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Sleep, Fatigue and Sleep

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A complete listing of his writings at <http://psychologywritings.synthasite.com/>.

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1. FATIGUE AND SLEEP

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1.1. INTRODUCTION

Xing et al (2019) began: "Sleep remains a relatively understudied phenomenon, despite being essential in some form to most vertebrate life. Although humans spend about one-third of their lives in the sleep state, an understanding and recognition of its importance for our well-being are severely lacking. Sleep of sufficient duration, continuity, and depth is necessary to maintain high cognitive performance during wake and to prevent certain physiological changes that may predispose individuals to many adverse health outcomes" (p1).

1.2. FATIGUE

Many individuals report feeling tired all the time (ie: subjective fatigue). There are a number of possibilities to explain these reports, including:

i) The pace and demands of modern life - There may be some truth to the "ever-present buzz of smartphone notifications" (Young 2016) (appendix 1A), and other demands of work, family, and life generally as the cause. But the complaint of being worn out by modern life and a wish for simpler times has been common throughout history (eg: in the 19th century steam power and the invention of the telegraph were the cause for some people) (Schaffner 2016).

ii) Lack of sleep - This is the cause for some individuals who suffer from insomnia, say, but the need for sleep and fatigue are not necessarily the same thing (Young 2016).

iii) Disruption of the circadian rhythms - The body follows a 24-hour rhythm which fits roughly to the day (alertness after waking and sleepiness increasing in the evening), but if this is disrupted or out of sync, a form of "permanent jet lag" can be experienced.

iv) An overactive immune system - A number of conditions could be due to inflammation (ie: autoimmune), and this leads to fatigue as the body seeks to fight "imagined invaders". Sedentary lifestyle, stress, and poor diet could all trigger higher levels of inflammation (Young 2016).

v) Stress and depression - Fatigue is a symptom of depression, and depression can be caused by stress. Long-term stress can lead to changes in hormones, and particularly to fatigue.

vi) Deficiency (eg: iron) and dehydration - Despite the marketing of supplements, deficiency does not explain feelings of fatigue for most people.

Because of the subjective nature of fatigue, it is difficult to establish objective information. A combination of these explanations could explain the large number who report fatigue (eg: one-fifth in a large US survey; Young 2016). Or people expect or have to do more and are surprised when tired from such demands.

1.3. SLEEP DURATION

On average, individuals need approximately eight hours of sleep per day to "function optimally", but towards half the adult US population do not have that on weekday nights (Xing et al 2019). This is due in part to environmental factors, like work schedule demands.

But sleep duration varies due to genetic factors. He et al (2009) described the first gene/mutation linked to short sleep (4-6 hours per night) (familial natural short sleep; FNSS), and with no negative consequences to such shortened sleep (Xing et al 2019) ¹.

Xing et al (2019) reported another gene/mutation leading to FNSS from experiments with mice. "Knock-out" mice were genetically engineered without the gene, and they spent significantly less time sleeping than controls

¹ Xing et al (2019) stated: "In our growing clinical database of FNSS, we have observed that FNSS subjects are healthy, energetic, optimistic, with high pain threshold, and do not seem to suffer from adverse effects of chronic restricted sleep. It is possible that there is a mechanism in these FNSS human and mice compensating for the negative effects normally caused by sleep loss. Alternatively, these FNSS humans and mice are impervious to the negative effects caused by sleep loss" (p5).

(average of 71 minutes less in 24 hours) ².

The gene, NPSR1 (neuropeptide S receptor 1), was first noticed in a human family (known as "K50226" for privacy reasons), where two individuals had noticeably less sleep (5.5 and 4.3 hours) (Xing et al 2019).

NPSR1 has been linked to part of the thalamus, which is critical to wakefulness (Ren et al 2018), and "found in some nuclei of basal forebrain regions, another known sleep regulatory area" (Xing et al 2019 p5).

1.3.1. Bedtime Regularity

As well as lack of sleep leading to health problems, bedtime regularity is also important.

Faust et al (2020) investigated resting heart rate (RHR) (which is a biomarker of cardiovascular health) and deviations in bedtime using data from the NetHealth study. This study involved 557 students who entered the University of Notre Dame in the USA in 2015-16, and were followed for four years.

RHR and sleep data were collected using a "Fitbit" worn "as much as possible". Data from this device were automatically uploaded to the study website, and was complemented by regular questionnaires. A "normal bedtime" was established using the median, and deviations were calculated in minutes for each night (outside a range of 30 minutes earlier or later than the median). Co-variates of physical activity, naps, and caffeine and alcohol consumption, for example, were measured.

Faust et al (2020) summed up the findings - "deviations from an individual's normal bedtime may prohibit RHR from slowing to its normal pace, resulting in a higher RHR throughout one's sleep session. Further, this short-term change to RHR may persist into the following day, with RHR returning to its normal pace by early evening. However, this extension only manifests when individuals go to bed later than their normal bedtime as opposed to earlier" (p3).

This study could not establish causality between later bedtime and increased RHR. It is possible that bedtime variability was part of a wider poor "sleep hygiene" (eg: less "sufficient sleep"; increased alcohol consumption), and this can be associated with later

² Xing et al (2019) admitted: "The main limitation of this study was the difference between the human and mouse sleep patterns. Despite the highly conserved genomic sequences, humans and mice display different features in sleep behaviours. Humans spend most sleep time at night and almost no sleep time during the day, whereas mice sleep both in the light and dark phases, with about 70% sleep time in the light phase and 30% in the dark phase. Moreover, mouse sleep is more fragmented than human sleep and does not occur in a consolidated bout as it does in humans. These differences probably result from varied sleep regulatory mechanisms between human and mice, which may contribute to differed phenotypes caused by the same genetic mutation" (p6).

health problems.

1.3.2. E-Cigarettes and Sleep

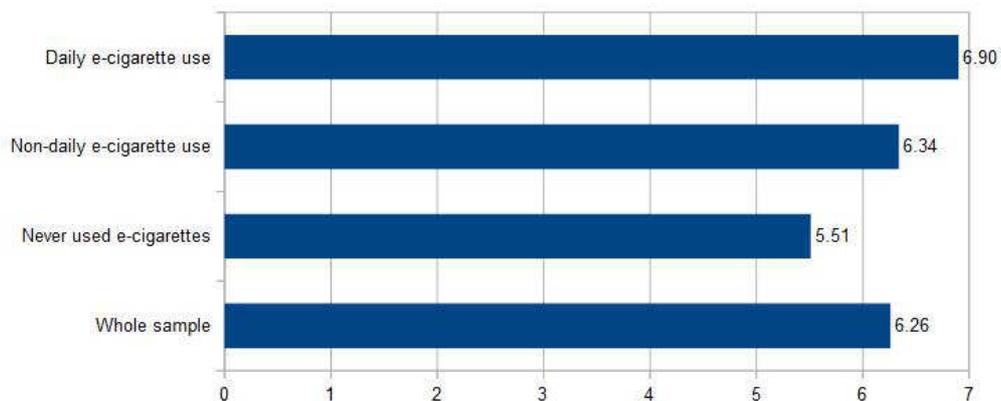
There is concern about the growing use of e-cigarettes while tobacco smoking is declining (appendix 1B). What are the consequences of e-cigarette use for sleep?

Previous research on tobacco smoking found more sleep disturbances among smokers, along with the effects of nicotine, like longer sleep onset latency, and reductions in REM and total sleep time (Brett et al 2020).

Brett et al (2020) investigated e-cigarettes and sleep with an online survey of 1644 US college students. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al 1989) was used to measure sleep characteristics, and there were questions about cigarette and e-cigarette use, and alcohol consumption ³.

Three groups were distinguished for comparison - never used e-cigarettes (n = 984), ever used (n = 546), and regular users (at least once a month) (n = 134).

E-cigarette "never users" had significantly better sleep health than "users" (figure 1.1), and this difference was stronger for both cigarettes and e-cigarettes combined (even controlling for alcohol use).



(Data from Brett et al 2020 table 2)

Figure 1.1 - Mean PSQI total score (out of 21) (controlling for gender and alcohol use, where a lower score is better sleep health).

This was manifest as fewer sleep disturbances (eg: waking

³ Data on illicit drug use was not collected.

frequently in the night; bad dreams), better subjective sleep quality (eg: feeling refreshed in the morning), less daytime dysfunction (eg: poor concentration; daytime sleepiness), and less regular use of sleep medication for "never users". Nicotine in e-cigarettes is assumed to be the mechanism of these sleep problems (Brett et al 2020).

1.3.3. Sleep Deprivation and Anxiety

Individuals with anxiety disorders often have sleep disturbances. But the direction of the relationship is not clear. Do anxiety disorders produce sleep problems or do sleep disturbances lead to increased anxiety?

Zenses et al (2020) produced evidence for the latter in their experiment on sleep deprivation. Forty volunteers at a Belgium university were allocated to one night's sleep deprivation or normal sleep⁴.

Anxiety was measured via a fear conditioning task. This involved showing three similar pictures of a neutral human male face and pairing one of them with a mild electric shock to the hand. Training (ie: the learning of the association) took place in the evening before sleep or not, and testing the next morning. Fear was measured in anticipation of the electric shock (threat expectancy rating - scored 0-10 in terms of certainty of electric shock following).

The sleep deprived group reported greater fear of an electric shock than the sleep group. This was particularly the case for faces that were similar to the paired one, and which did not lead to an electric shock. In other words, stimuli previously experienced as safe after sleep deprivation were perceived as threatening (figure 1.2). Zenses et al (2020) stated: "our results provide evidence that sleep disturbances may play a causal role in the development of anxiety disorders by increasing the extent to which a person expects danger" (p6).

Linked to this finding, Menz et al (2013) had found that REM sleep improved the ability to discriminate between threatening and non-threatening stimuli.

In Zenses et al's (2020) study, the threat expectancy rating was self-reported, and objective measures of fear did not differ between the two groups.

The researchers accepted that a sleep deprivation before training condition would have been useful. Also,

⁴ There was not complete randomisation to the two conditions. Zenses et al (2020) explained: "For practical reasons, we decided prior to advertising the study which nights would be sleep deprivation or regular sleep nights. However, participants did not know their assigned condition beforehand and we had no influence on who would sign up for which condition either" (p2).

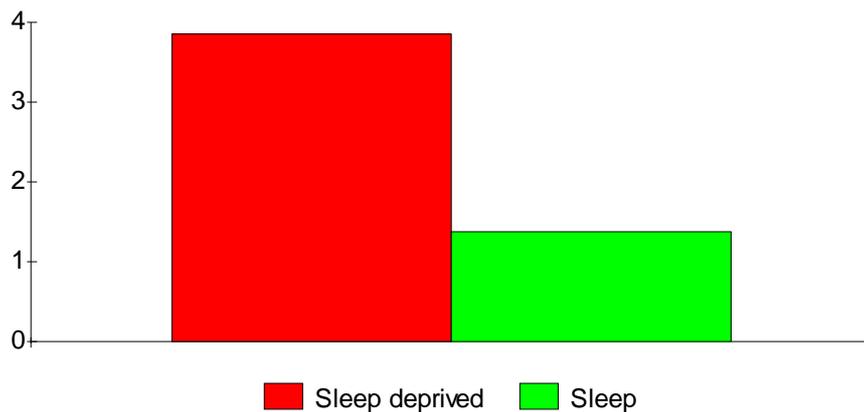


Figure 1.2 - Mean score (out of 10) for perceived threat of electric shock when shown a "safe" picture.

"introducing an additional night of (recovery) sleep before the test phase... would allow isolating the effect of sleep deprivation after learning because all participants would be well-rested during test. Conversely, allowing all participants to sleep during the night following the training phase and manipulating sleep during the night before the test phase would allow isolating the effect of the sleep-deprived state during test because memory consolidation after fear learning should have occurred to the same extent for all participants" (Zenses et al 2020 p7).

With any sleep deprivation study, there is the question of what the participants do when not sleeping. Zenses et al (2020) explained: "Depending on the experimental condition, participants either spent the following night sleeping at home (sleep condition) or were kept awake for 12 hr in the psychology library (sleep deprivation condition). Participants in the sleep deprivation condition were kept awake in groups of five-six participants, and were monitored by an experimenter until the beginning of the experimental session on day 2. During the night of sleep deprivation, participants were allowed to engage in activities, such as watching movies, talking to other participants and the experimenter, or reading. Participants in either condition were asked to not talk about the experiment during the course of the study" (p4).

There are potential confounders here. For example, the participants in the sleep condition going home and the lack of control over their behaviour, or the stress of the sleep deprivation condition of staying in groups and "wasting time" for 12 hours. How closely could the experimenter monitor the sleep deprivation?

1.4. WAKEFUL REST

The rat is well-studied in relation to spatial memory and sleep. When the animals navigate a novel environment, hippocampal place cells (which code for location) fire, and in subsequent sleep "the same cells re-express firing sequences corresponding to specific recent spatial experience (ie: the earlier travelled route is 'replayed'" (Craig et al 2016 p185). The attaching of electrodes to the rat's brain is done in this research, but this would not be ethical with humans (appendix 1C).

So, studies with humans on learning and sleeping involve testing recall. For example, with the learning of information before or after sleep, the former is more effective. In fact, "research shows that words and short stories are retained better for at least 7 days if their learning is followed immediately by a few minutes of wakeful rest rather than by novel sensory stimulation" (Craig et al 2016 p186). So, not just sleep, but wakeful rest is beneficial.

