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Disordered reward processing and functional connectivity in trichotillomania: A pilot study☆

Matthew P. White [a,*], William R. Shirer [b], Maria J. Molfino [b], Caitlin Tenison [a], Jessica S. Damoiseaux [b], Michael D. Greicius [b]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford University Medical Center, 401 Quarry Road, Stanford, CA 94305, USA
[b] Department of Neurology, Stanford University School of Medicine, USA

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ABSTRACT

Background: The neurobiology of Trichotillomania is poorly understood, although there is increasing evidence to suggest that TTM may involve alterations of reward processing. The current study represents the first exploration of reward processing in TTM and the first resting state fMRI study in TTM. We incorporate both event-related fMRI using a monetary incentive delay (MID) task, and resting state fMRI, using two complementary resting state analysis methodologies (functional connectivity to the nucleus accumbens and dual regression within a reward network) in a pilot study to investigate differences in reward processing between TTM and healthy controls (HC).
Methods: 21 unmedicated subjects with TTM and 14 HC subjects underwent resting state fMRI scans. A subset (13 TTM and 12 HC) also performed the MID task.
Results: For the MID task, TTM subjects showed relatively decreased nucleus accumbens (NAcc) activation to reward anticipation, but relative over-activity of the NAcc to both gain and loss outcomes. Resting state functional connectivity analysis showed decreased connectivity of the dorsal anterior cingulate (dACC) to the NAcc in TTM. Dual regression analysis of a reward network identified through independent component analysis (ICA) also showed decreased dACC connectivity and more prominently decreased basolateral amygdala connectivity within the reward network in TTM.
Conclusions: Disordered reward processing at the level of NAcc, also involving decreased modulatory input from the dACC and the basolateral amygdala may play a role in the pathophysiology of TTM.

1. Background and objectives

Trichotillomania (TTM) affects up to 1.5% of males and 3.4% of females (Christenson et al., 1991). Despite increasing research attention, the neurobiology of TTM is poorly understood, and there is considerable debate as to how best to conceptualize the illness. Initially thought to be an Obsessive Compulsive Disorder (OCD) spectrum illness, TTM also shares clinical features with Tourette's syndrome (Ferrao et al., 2009), Attention Deficit Hyperactivity Disorder (ADHD) (Chamberlain et al., 2005) and body-focused repetitive behavioral disorders such as skin-picking and nail biting (Chamberlain et al., 2009).

There is a paucity of research into the neurobiology of TTM. To date there have only been two fMRI studies of TTM, a negative study using an implicit sequence learning task (10 TTM subjects, 10 HCs, ROI based analysis) (Rauch et al., 2007) and a small symptom provocation study (9 TTM subjects, 10 HCs, whole-brain analysis), which found increased activation of the putamen, posterior cingulate, left temporal cortex, and precuneus in TTM subjects, although these results were mostly uncorrected for multiple comparisons (Lee et al., 2010).

Other methodologies have most frequently, if inconsistently, identified the striatum, particularly the left putamen, as a region of interest. Stein et al. using *Single Photon Emission Computed Tomography* ($n = 10$; ROI approach) found a reduction in left putamen perfusion with citalopram therapy, albeit not necessarily with symptom improvement (Stein et al., 2002). Using structural MRI, O'Sullivan found reduced left putamen volume (10 TTM vs. 10 HC; ROI approach) (O'Sullivan et al., 1997), and Chamberlain found increased left putamen grey matter density (as well as increased

☆ Previous presentation. A preliminary analysis of a subset of the data was presented orally at the Trichotillomania Learning Center Annual Conference on April 30, 2011. No written abstract or handouts were provided.

* Corresponding author.
E-mail address: mpwhite@stanford.edu (M.P. White).

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grey matter density in the left amygdalo-hippocampal formation, anterior cingulate and several other frontal areas; 18 TTM vs. 19 HC, whole brain analysis) (Chamberlain et al., 2008). However, Stein found no differences in striatal volume comparing 17 TTM to 12 HC's (ROI analysis) (Stein et al., 1997). The anterior cingulate was also shown to have reduced white matter integrity in a DTI study by Chamberlain (18 TTM vs. 19 HC, white matter mask) (Chamberlain et al., 2010). Cerebellar differences have been noted in more than one study, including reduced perfusion using Positron Emission Tomography (10 TTM vs. 10 HC, whole brain analysis) (Swedo et al., 1991) and reduced cerebellar volume (14 TTM vs. 12 HC, ROI analysis) (Keuthen et al., 2007).

The current exploration of reward processing in TTM results from several convergent lines of thinking. While TTM shares a certain compulsive quality with OCD, the experience of hair pulling is often described as soothing, even pleasurable, unlike the often-upsetting experience of performing rituals in OCD. Further, trials of serotonin reuptake inhibitors in TTM have been mixed and mostly disappointing, with the possible exception of clomipramine (Bloch et al., 2007). At the same time, a limited number of trials suggest that medications that affect the neurotransmitters glutamate (Grant et al., 2009) and dopamine (Van Ameringen et al., 2010; White and Koran, 2011) may be promising in the treatment of TTM. Both glutamate and dopamine are particularly concentrated in the nucleus accumbens (NAcc), a region often considered to be at the heart of reward prediction and feedback networks (Koob and Volkow, 2009). Taken together, these experiential and neurobiological indicators suggest that TTM may represent a problem of disordered reward processing (Blum and Gold, 2011; Stein and Lochner, 2006).

