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1 Basal ganglia volume and shape in anorexia nervosa

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19

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33Abstract

34Background: Reward-centred models have proposed that anomalies in the basal ganglia
35circuitry that underlies reward learning and habit formation perpetuate anorexia nervosa
36(AN). The present study aimed to investigate the volume and shape of key basal ganglia
37regions, including the bilateral caudate, putamen, nucleus accumbens (NAcc), and globus
38pallidus in AN.

39

40Methods: The present study combined data from two existing studies resulting in a sample
41size of 46 women with AN and 56 age-matched healthy comparison (HC) women. Group
42differences in volume and shape of the regions of interest were examined. Within the AN
43group, the impact of eating disorder characteristics on volume and shape of the basal
44ganglia regions were also explored.

45

46Results: The shape analyses revealed inward deformations in the left caudate, right NAcc,
47and bilateral ventral and internus globus pallidus, and outward deformations in the right
48middle and posterior globus pallidus in the AN group.

49

50Conclusions: The present findings appear to fit with the theoretical models suggesting that
51there are alterations in the basal ganglia regions associated with habit formation and
52reward processing in AN. Further investigation of structural and functional connectivity of
53these regions in AN as well as their role in recovery would be of interest.

54

55

561 Introduction

57Anorexia nervosa (AN) is a complex eating disorder characterised by severe malnutrition
58and relentless pursuit of thinness (American Psychiatric Association, 2013) . The mortality
59rate in AN is one of the highest among psychiatric disorders (Arcelus, Mitchell, Wales, &
60Nielsen, 2011; Papadopoulos, Ekblom, Brandt, & Ekselius, 2009) and treatment remains a
61significant challenge (Steinhausen, 2002, 2009). Shedding light onto the processes and
62mechanisms that perpetuate AN is therefore of interest. Current theoretical models of AN
63have proposed that anomalies in reward motivation and learning may play a key role in the
64maintenance of disordered eating (Kaye, Frank, Bailer, & Henry, 2005; Kaye, Fudge, &
65Paulus, 2009; Keating, Tilbrook, Rossell, Enticott, & Fitzgerald, 2012; O'Hara, Campbell, &
66Schmidt, 2015). Most recently, the reward-centred model of AN postulates that early on
67weight loss may be met with positive social and emotional consequences, such as
68admiration and approval, while weight gain may be met with negative appraisal, increasing
69the reward associated with caloric restriction (O'Hara et al., 2015). Over time the reward
70motivation associated with weight loss cues increases, and so the associated eating disorder
71behaviours become compulsive and are repeated despite aversive consequences, such as
72negative affect, social isolation, and poor physical health. Thus, these theoretical models
73highlight similarities between AN and addiction, both of which are considered to be
74disorders of compulsivity and share a number of characteristics such as obsessionality and
75preoccupation (Crane, Roberts, & Treasure, 2007; Fontenelle, Oostermeijer, Harrison,
76Pantelis, & Yücel, 2011; Lubman, Yücel, & Pantelis, 2004; Serpell, Livingstone, Neiderman, &
77Lask, 2002).

79 Along with prefrontal and motor cortices, basal ganglia circuitry, including the globus
80 pallidus and striatal regions, facilitates and supports reward-motivated learning and habitual
81 responding (Ashby, Turner, & Horvitz, 2010; Balleine, Delgado, & Hikosaka, 2007). Preclinical
82 studies have reported that reward-motivated decision making and acquisition of new
83 learned behaviours depend on striatal regions, such as the caudate, anterior putamen, and
84 nucleus accumbens (NAcc) (Goto & Grace, 2005; Gruber, Hussain, & O'Donnell, 2009; Yin,
85 Ostlund, & Balleine, 2008). Temporary deactivation or permanent destruction of these
86 regions impedes the acquisition of new rewarded actions, but does not negatively impact
87 execution of previously learned habitual behaviours (Salamone, Correa, Farrar, & Mingote,
88 2007; Schultz, 2016). The caudate, anterior putamen, and NAcc are also sensitive to
89 devaluation treatments, such as reduction in the expected value of outcome, and support
90 extinction of non-rewarded actions (Izquierdo & Jentsch, 2012; Trifilieff et al., 2013). The
91 posterior putamen and globus pallidus, on the other hand, have been proposed to facilitate
92 formation of rigid habits and automatic responses, which are resistant to devaluation
93 treatments and persist irrespective of consequences (Agustín-Pavón, Martínez-García, &
94 Lanuza, 2014; McFarland & Kalivas, 2001; Saga et al., 2016; Sommer, Costa, & Hansson,
95 2014). These preclinical findings are in line with results from human studies (Boisgontier et
96 al., 2016; Jahanshahi, Obeso, Rothwell, & Obeso, 2015; Tricomi, Balleine, & O'Doherty,
97 2009), which has sparked a great deal of interest in exploration of these regions in disorders
98 of compulsivity.

99

100 Anomalies in the above mentioned basal ganglia circuitry are believed to play a key role in
101 the maintenance of AN (O'Hara et al., 2015). In preclinical studies, mice exhibiting activity-
102 based anorexia (ABA) show reduced metabolism in regions associated with reward-

103motivated learning, including the anterior parts of the caudate, NAcc, and putamen
104(Barbarich-Marsteller, Marsteller, Alexoff, Fowler, & Dewey, 2005; van Kuyck et al., 2007).
105Furthermore, ABA rats show greater resistance to extinction of food aversion than control
106rats (Liang, Bello, & Moran, 2011). Similarly, human studies have documented reduced
107regional blood flow and metabolism in the caudate in people with acute AN compared to
108healthy comparison individuals (Gaudio, Wiemerslage, Brooks, & Schiöth, 2016; Phillipou,
109Rossell, & Castle, 2014) while weight restored AN participants show reduced regional blood
110flow in the posterior putamen (Kojima et al., 2005). Furthermore, studies investigating
111structural differences in these regions have documented grey matter reduction in the
112caudate, NAcc, and putamen in acute AN (Friederich et al., 2012; Phillipou et al., 2018;
113Titova, Hjorth, Schiöth, & Brooks, 2013). A few studies have also investigated structural
114anomalies in weight restored AN participants and have found reduced globus pallidus
115volume and increased grey matter volume in the putamen, NAcc, and caudate (Bernardoni
116et al., 2016; Friederich et al., 2012). Taken together, these findings appear to mirror to a
117degree the preclinical findings detailed above and lend support to the notion that eating
118disorder related behaviours in AN may be habitual and compulsive, and are pursued despite
119negative consequences.

120

121To our knowledge no studies to date have examined differences in the subcortical shape of
122the above mentioned basal ganglia circuitry in people with AN. While volumetric analysis
123can provide information about the overall size of a subcortical structure, vertex-wise shape-
124based analyses can detect alterations in the shape of subcortical structures and provides
125more information about regional anomalies in subcortical grey matter (Patenaude, Smith,
126Kennedy, & Jenkinson, 2011). Moreover, relative to other regional methods such as voxel-

127wise morphometry (VBM), vertex analysis provides more localised information about the
128geometric shape of the structure that is not sensitive to tissue-type segmentation or
129differences in prior smoothing (Patenaude et al., 2011). Therefore, examination of the shape
130of the basal ganglia circuitry in AN may be of interest. Indeed, a few recent studies have
131reported inward deformations in the shape of the caudate, NAcc, and anterior putamen
132and outward deformations in the posterior putamen and globus pallidus in disorders of
133compulsivity, including addiction, obsessive compulsive disorder (OCD), and trichotillomania
134(Choi et al., 2007; Garza-Villarreal et al., 2017; Isobe et al., 2018).

135

136The aim of the present study was to explore the morphometry of basal ganglia regions
137including the bilateral caudate, putamen, globus pallidus, and NAcc in light of the reward-
138centred model of AN (O'Hara et al., 2015). In addition to volumetric analysis we examined
139differences between people with AN and healthy individuals in the shape of these regions.
140To examine the volume and shape of these structures and increase statistical power,
141anatomical neuroimaging data was combined from two studies (Fonville, Giampietro,
142Williams, Simmons, & Tchanturia, 2014; Leppanen et al., 2017a). Based on previous
143structural findings outlined above, we hypothesised that people with AN would show
144generally reduced volume of the caudate, NAcc, and putamen. We also hypothesised that
145participants with AN would have inward deformations in the shape of these regions that
146could provide further information about more localised atrophy. Based on the preclinical
147findings and vertex-wise shape findings from other disorders of compulsivity, we also
148hypothesised that people with AN may show greater outward deformation in regions
149associated with habitual responding, namely the posterior putamen and globus pallidus.
150Within the AN sample, we also conducted additional exploratory analyses to examine

151 correlations between eating disorder characteristics, including body mass index (BMI),
152 eating disorder psychopathology, and duration of illness, on subcortical volumes and
153 shapes.

