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THEORETICAL REVIEW

Distinguishing sleepiness and fatigue: focus on definition and measurement

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Summary Sleepiness and fatigue are two interrelated, but distinct phenomena; observed in a number of psychiatric, medical and primary sleep disorders. Despite their different implications in terms of diagnosis and treatment, these two terms are often used interchangeably, or merged under the more general lay term of 'tired'.

Sleepiness is multidimensional and has many causes (multidetermined) and distinguished from fatigue by a presumed impairment of the normal arousal mechanism. Despite its ubiquity, no clear consensus exits as yet as to what constitutes sleepiness. Definitions of sleepiness, to date, are at best operational definitions, conceptualized so as to produce specific assessment instruments. As a result, while a number of subjective and objective measurement tools have been developed to measure sleepiness, each only captures a limited aspect of an otherwise heterogeneous entity.

Fatigue is an equally complex phenomenon, its nature captured by a number of conceptualizations and definitions. Measures of fatigue have remained subjective, with a 'gold standard' for its measurement remaining elusive. Despite a high prevalence and high degree of morbidity, fatigue has remained a relatively under appreciated symptom, from both a clinical and research point of view.

Introduction

It is not an uncommon experience for a clinician, both in sleep medicine and other fields, to be faced with the patient presenting with a chief complaint of being 'tired'. Such patients, and often their physicians, are usually unaware of the heterogeneity of potential symptoms inherent in this general lay term, not the least of which are the entities of sleepiness and fatigue. As a result, sleepiness and fatigue are two terms often used interchangeably, in both clinical practice and in the research literature, despite the distinct implications each of them has in terms of diagnosis and treatment. In fact, these two symptoms can be difficult to separate. This paper will attempt to outline the nature of both sleepiness and fatigue, with the ultimate goal of providing a framework for defining and evaluating between these two complex phenomena.

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Sleepiness

Definition and mechanisms

Sleepiness is an ubiquitous phenomenon, experienced not only as a symptom in a number of medical, psychiatric and primary sleep disorders, but also as a normal physiological state by most individuals over any given 24 h period. Pathology is inferred both when its presence becomes pervasive (as in narcolepsy) or in its absence (as in insomnia). Alternatively, sleepiness can be considered abnormal when it occurs at inappropriate times, or does not occur when desired. Consequently, no clear consensus has been reached as to when sleepiness is considered 'excessive', thus accounting, in part, for the 100-fold difference in prevalence estimates of daytime sleepiness; with a range of 0.3–35.8% found in various population studies.[1]

Furthermore, no clear consensus has been reached as to what precisely is entailed by the universal experience of 'sleepiness'. As several authors have pointed out, definitions of sleepiness are at best operational definitions, conceptualized so as to produce specific assessment instruments for particular aspects of an otherwise heterogeneous phenomenon.[2-4] One generally accepted, if not tautological, definition of sleepiness is that of one's tendency to fall asleep, also referred to as sleep propensity. This definition is based primarily on one of the first standardized assessment tools, the multiple sleep latency test (MSLT) and forms the basis of most measures of 'objective sleepiness', entailing as it were a readily observed behavioral and physiological phenomenon—the act of falling asleep. As several authors have commented, sleep propensity should be distinguished from somnolence or drowsiness, the transitional state between wakefulness and sleep associated with a number of subjective feelings and symptoms, sometimes referred to as 'subjective sleepiness'.[2,5,6] This more direct, phenomenological experience is presumably more encompassing than sleep propensity, correlating not only with a greater tendency to fall asleep but also a number of other sleep related variables including decreased cognitive and psychomotor performance, mood, motivation, autonomic and other physiological changes, fatigue and general 'sleep need'. This distinction between sleep propensity and somnolence or 'objective sleepiness' and 'subjective sleepiness' may also explain the subjective reports of sleepiness in patients with insomnia and psychiatric disorders, despite a lack of corroborating objective evidence,[7] as well as the differential responses to interventions as simple as caffeine ingestion.[8] 'Sleepiness', however, has become synonymous with the more restrictive definition of sleep propensity, a simplification that at the very least has allowed an approach to understanding sleepiness as more global, multidimensional phenomenon.

Johns[5,6,9] has provided one of the clearest conceptualizations of sleepiness as it applies to sleep propensity, using a four-process model of sleep and wakefulness. In this model the states of sleep and wakefulness are determined by the interaction between a sleep drive and a putative wake drive (which has until recently been relatively under appreciated in comparison with the sleep drive). Each drive, in turn, consists of primary and secondary components, accounting for the four-process model. Primary drives are derived from intrinsic neuronal activity in the central nervous system (CNS) with both the primary sleep and wake drives being influenced by circadian and ultradian rhythms. Secondary drives account for the effect of homeostatic, environmental (posture, light, etc.), and various behavioral factors. Each of the four processes is seen as varying independently from each other but with mutual and mainly inhibitory interactions. 'Sleepiness', or more specifically sleep propensity, is seen as a function not of the absolute magnitude of any particular drive, but the interaction between the total sleep drive (primary and secondary) and the total wake drive (primary and secondary). Other authors have also emphasized the need to consider sleep propensity as both a trait (long term, person specific) and state (short term, situational) phenomenon to account for the influence of primary and secondary processes.[3,10] The postulated division between opposing sleep and wake drives is consistent with advances in the understanding of the neurobiological determinants of sleep and wakefulness, with independent but mutually interacting sleep promoting and wake promoting neuronal systems being identified.[11] Implicit in such models is the understanding that sleepiness, in contradistinction to fatigue, is caused by an alteration or imbalance in sleep/wake mechanisms, a necessary and sufficient prerequisite. Fatigue may also result from such dysfunction, but not necessarily so.

