Dr Karren Towgood, Consultant Neuropsychologist with Re:Cognition, considers the impact of sleep deprivation and potential treatment regimes to help alleviate the significant detrimental effects of sleep deprivation on rehabilitation, recovery of function, mood, cognition and quality of life.

**Why do we sleep?**

On average we spend 36% of our time asleep, therefore if we live to the age of 90 we will have spent 32 years asleep (Foster, 2013). From this we can postulate that sleep serves an important function. Despite this sleep in the 20th century is not valued as it should be, with data suggesting we are sleeping less and less. In the 1980s we slept on average 8 hours per night, whilst in 2013 it was found that this had reduced to 6.5 hours sleep on average per night (Foster, 2013).

So what is sleep and why is it so important? Sleep is a complex amalgamation of physiological and behaviour processes which is made up of two separate states, rapid eye movement (REM) sleep and non-REM sleep. Discovery of REM sleep in the 1950s and observation that brain activity during REM sleep resembles that of the awake state led researchers to realise that sleep was an active process (Siegel, 2003).

Sleep is also an ordered process. The types and stages of sleep are organised in a series of cycles that repeat across the night (Espie, 2006). As we fall asleep we go into a transitional phase between wakefulness and sleep. This is a non-REM sleep stage called Stage 1. Stage 1 sleep lasts only a matter of minutes and then we progress to the second non-REM stage, Stage 2 sleep. Stage 3 and 4, also non-REM states, are often referred to as slow-wave sleep. During REM sleep the eyeballs move rapidly, whereas the rest of the body is usually almost paralysed. REM is a form of light sleep. It is during this stage of our sleep, which is estimated to comprise between 20-25% of our total sleep time, that we do most of our dreaming.

Two processes have been hypothesised to work together to regulate our sleep pattern, these are synaptic homeostasis and circadian rhythms (Espie, 2006). The interested reader is referred to Tononi and Cirelli (2006) and Pace-Schott & Hobson (2002) for further details on how these two processes are though to interact. Key areas of the brain thought to be involved in the process of sleep are illustrated in Figure 1 (over).
As Epsie (2006) has described sleep is not an optional extra in life, it is a fundamental requirement. There are a number of theories of why sleep is important, though as Siegel notes (2003) no one theory is as yet generally accepted or unequivocally proven. One theory of sleep which is particularly relevant for this paper is the proposed role of sleep in the promotion of memory consolidation (Diekelmann and Born, 2010). Consolidation refers to the process of turning initially labile memories encoded while awake into more stable representations that are integrated into network of long term memories (Diekelmann and Born, 2010). Memories are said to be replayed, modified, stabilised and enhanced while we sleep (Stickgold, 2006). Support for this proposed role of sleep has come from numerous studies that have shown that a period of sleep after learning enhances retention (for example see Stickgold, 2006 and Walker et al 2002). While a complete understanding of how these processes occur is not yet clearly established, the interested reader is referred Diekelmann and Born (2010) for further specific details of one hypothesised model. Sleep is also proposed to be important for allowing brain cells to restore and repair themselves, particularly after oxidative stress, to allow for brains to develop normally in early years (Siegel, 2003) and to allow for energy depletion to be reversed (Siegel, 2009).

**Impact of sleep deprivation**

Of relevance to understanding the importance of sleep in traumatic brain injury (TBI) cases is understanding the potential impact of sleep deprivation in the general population. Not surprisingly given the proposed role of sleep in memory consolidation sleep deprivation can produce a number of effects on our cognition (see Table 1).

From their review paper Lim and Dinges (2010) concluded that short term (one night) total sleep deprivation has significant negative impacts on cognition across all domains. Effect sizes range from
small to large (-0.125 to -0.762) with greater effect found on tasks of simple attention and vigilance. Effect sizes for working memory and complex attention were slightly smaller, falling in the moderate range. Interestingly, sleep deprivation was not however found to affect accuracy on measures of reasoning or crystallised intelligence. In addition, long term, short term and partial sleep deprivation has been found to have a negative effect on mood states (Goel et al, 2009). It has also been reported that chronic sleep restriction results in levels of cognitive impairment comparable to those seen following severe acute total sleep deprivation.

