**A. Scientific background**

Hoarding disorder (HD) is a common and disabling public health problem. HD is a newly recognized diagnostic entity in the DSM-5, affecting 44 million individuals in Europe alone (4% prevalence). HD is characterized by a difficulty in discarding items, irrespective of their value; this results in an accumulation of clutter that precludes the normal use of living spaces, causing significant distress or impairment (Fig. 1) 1. The accumulation of clutter leads to hazards such as fire, pest infestation, and eviction 2. While HD patients present aberrant neurocognitive and emotional processes, the mechanisms underlying HD remain elusive. Sleep disturbance hinders healthy adults’ neurocognitive and emotional processes, which have been shown to be aberrant in individuals with HD. Preliminary work we have conducted indicates that HD patients’ subjective sleep is worse than that of healthy individuals (Fig. 2). It is unknown which objective sleep parameters impact HD and whether modifying sleep can affect HD symptoms. The current project aims to address this knowledge gap and explore the role played by sleep disturbance in HD by assessing 1) how objective and subjective sleep impact an individual’s HD symptoms, neurocognition, and emotion; and 2) testing whether modifying sleep impacts an individual’s clinical symptoms of HD and cognition. We will refine the neuropathological underpinnings of HD and develop a scientifically informed sleep therapy program for individuals with HD.

HD is a disabling and understudied disorder. Hoarding disorder is a new diagnostic entity that has four defining features. Patients with HD have a) difficulty in discarding objects, irrespective of their value, b) due to their perceived importance; c) this leads to the accumulation of clutter, limiting the use of living spaces and d) causing significant distress or impairment. Most patients also acquire excessive quantities of items.1 HD impacts patients, their families, and society. The disorder is stigmatized and also increases the risk of chronic disease, pest infestations, and fire hazards. HD patients exhibit abnormal neural activity in their cognitive control and saliency circuits; the cognitive control network supports efficient resolution of simple conflicts and inhibition of prepotent actions 3,4. Patients with HD display hyperactivations in the major nodes of this network: the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), right inferior frontal gyrus (RIFG), and specific basal-ganglia nuclei. The saliency network adjusts arousal and attention based on the perceived relevance of a stimulus. HD patients display hyperactivation in the ACC and insula, which are the main nodes of this network; these patients also exhibit behavioral deficits in cognitive control, visual perception, and reaction speed. However, the neurocognitive abilities of patients with HD have yet to be systematically tested and the neuroscientific findings reported thus far have had little impact on treatments for this disorder.

**Fig. 1:** Clutter typical of hoarding disorder

Sleep disturbance impairs neural circuits that are relevant to HD. Sleep is central to physiological and mental functioning. Sleep disturbance impairs cognitive control and saliency networks, as well as attentional and emotional processes 5–8. Insufficient sleep is a common sleep disturbance 9, and restricting a healthy adult’s sleep even for a single night impairs their cognitive control and attention 10. Converging findings from imaging studies suggest that sleep restriction modifies neural activity and connectivity within the cognitive control and saliency networks, including DLPFC, RIFG 11, thalamus, insula, and ACC 12. Rapid eye movement (REM) sleep plays a unique role in regulating affective homeostasis; restricting REM sleep intensifies emotional reactivity toward both positive and aversive stimuli 13. Norepinephrine (NE) activity modifies arousal, reaching lowest levels during REM sleep. Altering the secretion of NE during sleep affects the likelihood of arousal 14. REM sleep may recalibrate phasic NE levels during the following day 13. The locus coeruleus is a major NE secreting nucleus 15 and its innervations to the prefrontal cortex (PFC) and the insula exemplify how arousal level can modify cognitive control and increase the saliency of a stimulus 16–18. The physiology of REM sleep modifies the reactivity of the insula and ACC to salient content 19 and may also modify HD symptoms. Sleep disturbance modifies brain circuits that are impaired in HD; thus, studying HD patients’ sleep is warranted. It is not known whether sleep restriction affects HD symptoms.

Patients with hoarding disorder exhibit subjective sleep disturbance. Sleep is understudied in relation to HD. The severity of HD patients’ symptoms is correlated with insomnia symptoms 20. HD patients reported worse sleep and more severe insomnia symptoms compared with these factors in a control group, even when controlling for depression, age, and gender (Fig. 2). These studies highlight the importance of sleep disturbance in HD; however, all of these studies used subjective sleep measures and none of them tested associations between sleep disturbance and patients’ cognition. Combining objective sleep measures with cognitive and clinical assessments will shed light on the neuropathology of HD.

Cognitive behavioral therapy (CBT) reduces sleep disturbance. Symptoms of insomnia are a common form of sleep disturbance 21, hindering cognition and decision making 22. These symptoms are defined as persistent difficulties to initiate or maintain sleep, despite motivation and an ability to sleep, causing distress or affecting an individual’s daily life 23. Insomnia patients display distinct objective sleep parameters 24. CBT for insomnia (CBTI) is a first-line insomnia treatment 25. CBTI focuses on modifying insomnia-related beliefs and perpetuating behaviors through the use of cognitive and behavioral interventions, which include tackling environmental factors (Table 3). CBTI improves patients’ objective and subjective sleep as well as their daytime functioning 25,26. CBTI can be efficacious when delivered online or via self-help applications and therapist support, allowing for rapid implementation in rural areas and during pandemics 27. CBTI has never been tested in patients with HD.

Fig 2. Mean ISI and PSQI scores in OCD (n=26), HD (n=38), and HC (n=22) 61, \*significance at .05 level. Error bars represent one standard error. ISI – insomnia severity index, PSQI – Pittsburgh Sleep Quality Index. A higher PSQI score denotes worse sleep quality.

