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Human slow wave sleep: A review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness

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Abstract. Recent findings concerning human slow wave sleep (hSWS-stages 3 + 4; delta EEG activity) are critically reviewed. Areas covered include the significance of the first hSWS cycle; hSWS in extended sleep; relationship between hSWS, prior wakefulness and sleep loss; hSWS influence on sleep length; problems with hSWS deprivation; influence of the circadian rhythm; individual differences in hSWS, especially, age, gender and constitutional variables such as physical fitness and body composition. Transient increases in hSWS can be produced by increasing both the quality and quantity of prior wakefulness, with an underlying mechanism perhaps relating to the waking level of brain metabolism. Whilst there may also be thermoregulatory influences on hSWS, hypotheses that energy conservation and brain cooling are major roles for hSWS are debatable. hSWS seems to offer some form of cerebral recovery, with the prefrontal cortex being particularly implicated. The hSWS characteristics of certain forms of major psychiatric disorders may well endorse this prefrontal link.
Key words. Human sleep; slow wave sleep; sleep loss; circadian rhythm; brain metabolism; thermoregulation; schizophrenia; depression; frontal cortex.

Introduction

Human slow wave sleep (hSWS) stages 3 + 4 (i.e. delta EEG activity)[118] seems to be a particularly vital form of sleep[70] that is increasingly coming under scrutiny. A major impetus for this is the evolving 'Process S' model of sleep and wakefulness, based on the (delta) EEG power of sleep[19,20,35]. Further interest in hSWS comes from biological psychiatry, and, for example, the intriguingly low levels of hSWS in various psychiatric disorders. From a more functional standpoint, there are recent findings suggesting associations between thermoregulation and hSWS. The aim of this critical review is to present an update on recent findings about hSWS.

Human SWS is typically detected by visual scoring of the EEG[118], but this method, based on a rather arbitrary amplitude criterion (> 75 μV), is now seen by many to be undiscerning for the accurate quantification of human delta activity (usually 0.5–3.5 Hz). The wide availability of computer packages for EEG analyses have rectified this apparent shortcoming, and 'slow wave activity' (SWA) is a resultant term commonly used to describe the quantified delta activity. However, we do not know much about the linearity of such hSWA data for example, whether a doubling of delta power means a doubling of whatever underlies or generates hSWA.

One might question any findings relating to hSWS that are based solely on visual analyses[118], attributing the results to an undiscerning methodology. But when more precise automated methods are used, these still tend to bear out (in a more sophisticated way) those based on the visual method. Visual scoring still has some merit, particularly as one can view the actual EEG, and there is a useful (albeit arbitrary) amplitude criterion for delta activity, which is usually not incorporated in standard Fourier analyses. Alternative period-amplitude analyses[48] overcome this latter problem, but the technique is more complex and not so readily available as is the Fourier method.

Distribution of hSWS over sleep

Within each of the first three non-REM cycles of a typical young adult's sleep the build-up of delta activity takes around 35 min to asymptote, but the decline is rapid[1]. These rise and fall rates diminish over the first three cycles. Normally, the first sleep cycle contains the most hSWS, and as there is relatively so much hSWS here, there is more to be lost, for example, during aging. Consequently, the first hSWS cycle is of particular interest. For many years Feinberg[48] has argued that it is here where our interest in hSWS should concentrate, wherein lie the major age differences in hSWS, rebound effects after sleep loss, and low hSWS levels in schizophrenia and depression.

The recent, substantial study by Merica and Gaillard[109] examined the cycle by cycle structure of 352 nights sleep from 147 adults (av. 28.3 y), and found that stage 4 sleep occupied 33% of the first cycle, 17% of the second, 6% of the third, 2% of the fourth and 1% of the fifth. In effect the values approximately halved for every successive cycle. Stage 3 sleep changed less, being respectively 12%, 11%, 8%, 5%, and 5% for cycles 1–5. Nevertheless, in a smaller group of older subjects (av. 39 y) with zero stage 4 sleep, stage 3 sleep showed an exponential fall over cycles 1–5 (occupying 17%, 9%, 4%, 1% and 0% of the cycles respectively). The interaction between hSWS and REM sleep revealed[109] a fine balance, not an antagonism – e.g. in subjects with low hSWS levels there was only a slight increase in REM sleep.

Although Feinberg[48] sees the key feature of hSWS being confined to the first hSWS cycle, he has recently amended this view[54]. When hSWS pressure is very high, following sleep loss[52], the first and second cycles merge, with the usual first REM period being suppressed. He now considers that it is this 'supranormal' first cycle that absorbs the entire extra hSWA demand. From earlier data[52] he points out that the hSWA levels in recovery sleep cycles 2 and 3 (integrated amplitude = 52 and 38 units respectively) are similar to the baseline cycles 2 and 3 (integrated amplitude of cycles 2, 3 and 4 = 56, 43 and 27 units respectively). Alternatively, if one considers recovery cycle 2 really to be cycle 3 (i.e. recovery cycle 1 = usual cycles 1 + 2; thus recovery cycle 2 = cycle 3, etc.), and compare this with baseline cycle 3 (i.e. 52 vs 43 units), and similarly compare recovery cycle 3 with baseline cycle 4 (i.e. 38 vs 27 units), then there is more hSWA in all the recovery cycles, not just the first one.

Other recent work also shows the hSWS recovery after sleep loss spreading beyond the first cycle. Gillberg and Åkerstedt[62] have re-analysed their earlier data[2] from one night of sleep reduction. As prior sleep loss lengthened, hSWA in the first recovery sleep cycle increased, and then began to 'spill over' into the second cycle. These and other findings that hSWS/hSWA within the first sleep cycle is the most liable to change, is not so remarkable as at first might seem. Given that hSWA is influenced by an exponential decay process, then common to all such processes, the equations show that the greatest rate of decay is at the time closest to zero, and that the initial rate of decay increases with the higher the initial value.

The circadian rhythm seems to have little effect on hSWS during more normal sleep regimens, but under a disentrained environment and with ad lib sleeping, the situation may be different[31]. Campbell and Zulley[31] claimed a prominent circadian influence on hSWS, whereby hSWS is inversely correlated with its proximity to the body core temperature circadian acrophase (i.e. the nearer in time to the temperature maximum, the more the hSWS). However, all major sleep periods between 20.00 h and 06.00 h were excluded from the analyses, as were naps under 30 min. There were large individual differences, with some subjects obeying the maxim and others not. The hSWS data were analysed as percentages,

but as naps varied in length, with shorter naps being nearer the acrophase, there is a distortion of these data. Thus, if hSWS is plotted in minutes (rather than as %) against the acrophase, then the circadian effect on hSWS almost disappears.