Wakeful rest has been shown to improve spatial memory in rats, but what about humans? Craig et al (2016) tested forty healthy young adults. The task was to learn the route around a virtual town. Then there was a ten-minute break, filled with wakeful rest or an unrelated perceptual task (spot-the-difference game), before a cognitive map test about the virtual town (ie: describe the position of nine landmarks).

The wakeful rest group were significantly more accurate in the cognitive map test. Craig et al (2016) explained: "When navigating an unfamiliar environment, our memory system automatically forms a flexible mental representation of the spatial relationships (ie: directions and distances) between objects in the world that are accessible from any perspective and vantage point, ie: a cognitive map. The present results suggest that the accuracy of such a newly formed cognitive map can be improved significantly via a post-navigation rest" (p191).

1.5. IMPROVING SLEEP QUALITY

Nearly half of the working population report poor sleep quality of some type (Chen et al 2020). "Mind-body exercises" may be beneficial to improve sleep quality.

Chen et al (2020) reviewed one type of such exercise - Pilates ⁵. "As a form of mind-body exercise, the Pilates exercise system mixes practical movement styles and ideas

⁵ Developed by Joseph Pilates in the 1920s.

of gymnastics, martial arts, yoga, and dance with philosophical notions, which are based on six fundamental principles: concentration, control, centering, flowing movements, precision, and breathing. Different from yoga, Pilates pays more attention to awareness, breathing, and core muscles" (Chen et al 2020 p2).

Chen et al (2020) found six randomised controlled trials (RCTs) evaluating Pilates for improving sleep quality. Overall, there was a significant improvement in subjective sleep quality, sleep latency (ie: quicker to fall asleep), total sleep duration, sleep efficiency (ie: more of time spent in bed asleep), sleep disturbances, and daytime dysfunction (from poor sleep) using Pilates as compared to a control group and measured by the PSQI. But there was no difference in use of sleep medication. Sub-group analysis based on age and health found no significant differences.

Any review and meta-analysis is dependent on the quality of the studies included. The score for methodological quality was fair to mild overall, while the heterogeneity of effects was moderate to high (ie: large differences in size of effect between studies).

A number of specific and general methodological points arise, including:

i) A small number of studies found.

ii) Details of randomisation, blinding, and drop-out rate were not always provided.

iii) "Pilates procedure processes, time of duration, and dosages varied from one study to another without a consolidated standard, which can be a potential source of clinical heterogeneity that affects the results" (Chen et al 2020 p5) (eg: 2 sessions per week for 12 weeks vs 3 sessions per week for six weeks).

iv) Clear selection and exclusion criteria by Chen et al (2020) - eg: only RCTs included.

v) Only studies published in English and Chinese (up to December 2019).

vi) The measurement of the outcome variables was the same in all studies (PSQI), but it is self-reported, whereas polysomnography would give objective measures of sleep.

vii) Countries of studies were Iran (2 studies), Spain (2), Brazil, and China.

viii) Four studies included only older/post-menopausal women (over two-thirds of all participants).

Wang et al (2019) performed a systematic review and meta-analysis of RCTs on four types of mind-body therapies (MBTs) (meditation, tai chi, qigong, and yoga) (published up to July 2018) for treatment of insomnia. Forty-nine relevant studies were found.

Wang et al (2019) summed up: "The overall effects of MBTs on improving sleep quality were significant..., but the effects on reducing the severity of insomnia symptoms were not significant" (p11). In terms of sub-group analysis, MBTs were better for healthy individuals with insomnia (as compared to those with physical conditions and resulting insomnia), and longer duration of treatment was also helpful.

The variety of comparison/control group (active - pharmacotherapy or cognitive behavioural therapy for insomnia (CBT-I); or inactive - waiting list or usual care) was a methodological issue. "In some studies, researchers used some active control conditions, such as CBT-I, pharmacotherapy, and sleep hygiene education. These active control conditions were also effective therapies or might improve sleep quality and reduce the severity of insomnia symptoms. Thus, compared with these active control conditions, MBTs might have similar effects and no obvious advantages over the former" (Wang et al 2019 p11).

There was great variety in the MBTs, which "made it difficult to draw definite conclusions about the effectiveness of particular MBTs and might also influence the overall effects" (Wang et al 2019 p11).

The PSQI was the outcome measure in many studies, and this is a subjective self-report method, though objective measures were also used in some cases.

1.6. APPENDIX 1A - PROBLEMATIC SMARTPHONE USE

Over the decade of the 2010s smartphone use by children and young people (CYP) has increased as have common mental disorders (CMDs) in that age group. Is there a relationship between the two events?

Sohn et al (2019) observed: "There is a public health uncertainty regarding a possible association between smartphone use and mental health in CYP, and in the UK, policy making has been hindered by a paucity of evidence" (p2). Studies are also contradictory. "One challenge is the date when the studies were carried out, often before the advent of widespread smartphone use, meaning the term screen-time may include televisions or personal computers, although it has a more common interpretation as a smartphone today. Other limitations include that longer use is assumed as harmful, and this may not necessarily be accurate" (Sohn et al 2019 p2).

It is further possible that problematic smartphone use (PSU) is the issue rather than smartphone usage

itself. The operationalisation of PSU has been "in such a way that it maps onto concepts of behavioural addiction: tolerance, withdrawal (dysphoria when the battery dies), preoccupation, neglect of other activities, subjective loss of control and continued use despite evidence of harm" (Sohn et al 2019 p2). The parallel is drawn with problem gambling which is associated with CMDs, whereas occasional gambling is not (Sohn et al 2019).

Sohn et al (2019) undertook a systematic review of forty-one relevant studies on smartphone use among CYP (published between 2011 and late 2017). Twenty-two of the studies were rated as poor methodological quality, and the others as moderate quality.

The median prevalence of PSU was 23.3%. It was linked to social networking, with female 17-19 year-olds as the most frequent sufferers.

There was a consistent association between PSU and CMDs, including depression (approximately three times more likely than non-PSU individuals), and anxiety (twice as likely), as well as stress, sleep problems, poor educational attainment (in a small number of studies), and suicidal ideation (in one study). "A range of different personality and emotional factors were investigated in relation to PSU. Somewhat paradoxically, traits associated with greater risk-taking (such as low self-control, impulsivity, emotional instability, and openness) and traits associated with avoidance of risk taking (such as perfectionism and conscientiousness), were more common amongst problematic smartphone users. An insecure attachment style, loneliness, and low self-esteem were all associated with PSU" (Sohn et al 2019 p5).

There were a number of methodological issues with the studies in the review, including:

i) The definition of PSU - This ranged from "a single criterion such as psychological withdrawal phenomena, to measurement of tolerance, withdrawal, loss of control, preoccupation, neglect of other activities and evidence of harm, which form the criteria for behavioural addictions" (Sohn et al 2019 p3).

ii) The measurement of PSU with a range of scales used, like the Smartphone Addiction Scale (SAS) ⁶ (Kwon et al 2013), and the Mobile Phone Problematic Use Scale (MPPUS) ⁷ (Bianchi and Phillips 2005).

⁶ Eg: "getting irritated when bothered while using my smartphone"; "won't be able to stand not having a smartphone".

⁷ Eg: "I can never spend enough time on my mobile phone"; "I lose sleep due to the amount of time I spend on my mobile phone".

iii) Type of design - All but three studies were cross-sectional, which means causality cannot be established.

iv) Country of study - Thirty studies took place in Asia. Usually studies from North America dominate reviews.

v) Measurement of outcome variables - eg: cut-off score for diagnosis of depression; self-reported symptoms vs diagnosis by clinician; variations in measurement of educational attainment.

Studies outside the time window, and not in the eight databases searched would have been missed.

1.7. APPENDIX 1B - ELECTRONIC CIGARETTES

The e-cig (electronic cigarette) is designed to resemble a conventional cigarette, but instead of burning tobacco, it delivers a vapour, which can include nicotine and particular flavours. It was first introduced in 2004 (Tavolacci et al 2016).

Establishing the prevalence of use is important. Tavolacci et al (2016) performed a cross-sectional study with college students in France, where e-cigarettes were introduced in 2007. The data were collected in late 2014 to early 2015 from 1134 students at two universities. The questionnaires were anonymous, and completed in lectures or at medical check-ups.

"Ever use" prevalence was 23% (n = 260)⁸, and "correct use" (defined as once or more in the last month) was 5.7% (n = 65)⁹. Of this latter group, 45% used every day or several times a week, and the remainder once a week or less. "Ever use" was significantly associated with current or former tobacco smoker status. It was also associated with frequent binge drinking and alcohol abuse problems.

Allem et al (2015) described two patterns of students experimenting with new things. "Emerging adults managing many transitions may not have time to experiment with e-cigarettes, while emerging adults managing fewer transitions may have excess time lending to idleness and experimentation with e-cigarettes" (Tavolacci et al 2016 p8).

Tavolacci et al's (2016) sample was two-thirds female. The data were self-reported, and cross-sectional

⁸ A Korean study reported 21.2% for "ever use", for example (Jeon et al 2016).

⁹ This was similar to Polish students (Goniewicz et al 2012), for example.

¹⁰, which limited the ability to make causal inferences ¹¹.

1.7.1. Renormalising Smoking?

The possibility that e-cigarettes may renormalise smoking among young people (ie: "a gateway to nicotine addiction and tobacco use") has been raised as a concern, including by the Australian government (Hallingberg et al 2020).

The "renormalisation hypothesis" has been challenged by the argument that e-cigarettes will "denormalise smoking" "through social display of an alternative behaviour, leading to displacement away from tobacco use for some young people who would otherwise have become smokers. From this perspective, alignment of e-cigarettes with tobacco in terms of regulatory frameworks paradoxically risks creating a perception that they are synonymous, potentially creating conditions for renormalisation to occur" (Hallingberg et al 2020 p208).

Hallingberg et al (2020) considered these two alternatives with UK data. If the renormalisation hypothesis is correct, the decline in smoking cigarettes will have slowed down in recent years. Alternatively, the decline will have increased if the denormalising argument is correct.

The data came from three nationally representative surveys of teenagers (covering 1998 to 2015) - Smoking Drinking and Drug Use Among Young People in England Survey (SDDU) (performed annually), Scottish Adolescent Lifestyle and Substance Use Survey (SALSUS) (biennial), and the Health Behaviour in School-aged Children (HBSC) survey and School Health Research Network (SHRN) survey in Wales (every 2-4 years). Smoking rates ("ever" and "regular") between 11 and 16 years old were the main outcome measures. The data were analysed before and after 2010 when e-cigarettes started to appear.

Over the time period of the data, "change in the rate of decline for ever smoking post-2010 was not significant, though a marginally significant ($p = 0.03$) slowing in the rate of decline occurred for regular smoking" (Hallingberg et al 2020 p209). Thus, there was no support for either hypothesis. In terms of attitudes towards smoking, there was a continued decline in teenagers agreeing that trying smoking or smoking was "OK" (Hallingberg et al 2020).

¹⁰ A cross-sectional study takes a "snapshot" of a situation at a particular time, though "this 'point' in time may in fact be a shortish period of time" (Bowers 2008 p76).

¹¹ The cross-sectional study is able to show the link between variables, even if not the duration of causal relationship (Bowers 2008).

1.7.2. Controversy

Vaping has always been controversial for some, but this is heightened by forty-seven deaths and over 2200 cases of lung injury in the USA linked to e-cigarette use recently (Hamzelou 2019).

The US situation appears not to be mirrored in other countries ¹². In fact, while the US Centers for Disease Control and Prevention (CDC) recommend "refraining from use of all e-cigarette, or vaping products", Public Health England described vaping as "95 per cent safer than smoking" (Hamzelou 2019) ¹³. The US problems may be related to chemicals found in illicit products (eg: tetrahydrocannabinol (THC) vaped by a large sample of e-cigarette-related lung injury cases) (Hamzelou 2019).

Other chemicals involved include vitamin E acetate (a synthetic form of the vitamin) in e-cigarette liquids in the USA (Hamzelou 2019).

1.8. APPENDIX 1C - MEASURING BRAIN ACTIVITY

"Memory replay" has been recorded in different areas of animal brains, including the visual cortex, parietal cortex, and motor cortex, and during both REM and NREM sleep (Eichenlaub et al 2020).

The offline "replay" of neural firing sequences during sleep has been shown recently in humans.

Indirectly there is evidence from non-invasive brain scans. For example, participants learned to associate odour cues with prior learning, and odour re-exposure during NREM sleep was associated with hippocampal activation during sleep (eg: Diekelmann et al 2011).

Invasive methods used with non-human animals is rare in humans. But opportunism does allow it. For example, Jiang et al (2017) used electrodes implanted in the brains of individuals during pre-surgical epilepsy monitoring. Patterns of electrical activity across the brain during waking (called "motifs") were very similar to those in subsequent sleep. "Furthermore, motifs occurring during the performance of a cognitive task were more likely to have more matches in subsequent sleep" (Eichenlaub et al 2020 p2).

Eichenlaub et al (2020) made use of microelectrodes placed in the brains of two paralysed individuals as part of a test of brain-computer interfaces (ie: controlling a

¹² Eight confirmed cases of lung injury in Canada, and seventy-four notifications to authorities of negative health effects in the UK (Hamzelou 2019).

