Original Article

Putamen Volume Differences Among Older Adults: Depression Status, Melancholia, and Age

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Abstract

Background: Individuals with major depressive disorder (MDD) may exhibit smaller striatal volumes reflecting deficits in the reward circuit. Deficits may change with age and be more pronounced among the melancholic subtype. Limited research has investigated striatal volume differences in older adults and by depression subtypes. **Method:** We used baseline data from the Neurocognitive Outcomes of Depression in the Elderly study. We examined volumetric differences in the putamen and caudate nucleus among older adults (60 years and older), comparing healthy control participants (n = 134) to depressed participants (n = 226), and comparing nonmelancholic depressed participants (n = 93) to melancholic depressed participants (n = 133). Group-by-age interactions were examined. **Results:** There were no significant group differences for the caudate nucleus. For the left putamen, investigation of the significant group-by-age interaction revealed that volume size was greater for the healthy controls compared to the depressed participants but only at younger ages (60-65 years); group differences diminished with increasing age. Examining volume by depression subtype revealed that the melancholic depressed participants had a smaller left putamen compared to the nonmelancholic depressed participants. Anhedonia symptoms were related to both smaller left and right putamen. **Conclusion:** Structural abnormalities in reward regions may underlie the anhedonic phenotype. Volume loss associated with MDD may attenuate in older age.

Keywords

striatum, reward, depression, melancholia, anhedonia, elderly

Growing evidence indicates that there are differences between those with major depressive disorder (MDD) and never-depressed individuals in the regions of the brain associated with reward sensitivity.[1-4] Reward processing depends on the striatum of the basal ganglia, including the caudate nucleus and putamen,[5] which have been implicated in the receipt and anticipation of reward.[6,7] Among individuals with MDD, there is evidence for functional dysregulation of the caudate and putamen during reward processing[4]; there is also structural evidence of reduced volumes of the caudate and putamen.[8-10] Reward sensitivity deficits may be particularly pronounced among those with the melancholic subtype of depression,[11] which is characterized by anhedonia or difficulty experiencing pleasure. Blunted reward processes may be a biological marker for depression risk[8,12,13] or differences may be the result of the effects of depression over time.[14]

Many studies have identified structural abnormalities in the basal ganglia of individuals who have depression, including samples of adolescents, young adults, middle-aged adults, and older adults.[8-10] However, not all depression studies have found such volume differences.[15,16] Indeed, in a meta-analysis, Schmaal and colleagues[16] examined magnetic resonance imaging (MRI) data to identify subcortical brain volume differences between patients with MDD (n = 1728) and controls (n = 7199) from 15 studies. Although they did report volume differences for some structures (eg, smaller hippocampus in MDD), no differences were found for the putamen or the caudate. Notably, their samples were comprised predominately of younger and middle-aged participants, and only 1 sample was comprised of older adults. On the other hand, in a meta-analysis

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of 41 studies across diverse age ranges, significant volumetric reductions in patients with MDD compared with healthy control participants were reported for the putamen and caudate nucleus.[17-19] Moreover, in a meta-analyses of older adults, Sexton and colleagues[20] identified reduced volume size of both the caudate nucleus and putamen among those with depression.

Discrepancies across studies may be due to the age of participants. Normal aging is associated with volume loss in the brain.[21] Accelerated volume loss has been found in middle aged[22] and older aged[12] individuals with MDD. The caudate volume declines by about 3.3% per decade; the putamen has been reported to decrease at 3.6% per decade.[23,24] In depression, however, it may be the case that hypoactivation of reward-related areas of the brain may uniquely interact with age-related volume decline—leading to accelerated volume loss in aging. In a recent cross-sectional study, researchers[12] did not find group differences between healthy controls and depressed participants (aged 18-60) for the putamen; however, they found an age by group interaction suggesting depressed participants showed accelerated volume loss in the putamen compared to controls.

An additional reason for the discrepancy in MRI findings across studies is that depression is a heterogeneous disorder—and, variability in findings may be related to subtypes of depression. Specifically, some studies have found that reward dysfunction is primarily exhibited among depressed individuals who have features of anhedonia.[11] Melancholic depression, in particular, is characterized by anhedonia—the reduced ability to experience pleasure.[25] Some have argued that melancholic depression should be considered a unique phenotype with identifiable biological and neurological substrates.[26] Thus, volume reduction in reward-related neural regions may be more evident among depressed individuals with the melancholic subtype. Consistent with this possibility, Soriano-Mas and colleagues[27] found that periventricular white matter proximal to the putamen exhibited age-related volume reductions in depressed patients with the melancholic subtype. In addition, in a functional MRI study, anhedonia severity was correlated with abnormal functional connectivity of the superior temporal gyrus and the caudate nucleus in patients with first-episode drug-naive MDD (mean age [standard deviation, SD] = 28.8[6.67]).[28]

There has been limited research examining whether structural differences in brain volume of areas associated with reward in older depressed participants may differ by depression subtype (eg, melancholic vs nonmelancholic depression). In 1 study that compared older melancholic depressed individuals with healthy controls, researchers found that melancholic depressed participants had volumetric reductions in several structures[27]; however, they did not examine differences in the putamen or the caudate.

