



Review

Trichotillomania: Neurobiology and treatment

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ABSTRACT

Trichotillomania is a disorder characterized by repetitive hair pulling, leading to noticeable hair loss and functional impairment. This paper provides an overview of what is known of trichotillomania from several perspectives. We begin by considering historical descriptions of hair pulling that ultimately contributed to the inclusion of trichotillomania as a formal diagnostic entity in the Diagnostic and Statistical Manual. Psychological factors involved in the mediation of symptoms are examined, including positive and negative reinforcement. The relationships between trichotillomania, other body-focused repetitive behaviours, and disorders of the putative obsessive-compulsive (OC) spectrum are surveyed. The review then explores findings from the available controlled treatment trials that utilized psychotherapy, pharmacotherapy, or both. Neural circuitry involved in the manifestation of hair pulling is then identified by considering data from animal models of the condition, along with neurocognitive and neuroimaging results from patients. Finally, we highlight important areas for future neurobiological and treatment research.

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1. Introduction

Trichotillomania is a psychiatric condition characterized by repetitive hair pulling, usually from the scalp and/or eyebrows, though any site can be affected. According to current diagnostic criteria, hair pulling is preceded by mounting tension, and is associated with subsequent relief, gratification, or pleasure (Diagnostic and Statistical Manual Version IV) (DSM-IV) (American Psychiatric Association, 2000). Hair pulling is one of several phenomenologically related grooming behaviours, along with nail biting and skin picking, which occur across species and in milder forms can be considered within the range of normal behaviour (Mansueto et al., 2007). The pathology of hair pulling in trichotillomania, therefore, exists in the focus, duration and extent of the behavior, as well as the resulting problems (noticeable hair loss and functional impairment). According to interviews conducted in a sample of 28 patients, symptoms impaired work productivity, disrupted family life, and led to avoidance of sports/social activities (Diefenbach et al., 2005). Trichotillomania has been associated with a variety of medical complications, including repetitive strain injury and the development of gastrointestinal obstruction following hair consumption, in case reports (e.g. see Dean et al., 1992; Bouwer and Stein, 1998; Keuthen et al., 1998; Frey et al., 2005).

There have been no population-wide epidemiological studies of trichotillomania. In a questionnaire-based study of 2500 US college students with a response rate of >90%, hair pulling resulting in noticeable hair loss was reported by 1.5% of males and 3.4% of females. Overall, 0.6% of the sample met DSM-III-R criteria for lifetime trichotillomania, strictly defined (Christenson et al., 1991c). In treatment trials, usually threefold or greater proportions of women than men have participated (Chamberlain et al., 2007d). Although this suggests trichotillomania may be more prevalent in women, it may be that males are reluctant to come forward for treatment, and/or more able to conceal hair loss by shaving. It has been suggested that hair pulling in very young children, known as 'baby trich', might constitute a distinct entity (Swedo and Rapoport, 1991). By contrast, archetypal trichotillomania starts in early puberty (11–13 years of age) and follows a relapsing-remitting course into adulthood. Amongst 772 subjects who responded to a magazine article about trichotillomania and were sent questionnaires about hair pulling, 123 replied (Cohen et al., 1995). Of these responders, most reported that they had not received treatment. Those who had received treatment reported disappointing outcomes.

2. Historical perspective: from Hippocrates to the DSM

The phenomenon of hair pulling has been recognized for centuries. Accounts of hair pulling are found in the Bible, Homer's *The Iliad*, and the plays of William Shakespeare (Christenson and Mansueto, 1999). The earliest references to hair pulling in the medical literature appeared in the works attributed to the Greek physician, Hippocrates. In *Epidemics I*, Hippocrates suggested that physicians should examine whether a person 'plucks his hair' as part of their general examination to determine if disease is present (Chadwick and Mann, 1983). In modern medical texts, it is actually trichophagia, the eating of hair, which appeared before accounts of hair pulling. In the late 18th century, the French physician Baudamant described a trichobezoar in a 16-year-old boy (Baudamant, 1777–1779). It was not until the 19th century that hair pulling was described as a discrete medical syndrome. In 1889, the French dermatologist Francois Hallopeau coined the term 'trichotillomania' (hair pulling 'insanity') in his account of a young man who pulled out all of his body hair (Hallopeau, 1889). In a follow-up account, Hallopeau attributed trichotillomania to

pruritis, but yet remarked that the skin and hair had a normal appearance; he described pulling as an attempt to seek relief from pruritis. Hallopeau considered the behavior chronic and lacking a cure, describing a failed attempt at treatment using mentholated camphor and by wrapping the person in rubber (Hallopeau, 1894).

Even with this long history in medical literature, trichotillomania was not formally incorporated into official psychiatric nosology until the revised third edition of the Diagnostic and Statistical Manual (DSM-III-R) (American Psychiatric Association, 1987). For DSM-IV, the phrase 'recurrent failure to resist impulses to pull' was removed, and one of the criteria was expanded to emphasise tension when attempting to resist (DSM-IV) (American Psychiatric Association, 2000). During the drafting of DSM-IV, trichotillomania was considered for inclusion in both the anxiety disorders (because of presumed similarities to OCD) and the disorders first presenting in childhood or adolescence, such as attention-deficit hyperactivity disorder (ADHD). As in the case of DSM-III-R, DSM-IV includes trichotillomania in the general category of Impulse Control Disorders Not Elsewhere Classified. As such, trichotillomania is currently classified alongside pathological gambling, pyromania, intermittent explosive disorder, and kleptomania (DSM-IV) (American Psychiatric Association, 2000). This categorization is somewhat arbitrary and there is an ongoing search for improved understanding of the neurobiology of these and other conditions, in order to provide a framework for more meaningful diagnostic classification.

3. Psychological models of trichotillomania

Positive reinforcement refers to the introduction of a hedonically positive consequence that strengthens a preceding response. In one study conducted in 30 patients, 39% reported pleasure or a sense of accomplishment from the act of pulling (Mansueto, 1991), suggesting that positive reinforcement may play a role in the mediation of symptoms. A negative reinforcement model, in which the response is strengthened as a means of avoiding punishment or reversing negative feelings, may apply to others with trichotillomania. For example, in a large study of 1697 individuals, 40% reported experiencing anxiety or an uncomfortable urge prior to pulling and that they wished to reduce these unpleasant feelings by the act of pulling (Woods et al., 2006a). A study of 186 patients identified formal depressive and anxiety disorders in 52% and 27% respectively (Christenson, 1995). An even greater percentage of individuals with trichotillomania are considered to have sub-clinical problems with depression and anxiety (Christenson and Mansueto, 1999). One study of individuals with trichotillomania ($n = 75$) found that negative affective states and poor self-esteem were described as the primary triggers for trichotillomania (Christenson et al., 1993). The impact of heightened levels of stress on psychosocial functioning has been examined in a study that compared individuals with trichotillomania ($n = 28$) to a control group (Diefenbach et al., 2005). Trichotillomania subjects reported lower life satisfaction, higher levels of distress, and lower levels of self-esteem. The lower self-esteem was related to concerns about appearance, feelings of embarrassment, and frustration with their inability to control the pulling. Thus, hair-pulling may initially serve to distract from life stressors and unpleasant cognitions but the resulting bald spots may in turn exacerbate anxiety, leading to an escalation of symptoms via positive feedback. Once ingrained and out of control, the repetitive habit becomes difficult to stop.

There has been speculation over the years as to whether trichotillomania is associated with childhood trauma. Azrin and Nunn believed that nervous habits may begin as a reaction to physical injury or psychological trauma (Azrin and Nunn, 1973). Cases of trichotillomania have been described in association with

early physical and/or sexual abuse (Singh and Maguire, 1989). Although one study of females with trichotillomania ($n = 60$) found that 18% had histories of childhood sexual abuse (Christenson et al., 1991a), this rate may not actually be different from that estimated for the background female population in general (12.8–24%) (National Research Council, 1993).

4. Trichotillomania and the putative obsessive-compulsive (OC) spectrum

Although trichotillomania is currently listed as an Impulse Control Disorder not Elsewhere Classified, several other conceptualizations should be considered. It has been proposed that trichotillomania constitutes one of several related body-focused repetitive (BFR) behaviours, along with skin picking and nail biting (Stein et al., 2007). BFR behaviours can be seen as constituting a spectrum from routine, commonplace, and harmless (e.g. the mild plucking of eye lashes for cosmetic purposes); through to extreme pathologic forms (e.g. chronic extreme hair pulling leading to noticeable deleterious hair loss, as in trichotillomania). One study compared the clinical characteristics of hair pulling and skin picking. Odlaug and Grant conducted a study in 33 patients with pathological skin picking, $n = 24$ patients with trichotillomania, and $n = 20$ patients with concurrent presentation of both disorders (Grant et al., 2007). Substantial clinical similarities were found across these groups in terms of age at onset, gender ratio, and psychosocial functioning. However, patients with skin picking spent more time engaging in symptoms and were less likely to have received psychotherapy.

It has also been proposed that trichotillomania may be viewed as a member of the putative OC spectrum of conditions. The repetitive motor symptoms of trichotillomania share some similarity with symptoms of other conditions, such as repetitive motor tics in Tourette's syndrome, or repetitive compulsive rituals in certain OCD symptom manifestations, such as tapping, touching, or other non-ideational compulsions (Miguel et al., 1997). Such symptoms can be viewed as pathologic 'habits'—i.e. repetitive thoughts/behaviors mediated by distributed cortico-basal ganglia circuitry (see later) (Swedo and Leonard, 1992; Rapoport, 1994; Stein et al., 1995; Graybiel and Rauch, 2000; Stein et al., 2006). According to the OC spectrum approach, it is believed that certain of these conditions share overlapping neurobiology and presumed aetiology (Christenson and Crow, 1996; Diefenbach et al., 2000; Elliott and Fuqua, 2000; Hollander and Rosen, 2000; Chamberlain et al., 2005; Grant et al., 2005; Grant and Potenza, 2006; Stein et al., 2006).