In light of the above considerations, one may begin to critically assess the efficacy of various assessment tools used to gauge and individual's level of 'sleepiness'.

Assessment of sleepiness

Subjective measures of sleepiness

One of the first, and still most widely used measures of subjective sleepiness is the Stanford Sleepiness

Scale (SSS, Appendix A).[12] The SSS consists of seven ranked statements describing various degrees of alertness/sleepiness from '1—feeling active and vital; alert; wide awake' to '7—almost in reveries; sleep onset soon; lost struggle to remain awake'. Subjects are asked to choose the one statement that best describes their present state of sleepiness. The developers of the scale claimed that they found ratings made every 15 min to be sensitive to discrete changes in sleepiness.[12]

A closer examination of the statements contained within the SSS reveals a mixture of adjectives describing sleep propensity, energy/fatigue and cognitive performance. Indeed, a factor analysis suggested a three-component factor in its structure ('alertness/sleepiness', 'loss of control', and a 'cognitive factor').[13] This would account for the lack of a significant correlation between the SSS and the multiple sleep latency test (MSLT).[8] Thus, as Johns[5] has pointed out, the SSS does not measure sleep propensity directly; limiting its validity as a measure of sleep propensity, but perhaps increasing it as a more global measure of 'sleepiness'.

A similar rating scale to the SSS is the 9-point Karolinska Sleepiness Scale (KSS) developed by Akerstedt and Gillberg.[14] Ordinal scales such as the KSS and SSS, however, may not be as sensitive markers of state sleepiness as simple Visual Analogue Scales (VASs).[15] whereby subjects are asked to indicate on a 100 mm line their subjective experience between two extremes. However unless appropriate care is given when querying subjects, ambiguities can arise as even VAS's querying how 'alert/drowsy' or 'very alert/very sleepy' one is, may not necessarily indicate sleep propensity if a direct measure of such is desired. On the other hand, a battery of VASs, given at a particular time, may best account for the multi-factorial nature of 'subjective sleepiness'. There are specific methodological issues in using Visual Analogue Scales, which are beyond the scope of this review but suffice it to mention, that the greatest utility of VASs is in longitudinal assessments of an individual combined with standardization of the range of the scale used if comparison between individuals are to be made.[15,16]

The SSS, KSS and VASs are all measures of state sleepiness, i.e. a subject's level of sleepiness at a particular time, which may be normal or abnormal. Such measures are more useful for research purposes, as in determining fluctuations in sleepiness in response to circadian factors, environmental stimuli, drug effects and so forth. Several attempts have been made to design subjective instruments to measure trait sleepiness, i.e. a subject's more enduring and stable level of daytime sleepiness. This is more relevant from a clinical point of view in determining the presence of pathology or simply predicting whether sleep onset is likely to occur at inappropriate times. The Epworth Sleepiness Scale (ESS, Appendix B), developed by Johns,[17] is a widely used and validated measure that falls into this category. The ESS is a self-administered questionnaire that asks subjects to rate their chance of falling asleep or dozing on a scale of 0–3 in eight soporific situations, ranging from 'Lying down to rest in the afternoon when circumstances permit' to 'In a car while stopped for a few minutes in traffic'. The sleep propensity on each of the items on the ESS have been shown to have significant but not close correlations to each other, thus covering a range of diverse soporific situations.[18] A total score from 0 to 24 is determined, with values over 10–11 indicating abnormal or pathological sleepiness.[19] The ESS has been shown to measure only one variable (presumably sleep propensity) with a high level of internal consistency and test-retest reliability over a period of 5 months in healthy subjects.[18,20] The original intent of the ESS was to measure sleep propensity over 'recent time', i.e. from week to week or longer, circumventing intraday and even day-to-day fluctuations.[17,20] More specifically the ESS is felt to measure average sleep propensity (ASP), postulated to be a general individual characteristic independent of any particular soporific situation a subject may be faced with. In this sense the ESS's measure of ASP represents an individual's trait level of sleepiness, while a particular state level of sleepiness is seen as a function of the subject's ASP, the soporific nature of a given situation ('somnificity') and subject-situation interactions depending on an individual's perception and response to each situation.[9,18]

The ESS has been shown to distinguish obstructive sleep apnea (OSA) from primary snoring. It correlates with respiratory disturbance index (RDI) and minimum oxygen saturation (SaO2).[5,17] It has been shown to improve with continuous positive airway pressure (CPAP) treatment for OSA over a period of 3-9 months.[20-22] However, some investigators have failed to find a significant correlation between the ESS and measures of OSA severity.[21,23-26] The scale has also been shown to indicate improvement in patients treated for narcolepsy.[21,27]

The main criticism of the ESS has been the fact that it relies on self-reporting of symptoms, leaving it open to misinterpretation, unintended bias and outright falsification for any number of reasons.[18] Several investigators have found significant but only modest correlations between the ESS and the 'gold standard' measure of objective sleepiness, the MSLT, in both normal and clinical populations,[17,18,23,24,28,29] while others have found no such correlation.[21,25,30] Of note, neither Johns[18] nor Chervin et al.[23] found a significant correlation between the MSLT and ratings from item 5 on the ESS 'Lying down when circumstances permit', which is presumably a close, albeit imperfect, simulation of MSLT conditions. Chervin et al.[23] also found that mean subjective sleep latency on the MSLT did not correlate with mean objective sleep latency, suggesting a significant role of recall bias (at least with respect to timing of sleep onset). While Johns[18] found no significant difference between ESS ratings filled out by patient or their spouses, Walter et al.[26] found a tendency for bed partners to give higher ESS scores than patients themselves. Olson et al.[24] found an overall close agreement between patient and spouse scores, but with more marked differences at lower ESS scores. Likewise a significant but again modest correlation has been found between the ESS and the maintenance of wakefulness test (MWT) in patients with narcolepsy[28] and sleep apnea.[31]

