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SLEEP RESEARCH IN SPACE: EXPRESSION OF IMMEDIATE EARLY GENES IN FOREBRAIN STRUCTURES OF RATS DURING THE NASA NEUROLAB MISSION (STS-90)

C. CENTINI AND O. POMPEIANO

Dipartimento di Fisiologia Umana, Università di Pisa, Via San Zeno 31, I-56127, Pisa, Italy

INTRODUCTION

The amount and quality of sleep are significantly affected during the space flight. Most space crew members suffer from insomnia, fragmentation of sleep, fatigue, and alterations of the circadian pattern of the sleep/wake cycle (53, 58, 86, 95, 110, 151). The amount and quality of sleep in space are critical to the astronaut performance. Just a few hours of sleep loss significantly affect brain function, leading to sleepiness and transient cognitive impairment (75). Also chronic sleep restriction leads to cumulative sleepiness, mood disturbance, and performance decrements (44).

The most important factors affecting sleep quality in space appear to be ambient noise, unscheduled operational events, and dual-shift work. Some of the sleep problems due to misalignment of circadian rhythms have been partially corrected in recent space missions, for example by maintaining a 24 h-day based on earth time (29). However, it remains to be determined whether changes in the gravity force *per se* can affect sleep and its homeostatic regulation. A few studies performed in space by using polygraphic recordings seem to support this hypothesis (cf. 73 for ref.). For instance, Frost *et al.* (53) reported that microgravity can directly influence the percentage of slow-wave sleep (SWS) and of paradoxical sleep (PS) or rapid eye movement (REM) sleep (REMS). The number of REMS episodes increased during the first sleep period in microgravity, and it returned to normal levels by the second night (137). An increase in REMS time and a decrease in REMS latency consistently occurred also after return to 1 G (43, 53).

Recently, it has become clear that, in addition to patterns of electrical activity (71, 72, 83, 123, 124), several cellular and molecular variables are also correlated with behavioral states. Such variables include activity of receptors, G-proteins and second-messengers, protein phosphorylation state and most remarkably gene expression in the brain (18, 19, 22, 23, 120, 121). These genes can be grouped in functional categories, coding for example for transcription factors, metabolic enzymes, and growth factors suggesting that several basic cellular functions are affected during the sleep-waking state (23).

Immediate early genes (IEGs) are one of the first and largest groups of genes so far identified as differentially expressed between sleep and wakefulness. IEGs are so-called because they are rapidly induced by a large number of extracellular stimuli, without need for *de novo* protein synthesis. Among the IEGs, the most studied

is certainly *c-fos*, which is considered a marker of neuronal activity and genomic activation (25, 141). *c-fos*-mRNA levels increase after 20 min of stimulus onset, while the corresponding protein product, Fos, which is synthesized shortly thereafter, peaks within 2-4 hours after the stimulus, and returns to the baseline within 6-8 hours (14, 69, 104, 156).

c-Fos and other IEGs are transcriptional regulators (25, 70, 77, 104, 156) and may modulate the transcription of a number of "late" target genes.

Previous work performed in our (18, 19, 120, 121) and other laboratories (4, 59, 60, 92, 113, 114, 157) showed that *c-fos* expression is low or absent in most brain regions, if the animals had spent most of the previous 3-8 hours *asleep*. Fos expression increased during sleep in two hypothalamic areas, the ventrolateral preoptic area vlPOA (157) and the median preoptic nucleus, MnPN (57, 67), where GABAergic neurons are located. *c-Fos* levels are high in many areas of the cerebral cortex, hypothalamus, thalamus and brainstem of animals that had been either spontaneously *awake* or sleep deprived for a few hours before sacrifice (18, 19, 120, 121; cf. 22, 23). The brainstem areas included the noradrenergic locus coeruleus (LC). If sleep deprivation continues for longer periods, the expression of Fos is significantly reduced in most brain areas, but remains high in the vlPOA and the MnPN of the hypothalamus, where Fos levels are roughly proportional to the duration of sleep deprivation (up to 24 hrs, 119, 120).

