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Neural Basis of Associative Learning in Trichotillomania and Skin-Picking Disorder

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Abstract

Disorders such as Trichotillomania (TTM) and skin-picking disorder (SPD) are associated with reduced flexibility and increased internally focused attention. While the basal ganglia have been hypothesized to play a key role, the mechanisms underlying learning and flexible accommodation of new information is unclear. Using a Bayesian Learning Model, we evaluated the neural basis of learning and accommodation in individuals with TTM and/or SPD. Participants were

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127 individuals with TTM and/or SPD (TTM/SPD) recruited from three sites (age 18 – 57, 84% female) and 26 healthy controls (HC). During fMRI, participants completed a shape-button associative learning and reversal fMRI task. Above-threshold clusters were identified where the Initial Learning-Reversals BOLD activation contrast differed significantly ($p<0.05$ FDR-corrected) between the two groups. *A priori*, effects were anticipated in predefined ROIs in bilateral basal ganglia, with exploratory analyses in the hippocampus, dorsolateral prefrontal cortex (dlPFC), and dorsal anterior cingulate cortex (dACC). Relative to HC, individuals with TTM/SPD demonstrated reduced activation during initial learning compared to reversal learning in the right basal ganglia. Similarly, individuals with TTM/SPD demonstrated reduced activation during initial learning compared to reversal learning in several clusters in the dlPFC and dACC compared to HC. Individuals with TTM/SPD may form or reform visual stimulus-motor response associations through different brain mechanisms than healthy controls. The former exhibit altered activation within the basal ganglia, dlPFC, and dACC during an associative learning task compared to controls, reflecting reduced frontal-subcortical activation during initial learning. Future work should determine whether these neural deficits may be restored with targeted treatment.

Keywords

trichotillomania; skin-picking disorder; associative learning; cognitive flexibility; functional neuroimaging

1. Introduction

Trichotillomania (TTM) and skin-picking disorder (SPD) are body-focused repetitive behavior disorders that commonly co-occur (1). The predominant clinical feature in these conditions is recurrent hair-pulling, respectively, or skin-picking, both of which may serve to reduce or prevent anxiety, despite adverse consequences. These behaviors have been associated with reduced cognitive flexibility (2), difficulty set shifting, and increased internally focused attention to the source of one's distress and repetitive behaviors (3,4). Plausibly, all of these features may portend a profile of cognitive vulnerability associated with TTM and SPD that involves difficulty with initial learning (5–7) and updating of new information. These vulnerabilities may be accompanied by neuroimaging-detectable signatures or neural targets for intervention. However, only a few small studies have examined the neural basis of learning in these clinical populations, with conflicting findings. For example, in one pilot study (n = 25), TTM was linked to abnormal fronto-occipital activation during set-shifting (8). In another study (n = 20), no neural differences between TTM and controls were found for implicit sequence learning (9). Larger scale studies are needed to more definitively determine the correlates of associative learning in TTM or SPD.

Bayes Theorem offers an optimal model for studying associative learning. This statistical approach calculates the probability of some event conditioned on another event, given the *a priori* independent, e.g., chance, probabilities of both events. Bayesian statistics can be used to model the chances of an event happening as a result of learning (10,11). This Bayesian approach enables the quantification of learning on a trial-by-trial basis, enhancing the precision with which both initial learning and updating new associations can be captured.

This is particularly relevant for TTM and SPD, where impairment is expected to involve deficits in initial learning, as well as effortful accommodation and consolidation. However, Bayesian models have not yet been used to explore learning flexibility in TTM and SPD.

The present study aims to utilize a Bayesian learning model to determine the difference in neural activation, as embodied by the brain fMRI BOLD signal, between TTM/SPD and HCs during initial learning. As fMRI typically measures brain states not absolutely, but by contrast, the initial learning phase of the associative learning paradigm is compared here to the reversal learning phase. The primary hypothesis is that patients with TTM and SPD will exhibit lower activation than controls during initial associative learning as compared to reversal learning in the basal ganglia, as these structures are implicated in both initial rapid learning and habit formation (12,13). We also conduct exploratory analyses in the dorsolateral prefrontal cortex (dlPFC), which is linked to organization of new information (14,15) and working memory (16), the dorsal anterior cingulate cortex (dACC) for its role in directed attention (17), reward and fear learning (18,19), as well as the hippocampus, which is associated with the transfer of knowledge from short to long term memory (20,21). Together, the activation of these regions of interest (ROIs) captures key nodes of the fronto-limbic and -subcortical circuitry active in learning processes, as well as areas of brain dysfunction implicated in impulse control disorders (22,23).

2. Methods

2.1. Participants

All participants provided written informed consent prior to participation in accordance with institutional guidelines and human subjects review boards. Study participants were adults, with ages ranging between 18 and 57 years, including 26 healthy controls and 127 individuals with TTM (n = 54), SPD (n = 47), or comorbid TTM+SPD (n = 26) recruited at Massachusetts General Hospital, University of Chicago, or University of California, Los Angeles (Table 1, for detail). Participants were recruited through clinics, referrals, and by advertisements. All participants (patients and controls) were assessed by a trained study evaluator for Trichotillomania and/or Skin Picking Disorder (TTM/SPD) diagnosis using the Trichotillomania Diagnostic Interview – Revised for DSM-5 (24), Keuthen Diagnostic Inventory for Skin Picking – Revised for DSM-5 (25), and other psychiatric diagnoses, using the Mini International Neuropsychiatric Interview 7.0 (MINI) (26). Disorder comorbidities were established using the MINI.

All eligible participants had normal or corrected-to-normal vision and were right-handed. Exclusion criteria for all participants included contraindications to MRI (e.g., ferromagnetic implants, severe claustrophobia) or positive pregnancy test. In the clinical group, comorbidity with psychiatric disorders was allowed, provided that TTM or SPD were the primary psychiatric condition (see Table 1). Psychiatric participants were excluded if there were psychotropic medication dose changes within the past three months or if the comorbid medical or psychiatric illness (e.g., current substance use disorder) was severe, requiring a higher level of care. All HCs had no current or lifetime history of any DSM-5 psychiatric disorder, including substance abuse, or other significant medical or neurological illness and were not currently taking any psychotropic medication. Due to our goal to focus on

this historically underrepresented clinical population, we aimed to recruit three times more patients than controls. This ratio should allow us the power to conduct both a case control study, and informative within group comparisons among patients.

