The effects of digital cognitive behavioural therapy for insomnia on cognitive function: A randomised, controlled trial

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Abstract

Study Objectives: We sought to examine the impact of digital cognitive behavioural therapy (dCBT) for insomnia on both self-reported cognitive impairment and objective cognitive performance.

Methods: The DISCO trial was an online, two-arm, single-blind, randomised clinical trial of dCBT versus wait-list control. Participants were aged 25 years and older, met DSM-5 diagnostic criteria for insomnia disorder and reported difficulties with concentration or memory. Assessments were carried out online at baseline, and 10 and 24 weeks post-randomisation. The primary outcome measure was self-reported cognitive impairment, assessed with the British Columbia Cognitive Complaints Inventory (BC-CCI). Secondary outcomes included tests of cognitive performance, insomnia symptoms, cognitive failures, fatigue, sleepiness, depression and anxiety.

Results: 410 participants with insomnia were recruited and assigned to dCBT (N = 205) or wait-list control (N = 205). At 10 weeks post-randomisation the estimated adjusted mean difference for the BC-CCI was -3.03 [95% CI: -3.60,-2.47; p<.0001, d = -0.86], indicating that participants in the dCBT group reported less cognitive impairment than the control group. These effects were maintained at 24 weeks (d = -0.96) and were mediated, in part, via reductions in insomnia severity and increased sleep efficiency. Treatment effects in favour of dCBT, at both 10 and 24 weeks, were found for insomnia severity, sleep efficiency, cognitive failures, fatigue, sleepiness, depression, and anxiety. We found no between-group differences on objective tests of cognitive performance.

Conclusions: Our study shows that dCBT robustly decreases self-reported cognitive impairment at post-treatment and these effects are maintained at 6 months.

Keywords: insomnia; cognitive function; cognitive behavioural therapy

Clinical trial registration: The trial is registered with the ISRCTN registry (ISRCTN89237370).

Statement of significance

We conducted the first study to investigate the effects of CBT, delivered via digital technology, on subjective and objective cognitive function in people with both insomnia and cognitive complaints. We found that CBT improves self-reported cognitive impairment relative to a waitlist control group at both post-treatment and 6 months follow-up, and that such differences are mediated in part via reduction in insomnia symptoms. We found no benefit of CBT on objective cognitive performance measured by computerised tasks.

Introduction

Insomnia is the most common sleep disorder and second-most prevalent psychiatric disorder in Europe[1,2]. People with insomnia report significant impairments to quality of life[3] and cite cognitive impairment as one of the chief consequences of sleep disruption[4]. Self-reported cognitive impairment manifests as difficulties with concentration, memory, attention and decision-making. While the literature on objective cognitive performance (assessed via neuropsychological tasks) is characterised by conflicting findings[5-7], meta-analyses reveal small-to-moderate deficits in working memory, inhibitory control, episodic memory and problem-solving[8,9]. More recent studies suggest that complex attention may be particularly affected[10]. Both objective and self-reported cognitive impairment may explain, at least in part, reduced work productivity and increased accident risk in those with insomnia[11,12].

Sleep is known to play a central role in brain plasticity, memory consolidation and optimal cognitive engagement[13]. Insomnia, therefore, is proposed to lead to impairment in cognition through its adverse effects on brain structure and function[14]. Indeed, insomnia is an independent risk-factor for cognitive decline and Alzheimer's disease[15,16], and may contribute to cognitive impairment observed in other highly co-morbid neuropsychiatric disorders[17].

Rescue of self-reported cognitive impairment through treatment is clearly important to patients[4] but to date few studies have assessed cognitive function in trials of cognitive behavioural therapy (CBT), the recommended first-line treatment. A recent review of this small literature[18] found that studies 1) assessed self-reported cognitive impairment using low-resolution questionnaire items; 2) rarely included objective performance measures of cognitive function; 3) evaluated cognitive function as secondary or exploratory outcomes;

and 4) often recruited small samples, with potentially confounding co-morbidities. The effect of CBT on cognitive function remains largely uncharacterized in adequately-designed studies. The present study, therefore, was specifically designed to examine the potential impact of an established digital CBT programme for insomnia (dCBT), relative to waitlist-control (WLC), upon both self-reported cognitive impairment and objective cognitive performance. We also aimed to determine whether change in insomnia symptoms mediates change in cognitive outcomes.

The primary hypothesis for the trial was:

1. dCBT will reduce self-reported cognitive impairment at the end of treatment (10 weeks) relative to WLC

The secondary hypotheses were:

2. dCBT will reduce self-reported cognitive impairment at follow-up (24 weeks) relative to WLC
3. dCBT will improve objective cognitive performance (in the following domains: simple attention, visual attention, episodic memory, working memory, and complex processing speed), relative to WLC (10 and 24 weeks)
4. dCBT will reduce insomnia severity and improve sleep efficiency relative to WLC (10 and 24 weeks)
5. Change in insomnia severity and sleep efficiency at week 10 will mediate change in self-reported cognitive impairment and objective cognitive performance at week 24

6. dCBT will lead to improvements in fatigue, sleepiness, self-reported cognitive failures, depression and anxiety, relative to WLC (weeks 10 and 24)

Methods

Study Design

The DISCO [*D*efining the *I*mpact of *S*leep improvement on *C*ognitive *O*utcomes] study was an online, two-arm, single-blind, randomised clinical trial of dCBT versus WLC. Participants meeting DSM-5 criteria for insomnia disorder were recruited from the community and screened, consented, assessed and randomised on a 1:1 basis to intervention or control using the online platform, Qualtrics (www.qualtrics.com). Participants in the intervention arm received access to the dCBT programme, Sleepio (www.sleepio.com)[19], while the WLC group received access to the same programme on completion of study follow-up (24 weeks). The study was conducted in the UK and approved by the University of Oxford Medical Sciences Inter-divisional Research Ethics Committee (R46116/RE001). The trial was prospectively registered with the ISRCTN (ISRCTN89237370) and the trial protocol published[20].