Despite these links to reward processing, there have been no task-activation fMRI studies addressing this hypothesis. Neither have there been any resting-state functional connectivity studies of TTM. The two methods are complementary: Task activation studies are particularly useful for evaluating between-group differences in brain activation in response to a certain task demand. Resting state methodology can explore how these brain regions connect to other brain regions, forming functional networks. Here, using both resting-state and task-activation fMRI, we sought explicitly to test the hypothesis that TTM can be characterized as a disorder of reward processing.

2. Methods and materials

2.1. Subjects

Subjects were recruited through online advertisements, the Trichotillomania Learning Center newsletter and trichotillomania support groups. After a complete description of the study, subjects signed an informed consent approved by the Stanford University Medical Center Institutional Review Board. The diagnosis of trichotillomania was made through clinical interview with a clinician experienced with trichotillomania; co-morbid diagnoses were screened using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) according to DSM-IV criteria (APA, 2000). All subjects (except three healthy controls used in the resting state analysis only) had hair-pulling severity measured with the Massachusetts General Hair Pulling Scale (MGHHPS) (Keuthen et al., 1995). Depression and anxiety were assessed with the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) respectively (Beck et al., 1988, 1961). All subjects were unmedicated and had been off all medications for three weeks. Exclusion criteria included use of psychotropic medications for three weeks prior to study enrollment, active substance abuse, active suicidal ideation, a diagnosis of bipolar disorder, or any psychotic disorder. These latter two diagnoses were excluded both for clinical concerns of being unmedicated and for possible difficulties attending to both resting state and task protocols. Seven of the healthy controls performed a different task than the MID task as an exploration of an experimental task paradigm; as such, they were included only in the resting state analysis to increase statistical power of this analysis. They otherwise were scanned under identical conditions in the identical scanner with an identical protocol. Because of problems with the task presentation software, 13 TTM subjects and 12 HC subjects were used in the task analysis.

There were no significant differences in age or gender for either the task-activation subjects or the larger resting state groups. Both the TTM and HC groups were predominantly female (79% of all resting state subjects). The TTM group had significantly greater BDI scores than HC subjects for both the MID task groups (mean TTM 8.5 ± 7.8; mean HC 0.5 ± 0.9; $p \leq 0.01$) and resting state groups (mean TTM 9.2 ± 9.8; mean HC 0.8 ± 1.1; $p < 0.0005$) and higher BAI scores for the resting state groups (mean TTM 4.1 ± 3.1; mean HC 1.1 ± 2.1; $p < 0.005$). As planned, the TTM subjects had significantly higher MGHHPS scores for both comparison groups. See Supplementary Table 1 for further information on subject demographics.

2.2. Reward task

The reward task was a modification of the Monetary Incentive Delay (MID) task developed and described previously by Knutson et al. (2003). The MID is a widely used task that allows for discrete analysis of anticipated monetary reward (or anticipated loss) separable from the outcome of monetary reward or monetary loss. The MID task has been shown to reliably activate the NAcc in response to reward anticipation (Figee et al., 2010). Our task was modified to reduce the total number of conditions, eliminating one "neutral" condition and simplifying the win/loss quantities from three possible values each to two values. See Supplementary Fig. 1 for further MID task details. Subjects performed two fMRI runs of 90 trials each, with each run divided into 45 "potential win" and 45 "potential loss" trials, equally divided into \$0, \$1 and \$5 trials. This resulted in 30 possible win trials, 30 possible loss trials and 30 "neutral" (zero dollar) trials per fMRI run.

2.3. fMRI data acquisition

All imaging was performed at the Richard M. Lucas Center for Imaging at Stanford University on a 3-Tesla General Electric Signa scanner using a standard whole-head coil. The scan session consisted of a 10 min resting state fMRI followed by two runs of the MID task.

For the resting state functional scan, we acquired 300 volumes (10 min) of 28 axial slices (4 mm thickness) parallel to the plane connecting the anterior and posterior commissures and covering the whole brain using a $T2^*$ weighted gradient echo spiral in/out pulse sequence (repetition time 2000 ms, echo time 30 ms, flip angle 80° and 1 interleave) (Glover and Law, 2001). We instructed subjects to "lie still with your eyes closed, try not to think of any one thing in particular and try not to fall asleep." For the MID task, each subject underwent two runs of 12 min each collecting 364 volumes per run using the same fMRI protocol. All data underwent physiologic noise correction for cardiac and respiratory artifact (Glover et al., 2000).

