
CRITICAL REVIEW

Systematic Review of Published Primary Studies of Neuropsychology and Neuroimaging in Trichotillomania

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Abstract

Objectives: Existing models of trichotillomania (TTM; hair pulling disorder) rely heavily on a biological predisposition or biological pathogenesis of the disorder, but fail to capture the specific neuropsychological mechanisms involved. The present systematic review aims to scope existing neuropsychological studies of TTM to explore gaps in current models. **Methods:** A systematic literature search was conducted to detect all published primary studies using neuropsychological and neuroimaging measures in a cohort of individuals experiencing TTM. Studies addressing neuropsychological function were divided into domains. Findings from imaging studies were considered within brain regions and across methodology. **Results:** Thirty studies with a combined 591 participants with TTM, 372 healthy controls and 225 participants in other types of control group were included. Sixteen studies investigated neuropsychological parameters, and 14 studies pursued neuroimaging technologies. Available studies that used neuropsychological assessments and reported a statistically significant difference between those with TTM and controls ranged in effect size from 0.25 to 1.58. All domains except verbal ability and visual ability reported a deficit. In neuroimaging studies, several structural and functional brain changes were reported that might be of significance to TTM. Only tentative conclusions can be made due to the use of multiple methodologies across studies, a major limitation to meaningful interpretations. **Conclusions:** Positive neuropsychological and neuroimaging results require replication, preferably with multi-site studies using standardized methodology. Increased standardized testing and analyses across the literature, as a whole, would improve the utility and interpretability of knowledge in this field. (*JINS*, 2018, 24, 188–205)

Keywords: Trichotillomania, Cognition, Systematic review, Neuropsychology, Neuroimaging, Brain

INTRODUCTION

Trichotillomania (TTM), otherwise known as hair pulling disorder, typically involves an overwhelming compulsion or urge to pull out one's own hair, and is associated with high levels of psychological distress. Several theories and models of TTM have been proposed and all rely heavily on a biological predisposition or biological pathogenesis; the biopsychosocial model (Franklin, Tolin, & Diefenbach, 2006), the stimulus regulation model (Penzel, 2003, 2008), the ethological model (Swedo, 1989), and the Affect regulation, Behavioral addiction, and Cognitive control model

for habit disorders more generally (Stein, Chamberlain, & Fineberg, 2006).

In a review of neuropsychological research in TTM, Stein and colleagues (Stein, O'Sullivan, van Heerden, Seedat, & Niehaus, 1998) concluded that both obsessive compulsive disorder (OCD) and TTM demonstrate cortical striatal involvement. In another review, it was acknowledged that evidence of brain regions associated with TTM was limited to either single studies or conflicting multiple studies; the authors of that review surmised that the cognitive domains of visuo-spatial learning and response inhibition were impaired in a proportion of people with TTM while set shifting appeared intact (Chamberlain, Odlag, Boulougouris, Fineberg, & Grant, 2009).

Six studies that explored neuropsychological function in TTM were reviewed by Walther, Ricketts, Conelea, and Woods (2010). While acknowledging contradictory findings,

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the authors noted that impaired cognitive flexibility is consistent with repetitive habitual motor patterns in TTM. Other reviews were more critical of the collected evidence. Duke, Keeley, Geffken, and Storch (2010), and Flessner, Knopik and McGeary (2012) could draw no clear conclusions given the diverse findings. Inconsistencies in both the neuropsychological and neuroimaging studies were highlighted, including conflicting results regarding inhibitory control and set shifting tasks, and mixed support for the involvement of frontal striatal circuits, the basal ganglia, and cerebellum (Flessner et al., 2012).

Finally, in the most recent reviews addressing the biological underpinnings of TTM, Johnson and El-alfy (2016) used a systematic search in which only three primary studies using either imaging or neuropsychological measures meet their selection criteria. A consistent theme of published reviews exploring the imaging and neuropsychological literature of TTM is the contradictory evidence, and/or sparse evidence in need of replication (Chamberlain et al., 2009; Flessner et al., 2012; O'Sullivan et al., 1997; Stein et al., 1998; Woods et al., 2006). No systematic review has been conducted to summarize neuropsychological and neuroanatomical research in TTM. The aim of the current review was to provide an up-to date systematic review of neuropsychological and neuroimaging studies in TTM.

METHOD

Literature Search

A literature search strategy was designed to detect published studies and was finalized before conducting the search. Studies were identified by searching electronic databases, and searching the references of included studies. A wide range of databases were searched using EBSCOhost, including: CINAHL; Health Source: Nursing/Academic Edition; Academic search Complete; Psychology and Behavioral Sciences Collection; Social Work Abstracts; ERIC; and SocINDEX (EBSCOhost, 2015). Search terms were: (trichotillomania OR hair pulling OR hairpulling OR hair-pulling) AND (neuropsych* OR attention OR neuroimaging OR fMRI OR neuropsychology OR neuropsychological OR biology OR neurobiology OR cognition OR cognitive).

Study Selection

Records were saved in a word document and the preferred reporting items for systematic reviews and meta-analyses (PRISMA; Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009) were followed. Once duplicates were removed, abstracts were screened and the inclusion criteria applied. Studies that clearly did not meet the inclusion criteria were rejected. For the rest, the full text was acquired to obtain adequate information about the inclusion and exclusion criteria. The references of studies in the full text appraisal assessment were searched. Reasons for excluding studies at the abstract and full text level were recorded.

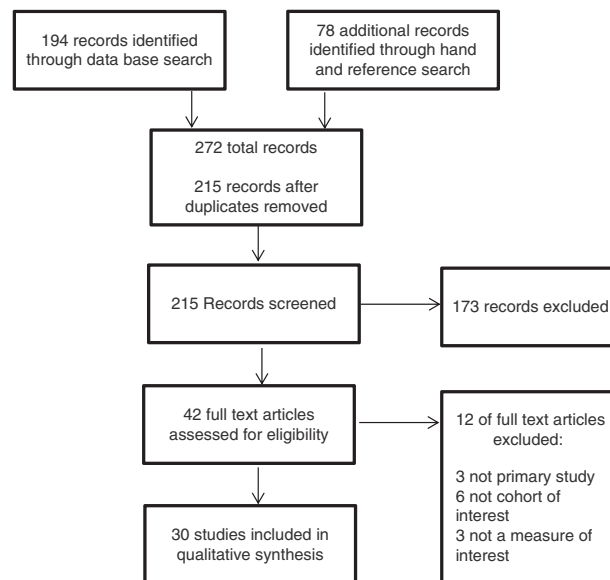


Fig. 1. PRISMA Flow chart from search results.

Search results with duplicates removed were assessed independently by two reviewers for adherence to inclusion/exclusion criteria. The inclusion criteria were: (1) the study must have reported primary research; (2) participants diagnosis of TTM confirmed by an appropriate healthcare professional; (3) data were quantitative; (4) the study used neuroimaging techniques, neuropsychological measures, or tasks measuring attention. Exclusion criteria were: (1) reviews and meta-analyses; (2) qualitative research; (3) the inclusion of children in the cohort. No limitations were made regarding quality of included studies, nor the design used so that an accurate picture of published research could be developed. The flow of studies through the screening process is presented in the PRISMA flow chart (Figure 1). When significant differences between TTM and healthy control (HC) groups were reported the effect sizes were calculated using Cohen's *d*; or Hedges' *g* for groups with different sample sizes. Effect sizes were considered: small ≤ 0.20 , $0.20 \leq$ medium < 0.50 , and large ≥ 0.80 (Cohen, 1992).

RESULTS

Two researchers (R.S. and M.R.) found 100% agreement for 30 studies that met inclusion criteria. One hundred and ninety-four search records were found through database searches, and 78 through hand searches and reference checks. After duplicates were removed 215 studies remained of which 42 full text articles were assessed for eligibility. Thirty studies, with a combined total of 591 participants with TTM, 372 HCs, and 225 participants in other types of control groups were included in this systematic review. Ten studies used an OCD comparison group, one study included a group of skin picking, one study a group of first degree unaffected relatives, and one study included a group of mixed anxiety disorders. This count was made on face value of reported

numbers. In practice, one participant or an entire cohort may have participated in multiple studies, for example, (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2006; Chamberlain, Fineberg, Blackwell, Robbins, & Sahakian, 2006; Chamberlain et al., 2007). One study pooled participants from multiple studies (Odlaug, Chamberlain, Schreiber, & Grant, 2013). The majority of studies were conducted with female participants from hospitals or specialist clinics, in the United States of America.

Neuropsychological Tests

Of the 16 studies that used neuropsychological measures, 12 compared TTM participants ($n = 11$ to 25) to HC groups ($n = 11$ to 26). Two studies used a within groups design to explore the effects of modafinil and naltrexone on neuropsychological performance. One study compared a cohort with TTM to skin picking. Table 1 summarizes these articles.