Thus, the current cross-sectional study examined differences in the structure (ie, volume) of neural regions associated with reward (ie, caudate nucleus and putamen) in a large sample (n = 226 depressed, n = 134 healthy controls) of adults ages 60 and older. First, we expected the depressed participants to have smaller volumes compared to healthy controls—and that these differences would increase with age. Secondly, examining differences by depression subtypes, we expected the melancholic depressed participants to have smaller volumes than the nonmelancholic participants, and further that these differences would increase with age.

Furthermore, we examined how characteristics of depression may be related to reduced volume size. Neurological deficits tend to be greater among older individuals with late-onset depression (first onset at 60 or later)[29] and among those with greater depression severity[30]; thus, we conducted exploratory analyses to determine whether later age of onset or depression severity would be associated with greater volume loss. Finally, we examined the extent to which the anhedonic symptoms, specifically, were associated with reduced volume size.

Methods

Procedures

We used data from the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study, a prospective cohort study that enrolled depressed patients (without dementia) aged 60 years and older, between 1994 and 2011. Depressed participants were treated using the study's protocol, based on a treatment algorithm designed to approximate a naturalistic approach that emphasizes the best regimen for each patient.[31]

Participants were assessed longitudinally with follow-up clinical interviews. Additionally, data were obtained from age-matched healthy nondepressed controls. The current analysis is restricted to individuals who were imaged with the same MRI scanner at baseline (in the initial stages of the NCODE study). Thus, for the current study, we examined only the cross-sectional baseline data obtained with the original MRI procedures.

Informed Consent

Written informed consent was obtained according to a procedure approved by the institutional review board (IRB) of Duke University. Further, the data analyses for the current project were approved by the Florida State University's IRB.

Participants

Participants included individuals (aged 60+) seeking treatment for depression, as well as healthy never-depressed controls (age 60+). Depressed participants were referred from the Duke Psychiatry inpatient and outpatient services and from the Duke General Internal Medicine Clinic. Patients met the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) criteria for a current major depressive episode. Patients were excluded if they presented with dementia or another major psychiatric illness and/or other neurological illnesses.

Never-depressed controls for the study were recruited from the Center for Aging Subject Registry at Duke University, which includes community-dwelling elders in the Durham,

Chapel Hill, and Raleigh (North Carolina) area who expressed willingness to participate in research.

Measures

Diagnostic assessment for MDD. At baseline, all participants were assessed for the diagnosis of MDD using the Duke Depression Evaluation Schedule (DDES).[32] The DDES is a structured interview that includes sections on demographic information, current life stress, and social support. The DDES also included the Diagnostic Interview Survey (DIS)[33] that allows for an assessment of *DSM-IV* current and lifetime major depression. Items on the DIS paralleled symptom criteria for *DSM-IV*[34] diagnosis of depression.

Melancholic subtype. Items within the DDES allowed for the identification of depressed participants who had the melancholic subtype. The criteria are as follows. To receive the melancholic subtype diagnosis, the depressed participant must meet the criteria for at least 1 of the 2 anhedonia-related symptoms: the reduced ability to experience pleasure in most or almost all activities and the diminished ability to feel better even for a brief time. Further, the individual must also meet the criteria for 3 (or more) of the following: depressed mood, depression worse in the morning, waking-up at least 2 hours earlier than usual, psychomotor agitation or retardation, weight loss, and excessive guilt.

Trained interviewers administered the DDES, and a geriatric psychiatrist interviewed all participants to confirm the study diagnosis.

Age of onset of depression. Depressed participants were asked the age at which they first experienced having depression. Depressed participants were defined as early onset (first episode before age 60) or late onset (first episode at 60 years or greater).[35]

Depression severity. For each depressed participant, a geriatric psychiatrist completed the Montgomery Asberg Depression Rating Scale (MADRS)[36] to determine the severity of depression at baseline. The MADRS has been used to assess depression in geriatric populations.[37] All 10 items had good-to-excellent interrater reliability.[38] The Cronbach α was .89.

Dementia screening. A geriatric psychiatrist screened participants for dementia during their initial clinical assessment based on examination, cognitive screening, the Mini-Mental State Examination (MMSE),[39] existing medical records, and consultation with referring doctors. Individuals were not enrolled if dementia was suspected or if the MMSE score remained below 25 after an acute course of treatment.

