

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

A. Y. Dombrovski<sup>1\*</sup>, G. J. Siegle<sup>1</sup>, K. Szanto<sup>1</sup>, L. Clark<sup>2</sup>, C. F. Reynolds 3rd<sup>1</sup> and H. Aizenstein<sup>1</sup>

<sup>1</sup> Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

<sup>2</sup> Behavioural and Clinical Neuroscience Institute, Department of Experimental Psychology, University of Cambridge, UK

**Background.** Converging evidence implicates basal ganglia alterations in impulsivity and suicidal behavior. For example, D<sub>2</sub>/D<sub>3</sub> agonists and subthalamic nucleus stimulation in Parkinson's disease (PD) trigger impulse control disorders and possibly suicidal behavior. Furthermore, 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.

**Method.** Fifty-two persons aged ≥60 years 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 magnetization prepared rapid acquisition gradient-echo (MPRAGE) magnetic resonance imaging (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 (MCQ) and delay aversion with the Cambridge Gamble Task (CGT).

**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 but not delay aversion. Secondary analyses revealed that SA had lower voxel counts in associative and ventral but not sensorimotor striatum.

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

Received 6 June 2011; Revised 4 September 2011; Accepted 7 September 2011; First published online 17 October 2011

**Key words:** Basal ganglia, corpus striatum, decision making, globus pallidus, putamen, reward, suicide.

## 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.* 2011). However, 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. We present preliminary evidence that, in vulnerable individuals, loss of basal ganglia integrity is associated with decisions focused excessively 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 & Strick, 2000). Haber & Knutson (2010) have proposed that, within these loops, reward-related representations are fed from ventral 'reward' circuits to dorsal 'cognitive' circuits through striatal-nigrostriatal spirals, giving rise to reward-guided behavior. During decision making, corticostriatal 'reward' circuits are thought to represent and integrate information relevant to the value of choices (Rangel *et al.* 2008). For example, as choice is made between immediate and delayed rewards (delay discounting), a value signal is represented in the striatum, anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) (Cardinal *et al.* 2001; McClure *et al.* 2004; Hariri *et al.* 2006;

\* Address for correspondence: A. Y. Dombrovski, M. D., Western Psychiatric Institute and Clinic, 100 N Bellefield Ave, Pittsburgh, PA 15213, USA.

(Email: dombrovskia@upmc.edu)

Kable & Glimcher, 2007). Although 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 the 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 seems 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 & Lees, 1985) and a high threshold for initiating action (Owen *et al.* 1993; Frank *et al.* 2007*b*). One remarkable exception is, again, the disruption of the indirect pathway with STN-DBS in PD, which seems 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, two out of 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 (Dombrowski *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 inter-temporal 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.

## Method

### *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  $\geq 60$  years with non-psychotic unipolar depression determined by SCID/DSM-IV: 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 (A.Y.D. or K.S.), 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 *et al.* 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, and major bleeding, as defined by a score of  $\geq 4$  on the BLS. All other attempts were classified as low-lethality. Violent means (shooting, cutting, jumping and hanging) were used by three out of 13 suicide attempters. 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 (A.Y.D. or K.S.) identified any attempts with a score of  $\geq 4$  on the BLS and any history of systemic hypotension  $> 5$  min or asphyxia or neurotoxic ingestion (e.g. polyatomic alcohols, methanol, or organic solvents); two out of 13. In addition to lethality, we assessed suicidal intent associated with suicide attempts, using the Beck 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/DSM-IV, and the Scale for Suicidal (SSI, 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/DSM-IV.

#### *Inclusion and exclusion criteria*

Our study was conducted at a university psychogeriatric in-patient unit and a late-life depression out-patient 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 (Conwell *et al.* 2000; Beautrais, 2002; Waern *et al.* 2002). Participants were recruited between January 2007 and April 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  $\geq 24$  on the Mini-Mental State Examination (MMSE; 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, schizo-affective disorder and exposure to electroconvulsive therapy in the 6 months preceding testing led to exclusion from 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 (HAM-D-17; 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 (ATHF; 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). 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 inter-rater reliability among our assessors were 0.95 for HAM-D, 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 2 weeks of in-patient admission or at the beginning of out-patient treatment. The Monetary Choice Questionnaire (MCQ), described below, was administered at baseline and at the 3-month follow-up assessment (Dombrowski *et al.* 2011). Data from the first administration were used in the current analyses. The Cambridge Gamble Task (CGT), 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 (MRI)*

Participants had high-resolution T1-weighted magnetization prepared rapid acquisition gradient-echo (MPRAGE) MRI scans on a 3-T Siemens Trio TIM scanner. T1-weighted brain MR images were processed using the automated labeling pathway (ALP) technique (Wu *et al.* 2006), which relies on atlas-based segmentation (a deformable registration approach) to measure regional volumetric differences between groups in predefined regions of interest (ROIs). 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 MR images. Using ALP, manually traced primary anatomic ROIs (putamen, caudate and pallidum) from the