Central to the notion of an OC spectrum are the terms 'impulsivity', and 'compulsivity' (Hollander and Cohen, 1996). OCD can be seen as the archetypal disorder of compulsivity, since compulsions are central to the diagnostic criteria. According to one view, compulsions represent failures to suppress repetitive behaviours that themselves reduce aversive emotional states, notably anxiety. Compulsive behaviours may thus be associated with high harm avoidance, high risk aversion, and low sensation seeking (Lochner et al., 2005; Stein and Lochner, 2006). By contrast, impulsivity can be viewed as a failure to inhibit behaviours motivated by reward, and may be associated with high sensation seeking and reduced harm avoidance. Thus, the impulsivity-compulsivity spectrum incorporates the range of OC spectrum disorders including OCD and trichotillomania. Both terms imply underlying problems with inhibitory control but perhaps stemming from different motivating factors driving the behaviours (Swedo and Leonard, 1992; Stein and Hollander, 1995; Stein et al., 1995; Chamberlain et al., 2005).

Despite a proposed relationship between OCD and trichotillomania, there are important differences as well as similarities

between these two conditions from several perspectives (see Stanley and Cohen, 1999 for excellent overview), and the notion of an OCD spectrum remains contentious (Elliott and Fuqua, 2000; Chamberlain et al., 2007d). OCD is thought to afflict similar numbers of men and women while in trichotillomania, the overwhelming majority of clinical trial recruits have been female (Chamberlain et al., 2007d). Compulsions in OCD are often driven by intrusive thoughts; by contrast, hair pulling is seldom driven by cognitive intrusions and obsessional thoughts are not listed in the diagnostic criteria. While trichotillomania symptoms typically initiate in early adolescence, OCD usually initiates in late adolescence (Himle et al., 1995). Treatment approaches also differ—for example, with exposure and response prevention being used for OCD, and habit reversal for trichotillomania; and with selective serotonin reuptake inhibitors (SSRIs) showing efficacy in the treatment of OCD but not, ostensibly, trichotillomania (see later).

Thus, the OC spectrum of disorders may represent a mixed group of illnesses whose central feature involves the performance of repetitive, unwanted acts. Key cross-cutting issues include demographics, co-morbidity rates, inheritance patterns, neurocognitive and brain imaging profiles, and treatment response. Comparison of candidate 'spectrum disorders' across these factors would have implications for determining optimal psychiatric classification. To further characterize the validity of the OC spectrum approach, large scale studies are needed in order to explore whether rates of trichotillomania in OCD patient relatives (and OCD in trichotillomania patient relatives) are disproportionately elevated relative to *other* axis-I conditions.

Few studies have directly compared clinical characteristics of trichotillomania with other OC spectrum disorders. In one such study (Lochner et al., 2005), in which 130 females with OCD and 49 females with trichotillomania were interviewed, interesting clinical differences between the two disorders emerged. For example, trichotillomania patients described significantly more novelty seeking than OCD patients, whereas OCD patients scored significantly higher on harm avoidance. The authors suggested the higher novelty seeking in trichotillomania pointed toward greater dopaminergic involvement in this disorder, also hinting that trichotillomania lies closer to a more impulsive risk-/novelty-seeking pole of an impulsive-compulsive spectrum. However, comorbidity in OCD involved a wider range of different diagnostic categories which extended to a significantly greater overlap with impulsive disorders such as intermittent explosive disorder. Thus impulsivity may also be an important component of OCD. Rather than viewing either disorder as lying at a point along on a single impulsive-compulsive dimension, the authors argued that compulsivity and impulsivity could represent orthogonal dimensions, with TTM sharing compulsive and impulsive components in common with other conditions characterized by stereotypical self-injurious habit symptoms, such as compulsive skin picking.

The same group of authors used the results of a cluster analysis of previously published OCD studies (Stein and Lochner, 2006) to refine their hypotheses. They identified 3 clusters of OC syndromes occurring together within OCD which they termed: (1) 'reward deficiency' (including trichotillomania, pathological gambling, hypersexual disorder and Tourette's disorder), (2) 'impulsivity' (including compulsive shopping, kleptomania, eating disorders, self-injury and intermittent explosive disorder), and (3) 'somatic' (including body dysmorphic disorder and hypochondriasis). Reward deficiency, a term thus applied to trichotillomania, implicates dysfunction of the dopaminergic reward system in the brain, which has been implicated in aberrant substance seeking behaviour and other related behaviours (Blum et al., 1996). Stein and Lochner concluded that OC disorders were unlikely to fall on any single phenomenological dimension and that multiple orthogonal constructs may be needed to map these relationships.

(Grant et al., 2007) have suggested that future research examining impulsive-compulsive neurocircuitry may identify a subtype of trichotillomania more akin to OCD, and another more akin to impulse disorders or addiction. In OCD, some types of symptom (i.e. hoarding) have been associated with poorer treatment outcome (Moritz et al., 2004). One proposed division of trichotillomania symptoms is into 'focused' versus 'automatic' subtypes. In the former, hair pulling is consciously undertaken and is the focus of the subject's attention at the time; in the latter, hair pulling is more habitual with the subject engaging in hair pulling without conscious awareness in a 'trance-like' or dissociative state (Christenson and Mansueto, 1999; du Toit et al., 2001). Given that automatic pulling has been associated with more severe symptomatology than focused pulling in trichotillomania (Flessner et al., 2008), it may also be that certain manifestations (or subtypes) of trichotillomania symptoms are more treatment resistant, although this has yet to be explored.

5. Treatment

As reviewed in depth elsewhere, there exist no formal treatment guidelines for trichotillomania, since the evidence base is limited (Bloch et al., 2007; Chamberlain et al., 2007d). This section considers key treatment studies conducted to date, and their limitations.

5.1. Psychotherapy

Psychosocial treatment data for trichotillomania are limited with 5 controlled studies published to date. In each published study, some form of cognitive behavioral therapy (CBT) has been examined. The strongest evidence appears currently to support habit reversal therapy (HRT) as the most effective first-line treatment for trichotillomania (Bloch et al., 2007).

In the earliest hair pulling study to employ CBT techniques, 34 individuals were randomized to receive a single 2-h session of either habit reversal training ($n = 19$) or negative practice ($n = 15$) (Azrin et al., 1980). Habit reversal training included: training subjects to use competing reactions (e.g. clenching fists), to recognize situations where they were likely to pull (awareness training), and to identify response precursors. Habit reversal also included relaxation training, prevention training, habit interruption, positive attention, and recording of hair pulling in a diary. Negative practice involved standing in front of a mirror and acting out the motions of hair pulling without actually doing so. Habit reversal resulted in a 91% reduction in hair pulling symptoms at a four-month follow-up, and was twice as effective as negative practice at reducing pulling frequency.

In a controlled study, the efficacy of acceptance and commitment therapy administered with habit reversal training (ACT/HRT) was investigated. This combination therapy included components designed to eliminate or reduce negative private experiences such as urges or emotional states (e.g. dysphoria) implicated in the pathogenesis of pulling behavior (Woods et al., 2006b). The 12 CBT completers reported significantly greater improvement in hair pulling symptoms versus a wait list control group ($n = 13$). The combined therapy group reported a 58% reduction in the number of hairs pulled per day compared to a 28% increase in the wait-list group. Subjects in the ACT/HRT group maintained this improvement at 3-month follow-up.

Group CBT has also been used in the treatment of trichotillomania. In a study of 24 patients, group behavioral therapy ($n = 12$) was compared to group supportive therapy ($n = 12$). The 8-session behavioral therapy group involved psychoeducation, awareness training, stimulus control (organizing the environment), competing response training (undertaking alternative responses incom-

patible with hair pulling), relaxation training, cognitive therapy, self-monitoring, motivation (rewarding oneself), and relapse prevention. Participants were required to undertake weekly homework assignments and to discuss progress within the group. After treatment, the behavioral therapy group showed significant reductions in trichotillomania symptoms compared to the support therapy group. However, follow-up at 1-month, 3-months and 6-months, showed a significant worsening of treatment gains for the behavioral therapy group (Diefenbach et al., 2006).

5.2. Pharmacotherapy

Several controlled pharmacological trials have been performed in trichotillomania, albeit with relatively small sample sizes, when compared to pharmacological studies undertaken in the context of other axis-I disorders, e.g. OCD. Most controlled pharmacological studies published to date have examined antidepressants, particularly the serotonin reuptake inhibitors (SRIs).

One study examined clomipramine compared to desipramine in a 10-week double-blind, cross-over (5 weeks for each agent) design, following 2 weeks of single-blind placebo lead-in (Swedo et al., 1989). Clomipramine showed superiority over desipramine in treating trichotillomania symptoms, although there was no parallel placebo arm to contextualise these findings. Fluoxetine has been studied in two randomized trials with disappointing results. In one study ($n = 15$ patients), fluoxetine was compared with placebo in a 6-week double-blind cross-over study, with a 5-week washout period between treatment arms (Christenson et al., 1991b). No significant differences were found between fluoxetine and placebo on measures of hair pulling urges, frequency or severity. In another controlled study, using a double-blind, placebo-controlled cross-over design, fluoxetine was evaluated in 16 subjects treated for 12 weeks, separated by a 5-week washout period (Streichenwein and Thornby, 1995). Again, fluoxetine failed to show significant improvement compared to placebo, on primary outcome measures.

O'Sullivan and Christenson performed a placebo-controlled, 6-week, randomized, double-blind parallel arm study of the opioid antagonist naltrexone (O'Sullivan and Christenson, 1999). Of $n = 17$ completers, 10 received placebo and 7 received 50 mg/day of naltrexone. Significantly greater improvement was noted for the naltrexone group on one measure of trichotillomania symptoms. Although two other measures of symptom improvement showed change in the anticipated direction for the naltrexone group, they failed to reach statistical significance, perhaps due to limited power on account of the sample size.

A recently completed study, presented as a poster abstract at the 19th Annual European College of Neuropsychopharmacology Congress, examined the efficacy of using an atypical antipsychotic (Olanzapine) in the treatment of trichotillomania (Van Ameringen et al., 2006). Antipsychotic medication was used based on the hypothesis that first and second generation antipsychotic agents are beneficial for motor tics (Jimenez-Jimenez and Garcia-Ruiz, 2001), and that similarities exist between the urges driving motor tics (Prado et al., 2008) and hair pulling. The study examined olanzapine in a double-blind placebo-controlled parallel fashion for 12 weeks ($n = 25$ subjects). According to the preliminary presented data, 85% of those assigned to olanzapine compared to 17% of those on placebo improved during the trial. The mean effective dose of olanzapine was 10.8 mg/day.