Participants

We aimed to recruit 404 participants and achieved a final sample size of 410 (205 in each arm). Participants were recruited from the community through multiple channels; for example, the study web-link was sent to contact lists of people who had previously expressed an interest in taking part in sleep research, and advertised on websites and social media platforms (e.g., Twitter and Facebook). Inclusion criteria were: 1) aged 25 years and over; 2) meet DSM-5 criteria for insomnia disorder according to the Sleep Condition Indicator[21]; 3) report difficulties with concentration or memory[22]; 4) have reliable internet

access; 5) read and understand English; and 6) currently reside in the United Kingdom. Exclusion criteria were: a) screen positive for or report diagnosis of additional sleep disorder[23]; b) report a diagnosis of mild cognitive impairment, dementia or neurological condition; c) take prescribed sleep medication on >2 nights in the past two weeks; d) currently receiving psychological treatment for insomnia; e) report a diagnosis of schizophrenia or bipolar disorder; f) report suicidal ideation with intent[24]; g) planned major surgery; h) life expectancy < 6 months; and i) habitual night, evening, or rotating shift-work. Participants with other mental and physical health problems, or receiving other types of treatments, were eligible to take part.

Randomisation and Masking

Simple randomisation with an allocation ratio of 1:1 was carried out using the randomisation function within Qualtrics Survey Software (Qualtrics, Provo, UT, USA) on completion of baseline measures. The research team therefore had no access to future allocations and were unable to influence randomisation. Other than the trial coordinator, who emailed participants their allocation, the research team remained blind to allocation. Contact between trial coordinator and participants was limited to standardised information, detailing instructions for dCBT access and completion of assessments, and did not cover therapy content or support.

Procedures

dCBT was delivered via the Sleepio programme, the efficacy of which has been established in several RCTs[19,25,26]. Detailed information is available elsewhere[19] but in brief, intervention ingredients, covering key cognitive and behavioural strategies, are introduced by an animated virtual therapist in a personalized but automated manner over six 15-20 minute

sessions. Participants also have access to a library of sleep-related articles and online community forum, and can participate in weekly live discussions with a sleep expert.

Participants randomised to the wait-list control arm were informed that they would be provided with access to dCBT at the end of the study (24 week follow-up). For both arms there was no restriction on what treatments or support participants could access during the trial, for sleep or any other health problem.

Outcomes

Demographic data were collected at baseline. Major assessments of primary and secondary outcomes were conducted at baseline, post-treatment (10 weeks post-randomisation) and follow-up (24 weeks post-randomisation). Participants received vouchers for completion of assessments (£5 for baseline; £10 for post-treatment; £15 for follow-up).

The primary outcome, self-reported cognitive impairment, was assessed with the British Columbia Cognitive Complaints Inventory (BC-CCI[27]), a six-item questionnaire assessing perceived cognitive problems in the past 7 days. Items are scored on a 0-3 scale (range = 0-18) and probe difficulties with concentration, memory, expressing thoughts, word-finding, slow thinking speed and problem-solving. Higher scores indicate greater perceived cognitive impairment.

Secondary outcomes included tests of cognitive performance, insomnia severity, sleep efficiency, cognitive failures, fatigue, sleepiness, depression and anxiety.

Cognitive performance was assessed via web-based test battery. The battery was developed by the UK Biobank Cognitive Psychology Sub-Group for Cognitive Assessments and comprised 6 tasks. Participants were advised to complete the tasks in a distraction-free environment and, where possible, at the same clock-time (across assessments), using the same device (across assessments). *Snap task (simple attention):* In this task, two cards (matching or non-matching) appear side-by-side on the screen. Participants are instructed to respond as quickly as possible when they see two matching cards, and withhold responses to non-matching cards (dependent variable: mean RT [msec] for correct responses on matching trials). *Trail making task (visual search, motor speed, mental flexibility)*: In the first part of this task (TRAILS-A) participants are required to join numbered circles in sequential order (dependent variables: RT [msec] to complete and number of errors). In part b (TRAILS-B) participants are asked to join together numbered circles and lettered circles in sequential order, shifting between sets (dependent variables: RT [msec] to complete and number of errors). *Reverse digit span task (working memory)*: In this task participants are presented with a series of numbers on the screen, increasing in string length across trials. Number strings disappear and participants are asked to insert the number string in reverse order using a mouse-click keypad (dependent variable: longest correct string of numbers). *Pairs matching task (episodic memory)*: In this task 6 pairs of cards (level 1, 3x4 matrix) or 8 pairs of cards (level 2, 4x4 matrix) are flashed on the screen and then disappear. Participants are asked to remember their location and subsequently identify matching pairs of cards (dependent variable: number of errors when matching pairs for levels 1 and 2). Progression to level 2 is contingent on achieving ≤ 1 error on level 1. *Symbol-digit substitution task (complex processing speed)*: In this task participants are asked to match a series of symbols to digits (dependent variable: number of correct matches in a 1-minute interval).

Insomnia severity was assessed using the Insomnia Severity Index (ISI)[28] and through calculation of sleep efficiency (%; derived from three items from the Pittsburgh Sleep Quality Index, PSQI[29]). Fatigue was measured with the Multidimensional Fatigue Inventory (MFI[30]), which comprises five sub-scales covering general, physical and mental fatigue, and reduced motivation and reduced activity; sleepiness was measured with the Epworth Sleepiness Scale (ESS[31]); everyday failures in perception, memory and motor function were measured with the Cognitive Failures Questionnaire (CFQ[32]); depression was measured with Patient Health Questionnaire (PHQ-9[33]); and anxiety was measured using two items from the General Anxiety Disorder scale (GAD-2[34]).