**Table 1.** Group characteristics

	Controls (C) <i>n</i> = 19	Non-suicidal depressed (D) <i>n</i> = 20	Suicide attempters (SA) <i>n</i> = 13	<i>p</i>	Post-hoc, Tukey HSD
Men	7/19	7/20	8/13	0.27	–
White	17/19	16/20	9/13	0.42	–
Age (years)	70.5 (7.5)	67.7 (7.0)	66.0 (6.4)	0.20	–
Years of education	13.7 (2.3)	14.8 (2.7)	13.7 (3.1)	0.38	–
MMSE ( <i>n</i> = 49)	28.2 (1.9)	28.6 (1.6)	28.0 (1.5)	0.60	–
DRS ( <i>n</i> = 45)	137.4 (3.1)	134.7 (8.7)	135.0 (4.6)	0.14	–
Pre-morbid IQ (WTAR) ( <i>n</i> = 32)	100.1 (14.7)	107.6 (14.4)	105.6 (14.3)	0.50	–
Current substance use disorders	–	0/20	4/13	0.010	–
Lifetime substance use disorders	–	4/20	6/13	0.11	–
Current anxiety disorders	–	3/20	9/13	0.002	–
Lifetime anxiety disorders	–	7/20	10/13	0.019	–
Depressive severity (HAM-D-17) in index episode	2.6 (2.1)	18.5 (3.6)	20.5 (4.4)	<0.0001	D = SA > C
Age at first depressive episode (years)	–	58.5 (19.6)	47.3 (23.3)	0.17	–
Mood disorders in first- and second-degree relatives	8/19	6/14	9/13	0.083	–
Burden of physical illness (CIRS-G) ( <i>n</i> = 105)	6.8 (2.6)	10.4 (2.9)	8.4 (3.5)	0.002	D > C
Intensity of antidepressant pharmacotherapy during current episode, ATHF score ( <i>n</i> = 25)	–	1.9 (1.7)	3.0 (2.8)	0.22	–
SSI score	–	–	27.1 (6.0)	–	–
Age of first suicide attempt (years)	–	–	49.3 (17.5)	–	–
BLS score	–	–	3.5 (2.6)	–	–
SIS score	–	–	17.6 (5.4)	–	–

MMSE, Mini-Mental State Examination; DRS, Dementia Rating Scale; WTAR, Wechsler Test of Adult Reading; HAM-D-17, 17-item Hamilton Rating Scale for Depression; CIRS-G, Cumulative Illness Rating Scale adapted for Geriatrics; ATHF, Antidepressant Treatment History Form; SSI, Scale for Suicidal Ideation; BLS, Beck Lethality Scale; SIS, Suicidal Intent Scale; HSD, Honestly Significantly Different.

Values are given as *n* or mean (standard deviation).

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 cerebrospinal fluid (CSF). For our secondary analysis of functional striatal subdivisions [Fig. 2a: associative striatum (precommissural dorsal caudate and precommissural putamen), sensorimotor striatum (postcommissural putamen) and limbic (ventral) striatum (nucleus accumbens and also the ventral caudate and the ventral putamen rostral to the anterior commissure)], we used manually traced regions as defined by 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 were stripped from the template and subjects' three-dimensional (3D) spoiled gradient recalled echo (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 the

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 obtained automatically. 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, as both of these image features contribute to the number of voxels labeled as 'likely gray matter' in the subcortical regions (Davatzikos & 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 *versus* larger delayed rewards, we used the MCQ (Kirby *et al.* 1999), which 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 *et al.* (1999). The MCQ identifies discount rates for small (US\$25–35), medium (US\$50–60) and large (US\$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 three 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 *et al.* (1999) and were natural log-transformed for analyses.

In addition, we used an experiential, real-time measure of delay aversion on the CGT. This metric reflects the difference in bets between two conditions: an ascend condition where the available bet starts small and increases in 5-s intervals on each trial, and a descending condition where the bet starts high and decreases in 5-s 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

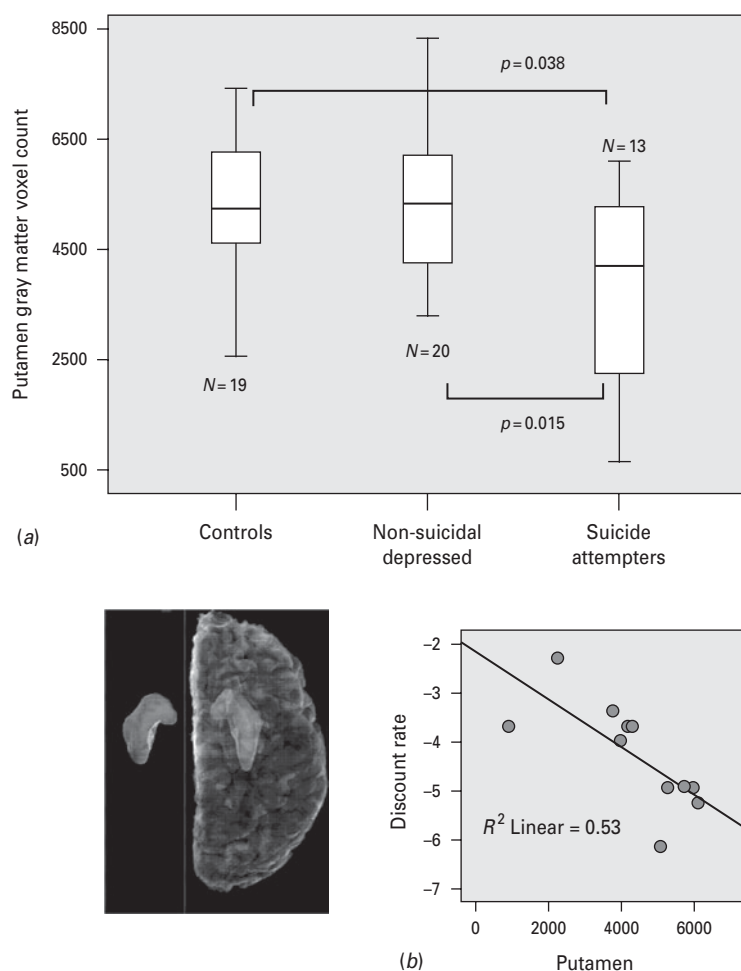
We used SPSS version 18.0 (SPSS Inc., USA) and MATLAB 7.6 (The MathWorks Inc., USA). All tests were two-sided. We compared groups on demographic and clinical characteristics using analyses of variance (ANOVAs) and  $\chi^2$  tests. For these and all subsequent ANOVAs, we examined *post-hoc* contrasts using the Tukey Honestly Significantly Different (HSD) test 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 ( $p=0.40$ ,  $0.49$  and  $0.25$  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 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 & 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 of 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 (BMI), 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/BMI 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 a 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 & 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.



