According to Jackson’s sleep-cognition hypothesis (1932), which postulates that cognitive deficits might be associated with alterations in sleep mechanisms and structure, several studies were carried out on sleep patterns of subjects with mental retardation of different etiologies (Pétre-Quadens & Jouvet, 1966; Pétre-Quadens, 1969; Castaldo & Krynicki, 1973, 1974; Grubar, 1983). The main findings of such studies were a reduction in percentage of rapid eye movement (REM) sleep and a prolonged latency of the first REM period in individuals with a mental handicap. Based also on the observation that, in animals, REM sleep percentage increases after intensive learning sessions (McGrath & Cohen, 1978; Mirmiran, van den Dungen, & Uylings, 1982) the hypothesis that REM sleep is involved in cognitive processes was postulated and REM sleep itself was indicated as an index of brain “plasticity” - i.e. the ability of the brain to retain information.

When REMs were considered, it was observed that patients with mental retardation also show a significant reduction in REMs separated by short intervals.
time intervals (< 1 sec) (Grubar, 1983). High-frequency REMs show a marked increase with age (Pétre-Quadens, 1980) and increase after training (Spreux, Lambert, Chevalier, Meriaux, Freixa et al., 1982). For these reasons, they were considered as an index of the brain “organizational” abilities - i.e., the ability to organize information from a random pool of elements into long-term memory.

**Sleep and Down syndrome**

Similarly to other groups of individuals with mental retardation, patients with Down syndrome show a significant reduction in the percentage of REM sleep (probably more evident in the most severely retarded subjects), a marked delay in first REM latency and a statistically significant decrease in high-frequency REMs during REM sleep (Colognola et al., 1988). In order to study the mechanisms of such a reduction in REM percentage, the effects of the administration of a drug, butoctamide hydrogen succinate (BAHS) an organic compound found in cerebrospinal fluid of normal subjects (Yanagisawa & Yoshikawa, 1973), on the sleep patterns of subjects with Down syndrome were repeatedly evaluated in different experimental protocols (Gigli, Bergonzi, Grubar, Colognola, Amata, et al., 1985; Gigli, Grubar, Colognola, Amata, Pollicina, et al., 1987; Grubar, Gigli, Colognola, Ferri, Musumeci, et al., 1985; Grubar, Gigli, Colognola, Ferri, Musumeci, et al., 1986). BAHS was able to increase the amount REM sleep in subjects with Down syndrome, similar to its effects in normal controls and in animals; however, high-frequency REMs were unaffected by the administration of this substance. On the other hand, intensive learning sessions were able to increase the ratio between high-frequency and low-frequency REMs but did not affect REM percentage (Gigli et al., 1985; Gigli et al., 1987). These results supported the basic hypothesis that the percentage of REM sleep in humans can be considered as an index of brain “plasticity” (reduced in the elderly and in children with mental retardation) and that the high-frequency REMs can represent an index of the brain ability to organize information (also involved in individuals with mental retardation) (Gigli et al., 1987). At the same time, such studies gave a neurophysiological basis to a psychopedagogical approach for the treatment of learning and memory disabilities in Down syndrome.

**Down syndrome and growth hormone production during sleep**

It is well known that, in normal subjects, growth hormone (GH) is released during sleep in a pulsatile pattern with peaks during slow-wave sleep (SWS) (Takahashi, Kipnis, & Daughaday, 1968; Van Cauter et al., 1992) and this mechanism seems to be mediated by hypothalamic neurons located around the ventral-medial nucleus projecting to the preoptic region (Sawchenco, Swanson, Rivier, & Vale, 1985).

The mean height of adults with Down syndrome is below 3 standard deviations of the mean for normal subjects, both in males and females (Penrose & Smith, 1966) and a dysfunction of GH production during sleep is strongly suspected in Down syndrome (Castells, Torrado, Bastian, & Wisniewski, 1992). Given the above sleep alterations, the relationships between sleep structure and GH production in a group of children with Down syndrome were studied (Ferri et al., 1996) and it was demonstrated that they show a clearly decreased peak amplitude of GH; however, a certain pulsatility was evident in all patients but synchrony with SWS was poor. Thus, it can be concluded that, if evaluated during sleep, GH release in Down syndrome often shows abnormalities.

Additionally, it should be considered that many subjects with Down syndrome have been reported to present obstructive sleep apnea (Marcus, Keens, Bautista, von Pechmann, & Davidson Ward, 1991) and that GH release is known to be reduced in children with this sleep disorder, probably because of the consequent sleep fragmentation, and it becomes normal if an effective treatment of apnea is started (Grunstein, Stewart, & Sullivan, 1992; Matsumoto, Sandblom, Schoene, Lee, Giblin, et al., 1985). Moreover, children with sleep apnea show short stature which can be corrected by treatment of the apnea (Broulliette, Fernbach, & Hunt, 1982; Goldstein, Wu, Thorpy, Shprintzen, Marion, et al., 1987).

**Sleep apnea in Down syndrome**

There have been many reports of obstructive sleep apnea (OSA) episodes occurring in patients with Down syndrome; in particular, Southall et al. (1987) found, in their group of 12 infants and young children with Down syndrome, that 50% of them were affected by OSAs. Marcus et al. (1991) reported that all of their overnight polysomnographic studies, performed in 16 patients with Down syndrome, were abnormal for the presence of OSAs in 63%, hypoventilation in 81%, and oxygen desaturation in 56%; Stebbens et al. (1991) reported OSAs in 10 of their 32 subjects with Down syndrome.

