Objective Measures of Cognitive Performance in Sleep Disorder Research

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KEYWORDS

• Sleep disorders • Neurocognitive testing • Cognitive domain • Cognition • Cognitive test battery

KEY POINTS

- Neurocognitive tests can provide an important addition to more traditional noncognitive sleep disorder measures.
- The use of neurocognitive testing in the field needs to be based on standardized practices and theory to conclude on and compare findings.
- We offer an extensive overview of empirical findings organized around neurocognitive tests and different cognitive domains.
- 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 and 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[2–4] 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 assessments 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 the various sleep disorders. An effective use of neurocognitive assessment must be based on standardized practices and have a firm theoretic basis.

The purpose of this review was 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 to clarify how different cognitive domains and processes are affected by sleep disorders and also how sensitive a particular test is for detecting impairments owing to sleep disruption. We conclude by suggesting neurocognitive tests for future research, classified by domain and the main cognitive processes involved.

The cognitive domains taken into consideration in the present review are motor skills, perceptual skills, processing speed, vigilance/sustained

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attention, selective attention, episodic memory (verbal/nonverbal), executive function (including working memory), 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), sleep-related breathing disorders (SRBD), insomnia and restless leg syndrome (RLS). Only studies completed between 2000 and the present date and based on comparing individuals with specific 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 the 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 a decreased ability to detect high-frequency sounds,[9] both an indication of impaired function of the perceptual system. Tests assessing perceptual skills however, are generally based on the detection of a stimulus and its orientation and location in space.[10] Such tests include the Visual Organization Test and the Judgment of Line Orientation. In a review by Fulda and Schulz,[11] no differences were found in perceptual skills between SRBD and normal controls, evaluated on tests such as Visual Organization Test, Thurstone Visual Matching Test, Judgment of Line Orientation, and the Physical Match and Sensory Motor task. In a recent meta-analysis, perceptual skills were found to be mildly affected by insomnia when assessed with tasks such as the Perceptual Reasoning Index and the Critical Flicker Fusion.[12]

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[13,14] or sleep deprivation[15] 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 (eg, Kilgore[15]). More work is needed in the field to conclude on the impact sleep disorders may have on perceptual skills. Future studies should clearly distinguish between tasks measuring the function of a perceptual system (sensation) and the perceptual processing of sensory stimuli (perceptual skills).

Motor Skills

Motor skills refer to motor coordination, dexterity and speed.[16] A wide variety of tests have been used to examine motor skills, also referred to as psychomotor function in sleep disorder research (eg, Devita et al[17] and Kilpinen et al[18]). These assessments include tests measuring fine motor coordination and motor speed such as the Mirror Tracing Task, Line Tracing, Rotary Pursuit Test, Finger Tapping Test, the Motor Sequence Learning Task, the Grooved Pegboard, the Purdue Pegboard Test, as well as various simple reaction time tests. Other tests perhaps more suited to assess attention and/or vigilance have also been used as an assessment of motor skills or information processing speed in the field. Note that the Psychomotor Vigilance Test (PVT) measures primarily vigilance and should not be used as an assessment of motor skills.

Ferini-Strambi and colleagues[19] found significantly slower reaction times for individuals with OSA compared with controls on a simple reaction time test. Devita and colleagues[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 significantly slower reaction times for the motor component in various different reaction time tests compared with normal controls. Khassawneh and colleagues[20] found no significant difference in performance on a simple reaction time test when comparing individuals with insomnia to a control group.

Studies have found impairments in motor speed, coordination, and dexterity for individuals with OSA compared with normal controls using the Purdue Pegboard Test.[19,21] Accordingly, in a review by Fulda and Schulz[11] and Aloia and colleagues,[22] a significantly impaired performance was found on the Purdue Pegboard Test for both individuals with SRBD and individuals with OSA compared with control groups. No impairment, however, was reported for individuals with insomnia on this task.[11,23] Furthermore, no impairment was reported in individuals with various sleep disorders for Finger Tapping Test, Grooved Pegboard, Sensory Motor Task, and Line Tracing Task in 2 reviews.[11,24] Rouleau and colleagues[24]

found no difference between individuals with OSA and a normal control group using the Rotary Pursuit Task and the Mirror Tracing Task, although more individuals in the OSA group seemed to have problems during the initial acquisition state of the latter task. Mathieu and colleagues[25] found that age rather than OSA explained differences in performance on the Mirror Tracing Task when comparing younger and older individuals with OSA. However, Neu and colleagues[26] found that individuals with OSA performed significantly worse on Finger Tapping compared with individuals with chronic fatigue syndrome. Similarly, Landry and colleagues[27] found that individuals with OSA demonstrated less learning on Finger Tapping compared with controls after an overnight sleep.

