the number of PET scans completed and (3) time spent on the study for Study 2. Approval for all methods was obtained from the Vanderbilt University Human Research Protection Program and the Radioactive Drug Research Committee.

Cognitive Assessment. Participants completed a battery of neuropsychological assessments during a separate session to verify that they had normal cognitive abilities. Mean performance on this test battery, the correlation of each measure with age and/or the difference between age groups, are displayed in Table 1. Participants in both studies displayed normal performance on cognitive tests. In Study 1 we found the expected age differences in measures of fluid intelligence (e.g. Digit Span, Numeracy, and Delayed Recall) and maintenance of crystallized intelligence (e.g. Vocabulary) across the adult life span. In Study 2, there was only a significant difference in delayed recall between younger and middle-aged adults; there were no other group differences in cognitive performance.

PET data acquisition and processing. PET imaging was collected at Vanderbilt University Medical Center. [^{18}F]Fallypride was produced by the PET radiochemistry laboratory following the synthesis and quality control guidelines described in US Food and Drug Administration IND 47,245. A 5.0 mCi slow bolus injection of [18F]Fallypride was followed by three, 3D emission scans in a GE Discovery STE scanner (3.25mm axial slices with in-plane pixel dimensions of 2.3x2.3mm). Prior to each emission scan, CT scans were collected for attenuation correction. Scanning lasted for approximately 3.5 hours, with two 15-minute breaks for participant comfort. Decay, attenuation, motion, and partial volume correction was performed on the PET scans and voxelwise BP_{ND} maps, which represent the ratio of specifically-bound [^{18}F]Fallypride to its free concentration, were calculated using the PMOD Biomedical Imaging Quantification software (see (Dang et al., 2016; Smith et al., 2017) for greater detail).

MRI data acquisition. Structural MRI scans were collected using a 3-T Phillips Intera Achieva MRI scanner using a 32-channel head coil. T1- weighted high-resolution anatomical scans (repetition time = 8.9 ms, echo time = 4.6 ms, field of view = 256 x 256, voxel dimensions = 1 x 1 x 1 mm) were obtained for each participant. These structural scans facilitated co-registration and spatial normalization of the PET data.

Partial volume correction. Using the Hammers atlas (Gousias et al., 2008; Hammers et al., 2003), both MRI and PET data were parcellated into 62 bilateral cortical, 12 bilateral subcortical, 3 posterior fossa, 5 ventricle, and 1 white matter regions of interest (a total of 83 regions). Following parcellation, the MRI and PET data were co-registered, PET data was resampled to MRI space, and then the partial volume correction (PVC) procedure available in PMOD's PNEURO module was applied to the PET data. PNEURO uses the GTM method (Rousset, Collins, Rahmim, & Wong, 2008; Rousset, Ma, & Evans, 1998), which restricts PVC to the PET signal of structurally defined regions of interest. To evaluate the co-registration between the MRI and PET data, we calculated quality control metrics using the PFUS module in PMOD 3.9 for a subset of 42 participants, including the oldest 10 participants in each study. It is our experience that due to gray matter loss with age, the oldest subjects are usually the hardest to co-register. The average Dice coefficient between PET data warped to MRI space and the MRI data itself, which is a ratio of the number of true positives compared to the number of true positives plus the number of false positives, was 0.86±0.02. This suggests that the registration methods were successful and consistent across the sample. Further, we tested whether there were

any age differences in registration quality control metrics provided by PFUS (sensitivity, specificity, Jaccard index) across the subsamples and found no relationship between age and any measure of registration quality. Time activity curves (TACs) from each region were extracted from the PET data after PVC and fit with a simplified reference tissue model (Lammertsma & Hume, 1996) using PMOD's PKIN module where a gray matter bilateral cerebellum ROI was used as the reference region (see Smith et al., 2017 for greater detail).

Regions of Interest Prior to analysis, brainstem, white matter, occipital lobes, and ventricles were excluded from consideration for analysis because these regions have no or extremely low levels of dopamine receptors. The cerebellum was also excluded because it was used as the reference region in the TAC modeling. To further limit the number of analyses, for each region of interest (ROI) we calculated the bilateral average BP_{ND} within each participant, giving a total of 33 bilateral ROIs. Within each study, we screened these bilateral BP_{ND} averages for outliers, cutting any values that were more than 1.5 times outside the interquartile range (Study 1: M = 3.15, Range = 0 to 17 participants excluded in each ROI, Study 2: M=2.08, Range = 0 to 8 participants excluded in each ROI). Because estimates of BP_{ND} in white matter was of no physiological interest in our analyses, we used the average white matter BP_{ND} for each study as a cutoff/threshold. For Study 1, average white matter BP_{ND} was 0.49±0.13 while for Study 2 average white matter BP_{ND} was 0.56±0.20. Regions with mean corrected BP_{ND} values at or below these white matter values were excluded from analyses. In Study 1, eleven regions were below the white matter BP_{ND} mean (middle frontal gyrus, precentral gyrus, anterior orbital gyrus, inferior frontal gyrus, superior frontal gyrus, lateral orbital gyrus, postcentral gyrus, superior parietal gyrus, inferiolateral remainder of parietal lobe, anterior cingulate gyrus and posterior cingulate gyrus ROIs) while in Study 2 no ROIs were below the white matter BP_{ND} mean. In many of these regions, these BP_{ND} values reflect that with aging, the levels of BP_{ND} drop below the threshold. This left us with 22 bilateral ROIs in both studies and 11 bilateral regions in Study 2, which are analyzed below. Pictures, scatterplots, and statistics for each ROI are available in an interactive app online at http://13.58.222.229:3838/agebp/. Data and code are available online at https://github.com/klsea/agebp or https://osf.io/h67k4/.

