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ORIGINAL INVESTIGATION

Effects of acute modafinil on cognition in trichotillomania

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Abstract
Rationale Individuals with trichotillomania often report significant difficulty resisting the urges and drive to pull hair.
Objectives The aim of this study is to examine whether modafinil improves motor inhibitory control, and other cognitive functions, in trichotillomania.
Methods Eighteen subjects with trichotillomania (mean age 33.4±12.8 years; 78% female) received a single dose of modafinil (200 mg) and placebo in a crossover double-blind design. Neurocognitive performance was assessed using the stop-signal, pattern recognition, rapid visual information processing and Tower of London tasks.
Results No effects of modafinil on cognition approached statistical significance on the test measures examined (all $p>0.10$).
Conclusions These results suggest that modafinil may not be useful for targeting impulse dyscontrol in trichotillomania. However, it remains possible that relatively small effects of modafinil on cognition could exert larger downstream effects on overt behaviour. Further trials using modafinil and other pro-cognitive agents are warranted.

Keywords Modafinil · Trichotillomania · Impulsivity · Cognition · Noradrenaline · Pharmacotherapy

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Introduction

Trichotillomania is an often disabling, under-recognised condition in which individuals repeatedly pull out hair, leading to noticeable hair loss (Keuthen et al. 1998; Woods et al. 2006; Flessner et al. 2009). The repetitive physical symptoms of trichotillomania suggest underlying dysfunction of motor inhibitory control processes (Chamberlain et al. 2006a; Stein et al. 2006). Recent research found that subjects with trichotillomania ($n=17$) exhibited impaired inhibitory control compared to healthy volunteers ($n=20$) on a stop-signal reaction time task (SSRT), which measures the ability of subjects to actively inhibit an already triggered motor command (Chamberlain et al. 2006a).

Response inhibition as a cognitive function is dependent on neural circuitry including the right inferior frontal gyrus (Aron et al. 2003), and is affected by manipulations of the noradrenaline system, but not of the serotonin system, in humans (Clark et al. 2005; Chamberlain et al. 2006b) and rats (Bari et al. 2009). These findings suggest noradrenaline and inhibitory network dysegulation in the pathophysiology of trichotillomania. Modafinil's behavioural (including pro-cognitive) effects are thought to stem in part from effects on noradrenaline transmission (Hou et al. 2005; Minzenberg et al. 2008), though this medication may also have dopaminergic effects (Volkow et al. 2009; Finke et al. 2010). In healthy volunteers and certain clinical groups (e.g. Attention Deficit Hyperactivity Disorder, ADHD), mod-

afinil has been reported to improve aspects of cognition (for reviews see e.g. Minzenberg and Carter 2008; Chamberlain et al. 2010).

Several studies have investigated the effects of acute modafinil administration on response inhibition and other tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Turner et al. reported improved response inhibition (SSRT) and executive planning (Stockings of Cambridge test), but not sustained attention (rapid visual information processing test, RVIP) in 20 healthy recruits given 200 mg modafinil compared to 20 subjects given placebo (double-blind design) (Turner et al. 2003). In a healthy volunteer study with 12 participants, modafinil (300 mg) failed to improve SSRT or RVIP versus placebo but did improve executive planning (double-blind crossover design). These beneficial effects were blocked by concurrent dosing with the alpha-receptor antagonist prazocin (Winder-Rhodes et al. 2009). Elsewhere, 100/200 mg modafinil (n=10 subjects per arm, placebo-controlled between-subjects design), had no benefits on RVIP or executive planning (Randall et al. 2003) and similar findings were reported with a sample of n=15 per arm (Randall et al. 2004). In a subsequent study with n=20 per arm, improved RVIP was found with 200 mg modafinil versus placebo (between-subjects design), with no benefits on executive planning (Randall et al. 2005). In 20 adults with ADHD, modafinil 300 mg improved SSRT, RVIP and executive planning versus placebo (double-blind crossover design) (Turner et al. 2004).

On the basis of these prior results, this pilot study sought to examine the potential pro-cognitive effects of modafinil in trichotillomania. We chose a 200-mg dose since this yielded the most robust effects in the studies already discussed. It was hypothesised that modafinil would improve aspects of cognition in subjects with trichotillomania, particularly response inhibition, since this function is impaired in the disorder (Chamberlain et al. 2006a).