154

1552 Materials and methods

1562.1 Participants

157The present study combined data from two previous studies (Fonville et al., 2014; Leppanen
158et al., 2017a) conducted between 2011 and 2014. After removing repeat scans from 12
159participants who had taken part in both studies, the combined sample consisted of 118
160unique adult female participants over the age of 18, which included 56 participants with
161current DSM-IV diagnosis of AN (amenorrhea not required) and 62 healthy comparison (HC)
162participants. Fifteen participants were excluded due to either substantial missing data or
163left-handedness. Another three AN participants were excluded for having BMI over 18.5 as
164there was uncertainty regarding whether these participants were weight restored or long-
165term recovered at the time. The final sample consisted of 100 right handed women. Forty-
166six participants had current diagnosis of AN, which was confirmed using the Structured
167Clinical interview for Diagnosis – Researcher version (First, Williams, Karg, & Spitzer, 2015).
168The AN participants were recruited from the South London and Maudsley specialist eating
169disorders service and through online advertisements (BEAT eating disorders charity).
170Twenty-three AN participants reported taking psychotropic medication during the time of
171the studies. Further information about the type of psychotropic medication the participants
172were taking was only collected as part of one of the studies and was available for 13 of the
173medicated AN participants (Supplementary Table 1). Fifty-four participants formed an age-
174matched HC group with no current or history of psychiatric disorders, which was confirmed
175using the SCID-R. The HC participants were recruited from the local community and King's
176College London students and staff.

178Participants were excluded if they reported acute suicidality, current or history of drug or
179alcohol misuse/abuse, any neurological disorders, or head trauma. Additionally, participants
180were excluded if they reported any MRI incompatibility, including pregnancy, any
181irremovable metal in or on the body, or claustrophobia. Prior to taking part all participants
182gave written informed consent and the two studies were approved by National Research
183Ethics Committees (11-LO-0952, 11/LO/0373). Both studies had prior ethical approval to use
184data later for further analysis. All research activities were conducted in accordance with the
185latest version of the Declaration of Helsinki (2013).

186

1872.2 Procedure

188The procedures in both studies were similar. In both studies all participants came to the
189King's College London Centre for Neuroimaging Sciences to undergo magnetic resonance
190imaging (MRI). Prior to the MRI, participants' height and weight were measured to calculate
191body mass index (BMI). Twenty-six women with current DSM-5 diagnosis of AN and 31 HC
192women took part in Study 1 between the years 2011 and 2014. In Study 1, the MRI session
193included a high resolution anatomical scan followed by three tasks which included two
194implicit facial emotion tasks reported elsewhere (Leppanen et al., 2017a, 2017b) and passive
195viewing of food and non-food images (Cardi, Leppanen, Mataix-Cols, Campbell, & Treasure,
1962018). Thirty-six women with current DSM-5 diagnosis of AN and 37 HC women took part in
197Study 2, which was conducted between the years 2011 and 2013. In Study 2, the MRI
198session included a high resolution anatomical scan followed by an implicit facial emotion
199task, embedded figures test, and the Wisconsin Card Sorting Test reported elsewhere
200(Fonville, Giampietro, Surguladze, Williams, & Tchanturia, 2014; Fonville et al., 2013; Lao-
201Kaim et al., 2015). Although a whole brain VBM examination using the data from Study 2 has

202been published (Fonville et al., 2014), the present study combined data from Study 2 with
203unpublished structural data from Study 1 and focused on vertex and volumetric analysis of
204specific, theory-driven regions of interest. Therefore, the present study should not
205constitute re-reporting published findings.

206

207As part of both studies participants were asked to complete self-report questionnaires
208providing their age and duration of illness (in years). Participants were also asked to
209complete the Eating Disorder Examination Questionnaire (EDEQ), a validated 36-item self-
210report assessment of eating disorder symptomatology over the past 28 days (Fairburn &
211Beglin, 1994), and a self-report questionnaire assessing current levels of anxiety and
212depression. The two studies used different questionnaires to assess anxiety and depression.
213In Study 1, participants were asked to complete the Depression, Anxiety and Stress Scale
214(DASS), which is a 21-item self-report measure assessing the level of depression, anxiety,
215and stress over the past 2 weeks (Lovibond & Lovibond, 1995). In Study 2, participants
216completed the Hospital Anxiety and Depression Scale (HADS), which is a 14-item self-report
217instrument assessing level of depression and anxiety over the past week (Zigmond & Snaith,
2181983). The internal consistency of the EDEQ (Cronbach's alpha = 0.96), DASS (Cronbach's
219alpha = 0.97), and HADS (Cronbach's alpha = 0.96) were high. To enable group comparisons
220across the two datasets, anxiety and depression subscales from the DASS and HADS were
221converted into z-scores. There was some missing data in the self-report measures in both
222studies: three AN participants did not report their exact age, 5 AN participant did not report
223their duration of illness, and one AN and one HC participant did not complete the EDEQ.

224

225Data from Study 1 and Study 2 will be henceforth be referred to as dataset 1 and dataset 2,
226respectively.

227

2282.3 Image acquisition

229Both studies used the same MRI scanner unit housed at the King's College London, Centre
230for Neuroimaging Sciences. The anatomical MRI was conducted with GE Signa 1.5T scanner
231unit (GE Medical Systems, Milwaukee, Wisconsin). Both studies used the same scanning
232parameters to acquire the T1-weighted anatomical magnetization-prepared rapid gradient-
233echo (MP-RAGE) images. The MP-RAGE images were acquired with 1.2 mm slice thickness,
2341.2 mm slice gap, 8° flip angle, 8.59 second repetition time, 3.8 second echo time, and voxel
235size of 1.2mmx1.2mmx1.2mm. Full brain coverage was achieved with 180 sagittal slices and
236an 8-channel headcoil was used to transmit and receive the signal.

237

2382.4 Statistical analysis

2392.4.1 Clinical and demographic data analysis

240All clinical and demographic data were analysed using R (R Core Team, 2018). Group
241differences in age, BMI, EDEQ, total score and anxiety and depression z-scores were
242examined using between-subjects t-tests. $P < 0.05$ was considered significant.

243

2442.4.2 Imaging data analysis

245All anatomical images were analysed with FSL (v5.0.11). The images were first preprocessed
246using *run_first_all*, which includes brain extraction, segmentation, formation of subcortical
247mesh and volumetric outputs, and boundary correction
248(<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide>). Following preprocessing, we used

249the *first_roi_slicesdir* function to generate summary images, which were visually inspected
250for segmentation errors by two authors (J.L. and F.S.), who were both blind to the diagnostic
251group each scan belonged to. Both authors inspected all summary images. Any images that
252showed evidence of poor segmentation according to either author were further assessed to
253find the cause of the segmentation error followed by re-running of the *run_first_all*
254function. The preprocessing and quality assessment procedures was repeated for four of the
255images due to segmentation errors that arose from coordinate mismatch.

256

257Information regarding volume (mm^3) of the subcortical regions of interest, namely the
258bilateral caudate, putamen, globus pallidus, and NAcc, were acquired using *fsstats*.
259Subcortical volumes were then entered into R (R Core Team, 2018) for statistical analysis.
260Group differences controlling for dataset were examined with multiple linear regressions
261(*lm*). Correlations between subcortical volumes and BMI, EDEQ total score, and duration of
262illness were explored. Prior to group comparisons and correlation analyses, differences in
263subcortical volume between the two datasets were examined. There were no significant
264differences between the two datasets (Supplementary Table 2). Thus, both datasets were
265analysed together. Still, dataset was entered as a discrete nuisance covariate in all vertex
266analyses, to ensure no group differences or correlations were present due to potential small
267differences between the two datasets. False Discovery Rate correction with $q = 0.05$ was
268used to adjust the p-threshold for multiple comparisons and $p < 0.003$ was considered
269significant.