**Fig. 1.** Putamen gray matter, suicide attempts and discounting of future rewards. (a) Suicide attempters (SA) had lower putamen gray matter gray matter voxel counts compared to the depressed (D) and healthy controls (C):  $F(2, 49) = 4.7$ ,  $p = 0.014$ ,  $\eta_p^2 = 0.16$ , *post-hoc*:  $SA < D = C$ . (b) 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 ( $r = -0.73$ ,  $p = 0.011$ ,  $n = 11$ ). The putamen image was generated using Brain Explorer 2 [Allen Institute for Brain Science: Seattle, WA ([www.brain-map.org](http://www.brain-map.org)) © 2011].

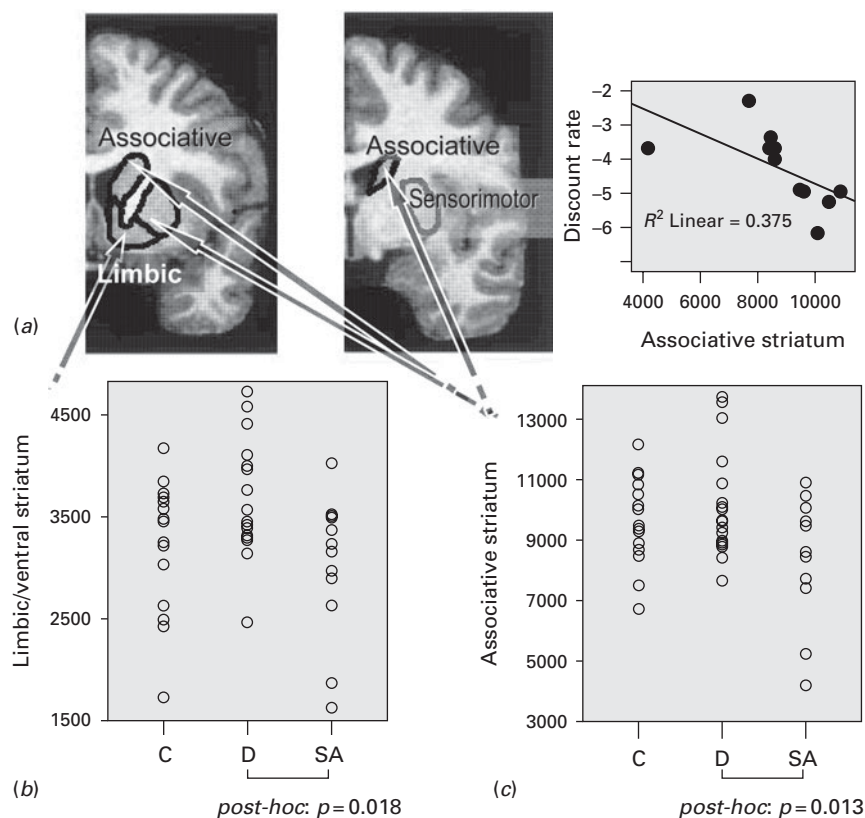
Suicide attempters were more likely to suffer from current substance use disorders and from current and lifetime anxiety disorders than the non-suicidal depressed participants. The two depressed groups did not differ significantly in severity of depression and psychotropic exposure. Suicide attempters 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 [ $F(2, 49) < 1.6$ ,  $p > 0.22$ ,  $\eta_p^2 \leq 0.06$ ].