Magnetic resonance imaging acquisition. Participants were imaged in a 1.5 T whole-body MRI system[40] using the standard head (volumetric) radiofrequency coil. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the canthomeatal line, and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment. The first set of images was obtained with an axial, multisection, T1-weighted pulse sequence (TR = 500 ms, TE = 15 ms) with a 256 × 192 data acquisition matrix, 5-mm section thickness, a 20-cm field of view (FOV), 1 excitation per phase-encoding increment (1 Nex), and a 32 KHz ($\pm$16 KHz) full imaging bandwidth. This was followed by a long TR (2500 ms), double-echo (TE = 30 and 80 ms) spin echo data-acquisition sequence using the same FOV, section thickness, bandwidth, and spacing, 256 × 192 data acquisition matrix, and 1 Nex. Saturation of spins outside the imaging volume (standard gap 15 mm) and flow compensation (gradient moment nulling) was employed to eliminate artifacts due to flowing blood and cerebrospinal fluid. These images were obtained in 2 separate acquisitions with a 5-mm gap between sections for each acquisition. The second acquisition was offset by 5 mm from the first so that the resulting data set consisted of contiguous sections.

To obtain high-resolution images for volumetric measurements, a dual-echo fast spin echo acquisition was obtained in the axial plane for morphometric analysis of cerebral structures, including lesion volumes. The pulse sequence parameters are TR = 4000 ms, TE = 30, 135 ms, 32 kHz ($\pm$16 kHz) full imaging bandwidth, echo train length =16, a 256 × 256 matrix, 3-mm section thickness, 1 excitation, and a 20-cm FOV. The images were acquired in 2 separate acquisitions with a 3-mm gap between sections for each acquisition (voxel size: 0.78 mm × 0.78 mm × 3 mm). The second acquisition was offset by 3 mm from the first so that the resulting data set consisted of contiguous sections with no gap.

Image Processing for Brain Volumes

The MRI data were processed on SUN workstations. Caudate volumes were evaluated using NIRL-modified version of MrX Software, which was created by GE Corporate Research and Development (Schenectady, New York) and originally modified by Brigham and Women's Hospital for image segmentation (Boston, Massachusetts).

As described in prior publications, colleagues[41-44] a supervised, semiautomated method was used to ascertain volumes of whole brain, cerebral hemispheres, caudate, lateral ventricles, and gray and white matter lesions. The segmentation protocol was based on the approach developed by Kikinis and colleagues[45] and Byrum and collegues.[46] Multiple MR contrast was used to identify different tissue classifications through a "seeding" process, in which a trained analyst manually selected pixels in each tissue type of interest (gray matter, white matter, cerebrospinal fluid, lesions, background). The brain was then segmented into tissue types, and nonbrain tissue stripped was away through a masking procedure. After this, specific regions of interest (ROI), including the caudate, were determined using tracing and connectivity functions. The final step was running a

Table 1. Demographics.[a,b]

Characteristic	Healthy Controls	All Depressed	F or χ^2	Nonmelancholic	Melancholic	F or χ^2
Sample size	n = 134	n = 226		n = 93	n = 133	
Sex (% female)	71.1%	69.8%	$\chi^2 = .82$	68.8%	69.9%	$\chi^2 = .09$
Age (years)	69.7 (6.1)	69.3 (7.3)	$F = 0.3$	68.7 (7.4)	69.7 (7.0)	$F = 0.204$
Education (years)	15.4 (1.8)	13.6 (3.1)	$F = 34.5$[a]	13.8 (3.1)	13.5 (3.1)	$F = 0.96$
Left putamen	3.6 (.64)	3.7 (.82)	$F = 0.335$	3.9 (.9)	3.6 (.73)	$F = 10.2$[b]
Right putamen	3.7 (.69)	3.7 (.79)	$F = 0.012$	3.8 (.85)	3.6 (.71)	$F = 5.04$[b]
Left caudate	3.6 (.64)	3.6 (.70)	$F = 0.0003$	3.6 (.77)	3.6 (.65)	$F = 1.3$
Right caudate	3.8 (.66)	3.7 (.7)	$F = 1.4$	3.8 (.70)	3.7 (.72)	$F = 0.06$

[a]$P < .01$. [b]$P < .05$.

summarizing program to calculate the volume of each tissue type within the specific ROI defined by the analyst.