While the ESS is often classified as a measure of 'subjective sleepiness', it should not be confused with a direct measure of somnolence as discussed above. More accurately, the ESS is a subjective assessment of sleep propensity.[19] However, as Johns[17] intended, subjects are specifically queried as to the estimated probability of falling asleep in a given situation, as opposed to the actual frequency of having done so, a design intended to circumvent lifestyle differences. This raises the possibility of subjects basing their estimates of sleep propensity on their subjective levels of somnolence, and hence contaminating the validity of the ESS as a measure of sleep propensity. Several investigators have found a number of potential confounding factors in the ESS including age,[23] gender,[25] psychological symptoms[24] and fatigue.[32] Also of interest Engleman[22] reported a significant correlation between the ESS and MSLT prior to CPAP treatment, but not after, suggesting the differential effects of treatment on different aspects of sleepiness, as measured by these two instruments.

A further limitation of the ESS is that in circumstances that the subject has not experienced the specific scenario presented by the scale the subject is asked to tell what his/her expectation of sleepiness in that scenario may be less of a behavioral rating scale and potentially introducing a form of bias between subjects.

While some have questioned both the validity and reliability of the ESS,[33] it has nonetheless become one of the most widely used tools for the assessment of sleepiness,[33] in large part because of its ease of use and cost effectiveness in comparison to more labor intensive instruments such as the MSLT and MWT.

Objective measures of sleepiness

The multiple sleep latency test. The multiple sleep latency test (MSLT) is one of the first and still most widely used measures of objective sleep propensity. In accordance with standardized guidelines[34] the MSLT is the best scientifically validated objective test of excessive sleepiness and it must be performed following an over night polysomnogram. The MSLT consists of 4-5 nap opportunities (sessions) at 2 h intervals across the day, beginning 1.5-3 h after waking up. Each session includes 20-30 min of electrophysiological and electrooculogram recordings. Subjects are asked to lie in a quiet darkened room and are encouraged to fall asleep. Electrophysiological recording is done with a standard recording montage with sleep latency being defined as the elapsed time from lights out to the first epoch scored as sleep. Electrooculogram (EOG) recording also allows for the detection of sleep onset of the rapid eye movement periods (SOREMPs). The nap opportunity is terminated after 20 min if no sleep has occurred, or 15 min after sleep onset to allow for the detection of SOREMPs. While the MSLT provides a distribution of sleep latencies across the day, the average sleep latency over the 4–5 nap opportunities is taken to be a measure of sleep propensity. A mean sleep latency of 10–15 min is generally considered indicative of mild or even normal level of daytime sleepiness; 5–10 min indicative of moderate sleepiness (or in the diagnostic arena a 'grey zone'); and <5 min indicative of severe or 'pathological' sleepiness.[34]

The MSLT has been demonstrated to have a high test-retest reliability in healthy normals over a period of 4–14 months ($r=0.97$),[35] but less so in insomniacs.[36] High inter-rater and intra-rater reliability has also been demonstrated for the MSLT in a clinical population,[37] an important consideration given its reliance on electroencephalographic (EEG) sleep onset scoring.

The MSLT has been demonstrated to be sensitive to manipulations in nocturnal sleep, including sleep restriction, sleep deprivation and sleep extension[29,38] as well as diurnal variation.[29,39] The MSLT has also been shown to be sensitive in detecting sleepiness in a variety of sleep disorders including narcolepsy, obstructive sleep apnea, idiopathic hypersomnia, periodic limb movement in sleep (PLMS) and use of sedative medications.[34] Certain authors[40] have found significant but modest correlations between the MSLT and measures of apnea severity, while others have not.[41]

There are a number of criticisms of the MSLT, beginning with the question of what precisely is being measured by this instrument. The MSLT, strictly speaking, measures the rate of falling asleep under a specific set of circumstances, a variable which is taken to indicate a subject's sleep propensity.[42] This is an operationalization of sleep propensity which is distinct form that of the ESS, which is a subjective assessment of one's *probability* of falling asleep in a number of situations. Thus one has two concepts of what constitutes sleep propensity, with a relationship to the more general term 'sleepiness' being even less clear, and it does not immediately follow that sleepiness entails solely being able to fall asleep rapidly when circumstances permit. Harrison and Horne,[43] for example, argued for a group of subjects with low MSLT scores but no other signs of sleep pathology or even sleepiness, described by the authors as 'high sleep ability without sleepiness'. Conversely one can hypothesize as to a group of subjects with 'high sleepiness without sleep ability', as in patients with psychophysiological arousal or depression. In this vein, several alternatives to scoring the MSLT have been proposed. For example, Clodoré et al.[39] suggested that sleep onset frequency on the MSLT may be a better indicator of diurnal sleepiness than mean sleep latency, while Pollack[44] found 'wake efficiency' (100% time asleep) to be the best measure of daytime sleep tendency.

The original designers of the MSLT intended it to be a measure of 'physiologic sleep tendency' akin to the primary sleep drive, in contrast to 'manifest sleep tendency' which is subject to a number of factors akin to secondary sleep and wake stimuli.[45] The MSLT is purported to measure such an underlying state as it measures sleep tendency under optimal conditions, i.e. in the absence of alerting stimuli (light, noise, recumbancy etc.). However, as several authors[6] have pointed out, the MSLT is not completely free of such stimuli which may include the effects of psychophysiologic arousal, the effects of the intrusive recording apparatus and so forth; with the potential of prolonging sleep latency in an otherwise sleepy individual. It is highly likely that trait anxiety plays a role in the results obtained in the artificial setting of the sleep clinic.