Our secondary analysis revealed that suicide attempters had lower voxel counts in striatal subregions involved in decision making compared to depressed controls; that is, in the associative striatum [dorsal caudate and dorsal precommissural putamen; Fig. 2c;  $F(2, 49) = 4.4$ ,  $p = 0.018$ ,  $\eta_p^2 = 0.15$ ,  $SA < D$ ] and limbic/ventral striatum [nucleus accumbens, ventral caudate and the ventral putamen rostral to the anterior commissure; Fig. 2b;  $F(2, 49) = 4.5$ ,  $p = 0.016$ ,  $\eta_p^2 = 0.16$ ,  $SA < D$ ]. By contrast, voxel counts in the sensorimotor striatum (postcommissural putamen) did not differ between groups [ $F(2, 49) = 0.04$ ,  $p = 0.96$ ]. The seeming lack of difference in associative striatum gray matter



**Fig. 2.** Secondary analysis: functional striatal subregions. (a) 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 (postcommissural putamen), and limbic (ventral) striatum (nucleus accumbens and also the ventral caudate and the ventral putamen rostral to the anterior commissure). Suicide attempters (SA) had lower voxel counts in the (b) limbic/ventral striatum [nucleus accumbens, ventral caudate and the ventral putamen rostral to the anterior commissure;  $F(2, 49) = 4.5$ ,  $p = 0.016$ ,  $\eta_p^2 = 0.16$ , SA < D] and (c) associative striatum [dorsal caudate and dorsal precommissural putamen;  $F(2, 49) = 4.37$ ,  $p = 0.018$ ,  $\eta_p^2 = 0.15$ , SA < D] compared to depressed controls (D), but did not differ significantly from healthy controls (C). (d) 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 ( $r = -0.61$ ,  $p = 0.045$ ).

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:  $F(1, 29) = 5.51$ ,  $p = 0.026$ ,  $\eta_p^2 = 0.16$ ; calcarine:  $F(1, 29) = 3.87$ ,  $p = 0.059$ ,  $\eta_p^2 = 0.12$ ] or whole brain volume [group:  $F(1, 29) = 4.89$ ,  $p = 0.035$ ,  $\eta_p^2 = 0.14$ ; whole brain:  $F(1, 29) = 9.44$ ,  $p = 0.005$ ,  $\eta_p^2 = 0.25$ ], the differences became apparent. However, in the case of ventral striatum volumes, the difference between suicide attempters and controls remained small and non-significant ( $p > 0.21$ ,  $\eta_p^2 < 0.06$ ).

#### 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 ( $r = -0.73$ ,  $p = 0.011$ ,  $n = 11$ ; Fig. 1b). This relationship was not seen in non-suicidal depressed elderly ( $r = 0.16$ ,  $p = 0.51$ ,  $n = 20$ ), and the correlation coefficients differed significantly ( $z$  score: 2.53,  $p = 0.011$ ). Similarly, in our secondary analysis, the preference for immediate rewards correlated negatively with associative striatum voxel counts ( $r = -0.61$ ,  $p = 0.045$ ; Fig. 2d), whereas the negative correlation with limbic striatum voxel counts was not significant ( $r = -0.49$ ,  $p = 0.13$ ). The correlation between an experiential measure of delay discounting (delay aversion on the CGT) and the putamen gray matter voxel count in suicide attempters was not significant ( $r = -0.15$ ,  $p = 0.66$ ). As in our larger behavioral study (Dombrovski *et al.* 2011), 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:  $F(2, 48) = 5.53, p = 0.007, \eta_p^2 = 0.20$ ; race: n.s.,  $\eta_p^2 = 0.03$ ] and age [group:  $F(2, 48) = 5.17, p = 0.009, \eta_p^2 = 0.18$ ; age: n.s.,  $\eta_p^2 = 0.03$ ] did not diminish the group differences in putamen gray matter voxel counts. Of note, 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 seemed to explain the additional variance beyond that explained by suicide attempts [group:  $F(1, 29) = 5.11, p = 0.031, \eta_p^2 = 0.15$ ; lifetime substance use disorders:  $F(1, 29) = 3.88, p = 0.059, \eta_p^2 = 0.12$ ]. By contrast, lifetime anxiety disorders did not explain any additional variance [group:  $F(1, 29) = 5.18, p = 0.030, \eta_p^2 = 0.15$ ; lifetime anxiety disorders:  $F(1, 29) = 0.02, p = 0.88, \eta_p^2 < 0.01$ ]. Group differences in basal ganglia integrity were also unchanged after excluding two participants with possible brain injury from the suicide attempts [putamen:  $F(2, 47) = 3.84, p = 0.028, \eta_p^2 = 0.14$ ] and when controlling for whole brain [putamen:  $F(2, 48) = 4.08, p = 0.023, \eta_p^2 = 0.15$ ] or calcarine [putamen:  $F(2, 48) = 4.41, p = 0.017, \eta_p^2 = 0.16$ ] volumes. Similarly, the correlation with delay discounting in suicide attempters was unchanged after controlling for calcarine volume (putamen:  $r = -0.74, p = 0.014$ ). As 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:  $F(1, 38) = 3.65, p = 0.036, \eta_p^2 = 0.16$ ; family history of mood disorders:  $F(1, 38) = 0.01, p = 0.91, \eta_p^2 < 0.01$ ; age at first depressive episode:  $F(1, 38) = 0.11, p = 0.90, \eta_p^2 < 0.01$ ].

### 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 (Fig. 3a), as would be predicted from our behavioral data (Dombrowski et al. 2011). In addition, low-lethality attempters had lower pallidum gray matter voxel counts, compared to depressed controls and high-lethality attempters (Fig. 3b).