5.3. Psychotherapy and pharmacotherapy: direct comparisons and combination treatments

Modified forms of habit reversal have been used in drug comparator studies. Twenty-three subjects with trichotillomania

were treated with 9 weekly sessions of CBT (a combination of habit reversal, stimulus control and stress management) ($n = 7$), clomipramine (up to 250 mg/d) ($n = 10$), or pill-placebo ($n = 6$). There was no control for the CBT arm. It was demonstrated that CBT significantly reduced the severity of trichotillomania symptoms compared to clomipramine and placebo over the course of the study. No long-term follow-up data were available to determine whether treatment gains were maintained over time (Ninan et al., 2000).

Van Minnen et al. investigated the efficacy of 6 sessions (12 weeks) of behavioral therapy compared to fluoxetine (up to 60 mg/d) or a wait-list control group, in patients with trichotillomania. The manualized behavioral therapy consisted of stimulus control, stimulus-response interventions, and response consequences. Forty-three subjects participated, with 40 completers (14 in behavior therapy, 11 in the fluoxetine group, and 15 in the wait list). During treatment, the behavioral therapy group improved significantly more than the other groups (van Minnen et al., 2003). Clomipramine did not significantly differentiate from the waiting list control condition. A 2-year follow-up of the same patients, however, showed that symptom improvement did not last for the therapy recipients (Keijsers et al., 2006).

One study has examined the effects of CBT combined with pharmacotherapy in sertraline non-responders (Dougherty et al., 2006). Forty-two subjects participated in a 12-week double-blind trial of sertraline versus placebo. Following initial treatment with sertraline or placebo, patients with less than a 40% decrease in hair-pulling severity scores received habit reversal therapy (two one-hour sessions) on top of their usual treatment regimen. Of the 42 initial recruits, there were 26 study completers. Of these, 13 had received single modality (4 sertraline, 9 therapy) and 11 had received dual modality. Two completers had received placebo only (placebo responders not receiving therapy) and were excluded from the analysis. The dual modality group showed significantly greater improvement on primary outcomes measures than the single modality group overall. These findings must be viewed with caution given the high attrition rate, and that sertraline responders were compared with non-responders.

5.4. Treatment: summary and future directions

Although there are many case reports on effective treatments for trichotillomania, the data from controlled trials are sparse. The one psychological treatment that has shown potential promise in treating trichotillomania is habit reversal therapy, or some modification thereof. The manualized treatments using habit reversal, however, have not been examined in confirmatory studies by independent investigators. In terms of pharmacotherapy, clomipramine has demonstrated greater efficacy than desipramine but this study lacked a placebo comparison condition. SSRIs have not yet shown robust benefit versus placebo. Pharmacological studies were limited by the small sample sizes, thus constraining power to detect treatment effects versus stringent control conditions. In those studies showing clinical benefits of treatments, long-term follow-up data were sparse. Double-blind trials with long-term follow-up are needed to examine these and other potentially beneficial pharmacological treatments, before firm treatment algorithms can be generated.

It would be valuable to explore other treatment targets. The noradrenergic antidepressant desipramine did not appear effective compared to clomipramine (Swedo et al., 1989), yet drugs with noradrenergic properties, such as the selective noradrenaline reuptake inhibitor atomoxetine, show efficacy in treating impulsive features of attention-deficit hyperactivity disorder (ADHD) (Robertson, 2006; Cheng et al., 2007) and may hold potential for trichotillomania. Glutamatergic agents such as N-acetyl cysteine

have been used with some success to treat behavioural addictions such as pathological gambling and would thus merit investigation in the context of treating trichotillomania (Fong et al., 2008).

6. Neurobiology

6.1. Animal models

Animal models represent useful tools for investigating the pathophysiology of psychiatric disorders such as trichotillomania, particularly those which closely mimic the behavioural and clinical manifestations of the disorders (Geyer and Markou, 1995; Mckinney, 2000; Geyer and Markou, 2002). Recent attempts have been made to develop experimental animal models of trichotillomania and other candidate OC spectrum disorders (see Moon-Fanelli et al., 1999 for excellent review). The existing models are either ethological or laboratory based. Ethological models focus on spontaneously arising repetitive or stereotypic behaviours, such as tail chasing, fur chewing and weaving (nest-building in birds) (Brown et al., 1987; Stein et al., 1994); and behaviours driven by conflict, frustration, or stress, such as excessive grooming, cleaning, and pecking (Stein et al., 1994). Even though the ethological models have high reliability and face validity, they have mainly practical limitations (for further details on validation criteria and animal models see Geyer and Markou, 1995; Geyer and Markou, 2002). Laboratory models on the other hand, are more practical but study behaviors that are induced and not spontaneous, for example resulting from pharmacological or genetic manipulations (Yadin et al., 1991; Ichimaru et al., 1995; Szechtman et al., 1998; Campbell et al., 1999a,b; Joel and Avisar, 2001; Greer and Capecchi, 2002; Chou-Green et al., 2003; Berridge et al., 2005; Tsaltas et al., 2005).

Barbering has been suggested as a mice model of compulsive hair pulling behaviour in trichotillomania. Driven by the fact that barbering, which involves abnormal whisker and fur trimming, is limited to a group of laboratory mice, Garner et al. (2004) suggested that it represents a form of abnormal behaviour and a possible mouse model of trichotillomania and OC spectrum disorders. The authors, in their research in laboratory mice, reported that barbering paralleled trichotillomania in terms of phenomenology (hair plucking from the scalp and around the eyes/genitals), demography (female biased, onset during puberty), and aetiology (genetic background), thus contributing to the model's face validity (Garner et al., 2004).

Bordnick et al. (1994) presented an avian model of trichotillomania based on feather picking disorder. A significant proportion of captive birds tend to pluck out their feathers at times of stress, or during states analogized to boredom (deprivation of sensory input). Psychogenic feather picking in birds is associated with feather loss or damage to body areas accessible by the bird's beak, arising from chewing, plucking, and destruction of feathers, thereby preventing normal growth (Moon-Fanelli et al., 1999). Preliminary data suggest that feather picking may respond to dopamine antagonists such as haloperidol (Iglauer and Rasim, 1993) and to the tricyclic clomipramine in some birds (Ramsay and Grindlinger, 1994). The latter finding is of particular relevance in light of the human study showing responsiveness of trichotillomania to clomipramine versus desipramine (Swedo et al., 1989), and given the efficacy of clomipramine in the treatment of OCD (Fineberg and Gale, 2004).

Finally, another candidate model of trichotillomania (and arguably OC spectrum disorders more broadly) is the *hoxb8* gene knockout mouse. Greer and Capecchi (2002) reported that, compared to their control counterparts, mice with mutations of *Hoxb8* gene groomed excessively to the point of hair removal and skin lesions. Mutant mice demonstrated normal cutaneous

sensation and there was no evidence of an inflammatory response suggesting that this behaviour was not due to skin or other abnormalities of the peripheral nervous system. This transgenic model is promising because the excessive grooming of *Hoxb8* mutants is similar to the excessive grooming seen in trichotillomania, thus offering face similarity to symptoms observed in OC spectrum disorders. Moreover, *Hoxb8* gene is expressed in the orbital cortex, the anterior cingulate, the striatum and the limbic system. It is noteworthy that these neural regions share remarkable overlap with those reported to be structurally abnormal in the largest MRI study of trichotillomania patients to date (see next section) (Chamberlain et al., 2008).

Although some of the above models offer very good symptom similarity (face validity) with human trichotillomania, another important method of validating such models is to show overlapping pharmacological response with the human disorder. This is difficult since human treatment studies are few. To the knowledge of the authors, it is not yet known whether barbering in mice or symptoms exhibited by *hoxb8* knockout mice respond to pharmacological treatments selectively. As noted, there is some evidence that avian feather picking responds to the tricyclic clomipramine, and that clomipramine is superior to desipramine in the treatment of human patients with trichotillomania.

6.2. Neuroimaging

The available neuroimaging studies conducted in patients with trichotillomania are few in number, and are chronologically summarized in Table 1. This section covers structural and functional neuroimaging in turn.

6.2.1. Structural findings

Much of the structural imaging research conducted in patients with trichotillomania has relied on 'region of interest' (ROI) approaches, in which certain brain regions are selected for comparison with controls beforehand, to minimize multiple comparisons. The selection of ROIs in trichotillomania research has largely focused on regions previously implicated in OCD, since there is a wealth of imaging data for this other condition and it may overlap with trichotillomania. In OCD, volumetric abnormalities of the orbitofrontal and anterior cingulate cortices, along with the caudate, amygdala, and hippocampus have been reported (Menzies et al., 2007a,b).

Amongst the trichotillomania structural magnetic resonance imaging (MRI) brain studies, one measured caudate volumes in trichotillomania cases ($n = 13$) versus controls ($n = 9$) (Stein et al., 1997), but detected no abnormalities. Elsewhere, reduced left inferior frontal gyrus and increased right cuneal cortex volumes were identified in trichotillomania patients compared to controls ($n = 10$ per group) (Grachev, 1997); and smaller left putamen volumes (ditto, same sample) (O'Sullivan et al., 1997). The putamen is involved in the generation of motor habits and responses, such as tics in Tourette's syndrome (Singer et al., 1993). Taking advantage of parcellation techniques (in which regions of the brain are anatomically demarcated, i.e. parcellated), one study identified reduced cerebellar volumes in trichotillomania patients ($n = 14$) compared to controls ($n = 12$) (Keuthen et al., 2006).

So far, a single study has sought to address whether distributed changes of neural circuitry exist in patients with trichotillomania, using voxel-based morphometry and MRI data in co-morbidity free patients (Chamberlain et al., 2008). This study found that patients with trichotillomania ($n = 18$) exhibited grey matter density increases, versus controls ($n = 19$), in several brain regions involved in affect regulation, motor habits, and top-down cognition (see Fig. 1).