¹³ This latter statement has been criticised because it is based on a comparison of the number of chemicals in e-cigarette vapour and tobacco smoke only (eg: Robert Tarran in Hamzelou 2019) (Ghosh et al 2018).

computer cursor with neural activity). As part of the training, participants were asked to imagine moving their head to control the cursor. The pattern of neural firing sequences was recorded. A pattern was more likely to appear in subsequent short, daytime naps (ie: NREM sleep) than in control situations (ie: no training or naps before training). This study suggested the replay of learning during sleep (Eichenlaub et al 2020).

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2. CIRCADIAN RHYTHMS

- 2.1. Entrainment
- 2.2. Twilight colour
- 2.3. References

2.1. ENTRAINMENT

The body runs on internal clocks that are near-24 hours (circadian rhythms). Light detection is crucial to maintaining these rhythms in relation to environmental changes (eg: seasonal day length variation).

The synchronising of the internal and external rhythms is known as entrainment. According to the discrete model of entrainment, a light stimulus at the will synchronise them. The light stimulus immediately shifts the internal clock to the environmental light-dark cycle which varies with the seasons, say.

The continuous model proposed that the light stimulus takes some time to synchronise the clocks. Alternatively, light signals at different times of the day have different effects. For example, bright light at night will shift the internal clock more than the same stimulus during the day (Webb and Herzog 2017).

Finding a "pill" to aid entrainment would be ideal in the modern world of shift work and "jet lag" (where the internal and external clocks are out of sync). A possible biochemical is the neuropeptide vasoactive intestinal polypeptide (VIP), which is released by the light sensitive suprachiasmatic nucleus (SCN) in the brain¹⁴. VIP is known to keep the cells of the SCN synchronised "to the same beat" (Webb and Herzog 2017). But high concentrations cause disarray ("phase tumbling") which could allow entrainment to happen faster.

Mice injected with high doses of VIP adapted quicker to sudden light-dark shifts (simulating jet lag) than controls (An et al 2013). This is done by habituating the mice to a certain schedule (eg: A: 1st 12 hours light/second 12 hours dark), and then suddenly shifting it (eg: B: 1st 12 hours dark/second 12 hours light). Jet lag is simulated as the internal clock follows schedule A while the environment is schedule B.

2.2. TWILIGHT COLOUR

Walmsley et al (2015) stated: "Twilight is

¹⁴ Information about light enters the eye and travels along the retino-hypothalamic projection (RHP) to the SCN. The RHP has a unique type of cell that is photosensitive (Walmsley et al 2015).

characterised by changes in both quantity ('irradiance') and quality ('colour') of light. Animals use the variation in irradiance to adjust their internal circadian clocks, aligning their behaviour and physiology with the solar cycle" (p1). These researchers concentrated on the changes in colour in their study, specifically "that, in mice, this primordial colour discrimination axis (equivalent to human blue-yellow colour vision) is an influential regulator of SCN activity, essential for appropriate circadian timing relative to the natural solar cycle" (Walmsley et al 2015 p2).

The mice were housed in controlled environments with 12-hour dark/12-hour light schedule when not being tested. Irradiance measurements had been collected from dawn/dusk transitions on thirty-six summer/autumn days in northern England, and these data were used in various light conditions in darkened chambers. Recordings were made of the electrical activity of neurons in the SCN as the measure of the response to light changes.

Mice were tested under simulated dawn/dusk transitions. Both quantity and quality of light were required to fully entrain the circadian rhythms of the animals. Specific cells in the SCN were found to respond to changes in colour occurring during twilight.

Response to light colour has also been shown in experiments by Lazopulo et al (2019), where fruit flies avoided blue light and preferred green light to red light at different times of the 24-hour cycle. The flies were kept individually in glass tubes which had three types of light (blue, green or red), and food was placed under the light (while a 12-hour dark/12-hour light schedule was maintained).

During the twelve hours of light, blue light was always avoided. Green light was preferred in the early morning and late afternoon when the flies were most active. "Such timed preferences are intuitively advantageous, because some of this activity is devoted to searching for food, and flies often find food in or under green trees and bushes" (Helfrich-Forster 2019 p43).

Lazopulo et al (2019) also tested these behaviours with flies with altered "clock" genes. The flies with no circadian rhythms always preferred green light throughout the 12 hours of the light period, while the flies with slowed or sped up circadian rhythms preferred green light at their body clock's early morning and late afternoon. So, the preference for green light is linked to the internal body clock.

It was also found that the aversion to blue light was not in response to photoreceptor cells in the eyes, but to pain-sensing neurons in the skin. "These neurons mediate escape responses to the fly to high temperatures, potentially harmful chemicals and mechanical stimuli"

(Helfrich-Forster 2019 p44).

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3. TWO DISORDERS OF SLEEP

- 3.1. Narcolepsy and H1N1 influenza and vaccine
 - 3.1.1. Review of evidence
- 3.2. Obstructive sleep apnea
 - 3.2.1. Menopause
 - 3.2.2. Dreaming
- 3.3. Appendix 3A - Mortality risk
- 3.4. References

3.1. NARCOLEPSY AND H1N1 INFLUENZA AND VACCINE

Narcolepsy, where individuals fall regularly and uncontrollably into sudden sleep, has been linked to a particular gene in dogs, and/or the hormone hypocretin/orexin (Nicholls 2012) ¹⁵.

Narcolepsy as an autoimmune disorder has also been proposed with an environmental trigger for the condition, like a respiratory infection (Nicholls 2012) ¹⁶.

For example, the onset of narcolepsy has been preceded by upper airway infections as the trigger (eg: Aran et al 2009 ¹⁷). Also links to the H1N1 influenza ("swine flu") vaccine (Pandemrix) as the trigger in children (eg: Swedish Medical Authorities in 2011) (Han et al 2011).

Han et al (2011) used Chinese data to show seasonal fluctuations in narcolepsy onset and H1N1 infections. Retrospectively the onset date of 629 patients with narcolepsy at a Beijing hospital between 1988 and 2011 were examined ¹⁸. Telephone interviews asked about recent history of seasonal influenza, H1N1 vaccination, and other diseases. Control data from two million individuals were also used.

Narcolepsy onset showed a circannual cycle (ie:

¹⁵ The most common symptoms are unintended sleep episodes, excessive daytime sleepiness (EDS), and cataplexy. The average age of onset is 12-25 years old. EDS can also occur with other sleep disorders like sleep deprivation, insomnia, and sleep apnea (Partinen et al 2012).

¹⁶ "Narcolepsy type 1 (NT1) is likely caused by an autoimmune-mediated destruction of hypocretin-producing neurons in the lateral hypothalamus. NT1 is almost always associated with cataplexy. In narcolepsy type 2 (NT2), there is no hypocretin deficiency or cataplexy" (Sarkanen et al 2018 p177). The International Classification of Sleep Disorders (3rd ed) (ICSD-3) distinguishes between type 1 and type 2, whereas ICSD-2 referred to narcolepsy with or without cataplexy.

The Brighton criteria (Poli et al 2013) are used to establish the level of certainty of narcolepsy (Sarkanen et al 2018):

- Level 1 - proven hypocretin deficiency by lumbar puncture.
- Level 2 - use of mean sleep latency test (MSLT) to establish EDS and cataplexy.
- Level 3 - use of MLST to establish EDS.

¹⁷ A US study that found that about two-thirds of patients with narcolepsy had anti-bodies for streptococcal infection (Han et al 2011).

¹⁸ Note that 70% of the sample were children at the time of onset.

lower in autumn and winter, and higher in spring and summer. Onset increased seven-fold in 2010 following the H1N1 2009-10 pandemic season. In both cases, narcolepsy onset significantly increased 5-6 months after influenza seasonal peaks and the H1N1 pandemic.

There was no relationship between narcolepsy onset and H1N1 vaccination (as only 5% of sufferers recalled a prior vaccination).

Altogether the findings suggested that influenza (including H1N1) was the trigger for the reactive immune response which led to narcolepsy onset. "Winter infections would initiate or reactivate an immune response that leads to hypocretin cell loss and narcolepsy in genetically susceptible individuals. Based on animal studies, approximately 80% cell loss is needed to exhibit symptoms, possibly explaining the 4- to 6-month delay between winter airway infection and narcolepsy onset occurrence" (Han et al 2011 p415).

Partinen et al (2012) investigated the changing incidence of childhood narcolepsy in Finland between 2002 and 2010¹⁹. There were 335 new cases in the study period, giving an annual incidence of 0.79 per 100 000²⁰. Twenty-six of these cases were individuals aged younger than seventeen years old (incidence rate of 0.31).

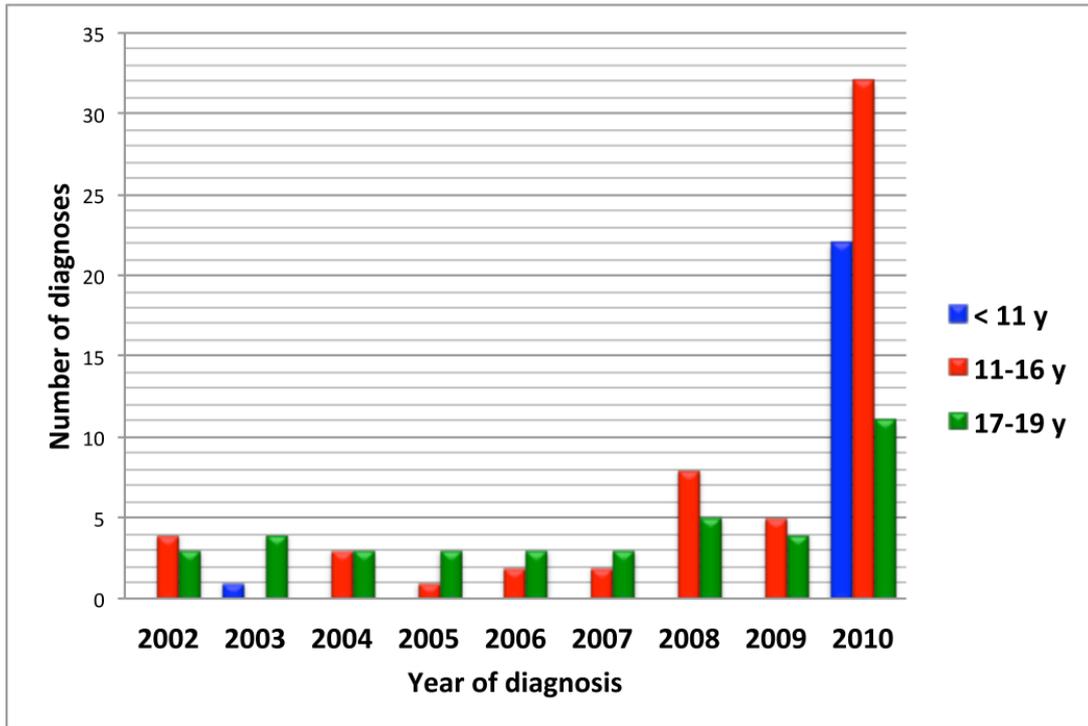
The vaccine for H1N1 (Pandermrix) was used in 2009-10. The incidence of narcolepsy was 1.88 in 2010 (54 of 101 cases were children and adolescents - incidence rate: 5.30). Thirty of these children and adolescents had received the vaccine within eight weeks prior to the onset of EDS (figures 3.1 and 3.2)²¹.

Partinen et al (2012) considered the reasons for the increased incidence: "Could the increased incidence be explained by the increased awareness of narcolepsy in 2010 compared to previous years - triggered by the intensive public discussion in Finland in August 2010 of the possible association of narcolepsy with Pandemrix vaccination? This is unlikely since in the majority of our patients the symptoms of sleepiness or cataplexy started abruptly before August 2010, and the parents had consulted health care personnel already during the winter or early spring 2010. At that time there had been no news or articles of the increase in narcolepsy incidence or its possible association with the H1N1 pandemic. Also, the symptoms of narcolepsy and cataplexy were so clear

¹⁹ "The incidence rates for narcolepsy were calculated by dividing the number of yearly-diagnosed narcolepsy patients by the total number of people in Finland in each age group during the same year" (Partinen et al 2012 p2).

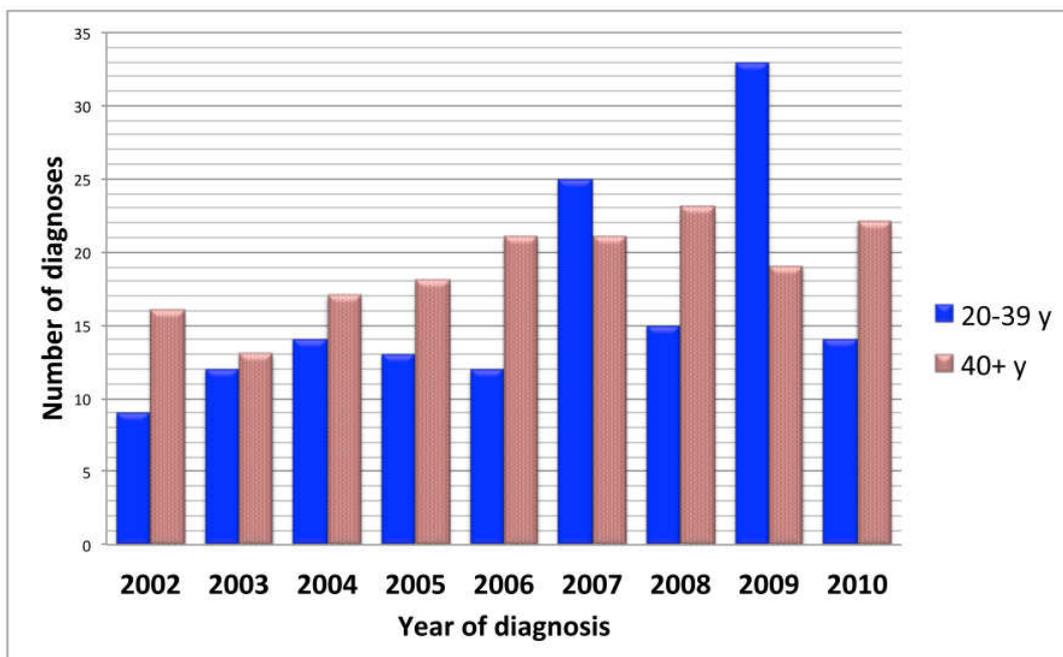
²⁰ Usual incidence in the general population is 1 per 100 000 (Sarkanen et al 2018).