Volumetric segmentation of the putamen was completed with the GRID program, an in-house extension of the MrX codebase (described above), which allowed improved visualization and segmentation of the putamen via a semiautomated determination of ROI volumes based upon a manual point counting method. Tracing of the putamen began on the most inferior slice on which the putamen was separable from the caudate. Hyperintensities were included if they appeared within the body of the putamen and were excluded if they appeared along the border. The globus pallidus and claustrum were excluded. If the lateral border of the putamen appeared to be fused with the insular cortex, the most posterior point at which they were separable was connected to the most anterior point at which they were separable. The superior border of the putamen was defined as the most superior slice on which it was visible.

Image analysis technicians were trained and supervised by experienced analysts. Analysts had to achieve a threshold of reliability across multiple scans before processing study data. Intraclass correlation coefficients were 0.9 for left caudate, 0.9 for right caudate, 0.8 for left putamen, and 0.7 for right putamen.

Data Analytic Plan

Initial analyses were conducted to describe the demographics of the participants. Descriptive statistics were calculated, and data issues such as skewness, kurtosis, and outliers were examined using PASW version 18.0. Of note, none of the variables included in the regression analyses (covariates or dependent variables) exhibited any skewness or kurtosis, and there were no outliers. Thus, no corrections were necessary.

Regression analyses were first performed for the sample as a whole, comparing healthy controls versus the depressed participants. Secondly, regression analyses were performed comparing nonmelancholic depressed participants versus the melancholic depressed participants. For each set of analyses, we compared baseline differences of the volume sizes of the left and right putamen and the left and right caudate. We controlled for gender, age, and years of education, and for the overall size of the cerebral brain volume. In addition to examining the main effect of age, in each analysis, we also examined the interaction between group and age. We clarified significant group-by-age interactions by observing the change in volume size associated with increased age by group (see simple slope analyses, Aiken and West[47]) and by conducting post hoc analyses examining group status as a function of age categories (60-65, 66-74, and 75+ years).

As described below, we also conducted exploratory regression analyses to determine whether depression-related characteristics contributed to increased volume loss. These variables included later age of onset, the severity of the depression, and anhedonic symptoms.

Missing data. Included in the regression analyses were individuals from whom we had complete data on all relevant variables. Among the participants, we had complete data for 134 healthy controls and 226 depressed participants. Among the depressed participants, we had complete data for 93 nonmelancholic and 133 melancholic participants.

There were 33 participants excluded from the analyses due to missing MRI data. Specifically, 11 healthy control participants and 22 depressed participants (11 nonmelancholics and 11 melancholics) were excluded. Logistic regression analyses were conducted to determine whether there were any observable differences between participants with complete and incomplete data. Among the healthy participants, we determined that there were no differences between those with missing data and those with complete data in relation to age, gender, and education. We then conducted a logistic analysis comparing the 22 depressed participants with missing data to the 226 depressed participants for whom we had complete data. We determined that there were no differences in relation to age, gender, education, age of onset, and severity of depression.

Results

Demographics and Clinical Characteristics

Table 1 presents demographic information for the healthy controls and the depressed participants. The only significant demographic difference between the groups was that the healthy controls had more years of education compared to the depressed participants (mean = 15.4 [SD 1.8] vs mean = 13.6 [SD 3.1], $F = 34.5$, $P < .01$). Table 1 also presents

Table 2. Left Caudate.

Whole Sample: Healthy Controls (n = 134) Versus Depressed Participants (n = 226)							
	B	SE	*P*	*F*	*df*	*P*	Adj. R^2
Step 1				17.04	5, 353	.001	0.18
Depression diagnosis	−.02	0.07	.644				
Sex	−.01	0.09	.886				
Education	−.02	0.01	.693				
Age	−.3	0.01	.001				
Cerebral volume	.31	0	.001				
Step 2				14.17	1, 352	.001	0.18
Age by group interaction	.01	0.03	.802				
Depression diagnosis: 0 = nondepressed, 1 = depressed							
Depressed participants: nonmelancholic (N = 93) vs melancholic (N = 133)							
	B	SE	*P*	*F*	*df*	*P*	Adj. R^2
Step 1				9.8	5, 231	.001	0.18
Melancholia subtype	−0.08	0.087	.352				
Sex	−0.07	0.12	.522				
Education	−0.01	0.02	.599				
Age	−0.27	0.01	.001				
Cerebral volume	0.002	0	.001				
Step 2				8.3	1, 230	.001	0.19
Age by group interaction	0.032	0.042	.46				
Depression subtype: 0 = nonmelancholic, 1 = melancholic							

demographics separately for individuals with nonmelancholic (n = 93) and melancholic (n = 133) depression. There were no significant differences between the nonmelancholic and melancholic participants, including age of onset. However, there was a significant difference in the severity of the depression at baseline between the nonmelancholic participants (mean = 25.98 [SD 8.3]) and the melancholic participants (mean = 28.38 [SD 7.7]). Specifically, controlling for age, gender, and education, we found depression severity to be greater for the melancholics compared to the nonmelancholics ($B = 2.2$, standard error [SE]) = 1.002, $P = .026$).