If rats are allowed to go back to sleep after a long period of sleep deprivation, a significant sleep rebound is observed, mainly characterized by the occurrence of episodes of REMS (139). Rats submitted to 4-8 days of total sleep deprivation by Cirelli *et al.* (21) showed an increase in Fos expression which affected not only pontine and medullary reticular structures possibly involved in REMS, but also regions of the limbic system such as the cingulate, retrosplenial and entorhinal cortex, lateral septum, amygdala, supramammillary nucleus (SuM), dentate gyrus, CA1 region of the ventral hippocampus and the subiculum. In these experiments, however, stress might have partially contributed to the observed pattern of Fos expression. To avoid this condition, prolonged episodes of REMS could be induced following activation of specific neurochemical systems.

In particular, observations made in *cats* have shown that REMS episodes could be induced by microinjection either of the cholinergic agonist carbachol in the peri-LCα, the laterodorsal (LDT) and pedunculopontine nuclei (PPN) (145) or of GABA agonist in the periaqueductal gray (PAG) matter and adjacent areas (as shown by Sastre *et al.*, 152, 153, 153b). Similar results were also obtained after microinjections of the same agents in the homologous structures of *rat* (Boissard *et al.*, 8, 9), such as the SLD, sublaterodorsal nucleus and the PAG, as identified in the atlas of the rat brain (117, cf. also 163). It is of interest that in the experiments by Sastre *et al.*, originally published in 1998 (153), REMS episodes were associated with an increase in Fos expression which affected not only the latero-dorsal tegmental structures of the pons, but also most of the structures of the limbic system, a finding which was later confirmed in the rat during the REM episodes following prolonged periods of sleep deprivation (Cirelli *et al.*, 1999, 21). These structures involved the

supramammillary nucleus (SuM), lateral septum, hippocampus, amygdala and caudate nucleus, indicating that the rinencephalon and striatum are targets of the excitatory system originating in the pons. Observations made by Jouvet (83, 84) had previously reported that this ponto-limbic system may induce prominent REM-related theta activity in mammals (cf. 118).

The main aim of our study was to use IEG expression as a marker of behavioural state in order to see: 1) whether rats of the STS-90 NASA Neurolab Space Mission showed either a pattern of normal sleep/waking activity or a pattern of sleep deprivation during space flight, and 2) whether they showed signs of sleep rebound after return to 1G. However, during the mission it was impossible for technical reasons to sacrifice the animals shortly after launch or the re-entry. For this reason, in addition to Fos, we studied the expression of Fos-related antigens (FRA), another class of IEGs whose expression persists in cells for longer periods of time (98, 108, 109, 155; cf. 128). These genes could then play an important role to detect the occurrence of long-term adaptive changes in the brain under different conditions.

A preliminary report on the Fos expression findings has been previously published (129).

METHODS

We examined two groups of adult male albino rats (Fisher 344, n = 24/group): a flight (FLT) group and a ground control group. Control rats were maintained at 1 G under the same temperature (23 ± 1 °C) and light conditions as FLT rats, and were housed in small cages similar to those used for FLT rats (Asynchronous Ground Control [AGC] group) (128). FLT rats were sacrificed at four different time points of the space flight (128): 1) FD2 = flight day 2, i.e. 24 h after launch (n = 4), when the gravity force increased in about 9 min from 1 G to 3 G before stabilizing to ~0 G; 2) FD14 = flight day 14, anticipated by two days, i.e. 12 days after launch (n = 9), when adaptation to microgravity had occurred; 3) R + 1 = re-entry day 1, i.e. 24 hrs after landing (n = 5), when gravity force increased in about 28 min from ~0 G to 1.5-1.6 G, before stabilizing to 1 G; and 4) R + 13 = re-entry day 13, actually delayed by one day, i.e. 14 days after landing (n = 6), when readaptation to 1 G had occurred. Control animals were sacrificed at corresponding time points.