²¹ Increased incidence of narcolepsy also reported in Sweden, France, England, Ireland and Norway in 2009-10 (Sarkanen et al 2018).



(Source: Partinen et al 2012 figure 1)

Figure 3.1 - Number of new diagnoses of narcolepsy in Finland in individuals under 20 years old by year of diagnosis.



(Source: Partinen et al 2012 figure 2)

Figure 3.2 - Number of new diagnoses of narcolepsy in Finland in individuals aged 20 years or older by year of diagnosis.

that they impaired the daily life of the children. It is very unlikely that similarly severe abrupt sleepiness with cataplexy and behavioural problems would have remained unnoticed before 2009-2010. In addition, the incidence of adult and childhood narcolepsy in Finland in 2002-2009 has been similar to that seen in other countries" (p6).

The researchers continued: "A likely trigger in our patients could be influenza vaccination, which took place in a close time-relation with the onset of narcolepsy. Vaccination may have induced or accelerated already pre-existing autoimmunity leading to a rapid destruction of the hypocretin cells among genetically susceptible children and adolescents... [But] We cannot formally rule out the contribution of other infectious agents (H1N1, seasonal influenza, enterovirus, rhinovirus, streptococcal infection, or some other microbial infections) together with vaccination that could have lead to the development of narcolepsy" (Partinen et al 2012 p7) ²².

Partinen et al (2012) asked another question: "Why were adult onset cases not increased? Theoretically it is possible that the vaccine precipitated onset in people who would have developed it later, anyway. In this case we should see a drop in adult incidence later during the coming years. Another possibility is that some children with multiple genetic predisposition factors are especially vulnerable to develop narcolepsy. In some other autoimmune diseases, such as in type 1 diabetes, early age onset is also often seen. It is also possible that the onset is more insidious in older adolescents and adults and thus there may be a delay in the diagnosis" (p8).

3.1.1. Review of Evidence

All the studies are observational, and have a number of limitations including (Sarkanen et al 2018):

a) Trouble in disentangling H1N1 infection and its vaccine as the cause of the narcolepsy onset.

b) Recall bias - eg: tendency to remember some events more than others.

c) Selection bias - eg: certain individuals more

²² "The adjuvant (AS03) in the Pandemrix vaccine is very potent, since it frequently induces local inflammatory reactions and occasional systemic side effects like fever. We can speculate that the inflammatory response was so strong that it included central nervous system affection" (Partinen et al 2012 p7).

likely to be involved in studies.

d) Ascertainment bias - eg: incorrect case confirmation; inaccurate gathering of information on symptom onset and vaccination date; lack of blinding to vaccination status.

"Simply an increase in attention towards this disease could lead to increase in the number of diagnosed cases without an actual rise in incidence" (Sarkanen et al 2018 p178).

Five outcome measures are used in studies (Sarkanen et al 2018):

i) Onset of symptoms (prone to recall bias as usually assessed retrospectively from a respondent);

ii) First healthcare contact (based on patient records, so more "objective");

iii) Date of referral to specialist (from patient records);

iv) Referral to MSLT (from patient records);

v) Final diagnosis (from patients records).

Sarkanen et al (2018) performed a systematic review and meta-analysis of studies on H1N1 influenza virus infection and vaccinations, and narcolepsy incidence. Up to November 2016, twenty-nine relevant studies were found, of which eleven provided quantitative data for meta-analysis.

The total number of narcolepsy cases was 376 vaccinated and 95 unvaccinated children and adolescents, and 133 vaccinated and 59 unvaccinated adults.

Sarkanen et al (2018) summed up: "In this meta-analysis we found a 5- to 14-fold increase in incidence of narcolepsy in children and adolescents and a 3- to 7-fold increase in adults in the countries where Pandemrix vaccine was widely used in 2009-2010 (Finland, France, Ireland, the Netherlands, Norway, Sweden and the UK). The risk in the observational studies is dependent on the used index date. Use of onset of symptoms as index date produced the highest risk followed by date of healthcare contact, referral to sleep studies, and date of diagnosis" (p183).

The authors ended on a positive note: "The vaccine attributable risk in children and adolescents was around 1 per 18,400 vaccine doses. Benefits of immunisation outweigh the risk of vaccination-associated narcolepsy, which remains a rare disease" (Sarkanen et al 2018 p177).

3.2. OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is "characterised by recurrent collapses of the upper airway during sleep and it is associated with intermittent hypoxia, sleep fragmentation, surges of sympathetic tone, and oxidative stress, finally resulting in increased cardiovascular risk and excessive daytime sleepiness" (Perger et al 2019 p35) ²³. Put simply, the individual temporarily stops breathing and the body reacts to it. It may not consciously wake the sleeper, but if this happens multiple times in the night, then deeper sleep is inhibited, and thus the EDS.

OSA can be assessed with a sleep laboratory-based polysomnogram that includes a measure of airflow through the nose and mouth, blood oxygen levels, snoring, and an electroencephalogram (EEG) of sleep and waking brain electrical activity. There are also questionnaires that can be used, like the Berlin Questionnaire (Netzer et al 1999) ²⁴. This involves eleven items covering snoring/apneas, fatigue/sleepiness, and obesity/hypertension (Gottlieb et al 2020) ²⁵.

OSA is associated with health problems like hypertension, type 2 diabetes, coronary heart disease, and even death (appendix 3A) (Gottlieb et al 2020). The mechanism is a combination of oxygen deprivation and the consequent stress on the body system, and sleep fragmentation in OSA (Gottlieb et al 2020).

The general prevalence of OSA is 22% for men, but 17% of women (Perger et al 2019). The prevalence, however, depends on the definition of hypopneas used. For example, a definition of a 4% decrease in blood oxygen saturation (as used in the Wisconsin Sleep Cohort Study ²⁶ ²⁷) leads to a prevalence estimate of 17.4% of women and 33.9% of men in the USA aged 30-70 years old with mild OSA (AHI 5 - 14.9/h ²⁸), and 5.6% and 13% respectively for

²³ Hypopnea (reduced breathing) and apnea (absence of breathing), which could be at least ten seconds in duration (Gottlieb et al 2020).

²⁴ Named after the Conference on Sleep in Primary Care in Berlin in 1996 from where it originated (Netzer et al 1999).

²⁵ Netzer et al (1999) reported it use with the first sample (n = 744). For example, 52% snored (half of these at least 3-4 times per week), 34% reported not feeling rested after sleep at least 3-4 times per week, and 19% had fallen asleep while driving (approximately 1 in 10 of those at least 3-4 times per week).

²⁶ This is a prospective longitudinal study began in 1988 with 30-60 year-olds working for various Wisconsin state agencies in the USA (Young et al 2008).

²⁷ This cohort is predominately non-Hispanic White (Gottlieb et al 2020). The Jackson Heart Sleep Study, for example, involved more African Americans, and their prevalence of OSA was 54% among 50 to 80 year olds (Gottlieb et al 2020).

²⁸ The apnea-hypopnea index (AHI) is the measure of the number of times that breathing stops per hour during sleep, and >15/h is classed as moderate to severe sleep apnea (Perger et al 2019). More formally, AHI is the number of apneas plus hypopneas per hour of sleep (Gottlieb et al 2020).

severe OSA (AHI \geq 30/h) (Gottlieb et al 2020).

OSA increases with age - eg: 27% of 30-49 year-old US men and 9% of women compared to 43% and 28% respectively aged 50-70 years old (Gottlieb et al 2020).

Body mass index (BMI) is also an important variable. For example, of individuals in the USA aged 30-49 years old with a BMI of less than 25 (low, normal weight), 7% of men and 1.4% of women had OSA compared to 45% of men and 14% of women with a BMI above 30 (ie: obese) (Gottlieb et al 2020).

3.2.1. Menopause

Men suffer from OSA much more than women with the exception of women after menopause (eg: 30% compared to 9% of pre-menopausal women, and a higher AHI; Heinzer et al 2018).

Among 589 women in the Wisconsin Sleep Cohort Study, post-menopausal ones were 2-3 times more likely to have OSA than younger women, adjusting for age, BMI, and smoking (Young et al 2003).

Following women over the transition from pre- to post-menopause, Mirer et al (2017) found a 4% increase in AHI each year ²⁹.

A number of factors have been proposed to explain the increased OSA post-menopause, including (Perger et al 2019):

i) Age - "Given that menopause is an ageing process and because age is a powerful predictor of sleep apnea, it is crucial to distinguish whether menopause itself is associated with greater risk of sleep apnea or whether it simply reflects an aging process similar to that in men" (Perger et al 2019 p36). Studies suggested a "partial role" for ageing.

ii) Quantity and distribution of body fat - Though OSA is generally associated with higher fat mass, again only a "partial role" for menopause-related fat mass, according to studies.

iii) Differences in endogenous sex hormones like oestrogen and progesterone - Studies provide inconsistent findings here.

iv) Pharyngeal dilating muscle activity - Put simply, airway obstruction increases in post-menopausal women (possibly linked to changes in sex hormones).

²⁹ The Sleep in Midlife Women Study was a sub-cohort of the Wisconsin Sleep Cohort Study.

Altogether, the different factors explain the increase in OSA in post-menopausal women (Perger et al 2019).

3.2.2. Dreaming

How does OSA impact dreaming? "Some studies have reported less dreams in OSA patients, and others have described that patients with OSA have increased dreams with emotional content, mainly violent and hostile" (BaHammam and Almeneessier 2019 p2).

BaHammam and Almeneessier (2019) provided a review of the studies.

i) Dream recall (six studies found) - The studies were contradictory with some reporting more dreaming among OSA patients than controls, and others less.

Different explanations have been proposed for the findings:

a) Less dream recall - OSA impairs dream recall, or frequent wakings from OSA reduces REM sleep and the opportunity to dream.

b) Increased dream recall - Frequent arousals leads to greater recall of dreams.

ii) Dream content (11 studies found ³⁰) - Some studies reported suffocation-related content, for example, BaHammam et al (2013); patients' reports include: "I dreamt that I fell in a deep well and was gasping for breath"; "that a person was holding my neck preventing me from breathing"; "I dreamt of drowning in dark water and was gasping for breath" (quoted in BaHammam and Almeneessier 2019).

As to whether OSA patients experience more nightmares was unclear from studies, partly due to difference definitions of nightmares.

Carrasco et al (2006) proposed an explanation for increased nightmares in that breathing problems during REM sleep trigger the limbic system and this generates highly emotional dream content.

BaHammam and Almeneessier (2019) summed up their review: "Although the number of studies investigating dreaming in patients with OSA is relatively small, the literature is intriguing and shows that altered sleep physiology due to recurrent obstructive events, frequent arousals, and repeated desaturations may influence dream

³⁰ Some of the studies are included in both topics.

recall and dream content in some patients. Nevertheless, studies were inconsistent and reported conflicting results" (p7).

The measurement of dreams is a key issue. One method is retrospective questioning in the morning (ie: post-sleep). The alternative, usually in sleep laboratories, is to wake the sleeper during REM sleep and ask them about dreaming. Not surprisingly, dream recall is higher using this latter method.

3.3. APPENDIX 3A - MORTALITY RISK

Sleep-disordered breathing (SDB) is a term used instead of or as well as OSA, as in the case of Punjabi et al (2009). They analysed data from the Sleep Heart Health Study on mortality. This longitudinal study recruited participants in the USA between 1993 and 1998 from other heart study cohorts (n = 6441). Details about sleep were collected from self-reports and physiological measures to give an AHI at baseline.

Follow-up occurred by April 2006. In total, 43% of men and 65% of women had no SDB compared to 8% and 3% respectively for severe symptoms. The latter were one and a half times more likely to die than the no SDB group, but, after controlling for cholesterol levels, AHI was associated with mortality for men only. Men aged 40-70 years old with severe SDB (AHI ≥ 30 /h) had the highest risk of death.

How SDB or OSA is measured is key in studies like this. Punjabi et al (2009) used polysomnographic equipment. "Apneas were identified if airflow was absent or nearly absent for at least 10 s. Hypopneas were identified when there was at least 30% reduction in airflow or thoraco-abdominal movement for at least 10 s" (Punjabi et al 2009 p2). Other studies have used snoring as a proxy measure, for example (Punjabi et al 2009).

Table 3.1 outlines some other methodological differences between this study and previous research.

Issue	Punjabi et al (2009)	Other Studies
Design	Prospective longitudinal	Eg: retrospective, case-controls
Sample	US general population (ie: not being treated for SDB)	Clinical populations (risk of referral bias)
Age	40 years +	Eg: elderly population only (Ancoli-Israel et al 1996)
Gender	Male and female	Eg: males only (Lavie et al 1995)
Length of follow-up	Up to 13 years	Eg: shorter
Control of confounding variables	Eg: other health problems; self-report of smoking status	Eg: less control: "lack of consideration of treatment effects" in clinical populations

Table 3.1 - Key methodological differences between Punjabi et al (2009) and other studies on SDB/OSA and mortality.