Statistical Analyses Despite the fact that the two studies were carried out by the same lab, using the same PET camera, protocol, and preprocessing and analysis pipelines, the two studies differed significantly in average BP_{ND} in many regions (Table 2). Because of this difference, our

baseline model included study, along with sex, which has been suggested to affect D2 receptor availability (Pohjalainen, Rinne, Någren, SyvÄlahti, & Hietala, 1998), as control variables to ensure that these variables did not exert an influence on estimates of D2 declines with aging. Age effects were tested with linear and quadratic regressions carried out using the lm command in the R programming language.

Baseline model

$$BPND = b_0 + b_1\, Study + b_2\, Sex$$

Linear model

$$BPND = b_0 + b_1\, Study + b_2\, Sex + b_3\, Age$$

Quadratic model

$$BPND = b_0 + b_1\, Study + b_2\, Sex + b_3\, Age + b_4\, Age^2$$

Model comparison was conducted contrasting these three regression models to each other within each region using the anova command in the R programming language, which tests the reduction in sum of squared error between models.

Percent change per decade (PCD) was calculated using the following steps for each region: (1) a linear model with a single predictor (age) was fit to the data, (2) using the resulting regression equation, the estimated BP_{ND} at age 20 and age 30 were calculated, and (3) percent change per decade was calculated using the following formula:

$$PCD = \frac{(BP_{ND\_30} - BP_{ND\_20})}{BP_{ND\_20}}$$

Confidence intervals for *PCD* were calculated the same way. For instance, the lower-bound was calculated as follows:

$$PCD_{LB} = \frac{(BP_{ND\_30\_LB} - BP_{ND\_20\_LB})}{BP_{ND\_20\_LB}}$$

Here we focus on complete reporting of effect sizes and confidence intervals rather than relying entirely on p-values which lead to somewhat arbitrary judgments of an effect being there or not (Cumming, 2014). The selection of a set of direct pairwise null hypothesis statistical tests would also be somewhat arbitrary given the large number of ROIs. What has been the standard p-value heavy approach has been criticized by statisticians e.g. (Wasserstein & Lazar, 2016). For the comparisons across regions, we are focused on estimation and comparison of estimated effects (Gardner & Altman, 1986). Non-overlapping confidence intervals indicate a significant difference at $p < .01$ (Cumming, 2009). We highlight a few significant differences but do not discuss every possible comparison.

Results

Average binding across regions of interest. Means and standard deviations of PVC-corrected BP_{ND} for each ROI are displayed in Table 2. As expected, BP_{ND} was highest in the striatum (ventral striatum: 37.16, putamen: 33.02, caudate: 26.9). The next highest BP_{ND} was observed in other medial and subcortical regions, but many of these values were an order of magnitude lower (pallidum: 14.83, subcallosal area: 9.23, insula: 2.44, thalamus: 2.43, amygdala: 3.02). The remaining frontal and temporal ROIs had mean BP_{ND} between 0.47 and 1.67.

Relative strength of linear age effects. The largest raw age slopes (unstandardized coefficients from linear regression) were observed in striatal regions with smaller slopes in frontal and temporal regions with no age differences in subcallosal frontal cortex, pallidum, or hippocampus (Figure 1). However, since mean BP_{ND} differed by orders of magnitude across regions, unstandardized regression slopes (i.e., unit difference in BP_{ND} per year difference in age) were not directly comparable. The point estimates for each age slope (collapsing across but not controlling for sex and study) in each region were converted to percentage differences per decade and then qualitatively compared across regions (Figure 2). Estimated percentage differences in receptor BP_{ND} by age decade (linear effects) were highest in most temporal and frontal cortical regions (~6–16% per decade), moderate in parahippocampal gyrus, pregenual frontal cortex, fusiform gyrus, caudate, putamen, thalamus, and amygdala (~3–5%), and weakest

in subcallosal frontal cortex, ventral striatum, pallidum, and hippocampus (~0–2%). Although there is a general trend of more anterior and lateral regions showing steeper effects of age than more posterior and medial regions, the confidence intervals around most of these point estimates overlapped. Thus, there was not a strong pattern of significant differences across anterior/posterior or medial/lateral gradients. However, the set of subcortical regions where we observed the smallest age differences (CI upper bound <5% per decade; putamen, amygdala, thalamus, ventral striatum, hippocampus, and pallidum) were significantly different than the set of cortical regions where we observed the largest age differences (CI lower bound >5% per decade; postcentral gyrus, middle frontal gyrus, lateral orbital gyrus, inferior frontal gyrus, anterior orbital gyrus, and posterior and anterior superior temporal gyri). See non-overlapping confidence intervals in Figure 2.

Non-linear effects of age. BP_{ND} in many frontal and temporal cortical regions were best fit by quadratic models (Tables 3–8). BP_{ND} in the straight gyrus/gyrus rectus, pre-subgenual frontal cortex, medial and posterior orbital gyri, fusiform gyrus, and all lateral temporal cortical regions showed concave-down quadratic effects of age such that BP_{ND} was reduced in middle age compared to young adulthood but then remained relatively stable (and low) until old age. Similar non-linear effects were observed in the insula and putamen such that there was a reduction in receptors during young adulthood (20–50 years old) that leveled off in middle age and older adulthood (+50 years old).