All neuropsychological measures were allocated to a cognitive domain for the purpose of organizing and making sense of the diverse measures used across studies. Domains were based on a prior neuropsychological review in OCD (Leopold & Backenstrass, 2015), to which we added neuropsychological tasks that had been used specifically in TTM studies. The domains were: processing speed, attention and vigilance, memory, verbal ability, visual ability, executive function, and motor and somatosensory function, as shown in Table 2.

DISCUSSION

Processing Speed

The most comprehensive exploration of processing speed was by Stanley, Hannay, and Breckenridge (1997) who reported statistically significant differences of approximately one standard deviation for: Trail Making B measured by trial time (TMT-B), and Weschler Adult Intelligence Scale - Revised (WAIS-R) Digit Symbol measured by the number of correct symbols. Confidence in these significant results is weakened by the number of participants with comorbid diagnoses and levels of anxiety, illustrated by a significant correlation between anxiety and TMT-B. People with TTM did not show a deficit in basic processing speed compared to controls when measured by the Trail Making Test A, or in processing speed associated with motor control, as measured by the length of time per trial of the Grooved Peg Board (Stanley et al., 1997).

In the single study that explored the effects of modafinil on neuropsychological function in TTM, no effect was found on visual processing speed or sustained attention, as measured by the Rapid Visual Information Processing Task (Chamberlain, Grant, Costa, Müller, & Sahakian, 2010). It is worth noting that the two processing speed measures that have been associated with TTM (TMT-B, WAIS-R Digit Symbol) are influenced by divided attention and were potentially confounded by substantial comorbidity. While it is possible that speed of processing is compromised in TTM when

attentional resources are challenged, the majority of evidence does not show processing speed impairments in TTM.

Attention and Vigilance

All studies discussed under Attention and Vigilance were conducted on TTM cohorts with numerous comorbidities, limiting the strength of conclusions that can be made. However, cohorts including multiple comorbid diagnosis more closely reflects TTM's actual clinical presentation and the consistency of findings across multiple studies increases confidence that conclusions are applicable to a wide general clinical group. No deficits were found on measures of focused attention: WAIS-R Delayed Recognition Span Test, Visual Search, the Attention Test (Stanley et al., 1997), and WAIS-R Digit Span (Bohne, Keuthen, Tuschen-Caffier, & Wilhelm, 2005; Bohne, Savage, Deckersbach, Keuthen, & Wilhelm, 2008; Bohne, Savage, et al., 2005; Keuthen et al., 1996; Stanley et al., 1997). This was not the case for divided attention, for which Stanley et al. (1997) reported deficits on: WAIS-R Digit Symbol, Paced Auditory Serial Addition Test (total score), and TMT-B.

Using an Endogenous Cueing Task, evidence was found that people experiencing TTM tend to use attentional disengagement at late stages of attentional processing when confronted with an image related to hair or general threat. The magnitude of attentional avoidance was large and related to TTM severity (Lee, Franklin, Turkel, Goetz, & Woods, 2012). Disengaging from emotional cues, and cues related to hair, may interfere with the encoding of memories.

Memory

Short-term verbal memory was not abnormal in TTM when measured using the WAIS-R Digit Span (Bohne, Keuthen, Tuschen-Caffier, & Wilhelm, 2005; Bohne et al., 2008; Bohne, Savage, et al., 2005; Keuthen et al., 1996; Stanley et al., 1997) or the California Verbal Learning Test (Bohne, Savage, et al., 2005; Stanley et al., 1997). Also, visual memory did not appear problematic in TTM. For example, people experiencing TTM did not differ from HCs on the Pattern Recognition Memory Test (Chamberlain et al., 2007), a particularly rigorous study that controlled for sex, age, verbal IQ, education, impulsivity, and depression; the Rey-Osterrieth Complex Figure Test (RCFT; Bohne, Savage, et al., 2005; Coetzer & Stein, 1999; Stanley et al., 1997; Stein, Coetzer, Lee, Davids and Bouwer, 1997); or on the Benton Visual Retention Test (Stanley et al., 1997). Additionally, modafinil did not influence the Pattern Recognition Memory Test (Chamberlain, Grant, et al., 2010).

There were some exceptions, specifically, three studies conducted with cohorts of TTM with multiple comorbidities. First, when the Stylus Maze was used as a measure of spatial memory, people with TTM made more errors and more rule violations than HCs, and performance on the Stylus Maze improved with a decrease in symptoms after clomipramine treatment (Rettew, Cheslow, Rapoport, Leonard, & Lenane, 1991).

Table 1. Studies with neuropsychological measures

Study, country, and participants	Neuropsychological measures	Main findings	TTM measures and task correlations	Anxiety levels and depression levels	Participant comorbidity and psychotropic medication
Rettew et al., 1991 USA 21 TTM, DSM-III-R 12 OCD, DSM-III-R 17 other anxiety disorder 16 healthy control	Money's Road Map Stylus Maze	Stylus Maze- TTM more route errors than HC*, other anxiety group more rule violations than TTM and HC**.	TSS (not reported) TIS (not reported) Correlations with Moneys Road Map, and Stylus Maze	ANX- not reported Dep- excluded if primary diagnosis, no scale	TTM- 2 panic LT, 9 GAD, 9 Dep LT, 2 bipolar, 7 drug or alcohol use, medication free. OCD- 10 Dep LT, 1 substance abuse, 3 panic, 4 bipolar, medication free. ANX- 10 social phobia, 5 panic and agor, 1 panic without agor, 1 GAD and somatization, 9 on medication. HC- 0, medication free
Stein et al., 1994 USA 13 TTM, DSM-III-R, 34 OCD, DSM-III-R, 16 healthy control	Multiple tests of coordination, involuntary movement, sensory function, and visuospatial function.	Visuospatial dysfunction- TTM more than HC*	Y-BOCS ($M = 8.6, SD = 11.7$) Correlations not reported	ANX- excluded if diagnosed, no scale. Dep- not significant	TTM- 1 OCD, medication free OCD- 0, medication free HC- 0, medication not reported
Keuthen et al., 1996 USA 20 TTM DSM-III-R 20 healthy control	Odd Man Out, Visual-Verbal Test, Rey-Osterrieth Complex Figure Test, Mental Rotation Test, Digit Span and Delayed Recognition Span Test from the WAIS-R.	Odd Man Out Test and Rey-Osterrieth Complex Figure Test (immediate recall)- TTM more errors than HC*	MGH-HPS (not reported) Correlation between- decreased resistance to pulling/behaviour and errors on Odd Man Out shapes.	ANX- not reported Dep- excluded if diagnosed, scale results not reported	Comorbidity not reported TTM & HC- medication free
Stanley et al., 1997 USA 21 TTM, 17 healthy control	The WAIS-R, multiple tests of Auditory perception and language, visual perception, somatosensory function, memory, motor ability, visual search, attention, concept formation, impulsivity and dichotic listening.	Divided attention tests, Paced Auditory Serial Addition Test, Trail Making B and Stroop- TTM poorer than HC**. Arithmetic and Digit Symbol from the WAIS-R- TTM poorer then HC** (Bonferroni corrected <i>t</i> test)	Not reported Correlations not reported	ANX- significant correlation with tasks Dep- significant correlation with tasks	TTM- 6 GAD, 5 social phobia, 2 simple phobia, 1 dysthymia, 1 bipolar, 1 panic with agor, medication free. HC- no Axis 1 diagnoses, medication not reported
Coetzer & Stein 1999 South Africa 11 TTM 11 OCD 11 healthy control	Comprehension, similarities, picture completion and block design from the South African WAIS. Stroop Test, Austin Maze, Hooper Visual Organization Test and Rey-Osterreith Complex Figure Copy.	Not significant	Not reported Correlations not reported	ANX- not reported Dep- excluded if diagnosed, not measured on scale	Comorbidity not reported TTM- some on SSRI, others not reported HC- medication not reported
Bohne, Keuthen et al., 2005 USA 21 TTM, DSM-IV 21 OCD, DSM-IV 26 healthy control	Block Cued Direct Forgetting Task. Participants were tested on free recall and recognition after being told to remember word lists, one list they were told to forget. Words related to TTM or neutral.	The OCD group recalled less words than the other two groups*, more TTM words were recognised by the TTM and OCD groups than the HC*. The TTM group rated TTM words as more negative than the OCD* and HC** groups.	MGH-HPS ($M = 14.1, SD = 4.8$) Y-BOCS ($M = 17.4, SD = 5.6$) Correlations not reported	ANX & OCD- not significantly different, but sig difference with HC	TTM- 4 social phobia, 3 specific phobia, 2 Dep, 1 eating disorder, 1 BDD, 1 = GAD, 1 panic with agor, 1 PTSD, 4 stable on medication. OCD- 7 social phobia, 4 BDD, 3 Dep, 1 Dysthymia, 1 GAD, 1 PTSD, 1 specific phobia, 13 stable on medication. HC-0, not on medication
Bohne, Savage et al., 2005 USA 23 TTM, DSM-IV	WAIS-R, Rey-Osterreith Complex Figure Test, California Verbal Learning Test, Tower of Hanoi,	Object Alternation Task- TTM made more perseverative errors than HC* and those	MGH-HPS ($M = 14.1, SD = 5.2$) Y-BOCS ($M = 16.9, SD = 5.0$) Not correlated	ANX & OCD- not significantly different, but significant difference with HC	TTM- 7 with Axis 1 disorders OCD- 10 with Axis 1 disorders HC-0