2.2. Associative Learning fMRI Task Paradigm

During fMRI, participants completed a shape-button associative learning and reversal task modeled after a probabilistic reversal-learning paradigm (27). Participants were shown abstract geometric shapes one-by-one in the center of a computer screen and were asked to press one of four keys resting under digits 1, 2,3, and 4 of the right hand during each trial to learn which key each of the set of six shapes was associated with (Figure 1). The shapes were white on black background and did not belong to any readily verbalizable category such as “circle”, “triangle”, etc. Hence, they had to be learned *de novo*. When the keypress was correct, the shape turned green, and when it was incorrect, the shape turned red. A blue circle was presented interspersed with the shapes, which turned green upon the selection of any button. The experiment had three phases: an Initial Learning block and two Reversal blocks (First Reversal and Second Reversal) lasting 102 trials each. In the Learning stage, three of the six shapes were shown at greater, pseudo-randomized frequency initially so that the participant could learn them more effectively, followed by a decrease in the frequency of presentation of those shapes and an increase in the frequency of the other three shapes for the second half of the Learning phase. In the First Reversal phase, the first half of shape-button associations were pseudo-randomized, leaving the second half of the shape-button associations unaltered. Subjects were expected to unlearn old associations and learn new ones, while also retaining the prior associations which had not changed. In the Second and last Reversal phase, the second half of the shapes were pseudo-randomized, while the first half remained associated to the same button as in First Reversal. Participants had 1.5 seconds to respond to each shape.

2.3. MRI Scanning

All MRI scans were completed at the Athinoula A. Martinos Center for Biomedical Imaging (MGH), the University of Chicago, or the University of California Los Angeles Health Sciences (UCLA). MRI data were collected at 3.0-T with 32-channel head coils using a Siemens Prismafit (MGH, UCLA) or a Philips Achieva (University of Chicago) scanner. Foam cushions were used to restrict head movements. Task images were displayed using a rear projection system and ePrime 2.0 stimulus presentation software (Psychology Software Tools, Inc., Pittsburgh). Task implementation and MRI acquisition followed strict protocols that were highly synchronized across the three recruitment sites. Data were checked for quality and cross-sites compliance after each session. Quality control included monthly acquisition of study protocol pulse-sequences on MRI phantoms to detec t and correct for potential scanner drift and site-to-site variation. The structural sequences included a high-resolution, four-echo, T1-weighted, magnetization-prepared, gradient-echo image (TR = 2310 ms, TE = 2.9 ms, flip angle = 9 °, voxel size = 1.0 x 1.0 x 1.0 mm) (van der Kouwe et al. 2008) for positioning and post-processing of fMRI. Functional images were acquired using a multiband SMS-3 T2*-weighted echo-planar-imaging (EPI) sequence sensitive to blood-oxygen-level dependent (BOLD) contrast (TR=2000 ms, TE=28 ms, flip angle=90°, voxel size = 3.2 x 3.2 x 3.1 mm).

2.4. Behavioral Analyses

In order to model behavioral data, we utilized a Bayesian inference model, which was applied during each trial and for each shape. For each trial, this Bayesian model produced a learning coefficient between 0 and 1, reflecting degree of learning; the closer the coefficient was to 1, the more the participant had learned the shape-button association. The learning coefficient was calculated as follows. First, the prior likelihood of a correct response was assumed to be 1/n where n was the number of key choices (four) available, which reflected the assumption that the participant was naïve to the shape-button associations at the start of every block and had an equal likelihood of choosing each button (including the correct association button) at chance. Next, this likelihood distribution was updated, independently for each shape, using Bayes's rule. During each trial *i*, the value of the standard deviation was updated such that after a new latent learning state x_i was applied, the maximum likelihood probability was equal to the probability that the participant correctly recalled the shape-button association after the first correct response (28). After reversals, the mean of the prior distribution was assumed to be $1/x_j$ where x_j was the latent learning state of the trial immediately before the reversal. This reflected the fact that participants are unlikely to respond correctly on the first trial after the reversal if they have learned the previous shape-button association correctly. The model was chosen this way because we had strong prior knowledge about the likelihood of answering an unknown association correctly and the likelihood of recalling an association. Trials with no response or participants who did not respond to more than 20% of the stimuli (n=18) were excluded from the analysis. Participants missed an average of 11.8% of trials ($SD = 4.2\%$). The latent learning states x_i for each trial *i*, were used as regressors for first level analysis of each participant's functional data.

2.5. fMRI Analyses

Analyses were conducted using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Raw data was slice time corrected, realigned and unwrapped, co-registered, convolved into three-dimensional space established by the Montreal Neurological Institute (MNI152), segmented, normalized, and smoothed. In first level models, Bayesian learning coefficients were input as parametric modulators to individual functional data. Next, a one-way ANOVA model was built to compare the groups in the Initial Learning-Reversals contrast, with study site was included as a covariate. Results were explored in anatomical ROIs, defined using the Wake Forest University Pick Atlas (29) bilaterally in the basal ganglia (single ROI consitituting the caudate body, head, and tail, and putamen), the dACC (BA 24 and 32), the dlPFC (BA 9, 8, and 46), and the hippocampus (see Figure 2). The basal ganglia were the primary *a priori* region of interest, but all significant findings survived AlphaSim false discovery rate correction at $p < 0.05$ with a minimum cluster size (k) of 15.9 voxels in the basal ganglia, 11.0 voxels in the hippocampus, 23.6 voxels in the dlPFC, and 32.9 in the dACC. MarsBaR toolbox for SPM (http://marsbar.sourceforge.net) was then used to extract average beta weight values from the significant clusters of activation found in these ROIs, for each subject. These beta weight values were used to estimate the magnitude of effects (Cohen's d). Post-hoc sensitivity analyses were conducted to examine the impact of sex, given a predominantly female (84%) sample. All 24 males were removed from the sample, and second level analyses were re-run with the remaining 129 females. Additionally,

exploratory analyses examined whether activation within significant clusters were associated with symptom severity on the Hair Pulling Urge Scale (HPUS) and Skin Picking Urge Scale (SPUS), clinical diagnosis (TTM vs. SPD vs. TTM+SPD), or anxiety disorder comorbidity, which was the highest frequency comorbidity in this sample.