270

271Vertex-wise subcortical shape analysis was conducted with FSL (v5.0.11) using *first_utils*
272(<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide>). Each participant's vertex-wise shape

273statistics are projected onto a group average surface and all meshes were reconstructed in
274Montreal Neurological Institute (MNI) space using rigid alignment transformation with 6
275degrees of freedom. Negative vertex-wise values indicate inward deformation in the shape
276of the subcortical structure, while positive values indicate outward deformation. Differences
277between the AN and HC groups were conducted using a non-parametric permutation test
278with 5000 permutations (*randomise*). Additional exploratory analyses were conducted
279examining correlations between vertex-wise values and BMI, eating disorder
280symptomatology, and duration of illness within the AN group. All results were corrected for
281multiple comparisons using the threshold-free cluster enhancement (TFCE) method (Smith
282& Nichols, 2009), which identifies clusters by enhancing voxels where the signal shows
283spatial contiguity. All p-values reported in the subcortical shape analysis section below are
284TFCE corrected p-values and $p < 0.05$ was considered significant. Prior to group comparisons
285and correlation analyses, differences in subcortical shape between the two datasets were
286examined. There were no significant differences between the two datasets in subcortical
287shape. Thus, both datasets were analysed together. Still, dataset was entered as a discrete
288nuisance covariate in all vertex analyses, to ensure no group differences or correlations
289were present due to potential small differences between the two datasets.

290

2913 Results

2923.1 Demographic and clinical characteristics

293 Demographic and clinical characteristics by group are presented in Table 1. The groups were
294 matched for age. As expected there was a significant difference in BMI, EDEQ total score,
295 anxiety z-score, and depression z-score such that the AN group had lower BMI and reported
296 more eating disorder symptomatology, anxiety, and depression than the HC group.

297

298 Table 1. Demographic and clinical characteristics

	AN	HC	
	M (SD)	M (SD)	t score, p-value
Age	27.51 (9.24)	26.35 (4.47)	t(58) = 0.76, p = 0.453
EDEQ Total	4.01 (1.01)	0.54 (0.51)	t(62) = 20.79, p < 0.001
Anxiety z-score	0.90 (0.67)	-0.77 (0.39)	t(69) = 14.88, p < 0.001
Depression z-score	0.85 (0.83)	-0.73 (0.31)	t(56) = 12.18, p < 0.001
BMI	15.73 (1.41)	21.49 (1.97)	t(95) = -16.96, p < 0.001
Duration of illness	11.39 (9.22)	N/A	N/A

(years)

299 AN = anorexia nervosa, HC = healthy comparison, EDEQ = Eating Disorder Examination
300 Questionnaire, BMI = body mass index, M = mean, SD = standard deviation, N/A = not
301 applicable

302

3033.2 Subcortical volume

3043.2.1 Differences between AN and HC groups

305 Subcortical volumes by group are presented in Table 2. Following correction for multiple
306 comparisons, there were no significant differences between AN and HC group in subcortical
307 volume controlling for dataset. There was also no significant difference between the two
308 datasets across groups.

310Table 2. Subcortical volume by group

Hemispher		AN	HC	t score, p value
e left	Volume	M (SD)	M (SD)	
	Caudate	3595.82 (368.18)	3668.41 (347.67)	Group: t(97) = 0.98, p = 0.330 Dataset: t(97) = -1.83, p = 0.071
	Putamen	4383.92 (443.59)	4437.08 (534.02)	Group: t(97) = 0.53, p = 0.597 Dataset: t(97) = -0.08, p = 0.935
	Globus	1322.97 (166.51)	1374.80 (173.03)	Group: t(97) = 1.50, p = 0.138 Dataset: t(97) = -0.77, p = 0.442
	pallidus	577.37 (84.95)	589.00 (124.63)	Group: t(97) = 0.52, p = 0.603 Dataset: t(97) = -0.45, p = 0.653
	NAcc	3620.95 (411.63)	3693.41 (336.76)	Group: t(97) = 0.93, p = 0.353 Dataset: t(97) = -1.93, p = 0.057
	Caudate	4204.35 (452.18)	4270.18 (523.61)	Group: t(97) = 0.67, p = 0.507 Dataset: t(97) = 0.12, p = 0.907
	Putamen	1458.66 (171.20)	1432.12 (171.36)	Group: t(97) = -0.79, p = 0.432 Dataset: t(97) = -0.78, p = 0.438
	Globus	486.46 (72.42)	524.30 (113.30)	Group: t(97) = 1.96, p = 0.053 Dataset: t(97) = 0.56, p = 0.577
	NAcc			
Right	Caudate	3620.95 (411.63)	3693.41 (336.76)	Group: t(97) = 0.93, p = 0.353 Dataset: t(97) = -1.93, p = 0.057
	Putamen	4204.35 (452.18)	4270.18 (523.61)	Group: t(97) = 0.67, p = 0.507 Dataset: t(97) = 0.12, p = 0.907
	Globus	1458.66 (171.20)	1432.12 (171.36)	Group: t(97) = -0.79, p = 0.432 Dataset: t(97) = -0.78, p = 0.438
	pallidus	486.46 (72.42)	524.30 (113.30)	Group: t(97) = 1.96, p = 0.053 Dataset: t(97) = 0.56, p = 0.577
	NAcc			

311AN = anorexia nervosa, HC = healthy comparison, NAcc = Nucleus accumbens, M = mean, SD

312= standard deviation

313

314

315

316

317

318

3193.2.2 Correlations with clinical characteristics

320Correlations between BMI, EDEQ total score and duration of illness, and subcortical volumes
321are presented in Supplementary Table 3. Following correction for multiple comparisons,
322there were no significant correlations between eating disorder characteristics and
323subcortical volumes.

324

325

326

327

3283.3 Subcortical shape

3293.3.1 Differences between AN and HC groups

330Group differences in subcortical shape controlling for dataset are presented in Table 3 and
331Figure 1. In the left hemisphere, the AN group had significantly smaller vertex indices in the
332caudate ($t = -4.44$, $p = 0.022$) and globus pallidus (C1: $t = -5.16$, $p = 0.001$; C2: $t = -4.97$, $p =$
3330.004) relative to the HC group. In the right hemisphere, the AN group had smaller vertex
334indices in the NAcc ($t = -3.52$, $p = 0.027$) and in the right globus pallidus (C3: $t = -4.33$, $p =$
3350.025) relative to the HC group. The AN group also had significantly greater vertex indices in
336two clusters in the right globus pallidus (C1: $t = 3.63$, $p = 0.027$; C2: $t = 4.11$, $p = 0.013$)
337compared to the HC group.

338

339Table 3. Group differences in subcortical shape

Hemisphere	Structure	Index	Voxels	Peak MNI coordinates			Peak F score, TFCE corrected p-value
				X	Y	Z	value
e	e						