Regression Analyses

Left and right caudate. After controlling for age, gender, education, and cerebral brain volume, there were no main effects of group status, and no significant group-by-age interactions. Although we should note that there was a tendency for the depressed participants to have smaller right caudate ($B = -0.08$, $P = .09$) compared to healthy controls (see Tables 2 and 3). No further analyses by other depressive characteristics were performed for the caudate nucleus.

Left putamen

Healthy control and depressed participants. After controlling for age, gender, education, and cerebral brain volume, group status (healthy control vs depressed participant) was unrelated to left putamen volume ($B = 0.04$, $P = .507$). However, the group-by-age interaction was significant ($B = 0.11$, $P = .024$), see Table 4. The interaction is depicted in Figure 1.

To clarify this significant interaction, we conducted additional analyses. Post hoc analyses revealed that the youngest aged participants (ie, 60-65 years) showed a significant group difference, with control participants having a larger left putamen compared to the depressed participants ($B = -0.323$, SE = .150, $P = .033$); however, the older aged participants demonstrated no difference between depressed and control participants (ie, 66-74, and 75+, $P > .10$). Simple slope analyses[47] also confirmed that the volume loss associated with increasing age was greater for the healthy participants compared to the depressed participants ($B = 0.253$, SE = .119, $P = .035$). Thus, it appears that the depressed participants' volume size did not decrease much with increased age, rather the healthy participants had a larger left putamen at the youngest age category (60-65 years), and then their volume size decreased with age becoming similar in size to the depressed participants.

Melancholic depressed and nonmelancholic depressed. Further analyses within the depressed group revealed that after controlling for age, gender, education, and cerebral brain size, the melancholic participants had smaller left putamen volume than the nonmelancholic depressed participants ($B = -0.306$, $P = .004$). The group-by-age interaction approached significance ($B = 0.09$, $P = .06$), see Table 4. Although melancholics had smaller left putamen compared to nonmelancholic participants overall, this difference tended to diminish with age, see Figure 2.

Table 3. Right Caudate.

Whole Sample: Healthy Controls (n = 134) Versus Depressed Participants (n = 226)							
	B	SE	*P*	*F*	*df*	*P*	Adj. R^2
Step 1				28.15	5, 353	.001	0.27
Depression diagnosis	−0.08	0.07	.09				
Sex	0.1	0.08	.07				
Education	0.01	0.01	.844				
Age	−0.3	0.01	.001				
Cerebral volume	0.48	0	.001				
Step 2				23.44	1, 352	.001	0.27
Age by group interaction	−0.02	0.03	.633				
Depression Diagnosis: 0 = non-depressed, 1 = depressed							
Depressed participants: nonmelancholic (n = 93) vs melancholic (n = 133)							
	B	SE	*P*	*F*	*df*	*P*	Adj. R^2
Step 1				17.24	5, 231	.001	0.267
Melancholia subtype	0.014	0.082	.865				
Sex	0.05	0.11	.718				
Education	0.001	0.014	.637				
Age	−0.031	0.006	.001				
Cerebral volume	0.002	0.001	.001				
Step 2				14.96	1, 230	.001	0.273
Age by group interaction	−0.066	0.04	.096				
Depression Subtype: 0, non-melancholic; 1, melancholic							

Table 4. Left Putamen.

Whole Sample: Healthy Controls (n = 134) Versus Depressed Participants (n = 226)							
	B	SE	*P*	*F*	Df	*P*	Adj. R^2
Step 1				9.9	5, 353	.001	0.11
Depression diagnosis	0.04	0.08	.507				
Sex	0.12	0.1	.051				
Education	0.04	0.02	.442				
Age	-0.28	0.01	.001				
Cerebrum volume	0.23	0	.001				
Step 2				9.21	1, 352	.001	0.12
Age by group interaction	0.11	0.04	.024				
Depression Diagnosis: 0 = non-depressed, 1 = depressed							
Depressed Sample: Non-Melancholic (n = 93) vs Melancholic (n = 133)							
	B	SE	*P*	*F*	Df	*P*	Adj. R^2
Step 1				5.12	5, 231	.001	0.084
Melancholic subtype	-0.306	0.11	.004				
Sex	0.103	0.14	.378				
Education	0.06	0.02	.363				
Age	-0.021	0.01	.002				
Cerebrum volume	0.16	0.001	.053				
Step 2				4.8	1,230	.001	0.093
Age by group interaction	0.09	0.05	.06				
Depression Subtype: 0 = non-melancholic, 1 = melancholic							

Depression characteristics. There was no effect of age of onset on the left putamen; however, increased symptom severity was associated with smaller left putamen ($B = -0.018$, $P = .01$). However, even controlling for these depression characteristics, the melancholic participants had smaller left putamen volume than the nonmelancholic depressed participants ($B = -0.267$, $P = .014$).