Discussion

This paper investigated regional differences in dopamine D2/3 (or D2-like) receptor BP_{ND} across the adult life span. As expected, the largest estimates of age-related differences per decade were observed in cortical regions (especially frontal and lateral temporal cortex), with more gradual loss of receptors in a subset of more medial cortical and subcortical regions. While we estimated declines of 8–16% in lateral temporal and many frontal cortical regions, we estimated striatal D2-like declines between 1.5 and 5% per decade. The estimates reported here are somewhat lower than those seen in a recent meta-analysis (Karrer et al., 2017), and could be due to our use of partial volume correction, an extremely healthy sample, or both. For instance, prior work from our lab on a subset of data from Study 1 noted that age-related changes in the uncorrected data more closely resemble those seen in the meta-analysis (Smith et al., 2017),

while another study showed that compared to more sedentary adults, age-related change in striatal D2 BP_{ND} is less steep in physically active adults (Dang et al., 2017). Thus, the estimated changes reported here likely reflect both the partial volume techniques used and the relative health of our sample.

There was partial evidence for a medial/lateral distinction across cortical and subcortical regions. We found partial evidence for relative preservation of more ventromedial aspects of frontal cortex (subcallosal) and subcortical regions (ventral striatum, pallidum, hippocampus). This set of regions is partially consistent with components of the "core affect" functional network from studies of emotional processing (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012) and the motivational loop described in anatomical and functional studies of dopaminergic frontostriatal circuits (Haber & Knutson, 2010; Seger & Miller, 2010). One exception is the moderate loss of receptors in the amygdala. One might expect more preservation in the amygdala relative to the hippocampus if the amygdala was primarily supporting affective function. Regardless, the relative preservation of dopaminergic function in the other medial regions may possibly account for the relative preservation of affective and motivational function with age.

There was some suggestive but weak evidence for an anterior-posterior gradient. Specifically, the point estimates of the linear effect of age on reductions in dopamine receptor availability were highest in frontal cortical regions. However, the confidence intervals around these estimates were very wide, so the higher rates of decline in these regions did not significantly differ from more posterior cortical regions or the majority of the other regions elsewhere throughout the brain. An important limitation is that these analyses were restricted to Study 2 because several areas had to be excluded from analysis in Study 1 due to their low BP_{ND} in older subjects. Thus, we may have been underpowered to detect small or medium effects of an anterior-posterior gradient given the smaller sample size in Study 2.

Although the steepest raw age slopes on BP_{ND} from the linear regressions were found in striatal regions, binding was also extremely high in these regions. Thus, even a large effect of age meant that the oldest adults still had relatively high levels of binding in striatum. This is why we chose to focus instead on the percentage age difference measures when making relative comparisons across regions. Although the percent per decade estimates did not control for study or sex (since these were dummy-coded categorical variables in the regression analyses), the

slopes used to compute the percentage scores were nearly identical to the slopes from analyses that included the study and sex covariates. However, in contrast to the still relatively high levels of binding in older age in striatal regions, in most cortical regions the oldest adults had almost no signal to distinguish from our white matter threshold (i.e., BP_{ND} approaching the binding values observed in white matter where there are no receptors). This was the case especially for regions showing curvilinear age effects where signal approached our threshold values as early as middle age. In fact, the evidence for these curvilinear effects may be confounded somewhat by a floor effect given that BP_{ND} has a lower bound of 0. An exception to this is the curvilinear effect in the putamen where the lowest values do not come close to approaching our threshold values. Much of the putamen is connected to the pre/motor cortex and lateral prefrontal cortex, and these corticostriatal loops are thought to mediate both motor and fluid cognitive abilities (Seger & Miller, 2010). Thus age-related change in the putamen is consistent with both age-related motor slowing (Deary & Der, 2005) and age-related change in executive function and cognitive control (Rubin, 1999). However, smaller ROIs that isolated subareas more connected with lateral and motor cortex would be needed to fully evaluate this explanation.

Additionally, across the sample within our striatal ROIs we report higher BP_{ND} values in the ventral striatum compared to the putamen, whereas the opposite pattern has been reported using fallypride in previous studies using uncorrected data (i.e., no PVC). Putamen BP_{ND} is higher than ventral striatum BP_{ND} in our uncorrected data as well (Study 1: ventral striatum BP_{ND} = 18.8, putamen BP_{ND} = 22.4). However, this relationship switches when using PVC. It is possible this occurs because the ventral striatum lies between ventricles and white matter; thus prior estimates of BP_{ND} in the ventral striatum likely included partial signal from neighboring ventricle and/or white matter in the estimates. Further, post-mortem studies comparing D2 receptor density in striatal subregions show a good deal of heterogeneity (Mawlawi et al., 2001), so it is not unreasonable for ventral striatal BP_{ND} to exceed putamen BP_{ND}.

We found little evidence to support change in BP_{ND} in the hippocampus. This was somewhat unexpected, as studies of gray matter volume have documented both declines (Raz et al., 2010) and accelerated declines (Fjell et al., 2013) in both cross-sectional and longitudinal data. There is also some evidence for age-related decline in hippocampal dopamine receptors in human and non-human animals (Stemmelin et al 2000; Kaasinen et al 2000). However, the previous evidence from human PET imaging did not use partial volume correction; thus, age

effects on BP_{ND} may have been somewhat confounded by age differences in gray matter volume. It is possible that there are age-related declines in hippocampal BP_{ND}, but we were unable to detect them due to our sample size, restricted range in BP_{ND}, and/or under-sampling of adults over the age of 65. In particular, given the greater variability in old-old age, future studies would benefit from over-sampling at the upper end of the human age range (Samanez-Larkin & D'Esposito, 2008). However, if there is true preservation of D2-like receptors in the hippocampus this would be an intriguing effect. Because memory performance has been linked to D2-like receptor binding in the hippocampus within older (Nyberg et al., 2016) and younger age (Takahashi et al., 2008) groups, age-related memory deficits have been suggested to be due to decline of the medial temporal lobes. However, these D2-like receptor effects have not been tested with cross-sectional age group or life-span designs. Our results may be viewed instead as consistent with the suggestion that many age-related memory deficits in healthy, disease-free adults are mediated by age-related changes in more frontal and/or lateral regions (Buckner, 2004).

