Objective evaluation of excessive daytime sleepiness

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Comprehensive Review

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Abstract

Excessive daytime sleepiness (EDS) is multifactorial. It combines, among other things, an excessive propensity to fall asleep ("physiological sleepiness") and a continuous non-imperative sleepiness (or drowsiness/hypo-arousal) leading to difficulties remaining awake and maintaining sustained attention and vigilance over the long term ("manifest sleepiness"). There is no stand-alone biological measure of EDS. EDS measures can either capture the severity of physiological sleepiness, which corresponds to the propensity to fall asleep, or the severity of manifest sleepiness, which corresponds to behavioral consequences of sleepiness and reduced vigilance. Neuropsychological tests (The psychomotor vigilance task (PVT), Oxford Sleep Resistance Test (OSLeR), Sustained Attention to Response Task (SART)) explore manifest sleepiness through several sustained attention tests but the lack of normative values and standardized protocols make the results difficult to interpret and use in clinical practice. Neurophysiological tests explore the two main aspects of EDS, i.e. the propensity to fall asleep (Multiple sleep latency test, MSLT) and the capacity to remain awake (Maintenance of wakefulness test, MWT). The MSLT and the MWT are widely used in clinical practice. The MSLT is recognized as the "gold standard" test for measuring the severity of the propensity to fall asleep and it is a diagnostic criterion for narcolepsy. The MWT measures the ability to stay awake. The MWT is not a diagnostic test as it is recommended only to evaluate the evolution of EDS and efficacy of EDS treatment. Even if some efforts to standardize the protocols for administration of these tests have been ongoing, MSLT and MWT have numerous limitations: age effect, floor or ceiling effects, binding protocol, no normal or cutoff value (or determined in small samples), and no or low test-retest values in some pathologies. Moreover, the recommended electrophysiological set-up and the determination of sleep onset using the 30-sec epochs scoring rule show some limitations. New, more precise neurophysiological techniques should aim to detect very brief periods of physiological sleepiness and, in the future, the brain local phenomenon of sleepiness likely to underpin drowsiness, which could be called "physiological drowsiness".

Keywords: Drowsiness, Excessive daytime sleepiness, Manifest sleepiness, Neurophysiological tests, Neuropsychological tests, Physiological sleepiness.

Introduction

Sleepiness is a physiological and behavioral "need state" or "need for sleep". It plays a key role in the regulation of the sleep/wake cycle, especially in the triggering of sleep onset at an individual's usual bedtime or during sleep deprivation. Sleepiness facilitates the transition from wakefulness to sleep or hinders the transition from sleep to wakefulness. "Physiological sleepiness", a.k.a. sleep drive, results from an imbalance between processes involved in the regulation of sleep and wake states, which are detailed in Section 1 of this article. Physiological sleepiness is not only driven by the prior duration of wakefulness and the prior amount of sleep but also changes across the day according to a circadian rhythm. When physiological sleepiness is severe, irrepressible, and persistent, sleep intrusion increases during wakefulness or during socially inappropriate situations; this condition is called excessive daytime sleepiness (EDS). However, there is no consensus on the definition of EDS. The *International Classification of Sleep Disorders* (3rd edition) [92] defines EDS as the "inability to stay awake and alert during major waking episodes, resulting in periods of irrepressible need for sleep or unintended lapses into sleep". In a position paper from a panel of European experts, EDS is rather defined as the subjective perception of an irrepressible need to sleep [53]. The clinical manifestations include: 1) The presence of a feeling of daytime sleepiness throughout most of the day, 2) The inability to stay awake in monotonous situations with unintended napping and possibly sleep attacks, 3) the acquired need for scheduled napping during the day, 4) Difficulty with sustained attention and vigilance, 5) Automatic behaviors, i.e. behaviors that are performed without conscious knowledge or full voluntary control and which can be attributed to EDS. To conceptualize EDS, Lopez et al [59] proposed three dimensions of EDS: excessive propensity to fall asleep, continuous non-imperative sleepiness (or drowsiness), and automatic behaviors. In this paper we focus only on excessive propensity to fall asleep and continuous non-imperative sleepiness. Excessive propensity to fall asleep corresponds to increased intensity of physiological sleepiness and therefore an inability to stay awake characterized by several voluntary daytime naps and/or involuntary sleep attacks not preceded by the prodromal feeling of sleepiness. Continuous non-imperative sleepiness corresponds to a lasting inadequate level of arousal also called drowsiness or "hypo-arousal" as described by Peter-Derex et al. [67], characterized by difficulty remaining awake and maintaining sustained attention and vigilance (i.e. brain fog). EDS is one of the dimensions characterizing the central disorders of hypersomnolence [53,59,67], the other dimensions being the excessive need for sleep, and sleep inertia, which

are described in two other articles of this special issue in NCCN. Importantly, EDS is associated with functional impairments in daily functioning and increases the likelihood of a road or workplace accident, with potentially serious consequences.

Identifying and quantifying EDS is a public health challenge, as EDS might be a consequence a) of several behavioral factors either voluntary or imposed by socio-economic factors, leading to insufficient or disrupted sleep, as manifested by social jetlag and shift work disruption, and b) of sleep disorders including sleep apnea syndrome, circadian disorders, central hypersomnolence disorders like narcolepsy and Idiopathic Hypersomnia (IH), other medical or psychiatric disturbances, or medications.

Carskadon and Dement [20] proposed a practical model for organizing the measurement of sleepiness. Sleepiness was divided into three factors: physiological sleepiness, manifest sleepiness, and introspective sleepiness. Physiological sleepiness corresponds to the underlying physiological drive to sleep. The intensity of this sleep drive is expressed by the speed with which an individual falls asleep, evaluated with neurophysiological measures. Manifest sleepiness corresponds to behavioral consequences of sleepiness and reduced vigilance. The measures of manifest sleepiness are as follows: behavioral signs of sleepiness, inability to volitionally remain awake, and deficit in performance on tests evaluating sustained attention during psychomotor or cognitive tasks. Introspective sleepiness concerns an individual's subjective perception and self-assessment of their sleepiness or drowsiness.

In this article, we present the objective investigations of EDS by examining tests that measure the two main dimensions of EDS: physiological sleepiness and manifest sleepiness. We first describe the test assessing the intensity/severity of physiological sleepiness. This neurophysiological test measures the duration of the wake-to-sleep transition, i.e. sleep onset latency. Secondly, we describe tests that measure the intensity/severity of manifest sleepiness. These neurophysiological and neuropsychological tests explore the ability to remain awake and/or cognitive performance, especially sustained attention. These tests have been used extensively to measure EDS in research and clinical studies and some are of clinical interest because they can confirm diagnoses or functional repercussions. We review the development of these objective measures of EDS and present recording techniques, protocols, interpretations, limitations and updated recommendations for their clinical use based on the task force of experts mainly appointed by the American Academy of Sleep Medicine (AASM) [50].

Basics of physiological sleepiness [35]

Sleepiness is mainly controlled by two internal oscillators: the circadian and homeostatic oscillators [14]. The homeostatic oscillator triggers a homeostatic drive that corresponds to the physiological need for sleep, known as homeostatic sleep pressure, which increases gradually during wakefulness and dissipates rapidly during sleep. On the other hand, during the biological day, the circadian oscillator generates a drive for wakefulness whose intensity is maximal at the end of the day. This maximal circadian drive for wakefulness is termed the "wake maintenance zone" or "forbidden zone of sleep". Thereafter, the drive for wakefulness dissipates rapidly to make way for the drive for sleep, the latter reaches its maximum at the end of the night. When sleep drive dissipates, the propensity to wake up appears. Thus, during a normal day, the buildup of sleep pressure is counteracted, in the late afternoon, by the circadian drive for wakefulness, especially during the wake maintenance zone, which allows the period of wakefulness to be extended. After this specific zone, the combination of higher homeostatic drive and rapid dissipation of circadian drive for wakefulness leads to sleep onset. After sleep onset, the rapid dissipation of homeostatic drive is counteracted by the circadian drive for sleep in order to extend the sleep period. As a result, homoeostatic and circadian drive interact to facilitate consolidated wakefulness throughout the day and consolidated sleep throughout the night.

These two types of drive interact with orexinergic neurons, especially the circadian one. Upon awakening, circadian drive originating from the suprachiasmatic nucleus inhibits the ventrolateral preoptic nucleus (VLPO) GABAergic neurons and activates the production of orexin and wake-active monoaminergic neurons in the brainstem and hypothalamus throughout the day, which contributes to consolidating wakefulness during this period. In the evening, circadian drive decreases, and the strength of homeostatic drive is maximal. One hypothesis is that adenosine, considered as the "sleep factor", inhibits wake-promoting cholinergic neurons in the basal forebrain via A1 receptors and disinhibits the sleep-active VLPO via A2 receptors. The VLPO inhibits orexinergic neurons and therefore also inhibits the wake-active monoaminergic neurons, finally triggering sleep onset and stabilizing sleep episodes. At the end of the night, when the strength of homeostatic drive is the lowest, the circadian drive begins to inhibit VLPO and to activate orexinergic neurons, so that the waking state begins again. Importantly, several factors such as age, stress and motivation interact with these main homeostatic and circadian processes, to modulate sleep/wake states[16,30,31].