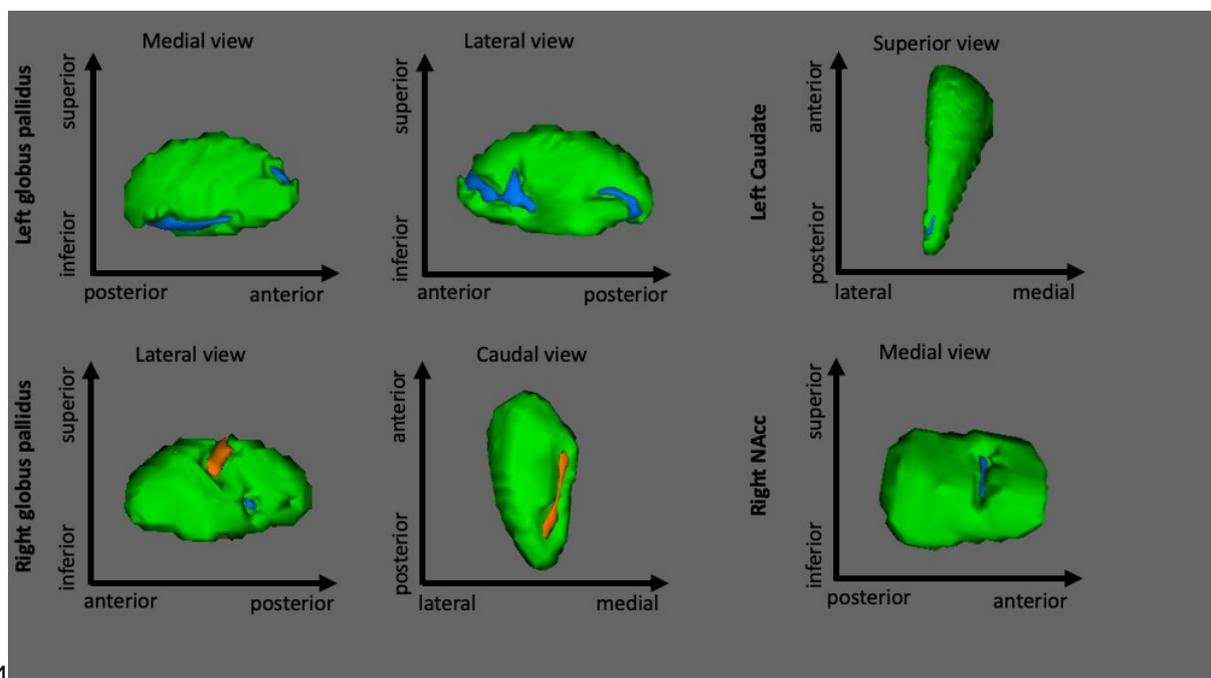
Left	Caudate	C1	16	-	-18	25	F = 9.85, p = 0.027
				19			
	Globus pallidus	C1	100	-	2	-6	F = 13.30, p = 0.001
				19			
		C2	67	-	-10	-3	F = 12.30, p = 0.003
				18			
Right	NAcc	C1	5	10	15	-4	F = 6.18, p = 0.041
	Globus pallidus	C1	27	17	-3	3	F = 8.46, p = 0.015
		C2	23	24	-11	-6	F = 6.33, p = 0.032
		C3	12	18	-8	-3	F = 9.37, p = 0.026

340TFCE = threshold-free cluster enhancement, NAcc = Nucleus accumbens, MNI = Montreal

341Neurological Institute

342

343Figure 1. Group differences in subcortical shape



344

345The blue clusters indicate smaller vertices in the AN group relative to the HC group and the

346orange colour indicated greater vertices in the AN group relative to the HC group. NAcc =

347Nucleus accumbens.

348

3493.3.2 Correlations with clinical characteristics

350There were no significant correlations between BMI, EDEQ total score, or duration of illness
351and vertex indices within the AN group. Within the HC group, there was a negative
352correlation between BMI and surface deformations in the anterior and lateral parts of the
353left putamen (Supplementary Table 4). There were no other significant correlations between
354vertex indices and BMI or EDEQ total score within the HC group.

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358

3594 Discussion

360The aim of the present study was to investigate differences in the volume and shape of basal
361ganglia structures hypothesised to play a key role in the maintenance of AN (O'Hara et al.,
3622015). Contrary to our hypotheses we did not find significant differences between AN and
363HC participants in left or right caudate, putamen, globus pallidus, or NAcc volume. However,
364as hypothesised, there was evidence of localised anomalies in the shape of the left caudate,
365bilateral globus pallidus and right NAcc in the AN group. In our exploratory correlation
366analyses we did not find any significant correlations between subcortical volume or shape
367and eating disorder characteristics.

368

369The present findings partly support and partly contradict our hypotheses showing inward
370deformations in the left caudate body and right NAcc, but also in the left ventral and
371internus globus pallidus, and right internus globus pallidus. These findings appear to suggest
372that the globus pallidus is a complex structure and may facilitate many function, not only
373habitual, rigid stimulus-response actions. Similar inward deformations in the left caudate
374body and right NAcc have been found in trichotillomania and crack cocaine addiction (Garza-
375Villarreal et al., 2017; Isobe et al., 2018). Such inward deformation of the striatum have
376been suggested as being linked to reward evaluation and reward-motivated decision
377making, possibly suggesting that such weighing of behaviour and outcome may disrupted in
378disorders of compulsion. Moreover, pathways linking the striatum to the ventral globus
379pallidus have been proposed to play a role in controlling behaviour (Aouizerate et al., 2004;
380Gillan et al., 2015; Narayanaswamy, Jose, Kalmady, Venkatasubramanian, & Reddy, 2013).
381Functional anomalies in this striato-pallidal pathway have been suggested to underlie

382repetitive, pathological behaviours in OCD (Aouizerate et al., 2004; Beucke et al., 2013). It
383has been suggested that this pathway fails to signal for the end of a behavioural routine,
384leading to a pathological loop which maintains the compulsive disorder-related behaviour
385(Aouizerate et al., 2004). As compulsivity is feature that has been linked to both OCD and AN
386(Montigny et al., 2013) and strong genetic correlation has recently been reported between
387AN and OCD (Watson et al., 2019), similar striato-pallidal functional anomalies may be
388present in AN. Thus, further investigation of potential anomalies in the functional and
389structural pathways that link these regions as well as the role they may play in the
390maintenance of eating disorder behaviours may be of interest.

391

392As hypothesised the present study revealed evidence of outward deformations in the
393middle and posterior internus globus pallidus in the AN participants. Similar outward
394deformations as well as increased grey matter in the middle and posterior internus globus
395pallidus have been documented in OCD (Shaw et al., 2015; Zarei et al., 2011). Furthermore,
396atypical increased activation in the globus pallidus and connected regions in the striatum,
397thalamus, and frontal cortex have also been reported to be linked to compulsive behaviours
398in OCD (Rotge et al., 2008). These findings appear to fit well with preclinical findings
399reporting that the posterior parts of the globus pallidus has a key role supporting and
400facilitating habitual, rigid behaviours (Agustín-Pavón et al., 2014; McFarland & Kalivas, 2001;
401Saga et al., 2016; Sommer et al., 2014). Therefore, further investigation of the functional
402connectivity of the posterior globus pallidus and its role in illness maintenance in AN would
403be of interest.

404

405 Our exploratory correlation analyses did not reveal any significant relationships between
406 basal ganglia volumes or shapes and eating disorder characteristics. Some previous studies
407 have reported significant relationships global grey matter and BMI in people with AN as well
408 as between BMI and grey matter increase following weight restoration in AN (Mainz,
409 Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Mühlau et al., 2007). However,
410 many previous studies have also failed to find significant correlation between brain structure
411 and self-reported clinical variables among people with AN (Boghi et al., 2011; Brooks et al.,
412 2011; Frank, Shott, Hagman, & Mittal, 2013; Mühlau et al., 2007; Suchan et al., 2010),
413 possibly highlighting the difficulty of using self-report measures. Future studies may benefit
414 from conducting longitudinal examinations to clarify the potential role of structural and
415 functional anomalies in these regions have perpetuating the illness.

416

417 4.1 Limitations

418 The present study is not without limitations. Firstly, we did not have a behavioural measure
419 to assess reward processing, learning, habit formation, or compulsivity. The use of such
420 measures would be necessary to confirm that the present basal ganglia deformations are
421 linked to reward learning and compulsivity. Therefore, future studies may benefit from
422 incorporating such behavioural measures and neuroimaging to further explore this potential
423 link in AN as well as its role in illness maintenance or recovery in a longitudinal setting.

424

425 The present study investigated the volume and shape basal ganglia regions, but not their
426 connections. Therefore, it is difficult to ascertain how the shape anomalies found may be
427 linked to each other. Future studies may benefit from further exploring structural
428 connections and pathways between these regions. A few studies have begun to investigate

429structural pathways in AN using diffusion tensor imaging (DTI) and have reported anomalies
430in white matter track in a number of regions including the corpus callosum and cingulum,
431but findings are still somewhat mixed (King, Frank, Thompson, & Ehrlich, 2018). Thus,
432further examination of the basal ganglia regions hypothesised to play a role in the
433maintenance of AN using DTI techniques may be of interest.