Table 1. (Continued)

Study, country, and participants	Neuropsychological measures	Main findings	TTM measures and task correlations	Anxiety levels and depression levels	Participant comorbidity and psychotropic medication
21 OCD, DSM-IV 26 healthy control Chamberlain, Blackwell et al., 2006 UK	Object Alternation Task, Wisconsin Card Sorting Test. Four Stage Visuospatial sequence task. Participants were asked to generate as many four red block sequences as possible on a screen before and after training.	with OCD more errors than TTM*. OCD group poorer performance than TTM and HC groups*	MGH-HPS ($M = 16.4$, $SD = 4.7$) Not correlated	ANX- excluded if diagnosed, no scale. Dep- excluded if diagnosed or >16 on MADRS, TTM & HC not significant, but OCD group sig more. No correlation with tasks	If Medicated, stable on medication for two weeks prior to participation TTM- no current Axis 1 disorders, medication free OCD- no current Axis 1 disorders, 16 on SSRI or medication free HC- 0
17 TTM, DSM-IV 20 OCD, DSM-IV 20 healthy control Chamberlain, Fineberg et al., 2006 UK	Stop-Signal Task. Participants pressed a button in response to arrows except when hearing an auditory tone. Intradimensional/ Extradimensional Shift Task. Participants learn a rule while guessing which of two stimuli are correct, the rule changes and so too must the participants guess it to be correct.	Reaction times for TTM were longer than OCD* and the OCD group were longer than the HC group*. The OCD group were poorer than the TTM* and HC* groups on the extradimensional shift condition.	MGH-HPS ($M = 16.4$, $SD = 4.7$) Correlated with stop signal reaction time	ANX- excluded if diagnosed, no scale. Dep- TTM and HC not significant, but OCD significantly higher. No correlation with tasks.	TTM- no significant comorbidities OCD- no significant comorbidities HC- not reported Medication free for 6 months before testing.
17 TTM, DSM-IV 20 OCD, DSM-IV 20 healthy control Chamberlain et al., 2007, UK	Pattern Recognition Memory Task, Spatial Working Memory Task, Tower of London, Information Sampling Task, Affective Go/no-go Task, Cambridge Gambling Task, Probabilistic Learning and Reversal Task.	Pattern Recognition Memory Task- OCD poorer than groups (immediate)*. Spatial Working Memory Task- OCD and TTM- more errors than HC*. Tower of London- OCD poorer than other groups*. Affective Go/no-go Task- OCD more errors than others* in the sad condition.	MGH-HPS ($M = 13.9$, $SD = 4.5$) Not correlated	ANX- excluded if diagnosed, no scale. Dep- excluded if diagnosed or >16 on MADRS, no significant difference. No correlation with tasks.	TTM- no significant comorbidities, medication free. OCD- no significant comorbidities, 16 on SSRI or medication free. HC- no current or history of Axis 1 disorders
20 TTM 20 OCD 20 healthy control Bohne et al., 2008 USA	Go/no-go Task. Participants pressed a button in response to one type of stimulus but not the other.	The TTM group performance was fast and inaccurate to slow and accurate*.	MGH-HPS ($M = 13.7$, $SD = 5.2$) Not Correlated	ANX- not significantly different between TTM and OCD, but significantly higher than HC. No correlation with tasks. Dep- not significantly different between TTM and OCD, but significantly higher than HC. No correlation with tasks.	TTM- 8 Axis 1 disorders OCD- 11 Axis 1 disorders HC- no current or past diagnosis Stable on medication two weeks prior
21 OCD, DSM-IV. 26 healthy control Chamberlain et al., 2010, UK, USA, Germany	Stop-Signal Task, Pattern Recognition Memory, Tower of London.	Not significant	MGH-HPS ($M = 14.6$, $SD = 3.9$) Correlations not reported	ANX- excluded if diagnosed, no scale. Dep- excluded if diagnosed or >10 on MADRS.	TTM- 1 panic, free of medication for 6 months.
18 TTM, DSM-IV Grant et al., 2011 UK, USA 39 TTM, DSM-IV 31, SP 33 healthy control	Intradimensional/Extradimensional Shift Task, Stop-Signal Task.	Stop Signal- reaction time was longer for SP than HC* and errors were greater for SP compared to TTM* and HC*.	CGI ($M = 4.56$, $SD = 0.75$) Not correlated	ANX- TTM & SP no significant difference, HC not tested. Correlation with SSRT for SP. Dep- TTM & SP no significant difference, HC not tested. Correlation with SSRT for SP.	TTM- 21 with comorbid disorders, 13 medicated SP- 22 with comorbid disorders, 15 medicated. HC- no current or LT diagnosis

Study, country, and participants	Neuropsychological measures	Main findings	TTM measures and task correlations	Anxiety levels and depression levels	Participant comorbidity and psychotropic medication
Han-Joo Lee et al., 2012 USA 13 TTM, DSM-IV 20 healthy control	Exogenous Cueing Task. Tests attentional engagement and attentional disengagement by requiring participants to respond to letters while pictures of TTM related pictures, general threat pictures, dysphoric mood pictures and neutral pictures.	At 1500ms the TTM group disengaged attention quicker from hair cues and threat cues compared to neutral cues *	MGH-HPS ($M = 20.2$, $SD = 4.7$) MIST-A automatic ($M = 23.1$, $SD = 7.8$) focused ($M = 45.0$, $SD = 15.9$) Not correlated	ANX- no significant difference between groups. Significant correlation with task. Dep- TTM significantly more than HC, significant correlation with task.	TTM- 5 Dep, 3 panic, 3 GAD, 1 ADHD, 2 on medication (no change in findings). HC- not reported
Odling et al., 2013 Denmark, USA 111 TTM, DSM-IV	Intradimensional/Extradimensional Shift Task, Stop-Signal Task.	TTM group made more Extradimensional shift errors than HC* and TTM group had longer reaction times on the Stop-Signal Task.	MGH-HPS (not reported) Correlations not reported	ANX- not reported Dep- not reported	TTM- grouped as internalizing and externalizing disorders, 37 stable on medication (no significant difference between medicated and unmediated group on tasks).
Grant et al., 2014 USA 51 TTM	Intradimensional/Extradimensional Shift Task, Stop-Signal Task.	Intradimensional/ Extradimensional Shift Task- cognitive flexibility improvement pre to post treatment, and compared to placebo*	MGH-HPS Naltrexone ($M = 16.2$, $SD = 4.8$) Placebo ($M = 18.3$, $SD = 3.8$) NIMH Naltrexone ($M = 12.0$, $SD = 4.0$) Placebo ($M = 12.9$, $SD = 3.9$) Correlations not reported	ANX- HAM-A, significant difference Dep- HAM-D, significant difference.	TTM- 27 with a comorbid disorder, 17 on medication.

Note. All studies adequately controlled for age of participants; TTM = trichotillomania; OCD = obsessive-compulsive disorder; HC = healthy control; ANX = anxiety; GAD = generalized anxiety disorder; Dep = depression; BDD = body dysmorphic disorder; PTSD = post-traumatic stress disorder; ADHD = attention deficit/hyperactivity disorder; agor = agoraphobia; SP = skin picking; LT = life time diagnosis; SSRI = selective serotonin reuptake inhibitor; DSM = Diagnostic and Statistical Manual of Mental Health Disorders; TSS = Trichotillomania Symptom Severity Scale; TIS = trichotillomania impairment scale; WAIS-R = Wechsler Adult Intelligence Scale Revised; MGH-HPS = Massachusetts General Hospital Hairpulling scale; MIST-A = Milwaukee Inventory for subtypes of Trichotillomania Adult version; Y-BOCS = Yale-Brown Obsessive-Compulsive scale; NIMH = National Institute of Mental Health Trichotillomania Symptom Severity Scale. CGI = Clinical Global Impressions Scale; MADRS = Montgomery-Asberg depression Rating Scale; HAM-D and HAM-A = Hamilton Depression and Anxiety Rating Scales; M = mean; SD = standard deviation.

* Significant at $\alpha = .05$.

