15. Effect of Physical Activity on the Circadian System in the Elderly

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Circadian rhythms, i.e. temporal variations with a period of approximately 24 hours, occur in several biological parameters, e.g. temperature, hormones and sleep-wakefulness and are involved in adaptation to the environmental periodicity [55]. The suprachiasmatic nucleus (SCN) in the hypothalamus is considered to function as the biological clock. With aging, morphological changes in the SCN are likely to have implications for functionality of the circadian timing system [36, 52]. In addition to the changes in the SCN itself, the strength of the environmental input signals received by the clock, the so called ‘Zeitgebers’, may decrease with aging. Elderly expose themselves, e.g. to less environmental light [12] and have, in addition, a lowered sensitivity of the eye to light [4]. Consequently the input the SCN receives from environmental light, the most important ‘Zeitgeber’ is less. It has recently been shown that the reduced circadian sleep-wake rhythm amplitude in aged rats can be restored to the level of young rats by means of increased environmental light [62]. In human studies, environmental light has shown to improve circadian rhythms in healthy elderly [13] and demented elderly [40].

In animal studies, physical activity level has shown to be another important modulator of circadian rhythms [61]. In human, several studies indicate a decrease in activity level with age (e.g. [18]) but, surprisingly, the effect of the activity level on the circadian amplitude in the elderly has not been evaluated. Most of the evaluated effects of exercise concern either day-time functioning or night-time sleep efficiency. In the present paper, it is argued that the day- and night-time effects reported in literature can parsimoniously be described as mediated by an enhancement of a circadian arousal amplitude. A model is put forward, proposing that the circadian circuity in the elderly is less sensitive to environmental input and in addition receives a reduced amount of input, resulting in a decreased circadian amplitude. This flattening of the circadian rhythm is reflected in suboptimal functioning during both day and night. Accurately timed increase in exercise, may boost the circadian amplitude and protect the circadian circuitry from deterioration, and thereby contribute to the well-being of the elderly. The aim of this paper is to evaluate only the effect of the activity level on the circadian amplitude in the elderly; other methods (e.g. photo therapy, increased social contacts, warm baths) have been proposed but will be reviewed elsewhere.

Circadian System and Its Physiological Changes with Aging

Many physiological and behavioural phenomena, including rest-activity, sleep-wakefulness, body temperature and levels of hormones show a marked circadian (i.e. ± 24 hour) rhythmicity (for a review see [1]). Such a rhythm is usually described with three parameters, i.e. period, amplitude and phase. The proper synchronisation of several circadian rhythms to each other and to the
environmental light-dark cycle appears to contribute to the well-being of man: desynchronisation of rhythms has been demonstrated in affective disorders, night shift work and jet lag [17]. The hypothalamic suprachiasmatic nucleus (SCN) is of crucial importance in the generation and synchronisation of circadian rhythms [38]. The SCN is capable of generating near 24 hour rhythms in the absence of environmental clues, i.e. in vitro [9, 38] and is therefore called a ‘circadian pacemaker’. With the aid of environmental clues, among which light is of major importance, the SCN synchronises the rhythms exactly to the 24 hour day, a mechanism referred to as ‘entrainment’ [38]. In man, the daily routine of social contacts, activity and meals are thought to contribute to the entrainment [60]. Of the inputs the SCN receives, the pathway of environmental light is best described. The SCN receives information about the environmental light-dark cycle by a direct retinohypothalamic projection and through an indirect retina-intergeniculate leaflet-hypothalamus projection. In addition to these projections the SCN receives inputs from other nuclei within the hypothalamus, the limbic forebrain, the reticular formation and the hormonal milieu [38]. Within the SCN oscillatory mechanisms have been described (cf. [35, 38]). The SCN efferents project predominantly to other nuclei within the hypothalamus [38].