All animals were maintained in a 12h: 12h light-dark (LD) cycle, with the exception of those of the R + 13 group, which were submitted to a constant dim red-light (LL). Prior to sacrifice, 50% of FLT and AGC rats were exposed to a light pulse of 300 lux for 60 min (light pulse, LP rats), while the others were not (no light pulse, NLP rats). The number of Fos and FRA-positive cells was usually slightly higher in LP than in NLP group (128, cf. also 129), but with a similar pattern of expression in either AGC rats and FLT animals. The present work refers to data obtained by comparing FLT and AGC animals in NLP conditions.

FLT and ground control rats were implanted by Dr. Fuller group with a small biotelemetry unit, which allowed monitoring body temperature and heart rate continuously. The telemetry informations were particularly measured from LD animals (n = 6 at launch; n = 4 at landing; Dr. C.A. Fuller, personal communication). Dr. Fuller group examined Fos induction by LP in the suprachiasmatic nucleus (SCN), which is the circadian pacemaker. The conclusion of Dr. Fuller group was that FLT rats in LD remained synchronized with the LD cycle except for their body temperature rhythm, which was markedly phase-delayed (55). As to the motor activity, no particular effect was found at FD2 (Dr. C.A. Fuller, personal communication). However, after landing, motor activity virtually ceased for 30 min, and was attributed in part at least to stress (*arrest reaction* ref. 11; or

freezing reaction ref. 148). This finding was likely to be associated and/or followed by episodes of postural atonia typical of PS. Once activity finally resumed, it remained at a lower level than measured at FD14.

In the Neurolab mission, launch occurred 2 hours after light-off (i.e. early in the rat's active phase), and landing occurred very close to the light-off transition. This timing was chosen to not confuse changes induced by launch or landing with the normal increase of all variables during the rat's active phase. In addition, all animals were sacrificed within the first 6 hours of their active period.

The brains were removed from the skull and dissected. In particular, a retrocollicular transection between the forebrain and the brainstem was made either by crew members in flight at FD2 and FD14, or by NASA technicians trained on the ground by members of our team, at R + 1 and R + 13 and all controls. Figure 1 represents schematically the level of transection of flight (FLT) and control (AGC) rats sacrificed at the different time points of the space flight. Both the forebrain and the brainstem were placed in separate vials containing appropriate fixative and maintained at 4° (128).

Coronal sections 40 μm thick of the entire brain were cut on a cryostat and Fos and FRA protein expression were visualized on free-floating sections using standard immunocytochemistry protocols (128). A polyclonal antibody against Fos (1:10.000; Oncogene Research Products, Cambridge, MA, USA) and a polyclonal antibody against FRA (1:2.000, kindly provided by Dr. Iadarola, NIH, Bethesda, MD, USA) were used. Qualitative evaluation of the intensity of Fos and FRA staining was performed in brain structures identified following the Paxinos and Watson atlas (117). Animal care was provided by a veterinarian crew member in flight and by specialized personnel on ground. All animal procedures complied with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

RESULTS

1. Changes in Fos expression.

At **FD2**, both FLT and AGC rats showed a large number of labeled cells in several brain areas including most cortical areas, septum, and hippocampal formation. Several hypothalamic areas were labeled like the medial preoptic area, septohypothalamic nucleus, arcuate nucleus, dorsomedial and ventromedial nuclei, posterior hypothalamic area, and supramammilary nucleus, SuM. The paraventricular thalamic nucleus was also labeled in both animal groups. Labeling was present in all areas of the (central) periaqueductal gray in AGC rats and mostly in its dorsomedial part in FLT rats.

