Defining and determining the properties of the human sleep homeostat

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Chapter 5

How ZZZs Are Manufactured: Mapping Slow Wave Activity Regulation across the Brain

Andrei Zavada, Arjen M. Strijkstra, Ate S. Boerema, Serge Daan, Domien G. M. Beersma
CHAPTER 5. SWA EFFICIENCY MAP

Abstract

The regulation of the timing of sleep is thought to be linked to the temporal dynamics of slow-wave activity (SWA, EEG spectral power in ∼0.75–4.5 Hz range) in the cortical NREM sleep EEG. In the two-process model of sleep regulation, SWA was used as a direct indication of sleep debt. Originally, this was done in a gross way, by measuring average SWA across NREM–REM sleep cycles, fitting an exponential curve to the values thus obtained and estimating its time constant. In later studies by Achermann, SWA was assumed to be proportional to the instantaneous decay rate of $S$ rather than as a direct reflection of $S$. Following up on this, we developed an extended model of SWA dynamics, in which effects of intrusions of REM sleep and wakefulness were incorporated. For each subject, a ‘gain constant’ can be estimated quantifying the efficiency of SWA in dissipating $S$. Since the course of SWA is variable across cortical locations, local differences are likely to exist in the speed of discharge of Process S, eventually leading to different levels of $S$ in different cortical regions. In this study we estimate the extent of local differences of SWA regulation on the basis of the extended model of SWA dynamics, for 26 locations on the scalp. We observed higher efficiency of SWA in dissipation of Process S in frontal frontal EEG derivations, suggesting that SWA regulation has a clear local aspect. This result further suggests that the process involved in (local) SWA regulation cannot be identical to the Process S involved (with Process C) in effectual determination of sleep timing—a single behaviour than cannot vary between locations on the scalp. We therefore propose to distinguish these two representations and characterize the former, purely SWA-related, as ‘Process Z’ (for zzz...).
5.1 Introduction

Sleep regulation research aims at the understanding of sleep behaviour and physiology. Even in the absence of full understanding of biochemical and neurophysiological functions of sleep, as well as of the underlying mechanisms, much is known about sleep homeostasis. In particular, studies of the dynamics of EEG Slow-Wave Activity (SWA, spectral EEG power in the delta frequency band) of the non-rapid eye movement sleep (NREM) have been successful in generating hypotheses concerning sleep homeostasis (Borbély, 1982; Daan and Beersma, 1983; Daan et al., 1984; Dijk et al., 1987a; Dijk and Czeisler, 1995).

The two-process model of sleep regulation (Borbély, 1982; Daan et al., 1984) is a widely accepted descriptive model of sleep timing. This model is based on two components: the homeostatic Process S, which increases during wakefulness and decreases in sleep, and a circadian Process C, which sets the limiting upper and lower thresholds to Process S, oscillating with a 24-hour period. Sleep is initiated when the level of $S$ reaches the upper threshold and terminated when it hits the lower threshold. The internal timing component, Process C, is independent from the homeostatic component, Process S (Daan et al., 1984; Dijk and Czeisler, 1995). Dissipation of $S$ during sleep follows an exponentially declining curve (towards $S = 0$). Similarly, an exponential increase towards an upper asymptote ($S = 1$) is assumed for the course of $S$ during wakefulness.

The time constant of the dissipation of $S$ was originally derived by fitting an exponential curve to average NREM sleep SWA values per cycle during sleep. The time constant of $S$ build-up was estimated by fitting an exponential curve to the NREM sleep SWA data at the end and beginning of a baseline night and at the beginning of a recovery night after sleep deprivation (Daan et al., 1984). The rise rate has been validated by measuring NREM sleep EEG data in naps after varying durations of waking (Dijk et al. (1987a); see, however, Werth et al. (1996)).