** Significant at $\alpha = .001$.

Table 2. Domains in which neuropsychological measures have been discussed and studies reporting significant results between groups with associated effect sizes

Neuropsychological task with studies reporting significant results	Processing speed	Attention	Memory	Verbal ability	Visual ability	Executive function	Motor
The Grooved Peg Board	x						
Trail Making Test A	x						
Rapid Visual Information Processing	x						
Trail Making Test B	x	x					
<i>Stanley et al 1997 (completion time)</i>	$d = 0.94$						
Digit Symbol WAIS – R	x	x					
<i>Stanley et al 1997</i>	$d = 1.05$						
Delayed Recognition Span Test WAIS–R		x					
Digit Span WAIS-R		x	x				
Information Sampling Task		x					
The Visual Search and Attention Test		x					
Endogenous Cueing Task		x					
<i>Lee et al 2012 (hair cues)</i>		$d = 0.89$					
<i>Lee et al 2012 (general threat cues)</i>		$d = 0.82$					
The Paced Auditory Serial Addition Test		x	x				
<i>Stanley et al 1997 (total scores)</i>		$d = 1.22$					
Spatial Working Memory Task			x				
<i>Chamberlain et al 2007 (between-search errors hard)</i>			$d = 1.05$				
The Benton Visual Retention Test			x				
Spatial Delayed Recognition Span Test			x				
Spatial Span, Weschler Memory Scale III			x				
The California Verbal Learning Test			x				
The Pattern Recognition Memory Test			x				
The Stylus Maze			x				
<i>Rettew et al 1991 (route errors)</i>			$d = 0.85$				
<i>Rettew et al 1991 (Rule breaks)</i>			$d = 0.25$				
Rey – Osterrieth Complex Figure Test			x				x
<i>Keuthen et al 1996 (immediate recall)</i>			$d = 0.69$				
Paced auditory addition test			x				
<i>Stanley et al 1997 (total score)</i>			$d = 1.22$				
Arithmetic WAIS-R			x				
<i>Stanley et al 1997 (scale score)</i>			$d = 1.06$				
Comprehension WAIS–R				x			
Vocabulary WAIS–R				x			
The Controlled Oral Word Association Test				x			
Similarities WAIS–R				x			
Auditory Discrimination Test				x			
The Token Test				x			
The Fused Dichotic Words Test				x			
Moneys Road Map					x		
Mental Rotation Test					x		
The Boston Naming Test					x		
Visual Form Discrimination					x		
Facial Recognition					x		
Judgement of Line Orientation					x		
The Austin Maze					x		
Hooper Visual Organisation Test					x		
Picture Completion WAIS–R					x		
Probabilistic Learning and Reversal					x	x	
The Wisconsin Card Sorting Test						x	
Bloch Queued Directed Forgetting Task						x	
Visual Verbal Test						x	

Table 2. (Continued)

Neuropsychological task with studies reporting significant results	Processing speed	Attention	Memory	Verbal ability	Visual ability	Executive function	Motor
Cambridge Gambling Task						x	
The Wisconsin Card Sorting Task						x	
The Tower of London						x	
The Tower of Hanoi						x	
Block Design WAIS-R						x	
Four Stages Visuospatial Sequence Task						x	
Object Assembly WAIS						x	
Information Sampling Task						x	
Picture Arrangement						x	
The Booklet Category Test						x	
The Stroop Neuropsychological Screening Test						x	
The Matching Familiar Figures Test						x	
The Object Alternation Task						x	
<i>Bohne et al 2005 (% of perseverative errors)</i>						$d = 0.81$	
Odd Man Out						x	
<i>Keuthen et al 1996 (shapes, set errors)</i>						$d = 0.87$	
The Intra-dimensional Extradimensional Shift Task						x	
<i>Odlaug et al 2013 (total errors adjusted)</i>						$g = 3.92$	
<i>Odlaug et al 2013 (extra-dimensional shift errors)</i>						$g = 0.58$	
GoNogo Task							x
Abnormality of Movement							x
The Finger Tapping Test							x
Finger localization, preferred hand, non-preferred hand, right left discrimination							x
The Tactual Performance Test							x
The Motor Functions Scale of Delivery and Nebraska Neuropsychological Battery							x
Stop-signal Task, Reaction Time							x
<i>Chamberlain et al 2006 (reaction time, ms)</i>							$d = 1.58$
<i>Odlaug et al 2014 (reaction time, ms)</i>							$g = 0.51$

Note. WAIS-R = Wechsler Adult Intelligence Scale-Revised; d = Cohen's d ; g = Hedges' g ; Effect sizes were calculated for between trichotillomania groups and HC groups when significant differences were reported; x = indicates the domain in which the test has been discussed.

The second exception was found with the immediate recall condition of the RCFT, whereby individuals with TTM had poorer performance than a normal control group (Keuthen et al., 1996). Furthermore, impairment on the RCFT was found to be associated with decreased left caudate volumes in those with TTM, however, tests between groups on the RCFT were not reported (Stein, Coetzer, et al., 1997; see below for a discussion of caudate involvement in TTM).

There is also mixed evidence regarding working memory impairment in TTM. Evidence supporting such a deficit was found in two studies, the WAIS-R Arithmetic, the Paced Auditory Serial Addition Test (Stanley et al., 1997), and the Spatial Working Memory Task (Chamberlain et al., 2007). However, evidence for intact performance was reported for the Spatial Delayed Recognition Span Test (Keuthen et al., 1996), the Spatial Span, and the Weschler Memory Scale-III (Bohne et al., 2008).

To summarize memory related findings, two studies found a spatial memory deficit in TTM compared to HCs (Keuthen et al., 1996; Rettew et al., 1991), and one study found a deficit

compared to OCD (Chamberlain et al., 2007). A deficit in working memory in TTM was found by Stanley et al. (1997). Effect sizes ranged from medium to large. However, the majority of evidence points to no memory deficits in TTM when traditional memory tasks are used. None of the reviewed memory tasks used stimuli associated with TTM, such as images of hair or words associated with hair pulling. Novel TTM-relevant stimuli may be required to activate the emotional and cognitive bias that elicit memory deficits in TTM.

Verbal Abilities

There is strong evidence to suggest that verbal abilities are not impaired in TTM, including when tests of general verbal ability or of specific verbal skills are used. No differences have been found between control groups and individuals with TTM or OCD when using such general measures of verbal ability as Vocabulary, Comprehension, and Similarities from WAIS-R (Bohne, Keuthen, et al., 2005; Bohne et al., 2008;

Bohne, Savage, et al., 2005; Coetzer & Stein, 1999; Stanley et al., 1997; Stein, Coetzer, et al., 1997). Similarly, specific tests of language (The Auditory Discrimination Test, The Token Test, The Diffused Dichotic Words Test, and the Controlled Oral Word Association Test) were not impaired in people with TTM (Stanley et al., 1997). This is not surprising considering the essential elements of TTM do not include verbal IQ or language deficits (American Psychiatric Association, 2013).

Visual Abilities

Of the TTM studies reviewed, no deficits were reported in visual abilities. Measures of complex visual perception, Visual Form Discrimination, Facial Recognition, and The Boston Naming Test, did not detect any deficits regardless of level of control for confounding variables (Chamberlain, Grant, et al., 2010; Coetzer & Stein, 1999; Keuthen et al., 1996; Rettew et al., 1991; Stanley et al., 1997; Stein, Hollander, et al., 1994). Spatial orientation tested by The Judgement of Line Orientation Test, and visual search abilities tested by the Visual Search and Attention Test were also found to be intact (Stanley et al., 1997).

Similarly, performance in visual spatial ability using the Austin Maze and the Hooper Visual Organization Test did not appear abnormal in people with TTM (Coetzer & Stein, 1999; Stein, Coetzer, et al., 1997); nor was spatial rotation when measured by the Moneys Road Map and The Mental Rotation Test (Keuthen et al., 1996; Rettew et al., 1991). No abnormalities of visual spatial function were found when assessed with the face-hand test, left-right confusion or the drawing of a cube (Stein et al., 1994), and the ability to perceive missing visual information, measured by WAIS-R Picture Completion (Coetzer & Stein, 1999; Stanley et al., 1997; Stein, Coetzer, et al., 1997), was not compromised. Furthermore, visual processing speed was not affected by modafinil (Chamberlain, Grant, et al., 2010).

Executive Function

Measures of perseveration have been widely used in TTM neuropsychological research due to the purported correspondence between repetitive behavior in TTM and rituals in OCD. However, the majority of studies reported no difference between individuals who experience TTM and HCs on measures of perseveration and set shifting. No deficits were found in a TTM cohort using the Wisconsin Card Sorting Test (Bohne, Savage, et al., 2005; Stanley et al., 1997), the Stroop (Coetzer & Stein, 1999; Stanley et al., 1997; Stein, Coetzer, et al., 1997), with initiating or set shifting measured by the Visual-Verbal Test (Keuthen et al., 1996), or when The Probabilistic Learning and Reversal Task was used (Chamberlain et al., 2007). In contrast, participants with TTM made more perseverative errors than HCs on the Object Alternation Task, though it is unclear how this finding relates to TTM as the number of perseverative errors were not correlated with symptom severity (Bohne, Savage, et al., 2005).

