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The temptation of suicide: striatal gray matter, discounting of delayed rewards, and suicide attempts in late-life depression

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Abstract

Background—Converging evidence implicates basal ganglia alterations in impulsivity and suicidal behavior. For example, D_2/D_3 agonists and subthalamic nucleus stimulation in Parkinson's disease trigger impulse control disorders and possibly suicidal behavior. Further, suicidal behavior has been associated with structural basal ganglia abnormalities. Finally, low-lethality, unplanned suicide attempts are associated with increased discounting of delayed rewards, a behavior dependent upon the striatum. Thus, we tested whether, in late-life depression, changes in the basal ganglia were associated with suicide attempts and with increased delay discounting.

Methods—Fifty-two persons aged ≥60 underwent extensive clinical and cognitive characterization: 33 with major depression (13 suicide attempters [SA], 20 non-suicidal depressed elderly), and 19 non-depressed controls. Participants had high-resolution T1-weighted MPRAGE MRI scans. Basal ganglia gray matter voxel counts were estimated using atlas-based segmentation, with a highly-deformable automated algorithm. Discounting of delayed rewards was assessed using the Monetary Choice Questionnaire, and delay aversion with the Cambridge Gamble Task.

Results—SA had lower putamen but not caudate or pallidum gray matter voxel counts, compared to the control groups. This difference persisted after accounting for substance use disorders and possible brain injury from suicide attempts. SA with lower putamen gray matter voxel counts displayed higher delay discounting on the MCQ, but not delay aversion on the CGT. Secondary analyses revealed that SA had lower voxel counts in associative and possibly ventral, but not sensorimotor striatum.

Conclusions—Our findings, while limited by small sample size and case-control design, suggest that striatal lesions could contribute to suicidal behavior by increasing impulsivity.

Keywords

suicide; basal ganglia; corpus striatum; globus pallidus; putamen; decision making; reward

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Introduction

Suicidal behavior has been linked to alterations in neural circuitry involved in cognitive control and reward processing (Ernst *et al.*, 2009, van Heeringen *et al.*). Yet, explanatory models of the pathway from neural abnormalities to suicidal behavior remain speculative and poorly specified. One of the missing links is the behavioral expression of neural pathology, an observable bias that would facilitate suicidal behavior. Below, we present preliminary evidence that, in vulnerable individuals, loss of basal ganglia integrity is associated with decisions excessively focused on the present at the expense of the future and with suicidal behavior.

The basal ganglia receive orbitofrontal and cingulate inputs and project back through thalamic nuclei, forming cortical-basal ganglia loops (Middleton and Strick, 2000). Haber and colleagues (Haber and Knutson, 2010) have proposed that, within these loops, reward-related representations are fed from ventral "reward" circuits to dorsal "cognitive" circuits through striatal-nigro-striatal spirals, giving rise to reward-guided behavior. During decision-making, cortico-striatal "reward" circuits are thought to represent and integrate information relevant to the value of choices (Rangel *et al.*, 2008). For example, as one chooses between immediate and delayed rewards (delay discounting), a value signal is represented in the striatum, anterior cingulate (ACC), and orbitofrontal cortex (OFC) (Cardinal *et al.*, 2001, Hariri *et al.*, 2006, Kable and Glimcher, 2007, McClure *et al.*, 2004). While the dynamics of these computations remain debated, it is likely that the disruption of parallel circuits emanating from the basal ganglia could lead to short-sighted or impulsive choices. This can be seen when activity in the direct and indirect pathways is altered by D_2/D_3 agonists and subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD). These treatments induce a stronger preference for immediate over larger delayed rewards (Housden *et al.*, 2010, Voon *et al.*, 2010) and trigger substance abuse, gambling, hypomania and inappropriate sexual behaviors (Weintraub *et al.*, 2006). From this literature, we conclude that the human ability to inhibit impulsive, stimulus-driven behaviors that are disadvantageous in the long run relies on the direct and indirect pathways in the striatum and pallidum, as part of integrated cortical-basal ganglia loops.

At the same time, accumulating evidence from both psychiatric and neurological studies suggests that basal ganglia alterations are associated with suicidal behavior. Following the first case report of idiopathic basal ganglia calcification with a suicide attempt (Trautner *et al.*, 1988), subsequent case-control studies found increased gray matter hyperintensities in the basal ganglia of older depressed patients with past suicide attempts (Ahearn *et al.*, 2001), low pallidum and caudate volumes in younger depressed suicide attempters (Vang *et al.*, 2010), and low caudate volumes in depressed patients with personal or family history of suicidal behavior (Wagner *et al.*, 2011). Likewise, early postmortem studies of suicide victims have found a reduced dopamine turnover in the basal ganglia (Arango *et al.*, 1997). Comparable effects are seen in Huntington's disease, where striatal degeneration appears to increase the risk for suicide (Di Maio *et al.*, 1993). By contrast, suicide rates are relatively low in PD (Stenager *et al.*, 1994) with its diminished mesencephalic dopaminergic input into the striatum, low impulsivity (Todes and Lees, 1985), and a high threshold for initiating action (Frank *et al.*, 2007b, Owen *et al.*, 1993). One remarkable exception is, again, the disruption of the indirect pathway with STN-DBS in PD, which appears to increase impulsivity and possibly promote suicidal behavior (Voon *et al.*, 2008). Finally, in a striking, even if uncontrolled, study of internal globus pallidus DBS for dystonia, 2/16 patients (both with a history of depression) committed suicide (Foncke *et al.*, 2006). Taken together, these observations suggest that, in the setting of depression, lesions to the striatopallidal complex could facilitate suicidal behavior.

These two lines of evidence informed the following hypothesis: the disruption of the direct and/or indirect pathway in the basal ganglia facilitates impulsive suicidal acts by promoting impulsive, myopic choice. In the context of the suicidal crisis, that would mean favoring suicide as an immediate solution and neglecting deterrents such as family and hope for a better future. The behavioral part of this hypothesis is supported by our observation of exaggerated preference for immediate rewards (or high delay discounting) in depressed elderly who had made low-lethality, unplanned suicide attempts (Dombrovski *et al.*, 2011). Late-life depression, with its high suicide rate and high prevalence of subcortical small vessel disease, provides an ideal patient population for testing the neural component of this hypothesis. To investigate whether myopic intertemporal choice in suicide attempters is associated with basal ganglia alterations, we examined gray matter voxel counts of the putamen, caudate, and pallidum and their correlations with delay discounting in suicide attempters, compared to depressed non-suicidal and healthy controls.