6.2.2. Functional findings

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) involve the injection of a radioactive isotope, in order to quantify metabolic activity and/or receptor binding. In a PET study, normalized resting cerebral glucose metabolic rates were found to be increased in the bilateral cerebellum and right parietal cortex, in patients with trichotillomania ($n = 10$) compared to controls ($n = 20$) (Swedo et al., 1991). In a qualitative study of a pair of genetically identical twins with trichotillomania, both showed decreased perfusion of the temporal lobes during SPECT, and the more severely affected twin showed more widespread temporal involvement (Vythilingum et al., 2002). One study used SPECT to explore brain changes following 12-week pharmacotherapy with the serotonin reuptake inhibitor (SRI) citalopram in patients with trichotillomania ($n = 10$) (Stein et al., 2002). Treatment was associated with significant reductions in symptom severity and reduced activity in frontal cortical regions, the left putamen, and right anterior-temporal lobe.

There has been one published functional MRI (fMRI) study of trichotillomania so far. Rauch and colleagues measured brain activation during an implicit sequence-learning task (Rauch et al., 2007). On this task, subjects were instructed to press one of four buttons in response to the position of asterisks appearing on a computer screen, whilst they were in the scanner. Task blocks comprised random sequences of asterisks ('Control' condition), and blocks in which the stimuli positions followed a 12-item sequence that repeated ('Implicit Learning' condition). By subtracting brain activation between Implicit Learning and Control conditions, the authors investigated brain circuitry mediating aspects of implicit motor pattern learning. No significant differences in brain activation were found between trichotillomania patients and controls.

6.2.3. Imaging: summary and future directions

The structural studies, discussed above, provide mixed support for the existence of volumetric decreases in trichotillomania patients versus controls in frontal regions, the putamen, and cerebellum. The single whole-brain study reported increased density of grey matter in frontal regions, the cingulate, and the putamen. One study in a group of trichotillomania patients suggested increased brain metabolic rates in patients versus controls, while another—in a pair of twins—suggested under-perfusion. SSRI treatment in patients with trichotillomania was associated with reduced activity in frontal regions and the left putamen. The only fMRI study so far found no significant differences between patients and controls in terms of brain activation during an implicit sequence learning task. Future studies should take advantage of other cognitive paradigms that have been adapted for use during fMRI, such as those tapping inhibitory control and motor learning. They could also investigate emotional processing in patients with trichotillomania.

6.3. Cognitive function

Cognitive deficits may be expected in trichotillomania, in light of the brain differences versus controls that have been reported in the above studies. Neuropsychological dysfunction has been reported across axis-I disorders and in some contexts has been associated with functional impairments and deleterious long term outcomes, such as in depression and schizophrenia (Chamberlain and Sahakian, 2004; Chamberlain and Sahakian, 2006). In the context of trichotillomania, the day-to-day impact of any deficits reported has yet to be characterized. Another critical issue concerns the trait versus state nature of cognitive dysfunction in trichotillomania—i.e. whether any reported deficits occur in people at increased genetic risk of the condition, perhaps reflecting a

Table 1
Neuroimaging studies of trichotillomania (TTM).

Study	Sample size	TTM subjects: % female; age (w/SD)	Psychiatric comorbidity (in TTM subjects)	Treatment status	Methodology	Key findings in TTM patients
Swedo et al., 1991	10T, 20C	100% F; 34.7 (5.2)	Free from current mood/anxiety disorders, and history of OCD or psychosis.	Free from psychotropic medications >4 weeks;? Psychotherapy status	Resting state PET + 18-F-fluorodeoxyglucose; ROI analysis in 46 regions including: cerebellum, superior parietal, prefrontal, orbitofrontal, anterior cingulate, and caudate (all bilateral)	Increased global metabolic rates in patients overall ($p = 0.0008$, uncorrected); increased metabolic rates in right superior parietal cortex and bilateral cerebellum after correction for global metabolic rates ($p < 0.05$ uncorrected for multiple comparisons)
Grachev, 1997	10T, 10C	100% F; 31.1 (10.0)	No OCD, Tourette's, psychosis, major depression, substance abuse	Free from psychotropic medications >4 weeks;? psychotherapy status	Same sample as O'Sullivan et al., 1997. 1.5T MRI; semi-automated brain segmentation method (grey and white); manual delineation of parcellation units	Reduced grey in left inferior frontal gyrus (triangularis); increased grey in right cuneal cortex; significant with bonferroni correction for 16 comparisons (48 undertaken)
Stein et al., 1997	17T, 9C, 13O	100% F; 32.5 (8.4)	No current major depression; no history eating disorder or psychosis. $n = 1$ social phobia, $n = 1$ specific phobia	Not indicated	1.5T MRI; left/right ventricular volume, bilateral total caudate volume, as proportion of TBV. Lentiform not assessed. 2x blinded raters	No significant group differences for caudate and ventricular volumes
O'Sullivan et al., 1997	10T, 10C	100% F; 31.1 (10.0)	No OCD, Tourette's, psychosis, major depression, substance abuse	Free from psychotropic medications >4 weeks;? psychotherapy status	Same sample as Grachev, 1997. 1.5T MRI; manual anatomic segmentation by blinded rater, verified by another blinded rater; semi-automated segmentation; ROIs included: cerebral hemispheres, cerebral cortex, white matter, caudate, putamen, and globus pallidus.	Reduced left putamen volumes ($p = 0.002$ uncorrected)
Stein et al., 2002	10T	100% F; 30.8 (7.2)	No major depression; otherwise not indicated	Free from current pharmacotherapy;? Psychotherapy status	SPECT + technetium-99m hexamethylpropyleneamine oxime. Conducted before and after 12-week citalopram therapy (20 mg daily titrated up to maximum 60 mg as tolerated). Asked to try to imagine hair-pulling during scan	Reduced activation following treatment in left and right hemispheres (inferior-posterior frontal and superior-anterior frontal); decreases elsewhere in right anterior-temporal area and left putamen. Uncorrected for multiple comparisons
Vythilingam et al., 2002	2T	100% F; 31 [TWIN PAIR]	No history of OCD or tics; no major depression at time of scan	Treatment naïve	SPECT + technetium-99m hexamethylpropyleneamine oxime; patients asked to allow themselves to feel the urge to pull during scans; visual inspection of perfusion	Decreased perfusion reported in temporal lobes
Keuthen et al., 2006	14T, 12C	100% F; 29.2 (6.7)	$n = 1$ general anxiety disorder, $n = 1$ specific phobia. Otherwise, free from axis-I disorder.	Free from psychotropic medications >4 weeks;? psychotherapy status	1.5T MRI; manual parcellation of regions into 32 units per hemisphere by blinded raters x2; TBV and head circumference recorded	Reduced total raw cerebellar volumes, significant for each hemisphere; no longer significant when corrected for TBV
Rauch et al., 2007	10T, 10C	100% F; 29.1 (7.4)	$n = 1$ general anxiety disorder; otherwise clear	No pharmacotherapy for >4 weeks;? Psychotherapy status	1.5T MRI; fMRI task in which volunteers responded to asterisks appearing in one of four locations on-screen; implicit motor sequence learning; SPM analysis for implicit learning versus rest contrast, collapsed across time	No activation abnormalities detected during implicit learning, in striatum or hippocampal formation
Chamberlain et al., 2008	18T, 19C	94% F; 37.4 (11.7)	None (MINI screen)	No psychological or pharmacological treatment for >6 months	1.5T MRI; automated segmentation into grey and white; automated analysis of between group cluster-wise density differences over whole brain	Increased grey density in left caudate/putamen and left amygdalo-hippocampal formation (19%); increased grey density in bilateral cingulate and right frontal cortices (28%). Corrected to <0.5 false positive clusters

T: trichotillomania, C: healthy controls, O: OCD cases; 1.5T: 1.5 Tesla; MINI: Mini-international Neuropsychiatric Interview; TBC: total brain volumes; MRI: Magnetic resonance imaging; PET: positron emission tomography; SPECT: Single proton emission computed tomography.