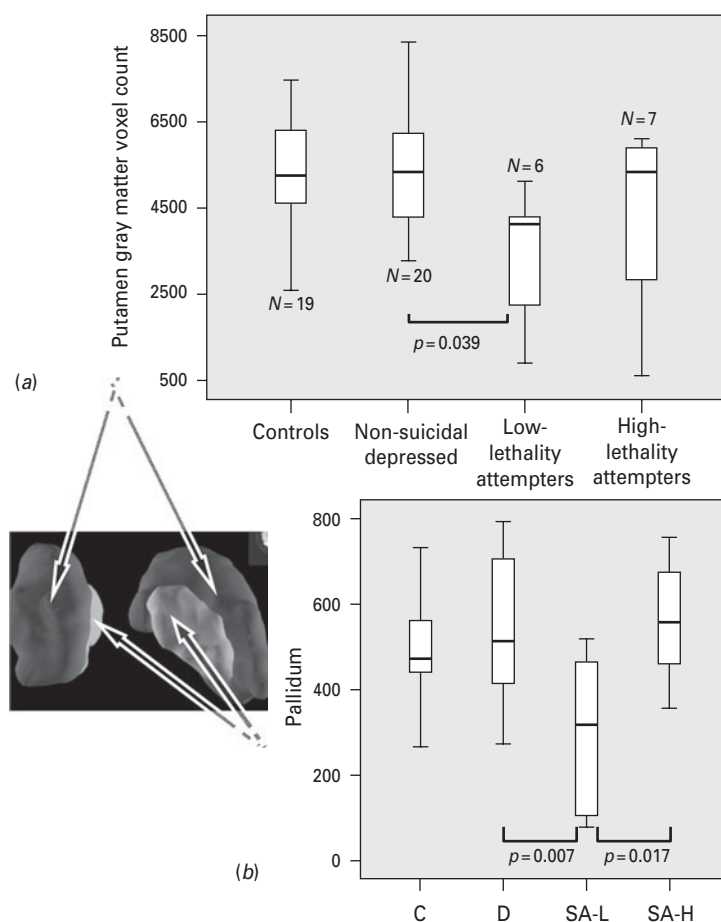
### Discussion

We found that (1) low gray matter voxel counts in the putamen were associated with suicide attempts in late-life depression and (2) structural abnormalities in the putamen were related to an exaggerated preference for smaller immediate *versus* 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 and also from anxiety and substance use disorders, even though lifetime substance use disorders did explain additional variance in putamen volumes. Although our findings should be viewed with caution because of the 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 the 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 (Weintraub et al. 2006; Housden et al. 2010; Voon et al. 2010) and suicidal (Di Maio et al. 1993; Ahearn et al. 2001; Vang et al. 2010) behavior. It is hard to say whether disintegration of any single nucleus is associated primarily with impulsivity and suicidal behavior, given the diffuse character of basal ganglia alterations seen in our sample, their close proximity, and in particular, 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. 1995, 2006), functional imaging evidence that the putamen is involved in reward processing and intertemporal choice (Luo et al. 2009) and a primate lesion study showing that the 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 STN-DBS (Frank et al. 2007a; Voon et al. 2008; Halbig et al. 2009).

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





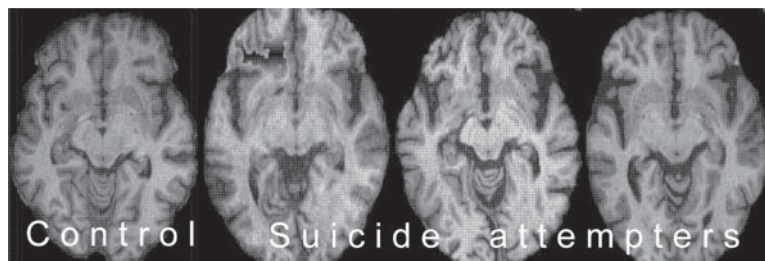
**Fig. 3.** Lethality of suicide attempts and basal ganglia gray matter voxel counts. Low-lethality suicide attempters (SA-L) had (a) lower putamen [ $F(3, 48) = 3.4, p = 0.026, \eta_p^2 = 0.17, \text{post-hoc: SA-L} < \text{D}$ ] and (b) lower pallidum [ $F(3, 48) = 4.3, p = 0.008, \eta_p^2 = 0.22, \text{post-hoc: SA-L} < \text{D} = \text{SA-H}$ ] compared to the control groups. SA-H, High-lethality suicide attempters; D, depressed controls; C, healthy controls. The putamen and pallidum image was generated using Brain Explorer 2 [Allen Institute for Brain Science: Seattle, WA (www.brain-map.org) © 2011].