Table 1: Summary of Cognitive Performance Effects of Sleep Deprivation Adapted from Goel et al (2009)

<table>
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<th>Effect</th>
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<tr>
<td>Involuntary micro-sleeps occur.</td>
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<td>Attention-intensive performance is unstable with increased errors of omission (lapses) and commission (wrong responses).</td>
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<td>Cognitive slowing occurs in subject-paced tasks, whereas time pressure increases cognitive errors.</td>
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<td>Psychomotor response time slows.</td>
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<td>Both short-term recall and working memory performances decline.</td>
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<td>Reduced learning (acquisition) of cognitive tasks occurs.</td>
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<td>Performance requiring divergent thinking deteriorates.</td>
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<td>Response suppression errors increase in tasks primarily subserved by the prefrontal cortex.</td>
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<tr>
<td>Response perseveration on ineffective solutions is more likely to occur.</td>
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<tr>
<td>Increased compensatory effort is required to remain behaviourally effective.</td>
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<tr>
<td>Tasks may begin well, but performance deteriorates as task duration increases.</td>
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<tr>
<td>Growing neglect of activities judged to be nonessential (loss of situational awareness) occurs.</td>
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Sleep and Traumatic Brain Injury (TBI)

Sleep disturbance are common following TBI, reported in between 30-75% of patients (Shekleton et al, 2010, Viola-Saltzman & Watson, 2012) though despite this it is one of the least studied symptoms of TBI (Sanders et al., 2013). Sleep disorders often seen in TBI include insomnia, hypersomnia, disturbances to sleep-wake cycles and excessive daytime sleepiness (Sinclair et al, 2014). Whilst the exact aetiology remains elusive, both primary factors such as brain pathology and secondary factors such as depression, anxiety, pain and maladaptive sleep behaviours, have been implicated (Sinclair, 2014).

Considering primary factors, Viola-Saltzman and Watson (2012) discuss how hypersomnia following TBI can result from disturbances to areas involved in maintaining wakefulness such as brainstem reticular formation, posterior hypothalamus and areas surrounding the third ventricle. Further, investigating sleep in TBI using polysomnography Shekleton et al (2010) found that individuals with TBI had a significantly higher proportion of slow wave sleep. They postulated that the TBI individuals experienced a higher pressure to sleep due to endocrine imbalances, neural plasticity, global reaction to trauma and diffuse damage to the homeostatic sleep system. In their study they also found that the TBI group had significantly lower melatonin production. Although they did not find an
association between melatonin levels and sleep disturbance they did find an association between melatonin levels and percentage of time spent in REM sleep. From this they concluded that TBI may disrupt structures which regulate the sleep-wake cycle, including synthesis of melatonin in the pineal gland. They also hypothesised that disturbed sleep in TBI also may impair neurogenesis and decrease cell proliferation. The role and association of secondary factors, such as pain, depression and anxiety, remains unclear (Ponsford et al., 2013). Fatigue may increase daytime sleeping, which in turn may affect night-time sleep quality. Sleep disturbance may exacerbate pain, or pain may exacerbate sleep disturbance.

**Sleepiness, fatigue and TBI**

Sleepiness and fatigue are two terms used interchangeably (Shen et al., 2006) and whilst important to separate for treatment recommendations in reality can be difficult to disentangle clinically. Neither fatigue nor sleepiness is thought to be a unitary phenomena with both often co-existing as a result of sleep deprivation. Patients usually don’t distinguish and group the two together under the common complaint of ‘tiredness’. Shen et al. (2006) define sleepiness as a ‘ubiquitous phenomena’ experienced both as a symptom in a number of conditions, but also as a normal physiological state experienced by most individuals. A lack of sleepiness results in insomnia and pervasive sleepiness can result in narcolepsy.

Fatigue, in contrast to sleepiness, has been defined by the North American Nursing Association as ‘the self-recognized state in which an individual experiences an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work (Carpenito, 1995). Fatigue is associated with significant levels of physical and psycho-social morbidity and in many illnesses fatigue is reported as one of the most severe and disabling symptoms (Shen et al., 2006).