There are important statistical caveats to the results reported here. In addition to study differences in average BP_{ND}, there was a significant difference in the average age between the two studies (Study 1: M= 49.43 years old; Study 2: M = 41.40 years old). Thus, because study and age are correlated with each other and we controlled for study in our models, the slopes reported in this manuscript may under-estimate age effects. Also, the inflection points of many of the best-fitting quadratic models (e.g. in the majority of the frontal lobes, lateral temporal lobes, the fusiform gyrus and the insula) was in early middle-age (between ages 35-45). This is earlier than we predicted based on longitudinal studies of gray matter volume, which suggested the inflection point is in the mid-fifties (Raz et al., 2005), and corresponds to an age range not included in Study 2. Future studies are need to determine if these inflection points are true age effects, an artifact of floor effects (as mentioned above), and/or the result of under-sampling of this age range in these samples.

One major limitation of this study is that it was cross-sectional in nature. The estimates of age differences reported here (e.g., percentage change per decade), and in the PET literature generally, are based on the assumption that cross-sectional studies accurately represent developmental trends. Until verified with longitudinal data, it remains possible that the age-related changes in dopaminergic function are at least partially a result of cohort effects.

Longitudinal studies of gray matter volume have estimated that cross-sectional studies can under-estimate the influence of aging (Raz et al., 2005) and similar longitudinal studies are necessary to determine to what extent this occurs in studies of the dopaminergic system. A longitudinal study is currently underway that should be able to address this question (Nevalainen et al., 2015). A second limitation of this study is that it focuses exclusively on D2-like receptor BP_{ND}, without considering age-related changes in D1-like receptor binding, dopamine transporters, dopamine synthesis capacity, or dopamine release. Each of these measures a distinct aspect of dopaminergic function, and by focusing on D2-like receptors, we are likely to be missing important aspects of age-related change or stability elsewhere in the system. For example, D1-like receptor binding has shown steeper declines with age while synthesis capacity appears to remain stable with age (Karrer et al., 2017). However, it is important to note that the regional variation of these effects have not yet been systematically evaluated.

Collectively, the data presented here suggests that dopamine BP_{ND} does not show the same regional pattern of age-related changes observed in studies of gray matter volume and white matter integrity. There was somewhat surprising evidence for preservation of dopaminergic function well into older age in a subset of ventromedial cortical and subcortical brain regions. These results may help clarify one paradox of aging: namely, that some dopamine-mediated cognitive functions are preserved with age while others show marked decline. While there are clearly age-related differences in dopaminergic function across the adult life span, these changes in function are not uniform and they do not show the same regional pattern of change than has been observed using other neuroimaging methods. New theories of adult brain development are needed that incorporate these and other challenging results. Hopefully these findings inspire future studies that could be used to modify existing or propose new theories of human brain aging that better account for the differential changes in cognitive, affective, and motivational functions across adulthood.

Tables

Table 1
Participant Characteristics

Variable	Study 1 (N=84)		Study 2 (N=48)		
	M (SD)	*r* [95% CI] with age	YA M (SD)	MA M (SD)	Group t-value [95% CI]
Age	49.43 (17.64)		25.78 (2.61)	55.65 (3.72)	
Gender	48F/36M		12F/11M	10F/10M	
Digit Span[a]	16.12 (3.96)	**–0.28 [–0.47, –0.07]**	20.52 (3.95)	21.85 (4.13)	1.07 [–1.18 , 3.83]
Numeracy[a]	11.81 (3.24)	**–0.27 [–0.46, –0.06]**	12.52 (1.5)	15.35 (7.88)	1.58 [–0.9 , 6.56]
Paired Associates Delayed Recall[b]	5.85 (2.34)	**–0.61 [–0.73, –0.45]**	7.22 (1.62)	5.95 (2.14)	**–2.16 [–2.46 , –0.08]**
Shipley Vocabulary Subscale[a]	33.67 (5.39)	0.15 [–0.07, 0.35]	33.3 (3.46)	32.1 (9)	–0.56 [–5.62 , 3.21]

Notes. Digit Span and Paired Associates Delayed Recall from the WMS-III, Wechsler Memory Scale-Third Edition, (Wechsler, 1997); Numeracy, (Peters, Dieckmann, Dixon, Hibbard, & Mertz, 2007); Shipley Vocabulary Subscale, (Shipley, 1940); Trails Test, (Corrigan & Hinkeldey, 1987).
YA = Younger adults; MA = older Middle Aged adults
Significant correlations denoted in bold.
No significant group differences in Study 2.
[a]Digit Span, Vocabulary, and Numeracy were not recorded for one participant in Study 1.
[b]Delayed Recall not recorded for five participants in Study 1.

Table 2. Mean (SD) for D2-like receptor availability (BPND) across two studies using [18F]Fallypride PET. Significant differences are denoted in bold.