Circadian disruptions, due to shift work and social jetlag, can modify circadian drive and increase sleepiness. The same applies to sleep loss, which increases the homeostatic drive and thus daytime sleepiness. Any dysfunction in the orexin hypothalamic neuropeptide system (observed in narcolepsy type 1) will also induce EDS.

Neurophysiological investigations of sleepiness

Principles of polysomnography

Neurophysiological investigations are based on the detection of sleep (propensity to fall asleep) or wakefulness (ability to stay awake) in soporific conditions and throughout the day using the recording of physiological parameters. According to a consensus international definition of sleep onset, the gold standard tool to quantify it is polysomnography (PSG), i.e. simultaneous recording of the electroencephalogram (EEG), the electro-oculogram (EOG) and the electromyogram (EMG). The recording montage should include at least 3 EEG recording derivations with at least 1 each for the frontal (F3-M2 or F4-M1), central (C3-M2 or C4-M1), and occipital (O1-M2 or O2-M1) derivations (M is the reference electrode over the opposite mastoid), left and right eye EOGs, mental/submental EMG, and electrocardiogram (EKG). Other EEG montages like Fz-Cz (or Fpz-Cz), Cz-Oz (or C3-Oz or C4-Oz), C4-M1 (or C3-M2) are considered as alternative EEG montages, as described in the current version of the AASM Manual for the Scoring of Sleep and Associated Events [8]. The AASM Manual provides rules for scoring sleep onset and sleep stages. Sleep stages are scored in 30-second, sequential epochs starting at the start of the study.

Sleep onset is identified by the first 30s-epoch of any unequivocal sleep stage (stage N1, N2, N3 or REM). An epoch is scored as a sleep stage if the majority (more than 50%, i.e. more than 15 seconds) of the epoch meets the criteria for the sleep stage considered. As sleep onset is commonly characterized in most individuals by the sleep stage transition “Wake to stage N1 sleep”, the definition of stage N1 is very important. Stage N1 criteria depends on the capacity of individuals to generate alpha EEG rhythms. In individuals who generate an alpha rhythm, N1 stages starts when the background EEG rhythm (usually alpha frequency, because eyes are closed) is replaced by low-amplitude, mixed frequency activity (LMFA, usually theta frequency (4-8hz)) for more than half of the 30s epoch. Generally, the appearance of theta frequency is accompanied by slow eye movements (initial deflection lasting less than 500 milliseconds). In individuals who do not generate an alpha rhythm, stage N1 commences with the earliest of

ANY of the following phenomena: 1) EEG activity in the range of 4–7 Hz with slowing of background frequencies by ≥1 Hz from those of stage Wake, 2) Vertex sharp waves, or 3) Slow eye movements. An international consensus has defined sleep latency as the duration, expressed in minutes, from light off to the first epoch of any sleep stage that characterizes sleep onset.

Objective measures of physiological sleepiness based sleep propensity: the multiple sleep latency test (MSLT)

The neurophysiological test that objectively measures the intensity of physiological sleepiness is the MSLT. The MSLT was developed to go beyond subjective sleepiness scales such as instantaneous sleepiness scales (Karolinska [1] or Stanford [42]) which assess levels of sleepiness throughout the day. The first experimental studies developed in Stanford by Carskadon and Dement in the years 1972-1978 [18,19] concerned the examination of sleep and wakefulness on a 90-min schedule to determine the speed at which a person falls asleep, thus assessing physiologic sleep drive across a 24hr period. The MSLT provides opportunities for napping throughout the day to quantify sleep drive via sleep onset latency. The assessment of sleepiness in different populations and in several settings (adolescents, young adults, elderly under various sleeping schedules or patients with EDS treated or not) led to the idea that the MSLT objectively measured daytime physiological sleepiness [64]. Standardized protocols for the MSLT were first published in 1986 by Carskadon et al. [17] and separate clinical and research protocols were established. In 1992, the AASM published a position paper that was a consensus opinion on the clinical use of the MSLT [81]. Attention was drawn to the fact that the setting in which the MSLT is used must be free from as many alerting factors as possible to enable the underlying physiological sleep tendency to be measured. In 2005, two founding papers were published by the AASM. One by Arand et al. [3] and the other by Littner et al [56] used an evidence-based approach to update the recommendations for the clinical use of the MSLT. The first paper summarized normative data, and through a Medline search of the publications on the MSLT, the usefulness and limitations of these tests in different pathologies and with different procedures or treatment. The second paper provided recommendations for the appropriate clinical use of the tests and replaced the recommendations of 1992.
In this article, we present in detail the updated standardized protocols for using the MSLT [50]. The characteristics of the MSLT are summarized in table 1.

Procedures

Patient preparation is an important step in the MSLT protocol.

Regular sleep timing and normal sleep duration (at least 6 h of sleep per night) evaluated by sleep diary or actigraphy for two weeks before MSLT are necessary to perform the test.

The MSLT can be scheduled when the sleep condition is stable. On the other hand, drugs with alerting, sedating and/or REM sleep-modulating properties should be discontinued at least two weeks before the MSLT [15] For medications or metabolites with longer half-lives (> 1 day), a longer washout, potentially up to 6 weeks, may be necessary.

Testing procedures

The MSLT should be performed after a minimum 7 hours in bed with at least 6 hours of sleep quantified by PSG. In line with AASM recommendations, treatment of Obstructive Sleep Apnoea-Hypopnoea (OSAH) should be used during the PSG **and MSLT** in patients with sleep related breathing disorders [50]. However, in recommendations of the Société Française de Recherche et Médecine du Sommeil (SFRMS), this point is not specified [93]. It is important to note that MSLT latency is sensitive to several factors, including the total sleep and the amount of slow wave sleep the night before the test.

On the day of the test, the patient should wear appropriate comfortable clothes. No external alerting factors, sedating or alerting drugs are allowed throughout the day. Stimulating activities (electronic devices and cell phones) and nicotine should be discontinued at least 30 minutes before a nap trial.

The MSLT consists of 5 nap trials. The patient is lying in bed for all nap trials in a quiet, dark room. The first nap should begin 1.5–3 hours after termination of nocturnal sleep. Each subsequent nap should begin 2 hours after the start of the prior nap. Only when the results lead to a clear diagnosis of narcolepsy after 4 naps, can a shorter 4-nap trial test be performed. Between nap trials, the patient should be out of bed and kept awake.

Very precise bio-calibration must be made before starting each nap trial. At the start of each nap, bedroom lights are turned off and the patient should be told the following: “Please lie quietly, adopt a comfortable position, keep your eyes closed, and allow yourself to fall asleep.” Testing starts immediately after the instructions have been given. A nap trial ends if the patient does not fall asleep in 20 minutes. If sleep onset occurs, the nap is continued for an additional 15 minutes to allow the occurrence of REM sleep.

There is also a research MSLT protocol that is slightly different from the clinical MSLT: each test is interrupted as soon as one epoch of any sleep stage is obtained to limit the amount of sleep that a subject is allowed.

MSLT interpretation

For each test, the sleep latency, expressed in minutes, is calculated. If no sleep occurs during a trial, a default latency value of 20 minutes is applied. The arithmetic mean of all naps (i.e. 4 or 5 naps) is calculated, including naps where the subject did not sleep. The number of naps involving REM sleep that began between 0 and 15 min after sleep onset (SOREM) is counted. An example of sleep onset REM is given in figure 1.

Cutoff values

The normative sleep latency of the MSLT is the one published in 2005, based on a small database or on a surrogate database of sleep latency [3]. Strikingly, there is no large systematically collected repository of normative MSLT data. In healthy adults from 18 to 80 years old, the mean sleep latency (MSL) was 11.6 +/- 5.2 minutes for a 5-nap test and 10.4+/- 4.3 minutes for a 4-nap test [3]. Normal values in control subjects vary from 7.4 to 15.2 with an SD from 1.1 to 7 minutes. In a recent systematic review, normal sleep latency in adults was 11.7 min (95% (CI: 10.8–12.6; 95% PI: 5.2–18.2) [45].

There is no clear published value of the MSL value according to age, even though a greater MSL has been reported in older subjects. A study including 129 young subjects (age 18-29) and 29 older ones (age 30-80) reported a MSL of 11.1 and 12.5 minutes, respectively, but no SD was indicated. In the paper by Arand et al [3], a MSL of 15.2 +/- 6 minutes was found in 80-year-old subjects, a value longer than in all other age groups. No effect of gender on MSL has been reported. In all cases, a MSL of less than 8 minutes indicates pathological sleepiness (sensitivity 94.5%, specificity 73.3%, patients with narcolepsy vs normal subjects), and less than 5 minutes is clearly pathological (sensitivity 80.9%, specificity 89.8% patients with narcolepsy vs normal subjects) [3,47].

Reliability data

The test-retest reliability of the 4-nap MSLT was 0.97 in healthy individuals on consistent sleep-wake schedules over a period of 4-14 months and was not affected by the retest interval (≤ 6 months versus > 6 months) or by the amount of sleepiness (MSL<5 minutes versus MSL ≥15 minutes) [91]. Reliability was also high in a clinical type 1 narcoleptic population; reported

interrater reliability for MSL ranged from 0.85-0.90 and intra-rater reliability was 0.87[29]. Evaluation of the presence of more than one SOREM also showed a high interrater agreement of 0.91 and of 0.78 for intra-rater agreement[29]. On the other hand, the MSLT has a poor test-retest reliability in narcolepsy type 2 and in idiopathic hypersomnia [58,72], so consistency results over time are likely unreliable for some diagnoses [83].