We report four outcomes beyond those that were pre-registered. We measured groups on the use of prescribed sleep medication and non-prescription sleep remedies at baseline, 10 and 24 weeks. Participants were asked to indicate *how many nights in the last two weeks have you taken*…(1) *sleeping pills prescribed by your doctor*; and (2) *non-prescription sleep remedies*. The cognitive test battery also included a test of reasoning (fluid intelligence task) at baseline, 10 and 24 weeks, where participants were presented with a series of problem-solving questions (dependent variable: total number of correct answers in 2-minute period). We measured proportion meeting 'caseness' for depression (defined as PHQ ≥10) at baseline, 10 and 24 weeks.

Serious adverse events (SAEs) were recorded if the research team were made aware of them, and were defined as death, suicide attempt, admission to hospital, or formal complaints about the dCBT intervention. We collected information on the following pre-defined adverse effects at 10 weeks using a standardised scale[35]: low mood, fatigue and/or exhaustion, extreme sleepiness, feeling agitated, bodily pain, headache and/or migraine,

euphoria and/or intense increase in mood, reduced motivation and/or energy, changes in hunger and/or appetite, blurred vision, dizziness and feeling irritable.

Statistical analysis

The study was powered at 90% to detect a minimum standardised effect size of 0.42 at post-treatment (week 10) at a 5% level of significance, accounting for 40% attrition from baseline.

Analyses followed intention to treat (ITT) principles and are reported according to the CONSORT statement for non-pharmacological interventions[36]. All analysis was conducted by the trial statisticians as partially blind (groups labelled A/B until analysis complete) using Stata version 14 (StataCorp). Summary statistics (means and standard deviations for continuous variables; frequencies and percentages for binary and categorical variables) are presented by randomised group without testing for baseline differences.

A linear mixed effects model was estimated using maximum likelihood for the primary outcome of self-reported cognitive impairment, measured by the BC-CCI. The outcomes at 10 and 24 weeks were included as the response. The baseline score was included as a covariate in the model along with time point (10 or 24 weeks), randomised group (dCBTi or WLC), and a patient specific random intercept to account for repeated measures. An interaction between time point and randomised group was included to estimate the treatment effect - the mean difference in scores between the dCBT group and the WLC group - separately at each time point. Of *primary interest* is the treatment effect at 10 weeks. 95% confidence intervals and two-sided p-values (significance level of ≤ .05) are reported with estimated effects. Bootstrapping was used to estimate confidence intervals where there was evidence of heteroscedasticity. Cohen's d statistics were calculated as the adjusted

treatment effect divided by the baseline standard deviation of the BC-CCI for the combined treatment groups. Unadjusted means by the two randomised groups are also reported. Secondary outcomes were analysed in the same way. For binary secondary outcomes, for which a linear model was not deemed appropriate, a logistic mixed model was estimated. Missing outcomes were assumed to be missing at random, conditional on the covariates in the model. Moderation of the cognitive functioning outcomes (BC-CCI, cognitive test battery) was assessed by including age at baseline in a three-way interaction in the linear mixed models. This enabled estimation of the difference in treatment effect associated with an increase in 1 year of age at both 10 and 24 weeks.

For cognitive variables showing a treatment effect at 24 weeks, causal mediation methods were used to investigate if changes in these outcomes at 24 weeks were mediated by changes in insomnia severity and sleep efficiency, respectively, at 10 weeks. Parametric regression models adjusting for the mediator measure at 10 weeks were used to test for the direct effect of the intervention on the outcome at 24 weeks. The indirect effect was estimated by multiplying the effect of the intervention on the mediator at 10 weeks and the effect of the mediator at 10 weeks on the outcome at 24 weeks, and bootstrapping was used to produce standard errors for the direct and indirect effects. Adjustment was made for baseline measures of the mediator and the outcome.

Differences in the frequency of self-reported adverse effects at 10 weeks were calculated and compared using chi-squared tests. The total number of adverse effects was also compared in a Mann-Whitney test.

No adjustment was made for multiple testing for the analyses performed on the primary and secondary outcomes as these hypotheses are pre-specified, correlated and related to each other[37].

Sensitivity analyses examined the robustness of the primary outcome analysis to different assumptions regarding departures from randomisation policies and missing data. A pattern mixture model was applied to the data which estimates the treatment effect under scenarios where the missing outcomes at 10 weeks are imputed as being higher or lower than the observed mean outcome. Additionally, it was assessed whether including baseline variables associated with missingness of the primary outcome at 10 weeks in the main analysis model changed the estimated treatment effect of the intervention on the primary outcome.

Role of the Funding Source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Recruitment commenced 18th October, 2016 and stopped on the 21st March, 2017 after the planned sample size was achieved. 2947 individuals were screened online; 509 were deemed eligible, while 410 participants completed baseline and were subsequently randomised (205 in each arm). Principal reasons for exclusion were not meeting insomnia criteria, shift work, possible sleep apnoea and possible restless legs syndrome (see Figure 1). Retention was 82% at 10 weeks and 74% at 24 weeks, and differed by group, with the

dCBT group less likely to provide outcome data than control (at 10 weeks: 76% for dCBT vs. 88% for control/ at 24 weeks: 66% for dCBT vs. 81% in control). An administrative error meant that 43 participants (n=28 dCBT, n=15 WLC), who did not complete outcome assessments at 10 weeks, were not sent a follow-up invitation at 24 weeks. In the dCBT arm, 60% of participants completed all 6 online treatment sessions, 73% completed ≥ 3 sessions, while 17% did not access the intervention at all.

[INSERT FIGURE 1: TRIAL FLOW]

The sample was predominately in middle-age (52.4 yrs, SD = 11.5; range 26-82), of white ethnic background (98%), comprised of females (87%), and the majority were university-educated (54%; see Table 1). Consistent with inclusion criteria, insomnia severity scores (ISI) were in the clinical range (mean = 18.2, SD = 3.7; see Table 2), and the majority of participants (62%) met 'caseness' for depression on the PHQ-9 (score of ≥10). At baseline, only 17% of the sample progressed to level 2 on the pairs-matching task so we did not analyse this variable as an outcome at 10 and 24 weeks.