In sum, motor skills as assessed with simple reaction time tests, Finger Tapping, and the Purdue Pegboard, are impaired in individuals with OSA. There is, however, little evidence of impaired motors skills in individuals with insomnia, or in sleep disorders in general for various other motor skills tasks listed elsewhere in this article. 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 tasks measuring executive function or selective attention. Both the Finger Tapping Test and the Purdue Pegboard Test are validated and reliable measures of motor skills.[16] These tests have been suggested as tools for evaluating professionals where coordination, motor speed, and dexterity is important.[28] For example, Ayalon and Friedman[29] found that shift work in resident doctors affected their performance on the Purdue Pegboard Test. Future studies should consider using the Finger Tapping Test, the Purdue Pegboard Test, or some variations of simple reaction time tests when evaluating the impact sleep disorders may have on motor skills.

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, and connecting numbers/letters in a sequence (Trail Making Tests A), where participants must complete the task as fast as possible.[16] Several studies have shown that individuals with OSA perform worse on the Digit Symbol Substitution Test compared with controls.[24,30–32] A comprehensive review by Kilpinen and colleagues[18] on the impact of OSA on information processing speed measured with tasks such as the Trail Making Test A and the Digit Symbol Substitution, along with motor control and pursuit tasks, showed a general slowing of information processing speed and psychomotor functions for individuals with OSA compared with control groups. Other studies, however, have found no difference between individuals with OSA and controls for the Trail Making Test A[32] and the Digit Symbol Substitution.[33,34] In the study by Saunamäki and colleagues[33] and Twigg and colleagues,[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 the Digit Symbol Substitution or the Trail Making Test A when comparing individuals with insomnia (medicated and not) with a control group.[23]

In sum, the studies reviewed in this article are almost entirely focused on OSA and processing speed. In general, there is some indication that processing speed, in particular as measured with the Digit Symbol Substitution, is affected by OSA, but there is insufficient empirical evidence to conclude on other sleep disorders. However, studies have shown that depriving normal individuals of sleep does impair their performance on Digit Symbol Substitution.[35] Furthermore, given 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 (eg, the Digit Symbol Substitution Test and the Trail Making Test A) and therefore it is important to use alternative tasks of processing speed that are nonmotor, such as inspection time.[37]

Vigilance and 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 toward 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 toward 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 (eg, Olaithe and Bucks[39] and Gagnon

et al[40]). Decreased 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 PVT, Continuous Performance Test, Choice Reaction Time Test, and Four Choice Reaction Time Test. Several studies have found impaired performance on the PVT test for individuals with OSA compared with control groups.[43–45] However, Djonlagi and colleagues[46] had different results, with OSA showing no impairment in performance on PVT compared with a control group. Both Li and colleagues[45] and Batool-Anwar and colleagues[43] found that worse performance on the PVT (more lapses and higher reaction times) for individuals with OSA correlated with increased subjective daytime sleepiness as measured with the Epworth Sleepiness Scale. Sforza and colleagues[47] found that errors (lapses and omissions) correlated significantly with both the apnea–hypopnea index and daytime sleepiness in individuals with SRBD. Lee and colleagues[6] found that performance on PVT (lapses and mean reaction times) correlated with quality-of-life measures, in particular, the physical domain for individuals with OSA. This finding was true even after controlling for body mass index, age, apnea severity, and depression. Mathieu and colleagues[25] examining younger and older participants and comparing OSA with a control group, found that individuals with OSA had longer reaction times on Four Choice Reaction Time Test and more lapses compared with controls. For the younger participants with OSA, increased time spent with oxygen saturation of less than 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 the severity of insomnia for older individuals (>65 years). Hansen and colleagues[49] found that PVT differentiated between individuals with sleep-onset insomnia and a control group during a total sleep deprivation period of 39 hours. With an increased number of hours during the sleep deprivation, vigilance as measured with lapses, response errors, and mean reaction time on PVT decreased significantly more for the insomnia group compared with controls. The exaggerated impact of sleep deprivation on individuals with insomnia was found both for the 10-minute version of the PVT and for a 3-minute version. Altena and colleagues[50] used a variation of the PVT, where participants responded to asterisks appearing on a computer screen at random time intervals (the simple vigilance task) and to a target letter (d) ignoring distractors (p) appearing also randomly (complex version). Their results showed that individuals with insomnia did not make more errors, but showed impaired response speed in the complex version compared with a control group, although no difference was found between the two groups in the simple version. Other studies have not found any impairment in performance for individuals with insomnia on Choice Reaction Time Test/Four Choice Reaction Time Test,[20,23] Continuous Performance Test,[51] alertness as measured with the Attention Network Test[52] and on an auditory PVT, both simple and complex.[53]