HD is difficult to treat. There are no FDA-approved drugs for the treatment of HD. The leading cognitive–behavioral model of HD suggests that symptoms result from distal factors (e.g., early experiences), cognitive deficits, and aberrant emotional responses that result in the acquisition of items and subsequent difficulty discarding them 28. Targeted CBT and peer workshops have been shown to be efficacious in treating the disorder 29–31. However, most patients continue to suffer from symptoms after the completion of treatment 32, and the acceptability of treatment is mediocre 33. The sleep disturbance that patients with HD experience may constrain any gains from treatment as such disturbance affects the relevant brain circuits and indeed CBT for HD does not modify subjective sleep disturbance 34. There is therefore an urgent need to develop new therapeutic interventions. Investigating the sleep of patients with HD may provide new therapeutic targets and refine our understanding of the underlying neuropathology of HD**.**

## Current experiment

I suggest that sleep disturbance impairs saliency, cognitive control, and emotional neural circuits in patients with HD. Patients who experience aberrant saliency, reduced cognitive control, and increased emotional reactivity will experience aggravated hoarding severity. The current study aims to address scientific and clinical knowledge gaps in our understanding of the role sleep disturbance plays in HD and its interaction with cognition, emotion, decision making, and clinical symptoms. I will test objective and subjective sleep patterns in a large sample of patients with HD, a clinical control group of patients with obsessive–compulsive disorder (OCD), and a control group of healthy adults (phase 1). I will then assess how impairing (phase 2) and improving sleep (phase 3) alters patients’ cognition and clinical symptoms.

# B. Research objectives and expected significance

Sleep is imperative for both mental and physical health. Sleep affects neurocognitive processes that play a central role in HD. CBTI can help to regulate these circuits 22. However, no studies of patients with HD have been performed that involved objective sleep measures; there have also been no studies that have explored how sleep interventions can affect HD symptoms. The overarching goal of this project is to study the role sleep disturbance plays in HD by characterizing patients’ sleep and testing how two types of sleep interventions can affect HD symptoms and patients’ cognition and clinical symptoms.

Validated tasks are necessary to understand the neurocognitive correlates of HD 35. Cognitive control differences between HD patients and healthy adults may result from lower levels of attention processes or arousal 36. We recently validated a new task used to tease apart cognitive control and lower-level attention processes (Fig. 4). This task allows us to test which neurocognitive processes differ among HD, OCD, and healthy participants. We will also report which neurocognitive processes are correlated with symptom severity. The findings of this project will be used to inform targeted brain-imaging studies incorporating objective sleep and neurocognition measures.

Regulating sleep improves cognition and emotional processes 19,37,38. CBTI can reduce depression 39 and improve cognitive control and saliency processing 22. Our study will be the first to test whether CBTI can have a beneficial effect on HD and OCD patients’ symptoms and neurocognition, while controlling for depression severity and age. Our results will have practical clinical implications, including whether sleep assessments are warranted during clinical intake, whether sleep represents a possible treatment target, and guiding future studies integrating CBTI components within existing HD and OCD therapies. Such advances could lead to drastic improvements in patients’ lives. This project will represent a major advance in our mechanistic understanding of HD and OCD, while also exploring a cost-effective sleep intervention.

## Specific aims

1) To test which objective sleep parameters differentiate HD patients from OCD patients and healthy adults. Significance: Characterizing HD patients’ objective sleep can illuminate the neuropathology of HD. Using patients with OCD and healthy participants as control groups will inform our understanding of obsessive–compulsive and related disorders and allow us to test the specificity of our findings.

2) To test which objective sleep parameters are associated with clinical symptoms and core neurocognitive processes in HD. Significance: Conducting within-group analyses while controlling for depression severity and age will test the clinical significance of the findings relating to aim #1 and guide the development of novel, personalized treatments.

3) To assess whether modifying sleep affects patients’ sleep, cognitive, and clinical symptoms. Significance: If sleep deprivation exacerbates HD symptoms and CBTI improves HD symptoms, then sleep represents a modifiable treatment target. Sleep interventions are cost-effective, and their dissemination would help numerous individuals who struggle with HD.

4) To assess which patients are more susceptible to sleep modifications. Significance: Identifying those HD and OCD patients who are more affected by sleep deprivation and/or benefit more from CBTI may help to refine treatment personalization and facilitate future clinical trials.

**C. Detailed description of the proposed research**

## **General working hypothesis**

Patients with HD report increased sleep disturbance compared with healthy individuals (Fig. 2). In healthy individuals, such disturbance affects neural circuits that are implicated in HD: cognitive control, emotional reactivity, and saliency processing. We hypothesize that sleep disturbance, and specifically REM sleep duration or stability, exacerbates HD by affecting these neural circuits and their behavioral correlates. We will test our hypothesis in three phases: 1) Comparing objective and subjective sleep and central neurocognitive processes in HD patients, OCD patients, and healthy participants; 2) investigating whether inducing sleep disturbance impacts patients’ clinical symptoms and central neurocognitive processes; and 3) investigating whether CBTI improves HD and OCD patients’ symptoms, sleep, and neurocognition. Together, our results will constitute a major advance in the field of HD and OCD, enrich the evolving research into sleep and the neuroscience of obsessive–compulsive and related disorders, and help to inform follow-up neuroimaging studies and clinical trials.

## **Research design and methods**

All studies will be approved by the Internal Review Board of Bar-Ilan University and the Helsinki committees of collaborating mental health clinics prior to the initiation of the study. Any medical findings will be reported to patients and their treating physicians.