[INSERT TABLES 1 & 2 – DESCRIPTIVE CHARACTERISTICS AND BASELINE SCORES OF OUTCOMES]

At 10 weeks post-randomisation the estimated adjusted mean difference on the primary outcome measure of self-reported cognitive impairment (BC-CCI) was -3.03 [95% CI: -3.60,-2.47; p<.0001, d = -0.86], indicating that participants in the dCBT group (unadjusted mean = 5.88, SD = 3.61) reported less cognitive impairment than the control group (8.91, SD = 3.87;

see Table 3). These large treatment effects were maintained at 24 weeks [estimated adjusted mean difference = -3.41, 95% CI: -4.06,-2.76; p<.0001, d = -0.96], with the dCBT group (unadjusted mean = 5.51, SD = 3.69) reporting less cognitive impairment than the control group (8.98, SD = 4.23). Effects were robust across sensitivity analyses investigating assumptions regarding missingness mechanisms for the outcome (see Supplementary Information).

[INSERT TABLES 3 & 4 – SECONDARY OUTCOMES]

Large treatment effects were observed for insomnia severity (ISI) at 10 weeks (d = -1.57) and 24 weeks (d = -1.60), and for sleep efficiency at 10 weeks (d = 0.91) and 24 weeks (d = 0.72), with the dCBT group reporting less insomnia symptoms and higher sleep efficiency scores (Table 3).

For objective cognitive performance, there were no significant group differences at 10 or 24 weeks, on any of the performance tests (d range = -0.09 to 0.11; see Table 4).

Treatment effects were observed for all five subscales (and total score) of the multidimensional fatigue inventory (MFI), at both 10 weeks (d range = -0.34 to - 0.70) and 24 weeks (d range = -0.42 to -0.76; see Table 3), with the dCBT group reporting lower levels of fatigue. Similarly, the dCBT group reported significantly lower levels of sleepiness (ESS) at 10 weeks (d = -0.42) and 24 weeks (d = -0.44). Consistent with the primary outcome, large treatment effects were found for self-reported cognitive failures (CFQ), with significantly

lower values in the dCBT group compared to control at 10 weeks (*d* = -0.83) and 24 weeks (*d* = -0.98).

At both 10 and 24 weeks dCBT was associated with less depressive symptoms compared to the control group (*d* = -0.68 and *d* = -0.64, respectively). Exploratory analyses, focusing on depression 'caseness' (defined as PHQ9 score ≥10), found a reduced likelihood of meeting 'caseness' in the dCBT group at both 10 weeks (adjusted risk ratio = 0.38, 95% CI: 0.21, 0.54) and 24 weeks (adjusted risk ratio=0.49, 95% CI: 0.28,0.70). For anxiety symptoms, dCBT was associated with significantly lower scores on the GAD-2 at 10 weeks (*d* = -0.39) and 24 weeks (*d* = -0.37).

Groups did not differ with respect to proportion using prescribed sleep medication (defined as ≥1 night in the past 14 days) at 10 weeks [adjusted odds ratio = 0.50, 95% CI: 0.13,1.98] or 24 weeks [adjusted odds ratio = 0.35, 95% CI: 0.07,1.79]. Compared to the control group, significantly fewer participants in the dCBT arm reported using non-prescription sleep remedies (defined as ≥1 night in the past 14 days) at both 10 [adjusted odds ratio = 0.20, 95% CI: 0.06,0.66] and 24 weeks [adjusted odds ratio = 0.10, 95% CI: 0.03,0.39].

We tested the extent to which treatment effects for cognitive variables at 24 weeks were mediated by change in insomnia symptoms and sleep efficiency at 10 weeks. Since there were no group differences on the objective cognitive tests we only assessed mediation for self-reported cognitive impairment (BC-CCI). The mediators (ISI scores and sleep efficiency) showed large treatment effects at 10 weeks (see Table 3). The proportion of the effect of the intervention on BC-CCI at 24 weeks that was mediated by change in *sleep efficiency* was

29.5% (see Table 5). The proportion of the effect of the intervention on BC-CCI at 24 weeks that was mediated by change in *insomnia severity* (ISI) was 60.4%.

[INSERT TABLE 5 – MEDIATION]

There was no evidence of moderation by age for the BC-CCI at 10 or 24 weeks, or for any cognitive task at 10 weeks (see Table S3). There was some evidence of moderation for two of the cognitive tasks at 24 weeks, although direction was not consistent. One task (simple attention) showed magnification of group differences with increasing age, while the other (episodic memory) showed attenuation. None of these effects were statistically significant after conservative adjustment for multiple testing.

There were no reported SAEs. For the 12 pre-specified adverse effects, there were no statistically significant group differences and the total number of endorsed adverse effects was similar in both arms (Table S4).

Discussion

Uptake of the dCBT intervention was high and, similar to previous trials[26,38], led to large reductions in insomnia severity, indexed via sleep efficiency and global ratings of insomnia symptoms. These sleep-related changes were accompanied by less frequent use of non-prescription sleep remedies in the dCBT arm versus control. We observed large treatment effects in favour of dCBT for our primary outcome, self-reported cognitive impairment, at both post-treatment (d = -0.86) and follow-up (d = -0.96). Group differences in self-reported cognitive impairment at follow-up were mediated, in part, by change in sleep efficiency and

global insomnia severity ratings at 10 weeks, suggesting a potential causal pathway to improved cognitive function via reduction in insomnia symptoms. Our secondary questionnaire measures (cognitive failures, fatigue, sleepiness, depression, anxiety) similarly showed treatment effects in favour of dCBT at both post-treatment and follow-up. In contrast, we did not observe treatment effects on any of our objective cognitive tests (see Figure 2).