At **FD14**, Fos expression was high in several brain areas of AGC rats, including the cerebral cortex, caudal part of the caudate-putamen, claustrum, septum and paraventricular thalamic nucleus. FLT animals showed a *moderately increased* Fos expression with respect to AGC rats in most cortical areas (Fig. 2, upper left) lateral septum, caudate-putamen, ventral pallidus, dorsal endopiriform nucleus, horizontal and vertical limbs of the diagonal band, dorsal dentate gyrus (specially in the upper blade), dorsal CA2 and 3, ventral dentate gyrus and subiculum. In the hypothalamus, Fos expression moderately increased in FLT with respect to AGC rats in the medial preoptic area, supramammillary, arcuate nuclei and posterior hypothalamic area. It decreased slightly in the median preoptic nucleus. Fos expression increased also in the dorsomedial periaqueductal gray (Bregma -5.30; 117).

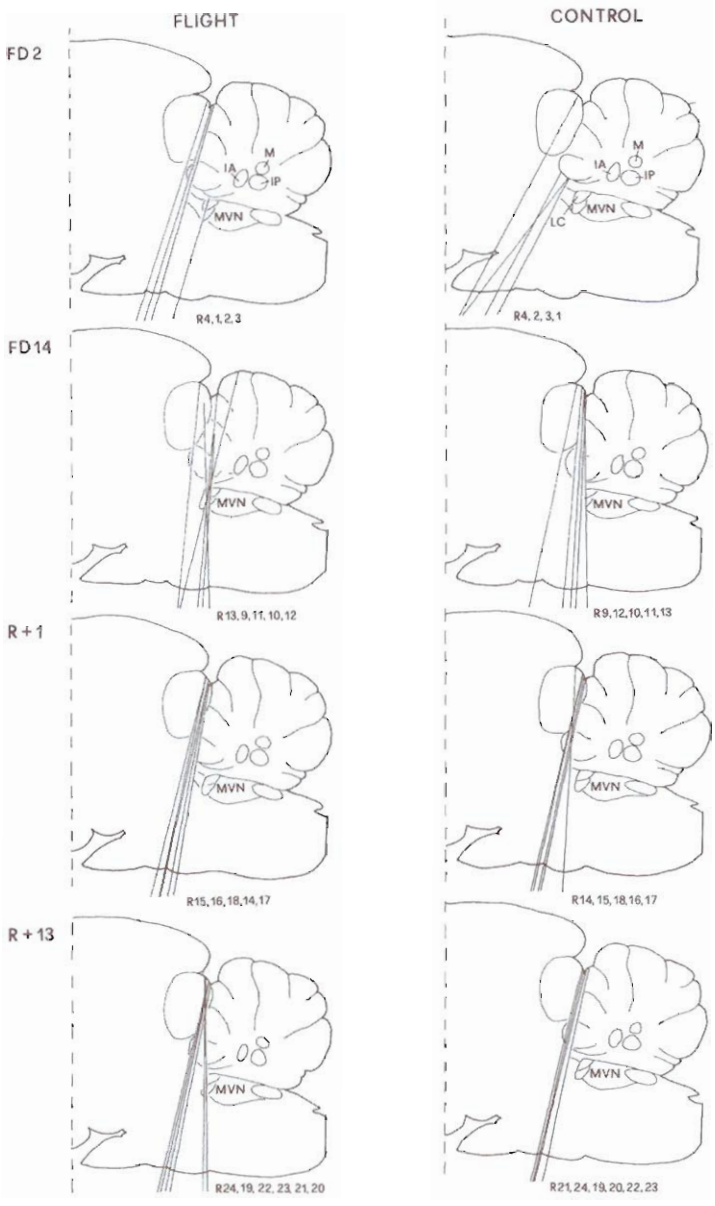

Fig. 1. – *Schematic representation of the levels of transection of the brainstem at mesopontine level performed at different time points of the space flight (FD2, FD14, R + 1, R + 13) both in FLT rats (left side) and control (AGC) rats (right side).*

The number of the rats used is indicated at the bottom of each transection level. Most of the transections are located just ventrally to LC.
Abbreviations used: LC, locus coeruleus (and subcoeruleus α); MVN, medial vestibular nucleus; M, medial (fastigial) nucleus, dorsolateral part; Int A, IA, interpositus anterior; IP, interpositus posterior.
The schemes are taken from the Paxinos-Watson atlas (cf. ref. 117).

