Article Title: Objective measures of cognitive performance in sleep disorder research: comprehensive overview of research and future perspectives

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Key Words.
Sleep disorders, neurocognitive testing, cognitive domain, cognition, cognitive test battery.

Key Points

- Neurocognitive tests can provide an important addition to more traditional non-cognitive sleep disorder measures.
- The use of neurocognitive testing in the field needs to be based on standardized practices and theory in order to conclude on and compare findings.
- We offer an extensive overview of empirical findings organized around neurocognitive tests and cognitive domain
- We propose neurocognitive tests and approach for future use of objective measures of cognition in sleep disorder research

Introduction

In addition to other more traditional sleep measures, neurocognitive assessment provides an important tool for determining the extent of sleep disruption, the general impact it may have on daily activities, as well as evaluating treatment efficacy. Long standing sleep disorders are known to have deleterious effects on general health [1] which in turn influences cognitive functioning [2; 3,4] and may in the long run, undermine occupational performance and social participation, ultimately leading to diminished quality of life [5,6]. Neurocognitive tests offer objective and reliable assessment of patients' status and progress. To date, however, there is no consensus on how to use neurocognitive assessment in sleep disorder research. The concept of cognitive domain has been used rather inconsistently in the field, with a particular domain being assessed through a single process or even very broadly using a variety of tests. Furthermore, the same test may be used to assess two different domains, making it hard to conclude how cognition is impacted by sleep disorders. An effective use of neurocognitive assessment must be based on standardized practices and have a firm theoretical basis.

The purpose of this review is to provide a platform for better standardizing the use of neurocognitive assessment in the field. We aim to do this by reviewing empirical results in sleep disorder research on the basis of the tests used and systematically mapping the different tests onto a corresponding cognitive domain. This approach will help clarifying how different cognitive domains and processes are affected by sleep disorders and also how sensitive a particular test is for detecting impairments due to sleep disruption. We will conclude by suggesting neurocognitive tests for future research, classified by domain and main cognitive processes involved.

The cognitive domains taken into consideration in the present review are: motor skills, perceptual skills, processing speed, vigilance/sustained attention, selective attention, episodic memory (verbal/non-verbal), executive function, and reasoning, decision making and emotional processing. We acknowledge that these cognitive domains are not fully independent and that there is not a complete consensus on how to classify cognitive abilities [7]. The sleep disorders considered in this review are: : obstructive sleep apnea (OSA) and other sleep-related breathing

disorders (SRBD), restless leg syndrome (RLS), insomnia, and severe sleep loss (SSL). Only studies completed during the period from 2000 to the present date and based on comparing individuals with the selective sleep disorders to a healthy control group are included in the current review.

OBJECTIVE MEASURES OF COGNITIVE DOMAINS IN SLEEP DISORDER RESEARCH

Perceptual skills

Various perceptual tasks have been used in sleep disorders research, including tasks assessing sensation rather than perception (the function of the perceptual system rather than processing of the sensory input in the brain). For example, studies have shown that people suffering from OSA have an impaired visual field [8] and decreased perception of high frequency sounds [9]. Perceptual skills refer to the identification of a stimuli and its orientation/location in space [10]. Tests assessing perceptual skills are often based on the identification of degraded objects [11] or alignment in space. Such tests include the Visual Organization Test (VOT), or the Judgement of Line Orientation Task (LOT). In a review by Fulda and Schulz [12] no differences were found in perceptual skills between SRBD and normal controls, evaluated on tests such as VOT, Thurstone visual matching test, LOT, Physical match and Sensory motor task. In a recent meta-analysis, perceptual functions were found to be mildly affected by insomnia when assessed with tasks such as Perceptual reasoning index and the Critical flicker fusion [13].

In sum, it is unclear to what extent perceptual skills are affected by sleep disorders. This aspect of neurocognitive functioning is rarely included in studies examining the impact of sleep disorder [14,15] or sleep deprivation [16] on cognitive performance. Yet, impaired perceptual skills, although not perhaps a problem in itself for individuals with sleep disorders, might impact higher order cognitive operations such as attentional control or updating information in working memory (e.g. [16]). More work is needed in the field in order to conclude on the impact sleep disorders may have on perceptual skills.

Motor skills

Motor skills refer to both motor coordination, dexterity and speed [11]. A wide variety of tests have been used to examine motor skills, also referred to as psychomotor function in sleep disorder research (e.g. [17,18]). These include tests measuring fine motor coordination and motor speed such as Mirror tracing task (MTT), Line tracing, Rotary pursuit task, Finger tapping task (FTT), the Motor sequence learning task (MST), the Grooved Pegboard (GPT) and the Purdue Pegboard test (PPT). Other tasks perhaps more suited to assess attention and/or vigilance have also been used as an assessment of psychomotor function or information processing speed in the field. The FFT, GPT and PPT are all validated and reliable measures of motor skill, both dexterity and speed [11]. The three tests have been suggested as tools for evaluating professionals where motor speed and dexterity is important [19]. Ayalon and Friedman [20] found that shift work in resident doctors affected their performance on PPT. Simple reaction time tests have also been used in the field to assess motor skills.

Ferini-Strambi et al [21] found a significantly slower RT for OSA individuals compared with controls on a simple reaction time test. Devita et al [17] used a computerized reaction time test where they distinguished between the perceptual component of reacting to stimuli (the time difference between stimuli appearing and removing a finger from a rest button) and the motor component (the time difference between removing a finger from a rest button and pressing a reaction button). In their study, individuals with OSA had a significantly slower RT for the motor component in various different reaction time tests compared with normal controls. Khassawneh et al [22] found no significant difference in performance on a simple reaction time test when comparing insomnia individuals to a control group.