In later studies, more attention has been paid to the detailed course of SWA. An extended model of SWA regulation was developed (Achermann et al., 1993). This model starts with a hypnogram and the value of SWA at the beginning of a sleep episode, and iteratively reconstructs the course of SWA using a set of parameters. These parameters define the rate of increase of SWA within NREM sleep bouts as well as the rate of SWA decrease due to intervening REM sleep and awak-
enings. It is further assumed that the instantaneous level of $S$ limits the maximal possible amount of SWA, and that SWA, in turn, influences $S$ through a certain factor called ‘gain constant’ ($gc$). This gain constant is thus a measure of efficiency with which SWA is dissipating $S$. Finally, it was shown by Achermann et al (1993) that the assumption of a constant tendency for $S$ to increase throughout all vigilance states (being overcompensated during sufficiently intensive NREM sleep) gives better simulations of the course of SWA. As a result, $S$ can eventually increase during NREM sleep, as in NREM sleep stage 1 with sufficiently low levels of SWA.

Process $S$ plays a slightly different, though related, role in the two process model (Daan et al 1984) and in the SWA model of Achermann et al (1993). It is primarily involved in the regulation of sleep timing in the two-process model, although the roughly exponential nature of the breakdown of $S$ implies that the decay ($dS/dt$) is proportional to $S$ and hence reflects SWA as well as $S$ does this. In the SWA model $S$ is primarily treated as a regulator of SWA. The characteristics of Process $S$ required to obtain optimal simulations of the course of SWA may not be identical to the characteristics required for the determination of sleep timing. An obvious problem is that SWA patterns in different areas of the cortex can be quite dissimilar, both at any given time (Cajochen et al., 1999) and along a stretch of time (Werth et al., 1997). To accommodate these dissimilarities, the $S$ in the sense of Achermann (1993) must, too, be made a local variable, while $S$ in the original two-process model must remain a single parameter for the whole brain as long as the brain can be either asleep or awake.

In our study we tested whether the simulation of SWA for different locations on the scalp requires different courses of $S$. To avoid any confusion about the meaning of the processes we are interested in, we will distinguish these locally-different instantiations of $S$ from the original Process $S$ involved in sleep timing, by the term ‘Process Z’. In contrast to the single Process $S$, there may be multiple instances of Process Z, at different sites of the brain.\(^1\)

\(^1\)The term is chosen in reference to the ‘many ZZZ’s manufactured’ by a Ukrainian taxidriver in Jonathan Safran Foer’s smashing novel ‘Everything is illuminated’, which itself rather keeps the reader awake.
5.2 Methods

5.2.1 Subjects and EEG data acquisition

Nine healthy young subjects (18–28 y.o.) participated in an experiment using visual stimulation. Subjects did neither smoke nor use drugs, and abstained from consumption of alcohol and coffee throughout the experiment. They did not rate as extreme morning or evening types on the Horne–Östberg Morningness-Eveningness scale (mean ± s.d. is 46.7 ± 7.86, falling within the ‘neither type’ range). Subjects signed an informed consent form. The experiment was approved by the Medical Ethics Committee of the Academic Hospital of the University of Groningen.

Subjects were asked to come to the lab for a habituation sleep night and a baseline sleep night before a visual stimulation experiment took place on the third day. The results of the visual stimulation will be published elsewhere. For the present analysis, only the baseline sleep EEGs were used. Before both habituation and baseline sleep nights, subjects stayed at home doing their normal routine, until they came to the lab at 20:00. After application of scalp electrodes subjects performed computerized test series of 35 min duration at 22:00 and 23:00. The test series contained questionnaires and event related potential trials, and did not include other visual stimulation. Subjects prepared to go to sleep at 23:40 and went to bed and the electrodes were connected to the EEG amplifiers around 23:55. At 00:00, lights were turned off until 08:00 the next morning.