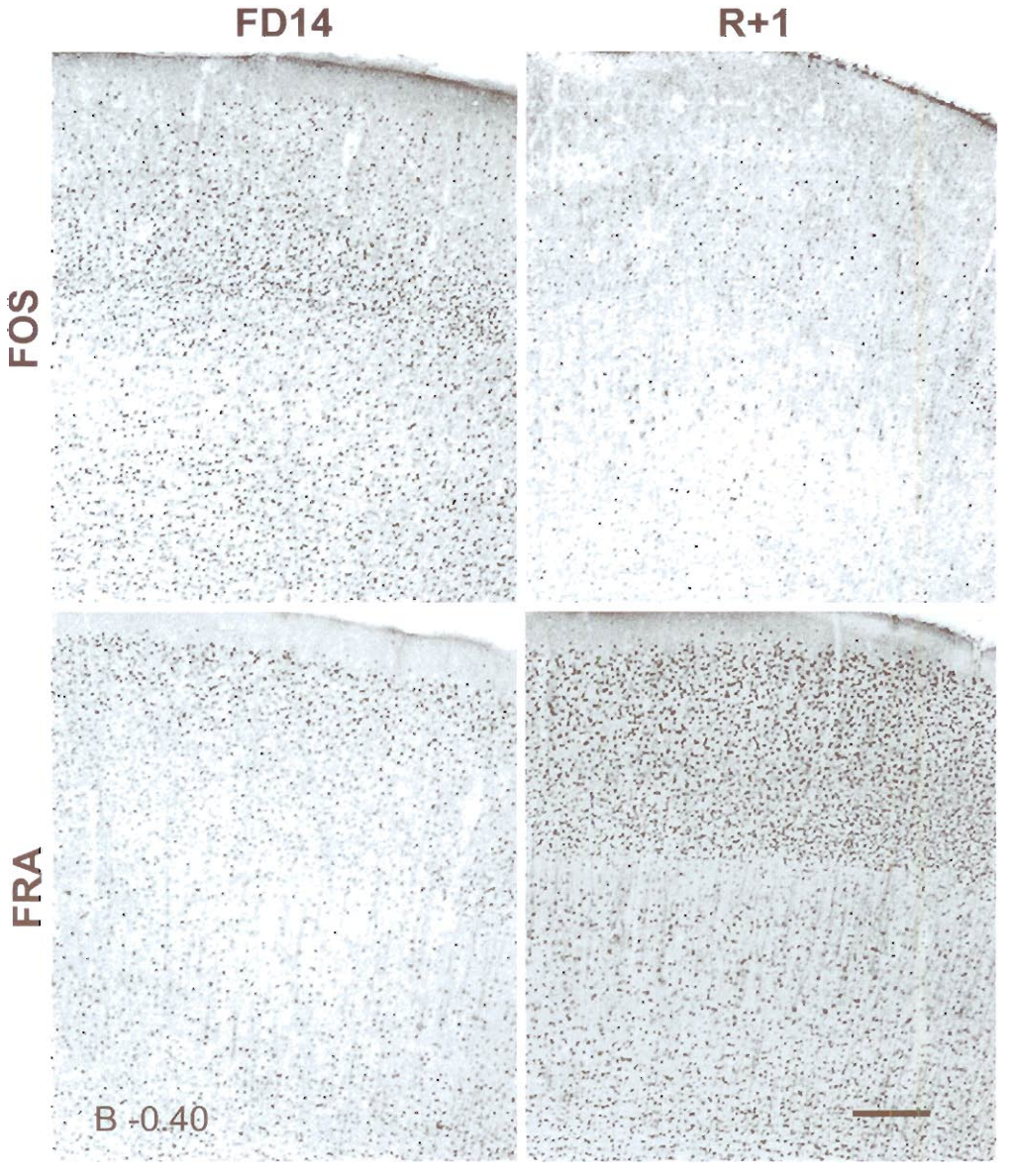

Fig. 2. – *Fos and FRA protein levels in two representative rats of the FLT group (no light pulse, NLP rats) sacrificed at FD14 (R7) (left side panels) and at R + 1 (R + 15) (right side panels), respectively.*