Specific indications for use of the MSLT

The MSLT is mainly indicated for the diagnosis of central disorders of hypersomnolence, i.e. narcolepsies (Type 1 and 2) and idiopathic hypersomnia [50,56,92].

MSLT in narcolepsies (type 1 et 2) must show a MSL < 8 minutes (90% of patients with narcolepsy have a latency below this value) and typically less than 5 minutes. Meta-analysis showed MSL in type 1 narcoleptic patients of 3.1 +/- 2.9 minutes. In addition, two or more SOREMs must be present on the MSLT. However, REM sleep onset on the PSG the night before the MSLT is a highly specific finding in the absence of another sleep disorder, but with low sensitivity. Therefore, it allows the "replacement" of one SOREM in the MSLT with a SOREM on the preceding PSG. The number of SOREM increases with decreasing sleep latency on the MSLT. Sensitivity of 0.78 and specificity of 0.93 were found when 2 or more SOREMs were considered for the diagnosis of narcolepsy. These typical MSLT findings rule out some diagnoses such as chronic fatigue syndrome and depression, which may mimic narcolepsy.

MSLT in pediatric narcolepsy type 1 must show MSL ≤ 8.2 minutes OR 2 or more SOREMs [69].

In a reappraisal consensus of European experts [53], proposing 3 new diagnostic categories of central disorders of hypersomnolence, MSLT is recommended for the diagnosis of "narcolepsy" (which includes type 1 and type 2 narcolepsy) and "idiopathic excessive sleepiness". The diagnosis of "narcolepsy" is certain (including MSLT evaluation) when a complaint of EDS is associated with typical cataplexy and MSL< 8 min and >1 SOREM (including nocturnal sleep). The diagnosis of idiopathic excessive sleepiness is certain when a complaint of EDS is associated with MSL <8min on the MSLT and PSG. "Probable" diagnoses are not described in this article.

New alternative MSLT parameters (neurophysiological parameters) have been proposed to better identify hypocretin deficiency in patients with hypersomnolence and in those with narcolepsy (better specificity and sensitivity). The sleep stage sequences preceding the SOREMs "wakefulness or stage 1 to REM" were significantly more frequent than "stage 2 to REM"

in narcolepsy compared to other hypersomnias [28,48]. Considering four different metrics (REM sleep latency < 5min, mean percentage of REM sleep during naps ≥40%; the number of transitions from wakefulness or stage 1 to REM ; and the REM duration), Lopez et al. [57] demonstrated that REM sleep duration ≥4.1min better identifies hypocretin deficiency in patients with a complaint of hypersomnolence (sensitivity of 0.87 and a specificity of 0.86) than other alternative MSLT parameters like sleep duration, REM sleep latency, and sleep stage transitions. Mean REM sleep duration ≥ 5.7 min identified patients with narcolepsy with a sensitivity of 0.77 and a specificity 0.82. On the other hand, conventional MSLT/PSG parameters identified hypocretin-deficient patients with a sensitivity of 0.87 and a specificity of 0.69, and 0.81/0.99 when combined with cataplexy.

In older patients with a complaint of hypersomnolence, sleep latency is longer and a lower rate of ≥2 SOREM was sometimes observed, resulting from the progressive increase in sleep latency seen in normal age and from the age-related decline in quantity of REM. These results must be considered when interpreting MSLT results in older patients, highlighting the reduced sensitivity of the usual MSLT in detecting narcolepsy in older adults [15,22].

In women with a complaint of hypersomnolence, sleep latency is shorter and a lower rate of ≥2 SOREM was observed than in men [15].

In idiopathic hypersomnia, after a night usually showing a long sleep duration, MSLT will show a mean sleep latency less than 8 minutes. However, in 2 large studies mean sleep latency was found to be 8.3 [2] and 7.8 minutes [89]. MSL values in IH are situated between those of narcolepsy and those of normal control subjects. If sleep latency is > 8 minutes, prolonged sleep monitoring is recommended with a 24 h or 36 h PSG (see the different procedures in another article of this review) or with wrist actigraphy during 7 days of unrestricted sleep. In a reappraisal consensus of European experts, MSLT is not recommended for the assessment and management of patients with IH [53].

Are there other indications for the MSLT ([92])?

In rare patients with insomnia and EDS, PSG and MSLT may be useful, particularly if narcolepsy is suspected. Otherwise, patients with non-comorbid insomnia have longer mean MSLT values than control subjects, suggesting hyper-arousal.

There is no indication for the use of MSLT in patients with phase-shifted sleep. The MSLT is sensitive to circadian effects. In phase-shifted sleep, it has been shown that the MSL is shorter during the night than during the day, and MSLT sleep latencies during night shifts following daytime sleep decreased from 23 pm to 5 am.

The MSLT is not indicated in medical or neurological illness as it does not correctly discriminate patients with sleep disorders and control subjects, except to detect some co-morbid pathologies (sleep-disordered breathing or periodic limb movements) on PSG.
Finally, the PSG and MSLT may help to differentiate long sleepers from patients with hypersomnia, OSAH or medical causes of hypersomnolence.

Limiting factors

As mentioned above, the normative sleep latency based on small samples is one of the limiting factors. In addition, many factors in the testing protocols can influence the results of MSLT (insufficient sleep, circadian rhythm sleep disorders, anxiety, physical activity, motivational aspects, iatrogenic effect of medications or substances on sleep latency and SOREMs [4])
In general, a basement or floor effect can limit discrimination of the sleepiest subjects. The MSLT is not sensitive to detect the most severe levels of sleepiness [3]). It is not uncommon to observe an abnormally short sleep onset latency (<8 min) in a good sleeper with no complaints of EDS or to observe normal sleep latency in patient complaining of EDS [66].
Finally, the MSLT has low sensitivity and specificity for diagnostic purposes [37,63] except for narcolepsy type 1.

Objective measures of manifest sleepiness based on measuring ability to stay awake: the maintenance of wakefulness test (MWT)

The neurophysiological test that objectively measures the ability to stay awake is the MWT. Like the MSLT, the MWT is a neurophysiological test. Unlike the MSLT, however, the MWT measures the manifest sleepiness. The MWT provides nap opportunities throughout the day to assess the potential threat of inappropriate, involuntary falling asleep. The MWT principally aims to determine manifest sleepiness [77].
In 1980-1982, it was observed that the MSLT did not change after surgery in most subjects with OSAH, though patients reported improvement of sleepiness. This suggests that the MSLT does not measure the ability to resist sleep and is not sensitive to changes in the state of arousal. Hartse et al. [39] were the first to propose a modification of the MSLT procedure where patients in a soporific environment are instructed to stay awake. Their protocol was effectively the precursor of the MWT. The test was then refined by Mitler et al [64]: patients were seated on a chair, in a quiet and dimly lit room with the instruction to stay awake. Four or five trials were given every two hours and were stopped after 20 minutes if the subject did not fall asleep.

Between 1982 to 1997, the trial duration varied widely (40min or 20min), as did the criteria for defining sleep onset ("3 consecutive epochs of stage N1 sleep or any single epoch of another sleep stage" or "at the first appearance of sleep, whether 10s of microsleep or the first epoch of any sleep stages"). In 1997, Doghramji et al [26] published a normative study of the MWT. They recommended 4 tests of 20min that terminated at the first occurrence of one epoch of any stage of sleep or after 20 min if sleep onset was not achieved.

It was not until 2005 that the AASM [56] recommended 4 tests of 40min for the MWT. In this section, we present the updated standardized protocols and recommendations for the MWT in detail [50]. The characteristics of the MWT are summarized in table 1.

Procedures

Patient preparation

Regular sleep timing and normal sleep duration (at least 6 hours of sleep per night) evaluated by sleep diary or actigraphy for two weeks before the MWT are necessary to perform the test.

The MWT can be performed when the patient is clinically stable and when treatments for any known sleep disorders are well established and effective.

In patients with sleep-disordered breathing who are being evaluated for the effectiveness of therapy, the clinician should ensure effectiveness (efficacy and adherence).

If the patient is taking medications with alerting or sedating properties chronically, then they should be continued at a stable dose.

Testing procedures

The MWT should be performed after the patient's major sleep period. Patients treated for OSAH should use their treatment during the night preceding the MWT but not during naps.

On the day of the test, the patient wears appropriate comfortable clothes. No external alerting factors, alcohol, marijuana, or other sedating substances are allowed. Stimulating activities (electronic devices and cell phones) and nicotine should be discontinued at least 30 minutes before a wake trial.

The MWT should consist of 40-minute wake trials. The patient should be seated in a comfortable position, in a bed or reclining chair, in a quiet dark room. The light source should deliver only dim light (approximately 0.1 lux at the corneal level) placed 30 cm off the floor 90 cm lateral to the patient's head. The first trial should begin 1.5–3 hours after termination of nocturnal sleep (at home or in a sleep clinic). Each subsequent trial should begin 2 hours after the start of the prior trial.

At the start of each wake trial, only a dim light is turned on and the patient should be instructed as follows: “Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light.” During the MWT, the subject is asked not to use self-stimulation strategies to avoid falling asleep. Testing starts immediately after instructions are given. Each trial is ended if unequivocal sleep occurs (3 consecutive epochs of stage N1 sleep or 1 epoch of any other sleep stage) or after 40 minutes.