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) (Russchen *et al.* 1985; Haber *et al.* 2006), 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),

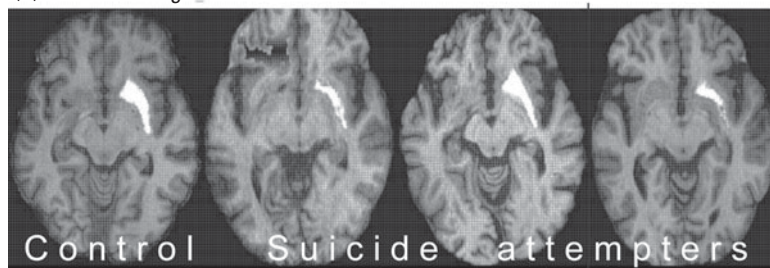
impulsive suicide attempters may have a lesion in the strategic delta system, which discounts rewards at a constant rate over time. Hence, their behavior may be governed primarily by the ‘impatient’ beta system sensitive to whether the reward is available immediately. In a suicidal crisis, such short-sighted 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

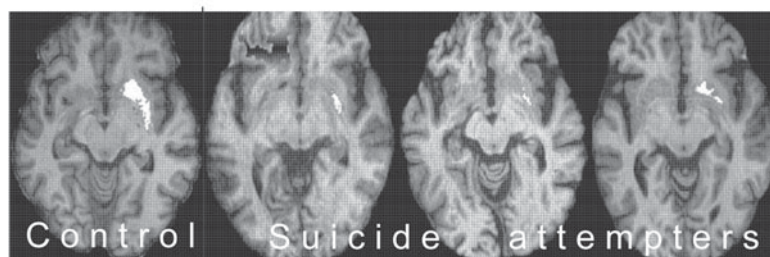
(a) Original T1 MPRAGE images



(b) Putamen segmented



(c) Likely gray matter voxels within the putamen



**Fig. 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 magnetization prepared rapid acquisition gradient-echo (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 (ALP) technique. Note that the artifact noted in the frontal lobe of the first suicide attempter does not affect the basal ganglia.

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 test formally 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 also be due to

white matter alterations. Furthermore, although 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.

Nevertheless, there are methodological strengths of our study that add confidence in our findings. The three-group design allowed us to control for effects of depression, and a careful characterization of cognitive and clinical status and also 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, we can 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 (Jollant *et al.* 2005, 2008, 2010; Dombrovski *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 the striatum could trigger impulsive suicidal behavior in vulnerable individuals.

### Acknowledgments

We thank C. Shollenberger for assistance with suicide attempt characterization and C. Nable and R. MacCloud for help with MRI data processing. The phrase 'temptation of suicide' belongs to Herman Hesse (*Steppenwolf*, 1927). This work received support from: National Institute of Mental Health (NIMH) grants K23 MH086620 and MH070471, R01 MH085651 and MH076079, and P30 MH079144, the American Foundation for Suicide Prevention Young Investigator award, the John A. Hartford Foundation, and the UPMC Endowment in Geriatric Psychiatry.

### Declaration of Interest

Dr L. Clark has served as a consultant to Cambridge Cognition. Dr C.F. Reynolds 3rd has received pharmaceutical supplies for his National Institutes of Health (NIH)-sponsored work from Forest Laboratories, Pfizer, Bristol-Myers Squibb, Wyeth, and Eli Lilly. All of the other authors have no biomedical financial interests or potential conflicts of interest.

### References

Ahearn EP, Jamison KR, Steffens DC, Cassidy F, Provenzale JM, Lehman A, Weisler RH, Carroll BJ,

Krishnan KR (2001). MRI correlates of suicide attempt history in unipolar depression. *Biological Psychiatry* **50**, 266–270.

Arango V, Underwood MD, Mann JJ (1997). Postmortem findings in suicide victims. Implications for in vivo imaging studies. *Annals of the New York Academy of Sciences* **836**, 269–287.

Beautrais AL (2002). A case control study of suicide and attempted suicide in older adults. *Suicide and Life-Threatening Behavior* **32**, 1–9.

Beck AT, Beck R, Kovacs M (1975). Classification of suicidal behaviors: I. Quantifying intent and medical lethality. *American Journal of Psychiatry* **132**, 285–287.

Beck AT, Kovacs M, Weissman A (1979). Assessment of suicidal intention: the Scale for Suicide Ideation. *Journal of Consulting and Clinical Psychology* **47**, 343–352.

Beck AT, Shuylar D, Herman I (1974). Development of suicidal intent scales. In *The Prediction of Suicide* (ed. A. T. Beck, H. L. P. Resnik and D. J. Lettieri), pp. 45–56. Charles Press: Bowie, MD.

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001). Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* **292**, 2499–2501.

Chen M, Kanade T, Pomerleau D, Schneider J (1999). 3-D deformable registration of medical images using a statistical atlas. In *Medical Image Computing and Computer-Assisted Intervention – MICCAI'99* (ed. C. Taylor and A. Colchester), pp. 621–630. Springer: Berlin.

Clark L, Dombrovski AY, Siegle GJ, Butters MA, Shollenberger CL, Sahakian BJ, Szanto K (2011). Impairment in risk-sensitive decision-making in older suicide attempters with depression. *Psychology and Aging* **26**, 321–330.

Cohen J, Cohen P (1983). *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. Erlbaum: Hillsdale, NJ.

Conwell Y, Lyness JM, Duberstein P, Cox C, Seidlitz L, DiGiorgio A, Caine ED (2000). Completed suicide among older patients in primary care practices: a controlled study. *Journal of the American Geriatrics Society* **48**, 23–29.

Davatzikos C, Resnick SM (2002). Degenerative age changes in white matter connectivity visualized in vivo using magnetic resonance imaging. *Cerebral Cortex* **12**, 767–771.

Deakin J, Aitken M, Robbins T, Sahakian BJ (2004). Risk taking during decision-making in normal volunteers changes with age. *Journal of the International Neuropsychological Society* **10**, 590–598.