Fatigue is often conceptualized along dualistic lines. Acute fatigue is thought to occur in healthy adults, has a rapid onset and short duration and is seen as having a normal protective function (Shen et al., 2006). Chronic fatigue primarily affects clinically disordered populations and is viewed as abnormal and excessive. It usually has an insidious onset, persists over time and is multi-factorial in origin (Shen et al., 2006).

Psychological fatigue, in contrast to physiological fatigue, is associated with a state of weariness and reduced motivation (Shen et al., 2006). Physiological fatigue is defined as a loss of maximal force generating capacity during muscular activity or a failure of a functional organ (Shen et al., 2006).

Central models of fatigue conceptualise fatigue as arising in the central nervous system, such as in the hypothalamic region, whereas peripheral models conceptualise fatigue as arising in the peripheral nervous system, such as impaired neuromuscular transmission (Shen et al., 2006). Primary fatigue is thought to encapsulate both central and peripheral fatigue processes (Ponsford 2012) whereas secondary fatigue is the result of the exacerbation of primary fatigue in circumstances such as sleep disturbance and pain.

Fatigue is a commonly reported symptom post-TBI and can be caused by sleep disorders, due to secondary factors or the result of primary factors such as brain pathology. Ponsford et al. (2012) investigated the association between fatigue and sleep disturbance in 140 participants with TBI and compared their results to 105 matched control participants. In this study they found a significantly higher degree of sleep disturbance in the TBI group with this disturbance related to self-reported levels of subjective fatigue.

The prevalence of fatigue in the general UK population has been estimated as 18% (Pigeon et al.,
In brain injured populations fatigue has been reported in 46% -60% of cases (Benbadis et al., 1999; Ponsford et al., 2013; Ponsford et al., 2012). A number of potential causes of primary fatigue in TBI have been postulated. These include diffuse axonal injury, impaired excitability of the motor cortex, and hypopituitarism (Bushnik et al, 2008). Causes of secondary fatigue include pain, depression, anxiety and sleep disorders. In TBI it is likely that the experience of fatigue represents a combination of primary and secondary causes (Ponsford et al., 2012). Another hypothesis put forward is that fatigue in TBI may result from the additional compensatory effort required to meet the everyday needs of life in the face of cognitive impairment (Ponsford et al., 2012).

Ponsford and her group have conducted a number of studies investigating the magnitude and impact of subjective ratings of fatigue following TBI. In one study Ponsford et al. (2012) studied a sample of 139 patients with mild to severe TBI. Patients had a mean age of 35, were mostly male (74%), had a mean education of 12 years and were assessed on average 10 months following their TBI. All patients were free from previous head injury, significant psychiatric illness or previous sleep disorder. Other important factors such as shift work or psychotropic medications were also controlled for. Patients were compared to a group of 78 matched healthy controls.

They generally found from sleep diary data that TBI patients reported longer sleep onset latency, poorer sleep efficiency and daytime napping. Results from their study suggested that individuals with TBI reported significantly higher scores on the fatigue severity scale and the causes of fatigue scale, with 64% of TBI participants reporting clinical significant fatigue levels compared to 35% of the control population. They also reported a greater impact of fatigue on their day to day life, with mental and physical activities both significantly contributing to fatigue. Fatigue was also significantly related to high anxiety and depression scores, suggesting an inter-relation between these variables.

Ponsford et al (2013) also investigated the factors that predicted subjective experiences of fatigue in the TBI population and found that older age was associated with a decline in some sleep variables, and greater injury severity increased the drive to sleep. Longer duration since injury was also associated with poorer sleep quality and daytime sleepiness, suggesting that without treatment sleep difficulties worsened across time (Ponsford et al 2013). Presence of anxiety, depression and pain was also associated with poorer sleep (Ponsford et al, 2013).