MWT interpretation

For each trial, the sleep latency is calculated. If no sleep occurs during a trial, a default latency value of 40 minutes is applied. The arithmetic mean of 4 wake trials is calculated, including trials where the subject did not sleep.

Cutoff values

The normal sleep latency of the MWT remains the one published in 1997, based on a small database or on a surrogate database of sleep latency. The wide variety of procedures and definitions of sleep onset have not simplified the establishment of normal values. In healthy adults from 30 to 69 years old, the MSL identified by 3 continuous epochs of stage 1 sleep or any single epoch of another sleep (“sustained sleep”) was 35.2 ± 7.9 minutes for a 4-trial 40-min MWT, and 18.1 ± 3.6 min minutes for a 4-trial 20-min MWT. On the other hand, the sleep latency to the first epoch of sleep or 10 seconds of sleep (non-conventional definition of sleep onset) on the 40-min MWT and 20-min MWT were 32.6 ± 9.9 and 18.1 ± 3.6 respectively. The distribution of sleep latencies is truncated for both procedures, with a large ceiling effect in over 75% of 40-min trials and in about 85% of 20-min trials. Strangely, in Arand's article [3], the normative value of the 40-min MWT has been changed to 30.4±11.2 minutes without explanation or evidence to support it. This updated normative value has been reported in the AASM recommendation in 2005 and 2021.

Tankere et al. [78] determined normal values in a population of well-treated non-sleepy OSAH patients (n = 76), and found a consensual sleep latency (defined as 1 epoch of any sleep stage) of 38.4±4.2 min. Eighty percent of well-treated non-sleepy patients did not fall asleep.

Age-related, but not gender-related, differences in MSL values exist for the MWT. Sleep latency values are lower in normal subjects 30-39 years of age compared with those of older normal subjects [26,76]. Regression across age shows an increase in sleep latency of approximately 2.5 minutes per decade for the MWT [3].

Reliability data

In the study of Tankere et al., the intra-scorer agreement on MSL was high but inter-scorer agreement was only fair (Cohen's kappa 0.54 for 33-min threshold, 0.27 for 19-min threshold), resulting in changes in latency category in 4%–12% of patients [78].

Specific indications for using the MWT

The MWT is mainly indicated to determine the effect of medications, substances, or other interventions compared to pretreatment or normal controls, or to determine the patient's nonpharmacologic state compared to normal controls.

There is no consensus regarding pathological values. Due to inconsistent data, the AASM recommendations in 2005 [56] stipulate that a MSL < 8.0 minutes on the 40-min MWT is considered abnormal and that values ≥ 8 minutes but < 30 minutes are of uncertain significance. In 1997, Doghramji et al. [26], applying the 2 SD definition of the lower normal limit, determined that the normal low cutoff point was 19.4 min for the 40-min MWT with sleep onset defined by 3 continuous epochs of stage 1 sleep or any single epoch of another sleep stage, and 12.9 min for the 40-min MWT with sleep onset defined by 10s of sleep or one epoch of any other sleep stage. Importantly, Doghramji's definitions of sleep onset do not correspond to the one currently accepted by international consensus, i.e. the first 30s-epoch of any sleep stage.

Using the normal lower cutoff determined by Doghramji et al, Sagaspe et al. [73,74] classified untreated OSAH patients in three classes in according MWT sleep latency: Very sleepy patients with sleep latency between 0 and 19 min, sleepy patients with a sleep latency between 20 and 33 min, and alert patients with sleep latency >33min. Here again, there is confusion concerning the definition of sleep onset. Sagaspe et al calculated sleep onset according to the current consensus (defined by first epoch of any sleep stages including N1), unlike Doghramji who measured sleep onset by 3 continuous epochs of stage 1 sleep or any single epoch of another sleep stage.

Driving ability has been determined by this classification. Sleepy and very sleepy patients with OSAH show impaired driving ability compared with non-sleepy patients and controls. In France, most sleep centers use this classification to identify sleepy and very sleepy patients. A recent study showed that no objective sleepiness test (MWT, SART or the PVT) is able to predict impaired driving (assessed by standard deviation of lateral position in driving simulator) in patients with narcolepsy [10]. In a recent review, Bijlenga et al. [9] confirmed the lack of reliability of the MWT for evaluating driving fitness in patients with central disorders of hypersomnolence.

By applying the 2 SD definition of normality, Tankere et al. [78] determined in a population of treated patients with OSAH that the normal lower cutoff point was 30 min for the 40-min MWT, with sleep latency defined as the first epoch of any sleep stage.

Are there other indications for the MWT?

According to the recent French legislation of 2022 on driving any kind of vehicle, the MWT can be used for the functional evaluation of the ability to drive in sleepy patients with moderate or severe OSAH. In addition, the Federal Aviation Administration uses the MWT for the functional evaluation of pilots' licenses in treated patients with OSAH.

Limiting factors

Even though the AASM has published and recommended updated procedures for the MWT, its most important limitation is the lack of consensus in defining a normative value and a pathological threshold. These thresholds have been defined in patients with OSAH, but they are not validated for all sleep disorders. Another issue is the definition of the lower normal limit. The MWT has an important ceiling effect (data not normally distributed among normal subjects) and the lower normal limit, calculated on 1, 1.5 or 2 standard deviations from the mean, may not be appropriate.

Neuropsychological investigations: objective measures of drowsiness based on measures of sustained attention

In this section, sleepiness is quantified in terms of cognitive performance, specifically vigilant attention, and it is universally agreed that vigilance is a component of cognition. Vigilant attention impaired by sleepiness can be restored by getting to sleep, e.g. by taking a nap, at least in non-pathological situations. Three mainly psychomotor tests that quantify sustained attention (i.e. drowsiness) are described hereafter: the Psychomotor Vigilance Task (PVT), the Sustained Attention to Response Test (SART) and the Oxford Sleep Resistance Test (OSleR). All these tests measure manifest sleepiness, i.e. the quality of the state of wakefulness, for which the ability to sustain attention is mandatory. The characteristics of each test are summarized in table 1.

The psychomotor vigilance task (PVT)

The PVT is a sensitive test of sustained attention and is widely recognized as the first-line measure of degradation of behavioral alertness or sustained attention [5] under sleep deprivation, whether acute [25,90], or chronic [86]. It is easy to administer, repeatable over time, and does not have a learning curve [43].

The PVT is a one-choice serial reaction time task in which a visual stimulus—typically a 10-millisecond counter or a black square— appears on the screen at random inter-stimulus intervals (2-10 s inter trials) (Figure 2). The subject's task is to press an answer button or touch the screen to make the stimulus disappear as quickly as possible without responding prior to the stimulus presentation. The subject has continuous feedback information on their reaction time. The intense stimulus load and the varying inter-trial intervals require a high level of vigilant attention.

The PVT was originally administered for 10 min (approximately 80 - 100 stimuli) with custom-built hardware (PVT-192) [25] or personal organizer (PSION organizer II) [36]. It can be administered on several types of device and shorter durations have been proposed and validated (3 or 5 minutes) [6,80]. A validated version for the Windows 10 operating system (PC-PVT 2.0) can be freely downloaded [49].

Generally, several outcome measures are calculated: mean and median reaction time (RT), fastest or slowest 10% RT, number of “blocks” or “lapses of attention” (very slow RT) and errors of commission (responses when no stimulus is present or false start). Median reaction times correspond to the average level of vigilance required to perform a task satisfactorily (global vigilance), whereas fastest 10% RT reflect optimal response capacities that can be recruited episodically above baseline cognitive level (optimal vigilance). “Blocks” were defined by Bills [11] as “a pause in the responses equivalent to the time of two or more average responses”. In 1949, Bjerner [12] defined “blocks” in terms of “lapses”. It was around 1985 that Dinges [25] labelled the lapse as a RT > 500 milliseconds (ms). This 500-ms criterion has since been recognized as the reference value for lapses. Lapses are comparable to errors of omission. They are generally associated with microsleeps [90], and lead to the inability to respond to stimuli. Lim et al [55] introduced the notion of catastrophic lapses, i.e. lapses lasting longer than 30 seconds and corresponding to a sleep attack. On the other hand, two other disengagements can also cause lapses: visual inattention and distraction [2]. Eye-tracking would be essential to differentiate between them, because lapses associated with microsleeps must be accompanied by eye closure or slow eye movement. The metric for the 10-min PVT

that optimally discriminates sleep-deprived subjects from alert subjects is response speed: the reciprocal metric mean (1/RT) [6]. Slowest 10%RT and lapses are also considered better parameters to study the effect of sleep deprivation on alertness than mean or median RT [6].

Studies on the effect of sleep deprivation and PVT performance have shown that response speeds and errors of commission are degraded after sleep deprivation in most subjects. RTs exhibit a time-on-task, modulated by time awake and time of day. On the other hand, certain individuals display minimal impairment during sleep loss, demonstrating an individual difference in response to sleep deprivation. The individual neurobehavioral responses to different sleep deprivations are stable and consistent, suggesting that there are trait-like differences in vulnerability [87]. However, the inter- and intra-individual variability in performance during sleep deprivation is task-dependent [33].