EEGs were recorded using a cap system with Ag/AgCl electrodes (Electro-Cap International, Inc., Eaton, Ohio, USA), on 26 positions on the scalp (F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, P9, P10, PO7, PO8, O1, Oz, O2, PO9, PO10, O9, O10). The left earlobe was used as reference, and the inion was used as ground. Data were amplified (500 µV/V) band-pass filtered between 0.16–30 Hz and sampled at 100 Hz. Besides EEGs, also EOG of the right eye was obtained, and EMG was measured on neck muscles. EEGs were scored for wake, movement time, REM sleep and NREM sleep on a 30-sec basis, using the criteria of Rechtschaffen and Kales (1968). For EEG quantification, the EEG analysis program BrainVision (Brain Products, Germany) was used. NREM sleep EEG was screened for artefacts (by 3-sec intervals), clean EEG epochs were Fourier transformed, and spectral power was calculated per 1 Hz frequency bin for a 1–7 Hz
EEG frequency range. Spectral power data from within a particular 30 sec interval were averaged. The EEG power data of each of the 26 derivations were entered into the model together with the vigilance state information to estimate the gain constant for that derivation.

5.2.2 The model

The modelling method follows the description of Achermann et al (1993), with a few minor modifications as detailed in Chapter 4. Table 5.1 gives an overview of the parameters of the model. These parameters are used to compute, at 30-sec intervals, the instantaneous rates of change of Z and SWA, from the initial value of SWA and the sequence of vigilance states. SWA fitting was done between the simulated and empirical SWA profiles throughout the night using a least squares method, by iteratively adjusting parameters until the resulting improvement of the overall fit was considered sufficiently small (< 0.05 %). SWA simulations were performed for each 1-Hz bin in the 1–7 Hz range. The fitting can fail if a parameter being adjusted goes outside of the arbitrarily set limits (Table 5.1). The equations are as follows:

\[
\frac{dS}{dt} = -gc \cdot SWA \cdot !WT + (S_U - S) \cdot rs, \quad (5.1)
\]

\[
\frac{dSWA}{dt} = rc \cdot SWA \cdot (S/S_U)(1 - SWA/S)\cdot!WT - f_{cR} \cdot (SWA - SWA_L) \cdot REMT - f_{cW} \cdot (SWA - SWA_L) \cdot WT, \quad (5.2)
\]

where SWA and Z are current values expressed as % of the mean SWA over all baseline pages scored as NREM; SWA_L is the lower asymptote for SWA, defined as 95% of the lowest SWA observed in all REM pages in baseline; Z_U is the upper asymptote for Z; rc, gc, rs, f_{cR} and f_{cW} are sleep parameters described in Table 5.1. WT = 1 on wake, else 0; REMT = 1 during and from t_a min before REM sleep, to allow for the SWA drop caused specifically by REM sleep, and for t_p min after completion of the REM episode, because effects REM interfering with SWA are still apparent for some time; t is time (in min). The operator ‘!’ is logical negation (thus !x = 0 for any x ≠ 0, and !0 = 1.

The current experiment does solely include baseline sleep and no additional sleep episodes, which are needed to determine the rise
Table 5.1  Parameters of the model. Initial values derived by Achermann et al. (1993) for 'normal' subjects. The rise rate ($rs$) was derived from (Daan et al., 1984).

For initial values, see Table 4.3 on page 60.

<table>
<thead>
<tr>
<th>Param. Unit</th>
<th>Description</th>
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<th>Limits</th>
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<tr>
<td>$rc$ min$^{-1}$</td>
<td>SWA rise constant</td>
<td>yes</td>
<td>0.02 ... 4</td>
</tr>
<tr>
<td>$f_{cR}$ min$^{-1}$</td>
<td>SWA fall constant triggered by REM</td>
<td>yes</td>
<td>0.06 ... 2</td>
</tr>
<tr>
<td>$f_{cW}$ min$^{-1}$</td>
<td>SWA fall constant triggered by Wake</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>$gc$ min$^{-1}$</td>
<td>Gain constant</td>
<td>yes</td>
<td>$(0.04 \ldots 2) \cdot 10^{-2}$</td>
</tr>
<tr>
<td>$S_0$ %</td>
<td>Level of $S$ at sleep onset</td>
<td>yes</td>
<td>50 ... 700</td>
</tr>
<tr>
<td>$S_U$ %</td>
<td>Upper asymptote of $S$</td>
<td>yes*</td>
<td>120 ... 1000</td>
</tr>
<tr>
<td>$t_a$ min</td>
<td>Anticipated effect of REM on SWA</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>$t_p$ min</td>
<td>Extension of effect of REM on SWA</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>$rs$ min$^{-1}$</td>
<td>Rise rate of $S$</td>
<td>no</td>
<td></td>
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</table>