### **Phase 1: Testing objective and subjective sleep**

Participants and recruitment strategy: We aim to recruit 150 participants (aged 18–65 years); 50 individuals with HD, 50 individuals with OCD, and 50 healthy controls (HCs) will participate in phase 1. HD and OCD patients will be recruited from major mental health centers and clinics (letters attached) and via advertisements in the media (please see the budget). HCs will be recruited through targeted social media advertisements, flyers, and emails to all staff members at Bar-Ilan University. Inclusion criteria: All groups – ability to complete the study procedures. HD – primary HD diagnosis, determined using the Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND), validated by a gold-standard self-report scale; and a Savings Inventory Revised (SIR) score ≥ 41 30. OCD – primary OCD diagnosis, determined using the DIAMOND and validated by a Yale–Brown Obsessive–Compulsive Scale (YBOCS) score ≥ 16. HC – ability to complete the study procedures.

Week 8

PSG 3

PSG 4

Week 16

Exclusion criteria: All groups – history of severe head trauma or neurological conditions. OCD and HD – A) psychosis spectrum disorders, moderate or severe substance-use disorders, co-morbid HD and OCD; B) Hamilton Depression Rating Scale 17 (HDRS-17) score > 19; C) active suicidality, determined by the Columbia Suicidality Severity Rating Scale (CSSRS); D) current CBT for HD or OCD; E) changes in pharmacotherapy in the past month; F) regular use of benzodiazepines. HC – A) current or history of any psychiatric or sleep disorders determined by the DIAMOND and the SCID module; B) regular consumption of arousal-regulating pharmacotherapy or drugs.

Fig. 3: Project outline post-screening. M - morning, E - evening. Participants will complete neurocognitive and clinical measures at M1-M4 and E1-E4 as well as at weeks 0, 4, 9, and 16 of phase 3.

 Procedure:

Screening. When a potential participant is identified, a member of the research staff will conduct a short screening interview over the phone, describing the study and checking the individual against the inclusion and exclusion criteria by asking them general questions. Eligible participants will then be invited to attend a screening session at Bar-Ilan University or in the referring clinic. At the screening session, individuals who agree to participate will review and sign an informed consent form. Participants will complete semi-structured interviews, self-report measures (Table 1), and perform short neurocognitive tasks (Fig. 4–6). Research staff will provide participants with actigraph watches. Actigraphy. Participants will wear actigraphs and complete sleep diaries for 2 weeks, to validate the actigraphy results (Table 1 and 2). Actigraphs measure objective sleep, daily activity, and bedroom luminance, with high ecological validity 40. PSG. After 2 weeks, participants will complete two consecutive PSGs at the Hadassah Medical Center sleep center (letter attached). The second night will act as a control for any “first night effect” (altered sleep patterns experienced by an individual during a first night in a sleep center). Participants will receive summary reports. Any aberrant findings will be sent to their physician.

Measures:

Clinical and self-reported measures. We will employ minimal and clinician-administered assessments to assess inclusion and exclusion criteria. Our self-reported measures have good psychometric properties and are the most commonly used tools to study our target constructs (Table 1).

Table 1: Details of screening measures.

|  |  |  |
| --- | --- | --- |
| **Assessment** | **Target construct** | **Reference** |
| **Clinician administered** |  |  |
| DIAMOND | HD, OCD, major psychopathologies | 41  |
| SCID sleep module | Sleep disorders | 42  |
| YBOCS | OCD severity | 43 |
| HDRS | Depression severity | 44 |
| CSSRS | Suicidality | 45 |
| **Patient rating – clinical** |   |   |
| SI-R | Hoarding severity | 46 |
| CIR  | Clutter severity (image rating; Fig. 1) | 47  |
| OCI-R | OCD severity | 48 |
| DOCS | OCD dimensions | 49  |
| DASS | Depression, Anxiety, Stress  | 50  |
| **Patient rating – sleep** |   |   |
| ISI | Insomnia Symptoms Index | 23 |
| PSQI | Sleep quality, sleep phase | 51, 52  |
| ESS | Daytime sleepiness | 53 |
| FOSQ | Impact of sleepiness on quality of life | 54 |
| ME | Circadian type | 55  |
| Consensus sleep diary a | Sleep patterns b  | 56 |
| Clinician administered: DIAMOND - Diagnostic Interview for Anxiety Mood and Obsessive–Compulsive and Related Neuropsychiatric Disorders; SCID - Structured Clinical Interview, DSM- 5; YBOCS - Yale–Brown Obsessive Compulsive Scale; HDRS - 17-Item Hamilton Depression Rating Scale; CSSRS - Columbia Suicidality Severity Rating Scale |
| Patient rating - clinical: SI-R - Savings Inventory Revised; CIR - Clutter Image Rating; OCI-R – Obsessive–Compulsive Inventory–Revised; DOCS - Dimensional Obsessive–Compulsive Scale; DASS - Depression Anxiety Stress Scale. |
| Patient rating - sleep: ISI - Insomnia Severity Index; PSQI - Pittsburgh Sleep Quality Index; ESS - Epworth Sleepiness Scale; FOSQ - The Functional Outcomes of Sleep Questionnaire; ME – Morningnesss\Eveningness. a We will add two items about medication and alcoholic and caffeinated drinks consumed in the previous day. b Participants will fill this out daily for 2 weeks. |

#### Objective sleep measures.

*Actigraphy.* The Phillips PRO Actiwatch tracks movements for up to 30 consecutive days, with a sampling rate of 32 Hz. Raw activity scores (in 1-minute epochs) are translated to sleep–wake scores based on validated computerized scoring algorithms. This will provide data relating to a participant’s bedtime, time in bed, total sleep time, sleep onset latency, wake after sleep, number of arousals, and sleep efficiency, as well as daytime activity. This actigraph is waterproof and, because its battery supports 30 consecutive recording days, participants will be able to wear it continuously throughout the study period.