In sum, there is strong empirical evidence for impaired vigilance and 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 or nonrestorative sleep on vigilance.[54] In addition, research has shown that the short (3-minute) version of the PVT is comparable with the longer 10-minute version in detecting the possible impact of lack of sleep on vigilance.[55,56] The short 3-minute version of the PVT may be ideal for testing elderly and vulnerable patient populations and for repeated testing.

SELECTIVE ATTENTION

Several reviews and meta-analyses have concluded that selective attention is significantly affected by sleep disorders.[22,38,39] 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 by Strauss and colleagues,[16] 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, the Posner paradigm, and the Induced Change Blindness task. In all these tests, participants are required to detect an item, object, or area in space, often located among distractors.

Giora and colleagues[13] used a Visual Search task when comparing individuals with OSA to a control group. Participants looked for a target letter (T) appearing among distractors (L, X, O) that varied in number. Their results showed a slower reaction time for individuals with OSA compared

with a control group, although search accuracy did not differ between the groups. Similarly, in Giora and colleagues,[14] individuals with insomnia did not differ from a control group in terms of search accuracy on the Visual Search task, but had significantly longer reaction times. Using the Posner paradigm, Woods and colleagues[57] found a significant difference in performance between participants with insomnia and normal sleepers. In their study, the participants with insomnia had a delayed reaction time on invalid trials of the task (ie, the target is not presented at the same side of a computer screen as the cue). Both Jones and colleagues[58] and Marchetti and colleagues[59] using the Induced Change Blindness, found selective attention impairments in patients with insomnia. In the Induced Change Blindness paradigm, a set of flickers is presented to the participant who then has to detect a change, either neutral (a neutral item missing from a picture) or sleep related (eg, a slipper missing from a picture), between the two flickers. In the study done by Marchetti and colleagues,[59] participants with insomnia had a clear bias in their selective attention by being significantly quicker to detect a change related to sleep, but significantly slower to detect a neutral change compared with a control group. Jones and colleagues[58] showed similar results, with individuals with insomnia being quicker to detect a sleep-related change but slower to detect a neutral change compared with normal controls. Although, Rouleau and colleagues[24] found a significant impairment in performance on a cancellation task for individuals with OSA compared with controls, Ferini-Strambi and colleagues[19] found no differences in performance on a cancellation task when comparing OSA to a healthy control group. Khassawneh and colleagues[20] used the Big Circle–Little Circle task to measure selective attention. In this task, participants respond to 1 of 2 circles, responding first to the smaller circle and then to the larger one. No difference was found in performance between individuals with insomnia and a control group.

In sum, very few studies have actually examined selective attention in relation to sleep disorders. In fact, many studies claiming to assess attention are rather assessing attentional control and/or vigilance. Using the Induced Change Blindness task, 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 individuals with insomnia 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 Visual Search are rarely used to assess selective attention, although Wermes and colleagues[60] concluded that reaction times in Visual Search is a reliable measure of selective attention. Future studies should use some of the tasks reviewed in this section when studying the impact that sleep disorders may have on selective attention, avoiding the potential confound with vigilance and executive control. The benefit of the Induce Blindness paradigm is that the task does not confound target detection with motor control.

Executive Function and 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 untimely or inappropriate responses.[61–63] It is currently widely accepted that executive functions include three main domains: (1) maintenance of information in working memory and updating of that information, (2) inhibitory control (including the control of attention), and (3) 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 Ballesio et al[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 domains, 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 with impairment in working memory, inhibitory control, and cognitive flexibility.[65] In a meta-analysis by Fortier-Brochue and associates,[66] insomnia had a significant impact on the working memory part of executive function (eg, maintaining, updating and manipulating information) while inhibitory control and cognitive flexibility were less affected.