2.4. Data processing and statistical analysis

2.4.1. MID task data

Task analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 4.1, part of FSL (FMRIB's Software Library, www.fmrib.

ox.ac.uk/fsl). To allow for T1 equilibration effects, the first 6 volumes of all scans were discarded. After motion correction, images were temporally high-pass filtered with a cutoff period of 150 s and smoothed using a 5 mm Gaussian kernel full-width at half maximum (FWHM) algorithm for the NAcc region of interest (ROI) analysis (because of the small ROI volume). For the whole brain analysis we used an 8 mm FWHM smoothing kernel to be consistent with other recent whole brain MID task studies (Beck et al., 2009; Figee et al., 2010). For the *anticipation condition* The BOLD response was modeled using a separate explanatory variable (EV) for each of the three conditions (reward anticipation, loss anticipation, neutral anticipation) as well as the button press. For each stimulus type, the presentation design was convolved with a gamma function to produce an expected BOLD response. The temporal derivative of this time course was also included in the model for each EV. Button press was orthogonalized with respect to each of the anticipation conditions. Data were then fitted to the model using FSL's implementation of the general linear model. For the *outcome conditions* a similar method was employed for the EVs of gain outcome, loss outcome and neutral outcome (outcome to a zero dollar trial) as well as button-press. Each subject's statistical data was then warped into a standard space based on the MNI-152 atlas. For each individual subject, runs were merged in a second level fixed-effects analysis. We used FLIRT (FMRIB's Linear Image Registration Tool) to register the functional data to the standard MNI atlas with 12 degrees of freedom affine transformation. Global signal and 6 motion parameters were modeled as nuisance covariates for all analyses described in this paper.

Mixed effects higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects). Depression scores (BDI) and anxiety scores (BAI) were demeaned and entered into the model as nuisance covariates. Because of our hypothesis that the NAcc would be differentially active in subjects with TTM, we masked our higher level analysis to a NAcc ROI consisting of a 7 mm diameter sphere located at MNI coordinates [−10,10,−9] and [10,10,−9]. These were located by visual inspection by Dr. Greicius on the standardized MNI atlas (to which all higher-level analyses were mapped) and did not overlap white matter. Due to the small size of the ROI we performed a voxel-wise analysis (two-tailed *t*-test) with significance set at family-wise error (FWE) corrected $p < 0.05$. We also performed a whole-brain mixed-effects higher-level analysis (two-tailed *t*-test), with a grey-matter mask, using a cluster-based threshold with $z > 2.3$ and $p < 0.05$ FWE corrected.

2.4.2. Resting state functional connectivity analysis

We performed functional connectivity analysis on 14 TTM subjects and 21 HC subjects. The data was preprocessed in FEAT using motion correction and FWHM smoothing of 6.0 mm (following the standard methodology used in our lab's resting state studies), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 75.0 s). fMRI volumes were registered to standard space images as in the task-related preprocessing.

For the functional connectivity analysis, we used the same left and right NAcc ROIs described earlier as seed regions. Using Feat-query we extracted the average time series for the left and right NAcc for each subject, with the time series averaged across all voxels in the ROI. Using each time series as an EV we then used FEAT to perform first level GLM analysis of all voxels positively or negatively correlated to each ROI. We then performed mixed effects higher-level analysis using FLAME. Initially, we performed a one group (one-tailed *t*-test) analysis using all subjects to obtain a group-level connectivity map, which we thresholded at a *z* score of 2.3 to create a mask for the two-group analysis. We then did a between-group analysis using FEAT (two-tailed *t*-test), masked to the one-sample *t*-test group mask, with BDI and BAI scores as nuisance covariates. The Z-statistics images were thresholded at $z > 2.3$ and $p < 0.05$ FWE corrected.

2.4.3. Dual regression

After preprocessing of the resting state data as described above, we performed dual regression following the technique of Filippini (Filippini et al., 2009) and as described by Damoiseaux et al. (2011). This involves three steps: First, running group Independent Component Analysis (ICA) using the MELODIC FSL tool on data of both groups together (TTM and HC subjects). ICA separates resting state data into temporally and spatially discreet components, many of which correspond to functionally connected brain networks. Here we used an equal number of subjects from each group (fourteen) so as not to skew ICA components in favor of a particular population and had MELODIC output 25 independent components. Second, using these 25 independent components as spatial regressors against each individual's resting state data, resulting in specific time courses for each independent component and subject which are, in turn used in a temporal regression against the individual's resting state data to estimate subject-specific spatial maps. Third, performing group-level analyses using nonparametric permutation testing (with 5000 permutations).

In this study, group ICA identified an independent component that was nearly identical to the reward network identified in the NAcc based functional connectivity analysis (see Supplementary Fig. 2). This network has been previously noted in other resting state fMRI and PET studies (Cauda et al., 2011) involving addiction (Upadhyay et al., 2010) and reward processing (Liu et al., 2010) but has not been highlighted in previous ICA studies as a resting state network linked to reward processing. We used this reward network as the basis for our dual regression analysis. To explore differences between TTM subjects and HCs, we performed, a 2-sample *t* test using "threshold-free cluster enhancement" (TFCE) as implemented in FSL (Smith and Nichols, 2009) and spatially masked with the reward network ICA component (thresholded at FWE corrected $p < 0.01$). Both corrected (FWE $p < 0.05$) and uncorrected ($p < 0.05$) results are presented.

3. Results

3.1. Behavioral data

There was no difference between reaction times for TTM and HC subjects for reward anticipation ($p = 0.11$), loss anticipation ($p = 0.59$) or all conditions combined ($p = 0.58$). There was no difference in the number of intrusions (premature button presses; $p = 0.87$) between the groups. As expected, based on the task design, there was no difference in monetary winnings.