3. Results

3.1. Behavioral

The average response accuracy across the whole task was 61.6% (SD = 13.5) in TTM/SPD and 65.3% (SD = 14.9) in the HC group. Average response accuracy did not differ between groups (F(1,151) = 1.57, p = .212). Additionally, average accuracy for the Initial Learning did not statistically differ (F(1,151) = 2.32, p = .130) in TTM/SPD (M = 56.7%, SD = 15.9) versus HC (M = 62.1%, SD = 19.1). Neither did accuracy for Reversals statistically differ (F(1,151) = .79, p = .377) in TTM/SPD (M = 64.1%, SD = 14.5) versus HC (M = 66.8%, SD = 14.6).

3.2. fMRI (Figure 3 and 4, Table 2)

In the basal ganglia *a-priori* analysis, the TTM/SPD group demonstrated a lower average difference score for the Initial Learning-Reversals contrast in the right basal ganglia (specifically, right caudate) compared to HCs. For the exploratory regions of interest, the TTM/SPD group similarly demonstrated a lower average difference score for the Initial Learning - Reversals contrast in several clusters of the dlPFC (bilateral BA 46, left BA 8, right BA 6) and left dACC (BAs 24 and 32). Follow up extractions (data not shown) of average activation for Initial Learning and Reversals blocks individually revealed that individuals with TTM/SPD consistently demonstrated lower activation in these regions during Initial Learning and higher activation during Reversals. By contrast, HC's demonstrated higher activation during Initial Learning and lower activation during Reversals. There were no significant group differences in the hippocampus.

3.3. Sensitivity and Post Hoc Analyses

All reported findings remained significant in post-hoc analyses conducted after removing males from the sample. Neither HPUS nor SPUS scores significantly correlated with activation for any ROI (all r's <.103; all p's > .256) among individuals with TTM/SPD. One-way ANOVAs comparing individuals with TTM, SPD, and comorbid TTM+SPD for all ROIs revealed a significant difference only in basal ganglia activation (F(2, 124) = 3.087, p = .049). Specifically, individuals with TTM showed reduced activation in the basal ganglia compared to individuals with comorbid TTM+SPD (Tukey post hoc test, p = .042, Supplemental Figure 1). There were no differences in activation for any ROI between patients with and without generalized anxiety disorder (all F's < 2.25, all p's > .136), social anxiety disorder (all F's < 1.11, all p's > .294), or major depression (all F's<1.18. all p's > .225). Finally, there were no significant differences in brain activation between those participants taking medications and those not taking anything (all F's < 2.13, all p's > .146).

4. Discussion

Obsessive-compulsive and related disorders such as TTM and SPD are associated with alterations in habit formation, which can negatively impact learning and flexibility. However, the study of learning processes and their underlying neural features has been limited in TTM and SPD. The present study utilized a Bayesian Learning Model and fMRI paradigm to address this gap in the literature. The primary results show that individuals with TTM/SPD HCs demonstrate lower engagement of the right basal ganglia, and the bilateral dlPFC and dACC significantly during initial learning as compared to reversal learning than HC individuals with TTM and SPD. Conversely, HC individuals demonstrate relatively greater activation in these regions during initial learning as compared to reversal learning. This study is the first to show individuals with TTM and SPD demonstrate fronto-subcortical alterations in associative learning neural circuitry.

The finding that individuals with TTM/SPD demonstrated lower neural recruitment of the basal ganglia during initial learning as compared to reversal learning than HC individuals is consistent with our hypothesis. It is also consistent with prior research reporting reduced basal ganglia volumes in TTM (22,30) and associations between severity of symptoms and symptom duration with reduced basal ganglia volumes in SPD (31). Thus, is appears that these disorders are associated not only with structural but also functional brain abnormalities within brain areas implicated in habit formation (12,13,32). The contrast comparing initial learning to the reversal phases implies that the fundamental deficit is with engagement during initial learning, with relatively greater engagement during the reversal phase. This is generally consistent with one prior study of TTM where increased activation (in this instance, right frontal) was observed during reversal (8). One possible interpretation is that individuals with TTM/SPD who are clinically prone to habit rigidity and inflexibility demonstrate a neural deficit associated with *novel* learning and subsequently require greater neural recruitment during learning accommodation. Increased activation during reversal may reflect a compensatory process, especially seeing as though this pattern of group differences was observed in the absence of behavioral performance differences.

Furthermore, individuals with TTM and SPD also under-engaged the dlPFC, and the dACC, in comparison to controls during initial learning, implicating broader frontosubcortical circuitry dysregulation. Indeed, largely medium effect sizes for the group comparison were observed across the basal ganglia, dlPFC, and dACC. It was somewhat surprising that hippocampal activity did not differ between the groups, especially in light of hippocampal dopaminergic alterations reported in other impulse control disorders such as Tourette's Syndrome (33,34). However, given that the hippocampus plays a key role in the transfer of knowledge from short to long-term memory and memory retrieval (21,22), this negative finding may reflect that neural dysfunction in TTM/SPD is more specific to cortico-striatal executive functions that facilitate organization, updating, and set-shifting during learning than mesolimbic memory systems.

Structural and functional alterations in the frontostriatal circuitry have also been widely implicated in reversal learning in obsessive-compulsive disorder (OCD) (22,23,35–37). As there exists substantial overlap in the phenomenological and clinical characteristics of

OCD (7), TTM, and SPD, and a high rate of co-occurrence of these disorders (38), our neuroimaging findings lend further credence to the possibility that these diagnoses share a common pathophysiological basis. However, only nine individuals in the current sample were diagnosed with comorbid OCD, precluding direct comparison of results in TTM/SPD patients with and without comorbid OCD. Our sample size did allow for exploratory evaluation of anxiety disorder comorbidity, where similar alterations in corticolimbic activation have previously been reported across a variety of tasks (39), but most notably for inhibitory control and salience processing (40). Interestingly, there were no differences observed between patients with and without comorbid GAD or social anxiety disorder in the dlpfc, dACC, or basal ganglia, raising the possibility that neural alterations of this circuitry *during associative learning* could be a more specific marker of body-focused repetitive behavior disorders.