434

435It is also of importance to note that structural differences do not necessarily indicate that
436there are any functional differences. Indeed, several studies that have investigated both
437brain structure and function have reported structural group differences in regions that have
438shown no functional group differences (Anurova, Renier, De Volder, Carlson, & Rauschecker,
4392015; Pereira et al., 2018; Tavor et al., 2016). One study found that less than 3% of the
440maximum voxels in voxel-based morphometry analysis matched those from a resting-state
441functional connectivity analysis (Pereira et al., 2018). Furthermore, studies attempting to
442map functional and structural connectivity studies investigating correlations between
443structural and functional MRI have found that although there are some links between
444resting state functional connectivity and structural pathways, direct functional connectivity
445has also been found between regions that show no direct structural connectivity
446(Damoiseaux & Greicius, 2009; Honey et al., 2009). Therefore, before firm conclusion
447regarding the role of basal ganglia regions in the maintenance of eating disorder behaviours
448in AN are drawn the function of these regions in relation to illness related variables should
449be examined.

450

451Although many recent studies have used a 3.0T MRI scanner unit, the present study used
452data acquired with a 1.5T MRI unit. The increased field strength of a 3.0T MRI unit has been

453suggested to improve signal-to-noise ratio leading to higher quality anatomical images
454(Takahashi, Uematsu, & Hatabu, 2003). A few studies comparison 1.5T and 3.0T MRI scanner
455units have reported that the 3.0T unit has greater sensitivity, particularly in detecting small
456scale structural anomalies in neurological disorders such as multiple sclerosis and
457Alzheimer's disease (Chow et al., 2015; Stankiewicz et al., 2011). 3.0T MR images have also
458been found to provide more clinically relevant information than images acquired using a
4591.5T MRI unit during pre-surgical review (Bingaman et al., 2004). However, a recent
460systematic review reported that the 1.5T and 3.0T units were equivalent and although
461differences were found they were largely too divergent to conclude that one was superior to
462the other (Wardlaw et al., 2012). This finding could explained by findings that improved
463signal-to-noise ratio at higher field strength may be offset by failure to take other
464differences into consideration such as increased T1 relaxation time (Takahashi et al., 2003).
465Thus, although using data acquired with a lower field strength MRI unit may have affected
466the present findings, the extent of the effect is unclear.

467

468It is uncertain to what extent and how the use of psychotropic medication impacted the
469present findings. A systematic review found that psychotropic treatment was associated
470with both structural and functional changes in a number of brain regions including the basal
471ganglia, in bipolar disorder, schizophrenia, and attention deficit with hyperactivity disorder,
472which in turn were associated with symptom improvement (Singh & Chang, 2012). In the
473present study we were unable to examine the impact of medication on basal ganglia volume
474and shape. Information regarding the type of medication participants were taking when the
475images were acquired was only collected as part of one study. Additionally, when this
476information was available it was clear that many participants were taking many different

477types of medication, which likely introduced heterogeneity to any investigation of impact of
478medication of basal ganglia volume and shape. Furthermore, information regarding how
479long participants had been taking psychotropic medication was not collected as part of
480either study. Future studies may benefit from controlling for the types of medication
481participants are taking in order to examine the impact of psychotropic medication of basal
482ganglia volume and shape.

483

484Finally, as the present study was cross-sectional in nature it is not possible to ascertain to
485what extent the findings may be related to state of malnutrition in AN (Phillipou et al.,
4862018). Furthermore, duration of illness, information regarding psychotropic medication,
487and eating disorder symptomatology were assessed through self-report. Thus, these
488measures could have been affected by uncertainty regarding the exact onset of illness and
489lack of insight into the illness. Additionally, we did not have sufficient information to
490regarding AN subtype to investigate differences between restricting and binge/purge AN
491participants. Future studies may benefit from linking with clinicians to gain information
492about illness subtype and to corroborate self-report measures with clinician report.

4934.2 Conclusions

494 Reward-centred theoretical models postulate that anomalies in the basal ganglia circuitry
495 that underlies reward processing, learning, and habit formation have a key role in the
496 maintenance of AN. The aim of the present study was to investigate the volume and shape
497 of key basal ganglia regions including bilateral caudate, putamen, NAcc, and globus pallidus
498 in women with and without AN. The study combined data from two existing studies
499 resulting in a sample size of 46 women with AN and 56 HC women. There were no
500 significant differences between the groups in the volume of any of the regions of interest.
501 However, there were small, localised group differences in the shape of these regions. The
502 results revealed areas of inward deformations in the AN group relative to the HC group in
503 the left caudate, right NAcc, and bilateral globus pallidus. Additionally there were small
504 areas of outward deformation in the AN group relative to the HC group in the right globus
505 pallidus. These findings are in line with the reward-centred models of AN and future
506 research may benefit from further investigation of the role of these regions in reward
507 processing in AN as well as their potential role in the maintenance of the illness in long term
508 would be of interest.

509

510

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5125 References

- 513 Agustín-Pavón, C., Martínez-García, F., & Lanuza, E. (2014). Focal lesions within the ventral
514 striato-pallidum abolish attraction for male chemosignals in female mice. *Behavioural*
515 *Brain Research*, 259, 292–296. <https://doi.org/10.1016/J.BBR.2013.11.020>
- 516 American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental*
517 *disorders (DSM-5®)*. American Psychiatric Pub.
- 518 Anurova, I., Renier, L. A., De Volder, A. G., Carlson, S., & Rauschecker, J. P. (2015).
519 Relationship Between Cortical Thickness and Functional Activation in the Early Blind.
520 *Cerebral Cortex (New York, N.Y. : 1991)*, 25(8), 2035–2048.
521 <https://doi.org/10.1093/cercor/bhu009>
- 522 Aouizerate, B., Guehl, D., Cuny, E., Rougier, A., Bioulac, B., Tignol, J., & Burbaud, P. (2004).
523 Pathophysiology of obsessive–compulsive disorder: A necessary link between
524 phenomenology, neuropsychology, imagery and physiology. *Progress in Neurobiology*,
525 72(3), 195–221. <https://doi.org/10.1016/J.PNEUROBIO.2004.02.004>
- 526 Arcelus, J., Mitchell, A. J., Wales, J., & Nielsen, S. (2011). Mortality Rates in Patients With
527 Anorexia Nervosa and Other Eating Disorders. *Archives of General Psychiatry*, 68(7),
528 724. <https://doi.org/10.1001/archgenpsychiatry.2011.74>
- 529 Ashby, F. G., Turner, B. O., & Horvitz, J. C. (2010). Cortical and basal ganglia contributions to
530 habit learning and automaticity. *Trends in Cognitive Sciences*, 14(5), 208–215.
531 <https://doi.org/10.1016/J.TICS.2010.02.001>
- 532 Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The Role of the Dorsal Striatum in
533 Reward and Decision-Making. *Journal of Neuroscience*, 27(31), 8161–8165.
534 <https://doi.org/10.1523/JNEUROSCI.1554-07.2007>

535Barbarich-Marsteller, N. C., Marsteller, D. A., Alexoff, D. L., Fowler, J. S., & Dewey, S. L.
536 (2005). MicroPET imaging in an animal model of anorexia nervosa. *Synapse*, 57(2), 85–
537 90. <https://doi.org/10.1002/syn.20160>

538Bernardoni, F., King, J. A., Geisler, D., Stein, E., Jaite, C., Nätsch, D., ... Ehrlich, S. (2016).
539 Weight restoration therapy rapidly reverses cortical thinning in anorexia nervosa: A
540 longitudinal study. *NeuroImage*, 130, 214–222.
541 <https://doi.org/https://doi.org/10.1016/j.neuroimage.2016.02.003>

542Beucke, J. C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., ...
543 Kathmann, N. (2013). Abnormally High Degree Connectivity of the Orbitofrontal Cortex
544 in Obsessive-Compulsive Disorder. *JAMA Psychiatry*, 70(6), 619.
545 <https://doi.org/10.1001/jamapsychiatry.2013.173>

546Bingaman, W. E., Triantafyllou, C., Wald, L. L., Wiggins, G., Kirk, G. P., Larsson, P. G., ... Grant,
547 P. E. (2004). Surgery for focal cortical dysplasia. *Neurology*, 62(6 Suppl 3), S30-4.
548 <https://doi.org/10.1212/01.wnl.0000114508.31261.e6>

549Boghi, A., Sterpone, S., Sales, S., D'Agata, F., Bradac, G. B., Zullo, G., & Munno, D. (2011). In
550 vivo evidence of global and focal brain alterations in anorexia nervosa. *Psychiatry*
551 *Research: Neuroimaging*, 192(3), 154–159.
552 <https://doi.org/10.1016/J.PSYCHRESNS.2010.12.008>

