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Damage to the dorsolateral prefrontal cortex is associated with repetitive compulsive behaviors in patients with penetrating brain injury

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ABSTRACT

Background Damage to cortico-striato-thalamo-cortical (CSTC) circuits is associated with the development of repetitive behaviours in animals and humans. However, the types of repetitive behaviours that are developed after injury to these structures are poorly defined. This study examines the effect of damage to separate elements of CSTC circuits sustained by veterans of the Vietnam War on obsessions, compulsions, and tics.

Methods We performed partial correlations (correcting for cognition, age, education, and global brain damage) between volume loss from traumatic brain injury in specific elements of CSTC circuits (lateral and medial orbitofrontal and dorsolateral prefrontal cortices, anterior cingulate cortex, thalamus, and basal ganglia) and scores on a modified version of the Yale-Brown Obsessive Compulsive Scale Symptom Checklist and the Yale Global Tic Severity Scale in 83 Vietnam war veterans with penetrating brain injuries at different sites throughout the brain.

Results We found that volume loss in the left dorsolateral prefrontal cortex was associated with the development of compulsive behaviours (r=0.32, padj<0.05) whereas volume loss in the basal ganglia was associated with the development of tics (r=0.33, padj<0.05).

Conclusion Our findings indicate that damage to specific CSTC elements can be associated with the development of compulsive behaviours and tics that are not necessarily accompanied by obsessions.

Key messages

What is already known on this topic

► Multiple studies have implicated a cortico-striato-thalamo-cortical (CSTC) circuit in obsessive-compulsive disorder and tics; however, the roles of individual circuit elements remain unclear. Human lesion studies have been used to establish many of our foundational theories about how different regions of the brain work but these studies have rarely been applied to psychiatric symptoms.

What this study adds

► In this study, we examine the relationship between lesions in particular brain regions and obsessions, compulsions, and tics by looking at a well-studied group of patients with penetrating traumatic brain injury, the Vietnam Head Injury Study cohort. We find that lesions in the left dorsolateral prefrontal cortex are associated with increased compulsions and lesions in the basal ganglia are associated with tics.

How this study might affect research, practice and/or policy

► This study suggests that damage to or dysfunction in certain CSTC circuit elements may be important in the development of compulsions and tics. This study may help in the development of novel targeted treatments to improve compulsions and or tics.

INTRODUCTION

The groundwork of our understanding of neurology and the human brain has been set by human lesion studies.[1 2] There has been less work exploring how psychiatric symptoms may relate to lesions in particular brain regions. This is despite the fact that neuropsychiatric symptoms are common after traumatic brain injury (TBI), especially penetrating TBI,[3] and psychiatric symptoms are difficult to model in animals, highlighting the importance of such work.

A number of studies in both humans and animals suggest that dysfunction in a cortico-striato-thalamo-cortical (CSTC) circuit including the dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus, and basal ganglia (BG) is involved in obsessive-compulsive disorder (OCD).[4] However, studies that have examined OCD patients to determine the contribution of regional brain dysfunction to OCD symptoms have had conflicting results.[5–7] Further complicating matters, some evidence suggests that this same circuitry may also be involved in the generation of tics in Tourette Syndrome.[8] Indeed, damage to regions of the frontal

cortex including the OFC and ACC have been associated with the development of multiple types of inappropriate repetitive behaviours in animals and humans.[9] A recent review of published case studies on the occurrence of tics after brain injury reported that tics and OCD symptoms co-occurred in 20% of cases and often involved injury to CSTC circuit elements including the BG.[10]

Movement disorders after brain injury, including compulsive repetitive behaviours and tics, are not uncommon and are reported in around 16%–33% of patients after severe head injury.[11] However, no study to our knowledge has attempted to correlate lesions of specific brain regions in a TBI cohort with specific OCD symptoms and tics. To evaluate the neural substrates of OCD symptoms and tics in patients with TBI, 83 patients with penetrating brain injuries to sites throughout the brain and 36 matched control subjects were examined using modified versions of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) Symptom Checklist to assess OCD symptoms and the Yale Global Tic Severity Scale (YGTSS) to assess for tics. Because some prior studies have found that OCD symptoms may be related to anxiety, we also assessed participants using the Hamilton Anxiety Rating Scale (HAM-A). We hypothesised that patients with TBI and damage to the CSTC circuit, including dlPFC, OFC, ACC, and BG, would have more obsessions, compulsions, and tics than patients with TBI without damage to the CSTC circuit.[12]