During extended sleep small amounts of hSWS may reappear after about 12 h[41,43,58]. This has led Broughton[22] to propose a bicircadian rhythm of hSWS. But as many subjects cannot maintain ad lib sleep for such a long time, significant periods of interim wakefulness may occur after about 9 h of sleep. A supplementary explanation by Horne[69] was based on the premise that wakefulness produces a need for hSWS, as might REM sleep (cerebral metabolic rate in REM sleep is like that of wakefulness). Thus, if the ratio of the normal values of hSWS to prior wakefulness is calculated for these subjects and applied to the summated wakefulness + REM sleep after the third (usually the last) hSWS cycle in the extended sleep, then the estimates obtained for the hSWS return in oversleep are very similar to the actual values. Whereas Broughton et al.[22] dismissed this notion, Dijk et al.[41,43] are more sympathetic, but point out that the hSWS return is small and inconsistent. Of course, the idea that hSWS immediately 'pays off' prior wakefulness in the way suggested[69] is probably too simple. More likely, some minimum consolidation period (e.g. 1–2 h) or buffer between cause and hSWS effect should be incorporated (see: 'Exercise and body heating'). Such a buffer might even vary in its characteristics according to the time of day.

Individual differences

Age

Both hSWS and hSWA decline with age; this is most evident in the first hSWS cycle, with the decline lying mostly in delta amplitude rather than in the incidence of delta waves[48,146]. Bes et al.[15] compared hSWS across the night for infants (16–52 weeks), children (1–6 y) and adults (20–36 y). For all groups hSWS peaked in the first cycle. Whereas for the latter two groups hSWS declined over the subsequent cycles, in the infants it remained fairly constant from the second cycle onwards, often alternating between zero and a fairly fixed hSWS quantity over the subsequent cycles. Bes et al. only used visual scoring of hSWS stages, but Ehlers and Kupfer[46] in their age study employed spectral analysis, a further delta quantification, and visual scoring. Men from three age groups were used: 21–30 y, 31–40 y, 51–70 y. The largest decline in hSWS was between the first two male groups, especially in the first sleep cycle, and there was a shift to higher delta frequencies. The oldest group had the most REM sleep.

Few studies have examined hSWS in the elderly. Recently, Spiegel et al.[133] reported that the common finding of a positive correlation between prior wakefulness and subsequent hSWS, is not evident in the elderly. In a five-year prospective investigation comparing hSWS and psychometric changes within elderly patients, the investigators found no correlations, and concluded that hSWS had no clear functional significance. But this applied to subjects with very diminished hSWS; many of them were demented and there was at least some neuropathology. Feinberg[47,48] has paid particular attention to age effects on hSWS, which he believes to be of functional significance. hSWS is absent at birth but then develops to reach its ontogenetic peak at around 5 y, which is maintained until around 10 y, when there is a steep decline, reaching the typical young adult level by about 20 y. hSWS then declines at a slower rate. Such changes seem to mimic the ontogenetic alterations in cortical synaptic density, which peak in the first decade and then undergo a substantial reorganisation during the second decade. Thus Feinberg[47] claims that there is an 'overproduction of neuronal elements' followed by a selective pruning or 'programmed neuronal cell death' involving a loss of equipotentiality in return for greater cortical specialisation. He[47] sees hSWS to be related to the functioning of the most plastic (programmable) neurones, and further postulates that in schizophrenia cortical organisation fails in late adolescence. He has also noted[48] that the ontogenetic development of hSWS/hSWA is similar to that of cerebral metabolic rate (CMR), with CMR rising steeply from birth to twice the adult level by early childhood, and then declining during adolescence.

Gender

Another outcome from the findings by Speigel et al.[133] was that age-for-age, their elderly women had double the amount of hSWS than had the men. This finding supports earlier reports on the sleep of the elderly[120,145], where women had 40–100% more hSWS (it must be remembered that hSWS levels are low for the elderly). A recent meta-analysis of sleep in old age[119] further endorses this. Whether or not there are significant gender differences in hSWS for young adults is still not clear, as there is a paucity of normal comparative data. A control group of 20–30 y subjects used by Webb[145] indicated significantly more hSWS for women. Reynolds et al.[121] have recently presented data on 151 age-matched (20–70 y) pairs of men and women suffering from depression. Apart from the usual age-related decline in hSWS, age-for-age, women had about 25% more hSWS than had men.

These apparent gender differences, if substantiated, are remarkable. If any association is to be made between waking CMR and hSWS (see: Conclusion), then it is interesting that there are also gender differences in CMR. For example, Gur et al.[64] found that for three age groups, under 20 y, 20–30 y, and over 30 y, women had markedly higher waking CMRs than had men (particularly in the prefrontal cortex).

Within-age groups

With careful scoring, stages 3 and 4 sleep can be differentiated reliably[17]. There is a high degree of intra-subject inter-night consistency with these stages, especially in young adults[17]. But there are large individual differences within age groups and gender[17,109], which might be attributable in part to deficiencies in visual scoring, but for the most part remain unexplained. For example, Bliwise and Bergmann[17] reported that stage 4 occupied between 8% and 50% of the first three hours of sleep in young adult males. In those subjects with low levels of stage 4 there were high amounts of stage 3, and vice versa. These individual differences were less apparent after the first 3 h of sleep. Possible correlations between hSWS levels and constitutional or psychological variables were not ascertained in this study[17].

Kerkhof[89] has found that morning vs evening 'circadian types' have different distributions of hSWS/hSWA over the night. Whereas hSWS/hSWA showed the more typical monotonic decline over the first four sleep cycles in morning types, for evening types there was no decline over the first two cycles. As one might expect, the daytime subjective alertness peak was earlier for the morning types (12.20 h vs 18.50 h) and their rectal temperature rhythm was advanced on that of the evening types by about 90 min. Morning types had a larger initial temperature fall at sleep onset, they claimed better sleep quality, and had significantly longer total sleep (476 vs 434 min). Another study[88] has shown that low levels of hSWS in young adults seem to be associated with slower reaction times and poorer time-estimation just after normal morning awakening. But whether these subjects were more likely to be evening types is not known.