Three hypotheses have attempted to explain the impairment in performance in sleep-deprived subjects. The first in time was the "lapse hypothesis" [90], which postulated that performance during sleep deprivation is relatively normal, until punctuated by microsleeps. Physiologically, they correspond to the sudden and often very brief intrusion of sleep into the waking state. This hypothesis posits that these sleep intrusions (lapses) are rare events that act intermittently on vigilance. However, sleep deprivation results in increased mean response speed, a high frequency of especially long response times (>500 ms) and errors of commission, which gradually increase throughout sleep deprivation, although some RT remain in the normal range. Based on these observations, David Dinges [27] introduced the notion of **"**wake-state instability" that fluctuates from second to second. The wake-state instability hypothesis posited that sleep deprivation progressively impacts cognitive performance due to the increase in homeostatic sleep pressure modified at certain times of day by circadian sleep drive, resulting in rapid, brief and uncontrolled sleep initiation (lapses). To maintain task performance and counter sleep intrusion, the subject must develop top-down compensatory strategies resulting in normal RTs for a short period of time. However, the compensatory effort made to resist sleep does not prevent all brief sleep intrusions in wakefulness and explains the presence of lapses. The wake state instability considers the number of lapses to be an index of state instability, whereas the number of false starts is taken to be an index of compensatory effort. At least, based on local sleep theory, Van Dongen et al. [85] suggested a bottom-up explication of wake state instability, which postulates that the unstable state is related to local, use-dependent sleep in neuronal groups involved in the PVT task.

Neuroimaging studies have demonstrated that during sleep deprivation, lapses are due to a decrease in brain activation in the fronto-parietal attention network (prefrontal cortex and

intraparietal sulcus, in the salience network (insula and medial frontal cortex) and sensorimotor areas identified as “task-positive” regions [60]. Conversely, there is thalamic activation resulting from the interaction between the arousing effects of task performance and the hypovigilant effect of sleep loss [60]. From a clinical point of view, PVT performance is better (fewer lapses and faster RT) in healthy controls than in patients with sleep-wake disorders. PVT performance is worse in patients with narcolepsy or hypersomnia than in subjects with insufficient sleep syndrome [79].

However, the PVT has not been used to quantify EDS, nor has it been used to diagnose sleep disorders. Moreover, there are no normative values for PVT. Age and gender are also major factors that may contribute to attentional failures [13,68]. The result of the PVT does not correlate with the results of the MSLT nor of the MWT [32,54]. Therefore, these studies suggests that the ability to stay awake as assessed by the MWT and the excessive propensity to fall asleep assessed by the MSLT are not associated with performance assessed by the PVT during sleep deprivation [33]. On the other hand, the PVT is associated with subjective daytime sleepiness in patients with OSAH, as assessed by the Epworth Sleepiness Scale (ESS) [54].

Sustained Attention to Response Task (SART)

The SART was developed by Robertson et al. in 1997 [71] to measure sustained attention in patients with traumatic brain injury. The SART is a go/no-go task in which the no-go target appears unpredictably and rarely. As it is based on a go/nogo paradigm, this test could be considered an inhibition test, but it is well known that the SART quantifies sustained attention rather than a putative response inhibition capacity [61].

For 4.3 min, 225 single digits (25 of each digit between 1 and 9) are presented centrally on a computer screen. The digits are presented in different sizes in a white font on a black computer screen. Each digit is displayed for 250 ms and then replaced by a 900 ms duration mask, composed of an X presented inside a 29-mm ring with a diagonal cross in the middle. The subject is instructed to press a key when the digits appear (a so-called “go trial”), with the exception of digit 3 (a so-called “no-go trial”) (Figure 3). Generally, the subject is instructed to attribute equal importance to accuracy and speed in performing the task, but the instruction "prefer accuracy over speed" is currently recommended (lower error count) [75]. In addition, a training/learning session is highly recommended.

Several outcomes are calculated [88] : mean reaction time (RT), RT variability, post error slowing, commission and omission errors. The mean RT is expressed in ms, calculated over

correct response trials. RT variability is quantified as the coefficient of variation of RT for correct response trials (standard deviation divided by the mean RT). Post-error slowing is the difference between the later and the earlier RT before a commission, divided by the mean RT of that session. The number of commission errors, with a maximum of 25, is the total number of errors (when the subject presses a key and the number 3 appears). The number of omission errors, with a theoretical maximum of 200 errors, is when the subject does not press the button when they are supposed to. The total error count, i.e. the sum of commission and omission errors, is also analyzed. The total error count or the SART error score is the primary outcome measure.

A meta-analysis has shown that SART scores depend on age. Older adults were slower than younger adults on go trials and more accurate than younger adults on no-go trials [84]. Men perform worse than women in the SART [38].

The SART was validated to measure sustained attention in 15 untreated patients with narcolepsy versus 15 matched controls [34]. It was administered prior to each of five MSLT sessions. The mean of all SART parameters obtained during 5 sessions was computed. For SART error score, the cut off is 5 (in healthy subjects median SART error = 2, 25th and 75th percentile = 1.3-4.0). The total error count is higher in the first session than in all others. In patients with narcolepsy, the median SART error score is 10.6 (6.1-18,7). The SART error score in patients with narcolepsy (with or without cataplexy), with idiopathic hypersomnia and OSAH is higher than the cut off determined by Fronczek et al. [34] (i.e. SART error score = 5).

In patients with narcolepsy, SART performance is not correlated with ESS score nor with the average sleep onset latency during the MSLT [34,88]. Another study demonstrated that the SART and the MWT do not reflect the same aspects of the narcolepsy burden [40]. The SART has been used to assess treatment effects in narcolepsy. Van der Heide et al. [40] demonstrated that SART performance (specifically log transformed commission errors and total error count) and ESS efficiently distinguished responders from non-responders to a wake-promoting drug, by using the Clinical Global Impression of Change (CGI-C) score but not the average mean sleep latency during MWT. Patients with higher baseline SART total errors were the responders to the wake-promoting drug. On the other hand, SART outcomes cannot differentiate patients with disorders of hypersomnolence [40]. In the proposal for a new classification of central disorders of hypersomnolence, European experts suggested that the SART should be an objective measure for assessing the impact of EDS on daily functioning. In addition, performance on the SART would make it possible to differentiate several subtypes of "Iidiopathic excessive sleepiness"[53].

The OSleR test (Oxford Sleep Resistance Test)

The OSleR is a sensitive test of sustained attention. Unlike the PVT and SART, however, it indirectly measures the subject's ability to maintain wakefulness [7]. The OSleR has been proposed by authors as a behavioral and cost-effective alternative to the MWT for measuring the ability to stay awake in monotonous situations.

The subject is instructed to press a button or apply a finger to a tactile sensor in response to dim light flashes generated by a light-emitting diode (LED) device placed at eye level, two meters away from the subject's head. The LED flashes regularly for one second every three seconds during 40 minutes (Figure 4). As stimuli are repeated regularly and not randomly (unlike the PVT), the OSleR creates a monotonous situation mimicking the MWT protocol. The subject is comfortably installed in a semi-seated position in a dark, noise-free room. The test is repeated 4 times a day, with a 2-hour interval between each session. The test is interrupted and ends automatically either if the subject fails to respond to 7 consecutive stimuli (i.e. 21 seconds), in which case the subject is considered to be asleep); or after 40 minutes in the absence of sleep. These 7 omissions represent 21 seconds of absence of reaction, which is slightly lower than the duration of a sleep epoch. An OSLeR "sleep latency" expressed in minutes is calculated, corresponding to the time between test start and the occurrence of 7 consecutive errors. Average OSLeR "sleep latency" is calculated by averaging the values obtained during the four tests. The term "sleep latency" used by the authors of OSLeR can be misleading. In fact, the sleep latency is usually used to define time elapsing until the first epoch of any sleep identified by polysomnography, which not the case in OSleR. The number of errors (omission) can be quantified: number of omissions per session ($OSLER_{OMIS}$) and number of omissions per minute of test duration ($OSleR_{OMIS/MIN}$) [70,76]. The percentage of the duration of the OSLeR test during which the patient makes errors can also be computed ([3 seconds × number of omissions/sleep latency duration in seconds] × 100) [62], with 3-6 consecutive errors indicating microsleep [70]. The fact that correct and missed responses are taken into account prior to sleep onset makes this test a sustained attention task [76]. Other protocols have been proposed, such as 3 tests during the day [70], without altering the diagnostic value.

To our knowledge, no study has observed the effect of age or sex on the "sleep latency" as defined by OSLeR.

OSLeR "sleep latency" is correlated with MWT sleep latency and with PVT outcomes in non-treated hypersomnia patients [7,52,62,70,76]. In addition, wake-promoting agents improve sustained attention assessed by the OSLeR, but not by the PVT [76]. Few studies have demonstrated the ability to differentiate between subjects with EDS and non-sleepy subjects (controls or treated patients), based on either mean sleep latency [7,46,62] or number of errors assessed by the OSLeR [23].

Indeed, the OSLeR test has mainly been used to measure EDS and the effect of treatments, (continuous positive pressure and wake-promoting agents) in patients with nocturnal respiratory disorders [65]. It would offer the advantage of a simple technique for objectively measuring daytime sleepiness compared to MWT, but no methodological consensus or specific normative data supporting clinical threshold scores are currently available.

Discussion

Neurophysiological tests (MSLT and MWT) are widely used in sleep centers to identify and quantify EDS with the aim of managing EDS and assessing the efficacy of treatments. Although MSLT and MWT both measure the latency to sleep onset, their results in the same subjects show poor correlation suggesting that they measure two different aspects of sleepiness (physiological and manifest).