METHODS AND MATERIALS
Subjects
Subjects were seen as part of the W.F. Caveness Vietnam Head Injury Study (VHIS), a longitudinal study of brain-injured veterans.[13] Overall, 83 brain injured patients and 36 control subjects were studied longitudinally. The 83 patients with brain injury included patients with lesions throughout the brain. Therefore, some of the 83 patients had lesions in the CSTC circuit and some did not. Individuals included in the current analysis were enrolled in VHIS and completed imaging in phase 3 and underwent psychiatric assessment in phase 4 of the study as detailed below. The imaging data for the current study were taken from phase 3 conducted from 2004 to 2007, and the OCD and tic symptom scales were obtained during phase 4 conducted from 2009 to 2013 at the National Naval Medical Center in Bethesda, MD. The Y-BOCS Symptom Checklist,[14] the YGTSS Symptom Checklist,[15] and the HAM-A[16] in addition to extensive neuropsychological testing were obtained on the 83 subjects with TBI. The structured clinical interview for the Diagnostic and Statistical Manual of Mental Disorders-IV Axis I—Patient Edition (SCID-I/P)[17] had been previously administered during phase 3 to all subjects by a psychiatrist trained to administer the SCID. The control subjects had served in Vietnam during the same years as the head injured subjects, were of the same age, and had comparable combat exposure.[13] All subjects gave informed written consent and all procedures were approved by the appropriate IRB. See table 1 for overall subject characteristics for the control subjects and the TBI patients included in this study. Significance testing for table 1 used two-tailed student t-tests corrected for multiple comparisons using the two-stage step-up method of Benjamini, Krieer, and Yekutieli for controlling the false discovery rate (FDR (Q)=1%).

Measures and definition of terms
As part of the VHIS, all of the subjects were required to bring a family member who had known them before and after their service as an informant. The administration of the symptom questions from the Y-BOCS[14 18 19] and the YGTSS[15] were adapted in three ways: (1) they were completed by both the participant and the informant about the participant's symptoms, (2) symptom ratings were given on a 5-point Likert scale of frequency ranging from "never" to "all of the time or almost all of the time", (3) participants and informants were asked to assess symptoms before and after the brain injury. We used the informant report, rather than the participant, because brain lesions, especially frontal lesions, can impair recognition and self-report of symptoms.[20 21] Before and after Likert scale measurements were used to assess changes in frequency of obsessions, compulsions, and tics. Informants for patients with TBI were asked to evaluate these symptoms before and after the brain injury occurred in the participant. Informants for the control subjects, who did not have a brain injury, were asked to assess current symptoms vs symptoms 5 years ago. The HAM-A, a self-report anxiety measure, was also administered to the participants.[16] The Y-BOCS was designed to have separate questions to assess obsessions and compulsions,[18 19] and this division of symptoms in the Y-BOCS has been supported by factor analyses.[14] Therefore, in presenting the data we have separately scored obsessions, compulsions, and tics. The primary outcomes used for the analysis are the current HAM-A and the preinjury to postinjury changes in obsessions, compulsions and tics reported for patients with TBI. Control participants were not included in the analysis. Current obsession, compulsion and tic scores for both patients with TBI and controls are presented in table 1. Predifferences and post differences in obsessions, compulsions and tics are also reported in table 1 for controls and patients with TBI. For the purpose of this study, obsessions were defined as unwanted ideas, images or impulses that intrude on thinking against the patient's wishes and efforts to resist them. Compulsions were defined as ritualised activities, behaviours, or thought patterns done repetitively and intentionally, often with the purpose of relieving perceived discomfort. Tics were defined as rapid, repetitive, non-rhythmic movements or vocalisations that could either be simple (eg, eye blinking) or more complex (eg, echopraxia).

Imaging
All of the brain-injured subjects received an axial non-contrast CT during phase 3 on a GE Medical Systems Light

Table 1 Demographic and clinical characteristics of subjects

	Control	Patients with TBI	P value
N	36	83	
Age	59.11 (3.89)	58.13 (2.94)	0.182
Education	15.40 (2.43)	14.76 (2.34)	0.186
Race	White: n=34 (94.4%); black: n=2	White: n=77 (92.8%); black n=4 (4.8%); Asian: n=1 (1.2%); Amer Ind: n=1 (1.2%)	
Ethnicity	Non-hisp: n=34 (94.4%)	Non-hisp: n=78 (94.0%)	
MMSE Total	29.59 (.62)	28.33 (2.29)	0.00001*
WAIS FIQ	111.51 (11.69)	103.24 (14.80)	0.0016*
WAIS PIQ	110.43 (12.26)	100.93 (16.22)	0.00007*
WAIS VIQ	110.69 (11.32)	104.53 (14.82)	0.0154
AFQT before injury	71.21 (18.22)	63.68 (23.69)	0.063
AFQT after injury or after service	72.63 (19.32)	64.26 (26.10)	0.055
HAM-A total	4.09 (4.31)	2.72 (3.69)	0.102
BDI total	11.61 (9.97)	9.43 (9.03)	0.264
Obsessions	4.41 (5.12)	5.35 (5.13)	0.361
Compulsions	13.33 (8.65)	14.01 (9.17)	0.700
Tics	1.36 (2.38)	2.28 (2.45)	0.059
Mean diff obsessions	0.10 (0.32)	0.10 (0.21)	1.0
Mean diff compulsions	0.18 (0.55)	0.22 (0.39)	0.694
Mean diff tics	0.07 (0.18)	0.13 (0.18)	0.099