Constitutional variables

The influence of constitutional variables such as body composition and physical fitness on hSWS levels is still problematic. Physical fitness does not seem to be a crucial factor itself. Paxton et al.[115] found that athletes who had not trained for several months and then underwent a rigorous training programme showed no change to hSWS levels (116 min and 121 min hSWS before and after; stage 4 = 78 and 75 min respectively). Nevertheless, these values were significantly above those of a sedentary control group (average hSWS = 90 min; stage 4 = 63 min). Meintjes et al.[108] reported a similar outcome after monitoring sleep in women before, during and after three months of intensive training; hSWS, unlike fitness, remained unchanged. A related study[44] by this group on men, came to the same conclusion.

The amount of lean tissue (lean body mass – LBM), versus body fat, may be related to hSWS levels, but the association is not straightforward and may well not be causal. For example, physical fitness may be a co-factor (e.g. fit people tend to be leaner). Paxton et al.[114] found that in both fit and unfit subjects, hSWS was negatively correlated with %LBM. These results contrast somewhat with those of Leiker et al.[98] who carried out more sophisticated measurements of LBM, and looked at lean and fatter men, both of whom also differed in physical fitness (but were not athletes). A significant fitness × body composition interaction was found for both hSWS and stage 4, but here it was the lean unfit subjects who had the most of these stages.

Whereas leanness and fitness may interact and correlate with hSWS, there may be other underlying (unknown) factors at work. One possibility may be thermoregulation and general body metabolic rate. As will be seen, these may affect hSWS in various ways, but may only be modulators of hSWS. Given that hSWS is a cortical phenomenon, emanating from a very advanced brain[70], we should perhaps view all the apparent body constitutional and thermoregulatory influences more as intervening variables rather than as being fundamental to hSWS. Or, to take another approach, maybe lean people may have higher waking alertness, and a more active (prefrontal) cortex (see below).

Sleep loss and prior wakefulness

An impressive positive correlation is found between the length of wakefulness and the amount of subsequent hSWS/hSWA. However, when wakefulness is shorter than usual this association may break down somewhat. This situation is best illustrated by the systematic study by Dijk et al.[39], of naps following waking periods of between 2 and 20 h duration following a normal night's sleep. The investigators analysed delta and theta activity levels (in 1 Hz bins), and from curve-fitting their data they concluded that these activities followed a monotonic function in relation to the duration of prior wakefulness. But at least for the lowest delta frequency (< 1 Hz) the actual data points also show a step function in hSWA power density for periods of wakefulness up to 10 h; beyond that there is little increase in hSWA up to 20 h wakefulness – i.e. there may be a more variable relationship between hSWA and prior wakefulness within normal waking periods than at first may seem.

Extending wakefulness beyond the norm implies sleep (hSWS) loss, which may be the real reason for the subsequent hSWS rebound, but one cannot easily separate out one factor from the other. The situation becomes more complex when sleep is restricted to say 100 min, with subjects remaining awake until the following night, as was the case in the study by Feinberg et al.[49]. Here, delta wave amplitude in the recovery sleep remained unchanged, although delta density increased (i.e. more delta waves, suggesting a delta rebound). It was claimed[49] that as it is the first hSWS cycle that really matters, the 100 min of sleep was sufficient, and the reason why delta activity in the recovery sleep was seemingly not affected. Implicit in these findings[49] is that wakefulness had been extended by some 5–6 h without apparently increasing hSWS, and the authors argued that it is the hSWS loss

that really matters rather than the length of prior wakefulness. This hypothesis was supported by the outcomes of two of their recent studies [52, 141] (the second a replication of the first). In both, subjects were deprived of the last 3–4 h of sleep (after all hSWS had been taken). Subsequent recovery sleep commenced at the usual time. Visual scoring showed no significant hSWS increase over baseline values for either study. Period-amplitude analysis revealed a significant (approx. 10%) increase in hSWA over baseline values in one study [52] but not in the other.

There is another explanation for this outcome. The summated stage 4 data over the first two cycles of the restriction night should have been the same as the levels of stage 4 in the first two cycles of the previous baseline night; but it was lower (Study 1: baseline = 21 min stage 4, restriction = 17 min; Study 2: baseline = 42 min stage 4, restriction = 38 min). Comparison of these restriction values (17 and 38 min) with those of the subsequent recovery nights (Study 1 = 24 min stage 4; Study 2 = 49 min) shows a clearer stage 4 rebound. A similar argument applies to total integrated amplitude data. Thus, it still seems that the length of prior wakefulness does influence hSWS, irrespective of hSWS loss. One explanation for the higher stage 4 levels during the baseline nights is that these nights also contained some hSWS rebound following an initial adaptation night.

Evidence pointing to recovery hSWS not being confined to the first sleep cycle comes from another impressive study by Dijk et al. [42], involving recovery sleep begun at 07.00 h, after 24 h of wakefulness. Circadian factors make REM sleep propensity high at this time. Nevertheless, hSWA was increased in the initial recovery sleep cycle, particularly during the first 20 min. The same happened in diminishing amounts for hSWA in cycles 2 and 3. Whilst there may have been some circadian attenuation of hSWA, this sleep was still largely under homeostatic control. Such a control of hSWS has been further demonstrated by Knowles et al. [91] who allowed subjects 3 or 6 h sleep under a delayed sleep regimen. A subsequent 3-h nap at 09.00 h showed hSWS to be highly positively correlated with a length of prior wakefulness. In a second study by this group [91], hSWS was subtracted out from the subsequent night's sleep by giving a prior 2-h daytime nap at various times. Nighttime hSWS declined as wakefulness decreased between the nap and main sleep.

The close relationship between wakefulness and subsequent hSWS is also showed by Brunner et al. [23]. Sleep was restricted to 4 h (sufficient for most hSWS to be taken) for two nights, followed by two recovery nights. This extra 3.5 h of wakefulness would add to the hSWS need on the second restriction and first recovery nights. Under baseline conditions stage 4 and hSWS averaged 32 and 75 min respectively, following about 16–17 h wakefulness. My own rough calculation gives 2 min of stage 4 and 4.5 min of hSWS per hour of wakefulness. On this basis the extra wakefulness would add an extra 7 min (total 39 min) and 16 min (total 91 min) to stage 4 and hSWS respectively during both the second deprivation and first recovery nights. The actual values for these two nights averaged 40 min for stage 4, and 89 min for hSWS. Such pro rata rough calculations also seem applicable to the increased hSWS found under chronic sleep restriction (e.g. five weeks of 1.5–2.0 h sleep reduction) [82].