3.2. Monetary Incentive Delay Task

ROI based analysis revealed significantly decreased activation in TTM subjects for *gain anticipation* in the left NAcc compared with HC subjects (corrected $p < 0.05$; Fig. 1). There were no between group differences for the condition of loss anticipation. For the outcome conditions, TTM subjects had relatively hyperactive right NAcc responses to both the *gain outcome* and *loss outcome* conditions compared with HCs (corrected $p < 0.05$; Fig. 1). The findings for gain anticipation, gain outcome or loss outcome in the NAcc did not correlate significantly with MGHHPS scores.

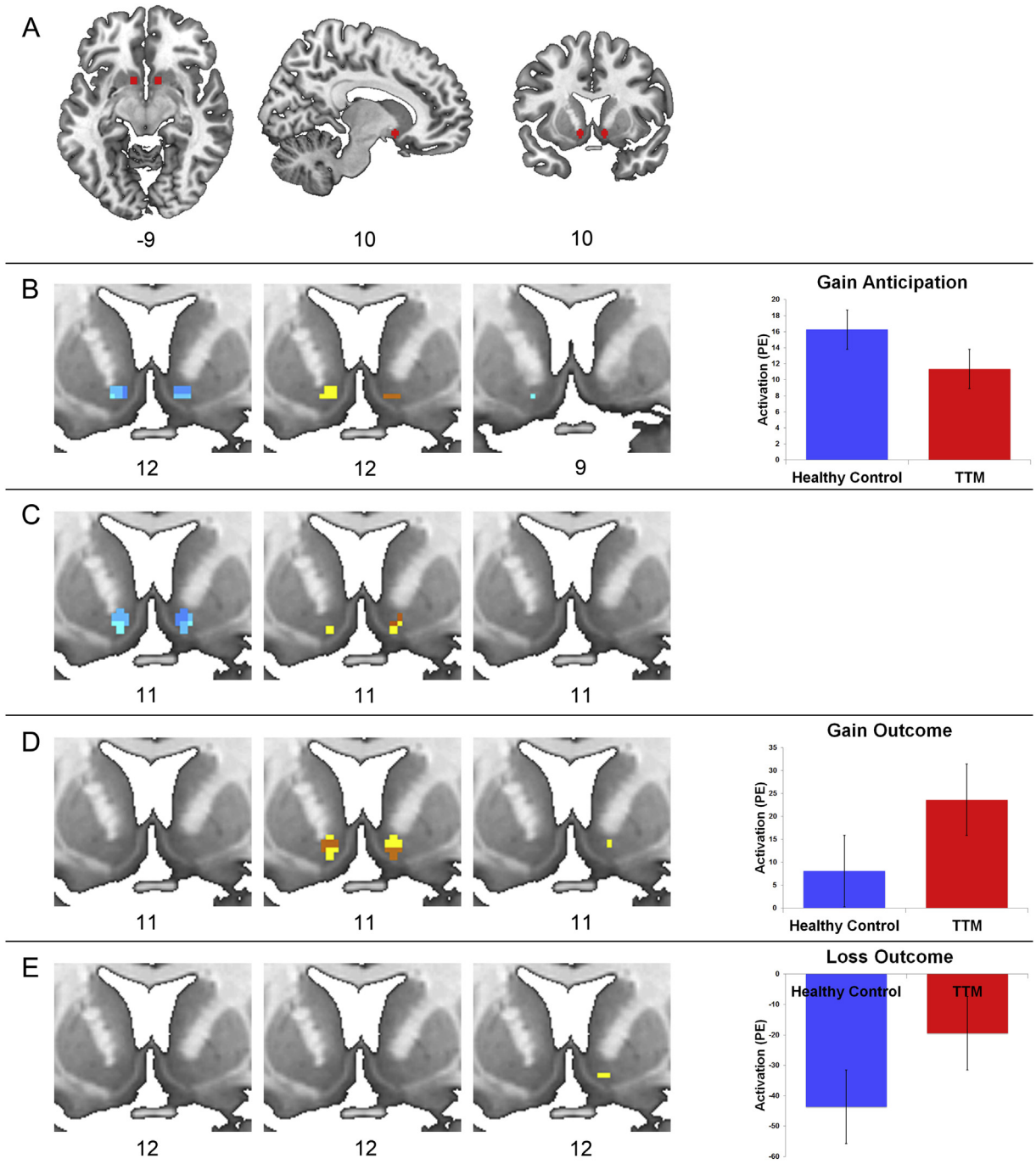

Fig. 1. Nucleus accumbens activation in the Monetary Incentive Delay Task. Nucleus accumbens (NAcc) activation in the Monetary Incentive Delay Task. A: NAcc ROI. B–E: From left to right, HC (blue), TTM (yellow/red) and difference maps (HC > TTM = blue; TTM > HC = yellow) for B: Gain anticipation; C: Loss anticipation (no difference); D: Gain outcome; E: Loss outcome (all $p < 0.05$ FWE corrected). Graphs on the right represent parameter estimates (PE) for regions of difference. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Whole brain analysis was significant only for the *loss anticipation* condition. TTM subjects showed less activation in the left putamen and insula (corrected $p < 0.001$, Fig. 2).