Patients and Methods

Study groups and characterization of suicidal behavior

To dissociate the effects of suicide attempts from those of depression, we studied two groups of participants aged 60 and older with non-psychotic unipolar depression determined by SCID/DSMIV: 13 who made suicide attempts and 20 people with depression but no history of suicidal thoughts or attempts. All participants provided written informed consent. The University of Pittsburgh Institutional Review Board approved the study.

Suicide attempters had made a self-injurious act with the intent to die (O'Carroll *et al.*, 1996) AND presented with thoughts of suicide at the time of study enrollment. Suicide attempt history was verified by a psychiatrist (AYD or KSz), using all available information: participant's report, medical records, information from the treatment team, and collateral information from family or friends. Significant discrepancies between these sources led to exclusion from the study. Medical seriousness of attempts was assessed using the Beck Lethality Scale (BLS) (Beck, 1975); for participants with multiple attempts, data for the highest-lethality attempt are presented. **High-lethality attempts** resulted in coma, need for resuscitation, unstable vital signs, penetrating wounds of abdomen or chest, third-degree burns, major bleeding, as defined by a score of ≥4 on the BLS. All other attempts were classified as **low-lethality**. Violent means – shooting, cutting, jumping, and hanging – were used in 3/13 suicide attempts. None of the attempts caused direct head injuries, however we assessed potential anoxic-ischemic or toxic brain injury, based on the BLS, medical records and the clinical interview. A psychiatrist (AYD or KSz) identified any attempts with a score of ≥4 on the BLS and any history of systemic hypotension >5 minutes or asphyxia or neurotoxic ingestion (e.g. polyatomic alcohols, methanol, or organic solvents); 2/13. In addition to lethality, we assessed suicidal intent associated with suicide attempts, using Beck's Suicide Intent Scale, SIS (Beck *et al.*, 1974). **Non-suicidal depressed elderly** were included in the study to detect effects of suicidal behavior above and beyond effects of depression. These participants had no current or lifetime history of suicide attempts or suicidal ideation as established by clinical interview, review of medical records, SCID/DSMIV, and Beck's Scale for Suicidal Ideation, (lifetime; (Beck *et al.*, 1979)). Participants were excluded from this group if they had indirect self-destructive behaviors.

Nineteen **control subjects** were included as the reference group. They had to have no lifetime history of any psychiatric disorder as determined by SCID/DSMIV.

Inclusion and exclusion criteria

Our study was conducted at a university psychogeriatric inpatient unit and a late-life depression outpatient clinic. To reduce heterogeneity in our study population, we focused on suicidal elderly with non-psychotic unipolar depression, the most common antecedent of late-life suicide (Beautrais, 2002, Conwell *et al.*, 2000, Waern *et al.*, 2002). Participants were recruited between January of 2007 and April of 2010. To exclude individuals with clinical dementia and to ensure that participants could engage in the task, all were required to have a score of ≥24 on the Mini-Mental State Exam (Folstein *et al.*, 1975). Sensory disorders that precluded cognitive testing, mental retardation, delirium, neurologic disorders (including stroke, epilepsy, brain tumors, and diagnosed neurodegenerative disorders), bipolar disorder, schizophrenia, schizoaffective disorder, and exposure to electroconvulsive therapy in the 6 months preceding testing led to exclusion from the study. All participants provided written informed consent. The University of Pittsburgh Institutional Review Board approved the study.

Cognitive and clinical characterization

We assessed current global cognitive function using the Dementia Rating Scale (DRS), testing initiation/perseveration, attention, construction, conceptualization, and memory (Mattis, 1988). Depression severity was measured with the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). Burden of physical illness was assessed with the Cumulative Illness Rating Scale adapted for Geriatrics (CIRS-G) (Miller *et al.*, 1992). We obtained medication lists from pharmacy records. We measured the intensity of pharmacotherapy for the current episode of depression with the Antidepressant Treatment History Form (Sackeim, 2001). The ATHF score is based on antidepressant trial duration in addition to the dose and also reflects the use of augmenting agents (e.g. antipsychotics, lithium). In order to capture exposure to psychotropic medications not included in the ATHF score, we additionally assessed exposure to sedatives/hypnotics, drugs with anticholinergic activity, and opioid analgesics. Intra-class correlation coefficients measuring interrater reliability among our assessors were 0.95 for HRSD, 0.97 for CIRS-G, and 0.99 for the DRS.

Study procedures

Clinical and cognitive data presented here were collected during the baseline assessment of a longitudinal study of late-life suicide. Baseline testing was performed within two weeks of inpatient admission or at the beginning of outpatient treatment. Monetary Choice Questionnaire, described below, was administered at baseline and at the 3-month follow up assessment (Dombrovski *et al.*, 2011). Data for the first administration were used in the current analyses. The Cambridge Gamble Task, described below, was administered at baseline (Clark *et al.*, 2011). Depressed participants continued to receive psychotropic medications as clinically indicated (Table 1).