[INSERT FIGURE 2 – FOREST PLOT]

This is the first trial to assess self-reported cognitive impairment as a primary outcome post-dCBT for insomnia. We recruited insomnia participants with cognitive complaints at baseline, reflecting perceived difficulty with memory and/or concentration. Baseline scores on the BC-CCI in our sample exceeded those observed in patients with major depression[27], while scores on the CFQ (everyday cognitive failures) were higher than those found in patients with multiple sclerosis[39]. Large improvements on both the BC-CCI and CFQ, and medium-to-large improvements on the *mental fatigue* sub-scale of the MFI, suggest dCBT effectively reduces perceived cognitive impairment; and these benefits are sustained at 6 months follow-up. This is an important finding because perceived cognitive impairment is one of the most salient concerns for patients with chronic insomnia, impacting upon a range of quality of life domains, including work performance and safety[12,40]. Further research is needed to determine whether the management of insomnia in the context of *specific* neurological and psychiatric conditions has the potential to improve self-reported cognitive and functional outcomes.

Although robust effects were observed in the subjective domain we found no evidence that dCBT engenders change in cognitive performance indexed via computerised tasks.

Divergent findings for subjective and objective cognitive function are common across a range of neuropsychiatric disorders, with reported impairment often not supported by task performance[41,42]. Subjective reports and task performance may probe different aspects of cognitive health[43]. It is important to note that subjective cognitive complaints, even in the absence of objective task-related impairment, have been associated with increased amyloid-β deposition, evolution of objective impairment over time, and subsequent dementia diagnosis[44,45]. While it is possible that our participants did not have objective cognitive impairment at baseline - and, therefore, limited capacity for change - we attempted to mitigate this by recruiting participants with persistent insomnia disorder *plus* cognitive complaints, a group more likely to display performance deficits[46]. Nevertheless, without a control group of normal sleepers (or normative data for comparison) we cannot confirm the presence of baseline impairment in objective cognitive performance. Below we offer several (non-exclusive) explanations for the null findings.

Our tasks map onto widely used neuropsychological measures that have shown sensitivity to insomnia (versus controls) in previous studies[9,47,48], but they were relatively simple, brief, and may not unmask subtle cognitive deficits[49]. For example, several studies reveal impairment (only) when cognitive load is high, particularly for the domain of attention[10,50]. A related point is that tests were performed outside of the laboratory, over the internet, and at a time convenient for participants. While we advised participants to maintain standard testing conditions (i.e. same device, clock-time, and distraction-free environment) across assessment points, variability introduced by the testing environment may have further reduced signal-to-noise ratio.

At least seven RCTs[38,51-55] have assessed the effect of CBT on objective cognitive performance in adult insomnia samples, four of which (including the present study) find no

evidence of benefit[38,54,55]. It is important to note that our study is the largest to date to test cognitive performance through objective computerised tasks, with the power to detect even modest effects. Impairments, if they reliably exist, may be trait-like and unresponsive to CBT. Alternatively, CBT may not sufficiently modify sleep physiology in order to bring about improvements in cognitive performance, consistent with findings from a recent meta-analysis[56]. These possibilities require dedicated interrogation in future studies.

Limitations of this work should be considered. We employed a waitlist control arm, which may slightly inflate effect size differences compared to a minimally active arm (e.g., sleep hygiene education), or behavioral placebo. Nevertheless, several studies show that the dCBT programme used in the present study convincingly out-performs sleep hygiene[26] and placebo[19] with respect to both sleep and daytime outcomes. Our sample was recruited online and may not be representative of treatment-seeking patients in clinical practice. For example, our sample was well-educated, with the majority holding a university degree, and the vast majority (87%) were female. We required participants to report cognitive complaints to enter the trial, which may have resulted in an over-representation of participants concerned about the effects of sleep disruption on cognitive function. However, research shows that perceived cognitive impairment is one of the most common consequences of insomnia.[4] We also excluded frequent users of hypnotics at baseline in order to limit confounding effects on our cognitive dependent measures; the extent to which our findings apply to those who regularly take sleep medication requires testing in future studies. Our sample included people from a broad age range (26-82 years), potentially introducing marked between-subject variability in the nature of sleep disruption, cognitive function and health (and their interaction). However, our aim was to conduct a randomised trial in a large sample of people with insomnia and perceived cognitive impairment; and we found no clear pattern of moderation by age. A key strength of our study is inclusion of people with common mental and physical health problems. For example, the majority of our sample met clinical

cut-offs for depression at baseline. Participants treated with dCBT were 62% less likely to meet 'caseness' at post-treatment, and 51% less likely at follow-up, relative to control. These results are consistent with emerging evidence showing that CBT for insomnia may exert anti-depressant effects[57]. Improvement in mood may represent an additional mechanistic pathway to restoration of cognitive function. Future study designs, capable of disentangling temporal changes in sleep, mood, and cognitive function, should be considered. A final point is that given the online nature of our trial we were not able to record sleep physiology and therefore the sleep profile of our sample is unknown. Emerging evidence suggests that insomnia disorder in combination with objective short sleep duration may have the most pronounced effects on cognitive performance[8,58]. Future stratification based on objective sleep parameters will help determine whether insomnia phenotypes have differential response on cognitive outcomes.

In conclusion our study finds that dCBT robustly improves self-reported cognitive impairment and that such improvements may operate via increased sleep efficiency and reduced insomnia severity. We found no evidence that dCBT improves objective cognitive performance relative to control, across a range of tasks and domains. The field requires rigorously-designed studies, incorporating sensitive measures of performance and sleep physiology in order to further delineate the effects of insomnia treatment on cognitive health.

Contributors

SDK and CES were chief investigators, conceived of the study, led study design, and wrote the manuscript. MEDH contributed to the design, was the principal trial coordinator, and helped to draft the manuscript. RE contributed to the design, supervised statistical analysis and helped to draft the manuscript. AM carried out the statistical analysis under the supervision of RE and helped to draft the manuscript. XO and AJ were trial coordinators and helped to draft the manuscript. KS and CAE contributed to the study design and helped to draft the manuscript. AL contributed to study design, supported sleep intervention access and helped to draft the manuscript. LB helped to draft the manuscript and conducted the literature search. All authors approved the final manuscript.