(*) $S_U$ is tied to $rs$ and not tuned independently:

$$S_U = (S_0 - S_{baseline,end} \cdot \exp(-t \cdot rs))/(1 - \exp(-t \cdot rs)),$$

$t$ being here 24 h less the duration of the baseline night.

rate of Process $Z$. The rise rate was therefore fixed at a value of $0.917 \times 10^{-3}$ min$^{-1}$, which Daan et al. (1984) have established for normal subjects in the experiments done by Borbély (1981). This parameter defines the rate with which $Z$ approaches its upper asymptote ($Z_U$) with time. As can be seen from Equation 5.2, $Z$ is rising irrespective of vigilance state because the term $(Z_U - Z)rs$ is always positive. However, due to the term $-gc \cdot SWA$, $Z$ receives an additional decrement depending on the current value of $SWA$, such that it will decline during sufficiently intense NREM sleep. Likewise, in sufficiently shallow NREM sleep, $Z$ will increase. This is where Achermann’s concept of $S$, here termed $Z$, departs from the original definition of Process S in the two-process model of Daan et al. (1984): Achermann (followed by us here) allows the sleep debt to increase with longer sleep.

In the analyses presented below, only the gain constant is included. The other two parameters being estimated, SWA rise constant ($rc$) and SWA fall constant triggered by REM ($f_{cR}$), were not found to have any systematic interdependencies in a previous study (Chapter 4), and are therefore not reported in the present article.

To visualize scalp maps of $gc$ values and to evaluate statistically differences between scalp maps, data were processed in LORETA, an EEG/ERP/electromagnetic tomography program. This freeware program uses a non-parametric statistical tool to estimate map differences
and single electrode differences within maps, using a randomization approach (Pascual-Marqui et al., 1994).

5.3 Results

Figure 5.1 shows the course of $Z$ and simulated Slow Wave Activity superimposed on the measured SWA profile in two subjects from the four medial derivations, Fz, Cz, Pz, and Oz. It can be seen that the course of $Z$ shows a rapid decrease during high SWA and a slower decrease or even increase during low SWA and REM sleep or wakefulness. Especially at the end of the sleeping episode, the rising $Z$ demonstrates a behaviour by which it is distinct from a putative course of Process S reconstructed from the same empirical SWA. In subject 2 (right), absence of scored REM between peaks of SWA in the first half of the night resulted in a straight course of the simulated SWA, exposing the degree of sensitivity of the method to the vigilance state history as well as to its accurate scoring.

By visual comparison, a gradual change in the relative amounts of SWA expressed in the first and next following NREM bouts is already noticeable, most clearly in subject 1 (Fig. 5.1, left column), but also in subject 2 (right column). This change is transformed into a gradient of the gain constant over the scalp, which is comprehensively given in gradient maps on Fig. 5.2.

It appears that large reductions in the level of $Z$ occur at Fz, as compared to the more posterior derivations. The figure thus suggests that the gain constant is larger in frontal than in more occipital derivations. In subject 2 (right), the four derivations shown were successfully modelled, but it can be seen that some troughs of measured SWA occur that are not well followed by the course of $Z$. In subject 1 (left) no gain constant could be found for the Oz derivation that would result in a successful fitting by the modelling procedure. Model failures occurred in 23% of a total of 1404 simulation runs in all subjects and all six 1 Hz EEG power data bins. Failures occurred most frequently in parieto-occipital (47%, interindividual s.e.m. 15) and occipital (28%, s.e.m. 13) derivations, and less frequently in parietal (20%, s.e.m. 10), central (16%, s.e.m. 13) and frontal (8%, s.e.m. 2) derivations. Most of them were in subject 1. The differences between electrodes may indicate that SWA regulation on parieto-occipital locations deviates from that in more frontal areas, sometimes to the extent that the
5.3. RESULTS