Johns[6,19] has also argued that the MSLT measures sleep propensity in only one given situation i.e. while lying in a quiet darkened room over a relatively short period (the day of the study). The ESS, in contrast, assesses sleep propensity in eight different situations, over a period of weeks, suggesting that the mean sleep propensity encompassed by the ESS score may be a more valid measure of the primary sleep drive, or at least has more ecological validity as a measure of general sleep propensity. This could account for the low correlation between the ESS and MSLT. Thus while the MSLT may be seen as a highly reliable and valid measure of objective sleepiness, given that it is conducted in a relatively optimally sleep conducive and controlled environment, this same context limits its generalizability, for instance, in an assessment of driving suitability for example.

Finally, from an operational point of view, the stratification of degrees of sleepiness based on MSLT scores and the designation of 'pathological sleepiness' is based on general consensus and open to dispute. Johns[19] suggested that the reference range of normal MSLT values, based on published studies, should be 3.2–20 min (mean $\pm$2 SD). This brings into serious question not only the validity of the accepted criteria, but also the test's discriminative properties. Conversely, excessively sleepy patients often exhibit very short sleep latencies on the MSLT with an inability of the test to distinguish degrees of sleepiness among them or pre and post treatment. This is called 'floor effect'.[46]

The maintenance of wakefulness test. The maintenance of wakefulness test (MWT)[47] was designed in part to provide a more sensitive and clinically valid measure of sleep propensity than the MSLT, specifically the ability to maintain wakefulness when called upon to do so, as opposed to allowing oneself to fall asleep. Several early studies demonstrated that simply instructing patients to 'try and stay awake', under the exact same conditions as the MSLT (the repeated test of sustained wakefulness-RTSW), resulted in significantly longer sleep latencies than the MSLT[46] and provided a more sensitive indicator of variation in sleepiness/alertness.[46]

The MWT, for which guidelines have been established,[48] extends this paradigm. Subjects are asked at two hour intervals to sit upright in bed in a quiet, darkened room and instructed to 'remain awake' for a specified period of time, with 20, 30 and 40 min protocols being described. For the 20 min protocol a mean value of 18.1$\pm$3.6 min has been described in normals, suggesting a lower limit of 10.9 min.[48] The MWT has been demonstrated to be sensitive to manipulation in sleep time.[46] The test has also been demonstrated to be capable of discriminating normals from patients with a variety of disorders associated with excessive daytime sleepiness including narcolepsy and OSA[48] and to be sensitive to treatment effects.[49]

Significant but modest correlations have been found between the MWT and MSLT.[50] Sangal et al.[50]

found a high level of discordance between the two measures, i.e. some patients with low MSLT scores were able to remain awake on the MWT, while some were unable to remain awake on the MWT but could not fall asleep quickly on the MSLT. A factor analysis in this study suggested that two factors: 'sleepiness' and 'alertness' accounted for 91% of the variance in the two measures, with sleepiness loading heavily on the MSLT and alertness loading heavily on the MWT. The authors, and many others subsequently, concluded that the MSLT and MWT measure different abilities, despite the fact that both relate to 'sleep propensity'. The MSLT is felt to measure physiological sleepiness, akin to the primary sleep drive; while the MWT measure alertness or 'wakefulness' presumably akin to the primary wake (arousal) drive with an additional influence of recumbancy (Bonnet and Arand[51] have shown that it is both the effects of instruction and posture which distinguishes MWT scores from MSLT scores).

'Alertness' or even 'wakefulness' in the context of the MWT is an operationalization of these terms to mean ability to resist sleepiness (i.e. remain awake), an attempt to provide objective measures of these variables. However, it should be noted that this concept of alertness is a distinct and more restrictive phenomenon than that entailed by the subjective experience of alertness, which would include not only an ability to resist sleepiness, but also other variables such as the ability to perform complex tasks and cognitive functions (sometimes referred to as vigilance), positive mood, motivation, and so forth; a relation analogous to that between sleep propensity and somnolence noted earlier.

As a measure of trait 'wakefulness' or wake drive, the MWT suffers from the same limitations as the MSLT, in particular, the fact that it measures only short term wakefulness (the day of the study), in only one, fairly soporific situation; rendering it incompletely distinct from the sleep drive, and limiting its generalization to other situations (such as driving). Nevertheless the MWT does provide a standardized measure of a subject's ability to remain awake under maximally soporific conditions (other than being recumbent), a potentially more clinically valid measure of sleep propensity for patients presenting with this very complaint ('I cannot stay awake') or in the context of safety or medical-legal assessments (i.e. driving safety).

Appendix C, Xin Chart, is a graphic form of data for the MSLT and MWT, which is provided based on published results.[52] The Xin Chart was organized by Xin Huang, a PhD researcher working in our laboratory.

Pupillometry. Pupillometry, in its most common form, involves seating patients in a darkened room and asking them to remain awake and fixate on a red target for a period of 15 min. Over this time period, pupil diameter measurements are made by means of an infrared pupillometer. Various pupillometer variables, related to spontaneous pupillary diameter variability, are felt to be indicative of sleepiness/wakefulness.[53] McClaren et al.[53] found a significant but modest correlation between a number of pupillometry variables and means of sleep latency on the MSLT. Furthermore they found a poorer ability of pupillometry to discriminate various degrees of excessive daytime sleepiness in a clinical (hypersomnolent) population in comparison with the MSLT. This is not surprising given that the pupillometry procedure is more akin to the MWT than the MSLT.