**Treatment recommendations**

Sleep disorders and problems with fatigue are highly common following TBI, and can have significant impact on the rehabilitation process and the individuals’ capacity to return to a full life. In addition, given the known impact of sleep deprivation and the proposed role of sleep in memory consolidation we would also expect that sleep disorders, together with fatigue, will have a direct impact on cognitive functioning. As such assessing and treating sleep disturbances and fatigue is an important consideration for expert witness evaluations in TBI. Whilst many individuals and professionals may expect sleep disorders and fatigue to naturally recover, the research evidence suggests this is not the case with insomnia symptoms commonly reported many years post-TBI (Oulette and Morrin, 2007).

Given the high prevalence of sleep disorders and fatigue in TBI objective and subjective assessments of sleep are an important first step in order to elucidate the factors contributing to sleep changes and fatigue. In addition, understanding the impact of secondary factors may have implications for effective and tailored treatment recommendations (Ponsford et al., 2013).

There are a number of useful resources to do this with one of the major starting points being use of a
sleep diary. While there are a number of sleep diaries available, and of course it is possible to develop these individually, it is recommended that a standardised sleep diary be used to allow comparison across subjects. One well known sleep diary has been developed by Carney et al (2013). In addition to gathering data about sleep onset latency, duration and duration of nocturnal awakenings it can also be useful for diagnosis of sleep disorders to gather information about the quality of that sleep.

Supplementing sleep diaries with other assessment data, such as about sleep quality, is also important. One well developed measure of sleep quality is the Pittsburgh Sleep Quality Index (PSQI; Buysse et al. 1989). This measure may prove particularly useful as it has been recently validated for use in TBI populations (Ponsford, 2013). It can also be important to understand the functional impact of sleep disorders in order to tailor recommendations. To measure aspects of sleep related quality of life impairment measures such as the Glasgow Sleep Impact Scale (GSII; Kyle et al 2012) are useful. Other useful tools for diagnosing sleep disorders, and in particular insomnia, are the Sleep Condition Indicator (Epsie et al. 2014) and the Insomnia Severity Index (Morrin et al., 2011).

Measurement of fatigue and the construct of ‘sleepiness’ is also another important component in assessment and planning treatment. Useful measures include the Fatigue Impact Scale (Fisk et al., 1994), Fatigue Severity Scale (Krupp et all, 1989), Causes of Fatigue (Ziino and Ponsford, 2005) and the Epworth Sleepiness Scale (Pepper et al 1993). In addition, consideration of the impact of sleepiness and fatigue on neuropsychological test performance is an important component of interpretation.

Whilst some causes of sleep disorders and/or fatigue following TBI, such as neuroendocrine disorders, are amenable to treatment (Bushnik et al, 2008) many cases can be difficult to treat with conventional treatments such as benzodiazepines (Viola-Saltzman & Waters, 2012). In addition, use of pharmacological agents may not be indicated because of their side effect profiles (Ponsford et al 2012, Sinclair et al 2014). However, some preliminary research data has suggested that melatonin may be of use in treating sleep disorders post-TBI (Kemp et al 2004). Modafinil has also been proposed as another potentially useful pharmacological treatment for fatigue and excessive daytime sleepiness. However, in their study with 53 participants with TBI Jha et al (2008) did not find that a dosage of 400 mg was more useful that placebo in the treatment of fatigue/sleepiness and, overall, research with this drug in TBI has generally been mixed (Sinclair et al, 2014).