3.3. NAcc functional connectivity

The one-sample *t*-test across both groups revealed NAcc functional connectivity for both left and right NAcc with the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), basal ganglia, thalamus, temporal cortex (including insula and amygdala), brain stem, and cerebellum (Fig. 3). Between-group differences were notable for reduced functional connectivity for TTM subjects between the dorsal ACC (dACC) and NAcc bilaterally (Fig. 3; corrected $p < 0.05$). Average connectivity scores for the dACC region for TTM subjects did not correlate significantly with MGHHPS scores, nor did they correlate significantly with observed task-based NAcc activation differences.

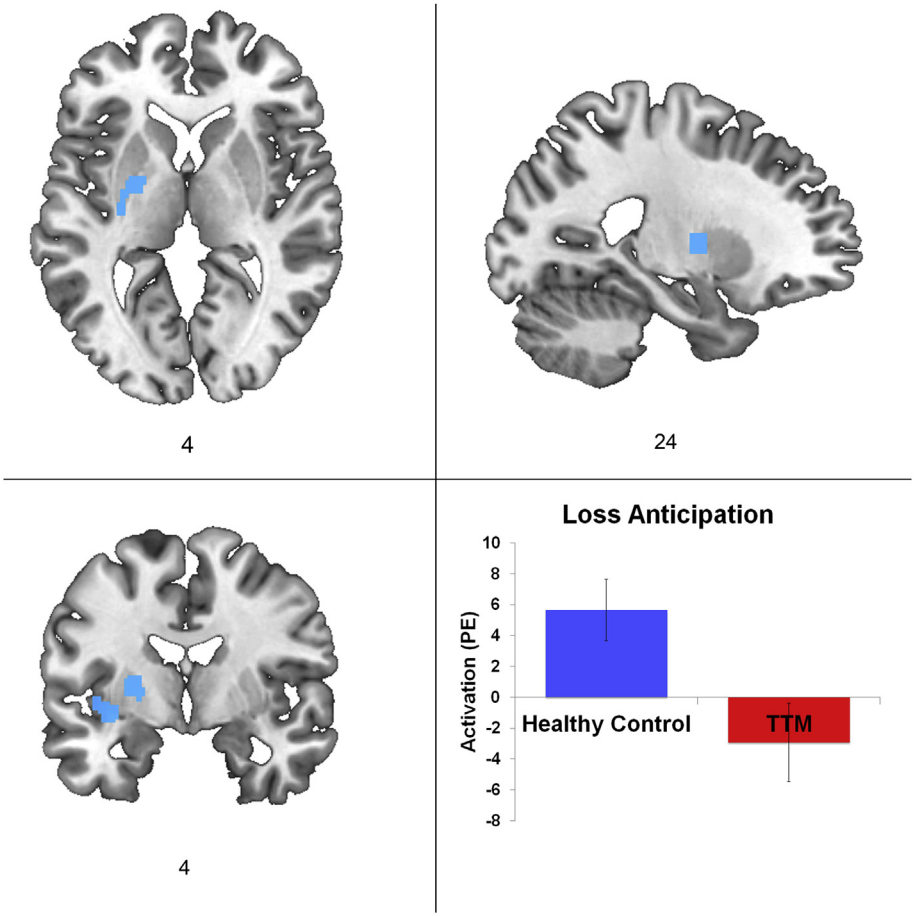

Fig. 2. Loss Anticipation: whole brain difference in Monetary Incentive Delay Task. Whole brain difference map for the Loss Anticipation condition in the Monetary Incentive Delay Task (HC > TTM; $p < 0.001$ FWE corrected). Graph on the lower right represent the parameter estimates (PE) for the region of difference (a continuous region including left putamen and left insula).

3.4. Dual regression

Dual regression of the reward network identified in group ICA showed decreased connectivity within this network for TTM subjects in a swath of temporal lobe extending from the right basolateral amygdala into the orbitofrontal cortex (corrected $p < 0.05$; Fig. 4). There were no regions where TTM showed increased connectivity to the network compared with HCs.

Because our ROI-based functional connectivity analysis showed decreased connectivity between the dACC and bilateral NAcc, we were especially interested in dACC connectivity within the reward network identified in ICA (as distinct from connectivity to the NAcc). Fig. 5 shows evidence of decreased dACC connectivity within the reward network of TTM subjects ($p < 0.05$ uncorrected) in a region similar to that identified by functional connectivity analysis. This region did not reach significance when corrected for FWE $p < 0.05$.

4. Discussion

This is the first resting state fMRI study of TTM, as well as the first fMRI study of TTM to explore reward-related task activation. Our findings present converging, if preliminary, evidence from both methodologies for dysregulated reward circuitry in TTM.

In our task-activation analysis using a relatively small sample-size, reduced NAcc activation to anticipated monetary reward parallels several findings in the fMRI addiction literature describing reduced NAcc activation to monetary reward anticipation in nicotine dependence (Buhler et al., 2010), and detoxified alcoholics (Beck et al., 2009; Wrase et al., 2007). Decreased NAcc activation to anticipated reward has also recently been reported in OCD (Figee et al., 2010), ADHD (Hoogman et al., 2011) and major depression (MDD) (Pizzagalli et al., 2009), although Knutson did not observe this difference in MDD (Knutson et al., 2008).