From a technical point of view, pupillometry measures changes in autonomic activity secondary to alterations in arousal and probably numerous other factors. While such changes in autonomic activity may, at face value, be related to state somnolence or vigilance, their relationship to sleep propensity remains to be elucidated. Pupillometry, despite offering a convenient way of measuring sleepiness/wakefulness, has found limited clinical use, in part because of its complicated nature, expense and lack of studies demonstrating its clinical utility.

Evoked potentials. Long latency cortical and 'cognitive' or 'event related' evoked potentials (primarily auditory) have been demonstrated to be altered in sleep and sleepiness, and altered in a variety of sleep disorders, including narcolepsy and OSA. While such evoked potentials may provide an objective means of assessing somnolence not observed with standard behavioral measures, their diagnostic use has been limited by a large degree of inter-subject variability.[54] Furthermore one may once again question the relationship between somnolence (or more specifically decreased cortical responsiveness) as measured by such potentials, and sleep propensity. Bastuji and Garcia-Larrea[54] have argued that evoked potentials may be more useful in assessing 'sleep inertia' in forced awakening paradigms.

Cognitive and psychomotor function. A number of cognitive and psychomotor tasks have been developed to test the effects of sleep impairment and treatments on cognitive and psychomotor performance.[55] Such measures, however, do not measure sleepiness or sleep propensity directly, but rather the effects of somnolence on the efficiency of brain functioning, as suggested by a functional magnetic resonance imaging (fMRI) study by Starbuck et al.[56] The relationship between sleepiness and cognitive/psychomotor performance may be determined by a number of factors including individual trait-like vulnerability.[57]

Alpha attenuation test. The alpha frequency of EEG power changes when individuals move from alertness toward sleepiness, namely, when eyes are closed the alpha frequency range decreases and when eyes are open it increases. The alpha attenuation test (AAT) is based on these findings. During the AAT, individuals are arranged in an illuminated room and instructed to open and close their eyes 8 times, with each opening and closing lasting for 1 min. Stampi et al.[58] found that, in eight of the 10 participants, the AAT correlated significantly with the MSLT. These correlations were higher than the correlations between MSLT and the subjective sleepiness measurements. Alloway et al.[59] did an AAT in 10 drug-free patients with narcolepsy–cataplexy and 10 normal persons matched for age and gender. The results showed that the ratio of mean eyes-closed to mean eyes-open alpha power was significantly smaller for narcoleptics than the normals. It was described that the AAT could substitute the MSLT to distinguish the patients with excessive daytime sleepiness, such as narcoleptics, from normal controls.

Fatigue

Scope of the problem

Fatigue, like sleepiness, is a highly prevalent phenomenon, associated with a significant level of physical and psychosocial morbidity. It is a commonly reported chief complaint in both primary and specialty medicine. Fatigue is the primary symptom of chronic fatigue syndrome (CFS), and is associated with a number of acute and chronic illnesses, such as rheumatoid arthritis, cancer and multiple sclerosis. It is also prevalent in certain medical treatments, such as radiation or chemotherapy. In many such cases fatigue is often one of the most important sources of disablement, often reported by patients with significant ill health as one of their most severe symptoms.[3,60–63] Fatigue has been identified as major debilitating and even life-threatening factor in working populations.[64]

Despite the ubiquity of fatigue as a chief complaint, it is often only identified and treated in a relatively small proportion of those affected. Several factors may contribute to this tendency. Firstly, some of the features of fatigue and excessive daytime sleepiness (EDS) may overlap, making the precise recognition of fatigue difficult. While researchers and clinicians in sleep medicine have made attempts to clarify the differences between fatigue and EDS, the broader medical literature, and most practitioners, are either unable or disinclined to distinguish between them. This may be, in part, due to the difficulty patients themselves have in distinguishing between these two symptoms. Terms regarding fatigue and EDS are frequently used interchangeably, or under the general rubric of being 'tired'. Even in sleep medicine, fatigue may not be properly recognized. Instead of sleepiness, some sleep apnea patients may experience fatigue as their prominent symptoms. One study, for example, found that 46% of CFS patients met the minimal polysomnographic (PSG) criteria for obstructive sleep apnea syndrome. In this, and other sleep disorders, fatigue may not be discussed as often as sleepiness.[4] Secondly, fatigue, whether conceptualized as a unitary or multidimensional phenomenon, is ultimately a subjective experience, and the measurements of fatigue are essentially subjective. To date, there is no objective 'gold standard' to measure fatigue. This has led some clinicians to overlook the existence of fatigue.[65] Finally, patients have been generally found to under-report fatigue.[4]

Defining fatigue

An accepted and sufficiently accurate definition of fatigue is the first step towards achieving the further aims of detecting fatigue and increasing the available means of treating it. However, such definitions have proven elusive, in part because fatigue is a complex phenomenon, involving a number of psychosocial and behavioral processes. As a result, various definitions have been proposed. Some of these existent definitions of fatigue have attempted to define it in terms of its source, while others have viewed it from a behavioural perspective, treating fatigue as impairment in performance. Some authors have distinguished normal fatigue from pathological fatigue, while others simply view normal fatigue as being acute and pathological fatigue as being chronic. Some consideration has also been given to psychological vs. physical fatigue.[61,65]

Currently, a number of conceptualizations of fatigue have considered it along dualistic lines.