P Value=unadjusted p value, with significance indicated by * for false discovery rate corrected p<0.05.
Numbers are reported as means with SD in parentheses except for Race and Ethnicity where number of subjects is reported and percentage of patients is reported in parentheses. 'Obsessions', 'compulsions', and 'Tics' refer to the mean score on the Y-BOCS and YGTSS Symptom Checklists (see Methods section for details of the measures). 'Mean diff obsessions', 'mean diff compulsions', and 'mean diff tics' refer to the mean difference between precompulsion and post compulsion, obsession, and tic score respectively (see Methods section for details of the measures).
n, number of subjects; MMSE, Folstein Mini-Mental State Examination; WAIS, Wechsler Adult Intelligence Scale; VIQ, Verbal IQ score; PIQ, performance IQ score; FIQ, Full Scale IQ score; AFQT, Armed Forces Qualification Test; BDI, Beck Depression Inventory II total score; HAM-A, Hamilton Anxiety Scale Total score

Speed Plus CT scanner in helical mode (clinical reviews of the subjects' CT scans from phase 4 indicated no obvious change in lesion size nor additional pathology). CT was used because the majority of subjects had residual metallic fragments in their heads, precluding MRI. Images were reconstructed with an in-plane voxel size of 0.4 mm × 0.4 mm, overlapping slice thickness of 2.5 mm and 1 mm slice interval. Lesions were manually traced by one rater and consensus was obtained after being reviewed by another rater who was blind to the results of the clinical evaluations. Percentages of each Brodmann area (BA) damaged were determined using the Analysis of Brain Lesion (ABLe) software[22] (see Refs. 13 23 for more details).

Regions of interest (ROIs) were defined prior to the analysis as components of the CSTC circuit that have also been associated with the development of inappropriate repetitive behaviours in humans in previous functional imaging and lesion studies (see Ref. 12 for a review). They were the right and left lateral and medial OFC, dorsolateral prefrontal (dlPFC), ACC, thalamus and BG.

The 'lesion score' of the cortical regions were defined at the sum of the percentages lesioned of the following BAs: lateral OFC (BAs 12, 45, 47), medial OFC (BA 11), dlPFC (BAs 4, 6, 8, 9, 10, 46, 44) and ACC (BA 24). Due to difficulty determining laterality and percentage involvement of subcortical structures, the 'lesion score' for the thalamus was coded as damage not present (0) or damage present (1). Subjects with damage to the substantia nigra, caudate, putamen, or the globus pallidus were considered to have BG involvement. The BG score was calculated by summing the BG structures involved (0–4). Hence, for both the cortical and subcortical ROIs, a higher lesion score indicates more severe damage. We did not have patients with ventral striatal damage isolated from dorsal striatal damage and so the more general designation 'basal ganglia' was used. Patients with damage to more than one ROI were included in each analysis (eg, a patient with damage to the dlPFC and thalamus would be included in both partial correlations).

Statistical analysis relating site of lesion to obsessions, compulsions and tics

Partial correlations were performed between the lesion scores for each ROI and the preinjury to postinjury change in obsessions, compulsions and tics (as assessed on the Y-BOCS and YGTSS Symptom Checklists), and the total HAM-A using the R statistical environment. The partial correlations were corrected for the following confounders: age, years of education, total volume loss on the CT scan, and change in cognition from preinjury to post injury as determined by the total Armed Forces Qualification Test (AFQT) score at phase 3 minus the preinjury result. The AFQT composed of several subtests including assessments of mathematics and verbal ability that the subjects received prior to their injury on their entry into the military and after their injury during their participation in the VHIS study, allowed us to measure the change in cognition associated with the injury. Pearson correlation coefficients are reported, and two-tailed tests were used to assess their significance. Unadjusted p values are reported in the table, but significance tags (eg, stars) are applied based on p values adjusted using the Benjamini-Hochberg approach for controlling the FDR.