Studies have found impairments in both motor speed and dexterity for OSA individuals compared with normal controls using the PPT [21,23]. Accordingly, in a review by Fulda and Schulz [12] and Aloia et al [24] a significantly impaired performance was found on the PPT for both SRBD and OSA individuals compared with control groups. No impairment was, however, reported for individuals with insomnia on this task [12,25]. Furthermore, no impairment was reported in individuals with sleep disorders for FTT, GPT, Sensory motor task and Line tracing task in two reviews [12,24]. Rouleau et al [26] found no difference between OSA individuals and a normal control group using the Rotary pursuit task and the MTT, although, more individuals in the OSA group seemed to have problems during the initial acquisition state of the MTT. Matthieu et al [27] found

that age rather than OSA explained differences in performance on the MTT when comparing younger and older individuals with OSA. However, Neu et al [28] found that OSA individuals performed significantly worse on FTT compared with individuals with chronic fatigue syndrome. Similarly, Laundry et al [29] found that OSA individuals demonstrated less learning on the FTT compared with control after an overnight sleep.

In sum, both motor speed and dexterity as assessed with simple reaction time tests, FTT and PPT, are impaired in individuals with OSA. There is however, little evidence of impaired motors skills in insomnia individuals, or in sleep disorders in general for various motor skills tasks listed above. More work is needed in the field to gain a comprehensive understanding of the impact sleep disorders may have on motor skills. Impaired motor skills may interfere with performance on various other tasks such as tasks measuring executive function or selective attention.

Processing speed

Processing speed refers to the ability to rapidly process information and perform various tasks (from simple to complex) such as symbol coding tasks, connecting numbers/letters in a sequence (Trail making test A, TMT A), where participants must complete the task as fast as possible [11]. Several studies have shown that OSA individuals perform worse on the Digit symbol substitution task (DSST) compared with controls [26,30–32]. A comprehensive review by Kilpinen et al [18] on the impact of OSA on information processing speed measured with tasks such as TMT A, and DSST along with motor control and pursuit tasks showed a general slowing of information processing speed and psychomotor functions for OSA individuals compared to control groups. Other studies however, have found no difference between OSA individuals and controls for TMT A [32] and DSST [33,34]. In the study by Saunamaki et al [33] and Twigg et al [34], a larger number of individuals in each group was used (n= 40-60) with the age ranging from approximately 20 to 70 years. No difference was found on DSST or TMT A when comparing individuals with insomnia (medicated and not) with a control group [25].

In sum, the studies reviewed here are almost entirely focused on OSA and processing speed. In general, there is some indication that processing speed, in particular as measured with DSST, is affected by OSA. Accordingly, studies on sleep deprivation have shown a significant impairment in DSST for sleep deprived individuals [35]. There is insufficient empirical evidence to conclude on

other sleep disorders. However, given the impaired performance on DSST for OSA individuals and sleep deprived individuals and the central importance of processing speed for efficient cognitive functioning [36], it is important to continue studying processing speed in sleep disorders. Also, it should be borne in mind that tests of processing speed are generally confounded by motor speed (e.g., DSST and TMT A) and it is important to attempt to find alternative tasks of processing speed that are non-motor [37].

Vigilance/sustained attention

Vigilance is the cognitive domain along with executive function that seems to be most affected by sleep disorders [38–40]. Vigilance refers to the ability to sustain attention over time and maintain alertness towards stimuli in the most immediate environment occurring at irregular intervals [41]. Deficits in vigilance caused by sleep deprivation include difficulties sustaining attention over time during continuous task performance, pauses in response time towards stimuli in the task environment (lapses) and response errors (responding too soon, pressing for too long or missing the target altogether) [42]. According to meta-analyses, vigilance is significantly impaired by various sleep disorders such as OSA, indicated by a large effect size [38]. Other reviews and meta-analyses have confirmed that vigilance is significantly affected by OSA (e.g. [39,40]). Reduced vigilance can lead to impairment in other more higher order cognitive functions such as executive control [40].

Vigilance is frequently measured with tasks such as the Psychomotor vigilance test (PVT), Continuous performance test (CPT), Choice reaction time test (CRTT) and Four choice reaction time test (FCRTT). Several studies have found impaired performance on the PVT test for OSA individuals compared with control groups [43,44,45]. Although see Djonlagi et al [46] for different results. Both Li et al [45] and Batool-Anwar et al [43] found that performance on the PVT for OSA individuals was related to scores on the Epworth Sleepiness Scale (ESS). Sforza et al [47] found that errors (lapses and omissions) correlated significantly with both AHI and daytime sleepiness in individuals with SRBD. Lee et al [6] found that PVT (lapses and mean RT) correlated with quality of life measures, in particular, the physical domain for OSA individuals. This was true even after controlling for BMI, age, apnea severity and depression. Mathieu et al [27] examining younger and older participants and comparing OSA with a control group, found that OSA individuals had longer reaction times on FCRTT and more lapses compared to controls. For the

younger participants with OSA, increased time spent with oxygen saturation below 90%, caused an increase in reaction time and lapses on the task.

In a large community cohort study [48] performance on PVT (response speed, not error) varied with severity of insomnia for older individuals (> 65 years). Hansen et al [49] found that PVT differentiated between sleep-onset insomnia individuals and control group during a total sleep deprivation period of 39 hours. With increased number of hours during the sleep deprivation, vigilance as measured with lapses, response errors and mean RT on PVT, decreased significantly more for the insomnia group compared to controls. The exaggerated impact of sleep deprivation on insomnia individuals was found both for the 10 minute version of the PVT and for a 3 minute version. Altena et al [50] used a variation of PVT, where participants responded to asterisks appearing on a computer screen at random time intervals (the simple vigilance task) and to target letter (d) ignoring distractor (p) appearing also randomly (complex version). Their results showed that insomnia individuals did not make more errors but showed impaired response speed in the complex version compared with a control group but no difference was found between groups in the simple version. Other studies have not found any impairment in performance for individuals with insomnia on CRTT/FCRTT [22,25], CPT [51], on alertness as measured with the attention network test (ANT) [52] and an auditory PVT both simple and complex [53].