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4. PHYSIOLOGY

- 4.1. Local sleep
 - 4.1.1. Unihemispheric sleep
- 4.2. Appendix 4A - Northern fur seal
- 4.3. References

4.1. LOCAL SLEEP

"Local sleep" was observed initially in rats (Vyazovskiy et al 2011). It was reported that "if a rat stays awake longer than usual, some cortical neurons show brief periods of silence that are basically indistinguishable from the off periods observed during slow-wave sleep. Meanwhile the rat is running around, its eyes open, tending to its business, as any awake rat would do" (Tononi and Cirelli 2013 p31).

Krueger et al (2019) observed: "Sleep is often viewed as an animal behaviour, yet the entire body is not required for sleep to ensue. Similarly, sleep is often viewed as 'of the brain, by the brain, and for the brain' [Hobson 2005], yet the entire brain is not required for sleep. Further, sleep, metabolism, inflammation, and plasticity share numerous regulatory molecular components. All these processes, including sleep, are initiated locally yet have emergent whole-body manifestations and functions" (p14). These researchers then argued that sleep is "a fundamental process of small neuronal/glial networks initiated by cell activity-dependent molecular signals" (Krueger et al 2019 p14).

This fits with the idea of "local sleep" (or the "local use-dependent sleep" hypothesis, or neuronal group theory of sleep function; Krueger and Obal 1993). Specifically, that "organism sleep can occur as a consequence of spontaneous state synchronisation of multiple local networks" (Krueger et al 2019 p19) (ie: that there is no "sleep centre" in the brain that controls the whole process). "Local sleep" is a "bottom-up" view as opposed to the "top-down" approach of a "sleep centre" (Krueger et al 2019).

Krueger et al (2019) outlined the key evidence for "local sleep":

i) Human experiments - eg: Kattler et al (1994): Excessive activation of the somatosensory cortex by using a hand vibrating device led to a small increase in EEG activity in that area of the brain in subsequent sleep.

ii) Animal studies - eg: Vyazovskiy et al (2011): Manipulating the sleep deprivation of rats while measuring local brain activity (ie: populations of cells)

found that "sleep-like states lacked synchrony across the cortex, with some populations seemingly remaining 'awake' as other populations 'slept'" (Krueger et al 2019 p17).

Unihemispheric sleep is also used as evidence for this hypothesis.

4.1.1. Unihemispheric Sleep

Within the daily rhythms, the most obvious is a period (or periods) of sleep and of wakefulness. However, some animals have evolved a middle way - unihemispheric slow-wave sleep (USWS) - where sleep occurs in one hemisphere of the brain while the other is awake. This has been observed in some marine mammals, bird species, and reptiles (Mascetti 2019).

The ventrolateral pre-optic (VPL0) nucleus in the hypothalamus of each hemisphere has been found in dolphins, for example, to determine which side of the brain sleeps, along with the brainstem (Kedziora et al 2012).

Recent research has suggested that some animals can experience USWS, and "normal sleep" (bihemispheric slow-wave sleep (BSWS) and REM) (eg: northern fur seals; figure; Lyamin et al 2017; appendix 4A). When on land, normal sleep is experienced, but in the water USWS is the case (Mascetti 2019).



(Source: US Fish and Wildlife Service; in public domain)

Figure 4.1 - Adult male northern fur seal.

4.2. APPENDIX 4A - NORTHERN FUR SEALS

With USWS at sea, seals can go as long as two weeks without REM sleep. "When they return to land they show little or no REM rebound. Their switch to from bilateral to unihemispheric non-REM sleep in water may make REM sleep unnecessary" (Lyamin et al 2018 p2000) ³¹.

Four juvenile seals, wearing data loggers including EEG readings to determine periods and type of sleep, were kept in seawater enclosures with or without access to a dry platform for 10-14 days. REM sleep was reduced to an average of three minutes per day in the water (compared to 80 minutes on land at baseline). A REM deficit of 98% was calculated (or average 765 minutes) while in the water. On the first day back on land, the amount of REM sleep was no greater than at baseline. "When returned from their 10-14 days in seawater to baseline conditions (sleeping on a dry platform), the seals were in good condition, as judged by their appearance, activity, interaction with the experimenters, weight, and appetite" (Lyamin et al 2018 p2002). Rats deprived of REM sleep for similar periods showed weight loss and reduced body temperature, for example (Kushida et al 1989).

It is thus assumed that REM sleep is involved in homeostasis (maintaining balance in the body systems), but Lyamin et al (2018) hypothesised that "a major function of REM sleep may be the reversal of the metabolic depression and cooling of the brainstem that result from prolonged bilateral non-REM sleep" (p2004). These brain changes are not an issue with USWS, and so less need for REM sleep.

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³¹ Humans show "REM rebound" -ie: more time in REM as a proportion of total sleep when allowed to sleep again. Rats in experiments showed a fivefold increase in REM sleep after 2-15 days of deprivation (Kushida et al 1989).

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5. DREAM CONTENT

- 5.1. Aggression in dreams
- 5.2. Recurrent dreams
- 5.3. References

5.1. AGGRESSION IN DREAMS

"Dream aggression" is "the feelings or acts of a character intended to hurt or annoy another character in a dream" (Zhang et al 2020 p2). Aggression in dreams varies from covert feeling of hostility to murder, with eight categories, according to one system of coding (Domhoff 1996).

Using this system of coding, about half of dreams include at least one aggressive interaction (Zhang et al 2020). Studies on gender differences in aggressive content are mixed, and the method of dream collection (questionnaire, diary, interview or sleep laboratory awaking) is relevant (Zhang et al 2020).

A commonly used method is the "Most Recent Dreams" (MRD) technique (Domhoff 1996), which involves recall of the last dream (whenever that was). Zhang et al (2020) performed a meta-analysis of twelve studies on gender differences in aggression dream content using this method.

The frequency of aggression was significantly higher in male than female dreams, and this was evident in children's and adult's, but not teenager's dream content.

Zhang et al (2020) argued that the findings supported the continuity hypothesis of waking life and dream content (Hall and Nordby 1972), which "claimed that dreams' characteristics were continuous with waking experiences, namely, whether awake or asleep, the individual maintains the corresponding personalities and characteristics" (Zhang et al 2020 p12). Generally, men are more aggressive in waking life, and this is reflected in their dream content.

5.2. RECURRENT DREAMS

Recurrent dreams are those with repeated content.

Oluwole (2019) surveyed 196 clinical students at a university in Nigeria with a questionnaire containing 106 dream themes. On average, thirty-three themes were reported (compared to eighteen among German undergraduates; Schredl et al 2004), and less than 2% of the sample had not experienced recurrent dream themes. The top recurrent dreams were seeing friends, colleagues, siblings, and parents, and success, and walking.

Being pursued was low in this study, but the highest reported by Japanese undergraduates.

Among US undergraduates (Griffith et al 1958), the most prevalent themes were falling, being attacked or pursued, and trying again and again to do something. Common to Canadian undergraduates (Nielsen et al 2003) were being chased or pursued, sexual experiences, and falling, while Chinese undergraduates (Yu 2008) reported seeing school teachers, studying, and being chased most often.

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6. SLEEP AND CIRCADIAN RHYTHMS AND ATHLETES

- 6.1. Overview
- 6.2. Time-of-day variations
- 6.3. Appendix 6A - Sargent and Roach (2016)
- 6.4. Appendix 6B - Miller et al (2017)
- 6.5. Appendix 6C - Lastella et al (2014)
- 6.6. Appendix 6D - Mah et al (2011)
- 6.7. References

6.1. OVERVIEW

The importance of sleep for athletes has grown in research interest in recent years, particularly in relation to recovery from training and competition, and for athletic performance (Lastella et al 2020).

The first study was Baekeland and Lasky (1966), who noted increased slow wave (deep) sleep in the night following high intensity exercise. Then few studies until Taylor et al (1997), "initiated a substantial increase in studies examining the impact of sleep in athletes, including relationships with training, competition, injury, psychological well-being, and performance" (Lastella et al 2020 p99).

Lastella et al (2020) looked at the topic using bibliometric techniques, which "aim to understand the research trends and focus, and contributions to scholarship of any field, country, institution, author or a journal" (p100).

An athlete was defined as an individual who "engages in physical activity or sports with the primary goal of improving performance to bolster athletic excellence and/or achievement" (Lastella et al 2020 p101), and included elite, semi-elite, retired, and recreational athletes, as well as eighty keywords in the search of the "Scopus" database (which includes over 23 000 peer-reviewed journals) up to mid-August 2019. The final analysis included 313 journal articles since 1966.

There was a sharp increase in publications in the last decade (2010-19) (n = 257). "Similar to sports nutrition research, sleep research in athletes has progressed, due to the well-established importance of sleep toward optimising recovery and performance. This trend may reflect the growing interests of athletic/sporting organisations and the scientific community in understanding the critical role sleep has on athlete health, recovery and performance. Technological advancements in sleep measurement, such as the implementation of research-grade accelerometers in athlete populations may have also contributed to the rise in research output" (Lastella et al 2020 p112).

The top country for recent studies was Australia,

followed by the USA, France, and the UK. "This increased production, mostly in developed countries, may reflect the globalisation of sport and the large investments made by governing bodies. For example, in the 2016-2017 financial year, the Australian government committed \$101 million (AUD) to high performance sports funding. For many countries, investment into sport is viewed in light of a virtuous cycle such that elite sporting success offers international prestige for the nation, a certain 'feel-good factor among the people' and ultimately can increase sport participation throughout the population" (Lastella et al 2020 p113).

The key areas of interest of researchers included:

i) Monitoring athletes' sleep (eg: Sargent and Roach 2016; appendix 6A).

ii) How different sports impact sleep (eg: Miller et al 2017; appendix 6B).

iii) How other aspects of an athlete's life impact sleep (eg: travel; Lastella et al 2014; appendix 6C).

The bibliometric analysis also showed the highest cited paper, which was Mah et al (2011). This found that increased sleep by around two hours per night (ie: sleep extension) improved athletic performance (appendix 6D). Surprisingly, this finding has only been confirmed by two other studies, but challenged by another (Lastella et al 2020).

Lastella et al (2020) noted the lack of research on daytime napping as a way to reduce sleep debt among athletes. Two studies were found only.

6.2. TIME-OF-DAY VARIATIONS

Circadian rhythms include differences in physical performance over 24 hours (eg: very short-term anaerobic performance is greater in the afternoon than the morning) (Pullinger et al 2020).

But sport involves repeated performance. Repeated-sprint performance, for example, has been studied in controlled situations (eg: using a treadmill). Findings include that mid-afternoon performance is better for average speed (Pullinger et al 2020).

But there is disagreement over fatigue from repeated-sprints over the day, for instance. "Observing significant changes in diurnal variation, may involve several contributing factors - such as type and intensity of the task, the motivation of subjects to perform the task, the time spent on the task and subject

familiarisation regarding the task to be performed... The chosen number of sprints, repetitions and training status of subjects differ between studies, making it difficult to compare findings" (Pullinger et al 2020 p452).

This led Pullinger et al (2020) to focus on a specific question in their review: "In healthy adolescent males, what is the magnitude of time-of-day differences in repeated-sprint performance outcomes between cycling and running in the evening (17:00 to 19:00 h) compared to the morning (06:00 to 09:00 h) during experimental trials?" (p452). Ten studies published up to June 2019 were found (with a total of 128 participants).

Most of the studies (n = 8) reported better performance on repeated-sprints in the afternoon compared to the morning. The difference in performance was up to 8%. But there was great variety in methodology between the studies, including:

a) Control of factors influencing body clock, like the light-dark cycle, and food intake.

b) Control of factors that influence performance (eg: room temperature; sleep and fatigue; fitness/training history of participants).

c) Number of repeated-sprints per day (5-10), length of sprints (eg: 25 m), and amount of recovery time (eg: 20-30 seconds).

d) Details of morningness-eveningness of participants.

e) Mode of exercise (running or cycling).

6.3. APPENDIX 6A - SARGENT AND ROACH (2016)

Professional sport is increasingly being scheduled for evening competition (to suit audiences, for example), but what is the impact upon an athlete's sleep?

Generally, poorer sleep is reported by athletes following evening competition in a variety of sports (Sargent and Roach 2016).

Studies using objective measures have mixed results (Sargent and Roach 2016). But "in some of these studies, only a small number of athletes were observed (9-12 athletes), not all of the athletes were professional (youth athletes), and some athletes had undertaken trans-meridian travel in the days leading up to competition (4-h time-zone shift)" (p667).