Working memory

Recognized working memory tasks that have been used in sleep disorder research include, the Backward Digit Span,[67] the Corsi Block Test, and the N-back Test.[68] Both the Backward Digit Span and the Corsi Block Test are among the most frequently used tests 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.[69]

Torelli and colleagues[70] found that individuals with OSA performed significantly worse on the Backward Digit Span than controls. Other studies, however, do not show an impaired performance on the Backward Digit Span when comparing individuals with OSA with a control group.[19,25,32,33,71] In the study by Torelli and colleagues,[70] only 16 individuals with OSA participated and most of them (n = 12) had severe OSA. Ferini-Strambi and colleagues[19] found no difference in performance on the Corsi Block Test and Canessa and colleagues[72] found no difference on the N-back Test when comparing individuals with OSA with control groups. Thomas and colleagues,[73] however, testing young individuals with OSA compared with controls, found that individuals with OSA had slower performance speed and less accuracy in the N-back Test. Using a comprehensive selection of working memory tests, Naëgelé and colleagues[74] found that individuals with OSA were not impaired on short-term span measures or dual task measures. They did, however, find a significantly impaired performance for individuals with OSA on the Paced Auditory Serial Addition Test, which is a highly speeded task, and on a modified Auditory Span task, where participants have to maintain a list of numbers as well as perform simple arithmetic transformation on the numbers.

In contrast with studies on OSA, studies on individuals with insomnia show a marked impairment in working memory. Both Haimov and colleagues[75] and Vignola and colleagues[23] found that performance on the Backward Digit Span was significantly impaired for individuals with insomnia. Similarly, Cellini and colleagues[76] found that young individuals with insomnia had a higher number of errors and less total accuracy on N-back compared with controls. Shekleton and colleagues[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 compared with controls. Lovato and colleagues[77] found no significant difference between older individuals with insomnia and controls on the Double Span Memory task when controlling for IQ.

Inhibitory control

Accepted neurocognitive tasks for measuring inhibitory control that are also used frequently in the field of sleep disorder research include the Stroop Test (also the Color–Word Interference Test), 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 (eg, letters) as fast as possible but refrain from responding to a particular stimulus or when a cue is given at random intervals. Outcome measures include accuracy and reaction time as well as stop signal reaction time.

Individuals with OSA have been shown to have impaired performance on the Stroop Test (increased error, not time) and the Flanker Test.[19,71,82] In a Canadian longitudinal study on aging with a large cohort, individuals with insomnia disorders (>45 years of age, n = 1068) did worse on the Stroop Test than those with no insomnia (n = 19,604) and insomnia symptoms only (n = 7813) after controlling for age, education, and sex.[83] Similarly, 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] Other studies have not found a significant difference in performance on the Stroop Test for insomnia[84] or RLS.[85]

Covassin and colleagues[86] compared eight individuals with insomnia with 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 and colleagues[87] found no difference in performance for individuals with insomnia and Angelelli and colleagues[89] found no difference in performance for individuals with OSA compared with a control group on the Go/No Go task. Mean age of participants was similar between the studies, but both Zhao and colleagues[88] and Covassin and colleagues[86] had very few participants (n < 15).

Cognitive flexibility (switching)

Recognized tests used to measure cognitive flexibility and also used in sleep disorder research include the Wisconsin Card Sorting Test, Trail Making Test B, and various attentional switching tasks such as the Task Switching Paradigm and the Switching to Attention Test. Werli and colleagues[71] found a significant difference between individuals with OSA and controls on both categories and perseverative errors on the Wisconsin

Card Sorting Test (see also Rouleau et al[24]). Other studies have, however, not found a difference on the Wisconsin Card Sorting Test when comparing individuals with OSA with healthy control groups.[25,90] de Almondes and colleagues[91] found no difference between individuals with insomnia and controls on the test (see also Vignola et al[23]). Similarly, no differences were found by Fang and colleagues[92] on the Wisconsin Card Sorting Test when comparing individuals with insomnia and control participants despite objective measures showing a difference in total sleep time and less sleep efficiency for individuals with insomnia. Although Ju and colleagues[93] found that individuals with OSA were significantly slower to complete the Trail Making Test B compared with a healthy control group and made more errors, other studies have not found any performance impairments on Trail Making Test B for individuals with OSA.[19,25,32,71,94] Similarly, no performance impairment on Trail Making Test B has been found for insomnia[23,84] or individuals with RLS.[85,95]