Moreover, it is noteworthy that we did not find any evidence of correlation between TTM or SPD symptom severity and activation within the regions of interest and raises the possibility that frontal-subcortical hypoactivation during learning reflects a 'trait' feature of TTM and SPD. This question should be evaluated in the future using at-risk or family designs, as it could facilitate early identification of risk for TTM and SPD. Notwithstanding, it is noteworthy that there was some variability in the pattern of results between TTM, SPD, or comorbid TTM/SPD. Specifically, individuals with TTM showed significant reduced activation in the basal ganglia compared to individuals with comorbid TTM+SPD. This finding could reflect the possibility that low basal ganglia activation during associative learning is especially characteristic of TTM, but also could simply be a function of greater variability due to the smaller sample of individuals with TTM+SPD comorbidity.

Our results should be considered in light of a number of limitations. Firstly, they were subject to natural fMRI data loss at an individual level due to missed/omitted trials and may have resulted in a reduction in statistical power. Missed/omitted trials, however, were excluded and constituted <12% of total trials. Secondly, while all participants had been diagnosed with either TTM, SPD, or both, many participants had other comorbidities, especially anxiety or mood disorders. While we were able to conduct exploratory analyses regarding GAD and social anxiety disorder, cell sizes for other comorbidities were too small to examine, but nonetheless could have introduced heterogeneity that may obscure the specificity of our results. Thirdly, although we undertook post-hoc comparisons to evaluate for potential differences between TTM, SPD, and their combination, the subgroups analysis was relatively small. Fourthly, this was a multicenter study with data acquired on three different MRI scanners. Rigorous measures were undertaken, however, to ensure site-to-site equivalence of behavioral and MRI endpoints and all primary study findings survived statistical adjustment for study site. Finally, all analyses were undertaken comparing Initial Learning to Reversal blocks, with post-hoc beta values extracted for individual blocks to understand the pattern of observed difference scores. However, it would have been ideal to have also acquired a "resting block" of the task, as the Reversal conditions likely constitute an active reference and mean activation from individual blocks does not have a true reference value.

As additional strengths, state-of-the-art MRI acquisition and post-processing protocols were employed and this was one of the largest neuroimaging studies to date of TTM and SPD, significantly impaired but historically understudied clinical populations.

5. Conclusions

Taken together, the basal ganglia, the dlPFC, and the dACC represent promising nodes of interest in the study of learning and learning accommodation in TTM and SPD. Given that TTM has previously been associated with response inflexibility (2), and that both disorders are clinically linked to impairments in habit formation, targeting these ROIs during psychotropic treatment could potentially alleviate or mitigate cognitive vulnerability to impulse control dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Statements:

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References

1. Snorrason I, Belleau EL, Woods DW. How related are hair pulling disorder (trichotillomania) and skin picking disorder? A review of evidence for comorbidity, similarities and shared etiology. Clin Psychol Rev. 2012 Nov;32(7):618–29. [PubMed: 22917741]
2. Bohne A, Savage CR, Deckersbach T, Keuthen NJ, Jenike MA, Tuschen-Caffier B, et al. Visuospatial Abilities, Memory, and Executive Functioning in Trichotillomania and Obsessive-Compulsive Disorder. J Clin Exp Neuropsychol. 2005 May;27(4):385–99. [PubMed: 15962686]
3. Chamberlain SR, Fineberg NA, Blackwell AD, Clark L, Robbins TW, Sahakian BJ. A neuropsychological comparison of obsessive-compulsive disorder and trichotillomania. Neuropsychologia. 2007 Jan;45(4):654–62. [PubMed: 17005210]
4. Clayton IC, Richards JC, Edwards CJ. Selective attention in obsessive–compulsive disorder. J Abnorm Psychol. 1999;108(1): 171–5. [PubMed: 10067003]
5. Cohen RJ, Calamari JE. Thought-Focused Attention and Obsessive–Compulsive Symptoms: An Evaluation of Cognitive Self-Consciousness in a Nonclinical Sample. Cogn Ther Res. 2004 Aug;28(4):457–71.
6. Stern ER, Muratore AF, Taylor SF, Abelson JL, Hof PR, Goodman WK. Switching between internally and externally focused attention in obsessive-compulsive disorder: Abnormal visual cortex activation and connectivity. Psychiatry Res Neuroimaging. 2017 Jul;265:87–97. [PubMed: 28024845]
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. Fifth Edition. American Psychiatric Association; 2013 [cited 2020 Oct 19], Available from: 10.1176/appi.books.9780890425596
8. Grant JE, Daws R, Hampshire A, Chamberlain SR. An fMRI Pilot Study of Cognitive Flexibility in Trichotillomania. J Neuropsychiatry Clin Neurosci. 2018 Oct;30(4):318–24. [PubMed: 30141727]
9. Rauch SL, Wright Cl, Savage CR, Martis B, McMullin KG, Wedig MM, et al. Brain activation during implicit sequence learning in individuals with trichotillomania. Psychiatry Res Neuroimaging. 2007 Apr;154(3):233–40.
10. Ahn W-Y, Haines N, Zhang L. Revealing Neurocomputational Mechanisms of Reinforcement Learning and Decision-Making With the hBayesDM Package. Comput Psychiatry. 2017 Dec;1:24–57.