Di Maio L, Squitieri F, Napolitano G, Campanella G, Trofater JA, Conneally PM (1993). Suicide risk in Huntington's disease. *Journal of Medical Genetics* **30**, 293–295.

Dombrovski AY, Clark L, Siegle GJ, Butters MA, Ichikawa N, Sahakian BJ, Szanto K (2010). Reward/punishment reversal learning in older suicide attempters. *American Journal of Psychiatry* **167**, 699–707.

Dombrovski AY, Szanto K, Siegle GJ, Wallace ML, Forman SD, Sahakian B, Reynolds 3rd CF, Clark L (2011). Lethal forethought: delayed reward discounting

- differentiates high- and low-lethality suicide attempts in old age. *Biological Psychiatry* **70**, 138–144.
- Epstein LH, Richards JB, Saad FG, Paluch RA, Roemmich JN, Lerman C** (2003). Comparison between two measures of delay discounting in smokers. *Experimental and Clinical Psychopharmacology* **11**, 131–138.
- Ernst C, Mechawar N, Turecki G** (2009). Suicide neurobiology. *Progress in Neurobiology* **89**, 315–333.
- Folstein MF, Folstein SE, McHugh PR** (1975). ‘Mini-mental state’. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189–198.
- Foncke EM, Schuurman PR, Speelman JD** (2006). Suicide after deep brain stimulation of the internal globus pallidus for dystonia. *Neurology* **66**, 142–143.
- Frank MJ, Samanta J, Moustafa AA, Sherman SJ** (2007a). Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science* **318**, 1309–1312.
- Frank MJ, Scheres A, Sherman SJ** (2007b). Understanding decision-making deficits in neurological conditions: insights from models of natural action selection. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* **362**, 1641–1654.
- Green L, Myerson J, Ostaszewski P** (1999). Discounting of delayed rewards across the life span: age differences in individual discounting functions. *Behavioural Processes* **46**, 89–96.
- Haber SN, Kim KS, Maily P, Calzavara R** (2006). Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. *Journal of Neuroscience* **26**, 8368–8376.
- Haber SN, Knutson B** (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**, 4–26.
- Haber SN, Kunishio K, Mizobuchi M, Lyndbalta E** (1995). The orbital and medial prefrontal circuit through the primate basal ganglia. *Journal of Neuroscience* **15**, 4851–4867.
- Halbig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, Tagliati M, Koller WC, Olanow CW** (2009). Subthalamic deep brain stimulation and impulse control in Parkinson’s disease. *European Journal of Neurology* **16**, 493–497.
- Hamilton M** (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* **23**, 56–62.
- Hariri AR, Brown SM, Williamson DE, Flory JD, de Wit H, Manuck SB** (2006). Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. *Journal of Neuroscience* **26**, 13213–13217.
- Housden CR, O’Sullivan SS, Joyce EM, Lees AJ, Roiser JP** (2010). Intact reward learning but elevated delay discounting in Parkinson’s disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology* **35**, 2155–2164.
- Jollant F, Bellivier F, Leboyer M, Astruc B, Torres S, Verdier R, Castelnaud D, Malafosse A, Courtet P** (2005). Impaired decision making in suicide attempters. *American Journal of Psychiatry* **162**, 304–310.
- Jollant F, Lawrence NS, Giampietro V, Brammer MJ, Fullana MA, Drapier D, Courtet P, Phillips ML** (2008). Orbitofrontal cortex response to angry faces in men with histories of suicide attempts. *American Journal of Psychiatry* **165**, 740–748.
- Jollant F, Lawrence NS, Olie E, O’Daly O, Malafosse A, Courtet P, Phillips ML** (2010). Decreased activation of lateral orbitofrontal cortex during risky choices under uncertainty is associated with disadvantageous decision-making and suicidal behavior. *NeuroImage* **51**, 1275–1281.
- Kable JW, Glimcher PW** (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience* **10**, 1625–1633.
- Kirby KN, Petry NM, Bickel WK** (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental Psychology: General* **128**, 78–87.
- Luo S, Ainslie G, Giragosian L, Monterosso JR** (2009). Behavioral and neural evidence of incentive bias for immediate rewards relative to preference-matched delayed rewards. *Journal of Neuroscience* **29**, 14820–14827.
- Mai JK, Assheuer J, Paxinos P** (1997). *Atlas of the Human Brain*. Academic Press: San Diego, CA.
- Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y, Cooper T, Kegeles L, Zarahn E, Abi-Dargham A, Haber SN, Laruelle M** (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: Amphetamine-induced dopamine release in the functional subdivisions of the striatum. *Journal of Cerebral Blood Flow and Metabolism* **23**, 285–300.
- Mattis S** (1988). *Dementia Rating Scale (DRS): Professional Manual*. Psychological Assessment Resources: Odessa, FL.
- McClure SM, Laibson DI, Loewenstein G, Cohen JD** (2004). Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507.
- McGirr A, Alda M, Seguin M, Cabot S, Lesage A, Turecki G** (2009). Familial aggregation of suicide explained by cluster B traits: a three-group family study of suicide controlling for major depressive disorder. *American Journal of Psychiatry* **166**, 1124–1134.
- Middleton FA, Strick PL** (2000). Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain and Cognition* **42**, 183–200.
- Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, Mulsant B, Reynolds 3rd CF** (1992). Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Research* **41**, 237–248.
- Monkul ES, Hatch JP, Nicoletti MA, Spence S, Brambilla P, Lacerda AL, Sassi RB, Mallinger AG, Keshavan MS, Soares JC** (2007). Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder. *Molecular Psychiatry* **12**, 360–366.
- Muranishi M, Inokawa H, Yamada H, Ueda Y, Matsumoto N, Nakagawa M, Kimura M** (2011). Inactivation of the putamen selectively impairs reward history-based action selection. *Experimental Brain Research* **209**, 235–246.
- O’Carroll PW, Berman AL, Maris RW, Moscicki EK, Tanney BL, Silverman MM** (1996). Beyond the Tower