In the switching tasks such as the Task Switching Paradigm and Switching to Attention Test, both attentional switching and response inhibition are evaluated.[96] Participants are required to switch between different tasks, for example, judging if a number is odd or even, and bigger or smaller than the number 5 in Task Switching Paradigm (eg, Sdoia and Ferlazzo[96] and Wilckens et al[97]) and switch between location and direction of arrows in Switching to Attention Test.[51] Which task the participant has to work on is indicated by a cue such as the shape of geometric figures (eg, Ballesio and colleagues[64] and Wilckens and colleagues[97]). Performing according to the same task rule results in a faster reaction times compared with when the participant switches from one task to another, this is referred to as switching cost.[96] In a study by Wilckens and colleagues,[97] older patients with insomnia were significantly worse in using a preparation time (time between cue and target) compared with a control group. Similarly, Shekleton and colleagues[53] found that patients with insomnia were significantly slower compared with controls to respond to the stimuli in the complex switching condition of the Switching to Attention Test (switching between location and direction). Interestingly, Shekleton and colleagues[53] found that only individuals with insomnia who reported short total sleep time (<6 hours) showed worse performance on the Switching to Attention Test compared with a control group but not those who reported longer total sleep time (>6 hours). Khassawneh and colleagues[20] found that individuals with insomnia and objectively measured short total sleep time (<6 hours) showed significantly higher response latency and errors on the Switching to Attention Test compared with a normal control group. However, Ballesio and colleagues[98] did not find impaired performance on Task Switching Paradigm after partial sleep deprivation (5 hours of sleep) for patients with chronic insomnia compared with controls.

Verbal Fluency tests and the Maze test 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 (phonemic fluency) or members of a particular category (semantic fluency) as they can for a given time period.[16,63,99] Both Ferini-Strambi and colleagues[19] and Salorio and colleagues[90] found a significantly impaired performance in individuals with OSA compared with controls for phonemic, but not semantic fluency. Werli and colleagues,[71] however, found that individuals with OSA did significantly worse on both semantic and phonemic fluency tests compared with controls. Other studies have not found any differences in phonemic fluency[24,70,74] or semantic fluency[70,93] for OSA compared with controls. Sivertsen and colleagues[84] found a significantly impaired performance for older individuals with insomnia on phonemic but not semantic fluency test. Pearson and colleagues[85] compared 16 individuals diagnosed with RLS with a matched control group and found that individuals with RLS had a significantly impaired performance on a semantic fluency test compared with controls. Other studies have not found any differences for Verbal Fluency for RLS.[95] Impaired performance on the Maze Test has been reported for individuals with OSA,[24] but not for individuals with RLS.[85]

In sum, various reviews and meta-analyses 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 chosen carefully 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 than for insomnia. Individuals with insomnia show impaired performance on all working memory tasks. However, most studies on working memory and OSA show no performance impairment in particular those studies using the

Backward Digit Span. In a comprehensive study by Naëgelé and colleagues,[74] OSA seemed to have little impact on short-term span or dual task working memory measures, but greater impact on more fast paced complex working memory tasks such as the Paced Auditory Serial Addition Test and the Auditory Span task.

Inhibition and attentional control are impaired in individuals with OSA and individuals with 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 the Wisconsin Card Sorting Test and the Trail Making Test B show no clear differences in performance of individuals with OSA, individuals with insomnia, and individuals with RLS compared with control groups. Both the Wisconsin Card Sorting Test and the Trail Making Test 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 for OSA, insomnia, and RLS. Although studies vary in terms of the number of participants and age, no systematic differences were found in demographics between studies that could explain the difference in results.

Episodic Memory (Verbal and Nonverbal)

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.[11,40] Measures also include learning when participants, for example, go repeatedly through the same word list. A variety of verbal memory tests exists and have been used in the field of sleep disorder research. The Auditory Verbal Learning Test tests immediate and delayed recall of semantically unrelated words.[16] In Logical Memory (the Wechsler Memory Scale), participants need to store and retrieve information from a story and in both the California Verbal Learning Test and the Hopkins Verbal Learning Test, participants work with semantically related information.[101] There is also the Verbal Paired Associates Test.[101] Meta-analyses and reviews indicate impaired verbal memory in OSA[102] and insomnia.[12] In fact, Wallace and Bucks[102] concluded that all aspects of verbal memory are impaired in individuals with OSA, that is, immediate and delayed recall as well as recognition and learning. According to Fulda and Schultz,[11] there is little indication of memory impairment in insomnia and SRBD.

Naëgelé and colleagues[74] used 16-word word lists where participants had to identify the category of each word as they went through the list (individuals with OSA compared with controls). They then tested immediate recall before and after an interfering task and a cued recall (repeated 3 times). The participants also completed a recognition test and a delayed free recall test. In general, individuals with OSA performed on par with normal controls, except on immediate free recall after interference. The authors concluded that impaired memory in individuals with OSA is isolated to the retrieval process, not the encoding, learning, or retention parts of verbal memory. Using a word list and immediate and delayed recall, Ju and colleagues[93] also found that immediate and delayed free recall is impaired for older individuals with OSA compared with controls, but not recognition memory. Other studies using the Auditory Verbal Learning Test have also found that individuals with OSA perform worse than controls.[26,70,71,103,104] Werli and colleagues[71] found only a difference in the delayed free recall of the Auditory Verbal Learning Test, whereas Neu and colleagues[26] found a difference in both immediate and delayed free recall when comparing OSA with controls. Neither study found any difference in recognition. Other studies have, however, not found any performance difference on the Auditory Verbal Learning Test when comparing individuals with OSA with controls.[24,25,84,105] Using the California Verbal Learning Test, Salorio and colleagues[90] found a significantly impaired overall recall, but not in retention for OSA compared with a control group.