In sum, there is strong empirical evidence for impaired vigilance/sustained attention in individuals with OSA. It is less clear to what extent vigilance and sustained attention is impaired in individuals with insomnia or other sleep disorders. Interestingly, for insomnia, studies show impaired performance on the original PVT but not on other measures of vigilance. The PVT has been deemed as perhaps one of the most sensitive measure of the neurocognitive impact of sleep deprivation [54]. The high signal load and the relatively short task performance time makes the PVT test ideal for detecting the impact of insufficient nonrestorative sleep on vigilance [55,54,56] and may therefore be well suited in the field of sleep disorder research.

Selective attention

Several reviews and meta-analyses have concluded that selective attention is significantly affected by sleep disorders [24,38,39]. However, studies in the field frequently use vigilance measures or executive function measures to examine attention, making it difficult to conclude about

selective attention. As pointed out in Strauss et al [11] it is hard to distinguish attentional selection in space from other cognitive processes such as perception, memory and motor control. Tests of selective attention include Cancellation tasks, Visual search tasks (VST), the Posner paradigm and the induced change blindness (ICB) task, where the participant needs to detect an item/object or a change among distractors or select an area in space.

Giora et al [15] used a VST when comparing individuals with insomnia to a control group. Participants looked for a target letter (T) appearing among distractors (L, X, O) that varied in number. Their results showed that insomnia individuals did not differ from the control group in terms of search accuracy, but had a significantly longer RT. Similarly, in Giora et al [14], the VST showed a slower RT for OSA individuals compared to a control group, while search accuracy did not differ between the groups. Using the Posner paradigm, Woods et al [57], found a significant difference in performance between participants with primary insomnia, and normal sleepers. In the study the participants with primary insomnia had a delayed reaction time on invalid trials of the task, invalid trials being trials when the target is not presented at the same side of a computer screen as a cue. Both Jones et al [58] and Marchetti et al [59] using the ICB found selective attention impairments in patients with primary insomnia and a delayed sleep phase syndrome. The paradigm is a task were a set of flickers is presented to the participant that has to detect a change, either neutral or sleep related, between the two flickers. In the study done by Marchetti et al. [59] participants with insomnia had a clear bias in their selective attention, by being significantly quicker to detect change related to sleep compared with controls. Interestingly though, for neutral change, individuals with insomnia were significantly slower to detect the change compared both with individuals with delayed sleep phase and normal sleepers. Jones et al. [58] showed similar results, with insomnia individuals being quicker to detect sleep-related change but slower to detect neutral change compared with normal controls. Although, Rouleau et al. [26] found a significant impairment in performance on a cancellation task for OSA individuals compared with controls, Ferini-Strambi et al [21] found no differences in performance on a cancellation task when comparing OSA to a healthy control group. Khassawneh et al [22] used the big circle-little circle task to measure attention. In this task, participants respond to one of two circles, responding first to the smaller circle and then to the larger one. No difference was found in performance between insomnia individuals and a control group.

In sum, very few studies actually study selective attention in relation to sleep disorders. Many studies claiming to be assessing attention are rather assessing attentional control and/or vigilance and selective attention tasks are generally compounded by motor speed. Using the ICB, studies have found attentional bias in individuals with insomnia who respond faster than normal controls to sleep related changes but slower to neutral changes. There is also some indication that insomnia individuals have a harder time disengaging attention from a selected area as demonstrated using the Posner paradigm. Furthermore, individuals with OSA have been found to do worse on a cancellation task and a visual search task. Tasks such as VST are rarely used to assess selective attention although Wermes et al [60] concluded that RT in VST is a reliable measure of selective attention.

Executive function/working memory

Executive function refers to various top down processes that regulate and control cognitive performance by guiding attention, updating information in working memory, overseeing attentional switching between tasks and inhibiting un-timely or inappropriate responses [61–63]. It is currently widely accepted that executive functions include three main domains; inhibitory control (including the control of attention), maintenance of information in working memory and updating of that information, and cognitive flexibility or set shifting [61,63]. For the most part, recent research on cognition in sleep disorders divides executive function into the three recognized domains (see [64]). However, in the literature as a whole, a variety of tasks are used to evaluate executive function, many of which are more suitable for evaluating other areas, such as attention, processing speed, or vigilance.

Both reviews and meta-analyses indicate strongly that executive function is impaired by various sleep disorders such as OSA [40,65], linking OSA to impairment in working memory, inhibitory control and cognitive flexibility [65]. In a meta-analysis by Fortier-Brochue [66], insomnia had a significant impact on the working memory part of executive function (e.g. maintaining, updating and manipulating information) while inhibitory control and cognitive flexibility were less affected. Recognized working memory tasks that have been used in sleep disorder research include, the backward digit span (BDS) [67], the Corsi block test and the n-back test [68]. Both BDS and Corsi block test are among the most frequently used test when evaluating the impact sleep

disorders may have on working memory [65]. Other tests used include double span memory task, and the Paced auditory serial addition test (PASAT) [69].