Basal ganglia gray matter integrity: structural magnetic resonance imaging

Participants had high-resolution T1-weighted MPRAGE MRI scans on a 3T Siemens Trio TIM scanner. T1-weighted brain MRIs were processed using the automated labeling pathway (ALP) technique (Wu *et al.*, 2006). ALP Technique relies on atlas-based segmentation (a deformable registration approach) to measure regional volumetric differences between groups in a number of pre-defined regions of interest. In an older group with highly variable ventricle size and shape, this technique offers a particular advantage in assessing basal ganglia structures, which adjoin the ventricles. The pathway combines a series of publicly available software packages (AFNI, BET, FLIRT, and ITK) and some locally developed programs (Wu *et al.*, 2005) to implement atlas-based segmentation of

MRIs. Using ALP, manually traced primary anatomic regions of interest (ROI) – *putamen, caudate,* and *pallidum* – from the AAL atlas (Tzourio-Mazoyer *et al.*, 2002), defined on the reference brain (MNI colin27) were transformed to fit each individual's anatomic image, and were then segmented into gray/white matter and CSF. For our secondary analysis of functional striatal subdivisions (Figure 2a) – *associative striatum* (precommissural dorsal caudate and precommissural putamen), *sensorimotor striatum* (postcomissural putamen), and *limbic (ventral) striatum* (nucleus accumbens as well as the ventral caudate and the ventral putamen rostral to the anterior comissure) – we used manually traced regions as defined by Martinez and colleagues (Martinez *et al.*, 2003) from the atlas of (Mai *et al.*, 1997). To reduce type I error, we combined right and left hemisphere data. Prior to registration, the skull and scalp was stripped from the template and subjects' 3D SPGR scans using the Brain Extraction Tool—BET (Smith, 2002), followed by erosion and dilation to remove additional skull and scalp (Wu *et al.*, 2005). The fully deformable registration model we use is similar to models described previously (Chen *et al.*, 1999). We have implemented this using the registration library in Insight Segmentation and Registration Toolkit (Yoo, 2004). This method starts with a grid-based piecewise linear registration and then uses a demons registration algorithm as a fine-tuning procedure for a voxel-level spatial deformation. The fully deformable registration allows for a high degree of spatial deformation, which seems to give it a particular advantage over other standard registration packages, such as AIR and SPM (Woods *et al.*, 1998). Images were visually evaluated by an operator to check for misalignment and to ensure that it did not distort voxel counts. Voxel counts of total brain volume, gray matter in the whole brain, and gray matter for each ROI were then automatically obtained. ROI gray matter voxel counts provided a measure of basal ganglia gray matter integrity. In older adults, we interpret ROI gray matter voxel counts as a combined measure of gray matter volume and gray-white contrast rather than volume alone, since both of these image features contribute to the number of voxels labeled as 'likely gray matter' in the subcortical regions (Davatzikos and Resnick, 2002). The current study was not designed to distinguish between low contrast and volume.

Delay discounting and delay aversion

To assess the preference for smaller immediate vs. larger delayed rewards, we used Kirby's Monetary Choice Questionnaire (MCQ) (Kirby *et al.*, 1999). The MCQ presents 27 choices between delayed larger monetary rewards and smaller rewards available immediately. Discount rates are inferred using a Bayesian procedure as originally proposed by Kirby (Kirby *et al.*, 1999). The MCQ identifies discount rates for small ($25-$35), medium ($50-$60), and large ($75-$85) delayed-reward amounts; their geometric mean is the overall discount rate. Higher discount rates reflect a preference for immediate rewards. To capture low discount rates potentially seen in the elderly (Green *et al.*, 1999), we added 3 choices with very small differences between immediate and delayed rewards. One of the choices was later randomly selected, and the chosen immediate or delayed reward was delivered to the participant as a debit card. Discount rates on the MCQ correlate strongly with more comprehensive measures of delay discounting [r=0.82; (Epstein *et al.*, 2003)]. Discounting data were missing for two participants. Discount rates were inferred using a Bayesian procedure and assuming hyperbolic discounting as originally proposed by Kirby and were natural log-transformed for analyses (Kirby *et al.*, 1999).

In addition, we used an experiential, real-time measure of delay aversion on the Cambridge Gamble Test (CGT). This metric reflects the difference in bets between two conditions: an ascend condition where the available bet starts small and increases in 5s intervals on each trial, and a descending condition where the bet starts high and decreases in 5s intervals. The difference between conditions reflects the tendency to take early bets over waiting to select a more optimal bet for the given odds (Deakin *et al.*, 2004).

Statistical analysis

We used SPSS 18.0 (SPSS Inc., Chicago, IL) and MATLAB 7.6 (The MathWorks Inc., Natick, MA). All tests were two-sided. We compared groups on demographic and clinical characteristics using analyses of variance (ANOVA) and chi-square tests. For these and all subsequent ANOVAs, we examined post-hoc contrasts using the Tukey HSD to control for type I error. To determine whether parametric tests would be appropriate for our primary analysis, we performed tests of normality on dependent measures. The distributions of caudate, putamen, and pallidum gray matter voxel counts did not significantly deviate from normality, as indicated by the Shapiro-Wilk test (p=.40, p=.49, and p=.25, respectively). Thus, in our primary analysis we first contrasted the measures of basal ganglia gray matter integrity – putamen, and pallidum likely gray matter voxel counts – in the three groups using an ANOVA. As our prior behavioral study has identified subgroups of suicide attempters with very high and very low discount rates (Dombrovski et al., 2011), we examined Pearson's product moment correlations between likely gray matter voxel counts and log-transformed discount rates by group. We also examined correlations between gray matter voxel counts and delay aversion on the CGT and tested the difference between independent Fisher's-Z-transformed correlation coefficients between the two depressed groups (Cohen and Cohen, 1983). In our secondary analysis, we contrasted the gray matter voxel counts for the functional subdivisions of the striatum – associative, sensorimotor, and limbic – in the three groups using an ANOVA, followed by tests of correlations with delay discounting as described above. Next, we examined the role of possible confounders in sensitivity analyses. We performed ANOVAs covarying for demographic characteristics that were imbalanced among study groups. Given the higher prevalence of substance use and anxiety disorders in suicide attempters, we evaluated the possibility that altered basal ganglia integrity in suicide attempters was attributable to effects these disorders. Next, we performed an ANOVA excluding two participants with possible brain injury from suicide attempts. Finally, various parameters can be used to control for effects of body size on regional brain volume: height, body mass index, whole brain volume, intracranial volume or specific brain areas that have minimal age-related variation. Some indices can be unreliable in older subjects, such as manual measurements of intracranial volume or the use of height/body mass index as a proxy for the intracranial volume (Rosano *et al.*, 2007). Aging has non-linear effects on different gray matter structures (frontal areas, medial temporal areas), rendering the use of the whole gray matter volume as control less accurate (Raz *et al.*, 2005). Thus, in addition to controlling for whole-brain gray matter volume, we chose to use the volume of the primary visual cortex (the calcarine area) to control for individual variations in brain size, as this is one of the regions with the least inter-subject and age-related variation (Raz and Rodrigue, 2006). Last, motivated by our earlier findings of high delay discounting in low- but not high-lethality attempters (Dombrovski et al., 2011), we explored differences in basal ganglia voxel counts between these subgroups.