Region	Overall BPND M (SD)	Study 1 BPND M (SD)	Study 2 BPND M (SD)	Study t-value [95% CI]
Ventral striatum	37.16 (8.01)	39.21 (7.66)	33.33 (7.27)	**-4.3 [-8.6, -3.17]**
Putamen	33.02 (4.87)	32.7 (5.09)	33.63 (4.41)	1.09 [-0.77, 2.64]
Caudate nucleus	26.9 (5.2)	25.92 (5.15)	28.64 (4.87)	**2.98 [0.91, 4.51]**
Pallidum	14.83 (3.47)	15.84 (3.28)	13.13 (3.12)	**-4.69 [-3.86, -1.57]**
Subcallosal area	9.23 (3.88)	9.86 (3.79)	8.03 (3.82)	**-2.53 [-3.27, -0.39]**
Amygdala	3.02 (0.65)	3.2 (0.64)	2.69 (0.56)	**-4.79 [-0.72, -0.3]**
Insula	2.44 (0.64)	2.33 (0.57)	2.64 (0.7)	**2.63 [0.08, 0.56]**
Thalamus	2.43 (0.39)	2.4 (0.34)	2.47 (0.47)	0.85 [-0.09, 0.22]
Anterior temporal lobe lateral	1.67 (0.48)	1.56 (0.37)	1.86 (0.59)	**3.21 [0.12, 0.49]**
Anterior temporal lobe medial	1.64 (0.45)	1.5 (0.35)	1.89 (0.5)	**4.8 [0.23, 0.56]**
Fusiform gyrus	1.62 (0.39)	1.55 (0.35)	1.75 (0.44)	**2.52 [0.04, 0.35]**
Superior temporal gyrus anterior	1.44 (0.52)	1.26 (0.4)	1.75 (0.56)	**5.29 [0.3, 0.67]**
Middle and inferior temporal gyrus	1.4 (0.45)	1.29 (0.36)	1.59 (0.54)	**3.49 [0.13, 0.48]**
Hippocampus	1.34 (0.43)	1.47 (0.44)	1.11 (0.3)	**-5.45 [-0.48, -0.23]**
Straight gyrus	1.23 (0.44)	1.05 (0.34)	1.52 (0.43)	**6.39 [0.32, 0.62]**
Medial orbital gyrus	1.19 (0.38)	1.03 (0.29)	1.45 (0.38)	**6.64 [0.3, 0.55]**
Subgenual frontal cortex	1.01 (0.55)	0.72 (0.35)	1.53 (0.43)	**10.71 [0.66, 0.97]**
Posterior orbital gyrus	0.94 (0.39)	0.78 (0.31)	1.19 (0.37)	**6.32 [0.28, 0.54]**
Lateral orbital gyrus	0.93 (0.45)		0.93 (0.45)	
Anterior orbital gyrus	0.93 (0.37)		0.93 (0.37)	
Inferiolateral remainder of parietal lobe	0.92 (0.42)		0.92 (0.42)	
Superior temporal gyrus posterior	0.82 (0.39)	0.7 (0.32)	1.05 (0.42)	**4.88 [0.21, 0.49]**
Posterior temporal lobe	0.81 (0.35)	0.72 (0.31)	0.98 (0.35)	**4.12 [0.13, 0.38]**
Cingulate gyrus anterior part	0.8 (0.2)		0.8 (0.2)	
Parahippocampal and ambient gyri	0.8 (0.27)	0.71 (0.18)	0.96 (0.33)	**4.96 [0.15, 0.36]**
Inferior frontal gyrus	0.79 (0.34)		0.79 (0.34)	
Superior frontal gyrus	0.78 (0.27)		0.78 (0.27)	
Postcentral gyrus	0.68 (0.46)		0.68 (0.46)	
Middle frontal gyrus	0.64 (0.38)		0.64 (0.38)	
Superior parietal gyrus	0.6 (0.39)		0.6 (0.39)	
Pre-subgenual frontal cortex	0.59 (0.24)	0.52 (0.2)	0.74 (0.25)	**5.2 [0.14, 0.31]**
Precentral gyrus	0.48 (0.29)		0.48 (0.29)	
Cingulate gyrus posterior part	0.47 (0.3)		0.47 (0.3)	

Table 3
Multiple Linear Regression Analyses of Frontal and Insula ROI's Age-related change in D2–like receptor availability (BP_{ND}) using [18F]Fallypride PET.

Model	Parameter	Medial orbital gyrus	Posterior orbital gyrus	Pre-subgenual frontal cortex	Straight gyrus	Subcallosal area	Subgenual frontal cortex	Insula
	N	126	124	126	128	123	124	128
Baseline	R^2	0.283***	0.252***	0.184***	0.263***	0.039*	0.506***	0.043*
Linear	Age	**-0.0057 [–0.009, –0.0024]**	**–0.0043 [–0.0078, –0.00086]**	–0.0016 [–0.0039, 7e-04]	**–0.007 [–0.011, –0.0032]**	–0.031 [–0.071, 0.0087]	**–0.0067 [–0.011, –0.0027]**	**–0.018 [–0.024, –0.012]**
	R^2 change	0.063***	0.036*	0.012	0.072***	0.019	0.042**	0.214***
Quadratic	Age	**–0.038 [–0.057, –0.019]**	**–0.028 [–0.048, –0.0072]**	**–0.016 [–0.029, –0.0023]**	**–0.041 [–0.062, –0.019]**	–0.077 [–0.32, 0.17]	**–0.029 [–0.053, –0.0057]**	**–0.065 [–0.099, –0.031]**
	Age2	**0.00034 [0.00014, 0.00054]**	**0.00024 [3.3e-05, 0.00046]**	**0.00015 [9.7e-06, 0.00029]**	**0.00035 [0.00013, 0.00058]**	**0.00049 [–0.002, 0.003]**	0.00024 [–7e-06, 0.00048]	**5e-04 [0.00015, 0.00085]**
	R^2 change	0.057***	0.03*	0.028*	0.047**	0.001	0.013	0.044**

Notes
Significant effects are denoted in bold.
Full regression tables can be found in the online application http://13.58.222.229:3838/agebp/.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 4
Multiple Linear Regression Analyses of Basal Ganglia ROI's Age-related change in D2-like receptor availability (BP_{ND}) using [^{18}F]Fallypride PET.