RESULTS

Patient demographics

Patients with and without TBI were matched for age, education, race, ethnicity and combat exposure. There were significant differences between control patients and patients with TBI on the Folstein Mini-Mental Status Examination (see table 1, MMSE, $p < 0.05$) and the Wechsler Adult Intelligence Scale (WAIS, $p < 0.05$ for full scale and performance scores) with control patients exhibiting better performance on the MMSE and WAIS. There were no significant differences in current anxiety, depression, obsessions, compulsions, or tics between controls and patients with TBI (table 1). Of the 36 control participants, 18 endorsed obsessions, 18 endorsed compulsions and 12 endorsed tics. Of the 83 patients with TBI, 59 endorsed

obsessions, 52 endorsed compulsions and 57 endorsed tics. One control subject and one patient with TBI had symptoms of OCD that met criteria for subthreshold OCD during their lifetime. No subjects met full criteria for OCD during their lifetime as measured by the SCID.

Lesion location and psychiatric symptoms

VHIS patients with TBI and brain damage at any site were included in the ROI analyses (n=83). Patients' preinjury to postinjury change in compulsions showed a significant association with lesion damage in the left dlPFC (r=0.32, $p_{adj} < 0.05$, table 2), with lesions in the left dlPFC associated with increased compulsions. The left lateral OFC also showed a moderate association with compulsions, but it was not significant after adjusting for multiple comparisons (r=0.27, p_{adj}=0.09). There was a significant association between patients' preinjury to postinjury change in tics and lesions in the BG (r=0.33, $p_{adj} < 0.05$) with lesions in the BG associated with increased tics. Regional damage to several other ROI showed moderate but non-significant associations with increases in tics, including the left lateral OFC (r=0.27, p_{adj}=0.07), right medial OFC (r=0.26, p=0.07), and left dlPFC (r=0.28, p=0.07, table 2). There were no ROI significantly correlated with changes in obsessions or current anxiety in our analysis (table 2).

DISCUSSION

The primary focus of this study was to examine whether lesions in certain elements of the CSTC circuit were associated with the development of OCD symptoms or tics in patients with TBI. Overall, we found that patients with TBI did not differ in the presence or severity of obsession, compulsions or tics compared with controls. Also, there were no significant differences in obsessions, compulsions or tics before and after brain injury in patients with TBI. Therefore, our findings suggest that general TBI is not specifically associated with the development of obsessions, compulsions or tics. However, when we examined whether damage to particular elements of the CSTC

Table 2 Partial Pearson correlations between regions of interest and measures

	Basal ganglia	Left lateral OFC	Right lateral OFC	Left medial OFC	Right medial OFC	Left dlPFC	Right dlLPFC	Thalamus	Left ACC	Right ACC
Compulsions	r=0.07, p=0.54	**r=0.27, p=0.019†**	r=−0.10, p=0.40	r=−0.01, p=0.90	r=0.10, p=0.40	**r=0.32, p=0.005***	r=−0.05, p=0.66	r=0.06, p=0.62	r=−0.07, p=0.52	r=−0.08, p=0.48
Obsessions	r=−0.06, p=0.60	r=0.13, p=0.26	r=−0.02, p=0.83	r=−0.12, p=0.30	r=−0.08, p=0.48	r=0.15, p=0.20	r=−0.09, p=0.42	r=0.01, p=0.92	r=−0.12, p=0.30	r=−0.10, p=0.38,
Tics	**r=0.33, p=0.004***	**r=0.27, p=0.020†**	r=0.01, p=0.96	r=0.15, p=0.21	**r=0.26, p=0.027†**	**r=0.28, p=0.017†**	r=0.08, p=0.48	r=0.10, p=0.38	r=0.09, p=0.45	r=−0.01, p=0.92
HAMA total score	r=0.12, p=0.31	r=0.12, p=0.31	r=−0.04, p=0.71	r=0.13, p=0.26	r=−0.04, p=0.74	r=0.09, p=0.46	r=−0.11, p=0.33	r=0.10, p=0.39	r=−0.05, p=0.68	r=−0.01, p=0.95

Uncorrected p values are shown, and those that remained significance after false discovery rate (FDR) correction are starred.
Controlled for age, total years of education, global brain volume loss, and Armed Forces Qualification Test (AFQT) change from preinjury to phase 3.
*FDR-corrected $p < 0.05$.
†FDR-corrected $p < 0.10$.
ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex.