Results

Demographic, cognitive and clinical characteristics (Table 1)

The three groups did not differ significantly in age, race, gender, education, and global cognitive function. Suicide attempters were more likely to suffer from current substance use disorders and from current and lifetime anxiety disorders than the non-suicidal depressed participants. The two depressed groups did not differ significantly in severity of depression and psychotropic exposure. Suicide attempters tended to have an earlier lifetime onset of depression, and a greater proportion of this group had a family history of mood disorders, but neither difference was statistically significant. Suicide attempters reported high suicidal intent and a wide range of attempt lethality.

Basal ganglia gray matter integrity (Fig. 1)

Our primary analysis revealed that suicide attempters had lower putamen gray matter voxel counts, compared to the control groups (Fig. 1a). Visual inspection of T1 images from subjects with the lowest gray matter voxel counts revealed an attenuated gray-white matter contrast and areas of T1 signal prolongation (Fig. 4). We found no group differences in caudate and pallidum gray matter voxel counts ($F[2,49]<1.6$, $p>0.22$, $\eta_p^2 \leq .06$).

Our secondary analysis revealed that suicide attempters had lower voxel counts in striatal subregions involved in decision-making – the associative striatum (dorsal caudate and dorsal precommissural putamen; Figure 2c; $F[2,49]=4.4$, $p=.018$, $\eta_p^2=.15$, SA<D) and limbic/ventral striatum (nucleus accumbens, ventral caudate and the ventral putamen rostral to the anterior commissure; Figure 2b; $F[2,49]=4.5$, $p=.016$; $\eta_p^2=.16$, SA<D) – compared to depressed controls. By contrast, voxel counts in the sensorimotor striatum (postcommissural putamen) did not differ between groups ($F[2,49]=0.04$, $p=.96$). The apparent lack of difference in associative striatum gray matter voxel counts between normal controls and suicide attempters was explained by the effects of body size. When we contrasted suicide attempters and healthy controls covarying for calcarine (group: $F[1,29]=5.51$, $p=.026$, $\eta_p^2=.16$; calcarine: $F[1,29]=3.87$, $p=.059$, $\eta_p^2=.12$) or whole brain volume (group: $F[1,29]=4.89$, $p=.035$, $\eta_p^2=.14$; whole brain: $F[1,29]=9.44$, $p=.005$, $\eta_p^2=.25$), the differences became apparent. However, in the case of ventral striatum volumes, the difference between suicide attempters and controls remained small and non-significant ($p>0.21$, $\eta_p^2<.06$).

Correlations with delay discounting

Much of the heterogeneity in suicide attempters' putamen voxel counts was explained by delay discounting: those with the lowest putamen gray matter voxel counts displayed a stronger preference for immediate rewards ($r=-.73$, $p=.011$, $N=11$; Fig. 1b). This relationship was not seen in non-suicidal depressed elderly ($r=.16$, $p=0.51$, $N=20$), and the correlation coefficients differed significantly (z-score: 2.53, $p= 0.011$). Similarly, in our secondary analysis, the preference for immediate rewards negatively correlated with associative striatum voxel counts ($r=-.61$, $p=.045$; Figure 2d), while the negative correlation with limbic striatum voxel counts was not significant ($r=-.49$, $p=.13$). The correlation between an experiential measure of delay discounting – delay aversion on the CGT – and putamen gray matter voxel count in suicide attempters was not significant ($r=-.15$, $p=.66$). As in our larger behavioral study (1), the preference for immediate rewards was related, albeit not significantly in this small sample, to poor planning of suicide attempts ($r=-0.51$, $p=0.109$). It was modestly correlated with the non-planning ($r=0.29$, $p=0.106$, $N=33$) and cognitive ($r=0.20$, $p=0.26$) subscales of the Barratt Impulsivity Scale, but not with the motor ($r=-0.04$, $p=0.84$) subscale.

Sensitivity analyses

Effects of race (group: $F[2,48]=5.53$, $p=.007$, $\eta_p^2=.20$; race: NS, $\eta_p^2=.03$) and age (group: $F[2,48]=5.17$, $p=.009$, $\eta_p^2=.18$; age: NS, $\eta_p^2=.03$) did not diminish the group differences in putamen gray matter voxel counts. Interestingly, when we accounted for lifetime substance use disorders as a predictor of putamen volumes in the two depressed groups (none of the controls had them by definition), they appeared to explain additional variance beyond that explained by suicide attempts (group: $F[1,29]=5.11$, $p=.031$, $\eta_p^2=.15$; lifetime substance use disorders: $F[1,29]=3.88$, $p=.059$, $\eta_p^2=.12$). By contrast, lifetime anxiety disorders did not explain any additional variance (group: $F[1,29]=5.18$, $p=.030$, $\eta_p^2=.15$; lifetime anxiety disorders: $F[1,29]=0.02$, $p=.88$, $\eta_p^2<.01$). Group differences in basal ganglia integrity were also unchanged after excluding two participants with possible brain injury from the suicide attempts (putamen: $F[2,47]=3.84$, $p=.028$, $\eta_p^2=.14$) and when controlling for whole brain (putamen: $F[2,48]=4.08$, $p=.023$, $\eta_p^2=.15$) or calcarine (putamen: $F[2,48]=4.41$, $p=.017$,

η_p^2=.16) volumes. Similarly, the correlation with delay discounting in suicide attempters was unchanged after controlling for calcarine volume (putamen: r=−.74, p=0.014). Since suicide attempters had a somewhat earlier onset of depression and were more likely to have a family history of mood disorders, we included these variables in a final sensitivity analysis. Only suicide attempt history was related to putamen gray matter counts (group: F[1,38]=3.65, p=.036, η_p^2=.16; family history of mood disorders: F[1,38]=0.01, p=.91, η_p^2<.01; age at first depressive episode: F[1,38]=0.11, p=.90, η_p^2<.01).