Torelli et al. [70] found that OSA individuals performed significantly worse on BDS than controls. Other studies however, do not show impaired performance on the BDS when comparing OSA to a control group [21,27,32,33,71]. In the study by Torelli et al [70], only 16 OSA individuals participated and most of them (n=12) had severe apnea. Ferini-Strambi et al [21] found no difference in performance on the Corsi block task and [72] found no difference on the n-back test when comparing OSA to control groups. Thomas et al [73] however, testing young OSA individuals compared with controls, found that OSA individuals had slower performance speed and less accuracy in the n-back test. Using a comprehensive selection of working memory tests, Naegele et al [74] found that OSA individuals were not impaired on short-term span measures or dual task measures. They did however find a significantly impaired performance on PASAT, which is a highly speeded task, and on a transformed auditory span task, where participants have to maintain a list of numbers as well as perform simple arithmetic transformation on the numbers.

In contrast to studies on OSA, studies on individuals with insomnia show a marked impairment in working memory. Both Haimov et al [75] and Vignola et al [25] found that performance on BDS was significantly impaired for individuals with insomnia. Similarly, Cellini et al [76] found that young individuals with insomnia had a higher number of errors and less total accuracy on n-back compared with controls. Shekleton et al [53] also found impaired performance on the n-back test among individuals with insomnia and short sleep duration, no difference in performance on the task was found for insomnia with normal sleep duration. In contrast, Lovato et al [77] found no significant difference between older individuals with insomnia and controls on the double span memory task when controlling for IQ.

Accepted neurocognitive tasks for measuring inhibitory control that are also used frequently in the field of sleep disorder research include the Stroop task (also the Color-Word Interference test, CWIT), the Simon task [78], the Flanker test [79], the go/no go [80] and the stop signal task [81]. These tasks not only require the individual to inhibit unwanted responses but also to direct attention to the relevant task related goal. When performing on the tasks the participant needs to respond to particular information (direction or color of stimuli) while ignoring other information (location or reading words). In the go/no go and the stop signal tasks, the focus is more on the inhibition of

response [63]. The participant must respond to stimuli (for example, letters) as fast as possible but refrain from responding to a particular stimulus or when a cue is given at a random interval. There are several outcome measures including accuracy and RT as well as stop signal RT.

In a Canadian longitudinal study on aging with a large cohort, individuals with insomnia disorders (>45 years of age, n=1.068) did worse on the Stroop test than those with no insomnia (n=19.604) and insomnia symptoms only (n=7.813) after controlling for age, education and gender [82]. Other studies have found a significantly impaired performance for individuals with insomnia (compared with control groups) on the Stroop test [75] and the Flanker test [52]. Individuals with OSA have also been shown to have impaired performance on the Stroop test (increased error, not time) and the Flanker test [21,71,83] Other studies have not found significant difference on the Stroop test for insomnia [84] or RLS [85].

Covassin et al [86] compared eight individuals with insomnia to eight good sleepers, using the stop signal task. They found that the individuals with insomnia had a harder time inhibiting their responses when the auditory cue was given. Studies have similarly found that both individuals with OSA [87] and insomnia [88] have a harder time preventing their responses to the no go stimuli. In contrast, Sagaspe et al [87] found no difference in performance for insomnia individuals and Angelelli et al., [89] found no difference in performance for OSA individuals compared with a control group on the go/no go task. Mean age of participants was similar between the studies but both Zhao et al [88] and Covassin et al [86] had very few participants (n<15).

Recognized tests used to measure cognitive flexibility and also used in sleep disorder research include the Wisconsin Card Sorting Task (WCST), Trail Making test (TMT) B, and various attentional switching tasks such as the Task Switching Paradigm (TSP) and the Switching to Attention Test (SAT). Werli et al [71] found a significant difference between OSA and controls on both categories and perseverative errors on the WCST (see also [26]). Other studies have, however, not found a difference in WCST when comparing OSA to healthy control groups [27,90]. Almodes et al [91] found no difference between insomnia individuals and controls on the WCST (see also [25]). Similarly, no differences were found in Fang et al [92] on WCST when comparing insomnia and control despite objective measures showing a difference in total sleep time and less sleep efficiency. Although, Ju et al [93] found that OSA individuals were significantly slower to complete the TMT B compared to a healthy control group and made more errors, other studies have not

found any performance impairments on TMT B for OSA individuals [94,21,27,32,71]. Similarly, no performance impairment on TMT B has been found for insomnia [25,84] or individuals with RLS [85,72].

In the switching tasks such as TSP and SAT, both attentional switching and response inhibition are evaluated [96]. Participants are required to switch between different tasks for example, judging if a number was odd or even, and bigger or smaller than the number 5 in TSP (e.g. [96,97]) and switch between location and direction of arrows in SAT [51]. Which task the participant has to work on is indicated by a cue such as the shape of geometrical figures (e.g. [64,97]). Performing according to the same task rule results in a faster RT compared to when the participants switches from one task to another, this is referred to as switching cost [96]. In a study by Wilkens et al [97] older insomnia patients were significantly worse in using a preparation time (time between cue and target) compared to a control group. Similarly, Shekelton et al [53] found that insomnia patients were significantly slower compared to controls to respond to the stimuli in the complex switching condition of the SAT (switching between location and direction). Interestingly, Shekelton et al [53] found that only individuals with insomnia who reported short total sleep time (<6 hrs) showed worse performance on SAT compared with a control group but not those who reported longer total sleep time (>6 hrs). Khassawneh et al [22] found that individuals with insomnia and objectively measured short total sleep time (<6 hrs) showed significantly higher response latency and errors on SAT compared to a normal control group. However, Ballesio et al [98] did not find impaired performance on TSP following partial sleep deprivation (5 hrs of sleep) for chronic insomnia patients compared with controls.