Figure 5.1 Simulation of SWA (thick black line) and Process Z (thin line) in the 2–3 Hz frequency range, plotted on top of the recorded SWA profile (solid grey area), in medial derivations obtained from two of our subjects. Z here has the same dimension as SWA (i.e., %) as in Achermann’s model. The original, dimensionless representation of Daan et al (1984) becomes thus \( Z/Z_U \). At the bottom of each panel, REM sleep is indicated as a half-height bar and NREM sleep as a full-height bar. Both subjects showed a decrease in SWA over the sleep episode. Subject 2 (right) had gain constant values of 0.013, 0.013, 0.011 and \( 0.009 \times 10^{-3} \text{ min}^{-1} \) in Fz, Cz, Pz, and Oz derivations. In Subject 1, the difference in peak SWA values between the first NREM bout and the next prominent bout is gradually diminishing from Fz to Pz, eventually even changing sign at Oz. Concurrently, \( gc \) decreases from \( 0.020 \times 10^{-3} \text{ min}^{-1} \) in Fz to 0.015 and \( 0.011 \times 10^{-3} \text{ min}^{-1} \) in Cz and Pz, resp.; derivation of \( gc \) did not succeed in Oz. Most such failures occurred in parietal and occipital derivations, and not in frontal derivations.
model is not sufficient to describe the data. The obvious reason for model failures was the increase of SWA over consecutive NREM sleep episodes, as often occurred in occipital derivations (e.g., lower left panel in Fig. 5.1).

Figure 5.2 shows scalp maps of the absolute gain constant \( (gc) \) values from all 26 measured scalp locations, for all six 1 Hz intervals overlapping with the delta band. The gain constant values are high in the lower frequencies, and highest in the 2–3 Hz band. This suggests that SWA is linked to \( Z \) closest in the 2–3 Hz frequency range. This is the frequency range where the largest rebound in SWA is observed following sleep deprivation (Dijk and Beersma, 1989), which led to the suggestion that this frequency range is the best representative in the context of sleep homeostasis.

In a statistical analysis, the 1–2 Hz map did not show significant deviation from a map with the overall average (TANOVA: \( p = 0.16 \)). The maps of the five higher 1 Hz frequency bin data deviated from the average map with a similar anterior-posterior cline (TANOVA: \( p < 0.01 \)). Table 5.2 shows the matrix of statistical assessment of differences between maps of different frequency bins of absolute \( gc \) values (in the lower-left triangle) and normalized \( gc \) value maps (in the upper-right triangle). For nearly all maps, differences in absolute \( gc \) value distributions were found, based on absolute differences and map differences combined, except for the 1–2 Hz vs 3–4 Hz and 5–6 Hz vs 6–7 Hz pairs. When absolute level effects were removed, the 1–2 Hz map still differed from all other maps, lacking the anterior-posterior cline in \( gc \). Additional map changes were found for 3–4 Hz vs 4–5 Hz and 4–5 Hz vs 5–6 Hz comparisons. Taken together, this indicates that \( gc \) behaves aberrantly in the 1–2 Hz, deviating from the distribution pattern with frontal high \( gc \) levels common to higher frequencies.