Exploratory analysis

Although the subgroups of low-lethality (N=6) and high-lethality (N=7) attempters were small, our exploratory analysis suggested that the group differences in putamen voxel counts were mainly driven by low-lethality attempters (Figure 3a), as one would predict from our behavioral data (Dombrovski *et al.*, 2011). In addition, low-lethality attempters had lower pallidum gray matter voxel counts, compared to depressed controls and high-lethality attempters (Figure 3b).

Discussion

We found that (1) low gray matter voxel counts in the putamen were associated with suicide attempts in late-life depression and (2) that structural abnormalities in the putamen were related to an exaggerated preference for smaller immediate vs. larger delayed rewards in suicide attempters. Correlations with delay aversion during a gambling task were small and non-significant. Our secondary analysis found alterations in associative and possibly ventral rather than sensorimotor striatum in suicide attempters. Our results held after accounting for the effects of possible brain injury from suicide attempts as well as anxiety and substance use disorders, even though lifetime substance use disorders did explain additional variance in putamen volumes. While our findings should be taken with caution due to small sample size and design limitations, they are consistent with the hypothesis that the disruption of the cortical-basal ganglia loop at the level of striatum/pallidum leads to short-sighted, present-focused decisions and thus facilitates impulsive suicidal acts in people with other vulnerability factors.

Our findings are in line with other evidence that striatal abnormalities are associated with impulsive (Housden *et al.*, 2010, Voon *et al.*, 2010, Weintraub *et al.*, 2006) and suicidal (Ahearn *et al.*, 2001, Di Maio *et al.*, 1993, Vang *et al.*, 2010) behavior. It is hard to say whether disintegration of any single nucleus is primarily associated with impulsivity and suicidal behavior, given the diffuse character of basal ganglia alterations seen in our sample, their close proximity, and primarily that these structures constitute functional circuits. That loss of *putamen* integrity was prominent and strongly correlated with delay discounting in suicide attempters is consistent with anatomical studies showing that the putamen receives projections from the OFC and ACC (Haber *et al.*, 2006, Haber *et al.*, 1995), functional imaging evidence that putamen is involved in reward processing and intertemporal choice (Luo *et al.*, 2009) and a primate lesion study showing that putamen is necessary for integrating reward value information over time (Muranishi *et al.*, 2011). Our findings also agree with extant evidence that disruptions of striatal output could contribute to impulsive and suicidal behavior, for example with stimulation of the internal pallidum (Foncke *et al.*, 2006) or with a relative increase in striatal output from the inactivation of the indirect pathway in subthalamic nucleus DBS (Frank *et al.*, 2007a, Halbig *et al.*, 2009, Voon *et al.*, 2008).

Impulsive suicide attempters in our study had alterations primarily in associative striatal subregions that process higher-order reward-related signals and receive projections from areas implicated in cognitive control and reward-based learning (dorsal ACC, dorsolateral

prefrontal cortex, and lateral OFC) (Haber *et al.*, 2006). The evidence for alterations in the ventral striatum, which processes low-order reward-related information and receives mostly limbic and paralimbic projections (ventromedial prefrontal cortex, amygdala and hippocampus)(Haber *et al.*, 2006, Russchen *et al.*, 1985), was less conclusive. Thus, in light of our functional understanding of corticostriatal projections, a lesion of the associative prefrontal-striatal circuit in suicide attempters would be expected to disrupt their ability to integrate more abstract reward-related information into their decisions. Indeed, suicide attempters with associative striatal alterations in our study tended to make choices that are short-sighted and driven by the superficial, easily accessed information (availability of immediate reward) as opposed to a more strategic approach that integrates reward magnitude and delay. Or, to use the beta-delta model of intertemporal choice (McClure *et al.*, 2004), impulsive suicide attempters may have a lesion in the strategic delta system, which discounts rewards at a constant rate over time. Hence, their behavior may be primarily governed by the "impatient" beta system sensitive to whether the reward is available immediately. In a suicidal crisis, such short-sighted decision-makers may be unable to realize the far-reaching consequences of their choices.

Overall, striatal alterations paralleled by increased delay discounting seen in suicide attempters bear a striking similarity to the observations of impulsive behaviors associated with excessive activity in the direct pathway (in PD patients receiving dopamine agonists) or inactivation of the indirect pathway (with STN DBS). Adding to the similarities, dopamine agonists trigger the impulse control disorders in PD patients with a family history of substance abuse and gambling (Voon *et al.*, 2007, Weintraub *et al.*, 2010). This phenomenon resembles the familial transmission of the impulsive-aggressive diathesis to suicidal behavior (McGirr *et al.*, 2009). Likewise, in our study, low putamen voxel counts were associated with high delay discounting only in suicide attempters but not in depressed controls. Altogether, these observations suggest that striatal alterations are, by themselves, not sufficient to produce impulsive and suicidal behavior, but could trigger it when superimposed on other vulnerabilities.

Limitations and strengths

Our findings are limited by small group sizes and a case-control design. These limitations made it impossible for us to formally test whether delay discounting mediated the effect of striatal alterations on suicidal behavior. Our inability to distinguish between gray/white matter contrast and gray matter volume also limits our findings, which could be also due to white matter alterations. Further, while small vessel disease is a likely cause of basal ganglia alterations in suicide attempters, we were unable to ascertain their etiology. Finally, the cross-sectional nature of our observations leaves them open to alternative explanations. For example, impulsive individuals may eat unhealthy foods, smoke, and neglect exercise, thereby hastening subcortical small vessel disease.

Yet, a number of methodological strengths add confidence in our findings. A three-group design allowed us to control for effects of depression, while a careful characterization of cognitive and clinical status as well as medication exposure enabled us to examine important covariates. Our use of a fully deformable approach to atlas-based segmentation improved our ability to handle aging-related variance in brain anatomy, particularly important in examining basal ganglia, which adjoin the ventricles.