Adams and colleagues[106] found that SRBD correlated with performance on the California Verbal Learning Test. Similarly, Cross and colleagues[83] found a significantly worse performance on the Auditory Verbal Learning Test, both immediate and delayed recall, in a large population-based cohort comparing insomniacs with controls. However, Sivertsen and colleagues[84] found no difference in performance on California Verbal Learning Test for older insomniacs compared with controls. In a study by Guo and colleagues[3] comparing insomniacs with controls, participants read out loud a list of object-related words and were then tested immediately and after a 5 minute 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 groups on the delayed recognition test. Vignola and colleagues[23] found no differences in individuals with insomnia compared with controls on immediate and delayed memory on the verbal paired associates test.

Using the Logical Memory Test, Mathieu and colleagues[25] found a significant difference in both immediate and delayed recall for individuals with OSA compared with control for both younger and older individuals. Similarly, Twigg and colleagues[34] found that individuals with OSA had impaired immediate and delayed recall compared with normal controls, but their recognition memory and maintaining information over time was intact. Ferini-Strambi and colleagues,[19] however, with fewer participants (n = 23 vs 60) found no difference between individuals with OSA and controls on the Logical Memory Test.

Studies suggest that immediate and delayed recall in visual memory is impaired in individuals with OSA.[102] Tests used to assess nonverbal memory include the Rey-Osterrieth Complex Figure, the Brief Visuospatial Memory Test,[101] the Wechsler Memory Scale (Visual Reproduction, Figural Memory, Visuospatial Delayed Recall and Visual Memory Test),[107] and the Wechsler Adult Intelligence Scale-Revised (Block Design). In the Visual Memory Test, participants are asked to recognize a target picture among distractors after viewing it briefly. Torelli and colleagues[70] found no significant difference in individuals with OSA compared with controls on the Visual Memory Test. In the Rey-Osterrieth Complex Figure Test, participants are asked to copy a complex figure and then reproduce the same figure from memory twice (immediate and delayed memory). Some studies have found that both individuals with SRBD[104,106] and those with OSA[24,70] perform worse on the Rey-Osterrieth Complex Figure Test compared with normal controls. However, other studies have not found any significant differences in performance.[19,34,84] Daurat and colleagues[108] found that the recollection of temporal and spatial memories is impaired in patients with OSA using the Brief Visuospatial Memory Test Revised. In the Wechsler Memory Scale Visual Reproduction subtest,[107] participants are shown visual designs and later asked to draw the designs as they remember them (immediate and delayed recall). Vignola and colleagues[23] found no difference in performance here for individuals with insomnia compared with controls.

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, because their performance on recognition tests seems intact. Similarly, although less empirical evidence exists on verbal memory in insomnia, individuals with insomnia also seem to do worse on recall than on recognition tests. The evidence for impairment in nonverbal (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 nonverbal tests for individuals with sleep disorders; however, it is possible that the difference between impairments in verbal and nonverbal 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 judgment[101] and can be measured with tests such as the Wechsler Adult Intelligence Scale (eg, Matrix Reasoning and Picture Arrangement subtests), the Ravens Progressive Matrices, and Colored Progressive Matrices. Reasoning is rarely included in reviews and meta-analysis in the field because it is seldom included in studies on cognition in sleep disorders. According to Fulda and Schulz,[11] no conclusion can be drawn regarding reasoning in SRBD owing to scarce evidence. 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. Studies have reported no impairment in performance on the Raven's test for individuals with OSA compared with controls.[19,70] In a study by Sivertsen and colleagues,[84] no differences were found in performance on Matrix Reasoning when comparing individuals with insomnia with controls. Furthermore, Pearson and colleagues[85] found no differences in performance on the Colored Progressive Matrices when comparing RLS with controls.

Although generally not included in meta-analyses and reviews, decision-making in relation to sleep disorders has been studied quite extensively and sleep deprivation in normal individuals has been found to impair decision-making under uncertainty.[109,110] The tasks used to assess decision-making, include, the Iowa Gambling Test, Game of Dice Task, Balloon Analog Risk Task, and the Bead Task.