Experimental procedures

Subjects

Eighteen adults (78% females; n=14) with a current primary diagnosis of trichotillomania were recruited, via advertisements on support websites for people with the disorder, in UK.

The Cambridge Research Ethics Committee approved the study and all subjects gave written informed consent. The study was formally exempted from clinical trial regulations by the Medicines and Healthcare Products Regulatory Agency, London, UK.

Procedures

Patients were interviewed using the Mini International Neuropsychiatric Inventory (MINI), a screening tool for axis-I disorders (Sheehan et al. 1998), supplemented with additional questions relating to DSM-IV criteria for the impulse control disorders (including trichotillomania). Depressive mood was assessed using the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979), and IQ with the National Adult Reading Test (NART; Nelson 1982).

Patients were enrolled on the basis of meeting full DSM-IV criteria for trichotillomania, being free from clinically significant levels of depression (not fulfilling DSM-IV criteria for major depressive disorder, and MADRS scores<10), and being free from psychological and psychopharmacological treatment for at least 6 months. Trichotillomania inclusion criteria also required absence of co-morbid OCD, pyromania, kleptomania and pathological gambling. Trichotillomania severity was assessed using the Massachusetts General Hospital Hairpulling Scale (MGH-HPS; Keuthen et al. 1995) at study entry. Exclusion criteria were: history of serious head injury, history of substance abuse, history of neurologic disorders (including epilepsy and tics), NART IQ<90, inability to understand the procedures, and contraindications to modafinil.

A double-blind, placebo-controlled within-subject design was used. Participants attended for two testing sessions, approximately 1-week apart. In one session, they received a single dose of modafinil (200 mg) and in another session they received a placebo. The order in which the participants received the drug was randomised and counterbalanced. Participants were tested approximately 2 h after oral administration of the drug, to coincide with peak plasma levels (Muller et al. 2004).

Neurocognitive assessment comprised a subset of tests from the CANTAB, including the stop-signal (SSRT), pattern recognition memory (PRM), RVIP, and Tower of London (TOL) tasks. As outlined above, these tests have been reported to be sensitive to effects of modafinil in some studies (see e.g. Turner et al. 2003; Randall et al. 2005; Winder-Rhodes et al. 2009). Tests were presented in a fixed order, which was identical between testing sessions (PRM, RVIP, TOL, SSRT).

The SSRT is a well-validated task quantifying the ability to suppress impulsive responses (Logan et al. 1984; Aron et al. 2003). Subjects observe a series of directional arrows appearing one at a time on a computer screen, and make speeded motor responses depending on the direction of each arrow, with a button box (left or right). On a subset of trials, an auditory beep occurs (the 'stop signal') which indicates that the subject should try to inhibit their response for that particular trial. By varying the time between presentation of the arrow and the occurrence of the stop signal dynamically, this task provides a sensitive estimate of the time taken by the subject's brain to stop a prepotent response, referred to as

the 'Stop-signal reaction time' (SSRT). Median reaction time for go trials is also recorded.

PRM is a test of memory whereby subjects make a forced choice of two stimuli per trial, one of which was previously displayed. The key measure is the percentage of correct recognition.

RVIP is a test of sustained attention, in which digits from 2 to 9 appear in a pseudo-random fashion, one per time, at a rate of 100 digits per minute. Subjects are requested to register responses on a press pad whenever they detect three-digits-target sequences. The three major RVIP outcome measures include mean latency, target sensitivity (A′) and response bias (B″).

TOL is a test of executive planning; subjects attempt to work out 'in mind' the minimum number of moves required to move a set of snooker balls displayed on-screen to match the appearance of a goal arrangement. Key measures are the mean attempts taken to obtain correct solutions and the mean response times for each difficulty level of the task (1 through 6).

Data analysis

Data were analysed using repeated-measures analyses of variance with drug condition (active/placebo) as the within-subject factor. For the TOL task, an additional within-subject factor of difficulty level (1/2/3/4/5/6) was included. Being an exploratory study, significance was defined a priori as $p<0.05$ uncorrected.