Placing our findings in the context of existing knowledge of brain alterations in attempted suicide, one may hypothesize that individuals with striatal alterations constitute a subgroup of impulsive suicide attempters. It is possible that orbitofrontal and amygdala structural changes noted in younger suicide attempters (Monkul *et al.*, 2007) represent pathology at different points in the corticostriatal loops; their behavioral correlates are yet to be

investigated. It is plausible that prefrontal alterations observed in younger suicide attempters are related to abnormal learning processes (Dombrovski *et al.*, 2010, Jollant *et al.*, 2005, Jollant *et al.*, 2008, Jollant *et al.*, 2010). If so, there may exist at least two distinct vulnerabilities: corticostriatal loop alterations paralleled by impulsive behavior and prefrontal alterations that disrupt learning from rewards and punishments in complex environments.

To conclude, we found that, in late-life depression, suicide attempts were associated with structural alterations in the putamen. These alterations were related to an exaggerated preference for immediate rather than larger delayed rewards in suicide attempters. These findings provide preliminary support for the hypothesis that the disruption of the cortical-basal ganglia loop at the level of striatum could trigger impulsive suicidal behavior in vulnerable individuals.

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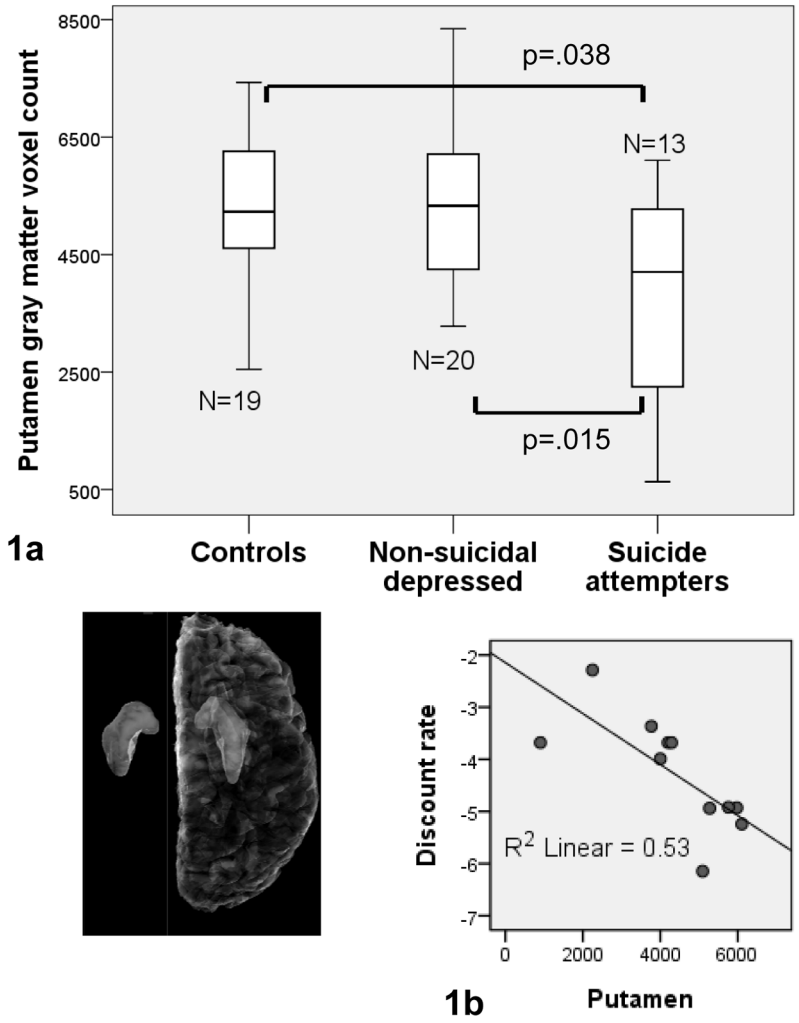

Figure 1. Putamen gray matter, suicide attempts, and discounting of future rewards

1 a–b. Suicide attempters had lower putamen gray matter voxel counts compared to the control groups (**1a**; F[2,49]=4.7, p=.014, η_p^2=.16, post-hoc: SA<D=C). **1b.** Suicide attempters with the lowest putamen gray matter voxel counts displayed a stronger preference for immediate rewards measured by the natural-log transformed discount rate (r=−.73, p=.011, N=11). The putamen image was generated using Brain Explorer 2 (Seattle (WA): Allen Institute for Brain Science. © 2011. Available from: http://www.brain-map.org).