The finding of relatively increased NAcc response to rewarding outcome is also consistent with studies of addiction using the MID task in cocaine addicts (Jia et al., 2011) and sober alcoholics (Bjork et al., 2008). TTM subjects' over-activation to rewarding outcomes could suggest that hair pulling may be over reinforced. In contrast, subjects with MDD show global NAcc hypo-responsiveness, including for rewarding outcomes as well as anticipation (Pizzagalli et al., 2009; Smoski et al., 2009).

Thus, with respect to reward anticipation and outcome, the findings of relatively decreased NAcc activation for reward anticipation and exaggerated response to reward outcome most closely parallel the literature on addiction. It is possible that this might represent a tonically under-active reward network that is to some degree "normalized" or pathologically stimulated by the behavioral outcome, regardless of valence, although this is highly speculative. In contrast, for rewarding outcomes, the NAcc is hypo-active in depression (Pizzagalli et al., 2009) and no different from controls in OCD (Figee et al., 2010). It should be noted that the OCD study used a whole brain analysis; an ROI based approach, as in this study, might have yielded different results.

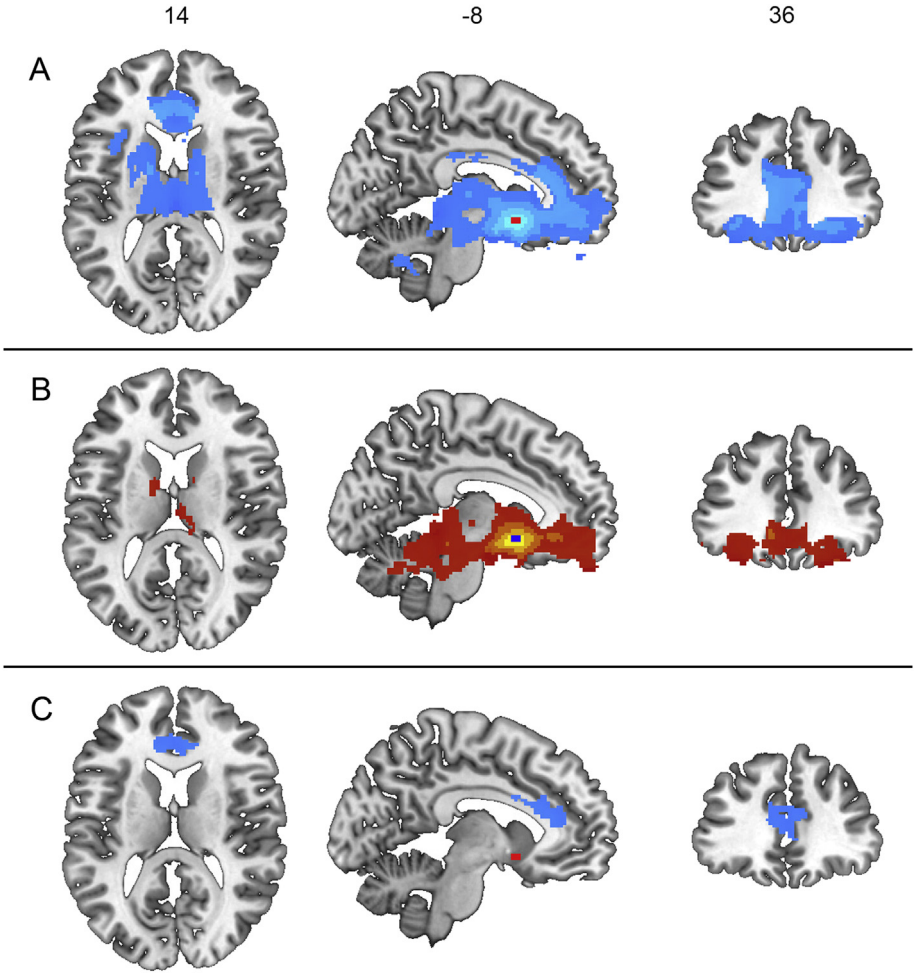

Fig. 3. Functional Connectivity to the Nucleus Accumbens. Resting state functional connectivity to the left Nucleus Accumbens (NAcc) for A: Healthy Controls (HC); B: TTM and C: HC > TTM (all $p < 0.05$ FWE corrected). Opposite color dots represent the NAcc seed. Connectivity maps for the right NAcc seed looked similar including a cluster in the dorsal anterior cingulate showing reduced connectivity in the TTM subjects.

Loss outcome is a less frequently reported finding in the reward-based literature; as such, comparisons with other illnesses are more difficult to make. The finding that TTM subjects show less deactivation to loss outcomes might suggest that the negative consequence of hair-pulling are under-represented. It is interesting to note that the left NAcc was under-active in reward anticipation, but the right NAcc over-responsive to rewarding outcome, although the significance of this laterality is unclear.