- of Babel: a nomenclature for suicidology. *Suicide and Life-Threatening Behavior* **26**, 237–252.
- Owen AM, Roberts AC, Hodges JR, Summers BA, Polkey CE, Robbins TW (1993). Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* **116**, 1159–1175.
- Rangel A, Camerer C, Montague PR (2008). A framework for studying the neurobiology of value-based decision making. *Nature Reviews Neuroscience* **9**, 545–556.
- Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex* **15**, 1676–1689.
- Raz N, Rodrigue KM (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews* **30**, 730–748.
- Rosano C, Aizenstein HJ, Studenski S, Newman AB (2007). A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **62**, 1048–1055.
- Russchen FT, Bakst I, Amaral DG, Price JL (1985). The amygdalostratial projections in the monkey. An anterograde tracing study. *Brain Research* **329**, 241–257.
- Sackeim HA (2001). The definition and meaning of treatment-resistant depression. *Journal of Clinical Psychiatry* **62** (Suppl. 16), 10–17.
- Smith SM (2002). Fast robust automated brain extraction. *Human Brain Mapping* **17**, 143–155.
- Stenager EN, Wermuth L, Stenager E, Boldsen J (1994). Suicide in patients with Parkinson's disease. An epidemiological study. *Acta Psychiatrica Scandinavica* **90**, 70–72.
- Todes CJ, Lees AJ (1985). The pre-morbid personality of patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* **48**, 97–100.
- Trautner RJ, Cummings JL, Read SL, Benson DF (1988). Idiopathic basal ganglia calcification and organic mood disorder. *American Journal of Psychiatry* **145**, 350–353.
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* **15**, 273–289.
- van Heeringen C, Bijttebier S, Godfrin K (2011). Suicidal brains: a review of functional and structural brain studies in association with suicidal behaviour. *Neuroscience and Biobehavioral Reviews* **35**, 688–698.
- Vang FJ, Ryding E, Träskman-Bendz L, van Westen D, Lindström MB (2010). Size of basal ganglia in suicide attempters, and its association with temperament and serotonin transporter density. *Psychiatry Research: Neuroimaging* **183**, 177–179.
- Voon V, Krack P, Lang AE, Lozano AM, Dujardin K, Schupbach M, D'Ambrosia J, Thobois S, Tamma F, Herzog J, Speelman JD, Samanta J, Kubu C, Rossignol H, Poon YY, Saint-Cyr JA, Ardouin C, Moro E (2008). A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain* **131**, 2720–2728.
- Voon V, Reynolds B, Brezing C, Gallea C, Skaljic M, Ekanayake V, Fernandez H, Potenza MN, Dolan RJ, Hallett M (2010). Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berlin)* **207**, 645–659.
- Voon V, Thomsen T, Miyasaki JM, de Souza M, Shafro A, Fox SH, Duff-Canning S, Lang AE, Zurowski M (2007). Factors associated with dopaminergic drug-related pathological gambling in Parkinson disease. *Archives of Neurology* **64**, 212–216.
- Waern M, Runeson BS, Allebeck P, Beskow J, Rubenowitz E, Skoog I, Wilhelmsson K (2002). Mental disorder in elderly suicides: a case-control study. *American Journal of Psychiatry* **159**, 450–455.
- Wagner G, Koch K, Schachtzabel C, Schultz CC, Sauer H, Schlösser RG (2011). Structural brain alterations in patients with major depressive disorder and high risk for suicide: evidence for a distinct neurobiological entity? *NeuroImage* **54**, 1607–1614.
- Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, Whetteckey J, Wunderlich GR, Lang AE (2010). Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Archives of Neurology* **67**, 589–595.
- Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, Moberg PJ, Stern MB (2006). Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Archives of Neurology* **63**, 969–973.
- Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC (1998). Automated image registration: II. Intersubject validation of linear and nonlinear models. *Journal of Computer Assisted Tomography* **22**, 153–165.
- Wu M, Carmichael O, Lopez-Garcia P, Carter CS, Aizenstein HJ (2006). Quantitative comparison of AIR, SPM, and the fully deformable model for atlas-based segmentation of functional and structural MR images. *Human Brain Mapping* **27**, 747–754.
- Wu M, Rosano C, Aizenstein HJ (2005). A morphological method to improve skull stripping of MR brain images. Paper presented at the Human Brain Mapping Conference, Toronto, Canada, 2005.
- Yoo TS (ed.) (2004). *Insight into Images: Principles and Practice for Segmentation, Registration, and Image Analysis*. AK Peters Ltd: Wellesey, MA.