The MSLT is the gold standard for measuring the intensity of physiological sleepiness following efforts to standardize the test in recent years. MSLT is also recommended in the International Classification of Sleep Disorders (ICSD-3) [92] for the diagnosis of central disorders of hypersomnolence, i.e. narcolepsies (type 1 and type 2) and idiopathic hypersomnia. Importantly, a diagnosis of hypersomnia should be made with as much clinical information as possible. The MSLT should not be the sole criterion for determination of excessive sleepiness and certification of a diagnosis. Such conclusions should be based on interpretation of the MSLT results in combination with the individual patient history or other medical relevant data (such as symptoms of EDS, cataplexy)

MWT, which measures the patient's alertness and/or ability to stay awake (manifest sleepiness), is recommended only to evaluate the evolution of EDS and thus the efficacy of treatment of EDS and/or the evolution of alertness over the course of the disease. In-some countries, MWT can be used for the functional evaluation of the ability to drive in sleepy patients. It is important to bear in mind that the MWT is not a diagnostic test. In the absence of a "consensus" normal value, there is no consensus pathological threshold. To recap, the lower the average latency, the

greater the manifest sleepiness and therefore the greater impact on daily functioning and risk of occupational or traffic injury. According to the AASM, a sleep latency <8min will be considered as abnormal, but there is an important grey zone between 8 and 30/35 min. This grey zone should be kept in mind when considering the three categories based on sleep latencies proposed by Philip et al. to estimate the risk of sleepiness-related accidents.

Since EDS encompasses sleepiness and drowsiness, it is necessary to measure sustained attention and its behavioral negative impact on daily functioning to improve the assessment of EDS and the diagnosis of "idiopathic excessive sleepiness". According to Lammers et al [53], the problems of sustained attention or vigilance may be the most disabling aspects for patients with hypersomnolence as opposed to EDS *per se*. The SART is recommended to measure sustained attention in "idiopathic excessive sleepiness" [53] because of the existence of a pathological threshold. But, under no circumstances can the SART be used as a diagnostic tool. The major problem is that useful clinical measures usually require normative values to determine a reliable cutoff. In both neuropsychological (PVT, SART and OSLeR) and neurophysiological (MWT) tests measuring manifest sleepiness, the lack of normative values makes it impossible to determine critical thresholds to differentiate pathological from normal manifest sleepiness. When normative data exist (SART and MWT), they are derived from very small groups of healthy subjects often studied in different protocols and with a wide range of "normal values", thus questioning the value of the test to discriminate controls from pathological subjects. In the future, research must focus on determining pathological thresholds. Since age affects all test results, pathological thresholds should be defined according to age, even for the MSLT.

Moreover, the processes for standardizing and harmonizing the MSLT and MWT should aim to improve the comparability of test results between sleep centers and to define appropriate reference intervals and decision thresholds. Sleep centers should therefore follow the recommended protocols precisely in the knowledge that many physiological, psychological and operational factors can affect the results of these tests and that EDS is measured in experimental conditions that are very different from those of daily life [66]. Attempts at standardization and harmonization have never been made for neuropsychological tests, so it is difficult to interpret results and use them clinically.

Even though new alternative MSLT parameters can better phenotype the central disorders of hypersomnolence, the definition of sleep onset by the AASM remains questionable. Firstly, the traditional epoch-by-epoch method of sleep scoring cannot identify sleep onset if the sleep episode is divided into two consecutive epochs. Secondly, the physiological transition from

wakefulness to sleep onset is gradual. The guidelines of the AASM do not consider the subject to be asleep if the sleep stage scoring criteria do not exceed 50% of the epoch. Thus, less than 50% (3 to 15 seconds of low-amplitude, mixed frequency) is scored as wakefulness. Sleep intrusion lasting less than 15 seconds in one epoch, called microsleep in wakefulness (between 3 and 15 s), is thus ignored (Figure 5).

Recent work has demonstrated that another method for detecting sleepiness during the MSLT or MWT, based on the occurrence of the first micro-sleep episode (between 1 and 15 seconds) or the occurrence of several micro-sleep episodes prior to sleep onset, can give the best objective measurement of sleep onset [24,41,82]. Studies are still needed to confirm the contribution of detecting micro-sleep episodes in predicting the risk of accidental drowsiness at the wheel [81].

The ocular signal *percentage of eyelid closure* (PERCLOS) can facilitate the detection of sleep under the conditions of the MWT, but sleep detection should not solely rely on ocular signals [51]. It has been shown that the PERCLOS increases with the extension of wakefulness and with the decrement of driving performance. Therefore, different measures of eye closure could be used to determine sleepiness or fatigue in drivers.

Last, the standard 3-electrode low-density EEG (LD-EEG) montage recommended by the AASM does not allow a spatial resolution, i.e. a global view of sleep, yet sleepiness has been shown to be a local phenomenon [21]. High-density EEG (HD-EEG) recordings utilize a higher number of scalp electrodes, thus improving spatial resolution. HD-EEG during sleep can be used to investigate localized changes in EEG, showing that sleep patterns can be observed in certain cortical regions during wakefulness. These local sleep intrusions during wakefulness could be considered as sleep onset [44] and offers the possibility to measure what could be called “physiological drowsiness”. The new markers of the wake -to-sleep transition allowing a definition of sleep onset and therefore EDS closer to sleep/wake physiology are presented in greater detail in the next article.

Conclusion

Sleepiness includes several dimensions which can be assessed by different tests. Tests such as the MSLT and MWT are internationally used; they have participated in standardizing practices, and much improved the diagnosis of central hypersomnolence disorders throughout sleep centers in the world, allowing comparison of results published in the literature.

However, a better understanding and standardization of the procedures to measure still under-

assessed dimensions of sleepiness is required. In this context, research into new electrophysiological analysis of brain signal to measure sleepiness opens new avenues for clinical neurophysiology applied to sleep medicine.

Declaration of Competing Interest

No conflicts of interest were reported for this study.

Acknowledgments and funding

JT is supported by the ANR (ANR-19-LCV1-0004 MEEGASAFE), VM has received funding from the European Union's Horizon Europe research and innovation program under the Marie Skłodowska-Curie grant agreement No. 101106577.

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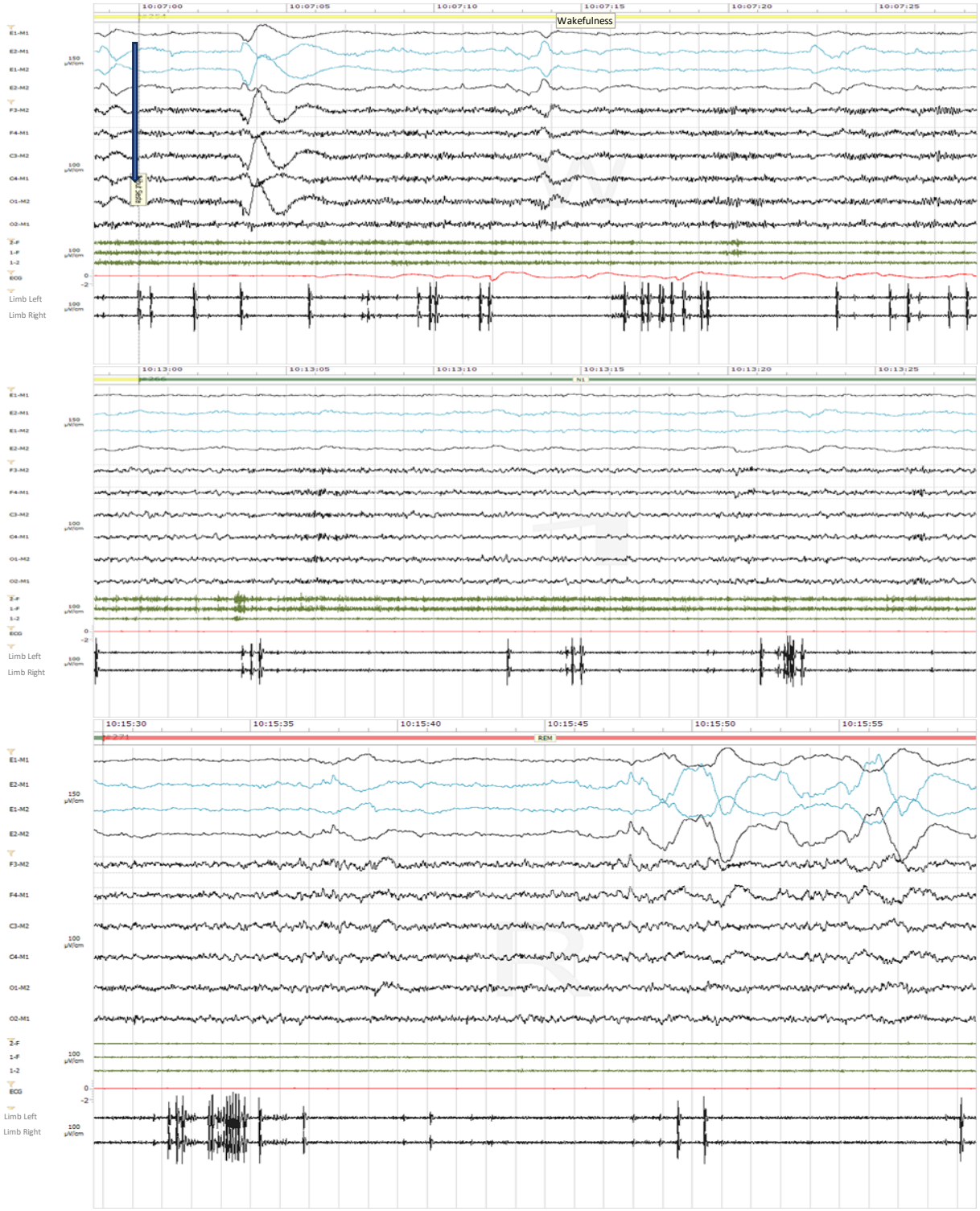

Figure 1: Three 30-second epochs recorded during a Multiple Sleep Latency Test. Epoch 1: wakefulness. Beginning of the test: 10:07:00. Epoch 2: first epoch of sleep N1 at 10:13:00. Sleep latency= 6 min. Epoch 3: REM sleep at 10:15:30. Latency of REM sleep =2min30sec from first epoch of sleep N1.