Verbal fluency tasks and the Maze task are also frequently used to assess cognitive flexibility [63]. In the fluency tests participants are asked to produce as many words starting with a particular letter or members of a particular category as they can for a given time period [63,99,11]. Pearson et al [85] compared 16 individuals diagnosed with RLS with a matched control group and found that RLS individuals had a significantly impaired performance on category fluency task compared with controls. Both, Ferini-Strambi et al [21] and Salario et al [90] found a significantly impaired performance in OSA individuals compared with control for phonemic not semantic fluency test. Werli et al [71] however, found that OSA individuals did significantly worse on both category and phonemic fluency tasks compared with controls. Other studies have not found any differences in

phonemic fluency [74,26,70] or category fluency [70,93] for OSA compared with controls. Sivertsen et al [84] found a significantly impaired performance for older insomnia individuals on phonemic but not category fluency task. No differences have been reported for verbal fluency for RLS [95]. Impaired performance on the Maze test has been reported for OSA individuals [26] but not for RLS individuals [85].

In sum, various reviews and meta-analysis indicate a strong impact of sleep disorders on executive function [38,65]. In fact, it has been concluded that executive functioning is the aspect of cognition that is most heavily impacted by sleep disorders [39]. Accordingly, it is clear from the present review that there are some impairments in executive function among individuals with sleep disorders. However, measures need to be carefully chosen and in order to conclude whether or not a particular sleep disorder affects executive function, all three domains must be examined (working memory, inhibition and control and cognitive flexibility). When it comes to impaired working memory, the results were more conflicted for OSA compared with insomnia. Although few studies have found impaired performance on n-back and PASAT for OSA individuals, most studies find no impairment, particularly for BDS. In contrast, individuals with insomnia show impaired performance on all working memory tasks. It has been pointed out in meta-analysis by Fortier-Brochue [66] that for insomnia, it is mainly maintenance and updating of information in working memory that is impaired not inhibition or cognitive flexibility.

Inhibition and attentional control is impaired in both individuals with OSA and insomnia. Tests such as the Stroop test and the Flanker test may be a good option for detecting this impairment in sleep disorders. For cognitive flexibility, studies using both WCST and TMT B show no clear differences in performance of OSA, insomnia and RLS individuals compared with control groups. Both WCST and TMT B are very popular and frequently used tests in clinical assessment but they may be more sensitive to serious frontal lobe problems rather then to the performance decrement caused by sleep disorders [64]. When measuring cognitive flexibility, switching tasks may be a better option in sleep disorder research. Studies have shown that individuals with insomnia have a harder time switching between tasks compared with normal controls. The results for fluency tasks are very conflicted but more studies have shown no significant difference in phonemic and category fluency for OSA compared with controls. Although studies vary in terms

of number of participants and age no systematic differences were found that could explain the difference in results.

Episodic memory (verbal and non-verbal)

Episodic memory refers to memory for particular events, recent as well as in the more distant past that are tied to time and place [100]. It is normally tested by measuring both immediate and delayed verbal and visual recall using both recognition and free recall [12,40]. Measures also include learning when participants, for example, go repeatedly through the same wordlist. A variety of verbal memory tests exists and have been used in the field of sleep disorder research. The Auditory Verbal Learning Test (RAVLT), tests immediate and delayed recall of semantically unrelated words [11]. In Logical Memory (Wechsler Memory Scale), participants need to store and retrieve information from a story and in both California Verbal Learning Test (CVLT) and Hopkins Verbal Learning Test (HVLT), participants work with semantically related information [101]. There is also the verbal paired associates test.

Meta-analysis and reviews indicate impaired verbal memory in insomnia [13] and OSA [102]. In fact, Wallace and Bucks concluded that all aspects of verbal memory are impaired in OSA individuals, immediate and delayed recall, recognition and learning. According to Fulda and Schultz [12] there is little indication of memory impairment in insomnia and SRBD. Vignola et al [25] found no differences in insomnia compared with controls on immediate and delayed memory on the verbal paired associates test. Naegele et al [74] used 16-word wordlists where participants had to identify the category of each word as they went through the list (OSA compared with controls). They then tested immediate recall before and after an interfering task and a cued recall (repeated three times). The participants also completed a recognition test and a delayed free recall test. In general, OSA individuals performed on par with normal controls, except on immediate free recall following interference. The authors concluded that impaired memory in OSA individuals is isolated to the retrieval process, not the encoding, learning or retention part of verbal memory. Using a word list and immediate and delayed recall, Ju et al [93] also found that immediate and delayed free recall is impaired for older OSA individuals compared with controls but not recognition memory. Other studies using RAVLT have also found that OSA individuals perform worse than controls [28,70,71,103,104]. Werli et al found only a difference in the delayed free recall of RAVLT. Neu et al [28] found significantly poorer performance for OSA individuals than controls

on both immediate and delayed recall on RAVLT but no difference in delayed recognition. Using the CVLT Salario et al [90] found a significantly impaired overall recall but not in retention for OSA compared with a control group. Other studies have, however, not found any performance difference on the RAVLT when comparing OSA individuals to control [26,27,84,105].

Adams et al found that SRBD correlated with performance on CVLT. Similarly, Cross et al [82] found significantly worse performance on RAVLT, both immediate and delayed recall in a large population based cohort, comparing insomniacs with controls. However, Sivertsen et al [84] found no difference in performance on CVLT for older insomniacs compared with controls. In a study by Guo et al [3] comparing insomniacs to controls, participants read out loud a list of object-related words and were then tested immediately and after five minuets delay (free recall) and again after a 20 minute delay (recognition). The results showed that individuals with insomnia were significantly worse at immediate and delayed free recall but no difference was between the group on the delayed recognition test.

Using the logical memory test, Mathieu et al [27], found a significant difference in both immediate and delayed recall for OSA compared with control for both younger and older individuals. Similarly, Twigg et al. [34] found that OSA individuals had impaired immediate and delayed recall compared with normal control but their recognition memory and maintaining information over time was intact. Ferini-Strambi et al [21], however, with fewer participants (n=23 vs 60) found no difference between OSA and controls on the logical memory test.