Model	Parameter	Caudate nucleus	Pallidum	Putamen	Thalamus	Ventral striatum
	N	130	129	129	127	129
Baseline	R^2	0.055*	0.151***	–0.007	0.02	0.124***
Linear	Age	**–0.15 [–0.2, –0.11]**	–0.022 [–0.055, 0.011]	**–0.13 [–0.18, –0.088]**	**–0.0071 [–0.011, –0.0033]**	**–0.1 [–0.18, –0.027]**
	R^2 change	0.248***	0.011	0.212***	0.097***	0.047**
Quadratic	Age	**–0.41 [–0.68, –0.14]**	0.038 [–0.16, 0.24]	**–0.53 [–0.79, –0.27]**	–0.014 [–0.036, 0.0091]	–0.31 [–0.77, 0.15]
	Age^2	0.0027 [–6.9e-05, 0.0055]	–0.00063 [–0.0027, 0.0014]	**0.0042 [0.0014, 0.0069]**	6.8e-05 [–1.7e-04, 3e-04]	0.0022 [–0.0026, 0.0069]
	R^2 change	0.02	0.002	0.053**	0.002	0.005

Notes
Significant effects are denoted in bold.
Full regression tables can be found in the online application http://13.58.222.229:3838/agebp/.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 5
Multiple Linear Regression Analyses of Medial Temporal Lobe ROI's Age-related change in D2-like receptor availability (BP_{ND}) using [^{18}F]Fallypride PET.

Model	Parameter	Amygdala	Anterior temporal lobe medial part	Fusiform gyrus	Hippocampus	Parahippocampal and ambient gyri
	N	131	130	127	129	127
Baseline	R2	0.136***	0.169***	0.044*	0.148***	0.198***
Linear	Age	**–0.013 [–0.018, –0.0066]**	**–0.011 [–0.015, –0.0069]**	**–0.0072 [–0.011, –0.0034]**	–0.0037 [–0.0078, 0.00038]	**–0.0033 [–0.0058, –0.00076**]
	R2 change	0.102***	0.162***	0.097***	0.021	0.041*
Quadratic	Age	**–0.037 [–0.072, –0.0011]**	**–0.032 [–0.054, –0.0091]**	**–0.037 [–0.06, –0.015]**	0.01 [–0.014, 0.035]	**–0.018 [–0.032, –0.0029]**
	Age2	0.00026 [–0.00012, 0.00063]	0.00022 [–1.4e-05, 0.00046]	0.00032 [8.7e-05, 0.00055]	–0.00015 [–4e-04, 1e-04]	0.00015 [–1.1e-06, 3e-04]
	R2 change	0.011	0.018	0.049**	0.009	0.023

Notes
Significant effects are denoted in bold.
Full regression tables can be found in the online application http://13.58.222.229:3838/agebp/.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 6
Multiple Linear Regression Analyses of Lateral Temporal Lobe ROI's Age-related change in D2-like receptor availability (BP_{ND}) using [^{18}F]Fallypride PET.

Model	Parameter	Superior temporal gyrus, anterior part	Anterior temporal lobe, lateral part	Middle and inferior temporal gyrus	Posterior temporal lobe	Superior temporal gyrus, posterior part
	N	130	131	131	131	129
Baseline	R2	0.194***	0.08**	0.091***	0.111***	0.179***
Linear	Age	**–0.012 [–0.017, –0.0081]**	**–0.01 [–0.017, –0.0089]**	**–0.0096 [–0.014, –0.0055]**	**–0.0051 [–0.0084, –0.0019]**	**–0.0086 [–0.012, –0.0053]**
	R2 change	0.163***	0.209***	0.128***	0.063**	0.137***
Quadratic	Age	**–0.048 [–0.074, –0.023]**	**–0.049 [–0.074, –0.025]**	**–0.055 [–0.079, –0.032]**	**–0.037 [–0.056, –0.018]**	**–0.043 [–0.062, –0.023]**
	Age2	**0.00038 [0.00012, 0.00064]**	**0.00038 [0.00013, 0.00064]**	**0.00048 [0.00024, 0.00073]**	**0.00034 [0.00014, 0.00053]**	**0.00036 [0.00016, 0.00056]**
	R2 change	0.039**	0.046**	0.082***	0.07***	0.06***

Notes
Significant effects are denoted in bold.
Full regression tables can be found in the online application http://13.58.222.229:3838/agebp/.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 7
Multiple Linear Regression Analyses of Frontal Lobe ROI's Age-related change in D2-like receptor availability (BP_{ND}) using [^{18}F]Fallypride PET in Study 2.

