

Sleep research, sleep medicine...

*...and the European Sleep
Research Society...*

Modern sleep research started in the 1930s and 1940s with the use of the electroencephalogram (EEG) – for the first time in humans – by H Berger in Germany to measure wakefulness and sleep, and by the observation by the Nobel laureate W R Hess in Switzerland that sleep can be induced in animals by the stimulation of a specific brain area, proving sleep as an active process of the brain.

Modern sleep medicine followed the discovery of the EEG and the recognition of different sleep stages, including the so-called REM sleep (characterised by Rapid Eye Movements, dreaming activity and physiological muscle paralysis/ atonia) first described in 1953 in the US. Centres for sleep medicine were founded in France, the Czech Republic, Italy and Germany in the late 1950s and 1960s. Such sleep disorders as narcolepsy, sleep apnea, and restless legs syndrome were discovered first in Europe.

The European Sleep Research Society (ESRS) was founded in 1972 ‘to promote interest in, and to facilitate the dissemination information about sleep research and related topics’. The ESRS now counts almost 1,000 full members and over 5,000 associated members who come from such different areas as neuroscience, physiology, pulmonary medicine, neurology, psychiatry, and psychology. This diversity of approaches and perspectives offers a unique opportunity for fruitful interactions and for a translational approach between basic and clinical disciplines. In that sense, the ESRS, as the entire field of sleep, ideally exemplifies the needs and opportunities of multidisciplinary approach in science and medicine.



The ESRS Board Members and the Presidents of National Sleep Societies of over 20 European countries during their meeting in Valencia, Spain, 1st May 2009

The Journal of Sleep Research is the official scientific organ of the ESRS, which organise biannually a scientific meeting.

The biology of sleep

Following the recognition of sleep as an active process of the brain (to be differentiated from anaesthesia and coma) and the existence of different sleep stages, research embarked in the elucidation of the mechanisms underlying sleep generation and regulation. Specific brain areas in the brainstem and in the so-called diencephalon were found to be essential for a normal sleep-wake cycle. Furthermore, the appearance of sleep and wakefulness was shown to reflect the interaction between two distinct regulative mechanisms, one dependent from the duration of wakefulness (homeostatic regulation) and the other one from the variation over the 24 hours of the activity of an ‘inner clock’ (circadian regulation).

More recently, it was also found that a genetic component (eg. the clock

gene PER3) partially determines an individual’s response to sleep loss and individual resistance to the accumulation of sleep pressure throughout the day. Functional investigations have yielded further evidence that cognitive performance and underlying cerebral activity differ mostly between morning and evening chronotypes under conditions of elevated sleep pressure. Additionally, homeostatic markers of sleep pressure have been shown to modulate activity in core cerebral structures for circadian regulation, demonstrating both in animal and human the interactive nature of circadian and sleep homeostasis processes.

The biological function of sleep remains a matter of debate. Besides a restorative function, it is now suggested that sleep plays an important role in brain plasticity mechanisms and memory consolidation. Imaging studies have congruently revealed continued expression and modulation of learning-related cerebral activity during post-training sleep

stages, eventually leading to performance improvement overnight and long-term reorganisation of the cerebral underpinnings of stored memories. Others have evidenced a prominent role of slow wave sleep oscillations as well as phasic events (eg. sleep spindles) in brain plasticity.

Recent combinations of functional neuroimaging and EEG have contributed to delineate better sleep-wake processes and the way they are generated and regulated in the human brain.

Sleep research in Europe

At present, about 130 centres are active in the field of sleep research in 24 different European countries. Approximately one-third of these centres are established in France, Germany, and Italy.

In more than 50 centres, research activity is aimed at the widening of basic aspects of sleep science. In about 50% of these labs, studies are directly carried out on humans, while animal models are used in the others. Basic sleep researchers in Europe are traditionally active in the study of the neurophysiologic, molecular and genetic determinants of regulatory processes underlying sleep occurrence, the relationship between sleep and cardio-respiratory, endocrine, metabolic, and thermoregulatory functions, the relationship between sleep and circadian rhythms, and the effects of sleep loss on vigilance and cognitive functions.

About 80 centres are active in the field of clinical sleep research, mainly in neurology, psychiatry, pulmonary medicine and paediatrics. Research activity deals with the whole spectrum of topics related to sleep pathology and sleep-related disorders from childhood to old age, in particular: insomnia, narcolepsy, sleep-disordered breathing, and movement disorders in sleep. Furthermore, the association between sleep and either psychiatric or neurological disorders, like Parkinson, stroke and epilepsy, is fruitfully approached.

Specific taskforces have been established by the ESRS that are aimed at improving the impact of research activity at a European level on the majority of the topics listed above.

Sleep medicine and sleep education in Europe

Over the past decades, sleep medicine has developed from a medico-scientific niche into a full-grown discipline, grounded in science, and worthy of respect and attention of the entire medical enterprise. The rapid expansion of its professional content has brought about a significant change in clinical practice, which now concentrates more on fundamentals of sleep pathology and is oriented towards multidisciplinary patient care. The year 2005 has been pivotal in this respect, as sleep medicine became an independent specialty in the USA. In the same year, sleep medicine was granted the status of a formally accredited medical subspecialty by the Chamber of Physicians in Germany.

For many years the ESRS has fostered the development of clinical sleep medicine. In 2004, a Committee was founded that interacted with European National Sleep Societies (ENSS) to create a framework from which new impetus could be given to guidelines in the field. In 2006, the ESRS issued European guidelines on accreditation of sleep medicine centres, and in 2009, European guidelines on certification of sleep professionals were published. Both landmark documents appeared in the *Journal of Sleep Research*. Through the ESRS Sleep Medicine and Educational Committees, efforts are being made to establish a curriculum for professionals in this specialty field.