Studies suggest that immediate and delayed recall in visual memory is impaired in OSA individuals [102]. Tests used to assess nonverbal memory include, Rey Osterrieth Complex Figure (ROCF), Brief Visuo Spatial Memory test [101], Wechsler Memory Scale, WMS (Visual Reproduction, figural memory) [106], WAIS-R block design and Visuo-spatial delayed recall and visual memory test. In the visual memory test, subjects are asked to recognize a target picture among distractors after viewing it briefly. Torelli et al [70] found no significant difference in OSA individuals compared with controls on the visual memory test. In Visual reproduction Wechsler [106] participants are shown visual design and later asked to draw the design as they remember it (immediate and delayed recall). Vignola et al [25] found no difference in performance here for individuals with insomnia compared with controls. In the ROCF subjects are asked to copy a

complex figure and then reproduce the same figure from memory (immediate and delayed memory). Some studies have found that both SRBD [104,107] and OSA [26,70] perform worse on ROCF compared with normal controls. However, other studies have not found any significant differences in performance [21,34,84]. Daurat et al [108] found that recollection of temporal and spatial memories is impaired in patients with OSA using the Brief Visuo Spatial Memory Test Revised.

In sum, it is clear that for verbal memory there is an impairment in both immediate and delayed free recall for individuals with OSA but not in retention of information as performance on recognition tests seems intact. Similarly, although less empirical evidence exists on verbal memory in insomnia, insomnia individuals also seem to do worse on recall than on recognition tests. The evidence for impairment in non-verbal (visual) memory is less clear than the evidence for verbal memory problems and warrants further investigation. Studies reviewed here tend not to show any impairments in performance on non-verbal tests for individuals with sleep disorders, however it is possible that the difference between impairments in verbal and non-verbal recall is the greater emphasis on attentional processes in verbal tasks such as list recall.

Reasoning, decision making and emotional processing

Reasoning refers to logical thinking and judgement making [101] and can be measured with tests such as the WAIS matrix reasoning and picture arrangement, the Ravens Progressive Matrices and Colored Progressive Matrices. In the Raven's test, participants need to choose visual design items from a set of distractors that logically fit in a given visual set. Reasoning is rarely included in reviews and meta-analysis since it is seldom included in studies on cognition in sleep disorders. According to Fulda and Schulz [12] no conclusion can be drawn regarding reasoning in SRBD due to scarce evidence. In a study by Sivertsen et al [84], no differences were found in performance on matrix reasoning when comparing insomnia individuals with controls. Also, no differences have been found in OSA individuals on the Ravens test compared with controls [21,70]. Pearson et al. [85] found no differences in performance on Colored Progressive Matrices when comparing RLS with controls.

Studies on sleep deprivation have found clear evidence that depriving individuals of sleep impairs decision making under uncertainty [109,110]. Although generally not included in meta-analysis and reviews, decision making in relation to sleep disorders has been studied quite extensively. The

tasks used to assess decision making, include, the Iowa gambling task (IGT), Game of Dice Task (GDT), Balloon Analog Risk Task (BART) and the Bead task.

In the IGT, the individual´s ability to learn from the consequences of the card selected and adapt his or her decision-making strategies accordingly is evaluated [111]. Cards are presented on a computer screen, half of them are advantageous (smaller rewards and smaller losses) and half are disadvantageous (large rewards but also occasional large losses). Most participants learn that, in the long run, choosing the advantageous cards is beneficial. Killgore et al., [109] found that following 49.5 hours of sleep deprivation participants became less sensitive to the benefits of the advantageous cards against the greater cost of the less frequent but larger penalties of the disadvantageous cards. In Chunhua et al [112] insomnia individuals showed less sensitivity to the risky cards in the IGT compared to a control group. Their results showed that for the first round of card playing there was no difference between those with insomnia and the control group. However, after the first round of card playing the insomnia individuals selected significantly fewer cards from the advantageous card deck compared to healthy control, suggesting that they had a harder time learning from the consequences of their card selection.

Examining untreated individuals with OSA, Delazer et al [94] found no difference between OSA and a healthy control group when looking at the performance on IGT. The OSA patients showed an average performance on IGT where they learned from the consequences of their card selection and over time selected more the advantageous cards over the disadvantageous cards as did the healthy control group. Interestingly however, when looking at the performance of the individuals, more individuals in the OSA group (13%) showed impaired performance (choosing the risky cards) compared to the healthy control group. Daurat et al [113] found that OSA individuals tended to select the risky decks significantly more frequently than a normal control group. McNally et al, [114] found a decreased learning effect during IGT for individuals with a higher risk of SRBD compared with lower risk individuals and healthy controls. To evaluate decision making abilities in subjects with RLS, Bayard et al [115,116] used both the IGT and GDT. GDT is a task where subjects are asked to maximize their income through a series of dice throws choosing between single numbers or combination for each throw. Both studies [115,116] showed reduced performances in RLS individuals for IGT (showing a more risk oriented decisions) but not for GDT (where probabilities are calculable).