11. Widge AS, Ellard KK, Paulk AC, Basu I, Yousefi A, Zorowitz S, et al. Treating refractory mental illness with closed-loop brain stimulation: Progress towards a patient-specific transdiagnostic approach. Exp Neurol. 2017 Jan;287(Pt 4):461–72. [PubMed: 27485972]
12. Graybiel AM. Building action repertoires: memory and learning functions of the basal ganglia. Curr Opin Neurobiol. 1995 Dec;5(6):733–41. [PubMed: 8805417]
13. Packard MG, Knowlton BJ. Learning and Memory Functions of the Basal Ganglia. Annu Rev Neurosci. 2002 Mar;25(1):563–93. [PubMed: 12052921]
14. Blumenfeld RS. Dorsolateral Prefrontal Cortex Promotes Long-Term Memory Formation through Its Role in Working Memory Organization. J Neurosci. 2006 Jan 18;26(3):916—25. [PubMed: 16421311]
15. Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, et al. Is There "One" DLPFC in Cognitive Action Control? Evidence for Heterogeneity From Co-Activation-Based Parcellation. Cereb Cortex. 2013 Nov;23(11):2677–89. [PubMed: 22918987]
16. Barbey AK, Koenigs M, Grafman J. Dorsolateral prefrontal contributions to human working memory. Cortex. 2013 May;49(5): 1195–205. [PubMed: 22789779]
17. Aberg KC, Kramer EE, Schwartz S. Interplay between midbrain and dorsal anterior cingulate regions arbitrates lingering reward effects on memory encoding. Nat Commun. 2020 Dec;11(1):1829. [PubMed: 32286275]
18. Maier S, Szalkowski A, Kamphausen S, Perlov E, Feige B, Blechert J, et al. Clarifying the Role of the Rostral dmPFC/dACC in Fear/Anxiety: Learning, Appraisal or Expression? Bruce A, editor. PLoS ONE. 2012 Nov 26;7(11):e50120. [PubMed: 23189183]
19. Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, et al. Individual differences in reinforcement learning: Behavioral, electrophysiological, and neuroimaging correlates. Neuroimage. 2008 Aug;42(2):807–16. [PubMed: 18595740]
20. Jarrard LE. On the role of the hippocampus in learning and memory in the rat. Behav Neural Biol. 1993 Jul;60(1):9–26. [PubMed: 8216164]
21. Myers CE, Shohamy D, Gluck MA, Grossman S, Kluger A, Ferris S, et al. Dissociating Hippocampal versus Basal Ganglia Contributions to Learning and Transfer. J Cogn Neurosci. 2003 Feb 1; 15(2): 185–93. [PubMed: 12676056]
22. O'Sullivan RL, Rauch SL, Breiter HC, Grachev ID, Baer L, Kennedy DN, et al. Reduced basal ganglia volumes in trichotillomania measured via morphometric magnetic resonance imaging. Biol Psychiatry. 1997 Jul;42(1):39–45. [PubMed: 9193740]
23. Kim C-H, Koo M-S, Cheon K-A, Ryu Y-H, Lee J-D, Lee H-S. Dopamine transporter density of basal ganglia assessed with [123 I]IPT SPET in obsessive-compulsive disorder. Eur J Nucl Med Mol Imaging. 2003 Dec 1;30(12): 1637–43. [PubMed: 14513291]
24. Keuthen NJ. The Keuthen Diagnostic Inventory for Skin Picking for DSM-5 (K-DISP-5). Unpublished.
25. Keuthen NJ. The Trichotillomania Diagnostic Interview for DSM-5 (TDI-5). Unpublished.
26. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22–33;quiz 34-57.
27. Cools R, Clark U, Owen AM, Robbins TW. Defining the Neural Mechanisms of Probabilistic Reversal Learning Using Event-Related Functional Magnetic Resonance Imaging. J Neurosci. 2002 Jun 1;22(11):4563—7. [PubMed: 12040063]
28. Yousefi A, Paulk AC, Basu I, Mirsky JL, Dougherty DD, Eskandar EN, et al. COMPASS: An Open-Source, General-Purpose Software Toolkit for Computational Psychiatry. Front Neurosci. 2019 Jan 11;12:957. [PubMed: 30686965]
29. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage. 2003 Jul;19(3):1233–9. [PubMed: 12880848]
30. Isobe M, Redden SA, Keuthen NJ, Stein DJ, Lochner C, Grant JE, et al. Striatal abnormalities in trichotillomania: A multi-site MRI analysis. Neuroimage Clin. 2018;17:893–8. [PubMed: 29515968]

31. Schienle A, Potthoff J, Wabnegger A. Voxel-based morphometry analysis of structural brain scans in skin-picking disorder. Compr Psychiatry. 2018 Jul;84:82–6. [PubMed: 29727807]
32. Graybiel AM. The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol. 2005 Dec:15 (6): 638–44. [PubMed: 16271465]
33. Gilbert DL, Christian BT, Gelfand MJ, Shi B, Mantil J, Sallee FR. Altered mesolimbocortical and thalamic dopamine in Tourette syndrome. Neurology. 2006 Nov 14;67(9): 1695–7. [PubMed: 17101911]
34. Steeves TDL, Ko JH, Kideckel DM, Rusjan P, Houle S, Sandor P, et al. Extrastriatal dopaminergic dysfunction in tourette syndrome. Ann Neurol. 2010 Feb;67(2): 170–81. [PubMed: 20225192]
35. Kehagia AA, Murray GK, Robbins TW. Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. Curr Opin Neurobiol. 2010 Apr;20(2): 199–204. [PubMed: 20167474]
36. Remijnse PL, van den Heuvel OA, Nielen MMA, Vriend C, Hendriks G-J, Hoogendijk WJG, et al. Cognitive Inflexibility in Obsessive-Compulsive Disorder and Major Depression Is Associated with Distinct Neural Correlates. Hashimoto K, editor. PLoS ONE. 2013 Apr 24;8(4):e59600. [PubMed: 23637737]
37. Gruner P, Pittenger C. Cognitive inflexibility in Obsessive-Compulsive Disorder. Neuroscience. 2017 Mar;345:243–55. [PubMed: 27491478]
38. Grant JE, Leppink EW, Tsai J, Chamberlain SR, Redden SA, Curley EE, et al. Does comorbidity matter in body-focused repetitive behavior disorders? Ann Clin Psychiatry Off J Am Acad Clin Psychiatr. 2016 Aug;28(3): 175–81.
39. Chavanne AV, Robinson OJ. The Overlapping Neurobiology of Induced and Pathological Anxiety: A Meta-Analysis of Functional Neural Activation. Am J Psychiatry. 2021 Feb 1;178(2): 156–64. [PubMed: 33054384]
40. Janiri D, Moser DA, Doucet GE, Luber MJ, Rasgon A, Lee WH, et al. Shared Neural Phenotypes for Mood and Anxiety Disorders: A Meta-analysis of 226 Task-Related Functional Imaging Studies. JAMA Psychiatry. 2020 Feb 1;77(2):172. [PubMed: 31664439]