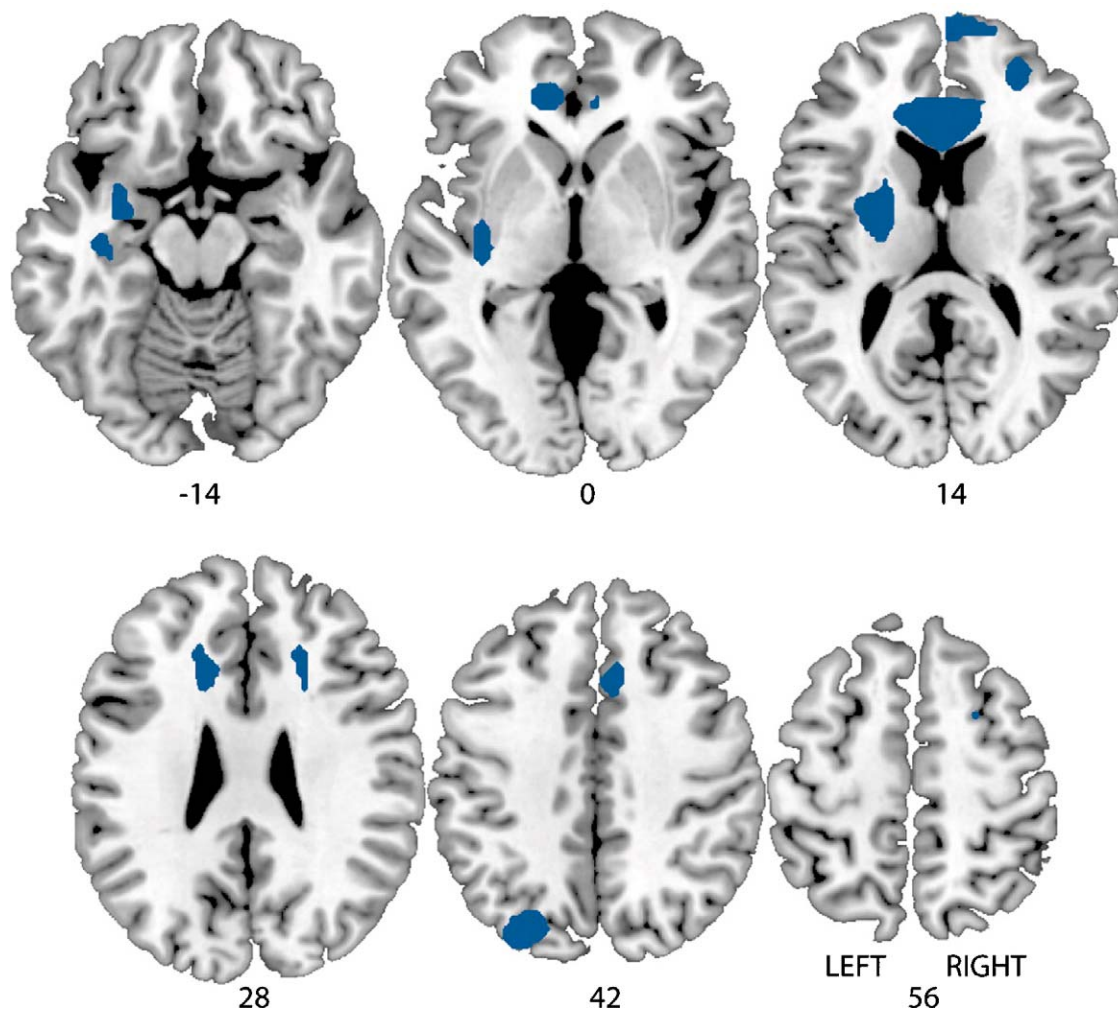


Fig. 1. Map of grey matter volume excesses (blue) in trichotillomania patients compared to healthy controls, superimposed onto template. Abnormalities were found in the left striatum, left amygdalo-hippocampal formation, and multiple cortical regions (including the cingulate, supplemental motor cortex, and frontal cortex). Representative slices (left) with z-coordinates indicated in MNI space. Expected number of false positive cluster tests < 0.5 over the whole map. Reprinted with permission from Chamberlain et al. (2008). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

vulnerability marker, or rather occur as a consequence of symptoms themselves (Chamberlain et al., 2007c,d). This issue is important since if objective vulnerability markers ('endophenotypes') can be identified, they can be used to empower research into aetiological factors contributing to the condition (Gottesman and Gould, 2003; Gould and Gottesman, 2006; Hasler et al., 2006; Braff et al., 2007). While these issues cannot be addressed yet, the following section surveys neuropsychological deficits reported in patients to date. Characterization of the neuropsychological profile of trichotillomania could inform how this condition should best be characterized as a nosologic entity, by identifying possible overlap between candidate spectrum disorders (Hollander et al., 2007). The available cognitive studies conducted in trichotillomania listed chronologically in Table 2 (Rettew et al., 1991; Martin et al., 1993; Keuthen et al., 1996; Stanley et al., 1997; Coetzer and Stein, 1999; Bohne et al., 2005; Chamberlain et al., 2006a,b, 2007b).

The first cognitive investigation in trichotillomania used the Stylus maze test, in which volunteers attempt to learn the correct path for navigating across a peg-board, using a stylus. The correct route is first demonstrated by an examiner (Kessels et al., 2002). This visuospatial learning task confounds multiple cognitive domains including memory, planning, motor execution, and error learning. Patients with trichotillomania ($n = 21$) showed problems on several indices from this test versus controls ($n = 16$) (Rettew

et al., 1991), but the treatment status of the sample was not indicated. In a subsequent study using a similar test (the Austin maze task) there was no evidence for deficits in trichotillomania patients ($n = 11$) who were free from current major depression and psychosis, versus controls ($n = 11$) (Coetzer and Stein, 1999), although again the treatment status was not indicated.

The Wisconsin Card Sorting Test (WCST) is a classic test of frontal (especially dorsolateral) cortex integrity, which measures rule learning and cognitive flexibility. Volunteers attempt to learn a rule about which of two cards is correct on the basis of feedback (trial and error). After a criterion is reached denoting learning has been accomplished, the rule is arbitrarily changed by the examiner (or computer), and volunteers attempt acquire the new rule, again based on feedback. Two studies have used the WCST in patients with trichotillomania, and both reported intact performance ($n = 21$ patients, $n = 17$ controls; $n = 23$ patients, $n = 26$ controls respectively) (Stanley et al., 1997; Bohne et al., 2005). More recently, set shifting was compared between trichotillomania cases, OCD cases, and controls using a computerized analogue of the WCST, the intra-dimensional (ID)/extra-dimensional (ED) set-shift task from the Cambridge Neuropsychological Test Automated Battery (CANTAB). ID shifting refers to maintaining attention on the same stimulus dimension (e.g. shape not colour) when new stimuli are presented on-screen; ED shifting refers to shifting

Table 2
Neuropsychological studies of trichotillomania (TTM).

Study	Sample size	TTM subjects: % female; age (w/SD)	Psychiatric comorbidity (in TTM subjects)	Treatment status	Cognitive tests administered	Key findings in TTM patients
Rettew et al., 1991	21T, 16C, 120	100% F; 33.0 (7.4)	Free from 'anxiety and depression'	Not indicated	Money's Road Map test; Stylus Maze test	TTM subjects were significantly impaired on Stylus Maze test
Martin et al., 1993	11T, 16C, 170	90% F; 32.3 (9.6)	Not specified; trichotillomania HamD scores suggest some depressive symptomatology	No pharmacotherapy for >6 weeks prior to testing; ?psychotherapy status	WAIS-R Vocabulary and Block Design subtests; Road-map test of directional dense; Room test; verbal fluency (letter based generation and category based generation); Simple and Choice Visual Reaction Time, Visual Search Task; CVLT	No significant differences between groups
Stein et al., 1994	13T, 16C, 340	100% F; 33.1 (9.9)	<i>n</i> = 1 had comorbid OCD; otherwise not indicated	No pharmacotherapy for >2 weeks; ? Psychotherapy	Neurologic soft signs battery including measures of movement, sensation, coordination, and visuo-spatial function	TTM group showed increased visuo-spatial dysfunction compared to the control group but not compared to the OCD group
Keuthen et al., 1996	20T, 20C	100% F; 29.9	No current depression, OCD, substance abuse, Tourette's, psychosis; otherwise status not indicated	No pharmacotherapy for >4 weeks; ? psychotherapy status	Odd Man Out test; Visual-Verbal test; RCFT; Mental Rotations test; Digit Spans subtest of the WAIS-R; Delayed Recognition Span Test	TTM group was impaired on RCFT immediate recall; increased loss of set errors on the Odd Man Out test
Stanley et al., 1997	21T, 17C	85.7% F; 34.5 (6.9)	<i>n</i> = 6 had current general anxiety disorder, <i>n</i> = 5 social phobia, <i>n</i> = 2 simple phobia, <i>n</i> = 1 bipolar, <i>n</i> = 1 dysthymia, <i>n</i> = 1 panic disorder w/agoraphobia	No current pharmacotherapy; ?psychotherapy status	Auditory discrimination test; RCFT; Visual form discrimination; facial recognition; judgement of line orientation; right-left discrimination; finger localisation; tactual performance; finger tapping; grooved pegboard; CVLT; BVRT; Booklet Category; WCST; visual search and attention; Trail making; auditory serial addition test; Stroop; MFFT; Fused dichotic words test	TTM group showed impairment on measures of divided attention (e.g. paced auditory serial addition test; trail making B; Stroop); intact on others including WCST
Coetzer and Stein, 1999	11T, 11C, 110	100% F; 32.8 (9.3)	Free from current major depression and psychosis; otherwise not indicated	Not indicated	Stroop test; Austin Maze test; Hooper Visual Organization test; RCFT	No significant differences between groups
Bohne et al., 2005	23T, 26C, 210	87% F; 37.4 (12.3)	<i>n</i> = 7 had current axis-I comorbidity - details not specified	<i>n</i> = 4 unspecified psychotropic medication; ?psychotherapy status	WAIS-R block design sub-test; RCFT; CVLT; TOH; OAT; WCST	TTM group showed increased perseverative errors on the OAT; intact on other measures (including WCST)
Chamberlain et al., 2006b	17T, 20C, 200	88.2% F; 36.1 (12.6)	None on MINI	No pharmacotherapy or psychotherapy for >6 months	Computerised Stop-Signal Task; computerised Intradimensional/Extradimensional Shift Task (set-shift test)	TTM group had impaired impulse control on Stop-Signal Task; intact on set-shifting
Chamberlain et al., 2006a	17T, 20C, 200	88.2% F; 36.1 (12.6)	None on MINI	No pharmacotherapy or psychotherapy for >6 months	Visuo-spatial sequence generation task requiring flexibility and implementation of trained strategy	TTM group intact on sequence generation and flexibility (OCD impaired)
Chamberlain et al., 2007b	20T, 20C, 200	% not indicated; 36.0 (12.4)	None on MINI	No pharmacotherapy or psychotherapy for >6 months	Pattern recognition, spatial working memory, Tower of London, Information sampling, affective go/no-go, Cambridge gamble, probabilistic learning and reversal	TTM group showed increased errors during spatial working memory on hard problems; intact on other tasks
Bohne et al., 2008	25T, 26C, 210	88% F; 38.0 (12.6)	<i>n</i> = 8 had current DSM-IV Axis-I comorbidities, details not specified	<i>n</i> = 5 unspecified psychotropic medication	Computerised go/no-go test	No significant differences between groups on primary measures

T: trichotillomania, C: healthy controls, O: OCD cases; BVRT: Benton Visual Retention Test; CVLT: California Verbal Learning Test, RCFT: Rey-Osterrieth Complex Figures Test, WAIS-R: Wechsler Intelligence Scale Revised, WCST: Wisconsin Card Sort Test, MFFT: Matching familiar figures test; OAT: Object Alternation Task; TOH: Tower of Hanoi; MINI: Mini International Neuropsychiatric Interview.