In BART participants are requested to inflate a digital balloon or collect a reward. After each inflate the amount the participant gains in a reward increases and can be lost if the balloon explodes [117]. Higher scores show a greater risk-taking propensity [118]. Heinrich et al [119] investigated the effect of induced hypoxia and poor sleep quality due to high altitude, showing that subjects become less risk oriented on BART after three days at high altitude. However, Demos et al [120] found no difference in performance on BART for partial sleep deprivation. Several studies using the bead task have shown impaired decision making in patients with RLS (e.g. [121,122]). In the beads task participants are shown two cups of coloured beads, one with mainly blue beads and another with mainly green beads. They are then asked to estimate from which cup a bead is drawn (the participant can wait a certain number of draws before giving an answer, so that the best strategy is to wait as much as possible instead of just "jump to the conclusion"), they were also informed about the "cost" in dollars for an incorrect choice of urn. The percentage of colors can vary between tasks (e.g. 60/40 or 80/20) and before any draw the participant is informed about the distribution in percentage of beads in the two urns [123,124]. In the study from Heim et al., [121] RLS individuals tended to jump to conclusion more than the control group. Similar results can be found in a previous study [122] where RLS individuals showed a more impulsive behaviour on the bead task than a control group, asking for fewer trials and giving answers with less information. Similar results were found in a recent study [125] where more impulsive behaviour was found in RLS individuals (with augmentation and augmentation + impulse control disorder) than healthy controls.

McNally et al, [114] suggest that the IGT could be a sensitive task (in sleep pathology) due to the double valence of the task, both in decision making and also in emotional functioning. In fact, studies have found impaired emotional processing with sleep deprived individuals rating neutral stimuli more negatively compared with rested individuals [126,127] and also demonstrating increased emotional sensitivity and decreased emotional empathy [112,128]. Heinrich et al [119] found that induced hypoxia and poor sleep cause impaired emotions recognition (better recognition of positive emotion at sea level and higher identification of neutral and sad expression at high altitude). But almost no work has been done on examining emotional processing in sleep disorders (although see [46], who found that OSA individuals rated their self perceived mood more negatively than controls). Chunchua et al [112], found no difference between insomnia individuals and control in evaluating emotional pictures, however, on a delayed recognition task the insomnia

individuals did worse in general but tended to remember better negative than positive and neutral pictures. De Almondes et al [91] found that insomnia individuals had impaired recognition of facial expression of sadness and fear compared with healthy controls. Furthermore, the impoverished emotional judgement was associated with poor performance on cognitive tests measuring inhibitory control, and cognitive flexibility.

In sum, there is no indication of impaired reasoning abilities in sleep disorders but more work is needed due to insufficient empirical work. However, decision making is impaired in individuals with OSA, insomnia and RLS. Studies show that individuals with various sleep disorders tend to make more risky choices and do not learn from negative consequences. Accordingly, there is also indication that emotional processing may be impaired in these individuals, with studies showing that sleep disruption can lead to a bias towards negative emotional stimuli and impaired emotional judgement.

SUMMARY AND FUTURE DIRECTIONS

As summarized above, numerous studies have established that various sleep disorders can entail cognitive difficulties which present as objectively measurable problems (e.g., [13,129]) but also as subjective complaints [130,13]. Using neurocognitive measures as objective daytime assessment of sleep disorders can therefore be an important tool in addition to traditional sleep measures. Cognitive measures can be useful to monitor patients‘ progress or decline [131], predict compliance [132] as well as providing patients with information about their cognitive status and validating their cognitive complaints.

All the sleep disorders considered in the current review, OSA and other SRBD, RLS, insomnia and SSL have been found to result in cognitive problems, at various levels of the cognitive system. According to meta-analyses the cognitive factors most often affected are attention, executive functions and memory (e.g., [129]). Cognitive components that are not commonly reported are language and visuoconstructional abilities. However, it should be kept in mind that it is hard to reach firm conclusions given the lack of standard practices in neurocognitive testing. As pointed out by Aloia et al [132], study results are determined by which areas of cognition are assessed and which are left out. Some areas, for example visuconstructional abilities, non-verbal memory and basic perceptual functions, are relatively seldom explored and thus knowledge on how these areas are affected by sleep disorders is

incomplete. Thus, domains that are reported to be affected, depend on the choice of tests in each particular study.

More than twenty years ago Décary, Rouleau and Montplaisir [133] proposed a neuropsychological test battery to be used in sleep apnea research. However, no particular combination of cognitive test is currently favored in sleep disorder research. Rather, a variety of tests have been used, both standardized clinical tests (e.g., Trail Making Test) as well as tests that have traditionally mostly been used in more basic cognitive research (e.g., the Brown-Peterson paradigm). Further, there has not been a systematic review of how to map cognitive tests onto domains of cognition and the concept of cognitive domain has been used rather inconsistently, which certainly is not unique to the sleep disorder field. The concept of cognitive domain has thus been used for a single component of a larger domain such as in Leng et al. [4] where delayed memory is used as a measure of the memory domain and in [13] where there are two separate working memory components (retention and manipulation). In other studies the cognitive domains are broader and even include components or tests that elsewhere are allotted to two different domains.

The lack of a standard cognitive battery for use in sleep research was discussed by Bucks et al [129] who made several recommendations. They pointed out, for example, the importance of taking into account the expertise required to administer and interpret cognitive tests and the population of interest (e.g., gender, age). However, they did not make specific recommendations regarding particular tests and how various domains should preferably be assessed.

How might then the ideal cognitive battery for sleep disorders look? First, one could consider separate batteries for clinical and research use. Research usually requires tests that take less time and that can potentially be administered online, even self-administrated [134]. Further, tests that have alternate versions for repeat testing could also be advantageous. However, this also applies to clinical testing. Research tests should also, to the extent possible, stress a single cognitive domain, as there will not be room for clinical interpretation of affected domains and perhaps not the required clinical expertise [129]. In clinical context the emphasis may be different as clinical interpretation comes into play.

Another important dimension to consider when chosing tests is age. Similar test batteries may not be appropriate for all ages. In some sleep studies the MMSE or the 3MS have been used as a measure of global cognitive function [4]. These tests lack sensitivity in young and otherwise

healthy populations but may be relevant in older populations where general cognitive decline or impending dementia are suspected. The impact general physical health or disease burden can have on cognitive functioning [135] is also particularly relevant in older patients in which case distentangling the cognitive impact of sleep disorders and other health issues might prove difficult when disease burden is not controlled for. Also, a long standing sleep disorder is a risk factor for dementia [136] which further complicates the picture in the elderly.