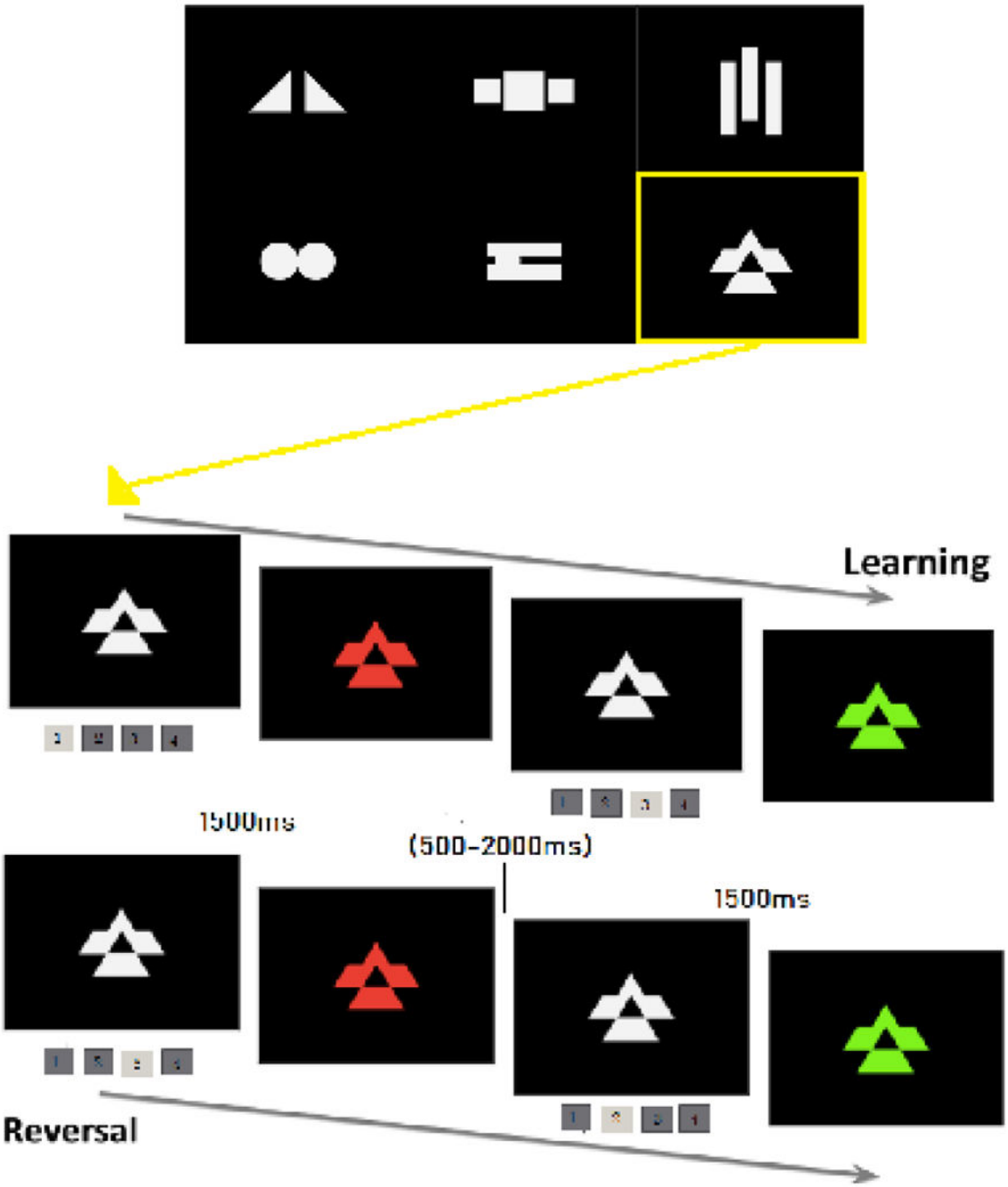


Figure 1.

Learning and Reversal Task Paradigm: Once the stimulus (1 out of 6) appeared on the screen, participants had to press a button (out of four possible ones). Participants had 1.5 seconds to respond to each shape. If the figure turned green, the correct button had been pressed, meaning that the association was correct. If the figure turned red, the participant had to try a new button next time the same stimulus was presented again. Here, in the Initial Learning block (top), the presented stimulus was associated with button number 3. However, in one of the Reversal blocks (bottom), the presented stimulus changed its association

to button number 2. Participants were then expected to press button number 2 when the stimulus above was shown, instead of button number 3