Data Sharing

The study protocol is freely available. Deidentified participant data and a data dictionary defining each field in the set will be available from the corresponding author upon reasonable request.

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Figure 1: Trial design of the defining the impact of sleep improvement on cognitive outcomes (DISCO) study.

Figure 2: Forest plot shows standardised effect sizes (Cohen's *d*) for dCBT versus WLC on outcomes at week 10. Polarity is adjusted for all outcomes such that positive effect sizes reflect superiority of dCBT over WLC.

Table 1. Descriptive characteristics of sample

Characteristic[a]	**dCBT (n = 205)**	**WLC (n = 205)**
Age, years		
Mean (SD)	52.5 (11.2)	52.4 (11.7)
Median, IQR	53 (46-59)	54 (44-61)
Gender[b], no (%)		
Male	30 (14.6%)	25 (12.2%)
Female	175 (85.4%)	180 (87.8%)
Ethnicity, no (%)		
White	200 (97.6%)	201 (98.1%)
Mixed	1 (0.5%)	1 (0.5%)
Asian	1 (0.5%)	3 (1.5%)
Caribbean	1 (0.5%)	0
Other	2 (1.0%)	0
Partnership status, no (%)		
No	44 (21.5%)	48 (23.4%)
Yes, living together	146 (71.2%)	141 (68.8%)
Yes, living apart	15 (7.3%)	16 (7.8%)
Children at home, no (%)		
No	124 (60.5%)	127 (62.0%)
Yes	81 (39.5%)	78 (38.1%)
Employment status, no (%)		
Full-time employed	80 (39.0%)	83 (40.5%)
Part-time employed	55 (26.8%)	47 (22.9%)
Unemployed	8 (3.9%)	10 (4.9%)
Retired	44 (21.5%)	50 (24.4%)
Full-time student	6 (2.9%)	3 (1.5%)
Part-time student	12 (5.9%)	12 (5.9%)
Age when finished education, mean (SD) in years		
	20.2 (5.3)	20.6 (6.1)
Highest level of qualification, no (%)		
None	3 (1.5%)	6 (2.9%)
GCSE	32 (15.6%)	19 (9.3%)
A-Level	17 (8.3%)	15 (7.3%)
College	34 (16.6%)	34 (16.6%)
University	58 (28.3%)	51 (24.9%)
Post-graduate	46 (22.4%)	67 (32.7%)
Other	15 (7.3%)	13 (6.3%)

Abbreviations: dCBT, digital Cognitive Behavioural Therapy; GSCE, General Certificate for Secondary Education; IQR, interquartile range; no, number of participants; SD, standard deviations; WLC, wait-list control.

[a] Percentages not adding up to 100% include missing values

[b] Response to the following questions: "*Are you… Male/Female/Non-Binary*

Table 2. Baseline scores for outcome variables

Baseline outcome scores		dCBT (n = 205)	WLC (n = 205)
Self-reported cognitive impairment (BC-CCI), mean (SD)			
	Total score	9.4 (3.4)	9.5 (3.7)
Sleep efficiency (PSQI), mean (SD)			
	%	60.4 (14.9)	61.3 (14.0)
Insomnia severity (ISI), mean (SD)			
	Total score	18.4 (3.7)	17.9 (3.6)
Sleep medication, mean (SD)			
	Sleeping pills prescribed by doctor, number of nights in last 2 weeks	0.36 (1.84)	0.37 (1.85)
	Non-prescription sleep remedies, number of nights in last 2 weeks	1.48 (3.26)	1.48 (2.94)
Sleepiness (ESS), mean (SD)			
	Total score	7.5 (4.6)	7.2 (4.8)
Fatigue (MFI), mean (SD)			
	General fatigue sub-scale	15.5 (2.8)	15.4 (2.7)
	Physical fatigue sub-scale	13.0 (3.8)	12.5 (3.6)
	Reduced activity sub-scale	11.8 (3.7)	11.2 (3.8)
	Reduced motivation sub-scale	12.2 (3.6)	11.9 (3.3)
	Mental fatigue sub-scale	13.9 (3.0)	14.0 (2.9)
	Total score	66.3 (12.7)	64.9 (12.1)
Self-reported cognitive failures (CFQ), mean (SD)			
	Total score	56.0 (14.2)	56.5 (13.8)
Depressive symptoms (PHQ-9), mean (SD)			
	Total score	11.9 (5.4)	11.4 (5.1)
Anxiety symptoms (GAD-2), mean (SD)			
	Total score	2.8 (2.0)	2.5 (1.9)
Cognitive performance			
Working memory, mean (SD)			
	Digit span task: longest correct string of numbers recalled in reverse format	5.84 (1.52)	5.74 (1.55)
Simple attention, mean (SD)			
	SNAP task: mean RT (msec) response for correct identification of matched cards (pair)	835.1 (258.0)	842.3 (257.9)
Complex processing speed, mean (SD)			
	Symbol-digit substitution task: number of correct matches of symbols and digits within 1 minute interval	22.2 (4.9)	21.9 (5.2)
Visual attention (TRAILS task), mean (SD)			
	TRAILS-A: Number of errors when connecting letters (A,B,C..) in sequential order	0.38 (0.80)	0.55 (1.72)
	TRAILS-A: Mean RT (msec) to connect letters (A,B,C..) in sequential order	34860.2 (15589.4)	35396.6 (12506.2)
	TRAILS-B: Number of errors when connecting letters and numbers (A-1, B-2, C-3,..)	0.98 (1.77)	1.35 (3.71)
	TRAILS-B: Mean RT (msec) to connect letters and numbers (A-1, B-2, C-3,..)	63204.8 (24451.4)	59837.0 (23796.3)