Model	Parameter	Anterior orbital gyrus	Cingulate gyrus anterior part	Inferior frontal gyrus	Lateral orbital gyrus	Middle frontal gyrus	Superior frontal gyrus
	N	47	46	46	45	44	43
Baseline	R2	-0.022	-0.021	-0.022	-0.018	-0.022	0.007
Linear	Age	**-0.014 [-0.02, -0.0077]**	**-0.0056 [-0.0092, -0.0019]**	**-0.014 [-0.019, -0.0086]**	**-0.018 [-0.025, -0.01]**	**-0.015 [-0.021, -0.0094]**	**-0.0092 [-0.014, -0.0047]**
	R2 change	0.324***	0.18**	0.401***	0.358***	0.396***	0.292***
Quadratic	Age	-0.018 [-0.095, 0.058]	0.00055 [-0.046, 0.047]	4e-04 [-0.066, 0.066]	-0.0077 [-0.1, 0.086]	-0.01 [-0.085, 0.065]	-0.0051 [-0.061, 0.051]
	Age2	5.8e-05 [-0.00087, 0.00099]	-7.4e-05 [-0.00064, 0.00049]	-0.00017 [-0.00097, 0.00063]	-0.00012 [-0.0013, 0.001]	-6.2e-05 [-0.00097, 0.00085]	-5e-05 [-0.00073, 0.00063]
	R2 change	0	0.001	0.003	0.001	0	0

Notes
Significant effects are denoted in bold.
Full regression tables can be found in the online application http://13.58.222.229:3838/agebp/.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 8

Multiple Linear Regression Analyses of Posterior Frontal and Parietal Lobe ROI's Age-related change in D2-like receptor availability (BP_{ND}) using [^{18}F]Fallypride PET in Study 2.

Model	Parameter	Cingulate gyrus posterior part	Precentral gyrus	Postcentral gyrus	Superior parietal gyrus	Inferiolateral remainder of parietal lobe
	N	47	40	40	42	46
Baseline	R2	-0.006	-0.018	-0.018	-0.022	-0.021
Linear	Age	**-0.0078 [-0.013, -0.0024]**	-0.0057 [-0.012, 0.00046]	**-0.017 [-0.025, -0.0089]**	**-0.0096 [-0.017, -0.0021]**	**-0.013 [-0.02, -0.0056]**
	R2 change	**0.161****	0.086	**0.328*****	**0.145***	**0.228*****
Quadratic	Age	0.034 [-0.033, 0.1]	0.017 [-0.059, 0.093]	-0.037 [-0.14, 0.061]	-0.013 [-0.11, 0.082]	-0.021 [-0.11, 0.072]
	Age2	-5e-04 [-0.0013, 0.00031]	-0.00028 [-0.0012, 0.00065]	0.00024 [-0.00095, 0.0014]	3.5e-05 [-0.0011, 0.0012]	9.4e-05 [-0.001, 0.0012]
	R2 change	0.029	0.009	0.003	0	0.001

Notes

Significant effects are denoted in bold.

Full regression tables can be found in the online application http://13.58.222.229:3838/agebp/.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Figures