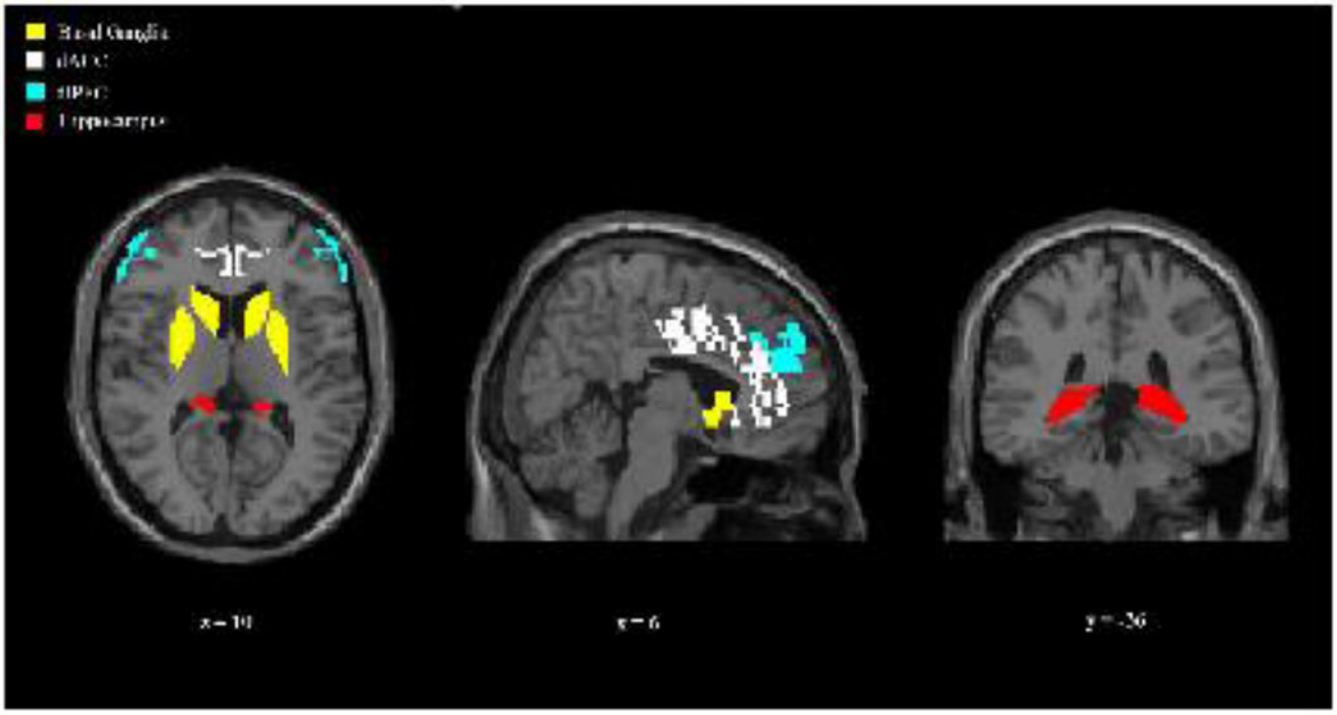
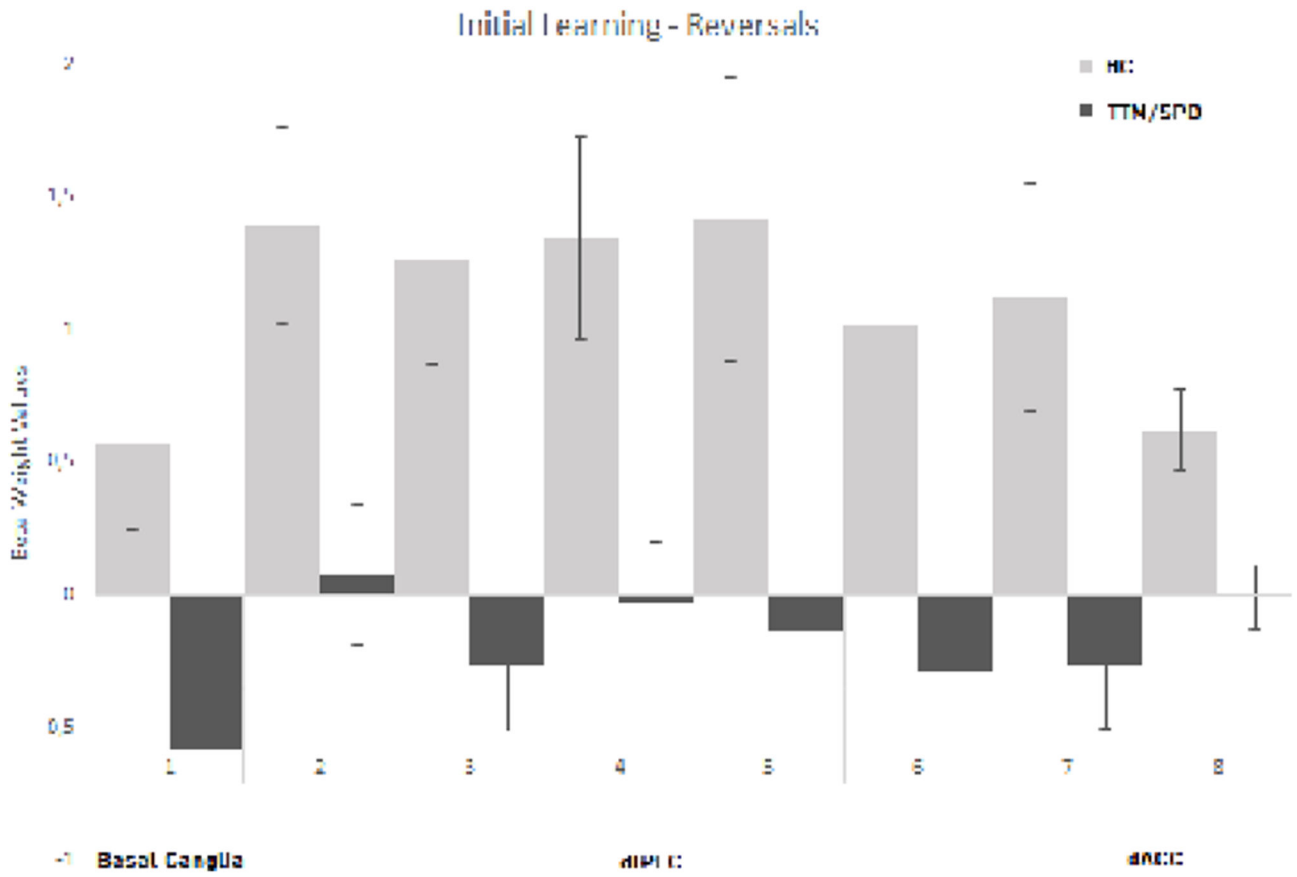
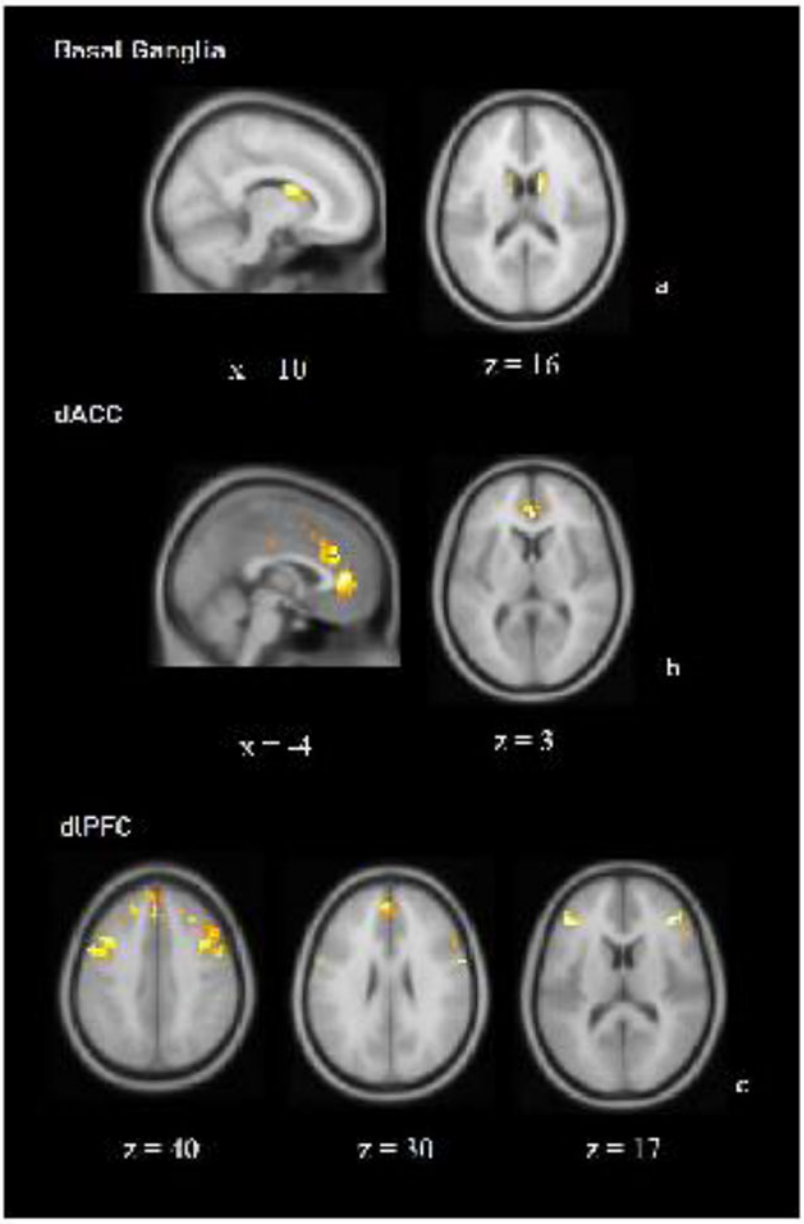