Acute vs. chronic fatigue

Acute fatigue generally occurs in healthy individuals, and is perceived as a normal protective function of the body. It has a rapid onset and is of short duration, and is usually linked with a single cause. After a rest, exercise, and/or stress management, acute fatigue is usually alleviated. Overall, it has minor or minimal effects on daily activities or quality of life. Chronic fatigue, on the other hand, primarily affects clinically disordered populations and is perceived as abnormal, unusual, or excessive. Chronic fatigue generally is insidious in onset, persists over time, and is usually multi-factorial in etiology. It is generally not relieved by usual restorative techniques. It negatively and significantly affects the daily activities and the quality of life of an individual.[61]

Physiological vs. psychological fatigue

Physiological fatigue is a loss of maximal force-generating capacity during muscular activity or a failure of the functional organ. It may be induced by excessive energy consumption; or the depletion of hormones, neurotransmitters or essential physiological substrates. Physiological fatigue may be associated with fever, infection, anemia, sleep disturbances, and pregnancy. Psychological fatigue, in contrast, has been defined as a state of weariness related to reduced motivation. Psychological fatigue has been associated with stress and other intense emotional experiences and may accompany depression and anxiety.[61,66]

Central vs. peripheral fatigue

Central models of fatigue imply a malfunction of the CNS, such as impaired transmission between the CNS and the peripheral nervous system, or dysfunction of selected areas of CNS such as the hypothalamic region. Peripheral models of fatigue, in contrast, view fatigue as resulting from dysfunction of the peripheral nervous system, such as impaired neuromuscular transmission at the motor-end-plate. Others, however, have used the term central to refer to a psychological etiology while using peripheral to refer to a physical etiology of fatigue.[4,61,65]

While dualistic approaches have proven to be popular, such definitions fail to capture the multidimensional nature of the fatigue. A number of other definitions for fatigue have been proposed. The North American Nursing Diagnosis Association has defined fatigue as: 'The self recognized state in which an individual experiences an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work'.[67] Ream and Richardson[68] defined fatigue as 'A subjective, unpleasant symptom which incorporates total body feeling ranging from tiredness to exhaustion, creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity'. Aaronson et al.[61] viewed fatigue as: 'The awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity'.

Our definition is that fatigue is an overwhelming sense of tiredness, lack of energy and a feeling of exhaustion, associated with impaired physical and/or cognitive functioning; which needs to be distinguished from symptoms of depression, which include a lack of self-esteem, sadness and despair or hopelessness.

Prevalence of fatigue

The prevalence rates of fatigue are high in the general population. Kroenke and Price[69] reported a prevalence rate for fatigue of 23.6% in a US population. An epidemiological follow-up sample indicated that 20% of the population had a lifetime prevalence of unexplained fatigue, lasting 2 or more weeks. A prevalence rate of 22% was found in a Norwegian sample,[70] and 18% in a UK sample.[4]

Fatigue is present in a variety of specific disorders including depression, cancer, renal failure, renal dialysis, and epilepsy. Among other conditions, fatigue has been reported in 46% of brain-injured patients, in 85% of multiple sclerosis patients, and in 50% of human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) patients.[30] Chervin[32] reported that fatigue (57%), tiredness (61%), and lack of energy (62%) are more frequent complaints than sleepiness (47%) in sleep apnea patients. In primary care, chronic fatigue is more common (20–25%) than excessive sleepiness (5–15%).[62]

Measurement of fatigue

A number of assessment tools with respect to fatigue have been developed. As noted, sleepiness has been measured both objectively with the MSLT and subjectively with, for example, the SSS or the ESS. However, as noted above, there is no objective tool to measure fatigue. It has been proposed that 'fatigability' is an objective inability to sustain power, which can be measured by electrophysiological methods, but to date, attempts to objectively measure fatigue have failed.[65] One study compared single-photon emission computed tomography (SPECT) scans between patients with chronic fatigue syndrome (CFS) and healthy persons when performing attention and working memory test. There were no group differences for the performance task, despite the fact that CFS subjects perceived them to require more mental effort to perform the task.[71]

Currently fatigue has typically been identified using a number of subjective scales. More than 30 scales are available for measuring fatigue. Seven of the most frequently used scales are described below.

Fatigue severity scale (FSS)

This nine-item fatigue severity scale is one of the best known and most used fatigue scales. The FSS items are principally measures of the impact of fatigue on specific types of functioning, relating to the behavioural consequences of fatigue rather than symptoms. The FSS has high internal consistency with Cronbach's alpha between 0.81 and 0.89. It is sensitive to change with time and treatment, and has good test-retest reliability. The FSS is able to distinguish patients with different diagnoses, such as between systemic lupus erythematosus (SLE) and multiple sclerosis (MS), and between chronic fatigue syndrome (CFS), MS and primary depression[65,72,73] Hossain et al.[62] successfully used the FSS to identify the shift workers with high fatigue from those with low fatigue.

Fatigue questionnaire (FQ)

The FQ originally consisted of 14 items with a subsequent revision to an 11-item questionnaire. The scale is comprised of two dimensions: Physical Fatigue and Mental Fatigue. This scale was developed for hospital and community studies with CFS and has been used in multiple studies. The FQ was found to be both reliable and valid. There was a high degree of internal consistency with a range of Cronbach's alpha of 0.88 and 0.90.[64] The validity of the FQ, in assessing fatigue, suggests that it is a useful tool for assessing fatigue in a variety of medical disorders. It has been used to assess fatigue in patients with cancer and HIV, and in other medical patients, and Gulf War veterans.[4,65,73,74]

Multidimensional fatigue inventory (MFI-20)

The MFI-20 is a 20-item self-report instrument. These items rate the severity of fatigue in the past week. The inventory covers 5 dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. It has good internal consistency and test-retest reliability. The MFI-20 was tested for its psychometric properties in cancer patients receiving radiotherapy, patients with CFS, psychology and medical students, army recruits and junior physicians. It was used to discriminate patients who had Parkinson's disease from those who did not have disease. The convergent validity of the MFI-20 was investigated by correlating the MFI subscales with a Visual Analogue Scale measuring fatigue with the correlation co-efficienct between 0.22 and 0.79.[61,73-75]