*PSG.* This device records electrical activity in the scalp (EEG), eyes (electrooculography), and muscles (electromyography), as well as expiratory/inspiratory nasal airway pressure, nasal/oral airflow, finger pulse oximetry, electrocardiogram, rib cage and abdomen movements, snoring, and body position. The sensors are put in place on the participant’s body, calibrated, and the signal quality is checked by a research technician.

The PSG results will be manually scored by Dr. Alex Gileles-Hillel and Dr. Joel Reiter, board-certified sleep physicians experienced in scoring PSG results in line with the American Association for Sleep Medicine guidelines (AASM; Table 2) (letter attached). The physicians will be blinded to a participant’s group.

|  |  |
| --- | --- |
| **Assessment** | **Target construct** |
| **General sleep measures** |  |
| Total sleep duration | Total time spent asleep |
| Sleep latency | Time taken to fall asleep |
| Time in bed | Amount of time in bed |
| Sleep efficiency | Sleep duration divided by time in bed |
| N1, N2, N3, REM proportion | Total time spent in each phase relative to general sleep time |
| Arousal index | Number of arousals |
| Wake after sleep onset | Time spent awake between sleep onset and final awakening |
| **REM and motor measures** |   |
| REM latency | Duration from first sleep epoch to first REM epoch |
| REM stability a | Proportion of arousals during REM |
| REM without atonia | Duration of REM with muscular activity  |
| REM density | Average number of eye movements during REM |
| Periodic limb movement index | Index of limb movements and periodic limb movement series |
| LM and PLMS arousals | Number of arousals due to motor movements |
| **Respiratory measures** |   |
| Apnea hypopnea index | Compound summary of apnea and hypopnea events |
| Respiratory distress index | An index assessing overall respiratory distress |
| Overall desaturation index | Overall number of oxygen desaturation events |
| Minimal desaturation | Minimal oxygen saturation throughout the night |
| **Spectral analysis** |   |
| Relative power | Power of each frequency band divided by total power |
|  |

Table 2: Main PSG measures and target constructs.

REM – rapid eye movement; LM – limb movement; PLMS – periodic limb movement in sleep

#### *Neurocognitive measures*.

*Attentional Networks Test-Dissociation (ANT-D).* ANT-D measures the efficiency of three major attentional networks – cognitive control, alertness, and orienting. Participants manually report the color of a single arrow (Fig. 4). Using a single arrow allows to dissociate interactions between orienting and alerting 57. Healthy participants demonstrate three significant main effects for three attentional networks with no interactions between the networks (Fig. 4). The primary outcome measure is the difference in reaction times (RTs) between the levels of each condition (e.g., incongruent and congruent).

*Emotional reactivity task*.This task measures the efficiency with which an individual can disengage from emotional images. Participants indicate the direction of a central arrow, while disregarding distracting flanker arrows (Fig. 5). A negative or a neutral image is presented before the arrows 58. The primary outcome measure is emotional interference (i.e., emotional reactivity), calculated by subtracting the RTs of correct answers following neutral images from the RTs of correct answers following negative images.

Fig. 4: ANT-D. Participants respond to the color of an arrow (red/blue). The button for red color is located on the right (“m”) and the button for blue color is located on the left (“c”). Alertness is modulated by playing a brief tone, (50 ms, 2000 Hz) in 50% of trials. Orienting is modulated with a visual cue – an asterisk appearing in a valid (50% of trials) or invalid location compared with the location of the following arrow. Congruency is modulated by the direction of the irrelevant arrow, which can be congruent or incongruent with the response button. A) An alerted, invalid trial. B) Results from healthy participants (n=22). Error bars represent one standard error. Cong - congruent; Incong - incongruent. (Linkovski et al., in prep). \* indicates a p-value < .05. Effect sizes: alerting ηp2 =.59, orienting ηp2 =.28, cognitive control ηp2 = .22. There were no significant interactions.

*Monetary incentive delay (MID)*.MID measures responses to potential monetary rewards and losses. Participants respond to a target stimulus before its disappearance at a predefined cutoff (Fig. 6). Prior to stimulus presentation, a cue specifies how much money will be gained or lost if the participant responds faster than the cutoff. Participants learn the amount associated with each cue prior to taking the task. The primary outcome measure is a slope of RT change as a function of the value of the cue. RT decreases when the cue value increases. The magnitude of this decrease is a measure of motivation. As the measure is a difference score, it is not confounded by psychomotor speed.

**Fig. 5**: Illustration of the emotional reactivity task. Participants indicate the color of a square (green/blue) preceded by an emotional or a neutral image.

Fixation

1,000 ms

100 ms

Image

Blank

Discrimination

50/100 ms

1,000 ms

Time

+

*Stroop task*. The Stroop task is a hallmark cognitive control measure 59. Participants manually respond to the ink color of a word while inhibiting semantic information that emerges from reading the word. The color and semantic meaning can be congruent (e.g., “Red”) or incongruent (e.g., “Red”). The primary outcome measure is the congruency effect (RT difference between congruent and incongruent conditions). The congruency effect has good test–retest reliability during multiple administrations within short time-spans, as reported in our earlier study 60. Participants will complete this task at screening and once again following the second PSG night.