553Boisgontier, M. P., van Ruitenbeek, P., Leunissen, I., Chalavi, S., Sunaert, S., Levin, O., &
554 Swinnen, S. P. (2016). Nucleus accumbens and caudate atrophy predicts longer action
555 selection times in young and old adults. *Human Brain Mapping*, 37(12), 4629–4639.
556 <https://doi.org/10.1002/hbm.23333>

557Brooks, S. J., Barker, G. J., O'Daly, O. G., Brammer, M., Williams, S. C., Benedict, C., ...
558 Campbell, I. C. (2011). Restraint of appetite and reduced regional brain volumes in

559 anorexia nervosa: a voxel-based morphometric study. *BMC Psychiatry*, 11(1), 179.
560 <https://doi.org/10.1186/1471-244X-11-179>

561Cardi, V., Leppanen, J., Mataix-Cols, D., Campbell, I. C., & Treasure, J. (2018). A case series to
562 investigate food-related fear learning and extinction using in vivo food exposure in
563 anorexia nervosa: A clinical application of the inhibitory learning framework. *European*
564 *Eating Disorders Review*. <https://doi.org/10.1002/erv.2639>

565Choi, J.-S., Kim, S. H., Yoo, S. Y., Kang, D.-H., Kim, C.-W., Lee, J.-M., ... Kwon, J. S. (2007).
566 Shape deformity of the corpus striatum in obsessive-compulsive disorder. *Psychiatry*
567 *Research: Neuroimaging*, 155(3), 257-264.
568 <https://doi.org/10.1016/J.PSYCHRESNS.2007.02.004>

569Chow, N., Hwang, K. S., Hurtz, S., Green, A. E., Somme, J. H., Thompson, P. M., ... Alzheimer's
570 Disease Neuroimaging Initiative. (2015). Comparing 3T and 1.5T MRI for mapping
571 hippocampal atrophy in the Alzheimer's Disease Neuroimaging Initiative. *AJNR*.
572 *American Journal of Neuroradiology*, 36(4), 653-660.
573 <https://doi.org/10.3174/ajnr.A4228>

574Crane, A. M., Roberts, M. E., & Treasure, J. (2007). Are obsessive-compulsive personality
575 traits associated with a poor outcome in anorexia nervosa? A systematic review of
576 randomized controlled trials and naturalistic outcome studies. *International Journal of*
577 *Eating Disorders*, 40(7), 581-588. <https://doi.org/10.1002/eat.20419>

578Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of
579 studies combining structural connectivity and resting-state functional connectivity.
580 *Brain Structure and Function*, 213(6), 525-533. [https://doi.org/10.1007/s00429-009-](https://doi.org/10.1007/s00429-009-0208-6)
581 0208-6

582Fairburn, C. G., & Beglin, S. J. (1994). Assessment of eating disorders: interview or self-report

583 questionnaire? *The International Journal of Eating Disorders*, 16(4), 363–370.

584 First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2015). *Structured Clinical Interview*
585 *for DSM-5, Research Version (SCID-5-RV)*. Arlington, VA: American Psychiatric
586 Association.

587 Fontenelle, L. F., Oostermeijer, S., Harrison, B. J., Pantelis, C., & Yücel, M. (2011). Obsessive-
588 Compulsive Disorder, Impulse Control Disorders and Drug Addiction. *Drugs*, 71(7), 827–
589 840. <https://doi.org/10.2165/11591790-000000000-00000>

590 Fonville, L., Giampietro, V., Williams, S. C. R., Simmons, A., & Tchanturia, K. (2014).
591 Alterations in brain structure in adults with anorexia nervosa and the impact of illness
592 duration. *Psychological Medicine*, 44(9), 1965–1975. [https://doi.org/DOI:](https://doi.org/DOI:10.1017/S0033291713002389)
593 [10.1017/S0033291713002389](https://doi.org/DOI:10.1017/S0033291713002389)

594 Fonville, Leon, Giampietro, V., Surguladze, S., Williams, S., & Tchanturia, K. (2014). Increased
595 BOLD signal in the fusiform gyrus during implicit emotion processing in anorexia
596 nervosa. *NeuroImage: Clinical*, 4, 266–273.

597 Fonville, Leon, Lao-Kaim, N. P., Giampietro, V., Van den Eynde, F., Davies, H., Lounes, N., ...
598 Tchanturia, K. (2013). Evaluation of Enhanced Attention to Local Detail in Anorexia
599 Nervosa Using the Embedded Figures Test; an fMRI Study. *PLOS ONE*, 8(5), e63964.
600 Retrieved from <https://doi.org/10.1371/journal.pone.0063964>

601 Frank, G. K., Shott, M. E., Hagman, J. O., & Mittal, V. A. (2013). Alterations in Brain Structures
602 Related to Taste Reward Circuitry in Ill and Recovered Anorexia Nervosa and in Bulimia
603 Nervosa. *American Journal of Psychiatry*, 170(10), 1152–1160. [https://doi.org/10.1176/](https://doi.org/10.1176/appi.ajp.2013.12101294)
604 [appi.ajp.2013.12101294](https://doi.org/10.1176/appi.ajp.2013.12101294)

605 Friederich, H.-C., Walther, S., Bendszus, M., Biller, A., Thomann, P., Zeigermann, S., ...
606 Herzog, W. (2012). Grey matter abnormalities within cortico-limbic-striatal circuits in

607 acute and weight-restored anorexia nervosa patients. *NeuroImage*, 59(2), 1106–1113.
608 <https://doi.org/10.1016/J.NEUROIMAGE.2011.09.042>

609 Garza-Villarreal, E. A., Chakravarty, M., Hansen, B., Eskildsen, S. F., Devenyi, G. A., Castillo-
610 Padilla, D., ... Gonzalez-Olvera, J. J. (2017). The effect of crack cocaine addiction and age
611 on the microstructure and morphology of the human striatum and thalamus using
612 shape analysis and fast diffusion kurtosis imaging. *Translational Psychiatry*, 7(5), e1122.
613 <https://doi.org/10.1038/tp.2017.92>

614 Gaudio, S., Wiemerslage, L., Brooks, S. J., & Schiöth, H. B. (2016). A systematic review of
615 resting-state functional-MRI studies in anorexia nervosa: Evidence for functional
616 connectivity impairment in cognitive control and visuospatial and body-signal
617 integration. *Neuroscience & Biobehavioral Reviews*, 71, 578–589.
618 <https://doi.org/10.1016/J.NEUBIOREV.2016.09.032>

619 Gillan, C. M., Apergis-Schoute, A. M., Morein-Zamir, S., Urcelay, G. P., Sule, A., Fineberg, N.
620 A., ... Robbins, T. W. (2015). Functional Neuroimaging of Avoidance Habits in Obsessive-
621 Compulsive Disorder. *American Journal of Psychiatry*, 172(3), 284–293. [https://doi.org/](https://doi.org/10.1176/appi.ajp.2014.14040525)
622 [10.1176/appi.ajp.2014.14040525](https://doi.org/10.1176/appi.ajp.2014.14040525)

623 Goto, Y., & Grace, A. A. (2005). Dopaminergic modulation of limbic and cortical drive of
624 nucleus accumbens in goal-directed behavior. *Nature Neuroscience*, 8(6), 805–812.
625 <https://doi.org/10.1038/nn1471>

626 Gruber, A. J., Hussain, R. J., & O'Donnell, P. (2009). The Nucleus Accumbens: A Switchboard
627 for Goal-Directed Behaviors. *PLoS ONE*, 4(4), e5062.
628 <https://doi.org/10.1371/journal.pone.0005062>

629 Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P.
630 (2009). Predicting human resting-state functional connectivity from structural

631 connectivity. *Proceedings of the National Academy of Sciences of the United States of*
632 *America*, 106(6), 2035–2040. <https://doi.org/10.1073/pnas.0811168106>

633Isobe, M., Redden, S. A., Keuthen, N. J., Stein, D. J., Lochner, C., Grant, J. E., & Chamberlain,
634 S. R. (2018). Striatal abnormalities in trichotillomania: A multi-site MRI analysis.
635 *NeuroImage: Clinical*, 17, 893–898. <https://doi.org/10.1016/J.NICL.2017.12.031>