Selective hSWS deprivation

There have been many findings showing that most of the hSWS lost during sleep deprivation is reclaimed [70]. In a recent imaginative study, Tilley et al. [139] terminated nighttime sleep after 50% of the usual hSWS had been taken. An ensuing afternoon nap allowed back 100%, 50% or 25% of the lost hSWS. Ad lib sleep the following night clearly showed that any lost hSWS remaining was regained. There was also an increase in REM sleep, but this seemed to be at the behest of the lost hSWS which extended sleep and may have accommodated the extra REM sleep.

Dijk and Beersma [38] selectively deprived subjects of hSWS during the first 5 h of sleep, by acoustic stimulation. hSWA rebounded in the following hour, but this did not produce any increase in ad lib sleep. In a second study [38] subjects were deprived of sleep for 24 h and allowed to sleep at 11.00 h. Then, hSWS was deprived as before, for 3 h. There was a significant hSWA rebound the next hour, again with no increase in total sleep time. However, the conclusion that increased hSWA pressure does not extend sleep [46] was not endorsed by Gillberg et al. [63] following a similar study. Here, night sleep was restricted to 4 h, followed by ad lib sleep at 11.00 h, when hSWS was suppressed by acoustic stimulation for 90% of the recovery sleep time (judged by means of a control group not undergoing this hSWS deprivation). Here, sleep was significantly lengthened, apparently to accommodate the recovery hSWS.

Increasing pressure for hSWS delays the latency to the first REM period (REM latency – REML), and it will be remembered that Feinberg et al. [51] believed this to be the cause of a missing first REM period following sleep loss. Whether the opposite is true, that decreased hSWS need leads to a shorter REML is another matter. Campbell and Gillin [30] tested the hypothesis that a shortened REML during nighttime sleep, as in depression, may be due to daytime naps containing hSWS. Their re-analysis of data from nap studies in normal subjects confirmed the significant negative correlation between nap hSWS levels and nighttime REML. But further examination of their findings shows that the relationship is not straightforward. For example, if the nap hSWS is zero, then the nighttime REML can vary between 0 and 40 min; and if the nap hSWS is between 0 and 25 min then REML is fairly constant at around 50 min. A positive correlation

is not evident until REML exceeds 50 min and nap hSWS exceeds 20 min.

The effects of selective hSWS deprivation on daytime performance is difficult to determine as the severe sleep disruption and loss in sleep continuity that is implicit in the method, together with the ensuing sleepiness, may well obscure more subtle (perhaps neuropsychological) effects of hSWS loss. Bonnett[18] briefly aroused subjects every time they entered stage 3 sleep. A control condition replicated the total number of arousals, with the aim of minimising the disruption to hSWS per se. But because sleep was interrupted every few minutes during the night under both conditions, sleep disturbance was marked. There was no difference between the conditions in the subsequent performance detriment at standard psychological tests.

Quality of wakefulness

Exercise and body heating

Acute increases in hSWS, especially stage 4, can be produced either by sitting subjects in a bath of warm water, typically at 40 °C (e.g. refs[26, 80, 87]) and raising core temperature by about 1.5–2.0 °C for at least 30 min during the day, or by raising core temperature less but for longer (e.g. subjects in a hot ambient environment for about 3 h[37, 130]. Delta EEG analyses endorse the hSWS increases[78]. For the bath heating, the longer the heating or the nearer it is to the nighttime sleep period, the greater the hSWS effect[26, 78]. As one might expect, too high a heating dose too near to sleep disrupts sleep and hSWS[78]. The relationship between the proximity of heating to sleep and the effect on hSWS is interesting. It may be due to a circadian dose-effect, with evenings being more potent than afternoons, or there may simply be a decline over the interim wakefulness in whatever sleep process is accelerated by the heating; the longer this wakefulness, the greater the decline.

We typically find[77, 78, 80] that passive heating increases stage 4 sleep by about 45% over baseline values, and hSWS by about 20% (the effect is primarily on stage 4). This effect is not in the first sleep cycle, but in the second and third. That is, a discontinuity seems to be added to the exponential decay of hSWS over the sleep cycles. The heating-induced rise in brain temperature, rather than in body temperature, appears to be the key to the hSWS effects[76], especially as specific brain rather than body heating has a similar result on hSWS[74].

Exercise does not necessarily raise hSWS. Certainly, it has no effect on hSWS in physically unfit (untrained) subjects[68, 70, 142] and may not affect hSWS even in fit (trained) subjects after long-duration lower intensity exercise[140], or after very short-duration high intersity exercise[27]. It has been postulated[68],with supportive findings[77, 80], that acute high intensity exercise in fit subjects leads to increased hSWS because of the accompanying body (i.e. brain) heating. Fit people can endure intense exercise for long periods of time and become sufficiently hot, unlike unfit subjects who have limited exercise endurance and do not become so hot. However, this level of heating is achieved in both fit and unfit subjects by the bath method[77, 78, 80]. In none of our studies was the hSWS increase accompanied by longer ad lib sleep.

A notable study by Bunnel and Horvath[28] woke subjects up after the second sleep cycle, after most of hSWS had been taken, and sat them either in a tepid (control) or hot bath for 20 min. Tympanic temperature rose by 2.4 °C and returned to normal within 1 h. Subjects then went back to sleep. There was a consolidation period, as the hSWS increase did not appear until the fourth cycle; the ensuing third sleep cycle remained unchanged.

Why a warm brain leads to more hSWS is still a matter for debate. Main possibilities seem to be a) increased brain temperature heightens waking brain activity and metabolism (Arrhenius's Law), maybe accelerating the accumulation of waking (or sleep) factors promoting hSWS; and b) the remaining small elevation in brain temperature (about 0.2 °C) at sleep onset after body heating (e.g.[80]) may be affecting other hSWS mechanisms, perhaps associated with thermoregulation[12]. This latter topic is returned to in the following section. A putative third reason involving muscle recovery ('body restitution') is unlikely[70], and given that hSWS is produced by the brain, not by muscle, hSWS measured alone is no index of muscle restitution. No sleep-after-exercise study has measured muscle recovery in sleep.