Notice the large number of Fos-positive cells in the somatosensory cortex at FD14, indicative of a state of waking, and the scarse Fos labeling in the corresponding cortical areas at R + 1, indicative of a rebound period of deep sleep, possibly SWS, as revealed 24 hours after the re-entry. Corresponding sections of the same rats stained with the FRA antibody showed only some slight FRA expression at FD14, still indicative of a beginning episode of waking, and a more prominent FRA labeling at R + 1, indicative of a state of very active waking, possibly associated with a state of stress, which occurred during the early part of the re-entry. Scale bar = 100 μm.

At **R + 1**, AGC rats showed a pattern of Fos staining similar to the one described above for FD14 AGC rats. Surprisingly, FLT rats showed *lower* levels of Fos immunostaining in most cortical areas (Fig. 2, upper right), caudate-putamen, lateral septum, some thalamic regions, such as the paraventricular and ventrolateral thalamic nuclei, dorsal and ventral dentate gyrus, dorsal CA2 and CA3 with respect to AGC rats. Fos staining slightly increased in FLT rats in the arcuate nucleus of the hypothalamus, as well as in the central nucleus of the amigdala (CeA), i.e. ~15 cells x section x side with respect to the controls, i.e. (1-2 labeled cells x section x side) (Fig. 3, upper right). This structure was poorly labeled in FLT rats sacrificed at FD2

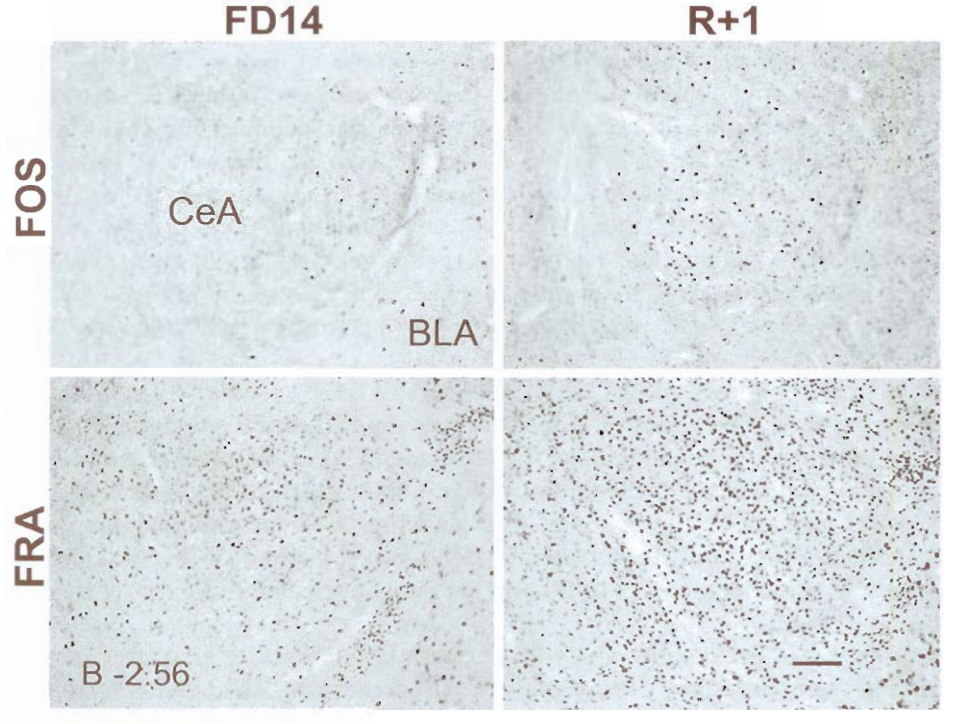

Fig. 3. – *Fos and FRA protein levels in the central nucleus of the amygdala (CeA) and the lateral and basolateral nucleus of the amygdala (BLA) of two representative rats in the FLT group (NLP rats) sacrificed at FD14 (R7) (left side panels) and at R + 1 (R15) (right side panels), respectively.*