#### Statistical analysis and expected results:

#### We will first characterize age, gender, depression, and stress differences among groups, using either independent sample t-tests or Mann–Whitney tests. We will also report the rates of sleep disorders in the groups. Our main analyses per testing domain follow.

##### *Analysis and expected results*: *Subjective sleep measures*

 Power analysis: Based on our preliminary data (Fig. 2), our proposed sample size will enable more than 95% power to detect a medium to large effect size with a type one error of .05. Expected results: We hypothesize that the HD and OCD groups will show greater levels of sleep disturbance (ISI and PSQI global scores), with more severe fatigue (ESS scores), and reduced daytime functioning (FOSQ scores). We anticipate a higher rate of eveningness tendencies in the OCD compared with the HD and HC groups, as seen in our preliminary data 61.

**Fig. 6.** Illustration of a monetary incentive delay trial. The cue predicts the amount that can be gained or lost.

Cue

250 ms

2-2.5 sec

Delay

Target

Outcome

160-260 ms

1,450 ms

+5.00

[25.00]

Time

##### Analysis and expected results: Objective sleep measures

*Actigraphy.* We will test differences in mean and intra-individual variability in sleep duration and efficiency using a location-scale mixed model. This is an extension of the hierarchical linear model approach, which allows the simultaneous analysis of the mean and interpersonal variance while accounting for missing data. It also enables testing group variance differences over and above the mean values 62. The dependent variables will be sleep efficiency/duration, with daily data treated as nested within subjects. The independent variable will be the group (HD, OCD, HC). We will also compare the frequency of differences among groups in delayed bedtimes and rise times, using a chi-square test. *Power analysis*: No actigraphy studies of HD have previously been conducted. We therefore conducted a power analysis for actigraphy and PSG based on a recent OCD study (Donse et al., 2017). Our sample size will allow a power of 90% to detect medium to large effects using a type one error of .05. *Expected results:* We hypothesize that the HD and OCD groups will exhibit greater intra-individual variance and reduced sleep efficiency. This would reflect a sparsely studied aspect of sleep disturbance in HD and OCD. We hypothesize that delayed bedtimes and rise times will be more prevalent in the OCD compared with the HD and HC groups.

*PSG*. We will test PSG data from the second night. We will use multiple analyses of covariance (MANCOVA) to compare the duration of sleep stages, relative power for alpha–theta frequencies, sleep efficiency, apnea hypopnea index, PLMI index, and REM without atonia (RWA) rates among groups. Age, gender, and depression severity will serve as covariates, with crucial alpha adjusted for false discovery rate correction. We will test the clinical significance of PSG differences by conducting a linear regression. For this, we will use the significant differences between groups identified by MANCOVA as being predictive of clinical severity when controlling for relevant covariates. We will use t-tests to compare rates of sleep disorders among the groups, including RBD, obstructive sleep apnea, and parasomnias. Sensitivity analyses will test whether differences in REM are due to serotonergic medications 64. *Power analysis*:No PSG studies of HD have previously been conducted. Therefore, we conducted a power analysis based on an OCD meta-analysis 65. Our sample size will allow a power of 90% to detect medium to large effects using a type one error of .05. PSG motor indices were not included in the meta-analysis, although 72%–90% of patients with OCD exhibit abnormal nightly movements 66,67. Expected results: We hypothesize that the OCD and HD groups will demonstrate reduced sleep efficiency with more pronounced reductions in REM duration and stability than the HC group. We hypothesize that the OCD group will exhibit elevated aberrant nightly movements (PLMI index and REM without atonia) compared with the HD group, as seen in pediatric cases of OCD 66,67.

*Analysis and expected results*: *Neurocognitive measures*

*ANT-D.* A three-way analysis of variance (ANOVA) will be carried out. Alerting tone (tone, no tone), orienting cue (valid, invalid), and congruency (congruent, incongruent) will be the independent within-subject variables; group (HD, OCD, HC) will be the between-subject independent variable; and RT will be the dependent variable. We will also perform a linear regression to test whether objective sleep efficiency, sleep duration, or group can predict the main effects of our three attention networks. *Power analysis*: The current sample allows for 85% power in detecting a medium-size effect with a type one error of .05, based on a cognitive control study 68. Alertness and orienting have not previously been tested in individuals with OCD or HD, and our results will thus set a benchmark for follow-up hypothesis-testing studies. Expected results:We anticipate that HD will have significantly larger congruency effect compared with that of OCD 69. We hypothesize that HD and OCD will demonstrate larger alerting effects and that across groups, alerting effects will be associated with sleep efficiency and duration.

*MID.* RTs will be analyzed using a repeated-measures ANOVA with cue (maximum loss, neutral, maximum gain) as a within-subject variable and group as a between-subject variable. Power analysis: This task has not previously been tested in individuals with HD. Our results will thus set a benchmark for follow-up hypothesis-testing studies. Expected *results*: In line with past studies, we hypothesize that RT will decrease as the cue value increases. We also hypothesize that patients with HD will exhibit a lower difference range, as each cue will be more salient to them than it will be to HCs, eventually reaching a ceiling effect. Therefore, we anticipate the HD group will exhibit a lower decrease with monetary changes and slower RTs to lower value cues compared with those of the OCD and HC groups, which will exhibit comparable RTs in this task 70.