Figure 2.
Bilateral masks of basal ganglia, dACC, dlPFC, and hippocampus



[1]Basal Ganglia, x = 12, y = 3, z = 17; [2]dlPFC, x = 63, y = 3, z = 26; [3]dlPFC, x = -46 , y = 35, z = 14; [4]dlPFC, x = 40, y = 38, z = 14; [5]dlPFC, x = -1, y = 38, z = 38; [6]dlPFC, x = -40, y = 16, z = 38; [7]dACC, x = -1, y = 38, z = 4; [8]dACC, x = -1, y = 32, z = 29

Figure 3.
Significant differences between groups in the basal ganglia, dlPFC, and dACC for the Initial Learning-Reversals contrast



Note: Peak clusters of activation: a. x=12, y=3, z=17. b. x=-1, y=38, z=4; x=-1, y=32, z=29 c. x=-46, y=35, z=14; x=40, t=38, z=14; x=-1, y=38, z=38; x=-40, y=16, z=38; x=63, y=3, z=26

Figure 4:
Significant results of a-priori and exploratory region of interest analyses for Initial Learning-Reverals in TTM/SPD vs. HC

Table 1.

Sample Demographics and Clinical Characteristics

Measures		HC		TTM/SPD		χ^2	*p*-value
		N	**%**	**N**	**%**		
Sex	Female	20	77	109	86	1.29	0.26
	Male	6	23	18	14		
Race	White	19	73	101	80	2.89	0.41
	Black	3	12	8	6		
	Asian	0	0	6	5		
	Mixed-Race	4	15	12	9		
Ethnicity	Latino/Hispanic	7	27	18	14	2.57	0.11
	Non-Latino/Hispanic	19	73	109	86		
Medication	Antidepressant	-	-	17	13.4	--	--
	Antianxiety	-	-	4	3.1		
	Antipsychotic	-	-	1	>1		
	Mood Stabilizer	-	-	1	>1		
Therapy style	Monotherapy	-	-	14	11.0		
	Pluritherapy	-		4	3.1		
Diagnosis	TTM	-	-	54	42.5	--	--
	SPD	-	-	47	37.0		
	TTM+SPD	-	-	26	20.5		
Current Psychiatric	Nail Biting	-	-	10	20.5		
Comorbidities	Major Depression *	-	-	13	20.5		
	Bipolar Disorder II	-	-	1	0.8		
	Panic Disorder	-	-	4	7.1		
	Agoraphobia	-	-	3	5.5		
	Social Phobia	-	-	16	23.6		
	Obsessive-Compulsive Disorder	-	-	9	11.0		
	Post-Traumatic Stress Disorder	-	-	6	7.1		
	Generalized Anxiety Disorder	-	-	22	44.9		
	Attention-Deficit/Hyperactivity Disorder	-	-	7	7.9		
		M	**SD**	**M**	**SD**	***t***	
Age		28.7	10.2	29.6	9.1	0.45	0.66
Hair Pulling Urge Scale [1]		0	0	10.6	8.1	6.4	<0.001
Skin Picking Urge Scale [2]		0	0	9.8	7.8	6.0	<0.001

* Non-parametric measures tested for significance using Chi-squared test. Parametric measures tested for significance using *t*-test.

[1] HPUS scores were missing for 2 HC and 4 TTM/SPD participants

[2] SPUS scores were missing for 3 HC and 3 TTM/SPD participants.

[*] Major Depression includes any patients meeting criteria for a current major depressive episode, recurrent major depressive disorder in current episode, or current major depressive disorder.

Table 2.

One-way ANOVA fMRI Results for HC vs. TTM/SPD for Initial Learning – Reversals Contrast

Contrast/Region	Hemisphere	BA	x	y	z	t-score	*p*	Cohen's *d*
HC > TTM/SPD								
Basal Ganglia	Right	48	12	3	17	2.65	0.004**	0.51
dlPFC								
	Left	46	−46	35	14	3.62	0.000***	0.64
	Right	46	40	38	14	3.42	0.000***	0.60
	Left	8	−1	38	38	3.38	0.000***	0.54
	Left	8	−40	16	38	3.09	0.001**	0.57
	Right	6	63	3	26	3.00	0.002**	0.53
dACC								
	Left	24	−1	38	4	3.46	0.000***	0.56
	Left	32	−1	32	29	2.88	0.002**	0.27
Hippocampus	No Results							
HC < TTM/SPM	No Results							