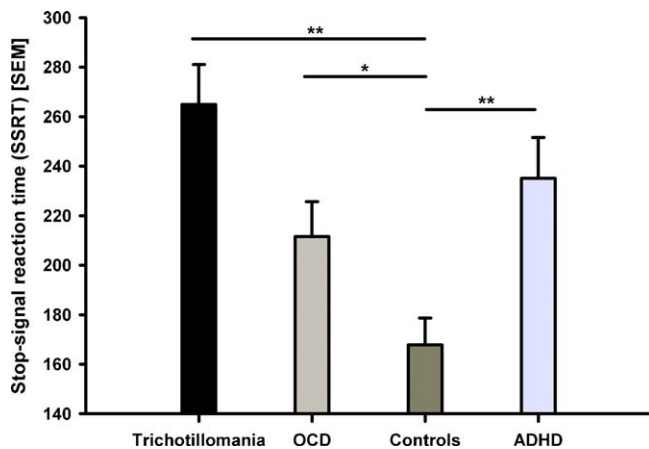


Fig. 2. Results from the stop-signal inhibitory control task. Left three bars: stop-signal reaction times in patients with trichotillomania, patients with OCD, and matched controls (Chamberlain et al., 2006a,b,c,d,e); right hand bar: stop-signal reaction time in adult patients with ADHD from a separate study, for visual comparison purposes (Chamberlain et al., 2007a,b,c,d). Error bars are SEM. * $p < 0.05$, ** $p < 0.01$, impaired versus controls.

attention between stimulus dimensions (e.g. from shape to colour, or *vice versa*) (see e.g. Clarke et al., 2005). Consistent with the WCST findings, untreated patients with trichotillomania ($n = 17$) showed intact performance on the task compared to controls ($n = 20$). By contrast, OCD patients ($n = 20$) exhibited cognitive inflexibility, i.e. difficulty inhibiting and shifting attention between stimulus dimensions (ED shifting) (Chamberlain et al., 2006b).

The repetitive physical symptoms of trichotillomania suggest underlying dysfunction of motor inhibitory control processes (Chamberlain and Sahakian, 2007). Motor impulsivity is classically assessed using tasks that require volunteers to make simple motor responses (e.g. pressing a button) on some computer trials but not on others. One study reported no overall performance deficits in largely un-medicated trichotillomania cases ($n = 25$) using a go/no-go task where participants responded to the letter 'X' but not the letter 'O' on-screen (or *vice versa*) ($n = 26$ controls) (Bohne et al., 2007). Another study used a stop-signal task that had been widely validated and shown to be sensitive to impulsivity in ADHD and right frontal lesions (Logan et al., 1984; Aron et al., 2007). Stop-signal tasks are behaviourally more sensitive than go/no-go tasks since they measure the ability of subjects to actively inhibit an already triggered motor command. These tasks use an individually tailored tracking algorithm, to estimate the time taken by the brain to suppress an already initiated response (referred to as the stop-signal reaction time, SSRT). As can be seen in Fig. 2, patients with trichotillomania ($n = 17$) exhibited impaired inhibitory control (i.e. increased SSRTs) versus controls ($n = 20$), comparable in magnitude to that previously reported in other studies of adult patients with attention-deficit hyperactivity disorder (ADHD) (Chamberlain et al., 2006b, 2007a). OCD patients ($n = 20$) also showed impaired inhibitory control, but to a lesser degree.

6.3.1. Cognition: summary and future research directions

The above studies indicate that a proportion of subjects with trichotillomania exhibit problems in cognitive domains relating to visuospatial learning and response inhibition, while set-shifting appears to be intact across studies. Response inhibition as a cognitive function is dependent on neural circuitry including the right inferior frontal gyrus, and is affected by manipulations of the noradrenaline system, but not of the serotonin system, in humans and rats (Chamberlain et al., 2006c,d,e, 2007a; Aron et al., 2007; Eagle et al., 2007; Robinson et al., 2007). Thus, these findings

suggest noradrenaline and inhibitory network dysregulation in the pathophysiology of trichotillomania.

Two fundamental issues need to be addressed in future cognitive studies. Firstly, the effect of co-morbidities (such as depression) on cognitive function should be clarified. Secondly, the effects of pharmacotherapy and psychotherapy on cognition in trichotillomania merit clarification, since it is known from other contexts that a variety of psychoactive drugs have cognitive effects (Robbins, 2000; Cools and Robbins, 2004).

7. Conclusions

Our understanding of trichotillomania and its overlap with other axis-I disorders, in terms of phenomenology, neurobiology and treatment, remains incomplete. Caution is required when attempting to generalize from the preliminary studies described herein in small samples, to trichotillomania as a disorder *per se*. Nonetheless, important insights have been gleaned from reviewing research to date. From a phenomenological perspective, trichotillomania can be thought of as a candidate member of the OC spectrum, which overlaps with OCD, Tourette's syndrome, and body-focused repetitive behaviours including skin picking and nail biting. While overlap may exist it is important to note differences between trichotillomania and these other conditions, for example with regard to treatment responsiveness. Mild hair pulling may be seen as a 'body-focused repetitive' (BFR) behavior that is commonplace and may be adaptive; the mechanisms by which such habits become ingrained, frequent, and pathological merits exploration. Little is known of how hair pulling symptoms evolve over time in individuals who ultimately exhibit clinical trichotillomania.

Brain abnormalities in neural regions involved in cognition (frontal cortex), affect regulation (amygdalo-hippocampal formation), and habit learning (putamen) have been implicated in trichotillomania, based on imaging patient studies, and animal models of the condition. Cognitive deficits relating to motor inhibition represent potential targets for intervention and could predispose to symptoms and impede functional recovery. Treatment algorithms are lacking, with habit reversal therapy showing efficacy but available at few sites. It is noteworthy however that habit reversal therapy is a relatively straight-forward form of psychotherapy that could be readily disseminated between sites. SSRIs appeared ineffective, and trials of novel agents such as newer noradrenaline reuptake inhibitors, antipsychotics, and anti-addictive pharmacotherapies would be valuable.

Future cognitive and imaging studies should recruit unaffected family members of people with trichotillomania to identify candidate vulnerability markers (Chamberlain et al., 2007c; Menzies et al., 2007a, b). Radioligand PET could be used to investigate whether trichotillomania is associated with abnormal binding of receptors involved in cognition and affective processing. Tasks related to inhibitory control that have been used behaviourally could be adapted for functional neuroimaging to investigate neural substrates.