Non-pharmacological approaches also offer potential benefit in the treating of sleep disorders and/or fatigue/sleepiness with effectiveness rates of 70-80% in the non-clinical population (Morin et al., 1999). The main goal of such treatments is to target factors such as unhealthy sleep hygiene, maladaptive sleep habits and dysfunctional beliefs or attitudes about sleep (Oulette and Morrin, 2007). The American Academy of Sleep Medicine (AASM) currently endorses a number of non-pharmacological treatment for sleep disorders in the general population (Morin et al., 1999). These include stimulus control therapy, a method which aims to train the patient to re-associate the bed and bedroom with sleep and re-establish a consistent sleep-wake cycle. One of the key factors in this approach is the advice to get out of bed again after 15 minutes if not asleep. Another useful approach endorsed by the AASM is relaxation training, such as progressive muscle relaxation and diaphragmatic breathing. Sleep restriction therapy, which involves restricting a patients' time in bed to initially match their average self-reported total sleep duration, is perhaps a more difficult approach to put in place, but also had proven efficacy (Kyle et al, 2015). A combination approach, often called cognitive behavioural therapy for insomnia (CBTI) which includes elements of the above but also incorporates therapy to address patients’ beliefs and attitudes about insomnia is highly
Non-pharmacological treatments have been shown to be useful in general cases of sleep disorders, with some limited evidence of their effectiveness with TBI (Oulette and Morin, 2004; Oulette and Morin, 2007). The study by Oulette and Morin (2007) is a useful guide to what might be expected from treatment recommendations for a combination approach such as CBTi. The study authors delivered eight sessions over an 8-10-week period, each session lasting approximately one hour and all sessions delivered by a psychologist. The content of the programme included stimulus control instructions to re-associate the bed, bedroom and bedtime with sleep, use of a sleep restriction procedure, cognitive therapy designed to address dysfunctional beliefs and attitudes about sleep, sleep hygiene techniques such as addressing lifestyle factors such as caffeine usage and environmental factors such as bedroom noise and temperature. A final component of their programme targeted fatigue by putting in place fatigue management strategies including adjustments to daily routines such as regular breaks, shorter total work hours and work-life balance adjustments. In addition to a focused CBTi programme such as discussed above, Ponsford et al (2013) also highlight the importance of addressing pain, anxiety and depression as part of the process of treating sleep disorders post-TBI. Treatment recommendations in expert witness reports addressing sleep and fatigue should look at building in additional sessions and expertise to tackle these issues, where applicable.

Another potentially promising treatment option that looks to target fatigue and daytime sleepiness is light therapy (Sinclair et al., 2014). In a randomised control trial Sinclair et al. (2014) delivered 45 minutes of home based blue light therapy one time a day for four weeks to 18-65 years old with a history of TBI, self-reported fatigue and/or sleep disorder. The study authors report a significant reduction in fatigue and daytime sleepiness in patients who received the blue light therapy when compared to yellow light and no treatment. This result was consistent with similar findings with blue light in the healthy population (Sinclair et al., 2014). They did however note that the degree of effectiveness across individuals was variable, and hypothesised that this variability was due to secondary factors such as fatigue, depression and anxiety (Sinclair et al., 2014). From this finding it may be useful to look at incorporating blue light therapy into a psychological programme which also addresses secondary factors, as described above.

Given the multi-dimensional nature of sleep and fatigue difficulties in TBI it is likely that treatment programmes incorporating several approaches will be the most effective.

Conclusions

- Sleep is an important component of our daily lives with hypothesised roles in memory consolidation, energy consumption and recovery from injury.
- Sleep disorders, fatigue and excessive daytime sleepiness are highly prevalent conditions following TBIs and can have significant detrimental effects on rehabilitation, recovery of function, mood, cognition and quality of life.
- Sleep disorders, fatigue and sleepiness following TBI can arise from a number of underlying causes, both primary and secondary, and assessing and understanding these causes is an important first step in any assessments conducted post-TBI.
- Once causes have been identified it is then possible for the expert witness to develop tailored treatment options. Some of these, whilst still under investigation, may prove particularly promising – such as bright light therapy and use of melatonin.
• Non-pharmacological treatment options, which have proven to be very useful in the general population, have also been indicated in TBI and it is the authors opinion that combined approaches such as CBT-I should be incorporated into all expert witness recommendations where either sleep, fatigue or sleepiness is identified as a factor post-TBI.

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Re:Cognition Health provides a comprehensive and innovative clinical approach to the diagnosis and treatment of all types of cognitive impairment.

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REFERENCES


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The Brain Injury Group is a national network of legal and other professionals supporting individuals and families affected by brain injury. www.braininjurygroup.co.uk


Shen, J., J. Barbera, and C. M. Shapiro, 2006, Distinguishing sleepiness and fatigue: focus on definition and measurement: Sleep Medicine, v. 10, p. 63-76.