Also of uncertain relationship to TTM was the finding of set shifting deficits with shapes but not letters on the Odd Man Out Test (Keuthen et al., 1996).

Cognitive inhibition was not found to be problematic in TTM when tested using a Block Queued Direct Forgetting Task, even though the words in the task were clearly of an emotionally negative valence (Bohne, Keuthen, et al., 2005). However, conflicting results have been found when cognitive flexibility and perseveration were investigated using The Intra-dimensional Extradimensional Shift Task. Two studies reported no deficits (Chamberlain, Fineberg, et al., 2006; Grant, Odlaug, & Chamberlain, 2011) whereas Odlaug et al. (2013) later reported deficits in extradimensional shift, though again no correlation was found between task performance and symptom severity. Furthermore, naltrexone increased cognitive flexibility, that is, reduced total errors on the Intra-extradimensional Shift Task, but did not influence reaction time (Grant, Odlaug, Schreiber, & Kim, 2014).

The majority of evidence exploring planning, problem solving, learning, and decision making in TTM supports the conclusion that these executive functions are intact in people with TTM. The aforementioned executive functions were not found to be problematic in TTM when measured using the Tower of Hanoi (Bohne, Savage, et al., 2005); the Tower of London (Chamberlain et al., 2007), including when modafinil was administered (Chamberlain, Grant, et al., 2010); the RCFT (Bohne, Savage, et al., 2005; Coetzer & Stein, 1999; Keuthen et al., 1996; Stanley et al., 1997; Stein, Coetzer, et al., 1997); the WAIS-R Block Design (Bohne, Savage, et al., 2005; Coetzer & Stein, 1999; Stanley et al., 1997; Stein, Coetzer, et al., 1997); The Probabilistic Learning and Reversal Task (Chamberlain et al., 2007); or when using the Object Assembly and Picture Arrangement Test from WAIS-III (Stanley et al., 1997).

There is no evidence to suggest that once a strategy has been taught to people with TTM they have difficulty implementing it, as measured by the four stages of the visuospatial sequence task (Chamberlain, Blackwell, et al., 2006). Moreover, the conceptual ability of using categories, as measured by the Booklet Category Test, was found to be intact in TTM participants (Stanley et al., 1997), as was decision making when measured by the Information Sampling Task and the Cambridge Gambling Task (Chamberlain et al., 2007).

Impulsivity has been proposed as a psychological construct underlying TTM (Flessner et al., 2012), yet no differences were found between those with TTM and a control group with the Matching Familiar Figures Test (Stanley et al., 1997), or with the Information Sampling Task (Chamberlain et al., 2007). These tests measure the dimension of reflection-impulsivity.

In summary, significant findings related to executive function require replication. The small number of studies reporting significant differences between groups within the domain of executive function may well reflect the 5% error rate inherent by the traditional use of $\alpha = 0.05$ to distinguish statistical significance. Furthermore, all tests found to have a significant difference between groups were not supported by correlations with symptom severity.

Motor

Studies in which motor functions were measured using a range of assessment methods reported no deficits in TTM (Stanley et al., 1997; Stein et al., 1994). However, a different picture emerged in studies using a narrower range of measures. The ability to suppress automatic motor reactions to an already triggered response was found to be impaired in TTM when measured using the Stop-Signal Task, (SST, Chamberlain, Fineberg, et al., 2006; Odlaug, Chamberlain, Derbyshire, Leppink, & Grant, 2014) whereas, results from Grant et al. (Grant et al., 2011) were inconclusive, with the TTM group performing midway between HCs and those with skin picking. Moreover, modafinil and naltrexone were found to have no bearing on reaction time associated with the SST compared to placebo control groups with TTM (Chamberlain, Grant, et al., 2010; Grant et al., 2014).

Motor inhibition was not impaired when tested using a GoNogo Task, although the correlation between reaction time and errors for those with TTM differed from HC and OCD groups (Bohne et al., 2008). Of interest, when the influence of emotion was added to motor inhibition using an Affective GoNogo Task, participants with TTM did not show impaired motor inhibition (Chamberlain et al., 2007). This is surprising given that emotion regulation has been touted as an underlying function of hair pulling in TTM (Arabatzoudis, Rehm, Nedeljkovic, & Moulding, 2017; Diefenbach, Mouton-Odum, & Stanley, 2002).

Critical Summary of Neuropsychological Studies

With a focus on studies using control groups, several systematic problems were identified in the reviewed literature on neuropsychological studies of TTM. Perhaps one of the more difficult limitations to overcome given the prevalence and secrecy of TTM, is that of small sample size. Not only may small sample sizes contribute to frequent type II errors it may also contribute to the lack of replicated results. Lack of replication is particularly striking when TTM is explored using neuropsychological measures. Indeed, replication of a statistically significant result when comparing those with TTM and HCs was only found on a single neuropsychological measure. Individuals with TTM were found to have impaired response inhibition during the SST compared to HCs (Chamberlain, Fineberg, et al., 2006; Odlaug et al., 2014); replication by an independent research group may clarify the magnitude of this impairment.

Neuropsychological tests often measure more than one cognitive process, and may span more than one domain with the same outcome measure. Grouping tests together based on targeted cognitive processes can help make sense of the results in relation to TTM, even though neuropsychological domains have not been statistically defined in TTM. For future research, a factor analysis of primary test results could help clarify which tests belong in various domains. Multiple tests of the same cognitive process could strengthen findings. In this review, results from primary studies were overwhelmingly not

statistically significant in all cognitive domains with a few exceptions in processing speed, divided attention, visual and working memory, executive function, and motor response inhibition. Of the statistically significant tests comparing TTM and HC groups, effect sizes ranged between 0.25 and 1.58.

Neuroimaging Studies

Fourteen published studies used neuroimaging techniques to examine patients with TTM. In controlled studies, the number of participants per study ranged from 10 to 18 in the TTM group and 10 to 20 in the HC group, one study comprised of a set of monozygotic twins and one study used a repeated measures design with 10 participants. Of the 11 studies that attempted to correlate imaging data with symptom severity, only five found a relationship (Table 3). Results are discussed below beginning with regions associated with fast automatic processing, and concluding with regions associated with complex cognition.

Nucleus Accumbens

In response to the Monetary Incentive Delay Task, the nucleus accumbens (NAcc) has been found to show decreased activation to reward anticipation and overactivity to gain and loss outcomes in TTM when compared to HCs (White et al., 2013). Even during resting state, the connectivity between the NAcc and the dorsal anterior cingulate was lower in those with TTM than a HC group (White et al., 2013). However, no relationship was found between NAcc function and symptom severity, participant comorbidity was not reported, and the TTM group experienced higher anxiety and depression than the HCs, which was not accounted for by the analyses. In contrast, left and right NAcc volumes were found to correlate with TTM symptom severity when TTM was measured by the Yale Brown Obsessive-Compulsive Scale and NAcc volume was measured in a whole brain analysis (Roos, Grant, Fouche, Stein, & Lochner, 2015).

Dorsal Striatum

The dorsal striatum is made up of the putamen and caudate nucleus. The first structural magnetic resonance imaging (MRI) study involving a TTM cohort is the only one to report decreased left putamen volumes, relative to HCs, using a region of interest (ROI) approach (O'Sullivan et al., 1997). Study limitations included a small sample size, possible confounding clinical level anxiety and subclinical depression, and the use of uncorrected tests for multiple comparisons. In contrast, a more rigorous study using a whole brain approach and powerful statistics found an increase in gray matter density in the left putamen (Chamberlain et al., 2008).