Several findings indicate deterioration of the circadian circuitry with aging. On the input side, the sensitivity of the eye to light declines with age, most markedly after the age of 60 [4]. In addition a decreased ultraviolet transmission through the ocular media with aging has been reported [7]. The information processing and rhythm generating part of the circadian circuitry, the SCN, shows a decrease in its size and number of cells expressing vasopressin, one of its major neurotransmitters, in subjects over 80 years old [52]. In the rat SCN the number of vasopressin and vasoactive intestinal polypeptide (VIP) expressing neurons decrease with aging [15, 45]. Several animal and human studies have looked at age-related changes in the output of the circadian system. The most prominent generally reported change is an overall reduction in the amplitudes of behavioural and physiological parameters. Amongst others, cortisol and melatonin, body temperature, sleep-wakefulness and rest-activity, may all show lower circadian amplitudes in the elderly [16, 36, 44, 54, 58]. In addition, for some parameters a shortening of the period and a phase advance in comparison with the light-dark cycle has been reported, which corresponds with earlier customary bedtimes and wake times [16, 44].

However, cognitive and electroencephalographic (EEG) parameters have to our knowledge not been assessed in any circadian rhythm study in the elderly. Some indication on the possible effect of aging on the circadian rhythms of these parameters may be derived by comparing publications addressing the effect of aging on either day time or night time measurements. In day-time EEG studies the elderly show a shift towards lower frequencies of the resting EEG, while sleep studies report a decrease in the lower frequencies [48, 49]. In EEG studies, wakefulness or arousal is associated with high frequencies, while sleep or rest is associated with low frequencies. Thus, the
combination of both sets of studies suggests a reduced circadian amplitude in EEG slow wave activity. A similar effect is found in task performance. Cognitive task performance has a circadian rhythm that parallels the temperature rhythm [30, 55]. The performance on several cognitive tasks given during the day worsens with aging but, interestingly, if subjects are awakened during the night, task performance is relatively better in the elderly and even more so in elderly insomniacs [8]. The lack of decrease in task performance after night-time awakening as compared to day-time performance was paralleled by a lowered arousal threshold and a reduced temperature drop during the night, suggestive of a damped circadian rhythm [8].

Phase, period and amplitude of circadian rhythms are undoubtedly effectively influenced by light as an environmental factor, as was shown in many animal and human studies (cf. [1, 17]). However, also the level of physical activity, an input to the circadian clock that in the present paper is considered to be an environmental stimulus, was found to affect the circadian rhythm amplitude in animal studies (e.g. [61]). Human studies have however, so far almost exclusively evaluated the effect of day-time activity on either day-time functioning or night-time sleep. In the present paper, the effect of activity will be evaluated mostly for day- and night-time functioning separately. In the final section an attempt is made to integrate the day- and night-time effects of activity within the framework of a circadian model. It is proposed that day- and night-time effects are at least partially controlled by the same underlying circadian oscillating mechanism.

Physical Activity and Aging

Activity in aging. Several studies report a decrease in day-time activity with aging (cf. [18, 56]). Also, the maximal oxygen uptake \( (\text{VO}_2\text{max}) \), a measure for physical capacity, declines from the age of 25 years on with approximately 1% per year and even faster in sedentary individuals (cf. [51]). However, the physical capacity does not decrease in every individual to the same degree as the between subject variability in motor performance also increases [50].

General health effects of physical activity. Exercise has been found to improve body functions; amongst others it normalises hypertension, reduces cardiac abnormalities and improves joint mobility, musculature, body composition and respiration [18, 25].

Effect of activity on day-time functioning. In addition to improved body functions several cognitive and behavioural effects of activity have been reported (cf. [18, 50]). Exercise may also alleviate depression and anxiety (cf. [32]).