Brain metabolism during wakefulness

Stage 4 and hSWS are significantly elevated (by about 30% and 23% respectively over baseline), following a subject's near-continuous assimilation of novel and interesting visual scenes (e.g. sightseeing, window shopping, cinema) over much of a 'busy' waking day[75]. Exercise levels were controlled for, although such exercise is unlikely to affect hSWS anyway[68]. By 22.00 h the subjects were unusually sleepy, and when eventually allowed to retire at their normal bedtime all fell asleep more rapidly. Interestingly, the hSWS increases did not appear in the first sleep cycle, but in the second and third. Sleep length and REM sleep were unchanged, and subjects woke up naturally at the usual times, feeling refreshed. This work complemented an earlier, similar study[81], where the main outcome was also increased hSWS. Both studies found a further small, significant rise in stage 4 on a second recovery night.

From laboratory-based measurements of cerebral metabolic rate (CMR) or cerebral blood flow (CBF) during heightened alertness and search behaviour[122, 125] it is fair to assume that these 'busy days' would have increased CMR, and maybe even imposed more wear and tear on cerebral neuronal and glial systems. Per hour, these increases in CMR would be less than those induced by the brain heating methods, but the overall effect may

have been similar as the duration of the 'busy days' was for much longer.

Apart from the visual cortex, an area of the cerebrum that would have been particularly affected by these days is the prefrontal cortex (PFC). Luria[101] proposed that the abilities to plan and direct the visual search of novel visual scenes and select aspects of the environment to attend to, as well as to shift and maintain attention, all centre on the PFC. These conclusions, endorsed by Stuss and Benson[135] and Fuster[57], are reflected in CMR studies[32, 122]. As will be seen, the PFC is the cortical region most metabolically active during wakefulness, and the least active during hSWS. Coincidentally or otherwise, hSWS and hSWA appear to be the most intense here. It would be worth investigating whether these 'busy' days produce different hSWA changes over the cortex, which are more apparent in the PFC. The possibility of differential decay dynamics for hSWA over the cortex also has implication for 'process S' theory. To conclude, both the 'busy' day and passive brain heating methods suggest that hSWS is not only affected by the length of wakefulness but also by its quality.

hSWS and thermoregulation

Why a slightly elevated core temperature at sleep onset should raise hSWS is a matter for debate. There are at least two views. Sewitch's 'thermodownregulation' hypothesis[128, 129] postulates that body temperature at sleep onset drives hSWS; the lower this temperature, the greater the ensuing hSWS. The other view, Berger's 'hSWS for hypothermia' hypothesis[12] argues the opposite, that as the function of hSWS is to conserve energy and bring down body temperature, then the higher the body temperature at sleep onset, the more the hSWS. Both proposals see hSWS to be a slave of thermoregulation.

Berger et al.[12] have shown a significant positive correlation between rectal (Tre) or tympanic (Tty) temperature at sleep onset and subsequent hSWS, particularly in the first sleep cycle. But one should be cautious about drawing conclusions as only a minority ($< 25\%$) of the variance can be accounted for. A recent study by Jordan et al.[87] only provided marginal support for Berger's hypothesis, and no support for that of Sewitch. Jordan et al. gave daytime hot bath treatment in the late afternoon and monitored Tre and oxygen uptake (VO_2) before and during the usual nighttime sleep. After the heating, Tre was still 0.19 °C higher than usual, at the start of the first hSWS cycle. After the initial 60 min of hSWS (which was increased) Tre still remained 0.14 °C higher. Thus, an elevated Tre at sleep onset might have enhanced hSWS, but the longer hSWS did not depress the elevated Tre. Further evidence that the coupling between hSWA and Tre is loose comes from two more studies. In extended sleep, the time courses of hSWA and Tre become disassociated[43], and in selective hSWS deprivation, Tre is unaffected, despite very little hSWS[8].

There is little evidence showing that metabolic rate falls to any remarkable extent during hSWS per se (especially in stage 4) compared with other sleep stages. At best this is under 5%[123, 131, 148]. The main fall in Tre during sleep occurs within one hour of sleep onset regardless of the sleep stage[61], and the major drop in metabolic rate attributable to sleep itself appears within 30 min of sleep onset[56]; that is, before hSWS usually starts. The other factor lowering core temperature and metabolic rate at this time is the circadian rhythm, which, of course, is present regardless of sleep.

The overall reduction in energy expenditure during sleep (irrespective of sleep stage) compared with that of relaxed wakefulness seems to vary according to the study, with a range from 8.5%[148] to 25%[56], being comprised of equal contributions from sleep itself and the circadian rhythm[56]. Interestingly, changes to the environmental temperature during sleep have an impact on REM sleep, but hSWS remains little affected unless sleep is grossly disturbed[99, 113].

It is unrealistic to claim that hSWS or even human sleep itself is primarily a hypometabolic/energy saving state[105], although this may well be the case for sleep in small mammals[70, 105]. Any energy saving afforded by human sleep must be incidental, and our sleep (especially hSWS) must have other, more important roles to play. Energy consumption during relaxed wakefulness in a young adult man averages about 4 kJ/min. If one were to sleep for 8 h at night rather than remain in a relaxed waking state, then the energy saved is around 250 kJ (= a small slice of bread). The energy saved during sleep by entering hSWS for 100 min rather than say, staying in stage 2, is about 20 kJ (= 1 peanut).

McGinty and Szymusiak[105] proposed that in wakefulness the brain is working at a temperature which is close to dangerous levels, and that another role for hSWS is a protective one to lower this temperature. However, the extent to which hSWS does this is debatable (see above). More important is whether or not the human brain runs 'too hot' at its usual 37 °C. Other detailed studies[29] indicate this to be quite a safe level as mammalian brains go, and comparatively low.

Heat loss during sleep appears to be greatest during hSWS, especially as sweat rate is highest in hSWS[124]. Of course, sweating is not a very effective method for thermolysis whilst asleep in bed, with a static microclimate. It is possible that this particular hSWS-linked sweating may have causes other than that of thermoregulation. For example, in sleep there is a loss of the usual cortical inhibition of sweating[94], and thus the resultant small fall in body temperature may be incidental, and not indicative of 'energy saving'.