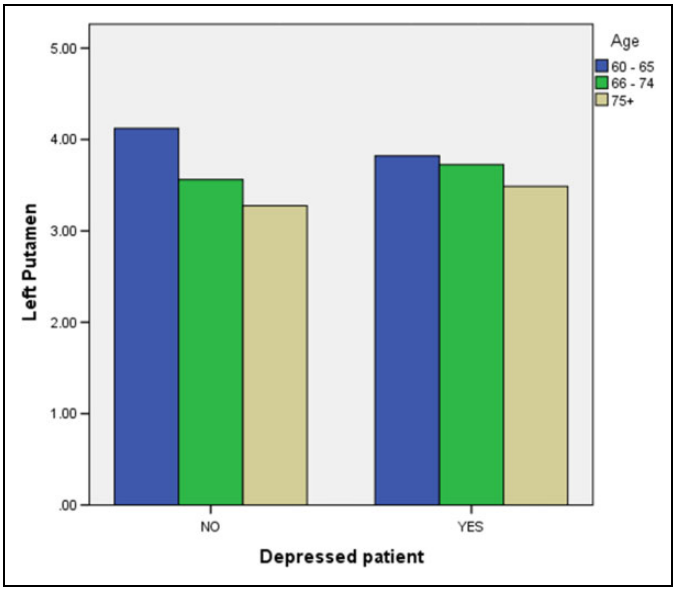

Figure 1. Left putamen: healthy controls versus depressed participants. Note: No main effect of group status (healthy controls vs depressed participant). Significant group-by-age interaction such that the increase in volume loss associated with aging was greater for healthy participants compared to the depressed participants.

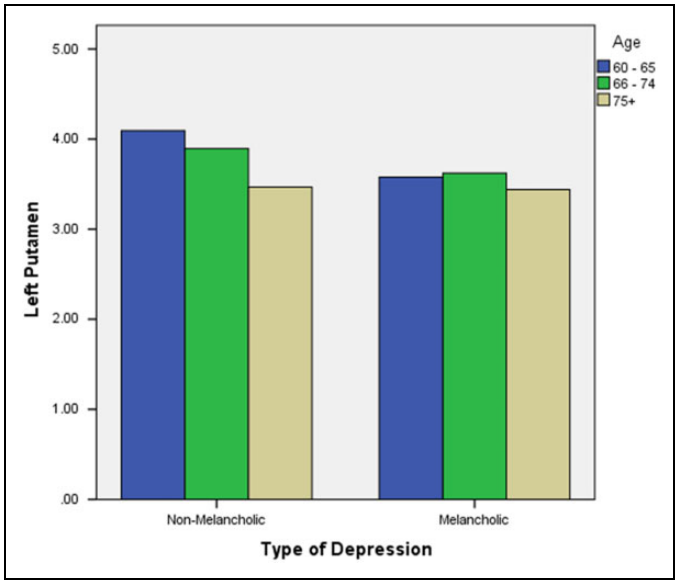

Figure 2. Left putamen: nonmelancholic versus melancholic. Note: Main effect of group status. Melancholics had smaller volume of the left putamen compared to nonmelancholic participants. Group-by-age interaction approached significance ($P = .06$), such that group differences diminished with age.

However, with the inclusion of these additional covariates, there was no longer an age by group interaction ($B = 0.084$, $P = .111$).

Moreover, considering each of the specific melancholic symptoms, only anhedonia symptoms were significantly related to the left putamen volume, such that responding positively to either of the anhedonia-related items predicted a smaller left putamen ($B = -0.462$, $P < .01$).

Right putamen

Healthy control and depressed participants. After controlling for age, gender, education, and cerebral brain size, group status (healthy controls vs depressed participants) did not predict right putamen volume ($B = 0.02$, $P = .758$). There was no significant age by group interaction ($B = 0.05$, $P = .327$), see Table 5.

Melancholic depressed and nonmelancholic depressed. Examining the right putamen volume within the depressed participants revealed that after controlling for age, gender, education, and cerebral brain size, the melancholic depressed participants tended to have a smaller right putamen volume compared to the nonmelancholic depressed participants ($B = -0.20$, $P = .07$). There was no significant age by group interaction ($B = -0.01$, $P = .839$), see Table 5.