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However, there were no data on respiratory patterns of subjects with Down syndrome without obvious risk factors for OSA; thus, in order to evaluate the eventual effects of CNS impairment on respiration in Down syndrome, the respiratory patterns during sleep of a group of 10 subjects with Down syndrome, aged 8.6-32.2 years, without relevant upper airway pathology were studied (Ferri, Curzi-Dascalova, Del Gracco, Elia, Musumeci, et al., 1997). The possible effects of sleep pattern and mental retardation on the results obtained were controlled by comparing data from Down syndrome with those obtained from a group formed by subjects with fragile X syndrome (6 males and 1 female, aged 10.0-15.42 years), another genetically determined type of mental retardation. Sleep structure was similar in both groups; however, subjects with Down syndrome showed significantly higher values of central sleep apnea and of oxygen desaturation than fragile X patients.

In patients with Down syndrome a significant preponderance of central, as opposed to obstructive, sleep apneas was found which also showed a significant age-related increase. Central apneas were mostly preceded by sighs, occurred more frequently during sleep stages 1 and REM, and were often organized in long sequences of periodic breathing. Sleep structure was not significantly modified by apneas and oxygen desaturation. In this study, it was hypothesized that the increase in central sleep apneas is related to a dysfunction of central respiratory control at the brainstem level in Down syndrome (Ferri et al., 1997).

The brainstem is suspected to be the probable site of dysfunction because a deficit in brainstem inhibitory mechanisms has already been suggested in Down syndrome, as an explanation for the shortening of the central conduction time of brainstem auditory evoked potentials, usually observed in these subjects (Gigli et al., 1984). In addition, this peculiar feature becomes more evident with age in patients with Down syndrome (Ferri, Del Gracco, Elia, Musumeci, & Stefanini, 1995).

Moreover, taking into account the sleep structure alterations usually seen in Down syndrome, as seen above, because of the absence of correlation between apnea indices and REM sleep features in the above results, sleep apnea does not seem to be responsible for the decrease in REM sleep percentage and the increase in REM latency in such a group of patients with Down syndrome.

Heart rate variability during sleep in Down syndrome
In order to confirm a brainstem dysfunction causing central sleep apnea, heart rate variability during sleep in a group of 7 patients with Down syndrome (mean age 13.9 years) was evaluated and compared with the results obtained in a group of 6 normal controls (mean age 12.8 years). Heart rate is under control of efferent sympathetic and vagal activities directed to the sinus node which is modulated by central brainstem (vasomotor and respiratory centers) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators (Malliani, Pagani, Lombardi, & Cerutti, 1991). Spectral analysis of heart rate variability is a quantitative reliable method for analyzing the modulatory effects of neural mechanisms on the sinus node (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) and two main components are currently considered: vagal activity which is the major contributor to the high-frequency component while the low-

![Figure 1. Ratio between the low-frequency and the high-frequency components of the spectrum of heart rate variability during sleep in patients with DS and normal controls.](image-url)

- **W** = wakefulness, **S1** = sleep stage 1, **S2** = sleep stage 2, **SWS** = slow-wave sleep, **REM** = rapid eye movement sleep
frequency component is considered by some authors to be a marker of sympathetic modulation and by others as a parameter including both vagal and sympathetic influences.

The spectral analysis of heart rate variability during the different stages of sleep and during epochs with or without episodes of central sleep apnea was also performed (Ferri, Curzi-Dascalova, Del Gracco, Elia, Musumeci, et al., submitted). The comparison between patients with Down syndrome and normal controls carried out only on epochs without apnea showed a significant alteration of the ratio between the low-frequency and high-frequency components in Down syndrome in all sleep stages, with a statistical significance for sleep stage 1 and slow-wave sleep (Figure 1). The sympathetic-correlated low-frequency component was always higher in Down syndrome; on the other hand, the vagal-controlled high-frequency component was always lower in the same group. Also in this study, a low frequency of obstructive sleep apnea was found because subjects were selected with the same criteria of the previous investigation on central sleep apnea (Ferri et al., 1997). The presence of this type of apnea, in patients with Down syndrome, induced a further significant increase in low-frequency and very-low-frequency components of heart rate variability, similarly to the effects of the presence of OSA already described in the literature (Schiomi, Guilleminault, Sasanabe, Hirota, Maekawa, et al., 1996).

This final study is additional evidence for impaired brainstem function in Down syndrome which is demonstrated by abnormalities in brainstem auditory evoked potentials, abnormal presence of central sleep apnea and impaired balance between sympathetic and vagal control of heart rate variability during sleep.

Finally, the altered balance between the sympathetic and vagal systems can be viewed also in psychophysiological terms, following the ideas of the so-called “Polyvagal Theory” (Porges, 1995) which states that the vagal system does not represent a unitary dimension and is formed by two distinct motor systems. The first one is the “vegetative status” originating in the dorsal motor nucleus, associated with passive automatic regulation of visceral subdiaphragmatic functions, the second is the “smart vagus”, originating in the nucleus ambiguus (NA), associated with the active processes of attention, motion, emotion, and communication, with supradiaphragmatic target organs. Thus, the changes reported in the autonomic function of subjects with Down syndrome, together with the already reported changes in central control of respiration (Ferri et al., 1997), might be physiopathologically connected with the basic mechanisms of their developmental psychomotor problems. In this respect, there is a need of further research.

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