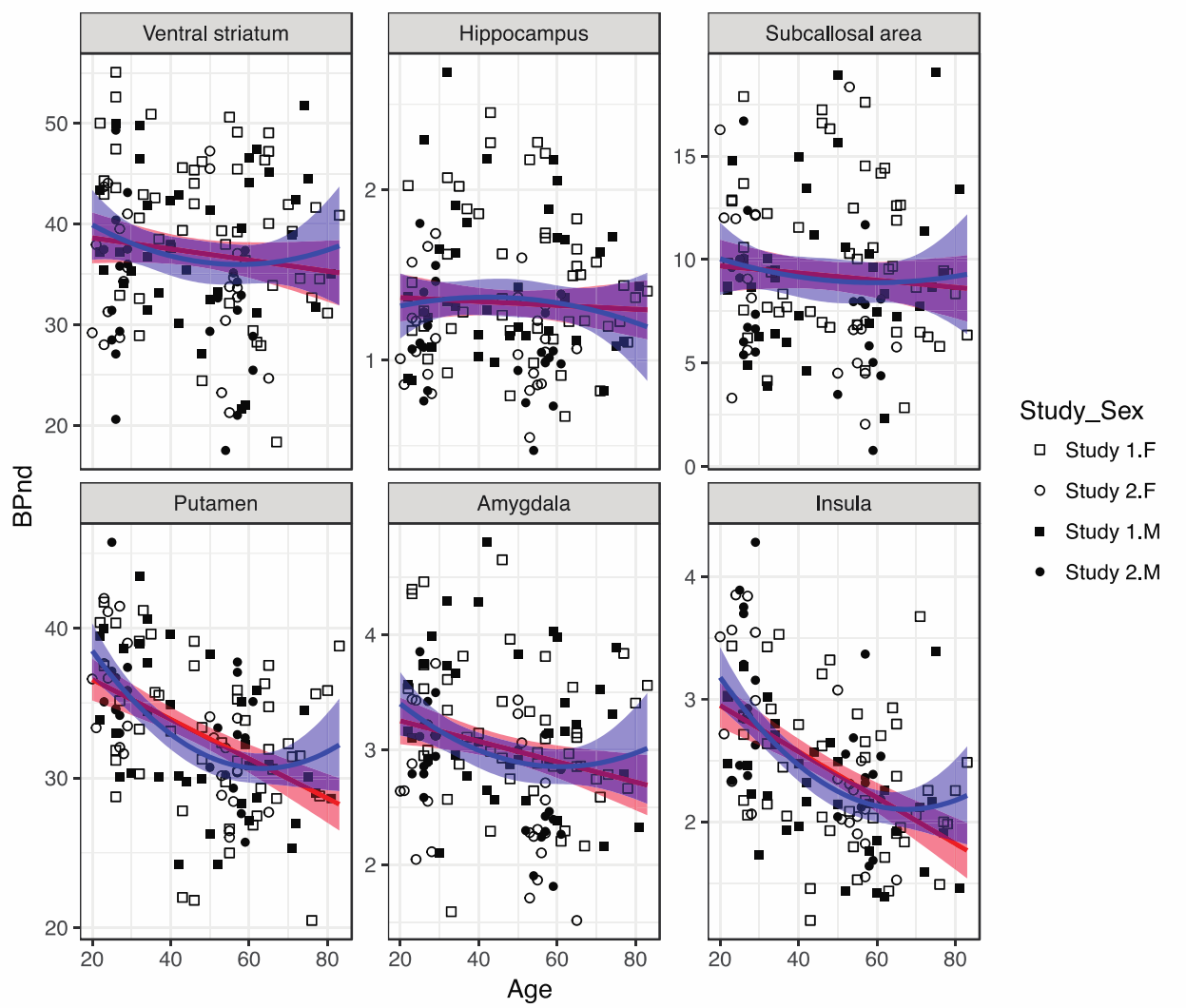

Figure 1: Linear and quadratic effects of Age on D2-BPND in select regions of interest. Pictures, scatterplots, and statistics for each ROI are available in an interactive app online at http://13.58.222.229:3838/agebp/

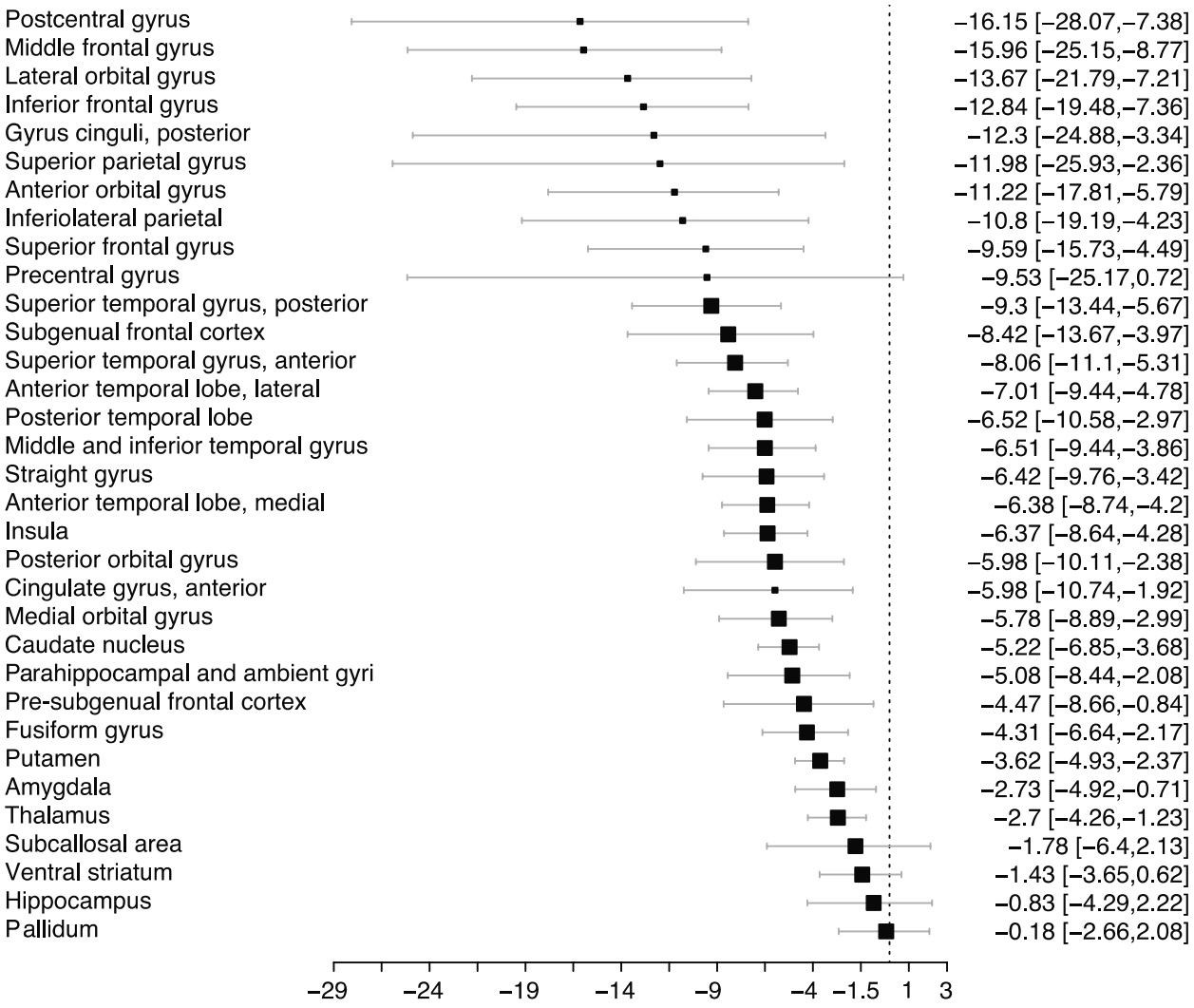

Figure 2: Percentage change in D2-BP$_{ND}$ per decade in regions of interest. Forest plot for all regions of interest. The position of the squares on the x-axis indicates the estimated percentage change in D2-BP$_{ND}$ per decade and the horizontal bars indicate the 95% confidence intervals of the estimate. Non-overlapping confidence intervals indicate significant differences at $p < .01$ (Cumming, 2009). The size of the squares are proportional to the number of individuals included in the analysis of that region (i.e., small squares indicate the estimate was based on Study 2 only, while large squares indicate the estimate was based on both Study 1 and 2).

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