Human growth hormone (hGH) and cortisol output

The role of hGH in sleep is debatable[70]. In adults it may have little to do with growth and tissue repair, being

perhaps a protective measure against the physiological effects of the fasting state of our relatively lengthy sleep[70]. On the other hand, in children it may well be more growth-associated, as most of their 24-h hGH output is confined to sleep. It was once thought that the sleep-related hGH release was intimately linked to hSWS, but it is now clear that the association is more tenuous. Born et al.[21] studied hGH release in normal subjects with and without hSWS deprivation (by acoustic stimulation, without awakening). Deprivation led to a dissociation between hSWS and hGH, as hGH output remained near normal. The authors considered that sleep onset was the major stimulus to the hormone's release. The technique appeared not to stress the subjects, as cortisol output remained normal. Jarrett et al.[85] came to similar conclusions after concentrating on hSWA rather than hSWS. Serum hGH was continuously sampled. Whilst there was some association between hSWA and hGH levels, it was not possible to demonstrate a clear relationship. Other complex mediating factors were presumed, with sleep onset seeming independently to affect hGH and hSWA. This conclusion was endorsed by another study from this group[86], based on depressed patients who had below-normal levels of sleep-related hGH output before, during, and after successful treatment (no medication). Nevertheless, some link between sleep-related hGH levels and hSWS in children and young adults is indicated in hGH-deficient subjects who have (approximately 25%) less hSWS than normal subjects[5]. There were intervening variables[5], as some of this hSWS difference may have been due to the longer sleep (i.e. less wakefulness) in the patients. To complicate matters further, in psychosocial dwarfism, sleep-related hSWS levels are very variable, and can be normal[136].

Ageing brings a fall in both hSWS and sleep-hGH output, but the links between these latter indices are still uncertain[117]. Such hGH reductions were mainly limited to the first 3 h of sleep[117]; then the levels were similar for both young and older men.

The relationship between nocturnal cortisol release and sleep is still controversial, particularly with regard to the influence of hSWS. In general, plasma cortisol levels increase over the night, regardless of whether the individual is asleep or awake, although, there are reports that hSWS may have some inhibitory effect on this hormone's output (Follenius et al.[55] for references). Follenius et al.[55] have questioned this latter view. They monitored plasma cortisol every 10 min during normal sleep and with sleep delayed by 4 h. Nocturnal cortisol output prior to this delayed sleep was no different from that at the same time of night with sleep. However, the first 20 min of each hSWS episode was significantly associated with declining plasma cortisol levels, which was particularly clear during the delayed sleep when hSWS now occurred at a time when cortisol output normally rises. Cortisol increases could not be linked to any particular sleep stage. The investigators could not clearly demonstrate a causal link between hSWS and cortisol either way; only a significant association was established.

Pharmacology

Most benzodiazepine hypnotics attenuate hSWS and hSWA, particularly over the first three cycles[1]. Feinberg et al.'s earlier results[50] with flurazepam suggest that the delta activity is of lower amplitude and is more diffusely spread over the night, leaving the total delta count relatively unchanged. In contrast, the 5HT2 receptor agonist Ritanserin produces remarkable dose-response rises in hSWS and hSWA. Idzikowski et al.[84] reported 90- and 120-min increases in hSWS over placebo levels following 10 mg and 30 mg doses respectively. Total sleep time increased only marginally (under 30 min) and REM sleep and REML were unchanged. Morning psychological performance was adversely affected.

Seganserin, a closely related compound, produces similar enhancements of hSWS, as has been shown by Dijk et al.[40]. The authors also used spectral analysis, and the enhanced hSWA was compared with that elicited by normal sleep deprivation. The drug-enhanced hSWA was bimodal, in the frequencies 0.5–1.0 Hz and 5.25–8.0 Hz, whereas after sleep deprivation the response was unimodal, at 1.25–2.0 Hz. As the authors point out, the hSWA changes after the drug may have an alternative physiological significance to that of normal hSWA, and may be affecting different underlying mechanisms. Unfortunately, little is known about possible thermoregulatory or neuropsychological sequelae of these drugs. By word of caution, pharmacological elevation of hSWS should not necessarily be viewed as beneficial. For example, if hSWS reflects cerebral recovery processes, then why is more recovery required following Ritanserin and Seganserin? Maybe these compounds are 'toxic' to the cerebrum, necessitating more recovery hSWS?

Pathological changes

Insomnia

Many chronic insomniacs have little hSWS, and Gaillard[59] has even proposed that insomnia may be a disease of hSWS. This controversial view has been promoted further by Sewitch[128] in her thermodownregulation hypothesis. Here, insomniacs are seen to have an anomaly in thermoregulation at sleep onset, and as core temperature is apparently unable to fall, hSWS is blocked. But as noted, this hypothesis lacks substantive support. Stress and anxiety also can lead to reduced hSWS, and it could be argued that it is this which keeps up core temperature and disturbs sleep in insomniacs, with the reduced hSWS being an artefact of the latter.

Sleepwalking

It has been known for some time that sleepwalking primarily occurs in hSWS. However, a new and substantive

study by Blatt et al.[16] on 24 young adult sleepwalkers has clearly shown them to have much more hSWS (129 min vs 86 min for controls). Also, the sleepwalkers had more (30 min vs 1 min) synchronous delta activity ('hypersynchronous delta'). Whether or not the sleepwalkers walked because they have unusually large and 'deep' amounts of hSWS, or whether the unusual hSWS is a symptom of sleepwalking, is a matter for speculation.

Alpha-delta sleep

This anomalous alpha activity in hSWS was first reported[65] in psychiatric patients with somatic malaise and fatigue. Subsequently, alpha-delta sleep has been found in patients with fibromyalgia ('fibrositis') and rheumatoid arthritis[102,110]. This alpha EEG can also pervade stage 2 sleep. According to one theory[132], distressing events induce psychophysiological arousal, linked to the generation of alpha activity, which interferes with a restorative role for hSWS, leading to musculoskeletal pain and fatigue.

However, the evidence for this causal link is not conclusive, as for example, a higher incidence of alpha-delta sleep has been reported in symptom-free subjects compared with fibromyalgic patients[127]. There are reports[111] of this activity being found in other illnesses such as the 'chronic fatigue syndrome' (this does have symptoms in common with fibromyalgia). Horne and Shackell[79] looked at alpha-delta sleep in fibromyalgic and healthy control subjects. Both groups claimed to be good sleepers. Mean percentage alpha-like activity in sleep stages 2, 3, and 4 were greatest for the fibromyalgia group, but were not significantly different from those of the controls. Overlap in the distribution of alpha-delta sleep between the two groups indicated that it is not directly related to musculoskeletal symptoms. Of greater importance was that spectral analyses showed much more frontal cortical prevalence of this activity (which may have been kappa rather than alpha activity) in the fibromyalgia group. Across both groups of subjects there seemed to be an association between the amount of this frontal activity during hSWS and what seems to be 'agitated sleep mentation'.