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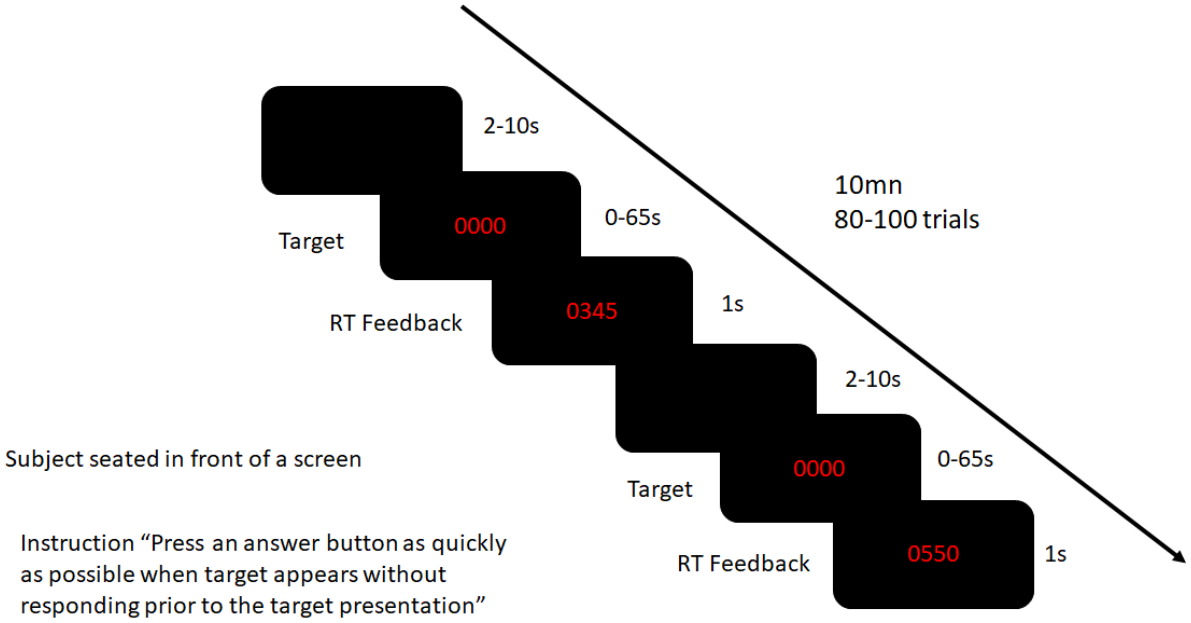


Figure 2: The serial flow of elements in one trial of the Psychomotor Vigilance Task (PVT) and standardized procedure

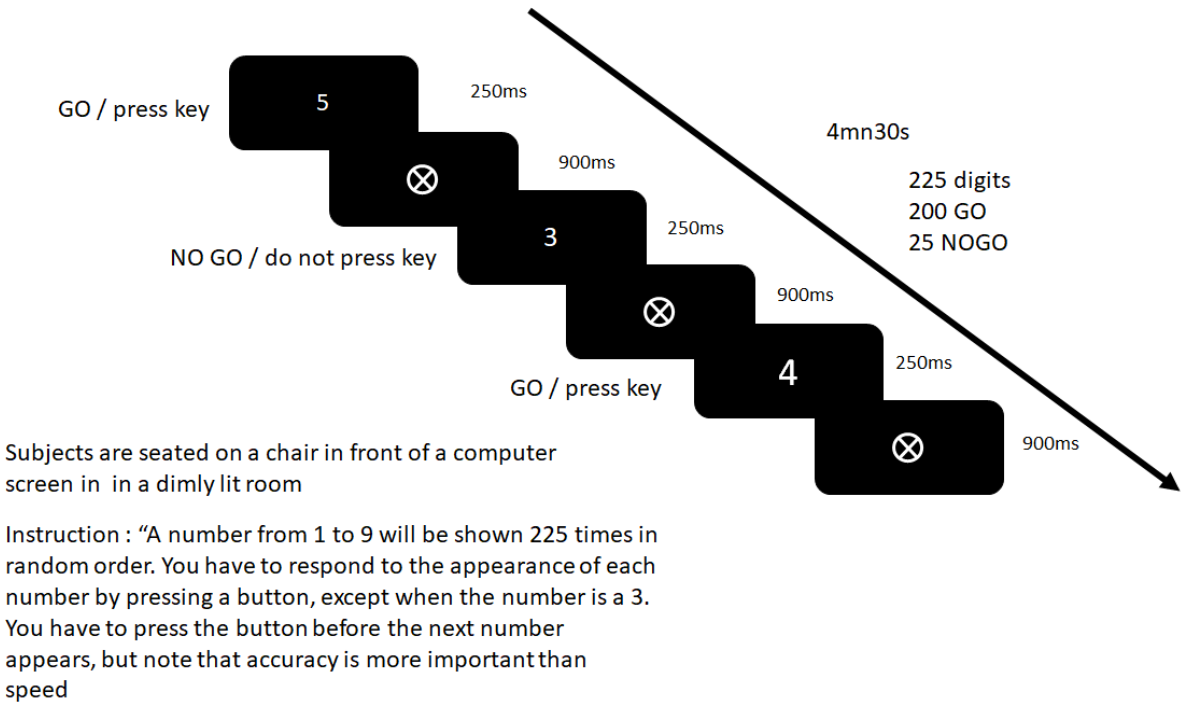
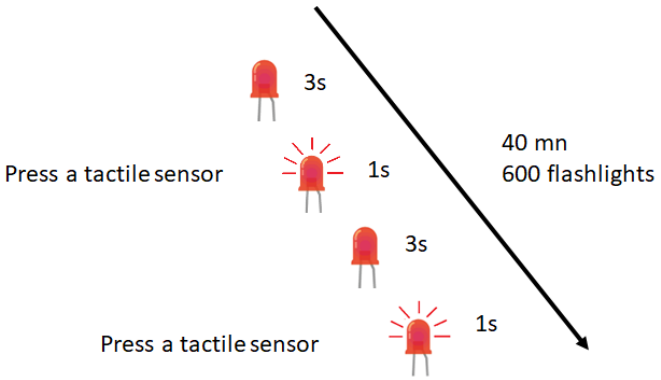


Figure 3: The serial flow of elements in one trial of the Sustained Attention to Response Task (SART) and standardized procedure.