With respect to the elderly, Baylor and Spirduso [2] found that the older women who are regularly engaged in aerobic exercise had shorter reaction times than sedentary older women. Bashore [3] concludes in a review that
reaction time is sensitive to activity level in the elderly, but not in young subjects, which may be interpreted as a ceiling effect. He concludes that the gain in reaction time is in premotor time rather than in actual contraction time, i.e. more on the central than on the peripheral level, as was previously suggested by other authors (e.g. [20]). Moreover, he stresses the point that effects are generally found only after a fitness program of sufficient vigour and duration to produce meaningful gains in fitness level. With respect to this, Blumenthal et al [6] reported a ceiling effect for the effect of exercise on psychological functioning if only healthy, highly educated and highly motivated elderly are selected. Dustmann et al [20] found that exercise improved the scores of elderly in a neuropsychological test battery. Shay and Roth [47] report better neurocognitive performance, especially visuospatial processing, in highly fit elderly. Dustmann et al [21] reviewed the effects of exercise on several tasks in the elderly and concludes that a general increase in response speed and cognitive and visual performance takes place. Furthermore, Dustmann et al [22] evaluated differences between highly fit and unfit young and elderly subjects on several EEG, ERP, cognition and stimulus sensitivity parameters. Interestingly, measures that indicated deterioration in the elderly as compared to the young were also lowered in unfit as compared to the highly fit.

Effect of activity on sleep. Positive effects of exercise on objective and subjective sleep quality have frequently been reported in young adults. A reverse effect, disruption of sleep by forced inhibition of activity has also been reported (cf. [28]). A positive effect was reported by Matsumoto et al [34], who found an increase in slow wave sleep, which was most pronounced in the second sleep cycle, after a whole day of exercise. Bunnell et al [10] reported a similar increase in slow wave sleep in the beginning of the night, and also showed a reduced night-time cortisol excretion. As cortisol has it's circadian trough during the night, this may be interpreted as an enhanced circadian cortisol rhythm. On the other hand, Paxton et al [41] could not find any effects of exercise on the amount of slow wave sleep, but concludes from reviewing previous studies that more extreme levels of exercise may be needed before effects can be detected. In later studies [37, 42] this group found that an athletic lifestyle, rather than fitness, was associated with shorter sleep onset latencies, more slow wave sleep and longer sleep. Athletic subjects that had become unfit because of a temporary abstinence from sports had an increased amount of slow wave sleep and a shorter sleep latency than non-athletes. This difference did not increase after they started training again. With respect to the elderly, we are aware of only two studies in relation to sleep and activity. Vitiello et al [59] found that elderly report improved subjective sleep quality after a six month period of exercise. Edinger et al [23] studied the effect of acute exercise in sedentary versus aerobically fit elderly and found that the fit group had more slow wave sleep, but that acute exercise did not affect the amount of slow wave sleep in either fit or unfit elderly. Several conclusions can be made from reviewing the literature. First,
that the most prominent effect of exercise on sleep is an increase in the amount of slow wave sleep, which is associated with depth of sleep. Second, that the effects may depend on the timing, type and intensity of the exercise, as well as on the physical condition of the subject. Third, exercise may have distinctive instantaneous and long-term effects. Fourth, as in most reports young adults were studied, and effects were more likely after extreme levels of exercise, ceiling effects are likely if nor sleep neither fitness is far from optimal. The effect of exercise on sleep might be more pronounced in people with sleep problems. However, studies of exercise effects on the sleep of insomniacs have, to our knowledge, not been undertaken.

Effect of activity on circadian parameters. To our knowledge, no one systematically studied the effect of activity on circadian parameters in the elderly. However, young adult and animal studies do indicate that activity influences circadian rhythms. Schmidt et al [46] report that activity accelerates the rate of re-entrainment of the circadian body temperature rhythm after a phase shift in man. Hamsters also accelerate their rhythm resetting after an enforced phase shift, but Van Reeth et al [57] report that aged hamsters are less sensitive to this activity-induced phase resetting, without being significantly less active. With respect to the shortened circadian period in the elderly (cf. [55]), a recent study on the circadian rest-activity rhythm in young and middle aged hamsters by Gnaedinger and Rosenberg [26] is of interest. They found that the period of the rhythm was influenced by the level of activity, but in a different way for young and older hamsters: whereas higher levels of activity tended to shorten the circadian period in young animals, it lengthened the period in old animals. A similar effect in aged human might counteract the decrease in circadian period (cf. [55]). Paxton et al [43] studied the effect of exercise on hormone secretion. Although they reported non significant effects on peak and area-under-the-curve measures, the graphs indicate that significant effects would likely have been found with time series analysis. Both the growth hormone and cortisol curves indicate an increased amplitude in their circadian rhythm in fit athletes as compared to unfit non-athletes. In conclusion, although to our knowledge the effect of activity on circadian parameters in the elderly has not yet been studied, young adult human studies as well as animal experiments suggest that the amplitude and period length might increase, i.e. normalise, after exercise. However, exercise might be less effective in the elderly having problems with phase shifting, as occurs in jet lag or night shift.