Episodic memory, mean (SD)		
Pairs matching task, Level 1: Number of errors when matching pairs of cards in 3x4 matrix	3.7 (2.9)	3.7 (3.0)
Pairs matching task, Level 2: Number of errors when matching pairs of cards in 4x4 matrix	5.9 (3.3)	5.4 (3.4)
Reasoning, mean (SD)		
Fluid Intelligence task: Total number of correct answers (in 2 mins) to series of problem-solving questions (/13)	5.48 (2.06)	5.59 (1.93)

Abbreviations: BC-CCI, British Columbia Cognitive Complaints Inventory; CFQ, Cognitive Failures Questionnaire; dCBT, digital Cognitive Behavioural Therapy; ESS, Epworth Sleepiness Scale; GAD-2, General Anxiety Disorder scale; ISI, Insomnia Severity Index; msec, milliseconds; MFI, Multidimensional Fatigue Inventory; PHQ-9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; RT, reaction time; SD, standard deviations; WLC, wait-list control

Table 3. Effects of digital Cognitive Behavioural Therapy (dCBT) vs Wait-list Control (WLC) on Primary and Secondary Outcomes (self-reported)

Assessment	Unadjusted, Mean (SD)		Adjusted difference (95% CI)	Cohen's d (95% CI)	p-value
	dCBT	WLC			
Self-reported cognitive impairment (BC-CCI)					
Week 10	5.88 (3.61)	8.91 (3.87)	-3.03 (-3.60, -2.47)	-0.86 (-1.02, -0.70)	<0.0001
Week 24	5.51 (3.69)	8.98 (4.23)	-3.41 (-4.06, -2.76)	-0.96 (-1.15, -0.78)	<0.0001
Sleep efficiency (PSQI)					
Week 10	78.05 (15.12)	64.54 (14.19)	13.21 (10.81, 15.61)	0.91 (0.74, 1.07)	<0.0001
Week 24	82.44 (15.87)	71.30 (16.07)	10.45 (7.82, 13.09)	0.72 (0.54, 0.90)	<0.0001
ISI total scores					
Week 10	10.65 (5.12)	16.19 (4.33)	-5.77 (-6.55, -4.99)	-1.57 (-1.78, -1.36)	<0.0001
Week 24	9.82 (5.41)	15.49 (4.84)	-5.88 (-6.80, -4.97)	-1.60 (-1.85, -1.35)	<0.0001
MFI total scores					
Week 10	57.86 (14.94)	64.74 (13.72)	-8.67 (-10.42, -6.91)	-0.70 (-0.84, -0.56)	<0.0001
Week 24	56.28 (15.33)	64.19 (14.16)	-9.48 (-11.54, -7.43)	-0.76 (-0.93, -0.60)	<0.0001
MFI General fatigue sub-scale					
Week 10	13.56 (3.35)	15.27 (2.86)	-1.92 (-2.38, -1.45)	-0.69 (-0.86, -0.52)	<0.0001
Week 24	13.35 (3.60)	15.15 (3.05)	-2.03 (-2.56, -1.50)	-0.73 (-0.91, -0.54)	<0.0001
MFI Physical fatigue sub-scale					
Week 10	11.58 (4.14)	12.37 (4.10)	-1.27 (-1.78, -0.76)	-0.34 (-0.48, -0.20)	<0.0001
Week 24	11.17 (4.07)	12.53 (4.10)	-1.80 (-2.37, -1.23)	-0.48 (-0.64, -0.33)	<0.0001
MFI Mental fatigue sub-scale					
Week 10	12.05 (3.44)	13.87 (3.30)	-1.90 (-2.41, -1.38)	-0.64 (-0.82, -0.47)	<0.0001
Week 24	11.52 (3.49)	13.72 (3.15)	-2.22 (-2.80, -1.65)	-0.75 (-0.95, -0.56)	<0.0001
MFI Reduced motivation sub-scale					
Week 10	10.24 (3.73)	11.72 (3.46)	-1.71 (-2.20, -1.21)	-0.51 (-0.66, -0.36)	<0.0001
Week 24	10.26 (3.69)	11.70 (3.55)	-1.58 (-2.15, -1.00)	-0.47 (-0.64, -0.30)	<0.0001
MFI Reduced activity sub-scale					
Week 10	10.43 (3.81)	11.51 (4.00)	-1.62 (-2.12, -1.12)	-0.43 (-0.56, -0.30)	<0.0001
Week 24	9.97 (3.89)	11.09 (4.11)	-1.61 (-2.15, -1.07)	-0.42 (-0.57, -0.28)	<0.0001
ESS total scores					
Week 10	6.51 (4.19)	8.04 (4.73)	-2.00 (-2.55, -1.45)	-0.42 (-0.54, -0.31)	<0.0001
Week 24	6.51 (4.39)	8.00 (4.73)	-2.10 (-2.69, -1.51)	-0.44 (-0.57, -0.32)	<0.0001
CFQ total scores					

Week 10	41.59 (15.61)	53.72 (13.60)	11.62 (-13.59, -9.66)	-0.83 (-0.97, -0.69)	<0.0001
Week 24	40.24 (15.66)	54.17 (14.63)	-13.72 (-15.90, -11.54)	-0.98 (-1.14, -0.83)	<0.0001
PHQ-9 total scores					
Week 10	7.68 (6.25)	10.86 (4.86)	-3.58 (-4.37, -2.79)	-0.68 (-0.83, -0.53)	<0.0001
Week 24	7.37 (6.16)	10.39 (5.22)	-3.35 (-4.20, -2.51)	-0.64 (-0.80, -0.48)	<0.0001
GAD-2 item scores					
Week 10	1.79 (1.91)	2.45 (1.91)	-0.76 (-1.02, -0.49)	-0.39 (-0.53, -0.25)	<0.0001
Week 24	1.71 (1.82)	2.30 (1.76)	-0.72 (-1.00, -0.45)	-0.37 (-0.51, -0.23)	<0.0001