Depression characteristics. Age of onset of the depression was not related to right putamen volume size, though the severity of depression tended to be associated with smaller right putamen ($P = .056$). In considering the specific melancholic symptoms, only the anhedonia symptoms were significantly related to volume such that responding positively to either of the anhedonia items predicted reduced right putamen volume ($B = -0.309$, $P = .013$; note 1).

Discussion

Major depressive disorder is thought to be associated with diminished reward sensitivity—evidenced by volumetric and functional deficits in the putamen and caudate nucleus.[1-4] Some evidence suggests that deficits may be more pronounced among those with the melancholic subtype of depression and among those who experience anhedonia.[11] Deficits in reward processing may comprise a biological vulnerability to depression onset[8,12] or may occur as a consequence of having depression.[14] The current study sought to build upon and expand previous literature by determining whether there were volume deficits in the putamen and caudate nucleus among older depressed participants compared to the nondepressed healthy control participants. The study also examined differences by depression subtype, contrasting participants with nonmelancholic depression to those with melancholic depression. Further, we examined if specific depression characteristics, including later age of onset, depression severity at baseline, and symptoms of anhedonia, were associated with reduced volume in depression.

Comparing healthy controls to depressed participants overall, there were no significant group differences in volume size for the putamen or the caudate nuclei. However, for the left putamen, the effect of depression on volume varied by age. Specifically, among the youngest participants studied (ie, 60-65 years), healthy individuals had a larger left putamen compared to the depressed participants; this difference was not evident among older participants (ie, 66-74, and 75+ years).

Although others have found differences,[8-10] our findings in MDD are more consistent with the recent meta-analysis conducted by the ENIGMA MDD working group, who also did not find differences between individuals with MDD and controls.[16]

Table 5. Right Putamen.

Whole Sample: Healthy Controls (N = 134) Depressed Participants (N = 226)							
	B	SE	*P*	*F*	*df*	*P*	Adj. R^2
Step 1				8.27	5, 353	.001	0.09
Depression diagnosis	0.02	0.08	.758				
Sex	0.14	0.1	.029				
Education	0.06	0.02	.313				
Age	−0.26	0.01	.001				
Cerebral volume	0.22	0	.001				
Step 2				7.05	1, 352	.001	0.09
Age–group interaction	0.05	0.04	.327				
Depression Diagnosis: 0 = non-depressed, 1 = depressed							
Depressed Sample: Nonelancholic (N = 93) vs Melancholic (N = 133)							
	B	SE	*P*	*F*	*df*	*P*	Adj. R^2
Step 1				4.4	5,231	.002	0.08
Melancholic subtype	−0.2	0.102	.07				
Sex	0.08	0.14	.548				
Education	0.02	0.02	.275				
Age	−0.022	0.007	.003				
Cerebral volume	0.001	0.001	.294				
Step 2				3.81	1, 230	.005	0.08
Age by group interaction	−0.01	0.05	.839				
Depression Subtype: 0, non-melancholic; 1, melancholic.							

We should also note that the depressed participants in the current study were receiving antidepressive medication which may have attenuated effects.[17] Moreover, inconsistencies in findings across studies might be related to variability in depressive phenotypes in the samples investigated. In relation to this possibility, the current study found differences in putamen volume by depression subtype (eg, melancholic vs nonmelancholic depressed) and as a function of anhedonic symptoms within the depressed group.

Specifically, melancholic depressed participants exhibited smaller left putamen volume and tended to have a smaller right putamen volume, when compared with the nonmelancholic depressed participants. Additionally, for the left putamen, this effect tended to be larger among younger participants but only at a trend level. It is important to note that depression severity was greater for the melancholics compared to the nonmelancholics—and, the severity of depression at baseline was related to smaller putamen volume. Nonetheless, even with the inclusion of depression severity in the analyses, depressed participants with the melancholic subtype were still found to have a smaller left putamen compared to those with the nonmelancholic subtype.

Moreover, we found that depressed participants endorsing either of the anhedonia symptoms (eg, reduced pleasure in all or most activities, the diminished ability to feel better even for a brief time) were characterized by smaller left and right putamen volume. Unlike severity and anhedonic symptoms, age of onset of depression was unrelated to putamen volume. Together, these findings are consistent with studies suggesting reward processing deficits are related to anhedonia specifically,[48,49] and with the possibility that the melancholic subtype has distinct structural neurological underpinnings that may represent a unique endophenotype of depression.[50] Our results also raise the possibility that reward circuit volume may relate more to symptoms of anhedonia rather than the melancholic subtype of depression.