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References

- APA, 2000. DSM-IV-TR. American Psychiatric Association.
- APA, 1987. DSM-III-R. American Psychiatric Association.
- Aron, A.R., Durston, S., et al., 2007. Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. *J. Neurosci.* 27 (44), 11860–11864.
- Azrin, N.H., Nunn, R.G., 1973. Habit-reversal: a method of eliminating nervous habits and tics. *Behav. Res. Ther.* 11 (4), 619–628.
- Azrin, N.H., Nunn, R.G., et al., 1980. Treatment of hairpulling (trichotillomania): a comparative study of habit reversal and negative practice training. *J. Behav. Ther. Exp. Psychiatry* 11, 13–20.
- Baudamant, M., 1777–1779. Description de deux masses de cheveux trouvees dans l'estomac et les intestines d'un jeune garcon age de seize ans. *Hist. Soc. R. Med.* 2, 262–263.
- Berridge, K.C., Aldridge, J.W., et al., 2005. Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's. *BMC Biol.* 3, 4.
- Bloch, M.H., Landeros-Weisenberger, A., et al., 2007. Systematic review: pharmacological and behavioral treatment for trichotillomania. *Biol. Psychiatry*.
- Blum, K., Sheridan, P.J., et al., 1996. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. *J. R. Soc. Med.* 89 (7), 396–400.
- Bohne, A., Savage, C.R., et al., 2005. Visuospatial abilities, memory, and executive functioning in trichotillomania and obsessive-compulsive disorder. *J. Clin. Exp. Neuropsychol.* 27 (4), 385–399.
- Bohne, A., Savage, C.R., et al., 2007. Motor inhibition in trichotillomania and obsessive-compulsive disorder. *J. Psychiatry Res.*
- Bordnick, P.S., Thyer, B.A., et al., 1994. Feather picking disorder and trichotillomania: an avian model of human psychopathology. *J. Behav. Ther. Exp. Psychiatry* 25 (3), 189–196.
- Bouwer, C., Stein, D.J., 1998. Trichobezoars in trichotillomania: case report and literature overview. *Psychosom. Med.* 60 (5), 658–660.
- Braff, D.L., Freedman, R., et al., 2007. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr. Bull.* 33 (1), 21–32.
- Brown, S.A., Crowell-Davis, S., et al., 1987. Naloxone-responsive compulsive tail chasing in a dog. *J. Am. Vet. Med. Assoc.* 190 (7), 884–886.
- Campbell, K.M., McGrath, M.J., et al., 1999a. Behavioral effects of cocaine on a transgenic mouse model of cortical-limbic compulsion. *Brain Res.* 833 (2), 216–224.
- Campbell, K.M., McGrath, M.J., et al., 1999b. Differential response of cortical-limbic neuropotentiated compulsive mice to dopamine D1 and D2 receptor antagonists. *Eur. J. Pharmacol.* 371 (2–3), 103–111.
- Chadwick, J., Mann, W.N., 1983. *Hippocratic Writings*. Penguin Books, translated by authors.
- Chamberlain, S.R., Sahakian, B.J., 2004. Cognition in mania and depression: psychological models and clinical implications. *Curr. Psychol. Rep.* 6 (6), 451–458.
- Chamberlain, S.R., Sahakian, B.J., 2006. The neuropsychology of mood disorders. *Curr. Psychiatry Rep.* 8 (6), 458–463.
- Chamberlain, S.R., Sahakian, B.J., 2007. The neuropsychiatry of impulsivity. *Curr. Opin. Psychiatry* 20 (3), 255–261.
- Chamberlain, S.R., Blackwell, A.D., et al., 2005. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci. Biobehav. Rev.* 29 (3), 399–419.
- Chamberlain, S.R., Blackwell, A.D., et al., 2006a. Strategy implementation in obsessive-compulsive disorder and trichotillomania. *Psychol. Med.* 36 (1), 91–97.
- Chamberlain, S.R., Fineberg, N.A., et al., 2006b. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *Am. J. Psychiatry* 163 (7), 1282–1284.
- Chamberlain, S.R., Muller, U., et al., 2006c. Neurochemical modulation of response inhibition and probabilistic learning in humans. *Science* 311 (5762), 861–863.
- Chamberlain, S.R., Muller, U., et al., 2006d. Noradrenergic modulation of working memory and emotional memory in humans. *Psychopharmacology (Berl.)* 188 (4), 397–407.
- Chamberlain, S.R., Muller, U., et al., 2006e. Neuropharmacological modulation of cognition. *Curr. Opin. Neurol.* 19 (6), 607–712.
- Chamberlain, S.R., Del Campo, N., et al., 2007a. Atomoxetine improved response inhibition in adults with Attention Deficit/Hyperactivity Disorder. *Biol. Psychiatry* 62, 977–984.
- Chamberlain, S.R., Fineberg, N.A., et al., 2007b. A neuropsychological comparison of obsessive-compulsive disorder and trichotillomania. *Neuropsychologia* 45 (4), 654–662.
- Chamberlain, S.R., Fineberg, N.A., et al., 2007c. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *Am. J. Psychiatry* 164 (2), 335–338.
- Chamberlain, S.R., Menzies, L.A., et al., 2007d. Lifting the veil on trichotillomania. *Am. J. Psychiatry* 164 (4).
- Chamberlain, S.R., Menzies, L.A., et al., 2008. Grey matter abnormalities in trichotillomania: morphometric magnetic resonance imaging study. *Br. J. Psychiatry* 193 (3), 216–221.
- Cheng, J.Y., Chen, R.Y., et al., 2007. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. *Psychopharmacology (Berl.)*.
- Chou-Green, J.M., Holscher, T.D., et al., 2003. Compulsive behavior in the 5-HT2C receptor knockout mouse. *Physiol. Behav.* 78 (4–5), 641–649.
- Christenson, G.A., 1995. Trichotillomania - from prevalence to comorbidity. *Psychiatric Times* 12 (9), 44–48.
- Christenson, G.A., Crow, S.J., 1996. The characterization and treatment of trichotillomania. *J. Clin. Psychiatry* 57 (Suppl. 8), 42–47 discussion 48–89.
- Christenson, G.A., Mansueto, C.S., 1999. Trichotillomania: descriptive statistics and phenomenology. In: Stein, D.J., Christenson, G.A., Hollander, E. (Eds.), *Trichotillomania*. American Psychiatric Press, Washington, pp. 1–41.
- Christenson, G.A., Mackenzie, T.B., et al., 1991a. Characteristics of 60 adult chronic hair pullers. *Am. J. Psychiatry* 148 (3), 365–370.
- Christenson, G.A., Mackenzie, T.B., et al., 1991b. A placebo-controlled, double-blind crossover study of fluoxetine in trichotillomania. *Am. J. Psychiatry* 148 (11), 1566–1571.
- Christenson, G.A., Pyle, R.L., et al., 1991c. Estimated lifetime prevalence of trichotillomania in college students. *J. Clin. Psychiatry* 52 (10), 415–417.
- Christenson, G.A., Ristvedt, S.L., et al., 1993. Identification of trichotillomania cue profiles. *Behav. Res. Ther.* 31 (3), 315–320.
- Clarke, H.F., Walker, S.C., et al., 2005. Prefrontal serotonin depletion affects reversal learning but not attentional set shifting. *J. Neurosci.* 25 (2), 532–538.
- Coetzer, R., Stein, D.J., 1999. Neuropsychological measures in women with obsessive-compulsive disorder and trichotillomania. *Psychiatry Clin. Neurosci.* 53 (3), 413–415.
- Cohen, L.J., Stein, D.J., et al., 1995. Clinical profile, comorbidity, and treatment history in 123 hair pullers: a survey study. *J. Clin. Psychiatry* 56 (7), 319–326.
- Cools, R., Robbins, T.W., 2004. Chemistry of the adaptive mind. *Philos. Transact. A Math. Phys. Eng. Sci.* 362 (1825), 2871–2888.
- Dean, J.T., Nelson, E., et al., 1992. Pathologic hair-pulling: a review of the literature and case reports. *Compr. Psychiatry* 33 (2), 84–91.
- Diefenbach, G.J., Reitman, D., et al., 2000. Trichotillomania: a challenge to research and practice. *Clin. Psychol. Rev.* 20 (3), 289–309.
- Diefenbach, G.J., Tolin, D.F., et al., 2005. Trichotillomania: impact on psychosocial functioning and quality of life. *Behav. Res. Ther.* 43 (7), 869–884.
- Diefenbach, G.J., Tolin, D.F., et al., 2006. Group treatment for trichotillomania: behavior therapy versus supportive therapy. *Behav. Ther.* 37 (4), 353–363.
- Dougherty, D.D., Loh, R., et al., 2006. Single modality versus dual modality treatment for trichotillomania: sertraline, behavioral therapy, or both? *J. Clin. Psychiatry* 67 (7), 1086–1092.
- du Toit, P.L., van Kradenburg, J., et al., 2001. Characteristics and phenomenology of hair-pulling: an exploration of subtypes. *Compr. Psychiatry* 42 (3), 247–256.
- Eagle, D.M., Tufft, M.R., et al., 2007. Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. *Psychopharmacology (Berl.)* 192 (2), 193–206.
- Elliott, A.J., Fuqua, R.W., 2000. Trichotillomania: conceptualization, measurement, and treatment. *Behav. Ther.* 31, 529–545.
- Fineberg, N.A., Gale, T.M., 2004. Evidence-based pharmacotherapy of obsessive-compulsive disorder. *Int. J. Neuropsychopharmacol.* 1–23.
- Flessner, C.A., Conelea, C.A., et al., 2008. Styles of pulling in trichotillomania: exploring differences in symptom severity, phenomenology, and functional impact. *Behav. Res. Ther.* 46 (3), 345–357.
- Fong, T., Kaleshstein, A., et al., 2008. A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers. *Pharmacol. Biochem. Behav.* 89 (3), 298–303.
- Frey, A.S., McKee, M., et al., 2005. Hair apparent: Rapunzel syndrome. *Am. J. Psychiatry* 162 (2), 242–248.
- Garner, J.P., Weisker, S.M., et al., 2004. Barbering (fur and whisker trimming) by laboratory mice as a model of human trichotillomania and obsessive-compulsive spectrum disorders. *Comp. Med.* 54 (2), 216–224.
- Geyer, M.A., Markou, A., 1995. In: Bloom, F.E., Kupfer, D.J. (Eds.), *Animal models of psychiatric disorders*. Psychopharmacology: the fourth generation of progress. Raven Press, New York, pp. 787–798.
- Geyer, M.A., Markou, A., 2002. In: Davis, K.L., Coyle, J.T., Nemeroff, C. (Eds.), *The role of preclinical models in the development of psychotropic drugs*. Psychopharmacology: the fifth generation of progress. LWW, pp. 445–455.
- Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160 (4), 636–645.
- Gould, T.D., Gottesman, I.I., 2006. Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav.* 5 (2), 113–119.
- Grachev, I.D., 1997. MRI-based morphometric topographic parcellation of human neocortex in trichotillomania. *Psychiatry Clin. Neurosci.* 51 (5), 315–321.
- Grant, J.E., Potenza, M.N., 2006. Compulsive aspects of impulse-control disorders. *Psychiatry Clin. N. Am.* 29 (2) 539–551, x.
- Grant, J.E., Levine, L., et al., 2005. Impulse control disorders in adult psychiatric inpatients. *Am. J. Psychiatry* 162 (11), 2184–2188.
- Grant, J.E., Odlaug, B.L., et al., 2007. Addicted to hair pulling? How an alternate model of trichotillomania may improve treatment outcome. *Harv. Rev. Psychiatry* 15 (2), 80–85.