Sargent and Roach (2016) reported a study of 22 professional male Australian Rules Football players over

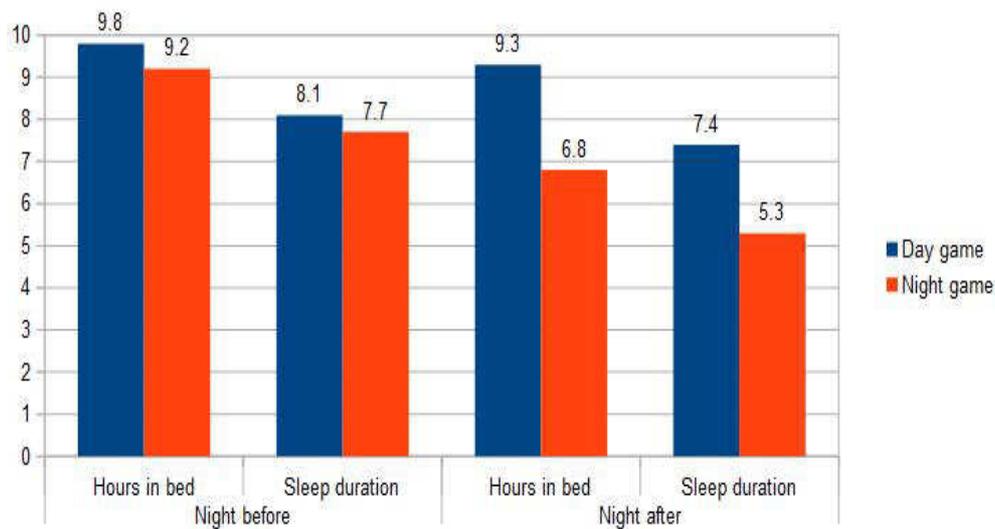
two weeks of pre-season that included a "day" game (starting at 3.45 pm) and an "evening" game (7.10 pm start). Sleep periods before and after the games were compared using sleep-diary and activity-monitor data.

a) Night before a game - Little difference between the day and night games.

b) Night after a game - There were significant differences here with sleep onset later, less time in bed and less sleep following the evening game (figure 6.1).

Disrupted sleep after an evening game may be due to physiological arousal from the game, and/or post-game activities including "players' social activities after the game and/or their post-game routines, such as recovery strategies, meals, showers, medical care, meetings and press conferences" (Sargent and Roach 2016 p669).

The study did not control for other factors that could have impacted sleep, like caffeine or alcohol use (Sargent and Roach 2016).



(Data from Sargent and Roach 2016 table 1 p669)

Figure 6.1 - Mean sleep length before and after games.

6.4. APPENDIX 6B - MILLER ET AL (2017)

Miller et al (2017) compared the sleep/wake behaviours of three groups of elite football players in Australia (16 Australian Rules football players, 28 rugby union, and seven soccer). All players kept a sleep diary and wore an activity monitor for seven days during

training.

The Australian Rules football players went to bed and got up earlier than the other two groups. There was no significant difference in total sleep time, but Australian Rules football players did take longer to fall asleep (sleep latency), and spent more time awake in the night (wake during sleep) (table 6.1).

Miller et al concluded: "Overall, the main finding of this study is that Australian Rules footballers experienced more sleep disturbances, compared to rugby union players and soccer players. An explanation of these findings is that the high training demand of Australian Rules football may have resulted in increased pain and movement during sleep, therefore increasing sleep disturbances... Since Australian Rules football is a considered to be a physiological hybrid of soccer and rugby union, it seems reasonable to suggest that the combination of high aerobic demand and high physical contact may explain the sleep disturbances observed in the current study" (p605).

	Australian Rules	Rugby Union	Soccer
Sample size	16	28	7
Bed time (24-hr clock)	22:55	23:36	23:12
Getting up (24-hr clock)	07:59	07:59	08:33
Total sleep time (hrs)	6.8	7.2	6.7
Sleep latency (mins)	18	10	10
Wake during sleep (mins)	70	57	56

Table 6.1 - Means for sleep behaviours in three groups of footballers.

6.5. APPENDIX 6C - LASTELLA ET AL (2014)

Studies of athletes travelling to altitude (from sea level) for competitions/tournaments report less deep sleep and less rapid eye movement (REM) sleep (eg: youth footballers; Sargent et al 2013). "Given that muscle recovery takes place during deep sleep, the reduction in deep sleep at altitude may limit athletes' post-exercise processes" (Lastella et al 2014 p718). With time at altitude, sleep disturbances decline (Lastella et al 2014).

But "international competition at altitude is often accompanied by trans-meridian travel, which causes a temporary misalignment between the internal body clock

and the local destination time" (Lastella et al 2014 p718). What is the combined effect of these two changes on sleep? Lastella et al (2014) attempted an answer in their study of sixteen members of the Australian U20s men's football team who travelled to their age group World Cup in Manizales, Columbia (2150 m about sea level) in 2011.

Data were collected on sleep/wake behaviour for three nights in Sydney, Australia (43 m above sea level), ten nights in Denver, USA (1600 m - low altitude), and six nights in Columbia via sleep diaries and wrist activity monitors. The travel involved an eight-hour time zone change.

Baseline mean total sleep time was 7.5 hours, and this was reduced to 6.9 hours in Columbia (and 6.6 hours in Denver). Self-reported sleep quality was poorer at altitude.

Appropriate exposure and avoidance of sunlight helped adapt to the new time zone, and it took 5-6 days to stabilise sleep to a new environment.

Noting the first game of the tournament against an altitude-native team (Ecuador), the researchers stated: "Data from this study indicate that 14 days at a new time zone and respective altitude provided a suitable adaptation period for football players to successfully compete against an altitude native team" (Lastella et al 2014 p719).

6.6. APPENDIX 6D - MAH ET AL (2011)

During the 2005 season, eleven male US college-level basketball players extended their sleep to at least ten hours per night for 5-7 weeks. The following key measures were taken during a 2-4-week baseline and during the study:

a) Sleep - daily sleep logs, regular sleep questionnaires, and actigraphy.

b) Athletic performance - hoop shooting accuracy, and timed sprinting.

In terms of athletic performance, shooting accuracy significantly improved between baseline and the end of the sleep extension period (eg: mean 7.9 to 8.8 out of 10 15-foot throws), and sprint time significantly decreased (from mean 16.2 seconds to 15.5 for 282 feet).

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7. IRON DEFICIENCY AND SLEEP DISORDERS

- 7.1. Iron deficiency
- 7.2. Appendix 7A - Miano et al (2019)
- 7.3. Appendix 7B - DelRosso et al (2018)
- 7.4. References

7.1. IRON DEFICIENCY

Restless legs syndrome (RLS) and periodic limb movements in sleep (PLMs) cause sleep problems as individuals produce small repetitive movements of the toes, ankles, or legs. They are neurological sensorimotor disorders, which have been linked to attention deficit hyperactivity disorder (ADHD) "with hypermotor restlessness as their common denominator" (Leung et al 2020 p1). ADHD-related sleep disorders (ADHD-SDs) have recently been categorised (eg: Miano et al 2019; appendix 7A).

Iron deficiency (ID) may be common to these disorders, as, for example, iron supplementation has been found to help RLS-induced insomnia (Leung et al 2020). Proposed mechanisms are derived from iron's central role in the brain as a co-factor in neurotransmitter synthesis, as well as in myelination and oxygen delivery. ID in humans and animals can lead to damage of diffuse brain structures, including the hippocampus, basal ganglia, and cerebellum" (Leung et al 2020 p2).

Leung et al (2020) argued for the investigation of ID (and the use of iron supplementation) in individuals with sleep problems, particularly "children with challenging sleep-wake behaviours". These researchers found 93 articles (up to mid-2017) on the subject in their scoping review.

Positive associations were found between ID and RLS, PLMs, sleep disordered breathing (SDB), general sleep disturbance (GSD), and ADHD-SDs in most studies. Iron supplementation was beneficial in a number of cases.

A new category of "restless sleep disorder" (RSD) was reported in two studies (eg: DelRosso et al 2018; appendix 7B).

Leung et al (2020) summed up: "the majority of the studies analysed here confirm that there is an association between ID and RLS-triggered insomnia and that iron supplementation is beneficial for patients with RLS. For PLMs, SDB, GSD, ADHD-SDs, and RSD, evidence was limited, but findings still support the need to investigate ID as first line. Hypermotor restlessness and hypo/hyperarousability (H-behaviours) are clinical features common to most of these disorders and clinical similarities between RLS, ADHD-SD, PLMS and RSD suggest a

common pathophysiology of the dopaminergic system for which iron is an important metabolic co-factor" (p9).

There was variety between the studies in the review in terms of methodology, including:

i) To investigate ID and sleep problems, or iron supplementation to improve them.

ii) Measurement of "iron status" (eg: serum iron; multiple iron index; cerebrospinal fluid (CSF) iron).

iii) Study design - eg: cross-sectional studies; cohort studies; case reports.

iv) Different sleep disorders investigated.

v) Samples - eg: size; co-morbidity with health problems; age; specific groups (eg: pregnant women); control/comparison group.

vi) The nature of supplementation - eg: oral or intravenous iron.

vii) Controlling of potential confounders and use of design controls like randomisation and blinding.

viii) Diagnosis and measurement of sleep problems.

The researchers justified their wide ranging review as a means to identify gaps in the literature, including the need for standardised diagnostic criteria for RLS, and the harmonisation of outcome measures (Leung et al 2020).

7.2. APPENDIX 7A - MIANO ET AL (2019)

Varied studies find that around one-quarter to a half of children with ADHD report sleep problems, most commonly sleep onset insomnia (Miano et al 2019). It is likely that "the link between ADHD and sleep is bidirectional; sleep disturbances can lead to behavioural and cognitive consequences that may mimic ADHD, and children with ADHD may have sleep disturbances originating from the same biochemical disturbances underlying their deficits in executive function and attention" (Miano et al 2019 p123).

Five patterns of sleep problems and ADHD can be summarised from the clinical reports (Miano et al 2019):

- Hypoarousal - "narcoleptic-like".
- Sleep onset insomnia.
- OSA.

- RLS/PLM.
- Micro-epileptic electrical activity during sleep.

But previous studies vary in the method used to diagnose the sleep disorder, including questionnaires, actigraphy, polysomnography, and clinical history (Miano et al 2019).

Miano et al (2019) performed what they believed was the first full sleep assessment on a sample of thirty medication-naive children with ADHD at a hospital in Switzerland (and compared them to 25 age-matched healthy controls). Both the children and parents completed sleep questionnaires, the children wore an actigraphic wrist monitor for one week, and one night in the sleep laboratory for polysomnography.

Twenty-eight of the ADHD sample were diagnosed with a sleep disorder, confirming the five patterns outlined above:

- Hypoarousal - 4 children.
- Insomnia - 5.
- OSA - 15.
- RLS/PLM - 8.
- Epileptic-like activity - 10 ³².

Compared to the controls, the ADHD group had low sleep efficiency (eg: longer to fall asleep and multiple awakenings).

Miano et al (2019) made the following argument: "We believe that our finding consolidates the idea of a key role of sleep and in particular chronic sleep deprivation as a predisposing background for ADHD. In all probability, the size and the reversibility of the executive dysfunctions induced by untreated chronic sleep perturbation depend on the children's developmental period in which the sleep impairment occurs as well as its duration" (p129).

The prevalence rate of sleep disorders was higher in this study than previous work. There are two possible reasons for this difference:

a) This study is more accurate than others because of the full sleep assessment rather than just single methods.

b) This study is less accurate because of methodological weaknesses like a small sample based on outpatients at one hospital, or the requirement of a dedicated collaboration of children and parents in the

³² Note that some children were diagnosed with more than one disorder.

study may mean "that those with sleep problems and their parents were more prone to participate" (Miano et al 2019 pp128-129).

7.3. APPENDIX 7B - DELROSSO ET AL (2018)

Diagnosis of sleep disorders in children is "not always straightforward", though up to half can have "sleep complaints" (DelRosso et al 2018).

DelRosso et al (2018) outlined a new condition for children. "The parents of these children with 'restless sleep disorder' (RSD) report that during sleep, children seem either 'restless' or present with 'excessive nocturnal motor activity' consisting of 'large movements' (frequent repositioning, moving both arms and legs, trashing the bed sheets and even falling out of bed). Parents perceive sleep disruption even if children do not get up from bed, and are often concerned that their child's sleep appears interrupted. Sleep patterns are reported to be consistent through the night and occur almost every night. Children have one or more daytime symptoms, most commonly daytime sleepiness (DelRosso et al 2018 p2).

The researchers described a cohort of fifteen children with RSD who attended a US children's hospital sleep centre in 2016-7. These were compared to fifteen cases with RLS, and 37 age-matched healthy controls.

Compared to controls, RSD and RLS children had less total sleep time per night, more awakenings, and less REM as a percentage of total sleep. But these two groups differed on leg movements during sleep (ie: less for the RSD group), and the RLS group took longer to fall asleep.

Altogether, DelRosso et al (2018) proposed the following diagnostic criteria for RSD:

A - "Restless sleep" or motor movements involving limbs, head and trunk (eg: moving around in bed; falling out of bed).

B - The motor movements are exclusively sleep-related.

C - Occurs almost every night.

D - Sleep latency and total sleep time are within normal range for age.

E - At least one of the following:

- Sleep disturbed;
- Daytime impairment;
- Irritability or hyperactivity.

F - No medical disorders that could explain the

behaviour.

The RSD children in the study had significantly lower iron levels than the RLS group, and there were no data collected on the controls. DelRosso et al (2018) speculated that "a common underlying pathway in motor/dopamine dysregulation as iron is a co-factor for tyrosine hydroxylase, precursor of dopamine; however, iron is also a co-factor in the biosynthesis of other neurotransmitters, for example, iron is also a co-factor for tryptophan hydroxylase, involved in the biosynthesis of serotonin. Studies in mice have shown that a decreased serotonin level in the brain increases motor activity levels. Serotonin has also been implicated in the mechanism of attention deficit hyperactivity disorder. It is too early in our research to speculate about the neurotransmitter involved in the pathophysiology of RSD, except that iron may be a key player" (p5).