Hypotheses on the mechanism of day- or night-time improvements after the exercise. Several authors have hypothesised on the mechanisms behind the improvements in day-time and night-time functioning with increased activity level. With respect to day-time functioning, the ‘health mediation’ model states that an age-related decrease in activity leads to a decline in health which, in turn, results in decrements in both physical and psychological
performance. However, this model cannot account for the observed lack of correlation between the effectivity of fitness on general health and on performance in the elderly [5, 31]. In a ‘genetic’ model, it has been argued that genetic background may predispose to both optimal brain functioning and a lifestyle with regular exercise. However, the idea that both fitness level and day-time functioning result from an underlying genetic disposition, is not supported by experiments in which trained rats had faster response times than their genetically identical untrained siblings (cf. [21]). Also, long-term studies that report improvements in sleep and performance after exercise argue against an underlying genetic disposition [22]. Another hypothesis (cf. [21]) suggested that fitness effects on day-time functioning might be due to improved oxygen transport and utilisation, resulting in a more efficient functioning of neurotransmitter systems. In rats, exercise has indeed been found to raise levels of dopamine, norepinephrine and serotonin (cf. [21]). Still, the oxygen hypothesis cannot explain the threshold effect: a gradual increase in the amount of exercise does not gradually improve day-time functioning, but rather a threshold in vigour or regularity of exercise should be reached before improvements occur.

With respect to sleep, Horne [29] reviewed the literature on the influence of exercise on sleep and concluded a similar threshold effect. To interpret this threshold effect, he put forward the hypothesis that an increase in deep body temperature might mediate the effect of exercise on sleep. Exercise in a cold environment, exercise of a low intensity and exercise by unfit people do not effectively increase deep body temperature and do not affect slow wave sleep. Deep body temperature is raised only with high levels of exercise, unlikely to be reached by unfit subjects. This hypothesis is supported by the fact that passive body heating, by means of hot baths taken at appropriate times, may increase slow wave sleep in a similar way [29]. Hot baths and exercise are both most beneficial for sleep when applied in the late afternoon (cf. [14]), when they increase the peak in the circadian body temperature occurring in the afternoon. Horne [29] suggests that the effect of an increase in deep body temperature on sleep might be mediated by prostaglandin D2, a sleep inducing substance sensitive to tissue heating (see also [39]). Although this model explains most of the contradictory findings in studies on the effect of exercise on sleep, it does not explain Horne’s earlier finding that prolonged increases in daytime brain work can have the same sleep enhancing effect, while the temperature is not affected.

Circadian Amplitude as Mediating Variable
The hypothesis we want to put forward is that the beneficial effects of activity on sleep- and wake-parameters are at least partially mediated by the same mechanism: enhancement of the circadian amplitude by stimulation of the SCN. There are several arguments for assuming the presence of a common mediating variable and, more specifically, a mediating variable of an oscillatory kind.
First, enhancement of an oscillator is a parsimonious way of describing two opposite effects of the same treatment: exercise enhances sleep and wakefulness, i.e. is both activating and deactivating. This opposite effect has been noted by De Vries [18], who summarised exercise as effectuating “a more vigorous individual who can also relax better”. Second, a treatment causing disturbance of the circadian rhythm induces cognitive impairment [19, 24]. Furthermore, the hypothesis is supported by the finding that the circumstances determining the effectiveness of exercise on sleep- and on wake-parameters are identical. Both sleep and wakefulness show the same threshold phenomenon: improvement is achieved only with high levels of exercise or in physically fit subjects [20, 21, 33, 47].