Notice the very limited number of Fos-positive cells in the FLT rats sacrificed at FD14, i.e. when the animal was presumably awake, and the increased number of Fos-positive cells observed in the FLT rat sacrificed at R + 1, i.e. when the animal showed a condition of sleep (possibly SWS) as detected after landing, i.e. during the early part of the reentry. As reported in the Discussion this episode was likely to be followed by a period of stress followed by a rebound of REM sleep, which most likely occurred during the late part of the re-entry. Corresponding sections of the same rats stained with the FRA antibody showed some expression in the CeA at FD14, still indicative of a waking state and a more prominent labeling at R + 1, indicative of a very active waking, possibly associated with a state of stress. In this case the labeling extended also to the lateral and the baso-lateral nuclei of the amygdala. Scale bar = 100 µm. This figure corresponds to Figure 8 of the paper by Pompeiano et al. 2004 (cfr. ref. 127), with the permission from Elsevier, Science, NL.

and FD14 (Fig. 3, upper left, cf. also 127). In the periaqueductal gray, Fos labeling decreased in the dorsolateral and dorsomedial parts and increased in the lateral part (0 *vs.* 8 cells x section x side) in FLT with respect to AGC rats (Bregma -5.30/-5.80, following Paxinos and Watson (117).

Rats sacrificed at **R + 13** showed generally low levels of Fos expression in several forebrain structures. In both AGC and FLT groups, one animal showed a slightly stronger labeling in the cerebral cortex, caudate-putamen and hippocampal formation.

2. Changes in FRA expression.

It was impossible to evaluate FRA labeling in **FD2** animals, because many slides showed freezing damage, specially from the FLT animals.

At **FD14**, a *moderate FRA expression* was observed in both AGC and FLT rats in several areas of the cerebral cortex (Fig. 2, lower left) and the limbic system (lateral septum, hippocampal formation ventral aspects), the caudate-putamen, claustrum, the amygdala (Fig. 3, lower left) and the paraventricular, thalamic and some hypothalamic nuclei. An *increase in FRA expression* in FLT with respect to AGC rats was also observed in the ventral part of the dentate gyrus and of CA1-3 (the dorsal aspect being difficult to evaluate), as well as in the supramammillary nucleus (SuM). FRA labeled cells also appeared to slightly increase in the lateral periaqueductal gray in FLT with respect to AGC rats (Bregma-5.30/-6.30 following Paxinos and Watson, 117).

At **R + 1**, FRA expression in FLT with respect to AGC rats was *very high* not only in some areas of the neocortex (Fig. 2, lower right), but also in some limbic forebrain regions, such as the cingulate, the retrosplenial (Fig. 4), and the entorhinal cortex, several components of the amygdaloid complex, such as the central, lateral and basolateral subnuclei (Fig. 3, lower right and Fig. 5A), the caudate-putamen (Fig. 5A), the lateral septum (Fig. 6A and Fig. 7), the bed nucleus of the stria terminalis, in particular the lateral part (Fig. 7) and the paraventricular and anterior hypothalamic nuclei (Fig. 8).

Some increase in FRA expression with respect to AGC controls also affected the hippocampal formation, particularly the ventral part of CA1-CA3 fields of the dorsal hippocampus (Fig. 9). An increase in FRA expression was also seen in the medial preoptic area (Fig. 6B and Fig. 7), a structure involved in the homeostatic regulation of REMS (cf. 67) as well as in the SuM, supramammillary nuclei (Fig. 5B). Labeling decreased in FLT with respect to AGC rats in the anterodorsal thalamic nucleus, but increased in the paracentral thalamic nucleus and in a restricted area of the lateral periaqueductal gray located immediately ventrolateral to the aqueductus (Bregma -6.04: 1.8 and 16.3 cells in AGC and FLT rats, respectively; Bregma -6.80/-7.04: 4.4 and 41.1 cells in AGC and FLT rats, respectively). Labeled cells were not seen in this area at any other time point of the mission.