- Graybiel, A.M., Rauch, S.L., 2000. Toward a neurobiology of obsessive-compulsive disorder. *Neuron* 28 (2), 343–347.
- Greer, J.M., Capecchi, M.R., 2002. Hoxb8 is required for normal grooming behavior in mice. *Neuron* 33 (1), 23–34.
- Hallopeau, M., 1889. Alopécie par grattage (trichomanie ou trichotillomanie). *Ann. Dermatol. Venerol.* 10, 440–441.
- Hallopeau, H., 1894. Sur un nouveau cas de trichotillomanie. *Annales de Dermatologie et de Syphiligraphie* 5, 541–543.
- Hasler, G., Drevets, W.C., et al., 2006. Toward constructing an endophenotype strategy for bipolar disorders. *Biol. Psychiatry* 60 (2), 93–105.
- Himle, J.A., Bordnick, P.S., et al., 1995. A comparison of trichotillomania and obsessive-compulsive disorder. *J. Psychopathol. Behav. Assess.* 17, 261–260.
- Hollander, E., Cohen, L.J., 1996. Impulsivity and Compulsivity. American Psychiatric Press, Inc.
- Hollander, E., Rosen, J., 2000. Impulsivity. *J. Psychopharmacol.* 14 (2 Suppl 1), S39–S44.
- Hollander, E., Kim, S., et al., 2007. Obsessive-compulsive disorder and obsessive-compulsive spectrum disorders: diagnostic and dimensional issues. *CNS Spectr.* 12 (2 (Suppl. 3)), 5–13.
- Ichimaru, Y., Egawa, T., et al., 1995. 5-HT1A-receptor subtype mediates the effect of fluvoxamine, a selective serotonin reuptake inhibitor, on marble-burying behavior in mice. *Jpn. J. Pharmacol.* 68 (1), 65–70.
- Iglauer, F., Rasim, R., 1993. Treatment of psychogenic feather picking in psittacine birds with a dopamine antagonist. *J. Small Anim. Pract.* 34, 564–566.
- Jimenez-Jimenez, F.J., Garcia-Ruiz, P.J., 2001. Pharmacological options for the treatment of Tourette's disorder. *Drugs* 61 (15), 2207–2220.
- Joel, D., Avisar, A., 2001. "Excessive lever pressing following post-training signal attenuation in rats: a possible animal model of obsessive compulsive disorder?" *Behav. Brain Res.* 123 (1), 77–87.
- Keijsers, G.P., van Minnen, A., et al., 2006. Behavioural treatment of trichotillomania: two-year follow-up results. *Behav. Res. Ther.* 44 (3), 359–370.
- Kessels, R.P., Jaap Kappelle, L., et al., 2002. Lateralization of spatial-memory processes: evidence on spatial span, maze learning, and memory for object locations. *Neuropsychologia* 40 (8), 1465–1473.
- Keuthen, N.J., Savage, C.R., et al., 1996. Neuropsychological functioning in trichotillomania. *Biol. Psychiatry* 39 (8), 747–749.
- Keuthen, N.J., O'Sullivan, R.L., et al., 1998. Trichotillomania: current issues in conceptualization and treatment. *Psychother. Psychosom.* 67 (4–5), 202–213.
- Keuthen, N.J., Makris, N., et al., 2006. Evidence for reduced cerebellar volumes in trichotillomania. *Biol. Psychiatry*.
- Lochner, C., Seedat, S., et al., 2005. Obsessive-compulsive disorder and trichotillomania: a phenomenological comparison. *BMC Psychiatry* 5 (1), 2.
- Logan, G.D., Cowan, W.B., et al., 1984. On the ability to inhibit simple and choice reaction time responses: a model and a method. *J. Exp. Psychol. Hum. Percept. Perform.* 10 (2), 276–291.
- Mansueto, C.S., 1991. Trichotillomania in focus. *OCD Foundation Newslett.* 5, 10–11.
- Mansueto, C.S., Thomas, A.M., et al., 2007. Hair pulling and its affective correlates in an African-American university sample. *J. Anxiety Disord.* 21 (4), 590–599.
- Martin, A., Pigott, T.A., et al., 1993. Lack of evidence for Huntington's disease-like cognitive dysfunction in obsessive-compulsive disorder. *Biol. Psychiatry* 33 (5), 345–353.
- Mckinney, W.T., 2000. In: Sadock, B.J., Sadock, V.A. (Eds.), *Animal Research and Its Relevance to Psychiatry*. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 7th edition. LWW, pp. 545–562.
- Menzies, L., Achard, S., et al., 2007a. Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain* 130 (Pt 12), 3223–3236.
- Menzies, L., Chamberlain, S.R., et al., 2007b. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci. Biobehav. Rev.*
- Miguel, E.C., Baer, L., et al., 1997. Phenomenological differences appearing with repetitive behaviours in obsessive-compulsive disorder and Gilles de la Tourette's syndrome. *Br. J. Psychiatry* 170, 140–145.
- Moon-Fanelli, A.A., Dodman, N.H., et al., 1999. Veterinary models of compulsive self-grooming: parallels with trichotillomania. In: Stein, D.J., Christenson, G.A., Hollander, E. (Eds.), *Trichotillomania*. American Psychiatric Press, New York, pp. 63–92.
- Moritz, S., Jacobsen, D., et al., 2004. Examination of emotional Stroop interference in obsessive-compulsive disorder. *Behav. Res. Ther.* 42 (6), 671–682.
- National Research Council, 1993. *Understanding Child Abuse Neglect*. National Academy Press, Washington.
- Ninan, P.T., Rothbaum, B.O., et al., 2000. A placebo-controlled trial of cognitive-behavioral therapy and clomipramine in trichotillomania. *J. Clin. Psychiatry* 61 (1), 47–50.
- O'Sullivan, R.L., Christenson, G.A., 1999. Pharmacotherapy of trichotillomania. In: Stein, D.J., Christenson, G.A., Hollander, E. (Eds.), *Trichotillomania*. American Psychiatric Press, Washington, pp. 93–124.
- O'Sullivan, R.L., Rauch, S.L., et al., 1997. Reduced basal ganglia volumes in trichotillomania measured via morphometric magnetic resonance imaging. *Biol. Psychiatry* 42 (1), 39–45.
- Prado, H.S., Rosario, M.C., et al., 2008. Sensory phenomena in obsessive-compulsive disorder and tic disorders: a review of the literature. *CNS Spectr.* 13 (5), 425–432.
- Ramsay, E.C., Grindlinger, H., 1994. Use of clomipramine in the treatment of obsessive compulsive behavior in psittacine birds. *J. Assoc. Avian Vet.* 8, 9–15.
- Rapoport, J.L., 1994. [The "obsessive-compulsive spectrum": a useful concept?]. *Encephale* 20 (4), 677–680.
- Rauch, S.L., Wright, C.I., et al., 2007. Brain activation during implicit sequence learning in individuals with trichotillomania. *Psychiatry Res.* 154 (3), 233–240.
- Rettew, D.C., Cheslow, D.L., et al., 1991. Neuropsychological test performance in trichotillomania: a further link with obsessive-compulsive disorder. *J. Anxiety Disorders* 5, 225–235.
- Robbins, T.W., 2000. Chemical neuromodulation of frontal-executive functions in humans and other animals. *Exp. Brain Res.* 133 (1), 130–138.
- Robertson, M.M., 2006. Attention deficit hyperactivity disorder, tics and Tourette's syndrome: the relationship and treatment implications. A commentary. *Eur. Child Adolesc. Psychiatry* 15 (1), 1–11.
- Robinson, E.S., Eagle, D.M., et al., 2007. Similar effects of the selective noradrenergic reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology*.
- Singer, H.S., Reiss, A.L., et al., 1993. Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. *Neurology* 43 (5), 950–956.
- Singh, A.N., Maguire, J., 1989. Trichotillomania and incest. *Br. J. Psychiatry* 155, 108–110.
- Stanley, M.A., Cohen, L.J., 1999. Trichotillomania and OCD. In: Stein, D.J., Christenson, G.A., Hollander, E. (Eds.), *Trichotillomania*. American Psychiatric Press, xx–xxx.
- Stanley, M.A., Hannay, H.J., et al., 1997. The neuropsychology of trichotillomania. *J. Anxiety Disord.* 11 (5), 473–488.
- Stein, D.J., Hollander, E., 1995. Obsessive-compulsive spectrum disorders. *J. Clin. Psychiatry* 56 (6), 265–266.
- Stein, D.J., Lochner, C., 2006. Obsessive-compulsive spectrum disorders: a multi-dimensional approach. *Psychiatr. Clin. North Am.* 29 (2), 343–351.
- Stein, D.J., Dodman, N.H., et al., 1994. Behavioral disorders in veterinary practice: relevance to psychiatry. *Comp. Psychiatry* 35 (4), 275–285.
- Stein, D.J., Simeon, D., et al., 1995. Trichotillomania and obsessive-compulsive disorder. *J. Clin. Psychiatry* 56 (Suppl 4), 28–34 discussion 35.
- Stein, D.J., Coetzer, R., et al., 1997. Magnetic resonance brain imaging in women with obsessive-compulsive disorder and trichotillomania. *Psychiatry Res.* 74 (3), 177–182.
- Stein, D.J., van Heerden, B., et al., 2002. Functional brain imaging and pharmacotherapy in trichotillomania. Single photon emission computed tomography before and after treatment with the selective serotonin reuptake inhibitor citalopram. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 26 (5), 885–890.
- Stein, D.J., Chamberlain, S.R., et al., 2006. An A-B-C model of habit disorders: hair-pulling, skin-picking, and other stereotypic conditions. *CNS Spectr.* 11 (11), 824–827.
- Stein, D.J., Garner, J.P., et al., 2007. Trichotillomania, stereotypic movement disorder, and related disorders. *Curr. Psychiatry Rep.* 9 (4), 301–302.
- Streichenwein, S.M., Thornby, J.L., 1995. A long-term, double-blind, placebo-controlled crossover trial of the efficacy of fluoxetine for trichotillomania. *Am. J. Psychiatry* 152 (8), 1192–1196.
- Swedo, S.E., Leonard, H.L., 1992. Trichotillomania. An obsessive compulsive spectrum disorder? *Psychiatr. Clin. N. Am.* 15 (4), 777–790.
- Swedo, S.E., Rapoport, J.L., 1991. Annotation: trichotillomania. *J. Child Psychol. Psychiatry* 32 (3), 401–409.
- Swedo, S.E., Leonard, H.L., et al., 1989. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). *N. Engl. J. Med.* 321 (8), 497–501.
- Swedo, S.E., Rapoport, J.L., et al., 1991. Regional cerebral glucose metabolism of women with trichotillomania. *Arch. Gen. Psychiatry* 48 (9), 828–833.
- Szechtman, H., Sulis, W., et al., 1998. Quinpirole induces compulsive checking behavior in rats: a potential animal model of obsessive-compulsive disorder (OCD). *Behav. Neurosci.* 112 (6), 1475–1485.
- Tsaltas, E., Kontis, D., et al., 2005. Reinforced spatial alternation as an animal model of obsessive-compulsive disorder (OCD): investigation of 5-HT2C and 5-HT1D receptor involvement in OCD pathophysiology. *Biol. Psychiatry* 57 (10), 1176–1185.
- Van Ameringen, M., Mancini, C., et al., 2006. A randomized placebo controlled trial of olanzapine in trichotillomania. *J. Eur. Coll. Neuropsychopharmacol.* 16 (4), S452.
- van Minnen, A., Hoogduin, K.A., et al., 2003. Treatment of trichotillomania with behavioral therapy or fluoxetine: a randomized, waiting-list controlled study. *Arch. Gen. Psychiatry* 60 (5), 517–522.
- Vythilingam, B., Warwick, J., et al., 2002. SPECT scans in identical twins with trichotillomania. *J. Neuropsychiatry Clin. Neurosci.* 14 (3), 340–342.
- Woods, D.W., Flessner, C.A., et al., 2006a. The Trichotillomania Impact Project (TIP): exploring phenomenology, functional impairment, and treatment utilization. *J. Clin. Psychiatry* 67 (12), 1877–1888.
- Woods, D.W., Wetterneck, C.T., et al., 2006b. A controlled evaluation of acceptance and commitment therapy plus habit reversal for trichotillomania. *Behav. Res. Ther.* 44, 639–656.
- Yadin, E., Friedman, E., et al., 1991. Spontaneous alternation behavior: an animal model for obsessive-compulsive disorder? *Pharmacol. Biochem. Behav.* 40 (2), 311–315.