Decreased activity in the left putamen was found in those experiencing TTM using single-photon emission computed tomography (SPECT) after selective serotonin reuptake inhibitor (SSRI) medication (Stein et al., 2002), and decreased activation of the left putamen was found in response to loss anticipation using functional MRI (fMRI)

Table 3. Imaging studies, cohorts, imaging methodologies and design, and significant findings

Study, country, and cohorts	Imaging technology, methodologies and design	Significant difference found between control and TTM group	Anxiety and depression	Correlation with TTM severity	Exclusion criteria, participant comorbidity, and psychotropic medication
Swedo et al, 1991 USA 10 TTM/ 20 HC	PET- global and ROI comparison of glucose metabolism during resting state and after clomipramine treatment. Scanned during resting state, using 18-F-fluorodeoxyglucose in a Scanditronix PC-1024-7B machine.	Higher global metabolic rate of glucose** Higher left** and right* cerebellum, right superior parietal area* (exploratory <i>t</i> tests).	ANX- excluded if diagnosed Dep- excluded if diagnosed ANX & Dep scales- chronic anxiety corr with cerebellum metabolic rates.	Caudate corr with TSS* Right cerebellum corr with Ward*	Excludes: affective or anxiety disorder, physical illness, mental retardation and psychosis, no medication 4 weeks before scan. Comorbidity: Axis II personality disorders and LT affective and anxiety disorders.
O'Sullivan et al, 1997 USA 10 TTM/ 10 HC	MRI- ROI comparison of volume. 1.5T GE, Signa System	Decreased left putamen* and decreased left lenticulate volume* (exploratory <i>t</i> tests).	ANX- not reported, no scale Dep- excluded if diagnosed, no scale	Not reported	Excludes: OCD, Tourettes, ADHD, psychosis, current major depressive disorder, substance abuse or dependence, or significant medical or neurological illness. Comorbidity: TTM- 4 LT dep, 2 LT substance dependence, HC- none.
Grachev, 1997 USA 10 TTM/ 10 HC	MRI- total and ROI of the neocortex comparison of volume. 1.5T GE, Signa System	Reduced left inferior frontal gyrus volume*, and enlarged right cuneal cortex volume* (Bonferroni corrected <i>t</i> test)	ANX- not reported, no scale Dep- excluded if diagnosed, no scale	Not reported	Excludes: OCD, Tourettes, psychosis, depression, substance abuse, significant medical or neurological illness, no psychoactive medication 4 weeks before study. Comorbidity: not reported
Stein et al, 1997 South Africa 17 TTM/ 12 HC/ 13 OCD	MRI- ROI comparison of volume of caudate and ventricles. 0.5T Elscin MRI	Not significant	ANX- not excluded, no scale Dep- excluded if diagnosed, no scale	Not significant	Excludes: major depressive disorder, eating or psychotic disorder, history substance abuse, medical or neurological illness. Some on SSRIs. TTM- 1 social phobia, 1 specific phobia, 10 Dep LT OCD- 4 Dep LT, HC- No Axis I disorders
Stein et al, 2002 South Africa 10 TTM	SPECT- WB, Before and after 12 weeks of citalopram treatment. Asked to experience the urge to pull during scan. Single photon emission computed tomography with 555MBq (15 mCi) technetium-99m hexamethylpropylene amine oxime. Dual detector gamma camera (Elscint, Helix).	Before-after medication; decreased activity on left and right, inferior-posterior frontal areas* and superior-anterior frontal areas*; plus the right anterior-temporal area* and left putamen* (exploratory <i>t</i> tests).	ANX- not reported, no scale Dep- excluded if diagnosed, measured with scale	Baseline: left mid-posterior frontal area corr with NIMH-OC Baseline: left superior-lateral frontal area, left mid and superior parietal regions, left caudate, right inferior-posterior and mid-posterior frontal areas corr with CCOCS	Excludes: Major depressive disorder, significant medical or neurological illness
Vythilingum et al, 2002 South Africa Identical twins.	SPECT- WB, asked to feel the urge to pull during the scan. Cerebral Perfusion Single-Photon Emission Computed Tomography (SPECT) Technetium-99m hexamethylpropyleneamine oxime imaging agent.	Medial temporal lobe, parietal lobe and parietal cortex, Paracingular cortex, anterolateral left frontal lobe, parieto-occipital cortex.	ANX- no scale Dep- no scale	The more severely affected twin had more temporal involvement.	Twin Mrs B more severe TTM than Mrs A. no history of OCD or tics. Mrs A. no history of OCD or Tics. Recurrent depression beginning 12 years old with TTM onset, not current

Study, country, and cohorts	Imaging technology, methodologies and design	Significant difference found between control and TTM group	Anxiety and depression	Correlation with TTM severity	Exclusion criteria, participant comorbidity, and psychotropic medication
Rauch et al, 2007 USA 10 TTM/ 10 HC	fMRI- ROI, Serial reaction time task, pressing one of four buttons that correspond to an asterisk positioned in one of four locations on the screen (errors and RT). 1.5T Siemens Sonatal scanner	Not significant	ANX & Dep- no significant difference between groups using a scale.	Not reported	Excludes: Axis 1 comorbid disorders, previous or current neurological disorder that may confound findings. Not on medication during study. TTM- 1 general anxiety. HC- 2 specific phobia
Keuthen et al, 2007 USA 12 TTM/ 12 HC	MRI- ROI comparison of cerebellum 1.5T Siemens Sonatal scanner	Smaller overall, left, and right cerebellum volumes* (<i>a priori</i>). Cerebellum cortex*, total vermis*, medial hemisphere*, lateral hemisphere*, right vermis smaller volumes* (exploratory <i>t</i> tests).	ANX & Dep- no significant difference between groups using a scale.	Left primary sensorimotor area corr with MGH-HPS* (<i>a priori</i>).	Excludes: OCD spectrum disorder or psychiatric condition, head injury, seizures or neurological or medical conditions, substance dependence, pregnancy. No psychotropic medications 4 weeks prior. TTM- 1 GAD. HC- 2 specific phobia
Chamberlain, et al, 2008 UK 18 TTM/ 19 HC	MRI- WB, comparison of gray matter between groups permeation cluster analysis. 1.5T GE Signa system.	No difference in overall gray matter density. Three clusters of higher gray matter density* 1. left putamen, left amygdala, left hippocampus; 2. Bilateral anterior/middle cingulate, bilateral supplemental motor area, bilateral frontal superior cortex, bilateral frontal superior medial cortex 3. Left superior occipital cortex, left middle occipital cortex, left superior parietal cortex, left inferior parietal cortex.	ANX- not excluded, no scale. Dep- excluded if diagnosed, significant difference between groups using a scale, statistically controlled in analysis.	Not significant	Excludes: history of neurological conditions and epilepsy, current depression, OCD, Tics, epilepsy. No treatment for 6 months. TTM- 1 panic and agoraphobia. HC- no Axis I disorders
Chamberlian et al, 2010 UK, USA 18 TTM/ 19 HC	DTI- WB, comparison of white matter integrity, Fractional anisotropy, using tract-based spatial statistics. 3T Siemens Allegra Magnetom Scanner.	Three clusters of reduced white matter integrity **. 1. Multiple temporal regions 2. Bilateral anterior cingulate cortices 3. Left pre-supplementary motor area.	ANX- not reported, no scale. Dep- excluded if diagnosed or, significant difference between groups using a scale, statistically controlled in analysis.	Not significant	Excludes: depression, OCD, pyromania, kleptomania, pathological gambling, head injury, substance abuse, neurological disorders, < 90 on the National Adult Reading Test, no treatment for 6 months TTM- comorbidity not reported HC- free of Axis I disorders
Roos et al, 2013 South Africa 16 TTM/ 13 HC	DTI- ROI, comparison of white matter integrity, Fractional anisotropy and mean diffusivity, axial diffusivity and radial diffusivity using permeation analysis. Diffusion tensor imaging. 3T Siemens Allegra Magnetom Scanner.	Not significant	ANX- excluded if diagnosed, TTM higher on scale. Dep- excluded if diagnosed, TTM higher on scale.	Fronto-striatal-thalamic pathway corr with duration of TTM and MGH-HPS*. Genu of the corpus callosum, and right anterior corona radiata corr with duration of TTM*. Left posterior corona radiata, and left posterior thalamic radiation corr with MGH-HPS*. Not significant	Excludes: substance or alcohol abuse/dependence, psychosis, psychiatric comorbidity, significant medical or neurological illness. Free of psychotropic medication or stable on them. TTM- 2 taking SSRIs, no comorbidity HC- no disorders

Table 3. (Continued)