In the Iowa Gambling Test, 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; one-half of them are advantageous (smaller rewards and smaller losses) and one-half are disadvantageous

(large rewards but also occasional large losses). Most participants learn that, in the long run, choosing the advantageous cards is beneficial. Examining untreated individuals with OSA, Delazer and colleagues[94] found no difference between individuals with OSA and a healthy control group when looking at the performance on the Iowa Gambling Test. The individuals with OSA showed an average performance, 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 with the healthy control group. Daurat and colleagues[112] found that individuals with OSA tended to select the risky decks significantly more frequently than a normal control group. McNally and colleagues[113] found a decreased learning effect during the Iowa Gambling Test for individuals with a higher risk of SRBD compared with lower risk individuals and healthy controls. In Chunhua and colleagues,[114] individuals with insomnia showed less sensitivity to the risky cards in the Iowa Gambling Test compared with 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 individuals with insomnia selected significantly fewer cards from the advantageous card deck compared with healthy controls, suggesting that they had a harder time learning from the consequences of their card selection.

To evaluate decision-making abilities in subjects with RLS, Bayard and colleagues[115,116] used both the Iowa Gambling Test and the Game of Dice Task. In the Game of Dice Task, the participants 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 worse performances for individuals with RLS for the Iowa Gambling Test (showing a more risk-oriented decisions), but not for the Game of Dice Task (where probabilities are calculable).

On the Balloon Analog Risk Task, 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] There is some indication that poor sleep quality may cause individuals to become less risk oriented on the Balloon Analog Risk Task.[119] However, other studies have not found any impact of partial sleep loss on performance on the task.[120] Several studies using the Bead Task have shown impaired decision-making in patients with RLS (eg, Heim et al[121,122]). In the Beads Task, participants are shown two cups of colored 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, the best strategy is to wait as much as possible instead of just "jump to the conclusion"). Participants are also informed about the cost in dollars for an incorrect choice of urn. The percentage of colors can vary between tasks (eg, 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 and colleagues,[121] individuals with RLS tended to jump to conclusion more than the control group. Similar results can be found in a another study,[122] where individuals with RLS showed a more impulsive behavior 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 behavior was found in individuals with RLS (with augmentation and augmentation plus impulse control disorder) compared to healthy controls.

McNally and colleagues[113] suggest that the Iowa Gambling Test could be a sensitive task (in sleep pathology) owing 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.[114,128] Heinrich and colleagues[119] found that induced hypoxia and poor sleep cause impaired emotions recognition. Almost no work has been done on examining emotional processing in sleep disorders. However, in one study[46] individuals with OSA rated their self-perceived mood more negatively than controls. Chunhua and colleagues[114] found no difference between individuals with insomnia and control in evaluating emotional pictures; however, on a delayed recognition task the individuals with insomnia did worse in general but tended to remember better negative than positive and neutral pictures. de Almodes and colleagues[91] found that individuals with insomnia had impaired recognition of facial expression of sadness and fear compared with healthy controls. Furthermore, the impoverished emotional judgment 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 owing to insufficient empirical testing. 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 an indication that emotional processing may be impaired in these individuals, with studies showing that sleep disruption can lead to a bias toward negative emotional stimuli and impaired emotional judgment.

SUMMARY AND FUTURE DIRECTIONS

As summarized elsewhere in this article, numerous studies have established that various sleep disorders can entail cognitive difficulties that present as objectively measurable problems (eg, Wardle-Pinkston et al[12] and Bucks et al[129]), but also as subjective complaints.[12,130] 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 patient progress or decline[131] and 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—namely, OSA, SRBD, insomnia, and RLS—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 (vigilance), executive functions and memory (eg, Bucks et al[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 in the field. As pointed out by Aloia and colleagues,[132] study results are determined by which areas of cognition are assessed and which are left out. Some areas, for example, visuconstructional abilities, nonverbal 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 20 years ago, Décary and colleagues[133] proposed a neuropsychological test battery to be used in OSA 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 (eg, the Trail Making Test), as well as tests that have traditionally mostly been used in more basic cognitive research (eg, 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 and colleagues,[4] where delayed memory is used as a measure of the memory domain and in Wardle-Pinkston and associates,[12] where there are 2 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 2 different domains.

The lack of a standard cognitive battery for use in sleep research was discussed by Bucks and colleagues,[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 (eg, sex, age). However, they did not make specific recommendations regarding particular tests and how various domains should preferably be assessed.