Fatigue assessment instrument (FAI)

The FAI is a 29-item fatigue assessment instrument that includes four subscales: Fatigue Severity, Situation Specificity, Consequences of Fatigue and Responsiveness to Rest/Sleep. The internal consistencies of the corresponding subscales are good to excellent with Cronbach's alpha values between 0.70 and 0.92.[76] The Fatigue Severity subscale has 11 items, eight of which correspond highly with the FSS mentioned above, indicating a good convergent validity.[76] Although its test-retest reliability is only moderate, the inventory, in general, has good psychometric qualities. The FAI is used to differentiate normal fatigue from medical disorders commonly recognized to have a large fatigue component and is able to distinguish differences between patients with different diagnoses.[76]

Fatigue impact scale (FIS)

This 40-item questionnaire is used to assess the impact of fatigue on different functioning areas, such as cognitive, physical and psychosocial functions. It has good internal consistency and reproducibility. The FIS was validated in a subject sample of patients with MS and hypertension. There were significant differences in the scores of these two groups. A discriminant function analysis was carried out in a group of CFS patients and a group of MS patients. The results showed that the FIS correctly classified 80.0% of the CFS group and 78.1% of the MS group when these groups were compared. This validation study indicates that the FIS has considerable merit as a measure of patients' fatigue symptoms.[77] The FIS is also a useful instrument to assess the impact of fatigue on patients' every-day lives.[77]

The brief fatigue inventory (BFI)

This nine-item scale was developed for screening and assessing clinical outcome in fatigued patients with cancer and it identified those patients with severe fatigue. The BFI is a reliable instrument. It is used for a rapid assessment of fatigue severity in both clinical screening and clinical trials. The BFI significantly correlated with two previously validated measures, the Profile of Mood States (POMS)

Fatigue subscale ($r=0.84$, $P<0.001$) and the Functional Assessment of Cancer Therapy (FACT) ($r=-0.88$, $P<$ 0.001), indicating that the BFI has good concurrent validity.[78]

Visual analogue scale for fatigue (VAS-F)

The VAS-F is an 18-item scale, which includes an Energy subscale (five items) and a Fatigue subscale (13 items). Six of the 13 Fatigue subscale items address behavioral manifestations of fatigue. The scale was developed to measure subjective symptoms of fatigue. It has good psychometric properties. The VAS-F was favourably compared with the Stanford Sleepiness Scale (SSS) and the Profile of Mood States and its internal consistency reliabilities are high.[61,64–66]

A number of other scales have also been reported. For example, Checklist Individual Strength (CIS), a 20-item scale, was developed to assess the severity and phenomenology of fatigue.[79] Functional Assessment of Cancer Therapy, Fatigue subscale (FACT-F), a 13-item instrument, is used to measure the severity and impact of fatigue in cancer patients.[80]

With respect to combined evaluation of sleepiness and fatigue, there are very few attempts to consider the interaction of fatigue and sleepiness as two separate but interacting processes.[81] There are even fewer attempts to assess these two qualities simultaneously and any attempt to do so usually draws the criticism that one is comparing apples and oranges in the sense that scales designed to measure 'sleepiness', e.g. the ESS, may focus on sleep propensity rather than sleepiness per se. If compared to the FSS, for example, both the format of the questions and the time frame, which the questionnaire covers, is different. In general, the scores obtained on the two questionnaires cannot be related to each other more than to indicate that one or another or both are in the pathological range. This is highly unsatisfactory. One exception to this is an adjectival checklist, the FACES, which sets out to measure the five 'faces' of fatigue and sleepiness.[82]

The FACES is a newly developed 50-item self-report questionnaire. It was modeled, in part, on a similar scale used in the field of pain. The FACES consists five subscales: Fatigue, Anergy, Consciousness, Energized and Sleepiness. The Fatigue subscale includes 15 items and the sleepiness subscale includes 10 items. Convergent and discriminate validity were evaluated by calculating correlations between FACES subscales and a number of independent indices. The results indicate that FACES offers a promising self-report instrument for the measurement of fatigue, sleepiness and related subjective experiences.[82] A limitation is that it is only applicable to English speaking populations.

Conclusion

The distinction between fatigue and sleepiness remains somewhat obscure, despite the development of a number of objective and subjective tools for measuring sleepiness, and numerous fatigue scales. Neither sleepiness, nor fatigue is unitary phenomena, each in themselves being complex, heterogeneous phenomena. Sleepiness and fatigue often coexist as a consequence of sleep deprivation, and are often grouped together by such patients under the complaint of being 'tired'. On closer examination, however, it can be seen that sleepiness and fatigue are two distinct, albeit interrelated symptoms.

Practice points

I As with sleepiness, no clear consensus has been reached as to what is entailed by the experience of 'fatigue'.
II Dualistic approaches, while popular, have failed to capture the multidimensional nature of this complex phenomenon.
III A lack of an objective test for fatigue, let alone a 'gold standard', has contributed to this lack of consensus, as well as causing fatigue to remain a relatively ignored as a legitimate subject for research.
IV As a result, fatigue has remained an under-recognized and under-treated phenomenon, despite its high prevalence and significant morbidity.

Research agenda

Further research should be directed toward not only the elucidation of the nature and treatment of each of these experiences, but also the relationship between them. We need to formulate a clear conceptualization of sleepiness and fatigue separately and then clarify the extent to which these energy states overlap and clarify in what ways they differ.