*Emotional reactivity*. An analysis of covariance (ANCOVA) will be performed to assess group differences, with the emotional interference index as the dependent variable, group (HD, OCD, HC) as the independent variable, and depression severity and age as the covariates. A regression analysis will be used to test the association between sleep parameters and the outcomes of this task. Sensitivity analyses will control for serotonergic medication confounds. Power analysis: The emotional reactivity task yielded large effect sizes in HCs in a previous study 58. Comparing subjective distress between individuals with HD and HCs in terms of emotional reactivity scales also previously yielded large effect sizes 71, suggesting that our sample size will allow for 95% power to detect medium to large effect sizes. Expected results:We hypothesize that the HD group will display heightened emotional reactivity compared with that of the OCD and HC groups. We also hypothesize that among individuals in the HD and OCD groups, sleep quality and REM stability will predict emotional reactivity.

*Stroop.* An ANCOVA will be used to assess group differences, with congruency effect as the dependent variable, group as the independent variable, and depression severity and age as covariates. Regression analyses will be performed to test which sleep parameters are associated with congruency effect. These results will be corroborated by running hypothesis-driven analyses of congruency effect in the ANT-D. Power analysis: The current sample will allow for 85% power in detecting a medium size effect with a type one error of .05 68. Expected results:We hypothesize that the HD group will exhibit a larger congruency effect compared with the OCD and HC groups, corroborating the findings from ANT-D.

## Phase **2: Testing the effects of sleep deprivation on neurocognition and clinical symptoms**

Working hypothesis: It is unknown whether sleep disturbance precedes clinical symptoms, results from these symptoms, or whether more complex interactions exist. We aim to test whether experimentally modifying participants’ sleep can affect disorder-relevant neurocognitive processes and clinical symptoms. We hypothesize that a) a night of sleep deprivation will enhance neurocognitive differences between the HD, OCD, and HC groups; and b) these neurocognitive differences will predict clinical symptoms during the following day. These results will inform follow-up studies examining which sleep stage or electrophysiological activity during sleep is driving these changes.

Participants: The same as in phase 1 (Fig. 3).

Procedure: After completing phase 1 (Fig. 3), the participants will return to the sleep center during the afternoon to perform the same neurocognitive tests and brief clinical assessments as in phase 1. They will then spend 24 hours awake in the sleep center, while engaging in recreational activities of their choice. They will complete the same neurocognitive measures the following morning and evening. Participants will refrain from napping until the final assessments are performed.

Methods: See phase 1.

Statistical analysis and expected results:

General approach: We will minimize psychomotor training effects by limiting the cognitive testing sessions and by conducting between-group comparisons in change scores pre- and post-sleep deprivation. We will reduce non-specific improvements due to task familiarity by including an initial training session for all tasks during the phase 1 screening. We will reduce stimulus familiarity by modifying the features of the perceptual tasks in each session: the colors used in ANT-D and Stroop, the shapes used in the MID, and the images used in the emotional reactivity task. The Stroop task will validate the effects in our cognitive battery with just three repetitions in phases 1 and 2. Our tasks have previously shown good test–retest reliability in healthy participants 58,72,73. Our design can evaluate test–retest reliability in individuals with HD and OCD and will enhance the validity of our findings. Secondary analyses will compare between-group changes from evening pre- to evening post-deprivation. All analyses will control for gender, depression, stress, and age. Power analysis: Sleep deprivation leads to large effect sizes on neurocognition, but no studies have previously explored this in patients with HD or OCD. Our study will thus set a benchmark for future hypothesis-testing trials. We will conserve statistical power by only analyzing those variables which differed between the HD and HC groups in phase 1. Regression analyses will be performed to test whether habitual sleep efficiency and duration (phase 1) predict changes in the main outcome measure of each task (specific aim 4).

*ANT-D*. A MANCOVA will be carried out, with changes in alerting, orienting, and congruency as dependent within-subject variables, time (pre- and post-sleep deprivation) as a within-subject independent variable, and group (HD, OCD, HC) as a between-subject independent variable. Expected results:We anticipate that the HD and OCD groups will exhibit larger changes in all attentional networks compared with the changes in the HC group. These results will be more pronounced following sleep deprivation.

*Stroop*. We will test between-group differences in congruency effect by performing an ANCOVA. The dependent variable will be the congruency effect and the independent variables will be group and time. *Expected results*: The HD group will exhibit a larger congruency effect compared with that of the HC and OCD groups. This interaction will be more pronounced following sleep deprivation.

*MID*. Reaction time changes will be analyzed using a repeated-measures ANCOVA, with cue (maximum loss, neutral, maximum gain) as the within-subject variable, time as the within-subject independent variable, and group as the between-subject independent variable. Expected results: In line with previous studies 74, we anticipate an interaction between group and cue such that participants with HD will exhibit larger differences in the gain vs. neutral cues compared with participants with OCD or the HCs. We anticipate this interaction will be larger following sleep deprivation, suggesting that sleep deprivation increases sensitivity to rewards in HD.

*Emotional reactivity*. An ANCOVA will be used to assess group differences, with the emotional interference change index as the dependent variable and group and time as independent variables. Expected results: We hypothesize that the HD group will display heightened emotional reactivity compared with that seen in the OCD and HC groups and that this interaction will be larger post-sleep deprivation.

## **Phase 3: Can improving sleep affect clinical symptoms and cognition?**

Working hypothesis: We hypothesize that sleep disturbance exacerbates HD and OCD symptoms and that improving patients’ sleep will alleviate them. This feasibility study will be the first to test whether targeting patients’ sleep disturbance using CBTI, an evidence-based insomnia psychotherapy, is feasible and acceptable. We hypothesize that CBTI will improve patients’ sleep, clinical symptoms, and cognition.