How, then, might 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 notion also applies to clinical testing. Research tests should also, to the extent possible, stress a single cognitive domain, because there will not be room for clinical interpretation of affected domains and perhaps not the required clinical expertise.[129] In a clinical context, the emphasis may be different as clinical interpretation comes into play.

Another important dimension to consider when choosing tests is age. Similar test batteries may not be appropriate for all ages. In some sleep studies the Mini-Mental State Examination or the Modified Mini-Mental State 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

Table 1
Suggested tests for sleep research and their corresponding cognitive domains based on theoretic groupings

Domain	Test[a]	Cognitive Processes[b]
Motor skills	Simple reaction time[139]	Motor speed/reaction time
	Purdue Pegboard Test[101]	Manual dexterity and coordination/speed
Perceptual skills	Line orientation[101]	Visuoperceptual ability, visual matching. spatial relations
	The Benton Visual Form Discrimination test[101]	Visual discrimination
Processing speed	Symbol Search[140]	Processing speed/psychomotor speed/ visual scanning
	Digit Symbol Coding[140]	Processing speed and many others (eg, short-term visual memory, implicit learning, psychomotor speed, visual scanning)
	Inspection time[37]	Nonmotor cognitive speed, perceptual speed, selective attention
Vigilance/sustained attention	PVT[138]	Sustained attention, reaction time
	Choice reaction time[139]	Vigilance/motor speed/reaction time/ decision-making
Selective attention	Cancellation task (eg, Bell test)[101]	Selective attention, scanning, motor speed
	Induced Change Blindness[59]	Selective attention, reaction times
Executive functioning	Corsi blocks[101]/Paced Auditory Serial Addition Test [101]	Maintenance and processing of information in working memory
	Stroop test[101]	Inhibition/attentional control
	Task switching paradigm[97]	Flexibility/set shifting
Visuoconstruction	Copy of Rey-Osterrieth Complex Figure[101]	Visuoconstructive abilities, planning/ executive function, motor speed
Episodic memory	Word list learning (eg, Rey Auditory Verbal Learning)[101]	Verbal memory (learning, immediate and delayed retrieval)
	Rey-Osterrieth Complex Figure - recall[101]	Nonverbal memory (learning, immediate and delayed retrieval)
Language	Naming tests (eg, Boston naming)[101]	Semantic retrieval
	Category Verbal Fluency[101]	Lexical access speed/cognitive speed
	Semantic priming[141]	Semantic memory integrity/motor speed
Reasoning/decision-making	Matrix reasoning (eg, from WAIS-IV).[140]	Visual/perceptual reasoning/attention and concentration
	Iowa Gambling task[113]	Evaluating choices based on consequences/ evaluating risks/decision-making under uncertainty
Global cognition	Addenbrooke test,[142] Montreal Cognitive Assessment[143] (older populations)	Nonspecific – taps into various cognitive factors
	Wechsler Abbreviated Scale of Intelligence[144] (for younger populations)	

[a] Note that in some cases there are several comparable tests available.
[b] These are not complete, but major components are indicated.

health or disease burden can have on cognitive functioning[135] is also particularly relevant in older patients, in which case disentangling 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 levels of the cognitive system. Because 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, because 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 (ie, healthy vs patient populations) (eg, Siedlecki et al[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.

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. In addition, the cognitive hierarchy is the basis for choosing the test, although 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 (eg, Digit Symbol Substitution Test and Matrix Reasoning).[145] Others are well-recognized neuropsychological test that have been used for decades in the clinic as well as in research (eg, the Auditory Verbal Learning Test, Rey-Osterrieth Complex Figure, and Purdue Pegboard Test).[101] Others are nonclinical tests (eg, reaction times, semantic priming, and Induced Change Blindness) or both nonclinical and experimental, such as the Iowa Gambling Test. 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 (eg, the PVT),[39] although practice effects when testing cognition should always be kept in mind, because they have even been found with simple reaction time tests.[146]

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, seems to be a simple cognitive task. This practice 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.

CLINICS CARE POINTS

- When using cognitive tests in the clinic, using appropriate normative data, stratified by age and education, is critical.
- Keep in mind that tests such as the Mini-Mental Examination Test, Addenbrooke, and Montreal Cognitive Assessment are only screening tests.
- In the clinic, it is important to distinguish between testing (ie, cognitive screening) and detailed professional neuropsychological evaluation.
- A diagnosis of dementia cannot be based on cognitive assessment only and medical history and other relevant information needs to be integrated with psychological assessment.

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