Previous studies have documented that volume loss in the brain occurs with increasing age.[51] These results were replicated in the current study—as we found a main effect of increasing age with volume loss in all analyses. However, inconsistent with predictions, we did not find evidence for a combined effect of depression and aging in terms of greater volume loss.[30] Our findings are inconsistent with those of Sacchet and colleagues[12]; they reported that with increasing age the volume loss in the putamen was accelerated among the depressed participants compared to the healthy controls. Inconsistencies in findings may be related to differences in the age of the samples: in their study, the average age of their depressed participants was 37.1 (SD 10.1), and participants were between 18 and 60 years of age—whereas in the current study, the participants were all 60 years or older. Perhaps, as Sacchet and colleagues found, there is accelerated aging of the putamen among young and middle-aged depressed individuals compared to controls. Our results suggest that volume loss in the putamen in older depressed individuals may stabilize or slow down; alternatively, age-related decline in volume among the nondepressed individuals may "catch up." This is an important area of further investigation, as the pattern

of volume loss over the lifetime among individuals with MDD may not be linear in relation to age.

For the caudate nucleus, we did not find any significant group effects or any significant age by group interactions. Our findings contrast with previous studies that find smaller caudate nuclei in depressed individuals compared to controls among middle-aged participants[9,10] and older age participants.[20,29] However, some studies have also failed to find such differences.[16,48] One factor that may have influenced our results was the exclusion of participants with clinically manifest dementia. Studies have found that cognitive impairment and dementia are associated with smaller caudate.[52] The extent to which comorbid depression and cognitive impairment together or individually contributed to smaller caudate among depressed samples is not well understood and is a potential area of future research.

The findings of the current study suggest that decreased volume in the putamen is associated with melancholic depression, and in particular, symptoms of anhedonia, in geriatric depressed patients. These results should be considered in light of findings that anhedonia in late life is associated with a more serious course.[53] As highlighted by Tadayonnejad and Ajilore,[26] specifying biological markers for each symptom domain in late-life depression may facilitate the development of symptom-oriented and individualized treatment options. We also need to keep in mind that in late-life depression, there may be important differences in the etiology, course, and treatment of the disorder related to whether or not the depression first occurred in early life or in late life. In this regard, and as discussed by Klein and Hajcak[54] and Vaidyanathan and colleagues,[55] it may be critical to parse the heterogeneity of depression using a temporal perspective. Future research should continue to examine high-risk individuals longitudinally (and starting at younger ages) to determine whether decreases in putamen volume precede the onset of depression, or arise as a function of depression, and also consider possible differences related to depression subtype. Researchers may also consider conducting similar analyses in nucleus accumbens and other reward-related regions not available in the current data set. Further, clarifying the course of development of putamen deficits in depression over time may inform clinical intervention. Future treatments could focus on preventing putamen volume loss or potentially mitigating the effects of such loss, either through medication[17] or activities that may contribute to neural regeneration, such as exercise.[56]

There are some limitations to be noted. First, we were not able to include NCODE participants recruited in recent years as they were not evaluated with the MRI protocol used in the current study. The MRI imaging data used in the current study were archival and did not have sequences consistent with the use of automated segmentation programs like Freesurfer,[57] in particular, a slice thickness (5 mm) that was too large. Nonetheless, manual segmentation, while time and labor intensive, is still considered the gold standard approach.[58] However, lower resolution of images may have contributed to lower reliability, in general, and for the putamen relative to the caudate. Future studies using more advanced MRI imaging techniques and applying automated segmentation tools to multiple brain reward regions have the potential to extend or improve upon the current study.

Another important consideration is that numerous group analyses (healthy controls vs depressed participants, and nonmelancholics vs melancholic participants) were conducted across several brain regions (eg, left and right putamen and left and right caudate nucleus). There were also additional exploratory analyses examining the role of the depression characteristics (eg, age of onset, depression severity, and anhedonia symptoms) in relation to volume size. These many analyses were conducted without controlling for multiple comparisons. Nevertheless, because this was one of the first studies to examine these issues with the inclusion of depression subtypes in the elderly patients, we viewed the results as a preliminary guide to future research. Thus, it will be important to determine whether the pattern of results that we observed can be replicated in future studies. Further, we should note that although we examined age of onset of depression (early vs late) in relation to volume size—this measure is limited in regard to determining whether the individual had long-term or chronic depression over the lifetime. Future research should employ a more sophisticated measure of chronicity. Similarly, future studies should consider the inclusion of a more nuanced measure of anhedonia (ie, Snaith-Hamilton Pleasure Scale).[59]

In conclusion, the association found between putamen volume and melancholic depression suggests structural abnormalities in reward-related regions may underlie the anhedonic phenotype. Further, the rate of volume loss in the reward center of the brain may vary between nondepressed individuals and depressed individuals across the life span.

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Note

1. Additional analyses revealed that there were no significant effects of group (e.g., healthy controls compared to melancholics and healthy controls compared to the nonmelancholics) in the prediction of the left and right putamen volumes.

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