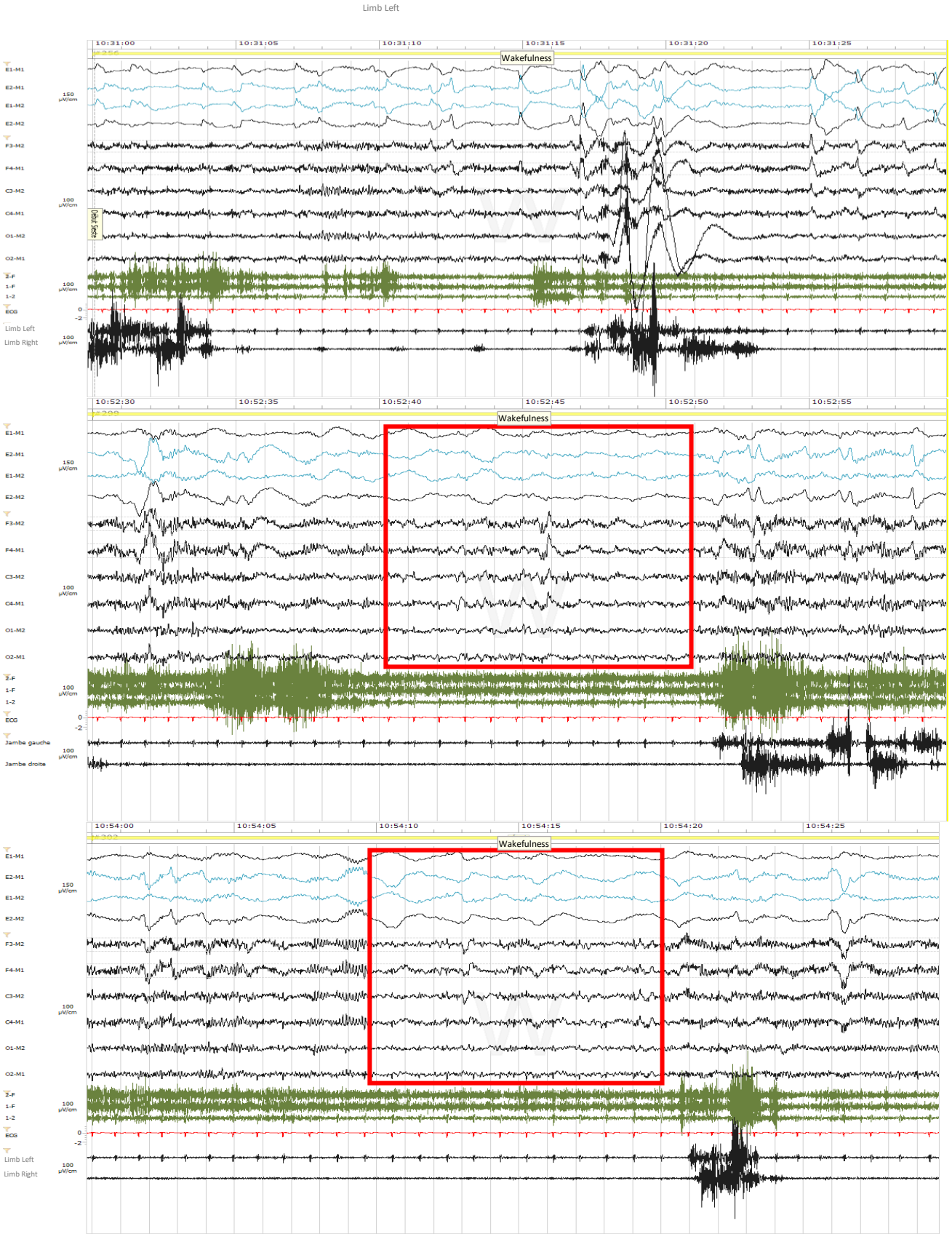


The subject is comfortably installed in a semi-seated position in a dark, noise-free room

Light-emitting diode device placed at eye level, two meters away from the subject's head

Instruction: "press the button on the device you are holding in your hand in response to the flash of light emitted by the diode"

Figure 4: The serial flow of elements in one trial of the Oxford Sleep Resistance Test (OSLeR) and standardized procedure.


Limb Left
10:31:00
10:31:05
10:31:10
10:31:15
10:31:20
10:31:25
Wakefulness
E1-M1
E2-M1
E1-M2
E2-M2
F3-M2
F4-M1
C3-M2
C4-M1
O1-M2
O2-M1
Z-F
1-F
1-2
ECG
Limb Left
Limb Right
150 µV/cm
100 µV/cm
0
-2
10:52:30
10:52:35
10:52:40
10:52:45
10:52:50
10:52:55
Wakefulness
Jambe gauche
Jambe droite
10:54:00
10:54:05
10:54:10
10:54:15
10:54:20
10:54:25
Wakefulness

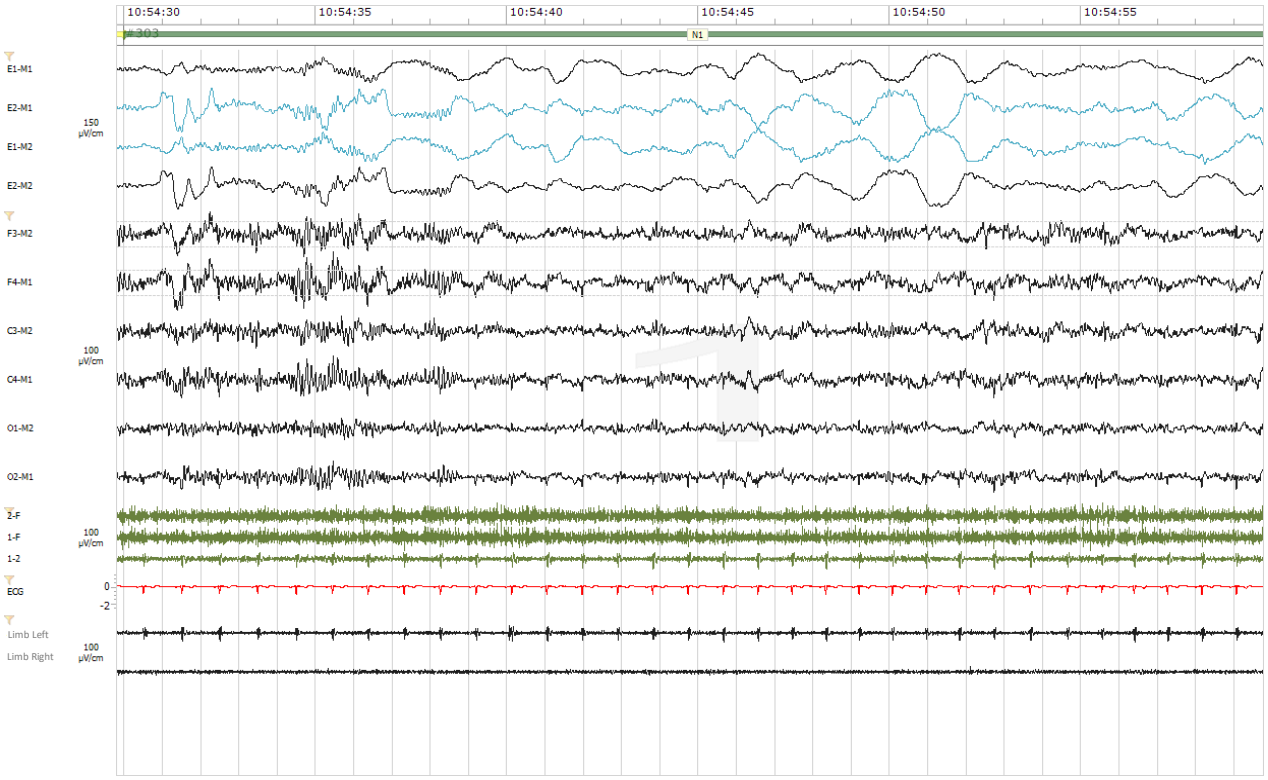


Figure 5: Three 30-second epochs recorded during Maintain Wakefulness Test. Epoch 1: wakefulness. Beginning of the MWT: 10:31:00. Epoch 2 (10:52:30): Wakefulness with a microsleep of 11 sec (red square). Epoch 3 (10:54:00): Wakefulness with a microsleep of 10 sec (red square). Epoch 4 (10:54:30). First epoch of sleep, N1. Sleep latency=23min30sec. The epochs 2and 3 are scored as Wakefulness because they do not meet the criteria for sleep onset (more than 15 seconds from any stage of sleep)

Neurophysiological tests			
	Main indications	Usefulness, normal and abnormal values	Limits
MSLT	Determination of the severity of daytime physiological sleepiness Diagnosis of central hypersomnias, (especially of NT1)	The most widely used test “Gold Standard” Recommended protocols for the administration of MSLT Validity in healthy subjects Normal mean sleep latency > 11 min. Abnormal : mean sleep latency ≤ 8 min ≥2 SOREM (including nocturnal sleep)	Normative values are ancient and on a small number of subjects Floor effects, poor discrimination of the sleepiest subjects Low sensitivity, specificity and consistency over time for some diseases (NT2, IH for exemple) Effect of REM suppressant drugs on presence of SOREM Effect of age on sleep latency Effect of sex not confirmed
MWT	Determination of the severity of manifest sleepiness Determination of the efficacy of the treatments against sleepiness (CPAP or drugs). Use, in France, for functional evaluation of driving license Not a diagnostic test	Recommended protocols for the administration of MWT The only test to measure “resistance to sleep” Normal mean sleep latency AROUND 35 min. Abnormal mean sleep latency < 8 min Grey Zone between 8 and 35 min	Normative values are ancient and on a small number of subjects Ceiling effect and difficulty to determine lower normal value No reliability data Objective control of sleep (PSG) just before the test is optional Effect of age on sleep latency Effect of sex, not confirmed

Neuropsychological tests			
	Main indications	Usefulness, normal and abnormal values	Limits
PVT	Evaluation of the evolution of manifest sleepiness during sleep deprivation protocol Evaluation of the daily functioning Not a diagnostic test	Widely used in healthy subjects No normal and abnormal values No correlation with MSLT and MWT Correlation with subjective sleepiness	No recommended protocols for the administration of PVT trait-like differences in vulnerability of sleep deprivation Important effect of age on reaction time. Effect of sex not confirmed
SART	Evaluation of the severity of manifest sleepiness Evaluation of the daily functioning Determination of the efficacy of the treatments against sleepiness (especially in patients with narcolepsy). Not a diagnostic test	Widely used in patients with central disorder of hypersomnolence Normal SART errors ≤5 Abnormal SART errors > 5 No correlation with MSLT and MWT	Normative values are validated on a small number of subjects No recommended protocols for the administration of SART Effect of age on SART performance Effect of sex not confirmed
OSLeR	Evaluation of the severity of daytime manifest sleepiness Determination of the efficacy of the treatments against sleepiness (especially in treated or not treated patients with OSA). Not a diagnostic test	Widely used in patients with OSA or in management of residual sleepiness in OSA. No normal and abnormal values Correlation with MWT and PVT	No recommended protocols for the administration of OSLeR No analysis of the effect of age and sex on OsleR sleep latency

Table 1 : Main indications, Usefulness, normal and abnormal values and limitation of neurophysiological and neuropsychological tests.