Type 2 schizophrenia

Many (but not all) schizophrenics have little hSWS and no stage 4 sleep compared with age-matched normal subjects[53]. However, some of these earlier findings were confounded by medication[90,138]. Recent studies have been aware of this problem, and have shed further light on this important area. Hiatt et al.[67] performed period-amplitude analysis on the EEG of medication-free patients and found them to average 30% less delta activity than age-matched controls. Visual scoring showed the patients to average 11 min stage 4 versus 47 min for the controls. All these effects were most evident in the first sleep cycle. Other recent findings endorse the low hSWS/stage 4 levels in schizophrenia[11], but there are major individual differences in hSWS among such patients[60]. Schizophrenia tends to present two clusters of symptoms, positive and negative. The former, of lesser interest here, include delusions, hallucinations, excitement, grandiosity, suspiciousness and hostility. Negative symptoms include inability to focus on relevant issues, paucity in speech, distractability, emotional flattening, lack of spontaneity, and stereotyped thinking. Patients often manifest one cluster more than another. Crow[33] has proposed a two-syndrome concept of schizophrenia with Type 1 patients having mostly the positive symptoms and Type 2 the negative ones. Not all patients can be so clearly categorised, but the dichotomy is becoming increasingly popular[106]. There is good evidence[3,34] that Type 1 symptoms are associated with hyperactivity of subcortical regions, and Type 2 symptoms with hypoactivity of the prefrontal cortex (PFC). There are often underlying neurochemical and/or neuroanatomical changes in both forms of the illness, but the causes and effects are a very debatable issue[3,4].

Concerning the topic of differences in hSWS between schizophrenics, Ganguili et al.[60] monitored never-medicated schizophrenics and found for the group as a whole, lower delta counts, averaging for the 1st, 2nd and 3+4th cycles 21, 13, 12 units respectively. In healthy controls these values were 33, 25 and 19 units. One particularly interesting finding in the patients was that delta activity levels during hSWS were inversely related to the magnitude of the negative symptoms; the worse the type 2 schizophrenia the lower the delta count, independent of age. But this outcome may be an artefact of the generally low levels of delta activity found in these patients. It should be noted that whilst REM sleep parameters were normal in the patients, their sleep was more disturbed, and one might consider that this disturbance could, at least in part, underlie the reduced hSWA.

Ganguili et al.[60] also reported on a group of major depressives who had even lower hSWA levels than had the schizophrenics. Mean delta counts for cycles 1, 2, and 3 + 4 in the depressives were 10, 12 and 13 units respectively; the main finding was a diminished delta count in the first cycle. The depressives also had a shorter REML than both the schizophrenic and control subjects. It was concluded[60] that the schizophrenics had a different constellation of abnormalities in the first sleep cycle compared with that of the depressives.

Despite the consistent sleep findings in schizophrenia (fragmented sleep, reduced total sleep time, less hSWS, shorter REM latency) none is specific to the disorder[90]. For example, low levels of hSWS are found in major depression, retardation and during stress, but it is not known whether or not the underlying reasons are the same or different. Schizophrenia is a heterogenous disorder (cf: Types 1 and 2), Also, low levels of hSWS/hSWA among these patients are associated with poorer attention and larger lateral ventricles[144]. The onset of Type 2

schizophrenia tends to begin in late adolescence, and Feinberg's neurodevelopmental model[47] suggests some form of maldevelopment in neuroplasticity that is linked to the hSWS abnormalities.

Kraepelin[93] proposed that schizophrenia 'attacks by preference the prefrontal areas of the brain' (p. 219). Whilst this may be an overgeneralisation, recent measurements of regional CBF (rCBF), regional CMR (rCMR), and magnetic resonance spectroscopy (MRS) make it increasingly apparent that there is some form of PFC degeneration in many Type 2 schizophrenics[6,14]. The 'hypofrontal pattern' in rCMR, which has been confirmed by several other studies[9,13], contrasts with the usual 'hyperfrontal' pattern in normal subjects. 'Hypofrontality' is not an epiphenomenon of medication, but seems to be more apparent in Type 2 patients. The recent MRS findings[116] are particularly indicative of this, and so are the PFC neuropsychological deficits in these patients[137,147]. The contingent negative variation (CNV), a slow EEG potential that is largely frontally generated, is abnormal in schizophrenia[143].

The PFC is highly developed in humans and is the last brain area for myelination to be completed (late adolescence). Hence a link with Type 2 schizophrenia. The PFC has complex connections with most other cortical lobes, the basal ganglia, the raphe and locus coeruleus, and may be able to control its own serotonergic and noradrenergic input[9,14]. There may even be some sort of PFC de-efferentation in these patients[13], particularly with the dopamine pathways. In summary, there may well be an association between the low levels of hSWS/hSWA and impaired functioning of the PFC, as exemplified by Type 2 schizophrenia. Evidence indicating hSWS generating mechanisms are impaired in this disorder comes from recent findings on the effects of Ritanserin on schizophrenics with low hSWS levels[10]. The drug had no effect on the patients, whereas it dramatically increases hSWS in normal subjects.

Severe depression

Many depressives have low levels of hSWS/hSWA, especially stage 4[66,97,107]. This reduction is most prominent in the first sleep cycle, and in middle-aged depressives[95]. The apparent importance of hSWS in depression has been highlighted by Kupfer and Reynolds[96], who, for example, have postulated that hSWS may be beneficial in protecting against psychiatric disorders and pathological ageing. From a different perspective, Kupfer et al.[95] have proposed that low hSWS levels in the first cycle are a good indicator of recurrent depression; better than is REML. This was demonstrated[95] in a two-year prospective study of 74 patients. Those who had more delta activity in the first than in the second sleep cycle (i.e. 'a delta sleep ratio' higher than 1.1) remained remitted for five times longer than those having a lower ratio. Interestingly, monthly interpersonal therapy further enhanced the remission in the high ratio patients. For the low ratio patients, maintenance medication was advocated. Kupfer and Reynolds[96] consider that as well as hSWS having an important role to play in depression, the associated alterations to endocrine responses may also be implicated[45]. Incidentally, unmedicated manic patients in mania do not present any hSWS changes compared with similarly aged healthy control subjects, although, total sleep time is significantly reduced, as is REML[83]. CMR studies indicate that severe depression, like Type 2 schizophrenia, is accompanied by a hypofrontal pattern; low levels of hSWS are also often found[9]. A substantial investigation by Baxter et al.[7] of unipolar and bipolar depressives found a significantly lower rCMR in the left dorsal anterolateral prefrontal cortex (alPFC a high-level integrating centre). This hypofrontality significantly positively correlated with Hamilton rating scale scores (i.e. the worse the depression the greater the hypofrontality). Medication not only improved these scores but reduced the hypofrontality. It was noted[7], however, that an alPFC abnormality might not be specific to depression, and may be present in certain types of schizophrenia. Obviously the question to ask is whether there is any correlation between this hypofrontality in depressives and their levels of hSWS/hSWA, comparable with the findings by Ganguili et al.[60] for schizophrenics? No such study has been performed.