circuit were associated with obsessions, compulsions or tics, we did find that damage to specific brain areas was associated with the development of compulsions and tics. Specifically, our results suggest that damage to the left dlPFC may be associated with the development of compulsive actions, behaviours, and thought patterns. Studies in the past have implicated the left and right dlPFC in OCD symptoms[24]; however, in this study, only left-sided lesions in dlPFC were associated with increased compulsions. While we do not have a simple explanation for this finding, a recent study suggested that the left dlPFC is important in context-dependent shifting of on-task and off-task thought.[25] Therefore, damage to the left dlPFC might be expected to decrease this shifting ability and may leave patients predisposed to enacting repetitive compulsive activities. Prior studies have shown that dysfunctional connectivity between dlPFC and putamen is associated with symptom severity in OCD.[26 27] The same study demonstrated that altered connectivity between these regions was associated with deficits in goal-directed learning. While the authors did not comment on the relationship between dlPFC-putamen disconnection and compulsivity specifically, a subsequent study demonstrated that deficits in goal-directed learning are associated with trait compulsivity.[28] Our study suggests that damage to the left dlPFC results in increased compulsivity in a TBI population. Interestingly, two recent meta-analyses found evidence that transcranial magnetic stimulation targeting the dlPFC can alleviate some symptoms in OCD.[29 30] However, a direct connection between altered dlPFC activity and compulsivity in OCD remains to be established.

In our cohort of patients with TBI, damage to the BG was associated with increased tics, similar to prior studies in animals and individual case studies.[31] The overall output of the BG is thought to inhibit motor activation[21 32] and prior studies in animals suggest that damage to or inactivation of the globus pallidus, one of the output nuclei of the BG, can result in a release of motor inhibition and repetitive stereotyped behaviours.[33] We speculate that this mechanism may also play a role in tic generation in patients with BG damage. One notable limitation of the current study is that the definition of tics we used does not allow tics to be well-distinguished from stereotypies. Whereas tics are associated with features such as premonitory urges and may be stress related or sometimes suppressible, stereotypies tend to cluster in longer periods and have a tendency to involve similar muscle groups in consistent patterns that may look rhythmic.[34] The YGTSS does not specifically distinguish between these aspects of the movements it identifies and quantifies. Notably, a recent study looking at the co-occurrence of stereotypies and tics in patients with Tourette Syndrome found that tics and stereotypies could be identified by the YGTSS and the Stereotypy Severity Scale (SSS), respectively. Future studies may benefit from including the YGTSS and SSS when there is concern for tics and/or stereotypy.[35]

While psychiatric illnesses are conceptualised as circuit-level disorders,[24] the results from this study highlight the possible involvement of individual CSTC circuit elements in the development of compulsions and tics in particular. Indeed, recent studies have suggested that compulsive behaviour may be an important transdiagnostic symptom that has the potential to be amenable to specific targeted brain interventions.[36–39] Our study adds to this literature by suggesting that dlPFC damage and dysfunction may play a role in compulsive behaviour and that BG damage and dysfunction may be involved in tics.

Our study has a number of important limitations. First, there were unequal numbers of patients in the different ROI groups, which could affect the power to detect associations. Second, the imaging and behavioural evaluations were performed at different phases of the study, and so separated by several years (although the lesions were stable between phases 3 and 4). Third, CT imaging of the BG and thalamus did not have the anatomical resolution of MRIs and our characterisation of damage to these regions was, by necessity, rudimentary. Fourth, all the patients in the current study are male. Fifth, the time elapsed between the brain injury, imaging, and assessment of symptoms may have confounded our results. Sixth, we employed modified versions of the Y-BOCS and YGTSS that were completed by an informant and assessed symptom presence and severity before and after brain injury (in the case of TBI subjects). Because the subjects sustained their brain injuries many years prior to their assessment, there was a chance for recall bias of the informant. All of the informants were family members and did know the patient before the brain injury. Finally, there were also some differences in the baseline characteristics of the subjects with TBI in the study and the control subjects. Despite these limitations, the present study is the first, to our knowledge, to examine the contributions of different CSTC circuit elements to obsessions, compulsions and tics in patients with focal penetrating TBI. A next step will be to test whether damage or dysfunction in the dlPFC or BG in other disorders, such as neurodegenerative illnesses, is associated with the development of compulsive behaviours or tics, respectively.

In summary, our results suggest that damage to the left dlPFC is associated with an increase in compulsions and damage to the BG is associated with the development of tics. Our findings contribute to understanding the role of particular CSTC nodes in compulsions and tics. Further work should explore whether there is circuit-level dysfunction occurring in these lesioned patients.

Research ethics Statement: This study obtained ethics approval by the IRB as detailed in the methods section of the paper.

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