Results

Subjects reported a mean (±SD) age of 33.4 (12.8) years and moderate trichotillomania severity (MGH-HPS total

Table 1 Cognitive tasks in trichotillomania subjects taking modafinil or placebo

	Mean±SD		Drug effect		
	Modafinil (n=18)	Placebo (n=18)	F	p	Cohen's d
Pattern recognition memory					
Percent correct	91.9±10.35	90.51±11.33	0.592	0.452	0.13
Rapid visual information					
Processing					
A′	0.93±0.05	0.87±0.22	1	0.332	0.39
B″	0.93±0.06	0.9±0.25	1	0.332	0.19
Response latency (ms)	414.72±63.69	408.28±117.52	0.063	0.805	0.07
Stop-signal reaction time					
SSRT (ms)	207.82±69.64	221.23±68.91	0.795	0.385	−0.19
Median 'go' RT (ms)	369.56±34.91	370.44±38.34	0.02	0.888	−0.02
Tower of London					
Attempts to correct solution			0.368	0.552[a]	
1-level difficulty	1.04±0.1	1.03±0.12			0.13
2-level difficulty	1.1±0.19	1.06±0.11			0.27
3-level difficulty	1.18±0.24	1.13±0.26			0.22
4-level difficulty	1.35±0.38	1.35±0.37			0.00
5-level difficulty	1.51±0.49	1.47±0.34			0.10
6-level difficulty	1.71±0.73	1.94±0.9			−0.29
Time to response (ms)			0.013	0.911[b]	
1-level difficulty	4,898.03±2,002.04	4,762.41±1,455.91			0.08
2-level difficulty	5,302.74±2,154.81	5,272.96±1,397.68			0.02
3-level difficulty	8,185.51±2,552.95	7,152.93±2,232.24			0.43
4-level difficulty	12,128.41±4,193.52	14,067.9±6,811.42			−0.34
5-level difficulty	28,126.5±21,281.34	33,172.03±17,743.9			−0.26
6-level difficulty	47,396.15±31,314.61	46,257.22±28,286.65			0.04

[a] Within-subject factor of difficulty level, main effect of drug condition reported. Significant main effect of difficulty (F=15.777, $p<0.001$), no significant drug condition by difficulty interaction (F=1.580, p=0.174)

[b] Within-subject factor of difficulty level, main effect of drug condition reported. Significant main effect of difficulty (F=28.092, $p<0.001$), no significant drug condition by difficulty interaction (F=1.302, p=0.272)

score of 14.56±3.88). One subject met DSM-IV criteria for panic disorder while the remainder were free from co-morbidities, as indexed by the MINI and supplementary questions. Unblinding at the end of the study indicated that order was fully counterbalanced (nine subjects received placebo-drug, and nine drug-placebo).

Results from cognitive tasks are presented in Table 1. No effects of drug approached statistical significance (all $p>0.10$).

Discussion

Contrary to our hypothesis, this study demonstrated that modafinil was not associated with any significant cognitive enhancing effects in trichotillomania, on the tasks examined. In particular, there were no effects on inhibitory control (stop-signal reaction time: $p=0.385$, Cohen's $d=0.19$), which was previously found to be impaired in subjects with the disorder versus matched controls (Chamberlain et al. 2006a). This study suggests that modafinil at a dose of 200 mg may not be useful in improving the motor inhibitory deficits underlying trichotillomania.

These results are relevant for the understanding and treatment of neuropsychological deficits in trichotillomania. Several limitations should be considered, including the relatively small sample size. However, assuming similar cognitive effects to those previously seen in healthy volunteers on the SSRT with modafinil (Turner et al. 2003), this study had >95% power to detect a similar beneficial effect (one-tailed; alpha 0.05). We did not record details of previous pharmacological and psychological treatments received, beyond 6 months prior to participation. Another limitation is that cognitive effects were assessed after a single fixed 200-mg dose of modafinil. It is still yet to be determined if modafinil taken in different doses, and over a period of time would be useful for the treatment of trichotillomania and its neuropsychological sequaelae. Furthermore, even relatively small effects on cognition could exert larger downstream effects on overt behaviour, and we cannot rule out this possibility with modafinil in trichotillomania. Hence, this study should not dissuade researchers from further exploring the potential utility of this medication.

There are currently no formally approved pharmacological treatments for trichotillomania and people with the disorder often report disappointing outcomes with available treatments (Woods et al. 2006; Chamberlain et al. 2009). Focusing on the underlying pathophysiology of trichotillomania in terms of impulse control, reward circuitry and affect regulation, may yet lead to more targeted pharmacotherapies.

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