636Izquierdo, A., & Jentsch, J. D. (2012). Reversal learning as a measure of impulsive and
637 compulsive behavior in addictions. *Psychopharmacology*, 219(2), 607–620.
638 <https://doi.org/10.1007/s00213-011-2579-7>

639Jahanshahi, M., Obeso, I., Rothwell, J. C., & Obeso, J. A. (2015). A fronto–striato–
640 subthalamic–pallidal network for goal-directed and habitual inhibition. *Nature Reviews*
641 *Neuroscience*, 16(12), 719–732. <https://doi.org/10.1038/nrn4038>

642Kaye, W. H., Frank, G. K., Bailer, U. F., & Henry, S. E. (2005). Neurobiology of anorexia
643 nervosa: Clinical implications of alterations of the function of serotonin and other
644 neuronal systems. *International Journal of Eating Disorders*, 37(S1), S15–S19.
645 <https://doi.org/10.1002/eat.20109>

646Kaye, W. H., Fudge, J. L., & Paulus, M. (2009). New insights into symptoms and neurocircuit
647 function of anorexia nervosa. *Nature Reviews Neuroscience*, 10(8), 573–584.
648 <https://doi.org/10.1038/nrn2682>

649Keating, C., Tilbrook, A. J., Rossell, S. L., Enticott, P. G., & Fitzgerald, P. B. (2012). Reward
650 processing in anorexia nervosa. *Neuropsychologia*, 50(5), 567–575.
651 <https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2012.01.036>

652King, J. A., Frank, G. K. W., Thompson, P. M., & Ehrlich, S. (2018). Structural Neuroimaging of
653 Anorexia Nervosa: Future Directions in the Quest for Mechanisms Underlying Dynamic
654 Alterations. *Biological Psychiatry*, 83(3), 224–234.

655 <https://doi.org/https://doi.org/10.1016/j.biopsych.2017.08.011>

656Kojima, S., Nagai, N., Nakabeppu, Y., Muranaga, T., Deguchi, D., Nakajo, M., ... Naruo, T.
657 (2005). Comparison of regional cerebral blood flow in patients with anorexia nervosa
658 before and after weight gain. *Psychiatry Research: Neuroimaging*, 140(3), 251–258.
659 <https://doi.org/10.1016/J.PSCYCHRESNS.2005.08.002>

660Lao-Kaim, N. P., Fonville, L., Giampietro, V. P., Williams, S. C. R., Simmons, A., & Tchanturia,
661 K. (2015). Aberrant Function of Learning and Cognitive Control Networks Underlie
662 Inefficient Cognitive Flexibility in Anorexia Nervosa: A Cross-Sectional fMRI Study. *PLOS*
663 *ONE*, 10(5), e0124027. Retrieved from <https://doi.org/10.1371/journal.pone.0124027>

664Leppanen, J., Cardi, V., Paloyelis, Y., Simmons, A., Tchanturia, K., & Treasure, J. (2017a).
665 Blunted neural response to implicit negative facial affect in anorexia nervosa. *Biological*
666 *Psychology*, 128. <https://doi.org/10.1016/j.biopsycho.2017.07.010>

667Leppanen, J., Cardi, V., Paloyelis, Y., Simmons, A., Tchanturia, K., & Treasure, J. (2017b).
668 fMRI study of neural responses to implicit infant emotion in anorexia nervosa.
669 *Frontiers in Psychology*, 8(MAY). <https://doi.org/10.3389/fpsyg.2017.00780>

670Liang, N.-C., Bello, N. T., & Moran, T. H. (2011). Experience with activity based anorexia
671 enhances conditioned taste aversion learning in rats. *Physiology & Behavior*, 102(1),
672 51–57. <https://doi.org/10.1016/J.PHYSBEH.2010.10.004>

673Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states:
674 comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression
675 and Anxiety Inventories. *Behaviour Research and Therapy*, 33(3), 335–343. Retrieved
676 from <http://www.ncbi.nlm.nih.gov/pubmed/7726811>

677Lubman, D. I., Yücel, M., & Pantelis, C. (2004). Addiction, a condition of compulsive
678 behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation.

679 *Addiction*, 99(12), 1491–1502. <https://doi.org/10.1111/j.1360-0443.2004.00808.x>

680 Mainz, V., Schulte-Rüther, M., Fink, G. R., Herpertz-Dahlmann, B., & Konrad, K. (2012).
681 Structural Brain Abnormalities in Adolescent Anorexia Nervosa Before and After Weight
682 Recovery and Associated Hormonal Changes. *Psychosomatic Medicine*, 74(6), 574–582.
683 <https://doi.org/10.1097/PSY.0b013e31824ef10e>

684 McFarland, K., & Kalivas, P. W. (2001). The circuitry mediating cocaine-induced
685 reinstatement of drug-seeking behavior. *The Journal of Neuroscience : The Official*
686 *Journal of the Society for Neuroscience*, 21(21), 8655–8663. Retrieved from
687 <http://www.ncbi.nlm.nih.gov/pubmed/11606653>

688 Montigny, C., Castellanos-Ryan, N., Whelan, R., Banaschewski, T., Barker, G. J., Büchel, C., ...
689 IMAGEN Consortium (2013). A phenotypic structure and neural correlates of
690 compulsive behaviors in adolescents. *PloS one*, 8(11), e80151.
691 doi:10.1371/journal.pone.0080151

692 Mühlau, M., Gaser, C., Ilg, R., Conrad, B., Leibl, C., Cebulla, M. H., ... Nunnemann, S. (2007).
693 Gray Matter Decrease of the Anterior Cingulate Cortex in Anorexia Nervosa. *American*
694 *Journal of Psychiatry*, 164(12), 1850–1857.
695 <https://doi.org/10.1176/appi.ajp.2007.06111861>

696 Narayanaswamy, J. C., Jose, D., Kalmady, S., Venkatasubramanian, G., & Reddy, Y. J. (2013).
697 Clinical correlates of nucleus accumbens volume in drug-naïve, adult patients with
698 obsessive-compulsive disorder. *Australian & New Zealand Journal of Psychiatry*,
699 47(10), 930–937. <https://doi.org/10.1177/0004867413491153>

700 O'Hara, C. B., Campbell, I. C., & Schmidt, U. (2015). A reward-centred model of anorexia
701 nervosa: A focussed narrative review of the neurological and psychophysiological
702 literature. *Neuroscience & Biobehavioral Reviews*, 52, 131–152.

703 <https://doi.org/10.1016/J.NEUBIOREV.2015.02.012>

704 Papadopoulos, F. C., Ekblom, A., Brandt, L., & Ekselius, L. (2009). Excess mortality, causes of
705 death and prognostic factors in anorexia nervosa. *British Journal of Psychiatry*, *194*(01),
706 10–17. <https://doi.org/10.1192/bjp.bp.108.054742>

707 Patenaude, B., Smith, S. M., Kennedy, D. N., & Jenkinson, M. (2011). A Bayesian model of
708 shape and appearance for subcortical brain segmentation. *NeuroImage*, *56*(3), 907–
709 922. Retrieved from
710 <https://www.sciencedirect.com/science/article/pii/S1053811911002023>

711 Pereira, A. M., Campos, B. M., Coan, A. C., Pegoraro, L. F., de Rezende, T. J. R., Obeso, I., ...
712 Cendes, F. (2018). Differences in Cortical Structure and Functional MRI Connectivity in
713 High Functioning Autism. *Frontiers in Neurology*, *9*, 539.
714 <https://doi.org/10.3389/fneur.2018.00539>

715 Phillipou, A., Rossell, S. L., & Castle, D. J. (2014). The neurobiology of anorexia nervosa: A
716 systematic review. *Australian & New Zealand Journal of Psychiatry*, *48*(2), 128–152.
717 <https://doi.org/10.1177/0004867413509693>

718 Phillipou, A., Rossell, S. L., Gurvich, C., Castle, D. J., Abel, L. A., Nibbs, R. G., & Hughes, M. E.
719 (2018). Differences in regional grey matter volumes in currently ill patients with
720 anorexia nervosa. *European Journal of Neuroscience*, *47*(2), 177–183.
721 <https://doi.org/10.1111/ejn.13793>