Study, country, and cohorts	Imaging technology, methodologies and design	Significant difference found between control and TTM group	Anxiety and depression	Correlation with TTM severity	Exclusion criteria, participant comorbidity, and psychotropic medication
White et al, 2013 USA 12-13 TTM/ 14-12 HC	fMRI- ROI, comparison of resting state functional connectivity and a monetary incentive delay task. The task requires the participant to react to a stimulus after a cue resulting in the win or loss of money. 3T GE Signa scanner	Decreased activation of the NAcc to reward anticipation* and overactivity of the NAcc to gain and loss outcomes*. Decreased activation in left putamen and insular in response to loss anticipation**. Reduced bilateral functional connectivity dorsal ACC and NAcc*. Decreased activation of temporal lobe from right baso-lateral amygdala to orbitofrontal cortex*. At resting state decreased connectivity of the dorsal anterior cingulate to the NAcc was found in TTM*. TTM had no increased connectivity.	ANX- excluded if diagnosed, TTM higher on scale. Dep- excluded if diagnosed, TTM higher on scale.		Excludes: psychotropic medication, active substance abuse, active suicidal ideation, bipolar disorder or psychotic disorder. Comorbidity not reported
Odlaug et al, 2014 Denmark, USA, UK 12 TTM/ 14 HC/ 10 first degree relatives'	MRI- WB, comparison of cortical thickness. Permeation cluster analysis. Structural imaging after task, 3T, Philips Achieva Quasar Dual 16 Ch system. (for the Stop-signal Task see Motor section).	Greater cortical thickness, as did relatives in the right middle and inferior frontal gyri, right lingual gyrus, left superior temporal cortex, and left precuneus	ANX- excluded if diagnosed, no scale. Dep- excluded if diagnosed, no scale.	Not significant	Excludes: comorbid disorders, unstable medical illness, pregnancy, inadequate contraceptives, thoughts of suicide, history of bi polar disorder, dementia, psychosis, substance use disorder, behaviour therapy or psychotropic medication in last 6 months, use of illicit drugs TTM- 1 taking lorazepam, LT depression, 3 LT anxiety disorder
Roos, et al, 2015 South Africa, USA 17 SP/ 17 TTM/ 15 HC	MRI- WB, comparison of volume and cortical thickness 3T Siemens Allegra MRI	Thinner parahippocampal gyrus*	ANX- excluded if diagnosed, no significant difference between groups. Dep- excluded if diagnosed, no scale.	Volumes of the left and right accumbens corr with YBOCS score	Excludes: LT psychosis, psychiatric comorbidity, and significant physical or neurological illness, pregnancy, not on stable medication for at least 3 months. TTM- 2 taking medication

Note. TTM = trichotillomania; HC = healthy control; OCD = obsessive-compulsive disorder; ANX = anxiety; Dep = depression; ADHD = attention deficit/hyperactivity disorder; GAD = generalised anxiety disorder; SP = skin picking; LT = Life time diagnosis; corr = a correlational relationship; WB = whole brain; ROI = region of interest; RT = reaction time; TSS = Trichotillomania Symptom Severity Scale; MGH-HPS = Massachusetts General Hospital Hairpulling scale; YBOCS = Yale Brown Obsessive-Compulsive Scale; CCOCS = Clinician Challenge Obsessive-Compulsive Scale; Ward = Ward obsessive-compulsive disorder rating of hair pulling severity; NIMH-OC = Mental Health-Obsessive Compulsive Scale; SSRI = selective serotonin reuptake inhibitor; NAcc = nucleus accumbens; ACC = anterior cingulate cortex; DTI = diffusion tensor imaging; PET = positron emission tomography; fMRI = functional magnetic resonance imaging; MRI = magnetic resonance imaging; SPECT = single photon emission computed tomography.

* Significant at $\alpha = .05$.

** Significant at $\alpha = .001$.

(White et al., 2013). Neither of these studies correlated the putamen with TTM symptom severity. Another study, which controlled for subclinical depression and anxiety, found that the serial reaction time task did not elicit functional differences between those with TTM and HCs in the cortical-striatal pathway (Rauch et al., 2007).

Regarding the caudate nucleus, left caudate volume was significantly correlated with symptom severity on the Clinician Challenge Obsessive-Compulsive Scale, albeit structural and functional differences between TTM and HCs were not reported (Stein, Coetzer, et al., 2002, 1997). Furthermore, a significant correlation between glucose metabolism in the caudate and The Trichotillomania Symptom Severity Scale was reported by Swedo and colleagues (Swedo et al., 1991). Additional complexity was added to the question of the role of the dorsal striatum in TTM by the findings of Roos, Fouché, Stein, and Lochner (2013). TTM severity was shown to correlate with white matter integrity of the internal capsule. The internal capsule projects through the caudate nucleus and putamen; it relays sensory and motor information from the cortex to the brainstem, and extends as the corona radiata. White matter damage or disorganization of the internal capsule, which passes through the ventral and dorsal striatum, was positively correlated with symptom severity using the Massachusetts General Hospital Hair Pulling Scale (MGH-HPS; Roos et al., 2015).

Hippocampus

Chamberlain et al. (2008) found that participants with TTM had increased gray matter density in the left hippocampus compared to HCs. Furthermore, mixed evidence has been reported regarding the parahippocampal gyrus. Roos et al. (2015) found it to be thinner on the right in people with TTM compared to HCs whereas others have found no such difference (Grachev, 1997; Odlaug et al., 2014). Roos et al. did not report statistical corrections for multiple analysis which may have influenced this result. A functional study also failed to find significant differences in hippocampus activation in those with TTM compared to HCs (Rauch et al., 2007).

Amygdala

Two studies reported significant findings regarding the amygdala in TTM. Using MRI to explore gray matter density, Chamberlain et al. (2008) found that those with TTM showed higher gray matter density in the left amygdala. White et al. (2013) found that during resting state the baso-lateral amygdala had decreased connectivity to the reward network in participants with TTM. Specifically, decreased activation of the connection between the right baso-lateral amygdala and the orbitofrontal cortex (White et al., 2013).

Cingulate

Only the anterior, not posterior, cingulate has been associated with significant findings in the literature. During resting state,

decreased connectivity of the dorsal anterior cingulate to the NAcc was found in individuals with TTM (White et al., 2013). Also, reduced white matter integrity between the orbital frontal cortices and anterior cingulate cortices have been reported (Chamberlain, Hampshire, et al., 2010). Not only is it possible that the connecting fibers of the cingulate contribute to TTM by disrupting communication to the orbital frontal cortices, increased gray matter density of the anterior and middle cingulate may further disrupt information processing (Chamberlain et al., 2008).

Yet the main fiber tract running the length of the cingulate gyrus, the cingulum, did not differ in activation after a reduction in symptoms post citalopram treatment (Stein et al., 2002). Nor were there activation differences in the left and right posterior cingulate cortex during an implicit sequence learning task (Rauch et al., 2007). Last, there were no differences in glucose metabolism of the anterior cingulate in TTM (Swedo et al., 1991). However, a correlation between left anterior cingulate glucose metabolism and symptom improvement measured by a clinician rated scale after clomipramine treatment was reported (Swedo et al., 1991).

Occipital Regions

Some studies report volume and density abnormalities in the occipital cortex in TTM. The left superior and middle occipital cortex areas were found to have increased gray matter density compared to HCs along with the left superior and inferior parietal areas with whole brain cluster analysis (Chamberlain et al., 2008). The right cuneal cortex and lingual gyrus was reported as enlarged in those with TTM in a study using a ROI approach to measure cortical volume, although comorbidity and anxiety were not reported in the study (Grachev, 1997). Of interest, in a whole brain comparison of cortical thickness, first degree relatives of those with TTM had an even thicker lingual gyrus than those with TTM (Odlaug et al., 2014). A study which did not include participants with any clinical level comorbidity and which used an ROI approach reported no differences in the degree of damaged or disorganized white matter measured by fractional anisotropy, axial diffusivity, and mean diffusivity. However, the left posterior corona radiata did correlate with the MGH-HPS (Roos et al., 2013). The posterior corona radiata projects from the brainstem to the parietal and occipital cortex.

Temporal Lobe

Using single SPECT, Stein et al. (2002) reported decreased activity in right anterior temporal lobe after citalopram treatment in 10 participants with TTM. Yet post-treatment increased activity in the right medial-temporal area was found while participants allowed themselves to experience the urge to pull; this increase in activity was correlated with TTM symptom severity (Stein et al., 2002). In the study of a set of twins with TTM, poor perfusion was found in both temporal lobes using SPECT, with wider areas of decreased

perfusion in the left lobe of the twin with more severe TTM (Vythilingum et al., 2002).

Parietal Regions

Abnormal structure and function of the superior parietal lobe would make logical sense in TTM as it includes the primary sensory cortex where the bulk of sensory information is processed. Indeed, the behavior of hair pulling involves fine-tuned tactile information from fingertips and the sensory experience of the hair leaving the skin. Abnormal white and gray matter has been reported as significantly different from HCs in those with TTM. Disrupted white matter integrity in the left primary somatosensory cortex has been found (Chamberlain, Hampshire, et al., 2010), although a subsequent study did not support white matter differences in this area (Roos et al., 2013).

Gray matter abnormalities of left superior parietal cortex and left inferior parietal cortex (Chamberlain et al., 2008) have been described. In addition, the precuneus cortical thickness has been reported as significantly thicker than HCs (Odlaug et al., 2014). Finally, the earliest study included in this review reported a higher ratio of glucose metabolism in the right superior parietal area compared to HCs using positron emission tomography (PET) (Swedo et al., 1991). A decrease in activity of the left mid and superior parietal regions correlated with clinician ratings of TTM severity before treatment (Stein et al., 2002).