5.4 Discussion

In this study we analyzed the temporal patterns of SWA at multiple electrode positions by applying an elaborated version of Achermann’s model of SWA regulation. The analysis was restricted to baseline sleep without sleep deprivations and thus was not aimed at a precise quantification of the rise rate of Process Z. Instead, we fixed the rise rate at the value Daan et al. (1984) established for normal subjects \((0.917 \times 10^{-3} \text{ min}^{-1})\). To investigate the effect of fixing the rise rate,
Figure 5.2  Distribution maps of the average gain constant ($g_c$) of all 26 derivations on the scalp ($n = 6–9$). The common pattern is characterized by higher $g_c$ values in frontal areas. The highest $g_c$ values occurred in the 2–3 Hz frequency bin. The frontal relatively high $g_c$ values are absent in the 1–2 Hz bin, where no difference in $g_c$ of any location with the scalp average $g_c$ could be detected (see text and Table 5.2).
Table 5.2  Significance of differences between $gc$ distribution maps between all 1 Hz frequency intervals overlapping with the delta range (Topographic ANOVA, * indicates significance at $p < 0.05$, **, at $p < 0.01$). Values in the upper right triangle: comparisons of absolute $gc$ values (indicating differences based on both level and map distribution); lower left triangle: within-map normalized values (indicating differences in map distribution only). The significance of map differences of 1–2 Hz to higher frequencies is evident in analyses of absolute and normalized data.

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we performed additional simulations of $gc$ using considerably higher (+30%: $1.2 \times 10^{-3} \text{min}^{-1}$) or lower (−30%: $0.6 \times 10^{-3} \text{min}^{-1}$) rise rates in the 2–3 Hz EEG frequency range data. These simulations resulted in small but similar $gc$ value changes in all derivations by on average +4% (0.895, s.e.m. 0.146) for the high value, and −5% (0.821, s.e.m. 0.134) for the low value, respectively. Rise rate variation thus appears to only marginally affect the gain constant. A previous experiment in which rise rate was a free parameter showed that although rise rate and gain constant were interdependent, the variation in rise rate was much larger than variation in $gc$ (Chapter 4). Thus, the fixing of the rise rate to a standard value is not considered of significant importance for the interpretation of the present results.

From the analysis of the gain constant in SWA regulation across multiple cortical locations we conclude that the essential hourglass mechanism of dissipation of Process Z represented by $gc$ is more clearly expressed in frontal areas. This is in accordance with Cajochen et al. (1999), who found a larger increase in frontal than in occipital SWA levels after sleep deprivation. In contrast, parieto-occipital areas appear to have lower gain constant, implying a smaller effect of local SWA on the decline of its regulating variable: $Z$. The increased frequency of unsuccessful fits in occipital areas suggests that Process Z has less explanatory power for the regulation of SWA at those locations. The
observed local variation in the course of Process Z as a function of time and the differences in the $Z$ level confirm our suspicion that Process Z is not identical across the cortex. As a consequence, Process S, supposed to control the timing of sleep, and Process Z, controlling SWA regulation, must be two different processes.

There is another argument consistent with our interpretation that $S$ and $Z$ are not exactly one and the same process. Achermann et al. (1993) have observed that SWA is simulated best under the assumption that $Z$ always has a tendency to increase, only visible during shallow NREM sleep (provided it is sufficiently shallow). Such shallow NREM sleep often occurs in the later hours of the night, when sleep need is satiated. At this time, $Z$ will effectively start increasing (as in Fig. 5.1, upper-left graph). Now, suppose the course of Process Z is to interact with Process C in order to determine the time of awakening. The increasing $Z$ in the later part of the night will approach the course of Process C at an acute angle, which will result in a relatively imprecise timing of sleep termination, considerably dependent on fluctuations in $Z$ and $C$. Therefore, the functional suitability of Process Z in the regulation of sleep timing is limited, which fact furnishes an additional argument for the separation of the classical sleep need regulating Process S of the original two-process model from the purely SWA-related Process Z.

This conclusion cannot be definitive as long as we do not have direct assessments of the rise rates in wakefulness. Nonetheless, the clear differentiation of the gain constant over different cortical areas must mean that attributing a role in predicting sleep timing to SWA can only yield global predictions since there is no independent evidence for the specific involvement of particular cortical areas in the timing process.

5.5 Acknowledgments

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