Dichotimised variables	Number of occasions (%)		Adjusted odds ratio (95% CI)	p-value
	dCBT	WLC		
≥ 1 night in past two weeks using prescribed sleep medication				
Week 10	12 (7.74%)	18 (9.94%)	0.50 (0.13, 1.98)	0.3245
Week 24	15 (11.0%)	17 (10.2%)	0.35 (0.07, 1.79)	0.5891
≥ 1 night in past two weeks using non-prescribed sleep remedies				
Week 10	23 (14.8%)	50 (27.6%)	0.20 (0.06, 0.66)	0.0084
Week 24	17 (12.5%)	47 (28.3%)	0.10 (0.03, 0.39)	0.0010

	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Risk of depression 'caseness' (PHQ-9≥10)		
Week 10	0.51 (0.39, 0.67)	0.38 (0.21, 0.54)
Week 24	0.59 (0.44, 0.78)	0.49 (0.28, 0.70)

Abbreviations: CFQ, Cognitive Failures Questionnaire; CI, confidence intervals; dCBT, digital Cognitive Behavioural Therapy; ESS, Epworth Sleepiness Scale; GAD-2, General Anxiety Disorder scale; ISI, Insomnia Severity Index; MFI, Multidimensional Fatigue Inventory; PHQ-9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviations; WLC, wait-list control

Table 4. Effects of digital Cognitive Behavioural Therapy (dCBT) vs Wait-list Control (WLC) on Secondary Outcomes of Cognitive Performance

Assessment	Unadjusted, Mean (SD)		Adjusted difference (95% CI)	Cohen's d (95% CI)	p-value
	dCBT	control			
Working memory: *Reverse digit span (longest string)*					
Week 10	5.98 (1.51)	5.82 (1.47)	0.18 (-0.09, 0.44)	0.11 (-0.06, 0.29)	0.2024
Week 24	5.77 (1.56)	5.80 (1.57)	-0.05 (-0.34, 0.25)	-0.03 (-0.22, 0.16)	0.7586
Simple attention: *SNAP task (RT, msec)*					
Week 10	780.96 (253.49)	821.47 (257.92)	-23.67 (-65.44, 18.11)	-0.09 (-0.25, 0.07)	0.2668
Week 24	778.24 (268.03)	794.17 (250.14)	10.78 (-34.01, 55.58)	0.04 (-0.13, 0.22)	0.6371
Complex processing speed: *Symbol-digit substitution (no. correct matches)*					
Week 10	23.38 (5.38)	23.09 (4.84)	-0.19 (-0.88, 0.50)	-0.04 (-0.18, 0.10)	0.5884
Week 24	23.56 (5.30)	22.45 (5.49)	0.47 (-0.26, 1.20)	0.09 (-0.05, 0.24)	0.2099
Visual attention: *TRAILS-A (RT, msec.)*					
Week 10	32599.15 (13395.06)	33215.06 (12085.34)	359.48 (-1749.11, 2468.07)	0.03 (-0.12, 0.17)	0.7383
Week 24	30394.71 (11042.08)	31896.53 (9625.50)	-91.93 (-2048.25, 1864.40)	-0.01 (-1.14, 0.13)	0.9266
Visual attention: *TRAILS-B (RT, msec.)*					
Week 10	54309.98 (19851.06)	55189.32 (18971.95)	-571.05 (-3542.61, 2400.52)	-0.02 (-0.15, 0.10)	0.7064
Week 24	55063.24 (25598.13)	54983.64 (24939.50)	-1014.27 (-45850.75, 2557.21)	-0.04 (-0.19, 0.11)	0.5778
Episodic memory: *Pairs matching task (no. of errors)*					
Week 10	3.38 (2.59)	3.49 (3.41)	0.03 (-0.50, 0.55)	0.01 (-0.17, 0.19)	0.9182
Week 24	2.85 (2.30)	3.18 (2.51)	-0.23 (-0.70, 0.24)	-0.08 (-0.24, -0.08)	0.3375
Reasoning: *Fluid intelligence task (no. correct answers)*					
Week 10	6.19 (2.15)	6.16 (2.01)	0.10 (-0.17, 0.38)	0.05 (-0.09, 0.19)	0.4666
Week 24	6.40 (2.14)	6.39 (2.04)	0.08 (-0.21, 0.37)	0.04 (-0.11, 0.19)	0.5824
Dichotimised variables	Number of participants (%)			Adjusted odds ratio (95% CI)	p-value
	dCBT	WLC			
TRAILS-A: *making at least one error*					
Week 10	31 (22.0%)	33 (20.5%)		1.29 (0.69, 2.40)	0.4217
Week 24	32 (25.4%)	30 (18.8%)		1.80 (0.94, 3.46)	0.0757
TRAILS-B: *making at least one error*					
Week 10	55 (39.0%)	57 (35.4%)		1.39 (0.79, 2.43)	0.2495
Week 24	49 (38.9%)	53 (33.1%)		1.60 (0.40, 1.86)	0.1233

Abbreviations: CI, confidence intervals; dCBT, digital Cognitive Behavioural Therapy; msec, milliseconds; RT, reaction time; SD, standard deviations; WLC, wait-list control

Table 5. The mediating effects of insomnia symptoms (10 weeks) on self-reported cognitive impairment (24 weeks)

Assessment	Mediation tested	Total effect		Direct effect		Indirect effect		Mediation, %
		Effect size (SE)	p-value	Effect size (SE)	p-value	Effect size (SE)	p-value	
BC-CCI (week 24)	Sleep efficiency (week 10)	-3.43 (0.31)	<0.0001	-2.35 (0.35)	<0.0001	-1.01 (0.15)	<0.0001	29.5%
BC-CCI (week 24)	ISI (week 10)	-3.45 (0.32)	<0.0001	-1.29 (0.34)	0.0002	-2.08 (0.22)	<0.0001	60.4%

Abbreviations: BC-CCI, British Columbia Cognitive Complaints Inventory; ISI, Insomnia Severity Index; SE, standard error