Motor Areas

The cerebellum is heavily involved in adjusting postural muscles, and programming and fine-tuning motor control; little surprise then that evidence of its involvement in TTM has been reported. A well-controlled study with no differences between groups on scales of anxiety and depression, and with a focus solely on the cerebellum, reported significant findings. Smaller overall cerebellum volumes were found in those experiencing TTM compared to HCs; as were left and right cerebellum volumes (Keuthen et al., 2007). Within the cerebellum, smaller volumes of the functional area of the left primary sensorimotor cluster were associated with more severe TTM.

Group differences were found for the vermis and medial and lateral hemispheres. It was also shown that, for those with TTM, volumes of the right thermal subterritory were smaller than in a HC group (Keuthen et al., 2007). These volumetric measures of the cerebellum support previous findings that the cerebellum may play a role in TTM. Specifically, Swedo et al. (1991) reported that glucose metabolism was higher in both the left and right cerebellum in those with TTM compared to HCs, and a correlation was found between symptom severity and activity in motor areas. However, Swedo et al. also reported a correlation between cerebellum metabolic rates and chronic anxiety, a possible study confound.

While correlations have been found between functional and volumetric measures and symptom severity with the cerebellum, this is not the case for other areas of the brain

involved in motor function. Whole brain analysis has shown increased gray matter in the bilateral supplemental motor area in people with TTM compared to HCs (Chamberlain et al., 2008), and white matter integrity in the connections with the left supplementary motor area were also compromised (Chamberlain, Hampshire, et al., 2010), even though volumetric differences with an ROI approach have not been found (Grachev, 1997). Structural differences between groups have been reported in brain areas associated with movement, but the lack of correlation with TTM symptom severity demonstrates that these structural differences cannot be accounted for by TTM symptoms, with the exception of the cerebellum.

Prefrontal Cortex and Frontal Lobe

Several studies have compared the volume of the frontal lobe or prefrontal cortex between those with TTM and those without. ROI approaches to volume measures have reported mixed results; Grachev et al. (1997) reported left inferior frontal gyrus volumes in those with TTM compared to those of HCs, while Stein, Coetzer, et al. (1997) found no difference at all. Other findings using whole brain analysis indicate greater cortical thickness (Odlaug et al., 2014). Doubt is cast on the idea of frontal gyrus volume contributing to TTM due to the lack of correlation with symptom severity.

Increased gray matter density was found in the bilateral frontal superior cortex and bilateral frontal superior medial cortex in TTM patients compared to HCs (Chamberlain et al., 2008). White matter integrity was reduced in the bilateral orbital frontal cortices (Chamberlain, Hampshire, et al., 2010). While the finding of reduced white matter integrity was not replicated in the orbital frontal cortices, the level of white matter integrity in the right anterior corona radiata was subsequently found to be correlated with the duration of TTM (Roos et al., 2013).

Using SPECT, decreased activity in several frontal areas was found after treatment with SSRI medication compared to baseline (Stein et al., 2002). In parallel with the reviewed literature of parietal areas, the only study to report correlations with symptom severity was Stein et al. (2002). Decreased activity indicated by SPECT findings of the left mid-posterior frontal area were found to correlate with the National Institute of Mental Health-Obsessive Compulsive Scale. Decreased activity in the left superior-lateral frontal area, the right inferior-posterior, and mid-posterior frontal areas of SPECT measures while experiencing the urge to pull correlated with clinician ratings of symptom severity before citalopram treatment (Stein et al., 2002). While before treatment a decrease in activation was correlated with severity, after treatment, an increase of activation was correlated with severity. The left-inferior lateral, inferior posterior, mid-posterior, and superior posterior frontal areas correlated with symptom severity (Stein et al., 2002).

Critical Summary of Imaging Findings

Based on studies using an HC comparison group, weak or no evidence was found for caudate nucleus and temporal lobe

involvement in TTM (Roos et al., 2013; Stein, Coetzer, et al., 1997; Sullivan et al., 1997; Swedo et al., 1991). Initial findings addressing reward circuitry and the nucleus accumbens in TTM point to an area of research which may, in the future, shed light on the underlying motivation for hair pulling, for example, negative emotions that are perceived as punishing, and the respite of which is perceived as rewarding (White et al., 2013).

Single studies have shown that volume, gray matter, and activity of the putamen differ from HCs, and have reported activation and structural abnormalities of the anterior cingulate and amygdala (Chamberlain et al., 2008; Chamberlain, Hampshire, et al., 2010; Sullivan et al., 1997; White et al., 2013). Mixed evidence was found for structural abnormalities of the hippocampal area in those with TTM (Chamberlain et al., 2008; Grachev, 1997; Odlaug et al., 2014; Roos et al., 2013). In the occipital regions, volume and density structural differences were reported, with the exception of white matter integrity (Chamberlain et al., 2008; Grachev, 1997; Roos et al., 2013).

Single studies have also reported gray matter and volume differences in several areas of the parietal lobe (Chamberlain et al., 2008; Odlaug et al., 2014). Within the parietal lobe, conflicting evidence was found regarding white matter dysregulation of the somatosensory cortex (Chamberlain, Hampshire, et al., 2010; Roos et al., 2013). Some evidence was found regarding cerebellum volume differences in TTM, including a relationship to symptom severity (Keuthen et al., 2007). Structural differences have been identified in other motor areas but without volume changes and correlations to TTM symptoms (Chamberlain et al., 2008; Chamberlain, Hampshire, et al., 2010; Sullivan et al., 1997). Finally, mixed evidence was found for frontal lobe volume differences with HCs, and some evidence for structural anomalies were reported (Chamberlain et al., 2008; Chamberlain, Hampshire, et al., 2010; Odlaug et al., 2014; Roos et al., 2013; Stein, Coetzer, et al., 1997; Sullivan et al., 1997).

Overall, the pool of available imaging literature in people with TTM was small, precluding robust conclusions. Seven studies used MRI to explore the volumes of various brain structures (Chamberlain et al., 2008; Grachev, 1997; Keuthen et al., 2007; Odlaug et al., 2014; Roos et al., 2015; Stein, Coetzer, et al., 1997; Sullivan et al., 1997). As each of these studies reported differing positive results and used different methodology, conclusions about structural volumes in TTM remain uncertain. Other studies were focused on the cerebral cortex, the results of which were markedly dissimilar (Chamberlain et al., 2008; Grachev, 1997; Odlaug et al., 2014; Roos et al., 2015). Two studies that explored white matter integrity using DTI also reported discrepant findings (Chamberlain, Hampshire, et al., 2010; Roos et al., 2013). Finally, knowledge of brain function and biological activity in TTM was restricted to five studies that used three techniques between them: PET (Swedo et al., 1991), SPECT (Stein et al., 2002; Vythilingum et al., 2002), and fMRI (Rauch et al., 2007; White et al., 2013).

All studies adequately matched age, gender, and handedness and included either the Structured Clinical Interview or the Mini International Neuropsychiatric Inventory for screening comorbid disorders. More generally, confounds were more rigorously controlled in imaging studies compared to studies using neuropsychological measures. Yet, control for comorbid depression and anxiety varied greatly between studies with various combinations of binary measures, scale measures, and the use of statistics to address anxiety and depression levels.

CONCLUSIONS

Our findings support previous conclusions that neuropsychological studies in TTM are sparse (Chamberlain et al., 2009; O'Sullivan et al., 1997; Stein et al., 1998; Woods et al., 2006), yet some patterns in the literature are beginning to emerge. The evidence reviewed here suggests that a substantial number of neuropsychological functions are intact in TTM, including processing speed, verbal abilities, visual abilities, focused attention, short-term memory, perseveration and set shifting, planning, problem solving and decision making, and general motor functions. However, some areas were found to show a deficit or consist of mixed results and would be worthwhile areas for future research, for example, divided attention, visual memory, working memory, and the ability to suppress automatic motor reactions. Replication is also required of the one study that found a tendency to use attentional disengagement when confronted with visual cues associated with hair pulling.

Some areas of the brain in TTM have been shown to have differences in either the structure or function compared to control groups without a correlation to TTM symptom severity, such as the putamen, hippocampus, and anterior cingulate. In other areas, such as the ventral striatum, caudate, amygdala, occipital lobe, cerebellum, and frontal lobe, reports of both differences between groups on structure or function and correlations with symptoms were reported, albeit not always within a study and with the same imaging technique. Yet research on most areas did not provide convincing evidence of involvement in TTM.

Future research involving neuropsychological testing would benefit from multi-center collaboration to increase sample size. Maintaining consistent data collection between sites may prove easier with neuropsychological testing than with imaging technology due to the complex settings and various models of scanning equipment. The existing neuropsychological literature would benefit from new research exploring various aspects of attention, motor impulse control, and memory using hair pulling related stimuli, as would future fMRI studies.

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