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8. BEREAVEMENT AND SLEEP DISTURBANCES

Bereavement and sleep disturbances are associated together. Lancel et al (2020) performed a review to establish the nature of the relationship. Eighty-five relevant articles (published up to early 2019) were used.

"The vast majority of the 27 well-controlled studies assessing subjective sleep variables reported increased sleep impairments in bereaved compared to non-bereaved controls" (Lancel et al 2020 p3). The sleep problems included poorer sleep quality, trouble falling asleep or staying asleep, and shorter sleep duration. Longitudinal studies showed that these problems declined with time, except individuals with "complicated grief" (CG) ("severe, persistent and disabling grief"; Lancel et al 2020) had longer-term sleep problems.

However, the small number of studies using objective sleep measures "did not show marked differences between bereaved and non-bereaved" (Lancel et al 2020 p4).

Higher grief intensity was associated with more severe or more frequent sleep problems. For example, Boelen and Prigerson (2007) found that grief symptoms at 6-12 months post-loss significantly predicted sleep disturbances 6-15 months later.

Four risk factors had been investigated in the studies (Lancel et al 2020):

i) Age - After controlling for increased sleep problems with age, younger individuals suffered more disturbances post-loss.

ii) Gender - Some evidence of more sleep disturbances for women post-loss, but not all studies agreed.

iii) Relationship to the deceased - Loss of a parent in childhood, and the loss of a child or spouse as an adult were worse for sleep problems.

iv) Type of death - In terms of natural/expected versus unnatural/unexpected deaths, the evidence was contradictory, but more sleep problems were associated with the latter.

There was a lack of evidence to establish the direction of causality - ie: poor sleep exacerbates grief or grief induces sleep problems.

The studies included in the review varied in methodological quality. "While some evidence has come from well-controlled studies, others were much weaker (eg: cross-sectional surveys among small samples, without adequate control groups)" (Lancel et al 2020 p6).

Ten studies were rated by the researchers as top quality.
There was also variety in the measurement of grief, sleep, and sleep problems.

a) Grief - eg: single items vs standardised questionnaires like the Texas Inventory of Grief (Faschingbauer et al 1977).

b) Sleep - Subjective (eg: PSQI) vs objective measures (eg: polysomnography).

Other methodological issues included the length of follow-up after loss, control of variables like pre-existing mental health problems, diagnosis of CG, demographic factors like age, and samples (eg: bereaved spouses/partners; children and adolescents).

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9. ADOLESCENT MOOD AND SLEEP DURATION

Insufficient sleep is common among adolescents (eg: 87% of US high school students had less the recommended number of hours - ie: 8-10 hours per night; Krueger and Friedman 2009). A meta-analysis by Lovato and Gradisar (2014) found a relationship between depression in adolescents and more wakefulness in bed (eg: longer to fall asleep; repeated awakenings).

Short et al (2020) investigated mood generally among adolescents and sleep duration with a review of 74 relevant studies. Shorter sleep duration was significantly associated with low/negative mood (eg: increased anger, depression, anxiety, and negative affect, and reduced positive affect). "Shorter sleep durations doubled the odds of adolescents experiencing reduced positive affect, and increased the odds of anger by 83%, depressed mood by 62%, negative affect by 60% and anxiety by 41%" (Short et al 2020 p6).

Based on two weeks of sleep diaries, Fuligni et al (2019) found that nine hours sleep per night was associated with optimal next-day mood, and this was especially important for younger adolescents, and individuals with higher levels of mental health problems.

In terms of explaining the relationship between sleep and mood, Short et al (2020) stated that reduced sleep "is known to effect brain regions implicated in mood and emotion regulation. Sleep loss reduced prefrontal activity and reduced functional connectivity between the prefrontal cortex and limbic regions. Sleep loss also reduces rapid eye movement (REM) sleep, which is implicated in the processing of emotional memories. Finally, sleep loss negatively effects cognitive functioning, many of which processes are needed for affective monitoring, reasoning and emotion regulation" (p8).

There was heterogeneity in the methodology and findings of the studies in the review, including (Short et al 2020):

i) The operationalisation/measurement of sleep - eg: studies with objective measures of sleep found stronger relationships than subjective measures. "This may be due to the superior validity of polysomnography and also the improved temporal association between sleep measurement and mood assessment in these studies. Studies using polysomnography typically assessed mood immediately following the objectively measured sleep period, whereas questionnaires ask about 'typical' sleep and not the sleep immediately prior to mood assessment. It is important to note, however, that sleep measurement tends

to be confounded with study design, as all studies using polysomnography were experimental" (Short et al 2020 p9).

ii) The design of the study - eg: experimental studies found the largest associations between mood and sleep duration, and this was probably due to control of extraneous variables related to sleep like academic pressure, and parental regulation of sleep. Confounding variables related to mood, like diet and home environment, were also an issue.

However, most studies were cross-sectional, which meant that the direction of causality could not be established.

iii) The country of study - Studies in North America had a larger association, but the researchers could not say whether this was "due to methodological differences of differences in vulnerability to sleep loss" (Short et al 2020 p9).

iv) The mood(s) measured - eg: negative vs positive; which negative moods.

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10. ALERTNESS AND DAYTIME TIREDNESS: THREE DIFFERENT ASPECTS

- 10.1. Call centre workers
- 10.2. An app for alertness
- 10.3. Young drivers and sleepiness at the wheel
- 10.4. References

10.1. CALL CENTRE WORKERS

Customer service employees (CSEs) (or call centre workers) are "main actors of this new age" (Etindele-Sosso 2020 p55).

Many of these workers have rotating shifts, which are known from other groups of workers, like nurses, to produce "a permanent disturbance of their circadian system" (Etindele-Sosso 2020 p55). Continuing the comparison with nurses and night shift workers, Etindele-Sosso (2020) pointed out that such "employments share characteristics like constant pressure to reach a certain objective and long working hours. This leads to several mental health issues and a general decrease of occupational health in workers from these areas" (p55).

These points for CSEs are mostly speculative as the research is limited, which led Etindele-Sosso (2020) to perform an exploratory study in Canada. Call centres in three cities were approached in 2016 and 2017, and 1200 employees agreed to complete an online questionnaire that covered sleep, mental health, and perceived social status (table 10.1).

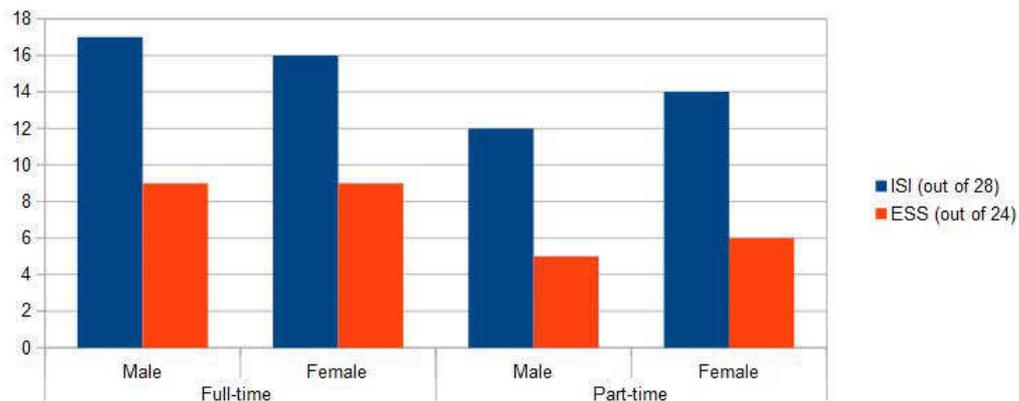
Questionnaire	Comment
Insomnia Severity Index (ISI) (Bastien et al 2001)	7 aspects of insomnia, each scored 0-4 (eg: early morning awakening; sleep onset delay). Cut-off score: ≥ 15 out of 28
Epworth Sleepiness Scale (ESS) (Johns 1991)	Measures daytime sleepiness with eight situations where individuals could fall asleep (each scored 0-3) (eg: watching TV; in a car while stopped for a few minutes in traffic). Cut-off score: ≥ 10 out of 24
Hospital Anxiety and Depression Scale (HADS)	Score for each scale (anxiety and depression): ≥ 11 = "clinical cases"
MacArthur Scale of Subjective Social Status	Measures perceived social status (pSES); scale 1-10 with a smaller number = lower pSES

Table 10.1 - Validated questionnaires used by Etindele-Sosso (2020).

The mean ISI score was 17 for men and 16 for women (ie: above the cut-off for "clinical insomnia"), while the mean ESS score was nine for both sexes (ie: just below the cut-off point). The mean score for anxiety was above the cut-off, but not for depression on the HADS. The mean score for pSES was below five. All these negative aspects were associated with length of time working as a CSE. Duration in position can be influenced by age, and this was controlled in the analysis.

The study had "difficulty in knowing what the exact role of each participant is in their respective companies, and this may be a limit because the level of stress experienced by a manager is different from the one experienced by an advisor..." (Etindele-Sosso 2020 p62). No details of medical history were collected, and certain confounders were not controlled (eg: sleep apnea - which causes excessive daytime sleepiness) (Etindele-Sosso 2020).

In summary, insomnia, sleepiness, anxiety and depression were common among the sample of Canadian CSEs. Full-time employees (the majority of the sample) scored higher than part-time employees (figure 10.1).



(Data from Etindele-Sosso 2020 table 2 p61)

Figure 10.1 - Mean scores on sleep measures for full-time and part-time CSEs.

10.2. AN APP FOR ALERTNESS

Consumer technology now allows for surveillance of sleep duration, and the consequent levels of alertness throughout the day. An app called the "2B-Alert App" has been developed to "learn" an individual's response to sleep deprivation and to make predictions about alertness (Reifman et al 2019).

The app is based upon a mathematical model called the "Unified Model of Performance" (UMP) (Ramakrishnan et

al 2015), which predicts psychomotor vigilance test (PVT) performance (a proxy measure for alertness) based on recent sleep loss/restriction, and the restorative effects of caffeine (Reifman et al 2019).

The "2B-Alert App" collects data on sleep schedule, and caffeine schedule, and a PVT (eg: reaction time) assesses alertness. Altogether, predictions of an individual 's alertness can be made from sleep/wake history, caffeine dosage, absorption rate and time of consumption, and time of day.

Reifman et al (2019) validated the "2B-Alert App" with twenty-one healthy young adults at an army research centre in the USA. Actigraphy data were collected for thirteen days and there was one night in a sleep laboratory.

The app needed 12 PVTs over 36 hours to become accurate. At its worst, the app made a prediction error of 10% for maximum alertness time in a 24-hour period.

In relation to the interest of the military in the "2B-Alert App", it can be used "to tailor personalised fatigue management strategies, facilitating self-management of alertness and safety in operational and non-operational settings" (Reifman et al 2019 p1).

10.3. YOUNG DRIVERS AND SLEEPINESS AT THE WHEEL

Young drivers are over-represented in sleep-related car crashes. It may be that their perceptions of the dangers of sleepiness are poor, or that they choose to continue driving when aware of increased sleepiness. Sleep-related factors may also be relevant (Watling 2020).

Watling (2020) explored this topic with 257 18-25 year-olds in Queensland, Australia. The completed a number of questionnaires on sleep, including the PSQI, ESS, the Sleep Timing Questionnaire (STQ) (Monk et al 2003) (that measures habitual sleep times), and the Experience with Sleepiness Questionnaire (ESQ) (eg: "When I feel sleepy, I can control my sleepiness to stay awake"). The Driver Behaviour Questionnaire (DBQ) (Reason et al 1990) was also completed.

Participants admitted to continuing to drive while sleepy "more often than not". After analysis of the different variables, four factors were significantly associated with continuing to drive while sleepy:

a) Being older - Though the age range was much less than studies which found that younger drivers were the greater risk to driving when sleepy.

b) Perceived ability to perform well when sleepy (ie: high ESQ score) - This variable had the strongest

association with driving when sleepy.

"Although laboratory-based studies have demonstrated that increased effort can, to a degree, overcome sleep-related impairment on simple cognitive tasks..., increased effort cannot completely overcome the impairment due to sleepiness on complex cognitive tasks... Moreover, sleep-deprived participants' perceptions of their actual performance levels can be erroneous... and applying extra effort to the task of driving does not result in any improvements in driving performance" (Watling 2020 p5).

c) More highway code violations (eg: speeding) (ie: sub-scale of DBQ).

d) Experience of previous sleep-related close calls.

The last two factors together, Watling (2020) "interpreted as an acceptance of engaging in risky driving behaviours" (p6).

Sleep-related factors, like sleep quality, were not associated with driving when sleepy.

This study did not collect data on psychological factors like impulsivity and risk-taking, nor medication and illicit drug use (Watling 2020).

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11. TWO STUDIES ON ANIMALS AND SLEEP

- 11.1. Cuttlefish
- 11.2. Starling
- 11.3. References

11.1. CUTTLEFISH

The basic principles of human sleep have been observed in studies with mammals, birds, and some reptiles (Iglesias et al 2019). These principles include two distinct brain states during sleep, commonly called rapid eye movement sleep (REMS) and non-REMS. Bouts of REM occur in humans every ninety minutes, but every ten minutes in rats, for example, or less than a minute in birds that have bouts of REMS (lasting 2-10 seconds in duration while bouts of non-REMS last 10-100 seconds) (Iglesias et al 2019). This ultradian rhythm (ie: cycles of REMS and non-REMS) lasts eighty seconds in reptiles, and it "appears to be an inherent characteristic of sleep in organisms that experience multiple stages of sleep" (Iglesias et al 2019 p1).