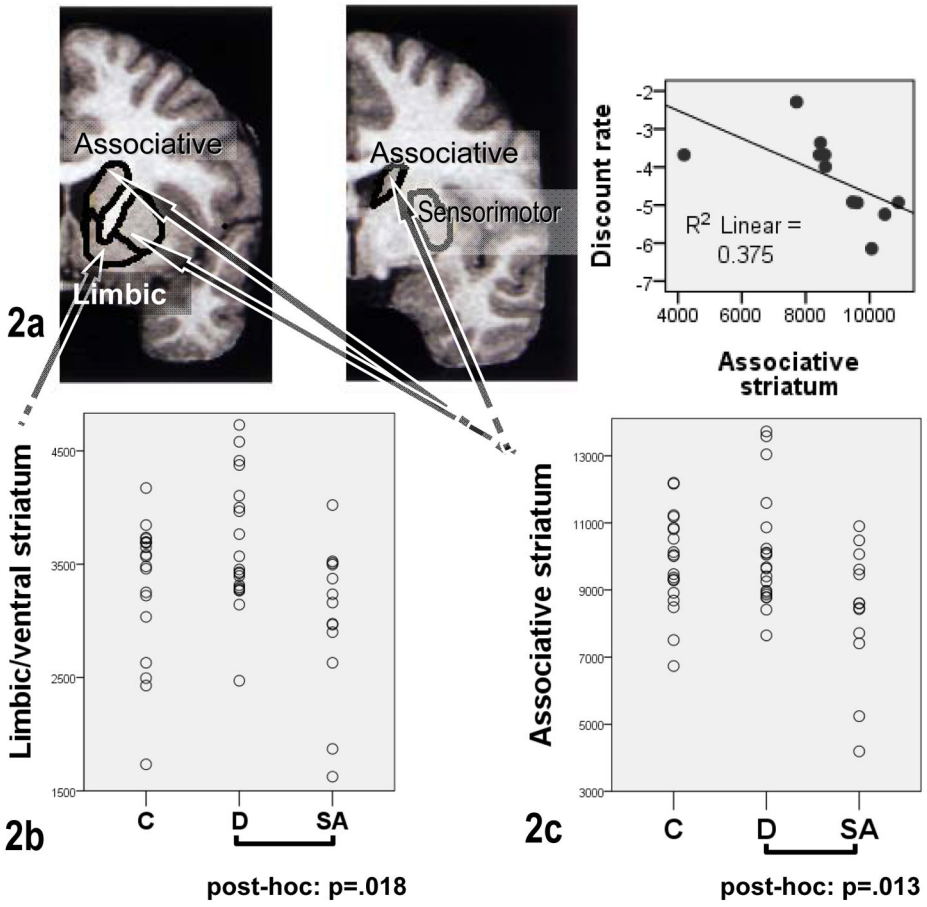

Figure 2. Secondary analysis: functional striatal subregions

2a. To examine the functional subdivisions of the striatum, we used manually traced regions as defined by (Martinez *et al.*, 2003) from the atlas of (Mai *et al.*, 1997): **associative striatum** (precommissural dorsal caudate and precommissural putamen), **sensorimotor** striatum (postcomissural putamen), and **limbic (ventral) striatum** (nucleus accumbens as well as the ventral caudate and the ventral putamen rostral to the anterior comissure). **Suicide attempters (SA) had lower voxel counts in the associative striatum** (dorsal caudate and dorsal precommissural putamen; **2c**; $F[2,49]=4.37$, $p=.018$, $\eta_p^2=.15$, SA<D) **and limbic/ventral striatum** (nucleus accumbens, ventral caudate and the ventral putamen rostral to the anterior commissure; **2b**; $F[2,49]=4.5$, $p=.016$; $\eta_p^2=.16$, SA<D), **compared to depressed controls (D)**, but did not differ significantly from healthy controls (C). **2d.** In suicide attempters, **low associative striatum** gray matter voxel counts were related to the **preference for immediate rewards** measured by the natural-log transformed discount rate ($r=-.61$, $p=.045$).

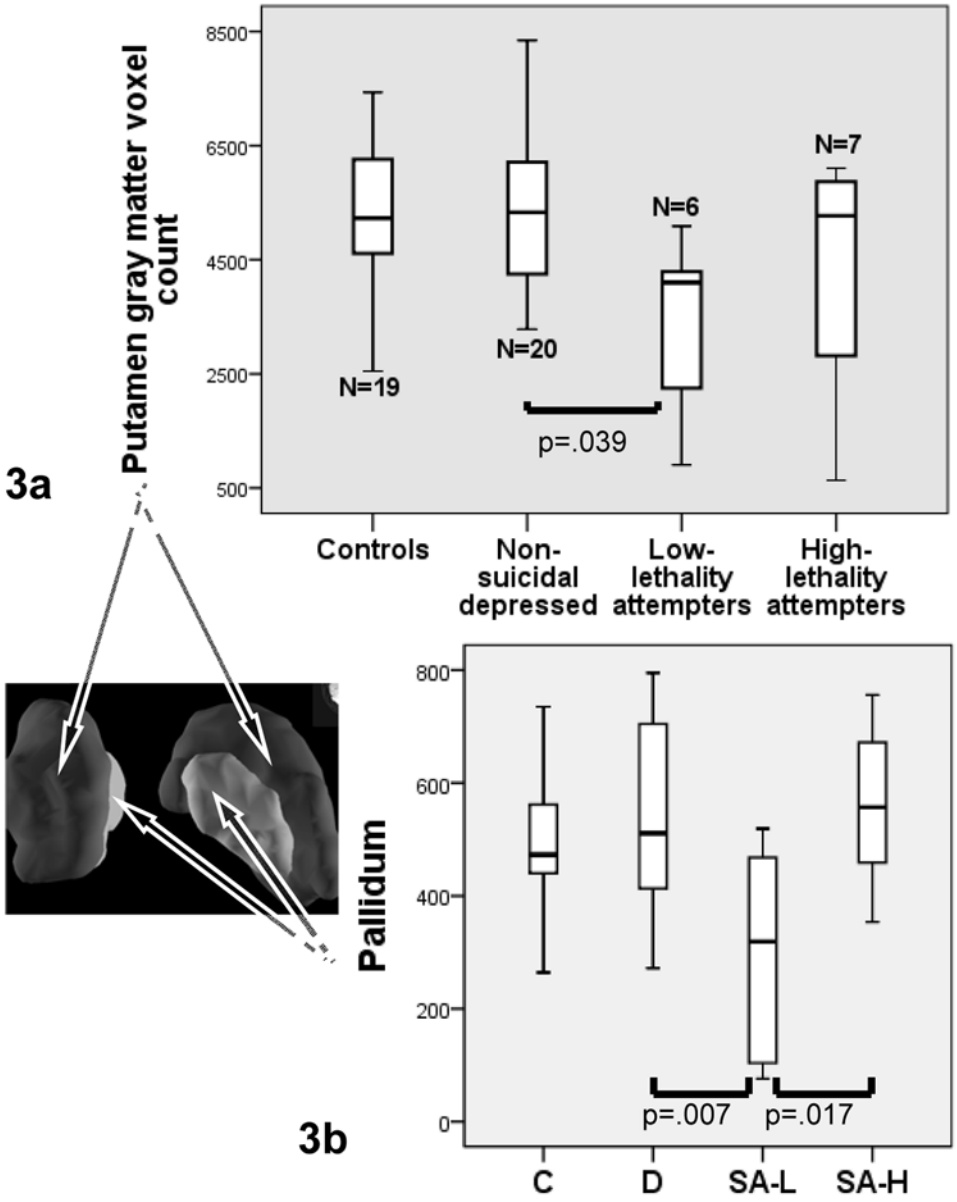

Figure 3. Lethality of suicide attempts and basal ganglia gray matter voxel counts

Low-lethality suicide attempters (SA-L) had lower putamen (**1a**; F[3,48]=3.4, p=.026, η_p^2=.17, post-hoc: SA-L<D) and pallidum (**1b**; F[3,48]=4.3, p=.008, η_p^2=.22, post-hoc: SA-L<D=SA-H) compared to the control groups. The putamen and pallidum image was generated using Brain Explorer 2 (Seattle (WA): Allen Institute for Brain Science. ©2011. Available from: http://www.brain-map.org).