722 R Core Team. (2018). R: A Language and Environment for Statistical Computing. Vienna,
723 Austria. Retrieved from <https://www.r-project.org/>

724 Rotge, J.-Y., Guehl, D., Dilharreguy, B., Cuny, E., Tignol, J., Bioulac, B., ... Aouizerate, B.
725 (2008). Provocation of obsessive-compulsive symptoms: a quantitative voxel-based
726 meta-analysis of functional neuroimaging studies. *Journal of Psychiatry &*

727 *Neuroscience : JPN*, 33(5), 405–412. Retrieved from
728 <http://www.ncbi.nlm.nih.gov/pubmed/18787662>

729 Saga, Y., Richard, A., Sgambato-Faure, V., Hoshi, E., Tobler, P. N., & Tremblay, L. (2016).
730 Ventral Pallidum Encodes Contextual Information and Controls Aversive Behaviors.
731 *Cerebral Cortex*, 27(4), bhw107. <https://doi.org/10.1093/cercor/bhw107>

732 Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of
733 nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology*,
734 191(3), 461–482. <https://doi.org/10.1007/s00213-006-0668-9>

735 Schultz, W. (2016). Reward functions of the basal ganglia. *Journal of Neural Transmission*,
736 123(7), 679–693. <https://doi.org/10.1007/s00702-016-1510-0>

737 Serpell, L., Livingstone, A., Neiderman, M., & Lask, B. (2002). Anorexia nervosa: Obsessive–
738 compulsive disorder, obsessive–compulsive personality disorder, or neither? *Clinical*
739 *Psychology Review*, 22(5), 647–669. [https://doi.org/10.1016/S0272-7358\(01\)00112-X](https://doi.org/10.1016/S0272-7358(01)00112-X)

740 Shaw, P., Sharp, W., Sudre, G., Wharton, A., Greenstein, D., Raznahan, A., ... Rapoport, J.
741 (2015). Subcortical and cortical morphological anomalies as an endophenotype in
742 obsessive-compulsive disorder. *Molecular Psychiatry*, 20(2), 224–231.
743 <https://doi.org/10.1038/mp.2014.3>

744 Singh, M. K., & Chang, K. D. (2012). The neural effects of psychotropic medications in
745 children and adolescents. *Child and Adolescent Psychiatric Clinics of North America*,
746 21(4), 753–771. <https://doi.org/10.1016/j.chc.2012.07.010>

747 Smith, S., & Nichols, T. (2009). Threshold-free cluster enhancement: Addressing problems of
748 smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*,
749 44(1), 83–98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>

750 Sommer, W. H., Costa, R. M., & Hansson, A. C. (2014). Dopamine systems adaptation during

751 acquisition and consolidation of a skill. *Frontiers in Integrative Neuroscience*, 8, 87.

752 <https://doi.org/10.3389/fnint.2014.00087>

753 Stankiewicz, J. M., Glanz, B. I., Healy, B. C., Arora, A., Neema, M., Benedict, R. H. B., ...

754 Bakshi, R. (2011). Brain MRI lesion load at 1.5T and 3T versus clinical status in multiple

755 sclerosis. *Journal of Neuroimaging : Official Journal of the American Society of*

756 *Neuroimaging*, 21(2), e50-6. <https://doi.org/10.1111/j.1552-6569.2009.00449.x>

757 Steinhausen, H.-C. (2002). The Outcome of Anorexia Nervosa in the 20th Century. *American*

758 *Journal of Psychiatry*, 159(8), 1284-1293. <https://doi.org/10.1176/appi.ajp.159.8.1284>

759 Steinhausen, H.-C. (2009). Outcome of Eating Disorders. *Child and Adolescent Psychiatric*

760 *Clinics of North America*, 18(1), 225-242. <https://doi.org/10.1016/J.CHC.2008.07.013>

761 Suchan, B., Busch, M., Schulte, D., Grönermeyer, D., Herpertz, S., & Vocks, S. (2010).

762 Reduction of gray matter density in the extrastriate body area in women with anorexia

763 nervosa. *Behavioural Brain Research*, 206(1), 63-67.

764 <https://doi.org/10.1016/J.BBR.2009.08.035>

765 Takahashi, M., Uematsu, H., & Hatabu, H. (2003). MR imaging at high magnetic fields.

766 *European Journal of Radiology*, 46(1), 45-52. [https://doi.org/10.1016/S0720-](https://doi.org/10.1016/S0720-048X(02)00331-5)

767 [048X\(02\)00331-5](https://doi.org/10.1016/S0720-048X(02)00331-5)

768 Tavor, I., Parker Jones, O., Mars, R. B., Smith, S. M., Behrens, T. E., & Jbabdi, S. (2016). Task-

769 free MRI predicts individual differences in brain activity during task performance.

770 *Science (New York, N.Y.)*, 352(6282), 216-220.

771 <https://doi.org/10.1126/science.aad8127>

772 Titova, O. E., Hjorth, O. C., Schiöth, H. B., & Brooks, S. J. (2013). Anorexia nervosa is linked to

773 reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM

774 studies. *BMC Psychiatry*, 13(1), 110. <https://doi.org/10.1186/1471-244X-13-110>

775Tricomi, E., Balleine, B. W., & O'Doherty, J. P. (2009). A specific role for posterior
776 dorsolateral striatum in human habit learning. *European Journal of Neuroscience*,
777 29(11), 2225–2232. <https://doi.org/10.1111/j.1460-9568.2009.06796.x>

778Trifilieff, P., Feng, B., Urizar, E., Winiger, V., Ward, R. D., Taylor, K. M., ... Javitch, J. A. (2013).
779 Increasing dopamine D2 receptor expression in the adult nucleus accumbens enhances
780 motivation. *Molecular Psychiatry*, 18(9), 1025–1033.
781 <https://doi.org/10.1038/mp.2013.57>

782van Kuyck, K., Casteels, C., Vermaelen, P., Bormans, G., Nuttin, B., & Van Laere, K. (2007).
783 Motor- and food-related metabolic cerebral changes in the activity-based rat model for
784 anorexia nervosa: A voxel-based microPET study. *NeuroImage*, 35(1), 214–221. [https://](https://doi.org/10.1016/J.NEUROIMAGE.2006.12.009)
785 doi.org/10.1016/J.NEUROIMAGE.2006.12.009

786Wardlaw, J. M., Brindle, W., Casado, A. M., Shuler, K., Henderson, M., Thomas, B., ... Group,
787 T. S. C. (2012). A systematic review of the utility of 1.5 versus 3 Tesla magnetic
788 resonance brain imaging in clinical practice and research. *European Radiology*, 22(11),
789 2295–2303. <https://doi.org/10.1007/s00330-012-2500-8>

790Watson, H. J., Yilmaz, Z., Thornton, L. M., Hübel, C., Coleman, J. R. I., Gaspar, H. A., ... Bulik,
791 C. M. (2019). Genome-wide association study identifies eight risk loci and implicates
792 metabo-psychiatric origins for anorexia nervosa. *Nature Genetics*, 1.
793 <https://doi.org/10.1038/s41588-019-0439-2>

794Yin, H. H., Ostlund, S. B., & Balleine, B. W. (2008). Reward-guided learning beyond dopamine
795 in the nucleus accumbens: the integrative functions of cortico-basal ganglia networks.
796 *European Journal of Neuroscience*, 28(8), 1437–1448. [https://doi.org/10.1111/j.1460-](https://doi.org/10.1111/j.1460-9568.2008.06422.x)
797 [9568.2008.06422.x](https://doi.org/10.1111/j.1460-9568.2008.06422.x)

798Zarei, M., Mataix-Cols, D., Heyman, I., Hough, M., Doherty, J., Burge, L., ... James, A. (2011).

799 Changes in Gray Matter Volume and White Matter Microstructure in Adolescents with

800 Obsessive-Compulsive Disorder. *Biological Psychiatry*, 70(11), 1083–1090.

801 <https://doi.org/10.1016/J.BIOPSYCH.2011.06.032>

802 Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta*

803 *Psychiatrica Scandinavica*, 67(6), 361–370. Retrieved from

804 <http://www.ncbi.nlm.nih.gov/pubmed/6880820>

805

806