Participants and recruitment strategy: Participants will comprise patients with HD and OCD patients who completed phase 2. Depending on the enrollment rates at 12 months, we will add recruitment efforts and enroll HD and OCD patients who are experiencing clinically significant insomnia symptoms to this phase alone. Our preliminary data suggest a high prevalence of clinically significant insomnia symptoms in patients with HD (24%) and OCD (27%) 61. Patients will be divided into subgroups based on their insomnia symptoms (Fig. 3). Patients reporting clinically significant insomnia symptoms (ISI > 10) will be assigned to CBTI groups, and the remaining patients will comprise the clinical control groups. Inclusion criteria: The same as phase 1. Exclusion criteria: The same as phase 1, as well as individuals with untreated objective sleep disorders identified during phase 1.

Procedure: Participants will complete a standard 8-week CBTI course with special emphasis placed on environmental factors relevant to HD, such as bedroom clutter (Table 3). Participants will repeat the neurocognitive and self-reporting measures from phase 1 at: A) baseline, B) mid-treatment (week 4), C) one-week post-treatment (week 9), and D) 2-months post-treatment (week 16). They will complete 2 weeks of actigraphy during the final weeks of treatment (weeks 8–9) and two PSG nights at Hadassah Medical Center (week 9) (Fig. 3). CBTI will be conducted by graduate-level psychologists under supervision and following in-person training. Prof. Rachel Manber, a CBTI expert who developed a national CBTI training initiative across the Veterans Health Administration system, will oversee the CBTI training and quality assurance (letter attached). Prof. Manber will also train therapists on how to assess and address HD-related aspects of the sleep environment.

Measures: See phase 1 (Table 1; Fig. 4–6). We will add two self-report measures: 1) *Insomnia Treatment Satisfaction Scale (ITSS)*, which assesses the impact of CBTI on insomnia and seven major life areas (energy level, work productivity, coping, life enjoyment, hopefulness, self-esteem, and mood) 76; and 2) *Treatment Components Adherence Scale (TCAS)*, which assesses adherence to the behavioral and cognitive components of CBTI 77. Participants will complete the ITSS and TCAS upon treatment completion. The therapists will report environmental factors that are affecting participants’ sleep.

TheCBTI

|  |  |
| --- | --- |
| Session | Main content |
| **1** | Assessment: Sleep history, habits, cognitions, and environmental factors such as bedroom clutter. Review the sleep diaries from phase 1. |
| **2** | Psychoeducation and behavioral techniques: The main techniques are 1) stimulus control, e.g., leaving bed when not falling asleep; 2) sleep restriction therapy, e.g., scheduling a regular sleep time; and 3) mitigating environmental factors, e.g., moving bed clutter to another room. |
| **3** | Cognitive techniques and troubleshooting: 1) “constructive worry” – prescribing a pre-bedtime and writing worries and tangible actions to mitigate them; 2) thought recording – a standard CBT practice applied to sleep. Writing down maladaptive sleep thoughts, their context, and associated emotions. We will work on creating alternate adaptive beliefs. |
| **4-5** | Review of sessions 2 and 3, and modifications to behavioral and cognitive techniques. |
| **6** | Summary and future action plans. |

Statistical analysis and expected results:

General: All analyses will use the intent-to-treat principle and include all participants who started CBTI with their last observation carried forward. Power analysis: This will be the first study to test the use of CBTI in patients with HD or OCD. The outcomes will guide power calculations for follow-up hypothesis-testing trials.

Insomnia symptoms: Two ANCOVAs will be carried out to compare ISI pre- and post-treatment in HD and OCD patients, with ISI score as the dependent variable, time (baseline, post-treatment) and treatment (CBTI, no treatment) as independent variables, and age and depression severity as covariates. Separate mixed-effects regression models will be used to test ISI change over time. Expected results: We hypothesize that both HD and OCD patients will demonstrate reduced insomnia symptoms following CBTI.This would represent a novel therapeutic and conceptual advance in the treatment of HD and OCD, as a patient’s sleep is not addressed in current treatments.

Treatment feasibility and acceptability. *Completion rates*:TCAS and ITSS scores will be reported, in line with previous treatment-development studies 76. Expected results: We hypothesize there will be a high degree of treatment feasibility and acceptability in patients with HD or OCD.

Clinical measures: We will test the impact of CBTI on HD and OCD outcomes by using two ANCOVAs with a clinical measure (SIR for HD and YBOCS for OCD) as a dependent variable and time (baseline, mid-treatment, post-treatment, follow-up) and treatment (CBTI, no treatment) as independent variables. The number of responders in each group will be reported, using an a priori criterion of 35% improvement 79. Expected results: We hypothesize that CBTI will reduce the severity of HD and OCD and that this reduction will persist over 2 months. If successful, and pending replication, our results may constitute a new treatment option for patients with HD or OCD and lead to follow-up treatment-development studies integrating CBTI and CBT for HD and OCD. Integrating CBTI and CBT has previously yielded positive results in different fields 80.

Neurocognitive processes: Three, repeated-measures ANCOVAs for HD and OCD will be used for ANT-D, MID, and the emotional reactivity task, with RTs as dependent variables and time (pre-treatment, post-treatment) and treatment (CBTI, control) as independent variables. All analyses will be controlled for age, gender, and depression severity. Expected results: We hypothesize that CBTI will increase the alerting effect in the ANT-D task in both groups, reduce the loss of sensitivity of HD participants in the MID, and decrease emotional reactivity in the OCD and HD CBTI groups compared with their control groups.

Subjective sleep measures: A three-way ANCOVA will be used, with sleep scores as dependent variables (PSQI, ESS, FOSQ) and time (baseline, mid-treatment, post-treatment, follow-up), group (HD, OCD), and treatment (CBTI, no treatment) as independent variables. Expected results: We hypothesize that sleep quality and daytime functioning will increase in patients with HD or OCD.