The finding of reduced left putamen activation in the loss anticipation condition, while again based on a small sample size, is intriguing because the left putamen has been one of the most consistently implicated regions in the limited imaging studies of TTM. The putamen is a dopamine rich structure that plays a role in controlling complex motor activities, and (DeLong and Wichmann, 2007) in regulating automatic stimulus-response (i.e. habit) behaviors (Balleine and O'Doherty, 2009). The putamen may also play

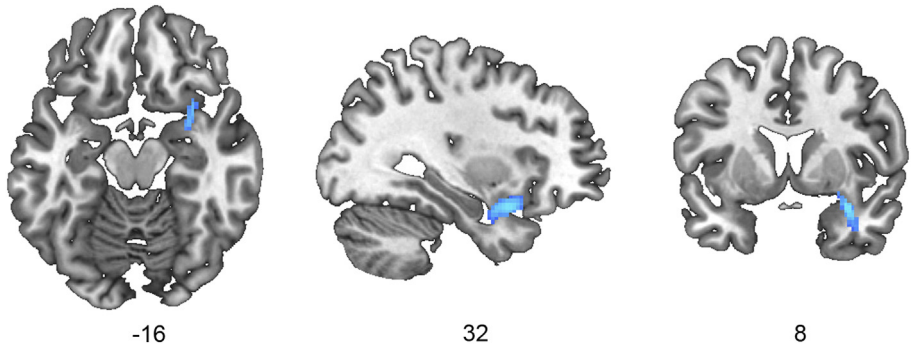

Fig. 4. Dual regression: Differential connectivity within the reward network. The basolateral amygdala demonstrates greater resting state connectivity within the reward network for healthy controls > TTM ($p < 0.05$ FWE corrected).

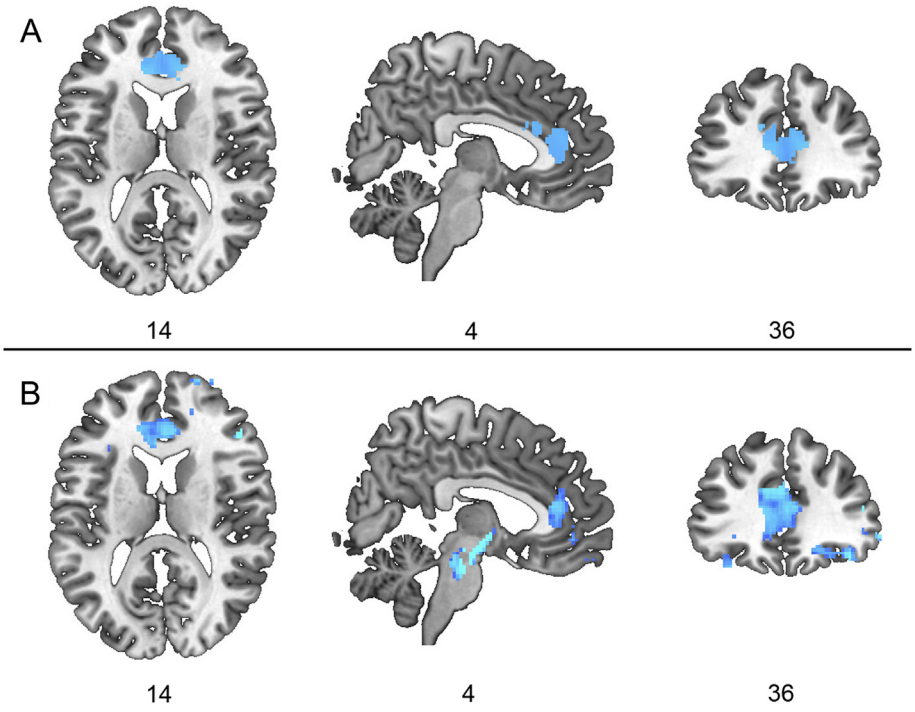

Fig. 5. Seed-based analysis and dual regression converge on reduced dorsal anterior cingulate connectivity in the reward network. A: Seed-based functional connectivity analysis shows decreased functional connectivity of the dorsal anterior cingulate (dACC) to the Nucleus Accumbens (NAcc) in TTM compared with healthy controls ($p < 0.05$ FWE corrected). B: Dual regression to the reward network also demonstrates decreased connectivity of the dACC to the reward network in TTM, albeit less robustly ($p < 0.05$, uncorrected).

a role in impulsivity and addiction: Increased putamen D2 and D3 receptor availability has been associated both with methamphetamine addiction and increased measures of impulsivity (Lee et al., 2009).

Resting state functional connectivity analysis using a slightly larger sample revealed decreased dACC connectivity to the NAcc bilaterally using seed-based functional connectivity analysis, and – less robustly – decreased dACC connectivity within the reward network overall using dual regression analysis. This region of the dACC sits at the junction of dorsal cognitive control regions and rostral and ventral limbic regions. It has been implicated in these overlapping functions such as appraisal of emotional information, emotion regulation and top-down inhibitory control (Etkin et al., 2011; Shackman et al., 2011). It may also play a role in reinforcement-based learning and decision-making (Liu et al., 2010; Rushworth et al., 2011). Volkow has posited that disruption of cingulate glutamatergic projections to the NAcc may contribute to increased compulsivity and decreased cognitive control in addiction (Kalivas and Volkow, 2005). Resting state functional connectivity of the dACC to the striatum (particularly the putamen and its transition zone to the NAcc) has previously been shown to correlate inversely to severity of nicotine addiction (Hong et al., 2009). The only Diffusion Tensor Imaging (DTI) study of TTM found disrupted white matter integrity in this portion of the ACC (Chamberlain et al., 2010).