We propose that when testing possible cognitive impairments among patients with sleep-disorders it is important to cover cognitive factors at all level of the cognitive system. As sleep disorders are likely to have diffuse cognitive effects most, if not all, cognitive domains should be addressed to some degree and more than one test should be used for each domain as most tests are not pure measures of a single cognitive factor. We fully acknowledge that the various cognitive domains are not fully independent and that there is not a complete consensus on how to classify cognitive abilities into domains [7]. Also, groupings of tests into cognitive domains may depend on whether the groupings are done theoretically or by using factor analysis on a large battery of tests. Furthermore the factor structure may also depend on the populations studied (i.e., healthy vs. patient populations) (e.g., [137]). It is important to be cognizant of this issue and be able to address it, for example in justifying choice of tests and in conceptualizing and interpreting results.

Based on our review and having taken the various levels of cognition and cognitive domains into consideration, tests that are appropriate for sleep disorder research have been listed in Table 1 along with the domain they belong to.

Table 1 inserted here

The list in Table 1 is not the ultimate and final list of tests to be used in sleep research. Rather it is presented as a framework and a way to think about cognitive testing in sleep research. Thus, as shown, we present two very different motor tests that assess basic stimulus-reaction times and dexterity that is also speed-related. Also, the cognitive hierarchy is the basis for choosing the test while it should not be forgotten that the domains intersect. Given the usual time constraints in research it is unlikely that it is possible to administer all tests in every study. However, we believe that with 90 minutes of testing sampling from all domains can be done.

Given the amount of useful information that can be obtained with cognitive testing this is time well spent.

Many of the tests listed in Table 1 exist as a part of well developed psychological tests such as the Wechsler Intelligence Scales (e.g., DSST and Matrix Reasoning) [138]. Others are well recognized neuropsychological test that have been used for decades in the clinic as well as in research (e.g., RAVLT, ROCF and Purdue Pegboard Test) [101]. Others are non-clinical tests (e.g., reaction times, semantic priming and ICB paradigm) or both non-clinical and experimental, such as the Iowa Gambling task. All the tests listed have an extensive literature behind them and are known to be valid and sensitive and the clinical tests have extensive normative literature [101]. Also, many of the tests that are generally used as paper-and pencil tests have been digitized or can be digitized and run on computers. Further, some of the tests are appropriate for repeat testing and have minimal practice effects (e.g., PVT) [139] although practice effects when testing cognition should always be kept in mind as they have even been found with simple reaction time tests [140].

Neurocognitive testing is a complex procedure and goes beyond pure testing. When planning a cognitive test battery it is important to be aware of the many cognitive processes required for solving what, on the face of it, appears to be a simple cognitive task. This will result in a more balanced test battery which in turn should ease the interpretation of results. In the best of worlds a standardized neurocognitive battery, used across a variety of sleep disorders and in multiple centers across the world would be ideal. This approach would facilitate comparisons of studies, across disorders and different populations. A standardized battery has been suggested before [133] but it did not reach the sleep research community as a whole. Perhaps the time is now ripe and we call for a consensus on the use of cognitive measures in sleep research.

Tables.

Table 1

Suggested tests for sleep research and their corresponding cognitive domains based on theoretical groupings

Domain	Test *	Cognitive Processes**
Motor skills	Simple reaction time	Motor speed/reaction time
	Purdue Pegboard Test	Manual dexterity and coordination/speed
Perceptual skills	Line orientation	Visuoperceptual ability, visual matching. spatial relations
	The Benton Visual Form Discrimination test (VFD)	Visual discrimination
Processing speed	Symbol Search (SS)	Processing speed /psychomotor speed/visual scanning
	Digit Symbol Coding (DSST)	Processing speed and many others (e.g., short-term visual memory, implicit learning, psychomotor speed, visual scanning)
	Inspection time (IT)	Non-motor cognitive speed, perceptual speed, selective attention
Vigilance/sustained attention	Psychomotor vigilance test (PVT)	Sustained attention, reaction time
	Choice reaction time	Vigilance /motor speed/reaction time/decision making
Selective attention	Cancellation task (e.g., Bell test)	Selective attention, scanning, motor speed
	Induced Change Blindness (ICB)	Selective attention, reaction times
Executive functioning	Corsi blocks/PASAT	Maintenance and processing of information in working memory
	Stroop test	Inhibition/attentional control
	Task switching paradigm	Flexibility /set shifting
Visuoconstruction	Copy of Rey-Osterrieth Complex Figure	Visuoconstructive abilities, planning/executive function, motor speed
Episodic memory	Word list learning (e.g.,Rey Auditory Verbal Learning (RAVLT))	Verbal memory (learning, immediate and delayed retrieval)

	Rey-Osterrieth Complex Figure - recall	Non-verbal memory (learning, immediate and delayed retrieval)
Language	Naming tests (e.g., Boston naming)	Semantic retrieval
	Category verbal fluency	Lexical access speed /cognitive speed
	Semantic priming	Semantic memory integrity /motor speed
Reasoning / Decision making	Matrix reasoning (e.g., from WAIS-III test).	Visual /perceptual reasoning /attention and concentration
	Iowa gambling task	Evaluating choices based on consequences/evaluating risks/decision making under uncertainity
Global cognition	Addenbrooke test, MOCA (older populations) WASI (for younger populations)	Nonspecific – taps into various cognitive factors

*Note that in some cases there are several comparable tests available

** These are not complete, but major components are indicated

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