In other organisms, like the common European cuttlefish (*Sepia officinalis*), a "quiescent sleep-like" (QS) state has been observed (Frank et al 2012) (figure 11.1), and approximately 10% of a 24-hour period is spent in it (Iglesias et al 2019).

Whether the QS state is sleep depends on the definition of sleep, which usually has three key criteria (Iglesias et al 2019):

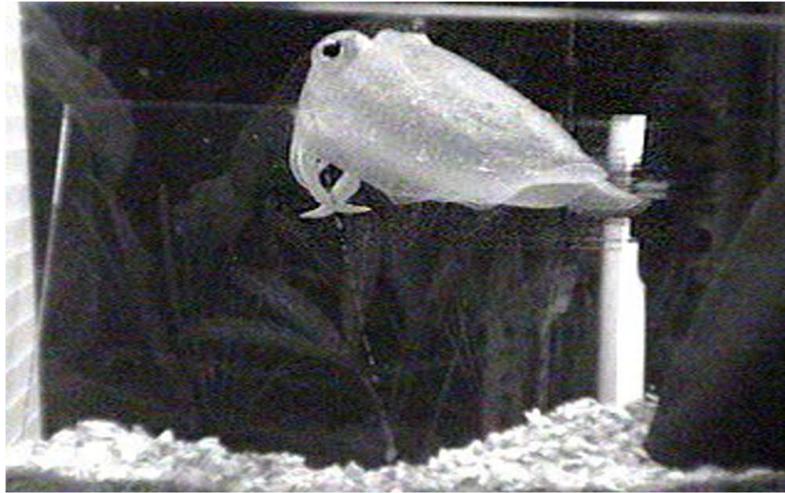
- i) An increased threshold of arousal compared to "waking" (ie: slower to respond).
- ii) A rapid reversal to an alert state.
- iii) "Rebound sleep" - After sleep deprivation, there is an increase in the time spent in sleep.

Criteria (ii) and (iii) have been observed in the QS state of the cuttlefish by Frank et al (2012).

Iglesias et al (2019) (the same research team) built upon this study with an investigation of REMS-like behaviours, and on ultradian rhythm with the QS state. During the REMS-like phase, the cuttlefish's behaviour is "characterised by rapid chromatophore changes (skin skin brightness and patterning), skin-texture changes, REM and arm twitching" (Iglesias et al 2019 p1).

Six captive-bred cuttlefish were video-recorded in their individual tanks (for between 50 to 280 hours). Fifty-five REMS-like periods were recorded.

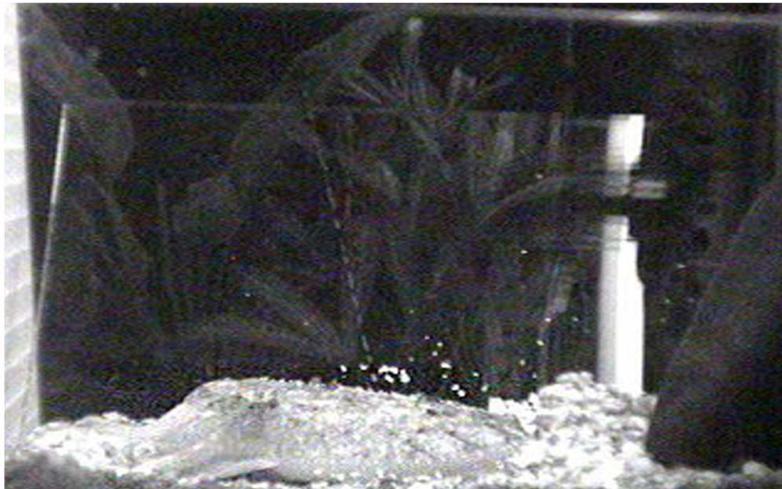
A



B



C



(A = swim; B = hover; C = quiescence)

(Source: figure 1 Frank et al 2012)

Figure - Photographs of three behaviours observed by Frank et al (2012).

Iglesias et al (2019) concluded that "cuttlefish in a quiescent, sleep-like state periodically undergo a REMS-like state, characterised by (i) general immobility with occasional muscle twitching (arms and neuromuscular chromatophore organs), (ii) rapid horizontal movements of the eyes, (iii) alternating QS and REMS-like states in a predictable ultradian rhythm and (iv) a significant increase in the number and unusual combinations of neurally controlled skin pattern changes compared with those in the awake state" (p5).

This parallels findings with octopuses (eg: Brown et al 2006).

Because of the artificial nature of the cuttlefishes' lives in the study, the researchers had to consider alternative explanations for their findings. Iglesias et al (2019) stated: "None of the animals were in visual contact with other animals or with humans; it is possible - but highly unlikely - that the body pattern changes seen during the REMS-like state in these experiments were a result of artifactual stimulation outside of the experimental chamber, such as ground-transmitted vibrations. Given that the system had a continuous inflow of local seawater, it is also possible that a chemical cue was responsible for eliciting these body patterns; however, all tanks received the same water and the REMS-like state was not observed in multiple cuttlefish simultaneously. Thus, it is highly likely that the cuttlefish were indeed exhibiting a typical behaviour associated with the sleep-like state" (pp6-7).

So, the "data suggest that cephalopods, which are molluscs with an elaborate brain and complex behaviour, possess a sleep-like state that resembles behaviourally the vertebrate REM sleep state, although the exact nature and mechanism of this form of sleep may differ from that of vertebrates" (Iglesias et al 2019 p1). This has implications for the understanding of the evolution of REMS.

11.2. STARLING

The compensatory rebound in sleep after a period of deprivation is taken as evidence that sleep is homeostatically regulated. Studies have shown clear homeostatic regulation of NREMS on mammals (particularly laboratory studies of mice and rats; eg: Friedman et al 1979), and also REMS rebounds, but these are "less predictable compared with NREM sleep. In fact, it is still debated whether REM sleep is homeostatically regulated at all, and, if so, whether that is in relation to prior wakefulness or perhaps preceding NREM sleep. Other factors that influence REM sleep are, for example, environmental temperature and stress (van Hasselt et al

2020 p2).

van Hasselt et al (2020) looked at a non-mammal species, namely the European (or common) starling (*Sturnus vulgaris*) (figure 11.2). Twelve captive birds were studied. Electrodes were implanted in the brain to allow measurement of electrical activity via micro-data-loggers, and to gain an accurate picture of waking and sleep. The birds experienced three conditions, each for three days - control (no restrictions on sleep), four hours of sleep deprivation (4SD), and eight hours of deprivation (8SD). The birds were kept awake by tapping the cage when they appeared to be falling asleep. The laboratory environment was controlled at 12 hours of light and twelve hours of darkness, and food and water were freely available as required ("ie: ad libitum").



(Source: Wilhelm von Wright (1828) <https://www.doria.fi/handle/10024/43328>; in public domain)

Figure 11.2 - Drawing of European starling.

In the control/baseline condition, the starlings slept for most of the dark phase, and the vast majority of that was NREMS (average 98.4%). Thus REMS was an average of 1.6% of total sleep time.

After 4SD and 8SD, the starlings showed a small compensation for NREMS (ie: longer duration and more intense), but no compensation for REMS. The compensation in NREMS occurred in the next night's sleep after sleep deprivation, not immediately after. The sleep rebound was similar in both SD conditions.

The changes in electrical activity of the brain during NREMS rebound was different to that recorded in studies with mammals. Also mammalian studies have found differences in sleep rebound based on the length of sleep deprivation. van Hasselt et al (2020) explained that "while it is often assumed that sleep in mammals and other animals such as birds represent similar states that have a common evolutionary origin, it is not excluded that a primitive common sleep state evolved into more complex states with different functions in different taxonomic groups. Thus, homeostatic regulation of sleep in relation to the duration of wakefulness as it is found in mammals may not be present in exactly the same way in birds" (pp7-8).

There are studies of birds in natural conditions that show little sleep for long periods and then partial sleep rebound. For example, male pectoral sandpipers spend around three weeks of the breeding season (in permanent daylight in the Arctic) in intense competition for females with very little sleep (Lesku et al 2012). "Interestingly, the males that slept the least ultimately produced the most offspring suggesting that decreased performance is not an inescapable outcome of sleep loss" (van Hasselt et al 2020 p8).

It could be possible that sleep homeostasis is not important in birds (van Hasselt et al 2020). Another point to note was the low percentage of REMS during baseline. Other studies have found variable and higher rates - eg: quail (around 6% of total sleep time), turtle doves (around 5%), white-crowned sparrows (16%), and zebra finches (25%) (van Hasselt et al 2020).

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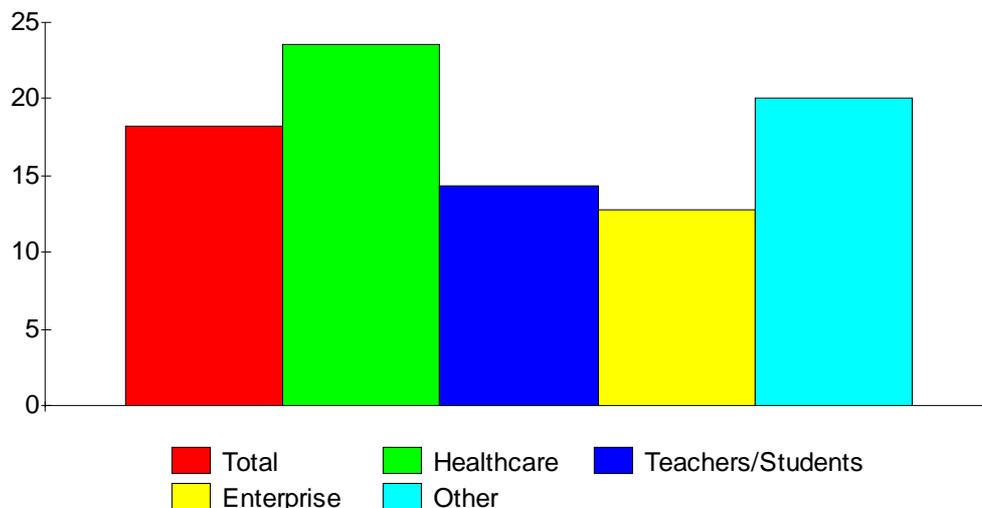
12. SLEEP QUALITY AND COVID-19 IN TWO EARLY OUTBREAK CHINESE STUDIES

Covid-19 emerged in Wuhan, Hubei Province, China in December 2019, and then spread nationally (and internationally) (Li et al 2020).

Huang and Zhao (2020) undertook an online survey in China in early February 2020. A total of 7236 individuals responded to social media invites to participate (of which 2250 were healthcare workers).

The survey included questions about covid-19 knowledge, anxiety, depression, and sleep quality. The latter used a Chinese version of the Pittsburgh Sleep Quality Index (PSQI) (Liu et al 1996), and concentrated on the past two weeks.

Overall, 18.2% of participants scored above the cut-off on the PQSI for "poor sleep", but this was higher for healthcare workers (23.6%) (figure 12.1). There was no overall age difference in sleep quality, but anxiety and depression were higher among under 35s (compared to over 35s).



(Enterprise = business and public sector employees; Other = freelancers, retirees, and social workers)

(Data from Huang and Zhao 2020 table 4)

Figure 12.1 - Percentage classed as "poor sleep" in 4 occupational groups.

More time spent focusing on covid-19 (based on information seeking about it - ie: >3 hours per day) was associated with anxiety, and poor sleep quality.

The study suggested two routes to poor sleep. Firstly, among the general population via anxiety about

covid-19, which was a very new event at the time of the survey. But healthcare workers had poor sleep from occupational stress and lack of time in the face of the epidemic.

Li et al (2020) studied a convenience sample of healthcare professionals in two areas of China in the first week in March 2020. Hubei Province was classed as a high risk for covid-19 at that time, and Jiangsu Province as a low risk area. The internet survey was completed by 253 individuals from the former area and 134 from the latter. The Chinese version of the PSQI was the measure of sleep quality.

The mean PSQI score of the Hubei sample was 9.7 (out of 21) compared to 7.7 in Jiangsu ³³. This is a significant difference as in the percentages of the sample scoring greater than seven - 62% and 49% respectively.

The Hubei sample self-reported significantly poorer health in response to the question, "How do you rate your health status at present?" (scored from 1 (very poor) to 5 (very good)) (mean 3.3 vs 3.5).

Poor sleep quality in the Hubei sample was associated with fear of infection ³⁴, fatigue from wearing personal protective equipment ³⁵, and worrying about own family ³⁶. In the Jiangsu sample, only dizziness during wearing protective equipment was associated significantly with poor sleep quality.

In both groups, controlling for other variables, poor self-rated health and poor sleep quality went together.

The study did not collect a lot of information (eg: stress; social support) because of the desire to keep the survey brief for the hard-pressed workers.

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³³ Note that a score of seven or above is classed as "poor sleep".

³⁴ The mode of transmission was not clear in the early days, and five healthcare professionals had died in early February according to official figures (Li et al 2020).

³⁵ The workers wore masks, three pairs of gloves, goggles, outer gowns, and boots, for example.

³⁶ Many of the staff in Hubei were from other areas brought in to help, and so could only contact their families occasionally.