Whether the manipulation of hSWS has any central role to play in the treatment of depression is also a matter that is unresolved[149], but there seems to be a positive correlation between mood improvement and the hSWS rebound in depressives after sleep deprivation[95].

Conclusions

Recent studies on the cat, by Steriade et al.[134] show that cortical SWA is somehow driven or synchronised by thalamic oscillatory neurones. But hSWA is not simply a passive reflection of thalamic activity, particularly as the large amplitude of the hSWA as reflected by the scalp EEG shows that it is not the result of passive transmission of delta activity from the thalamus through the relatively thick mass of the cortex; this hSWA is being regenerated by the cortex itself. As Livingstone and Hubel[100] have pointed out, also from working on the cat, during SWA the cortex is in a peculiar state of sensory isolation, with the decreased responsiveness perhaps 'reflecting whatever recuperative processes the brain undergoes during sleep' (p. 561). The corticofugal projections to the thalamus indicate some form of reciprocity in SWA, through what Steriade et al.[134] term 'resonant thalamocorticothalamic loops' (p. 3201). Maybe the sleeping cortex permits itself to be driven by the thalamus in this way so that the cortex can obtain some form of rest/recovery?

Does hSWS/hSWA indicate any major function of sleep? Has it roles that are qualitatively or quantitatively different from other forms of human sleep? These are still

open questions. It has been argued [70] that whatever major functions human sleep may have, these centre on the cerebral cortex, rather than on the rest of the body. But there may be subtle phylogenetic differences in the various functions of mammalian sleep. For example, the rodent and human both show cortical SWA during sleep, but because much of the human cortex has evolved quantitatively and/or qualitatively different roles to those of the rodent (cf: the considerable rodent/human differences both in encephalisation, and in the cortical nerve/glial cell ratio particularly with respect to the PFC), then sleep and hSWA may present subtly different roles for the cortices in these animals [70]. On the other hand, it is reasonable to argue that SWA has a key energy conservation role for the rodent, whereas this is not realistic for humans [70].

An emerging point from this review of human SWA is that the PFC seems particularly involved in the manifestation of hSWS. Not only is hSWS at its most intense here [25], but this is where rCMR during sleep [103, 125] is at its lowest [24]. In contrast, the PFC has the greatest waking rCMR (hyperfrontality [24, 104, 122]), and where waking EEG frequency is at its highest compared with elsewhere over the cortex [104] (frequency is positively correlated with CMR). Coincidentally or otherwise, the PFC is where hSWS is at its most intense. Thus it might simply be argued that the reason why hSWS and what appears to be more intense 'cerebral rest' (vis-a-vis rCMR values) are most evident in the PFC, is that this is where waking activity is greatest. So the buildup during wakefulness of some sleep process, neurotransmitter, peptide, etc. may be more intense here. Brain heating or other ways of increasing brain metabolism may simply accelerate this buildup.

But the PFC may have a more subtle role to play, as the integrity of this area seems to be important for the generation of hSWS/hSWA. Impairment to this region, as in Type 2 schizophrenia, seems to attenuate hSWS throughout the cortex, not just in the PFC. Unfortunately, apart from the clinical findings, there are only incidental data from normal subjects to support this latter notion. For example, coherence analysis of the EEG [112], shows that the PFC is a focus for hSWA (coherence reflects connectivity between parts of the cortex). Ageing leads to a marked diminution in hSWS, and interestingly, the most marked age changes in cerebral morphology are in the PFC [36, 119].

Clearly, hSWS is not solely generated by the PFC. *But inasmuch that this area recruits and coordinates other cortical regions for the various tasks in hand during wakefulness* [57, 92, 135], *so may it act in a similar manner during hSWS. The high rCMR involved in this recruiting during wakefulness may necessitate greater PFC recovery during hSWS.* Of course, the PFC might only be a link in a chain, with the real cause for hSWS to be generated coming from the thalamus, or elsewhere. However, it has been suggested (see above) that the role of the thalamus is to facilitate rather than to stimulate the cortex into generating hSWA.

The full functions of the PFC are unresolved, but key roles seem to be maintaining wakefulness and non-specific arousal, as well as recruiting other areas of the cortex. The PFC has other major functions [57, 92, 135], e.g. planning, high-level perception, sensory comparisons, decisions to act, discrimination, directing and maintaining attention and novel goal-directed behaviour (including speech articulation and expression), and scanning eye movements. PFC damage does not affect old and well-rehearsed lengthy routines, but instead, the abilities to respond to a new situation or to execute a novel sequence of acts. Flexible, original thinking is far more affected than is performance at 'concrete' tasks such as IQ tests. There may be some association, causal or otherwise, between abilities at the above tasks, the functional integrity of the PFC, and the manifestation of hSWS in healthy subjects. This potential focus for future research might be complemented by more sophisticated 'busy day' studies placing increased demands on the PFC. Another avenue for exploration is whether total sleep loss produces marked (reversible) PFC deficits in behaviour. Findings so far, indicate this seems to be so [71–73]. Of course, whether these deficits are associated with a loss of hSWS rather than of sleep in general, is another matter.

In relation to Type 2 schizophrenia and severe depression, there is the problem of cause and effects between the symptoms, hypofrontality, PFC impairment and hSWS. Is the onset of certain forms of depression, for example, due to interpersonal problems, leading to less interest in the outside world, less use of the PFC, some sort of degeneration here, neuropsychological deficits, hypofrontality and low hSWS? That is, the PFC change is secondary, whereas in Type 2 schizophrenia it may be primary – a neurological/neurochemical disease process of the PFC predisposing to the manifestation of this disorder.

Human sleep is an extremely complex process and hSWS only represents a facet of sleep and its function. This review has concentrated on hSWS, and excluded the remainder of sleep which also must have key roles to play. One must not fall into the trap of dichotomising human sleep as hSWS vs non-hSWS, as has been the case with REM vs non-REM sleep, which for many years narrowed our outlook on sleep to the exclusion of many of its other fascinating phenomena.

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