Appendix A. Stanford Sleepiness Scale (SSS)

For the following scale please check (√) the one statement that best describes you at present. Table A1

Table A1

1	Feel active and vital; alert, wide awake
2	Functioning at a high level, but not at peak, able to concentrate
3	Relaxed; awake; not at full alertness, responsive
4	A little foggy, not at peak; let down
5	Fogginess; beginning to lose interest in remaining awake; slowed down
6	Sleepiness; prefer to be lying down; fighting sleep; woozy
7	Almost in reverie; sleep onset soon; lost struggle to remain awake

Appendix B. Epworth sleepiness scale (ESS)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Using the following scale, circle the most appropriate number in the chart for each situation.

0 = would NEVER doze 1 = SLIGHT chance of dozing

2 = MODERATE chance of dozing 3 = HIGH chance of dozing Table B1

Appendix C. Xin Chart

Chart 1 provides the means and standard deviations (SD) for MSLT and MWT tests. It can be used to plot an individual patient's results and to give a quick

Table B1

Situation	Chance of dozing			
1. Sitting and reading	0	1	2	3
2. Watching TV	0	1	2	3
3. Sitting, inactive in a public place (e.g. a theatre or a meeting)	0	1	2	3
4. As a passenger in a car for an hour without a break	0	1	2	3
5. Lying down to rest in the afternoon when circumstance permit	0	1	2	3
6. Sitting and talking to someone	0	1	2	3
7. Sitting quietly after a lunch without alcohol	0	1	2	3
8. In a car, while stopped for a few minutes in the traffic	0	1	2	3

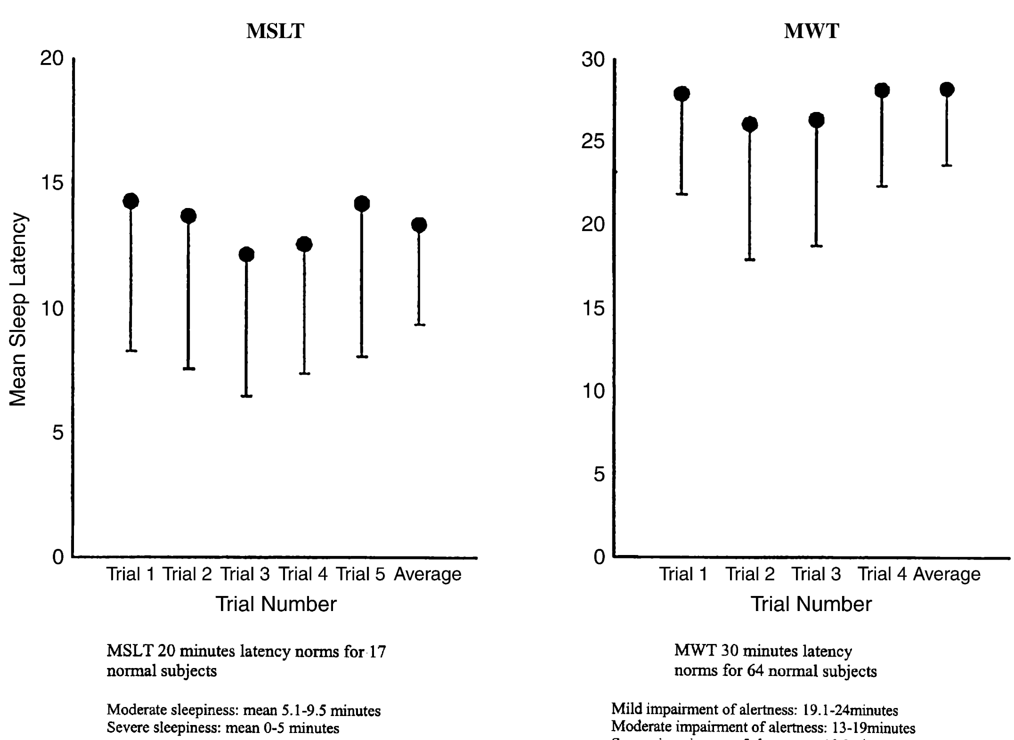

Chart 1.

Table D1

During the past week, I have found that:	Completely Disagree		Neither Agree Nor Disagree			Completely Agree	
	←	-	-	-	-	-	→
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life	1	2	3	4	5	6	7

graphic presentation of whether the results are normal.

Appendix D. Fatigue severity scale (FSS)

Using the following scale, circle the most appreciate number in the chart.

1 = Completely disagree 4 = Neither agree nor disagree 7 = Completely agree Table D1

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Glossary

Cronbach's alpha: A statistic that is used to estimate the reliability of a test.

Chronic fatigue syndrome (CFS): A disorder with fatigue as its major symptom. CFS patients sometimes feel too fatigues to do normal activities or are easily exhausted with no apparent reason. This condition can be months or years.

Electrooculogram (EOG): A study using electrodes placed around the eyes to detect electrical activities associated with eye movements.

Functional magnetic resonance imaging (fMRI): An instrument uses radio wave and a strong magnetic field to measure the quick tiny metabolic changes that take place in an active part of the brain.

Motor-end-plate: A flattened end of a motor nervous cell that transmits neural impulses to a muscle.

Multiple sclerosis (MS): A chronic disease of the central nervous system.

Periodic limb movement in sleep (PLMS): A common sleep disorder with repetitive movements, most typically in the lower limbs, which occur about every 20–40 s.

Polysomnography (PSG): A sleep diagnostic test during which a number of physiologic Variables are measured and recorded during sleep.

Single-photon emission computed tomography (SPECT): A type of nuclear imaging test that shows blood flows to tissues and organs.

Sleep apnea: A breathing disorder characterized by brief interruption of breathing during sleep.

Systemic lupus erythematosus (SLE): A chronic rheumatic disease that affects many parts of the body.