The basolateral amygdala, which showed decreased connectivity to the reward network in our dual regression analysis of the slightly larger sample, has been implicated in encoding expected reward value via direct excitatory dopaminergic projections to the NAcc (Ambroggi et al., 2008). It is consistent, therefore, that TTM subjects, who under-activate the NAcc in anticipation of reward, should also have reduced basolateral amygdala connectivity to the reward network. As such, mismatches between under-anticipated reward and over-valued outcome may lead to maladaptive behaviors, such as hair pulling. This finding should be considered preliminary, as this region also may extend into the orbito-frontal cortex, a region associated with inhibitory modulation of striatal circuits. Reduced OFC connectivity to the reward network would instead suggest lack of top-down control, akin to the dACC findings. A larger sample size would likely help to confirm and localize this region of decreased connectivity in TTM.

In sum, this small pilot study offers preliminary evidence of dysregulated NAcc activity as well as decreased functional connectivity between the dACC and the NAcc and between the basolateral amygdala/OFC and the reward network. Both the dACC and the basolateral amygdala have glutamatergic and dopaminergic projections to the NAcc a dopamine and glutamate rich region. This may be relevant to recent clinical inroads in the treatment of TTM using agents that modulate glutamate (Grant et al., 2009) and dopamine (Van Ameringen et al., 2010; White and Koran, 2011).

The main limitation of this study is the relatively small simple size, particularly for the MID task portion of the study. Furthermore, this study included both “automatic” and “focused” pullers, an increasingly recognized distinction in TTM that was evolving during the course of this study (Flessner et al., 2009). It is possible that disordered reward processing in the ventral striatum may be present in a subset of subjects with TTM, such as those with more focused pulling, whereas those with more automatic pulling may have problems of more dorsal striatal circuitry.

A broader criticism pertains to the *a priori* focus on the NAcc and the reward network. It is likely that the neurobiology of TTM involves a complex interplay of dysregulated regions or circuits beyond those explored here, including circuitry responsible for motor response inhibition, other limbic structures, and cerebellar networks.

A significant strength of the study is the multi-modal approach, involving both resting state analysis and task-activation paradigms. The progression of evidence from dysregulated NAcc activation, to

disrupted functional connectivity between the dACC and NAcc, to alternations in connectivity to the reward network as a whole (including basolateral amygdala and dACC) makes a compelling case for developing theories about reward processing and motivational control in TTM. A second strength of this study is the use of anxiety and depression scores as nuisance covariates, which significantly improves study validity, especially given the higher levels of depression and anxiety in the TTM subjects. As such the results should reflect differences in TTM vs. healthy control subjects and not group differences in anxiety and depression. Further, use of medication-free subjects similarly guards against the possibility that our results reflect a primary medication effect.

It should be mentioned that the term "reward" might more appropriately be conceptualized as "behavioral prediction and feedback" or "motivation and reinforcement" network. Also, while TTM may share some neurobiologic features with addictions, to reframe TTM as an addiction would oversimplify this complex illness. Indeed, the lack of significant addictive co-morbidity reported for TTM speaks to some unique aspect of this challenging disorder. As such, disordered reward processing should be considered alongside other findings in the clinical, cognitive neuroscience, and imaging literature in seeking to formulate a neurobiologic understanding of TTM.

Future studies could explore the role of hair pulling itself in modulating this reward network as well as the relationship of this network to attention, mood regulation and impulsivity. Studies of sub-populations (i.e. focused pullers vs. automatic pullers, more recent vs. chronic pullers) might also help clarify the role of reward dysregulation in TTM. Further, examinations of dopaminergic and glutamatergic activity in these regions and the effect of emerging treatments in their activity may be of great interest and should aid in the development of more targeted and efficacious treatments.

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Contributors

Matthew P. White M.D. conceived, designed and sought funding for the study. He is primarily responsible for data analysis and preparation of the manuscript.

William R. Shirer B.S., Research Assistant, performed MRIs, wrote software scripts used in the data analysis and prepared figures.

Maria Molfino, Research Assistant, performed MRIs, wrote software scripts used in the data analysis and prepared figures.

Caitlin Tenison, Research Assistant, performed preliminary analysis on the Monetary Incentive Delay Task.

Jessica S. Damoiseaux, Postdoctoral Fellow, wrote the software scripts used in the dual regression analysis and advised on resting state analysis and FSL.

Michael D. Greicius advised on all stages of study design, analysis and manuscript preparation.

Conflict of interest

Dr. White, Mr. Shirer, Ms. Molfino, Ms. Tenison, and Dr. Damoiseaux have no disclosures. Dr. Greicius receives consultant fees from Genentech and Pfizer and royalties on a shared patent with Phillips.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2013.05.014.

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