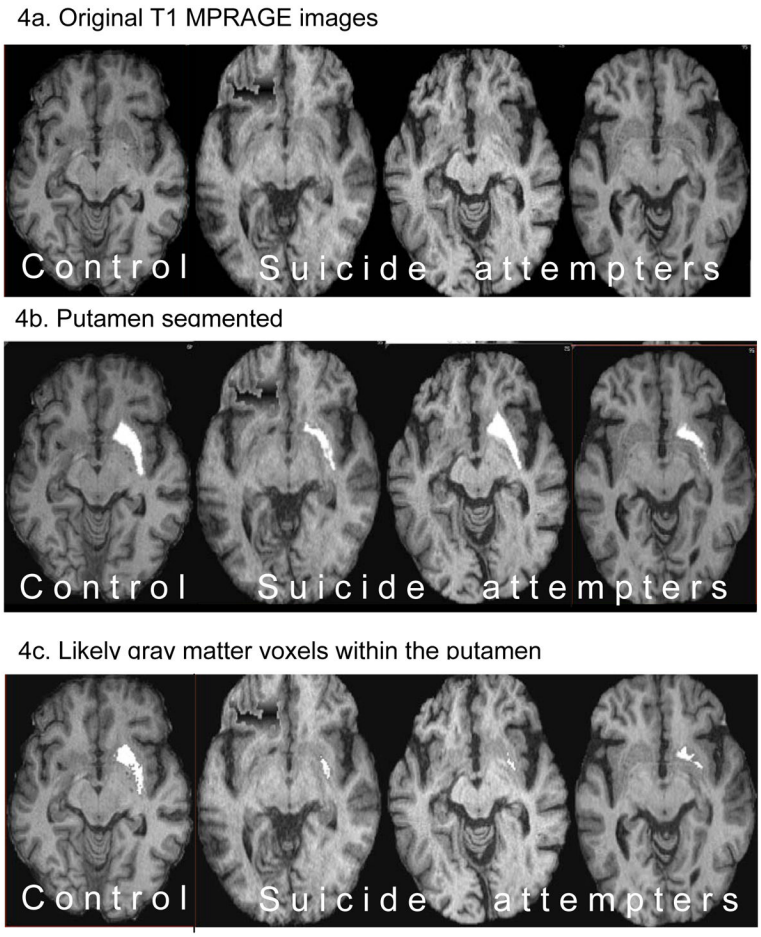

Figure 4. Putamen images from four representative subjects (neurological convention)
These T1 images illustrate gray matter changes in the putamen of suicide attempters, contrasted with an intact control participant. The original T1 MPRAGE image shows poorly defined putamina with an effaced gray/white matter contrast in the suicide attempters. The second row shows segmentation accuracy for the entire right putamen. The third row displays likely gray matter voxels, as segmented by the Automatic Labeling Pathway. NB: the artifact noted in the frontal lobe of the first suicide attempter does not affect the basal ganglia.

Table 1

Group characteristics

	Controls (C) N=19	Non-Suicidal Depressed (D) N=20	Suicide attempters (SA) N=13	p	Post-hoc, Tukey HSD
Men, N	7/19	7/20	8/13	.27	-
White, N	17/19	16/20	9/13	.42	-
Age, years (SD)	70.5 (7.5)	67.7 (7.0)	66.0 (6.4)	.20	-
Years of Education, mean (SD)	13.7 (2.3)	14.8 (2.7)	13.7 (3.1)	.38	-
Mini-mental status examination (N=49), mean (SD)	28.2 (1.9)	28.6 (1.6)	28.0 (1.5)	.60	-
Dementia rating scale (N=45), mean (SD)	137.4 (3.1)	134.7 (8.7)	135.0 (4.6)	.14	-
Premorbid IQ, Wechsler Test of Adult Reading (N=32), mean (SD)	100.1 (14.7)	107.6 (14.4)	105.6 (14.3)	.50	-
Current substance use disorders, N	-	0/20	4/13	.010	-
Lifetime substance use disorders, N	-	4/20	6/13	.11	-
Current anxiety disorders, N	-	3/20	9/13	.002	-
Lifetime anxiety disorders, N	-	7/20	10/13	.019	-
Depressive Severity (HRS16) in index episode, mean (SD)	2.6 (2.1)	18.5 (3.6)	20.5 (4.4)	<.0001	D=SA->C
Age at first depressive episode	-	58.5 (19.6)	47.3 (23.3)	.17	-
Mood disorders in first- and second-degree relatives,	8/19	6/14	9/13	.083	-
Burden of physical illness (Cumulative Illness Rating Scale adapted for Geriatrics) (N=105), mean (SD)	6.8 (2.6)	10.4 (2.9)	8.4 (3.5)	.002	D>C
Intensity of antidepressant pharmacotherapy during current episode, Antidepressant Treatment History Form Score (N=25), mean (SD)	-	1.9 (1.7)	3.0 (2.8)	.22	-
Scale for Suicidal Ideation, mean (SD)	-	-	27.1 (6.0)	-	-
Age of first suicide attempt, mean (SD)	-	-	49.3 (17.5)	-	-
Beck's Medical Lethality Scale, mean (SD)	-	-	3.5 (2.6)	-	-
Beck's Suicidal Intent Scale, mean (SD)	-	-	17.6 (5.4)	-	-