The ESRS organises an annual sleep training course, which is sponsored by the EU. In 2007, the ESRS has been financed by the European Union within the frame of the FP6 'Marie Curie' programme for a four-year project entitled 'Training in

Sleep Research and Sleep Medicine'. This programme, which involves 160 young trainees, consists of annual teaching courses and practical training periods in different sleep research/medicine centres around Europe.

Teaching and training courses organised by ENSS are also endorsed by the ESRS. This endeavour aims at formalising the field and to help other countries in Europe in the achievement of official recognition for sleep medicine as a specialty field.

Sleep disorders: frequent, relevant, treatable...often neglected

Sleep disorders are very common (>10% of the population) and their frequency generally increases with age. Sleep disorders can have profound effects on daytime functioning, quality of life but also on the risk of cardiovascular disorders and mental health. Furthermore, sleep disorders may represent the first symptom of an underlying medical disorder such as depression or Parkinson's. The presence of sleep disorders may affect also the course of other medical conditions such as headache, epilepsy, and stroke. Finally, sleep disturbances and sleep loss are a frequent cause of driving accidents.

Patients with sleep disorders can present with complaints of poor sleep (insomnias), excessive daytime sleepiness (hypersomnias), and undesired events during sleep (parasomnias, such as sleepwalking and violent behaviours in sleep). Several causes – sometimes in combination – including psychiatric, medical and neurological disorders but also medications, illicit drugs, alcohol can lead to similar sleep problems. Sometimes a specific cause for a sleep disorder cannot be found: in such cases, genetic but also psychosocial factors may play an important role.

Sleep disorders should be managed first by General Practitioners. The

absence of a curriculum in sleep and sleep disorders in many (if not most) European countries prevents, however, an adequate education of medical professionals. This lack of awareness and teaching contrasts not only with frequency and relevance, but also with good diagnostic and treatment possibilities of sleep disorders.

In trained hands, most sleep disorders can in fact be accurately diagnosed and well managed without the need for expensive investigations in specialised sleep centres. In selected cases, such investigations are, however, needed for proper diagnosis.

A variety of treatment options are available for patients with sleep disorders. The correct and skilled use of hypnotics, dopaminergic agents, antidepressants, melatonin, behavioural treatment, changes in sleep habits, devices delivering a positive pressure in the upper airways during sleep will eventually improve their condition.

Insomnia: affects 15% of the population, predicts depression and causes dramatic health costs

Insomnia is one of the most frequent subjective complaints, affecting chronically 10-15% of the population and causing 15% of GP consultations in Germany. Impaired sleep initiation and maintenance persisting for at least four weeks define insomnia and are a hallmark of numerous psychiatric disorders, frequently occur in many medical conditions and may constitute a disorder called primary insomnia. Insomnia has a prominent negative effect on quality of life and induces dramatic health cost. In addition, patients with longstanding sleep problems are particularly prone to depression and recent research suggests that reduced sleep quality and quantity might increase physical health risks. Particularly obesity and diabetes seem to be linked to persisted sleep disturbances. The increasing demands on individuals and more and more flexible schedules of private activities and work, including

shift work, are prominent challenges for the sleep regulation brain networks resulting in a '24-hour society' in vigilance and performance problems potentially leading to lapses of attention, which sometimes may have dramatic consequences (eg. the Exxon Valdez catastrophe).

Obstructive Sleep Apnea (OSA): a cause of daytime sleepiness and a risk factor for arterial hypertension, stroke and cardiac disorders

OSA is defined by symptoms such as excessive daytime sleepiness and daytime functioning impairment, with more than five obstructive events per hour occurring during sleep. The prevalence of the disease is very high ranging from 5 to 15%, increasing linearly up to 60 years old. Regarding OSA morbidity, there is now substantial evidence that there is a causal relationship between OSA and Excessive Daytime Sleepiness, with cognitive impairment, including increased risk of traffic accidents, and cardiovascular morbidity and mortality. The cardiovascular consequences seem to appear early in the disease, eg. occurrence of atherosclerosis without significant classical cardiovascular risks during OSA. A more recent field of research is the metabolic impact of OSA. In the general population, OSA is associated with glucose intolerance. OSA severity is also associated with the degree of insulin resistance. Prevalence of the Metabolic Syndrome is higher in patients with OSA than in obese subjects without OSA. Treatment with continuous positive airway pressure (CPAP) seems to improve glucose metabolism both in diabetic and non-diabetic OSA but mainly in non-obese subjects.

The cellular and molecular mechanisms of the cardiovascular consequences as well as the relative role of obesity and OSA in the pathogenesis of metabolic alterations are still largely unknown. Both are intensively studied in clinical and experimental models. Although most of

the general population cohorts come from the US, many pathophysiological studies and most interventional studies have been conducted in Europe.

Restless legs syndrome (RLS): one of the most common neurological disorders

RLS is characterised by sensory discomfort localised in the extremities, which leads to an urge to move them, and which appears at rest and in the evening hours. RLS can be a cause of chronic insomnia and often reduces severely the sleep and life quality of affected patients. RLS affects 5-15% of the general population but is even more frequent in pregnant women, and patients with iron deficiency and renal failure. The diagnosis is usually made on clinical grounds. Treatment with dopaminergic drugs is effective in a few days in most patients.

Restless legs together with narcolepsy are a sleep disorder for which a genetic predisposition has been recognised. This offers new avenues for better understanding of the cause and future treatment of these conditions.



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