Objective sleep measures: Actigraphy and PSG:Separate, repeated-measures ANCOVAs will be used to test whether CBTI modifies aberrant sleep parameters in HD and OCD patients, detected in phase 1. The independent variables will be time (baseline, post-treatment) and treatment (CBTI, no treatment). Depression severity and baseline clinical severity will be the covariates. Expected results:We hypothesize that CBTI will improve objective sleep measures in both the HD and OCD groups.

Facilities and personnel

Dr. Linkovski is an experienced psychologist who has concentrated his clinical and scientific efforts on the study of HD and OCD. He has been assessing and treating patients suffering from these psychopathologies for the past 9 years. He has received training from professionals experienced in clinical assessments (Prof. Anthony Pinto), as well as CBT and therapeutic interventions for HD and OCD (Prof. Gideon Anholt, Dr. Anthony Lombardi, and Mr. Lee Shuer). Dr. Linkovski completed a postdoctoral fellowship at the Department of Psychiatry and Behavioral Sciences at Stanford University, where he focused on advanced clinical training, large-scale clinical trials (Prof. Carolyn Rodriguez), and basic sleep research (Prof. Ruth O’Hara and Prof. Makoto Kawai). Dr. Linkovski has mentored more than 25 graduate and undergraduate students in the past 6 years, in both clinical and research settings. In the past year, Dr. Linkovski initiated his laboratory at Bar-Ilan University; he is now mentoring the graduate and undergraduate students who are setting up the proposed study, as well as clinicians who will serve as independent evaluators. Dr. Linkovski’s laboratory includes three experimental rooms equipped with the relevant hardware and software to conduct this study and three shared clinical interview rooms. Bar-Ilan University has allocated space to open its sleep center. I am submitting an additional ISF equipment grant to purchase a PSG. An ISF-funded sleep laboratory will simplify participant access, reduce costs, and expand PSG usage. I will train graduate students in sleep scoring while receiving support from Drs. Reiter and Gileles-Hillel. Prof. Rachel Manber, a CBTI expert, will assist in CBTI implementation and quality assurance. Dr. Linkovski is collaborating with Prof. Rodriguez on several ongoing neurocognitive and clinical projects pertaining to HD and OCD, as well as PSG studies in pediatric OCD with Profs. O’Hara and Kawai. He is conducting the first study to test whether a neurosurgical procedure for OCD affects sleep, with Prof. Hagai Bergman and Dr. Renana Eitan (Hebrew University). These global leaders will be available to provide ad hoc advice on the theoretical and practical aspects of this study.

Potential pitfalls and contingency plans

Recruitment: Recruiting 3 to 4 patients each month will be sufficient and expected based on our previous experience in recruiting HD and OCD patients. There are no Israeli researchers studying HD or psychologists who specialize in HD; therefore, our initial patient pool may be small. However, HD is equally prevalent across societies 81–83. To maximize the recruitment rate, we are collaborating with one of the largest medical centers for mental health in Israel, the Jerusalem Center for Mental Health (which treats more than 2,300 patients); a large, specialized CBT center (“Cognetica”); and the Bar-Ilan University clinic. In addition, we will recruit participants through social media and local newspapers. We will contact additional Israeli clinics and medical centers as needed. Having the same participants completing phases 1 to 3 will allow for longitudinal analyses and enhance the statistical power. We will assess enrollment on a yearly basis and consider recruiting different patients for each phase. Meeting our recruitment goals will allow us to test our primary hypotheses, driving future randomized clinical trials and longitudinal studies.

Participant characteristics: The menstrual cycle may affect sleep. We will ask female participants to indicate the time elapsed since their most recent period. This information will be used to optimize scheduling and for post hoc analyses. However, we will not exclude participants who choose not to provide this information.

COVID-19: The COVID-19 pandemic has impacted clinical research by limiting in-laboratory sessions. I will mitigate this in the following ways: 1) Subjective questionnaires and clinical interview reports will be completed using the Qualtrics secured system. A HIPPA approved Zoom license will be purchased so that clinical interviews and CBTI sessions can be conducted remotely. 2) Our neurocognitive tasks will be created using E-Prime software, allowing accurate data collection. Research staff will provide participants with identical laptops and sanitize them after each use. 3) For the actigraphy, we will sanitize the actigraphs between participants, according to the manufacturer’s guidelines. 4) For the PSG, in cases of extended quarantine measures (more than 6 weeks) during the study period, we will consider conducting the PSG at participants’ homes or using mobile sleep-staging devices 84. Dr. Linkovski has previously administered 50 in-home PSGs as part of an ongoing study at Stanford University. Any modifications will be approved by the relevant health authorities and review boards.

Significance of the study

1. Characterizing objective sleep in individuals with HD: Our study will be the first to explore objective sleep in individuals with HD, while providing additional information on the divergent and convergent sleep characteristics among obsessive–compulsive and related disorders. This may help to improve our mechanistic understanding of the role sleep plays in HD and OCD and may also guide treatment development.
2. Testing whether sleep modifications affect participants’ sleep and clinical outcomes: Testing how sleep modifications can affect clinical symptoms and neurocognition will provide preliminary directional connections for the role sleep plays in the etiology and/or maintenance of these disorders.
3. Piloting a new therapeutic intervention: If CBTI proves effective for HD and OCD, it may represent an affordable, scalable intervention. This will lead to large-scale follow-up research projects, grant applications, and – most importantly – improvements to millions of people’s lives.

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