We propose that two mechanisms are involved in exercise-enhanced circadian functioning. First, the mechanism that Horne [29] proposed to mediate the acute effect of exercise on sleep should be extended to both day-time and night-time. Vigorous exercise raises the deep body temperature and thus, when appropriately timed, increases the circadian temperature amplitude. With respect to this, Johnson et al [30] have recently shown in young adults that cognitive task performance has a circadian rhythm that parallels the temperature rhythm, and several authors have indicated that circadian rhythm dampening may underly sleep complaints in the elderly (e.g. [16]). Thus, we suggest that an acute increase in the amplitude of the circadian temperature rhythm is accompanied by improvements in day-time functioning and night-time sleep. In this view it is interesting that it has recently been suggested that an increase in the deep body temperature may also play a role in the enhancement of sleep after exposure to bright daylight, the most important modulator of circadian rhythms [11].

We propose that a second mechanism is involved in the enhanced circadian amplitude in the physically fit, even when they are momentary abstaining from exercise [42]. A repeated increase in the circadian amplitude, as occurs in frequently exercising subjects, may protect the circadian neuronal circuitry from age-related deterioration. This theory, that has been paraphrased as ‘Use it or lose it’ [53], states that activation of nerve cells within the physiological range prevents their degeneration and may even restore their function in aging and neurodegenerative disease. According to Swaab [53], activation can be accomplished, depending on the neural system involved, by internal stimuli like hormones, growth factors and transmitters or by environmental stimuli, such as light for the SCN. A repeated increase in circadian temperature amplitude or enhanced synaptic input by exercise may thus also positively affect the SCN. Based on the ‘use it or lose it’ model, exercise may also be important for the protection of other parts of the brain from deterioration. Vigorous motor activity is accompanied by increased amounts of sensory and proprioceptive stimuli [61], and thus generally arousing, which, in the ‘use it or lose it’ model, could spare brain areas involved in arousal regulation. This possibility is supported by the fact that exercise has been shown to increase stimulus sensitivity (cf. [3]). Thus, exercise may
counteract the decrements in the visual, auditory, kinaesthetic, somatosensory and vestibular sensory systems that have been described in the elderly [48]. In conclusion, exercise is hypothesised to activate the SCN by increased synaptic input or by boosting the circadian temperature amplitude.

To our knowledge, no studies simultaneously investigating the effect of exercise on both day-time and night-time parameters in the elderly have been performed. Although some studies report a lack of correlation between day-time and night-time parameters under non-experimental conditions in healthy subjects [27, 49], which is likely to reflect constitutional inter-individual variance, we expect that the amount of change after appropriate exercise will in fact become more obvious when studied over the entire day/night cycle. Therefore, we are presently studying the effect of aerobic exercise in elderly men on day-time performance, night-time sleep and circadian rest-activity patterns. In this experimental set-up, the contribution of an enhanced circadian rhythm as a mediating variable for several cognitive and sleep effects will be evaluated. It is hypothesised that positive effects of exercise on several sleep and cognition parameters will not be scattered over individuals but rather that effects will be coupled i.e. elderly showing most profit from exercise on sleep parameters will also show more prominent changes on the cognitive parameters. Our preliminary results indicate that fitness improvement after a three month training period in elderly men is accompanied by: (a) better sleep, i.e. less awakenings after sleep onset and more slow wave sleep; (b) better day-time functioning, i.e. increased vigilance, decreased reaction times, less errors in task performance and shortened P300 latencies in an event related potential paradigm; (c) less fragmentation in the circadian rest-activity rhythm. These preliminary data support our idea that physical activity might improve the functioning of the circadian system, and thus brain function in general, in the elderly.

Acknowledgements

References

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