Rat sacrificed at **R + 13** showed low to moderate levels of FRA expression in several brain areas, including the cerebral cortex and caudate-putamen of both FLT and control rats.

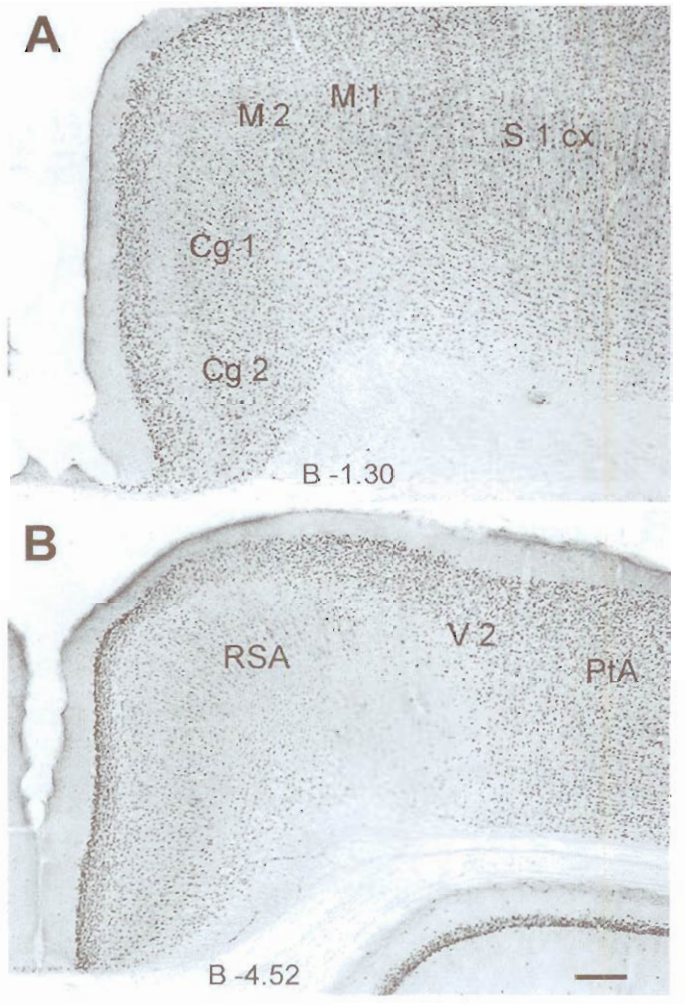

Fig. 4. – *In A, FRA immunoreactivity in the cingulate cortex, area 1 (Cg1) and area 2 (Cg2), in the primary (M1) and secondary (M2) motor cortex and in the somatosensory cortex (S1 cx) of a rat (R17) sacrificed at the re-entry (R + 1) (Bregma –1.30).*

In B the FRA immunoreactivity also affects the retrosplenial agranular cortex (RSA), the secondary visual cortex (V2) and the parietal association cortex (PtA) (Bregma –4.52). Scale bar is 200 μm.

DISCUSSION

Section 1. Effects of space flight on the sleep-waking activity.

Studies conducted in human subjects had previously shown that sleep can be considerably disrupted during space mission (53, 58, 86, 95, 110, 151). This has practical implications since sleep loss affects performance by causing attention deficits, decrease in short-term memory, speech impediments, perseveration and inflexible thinking (cf. 68). Not only total sleep deprivation but also sleep restriction causes cumulative sleepiness, mood disturbance and performance decrements (44).

Polygraphic recordings of sleep and assessment of subjective sleep quality during Skylab Missions (53), space shuttle missions (103, 151) and Mir missions (62, 63) have documented that on average sleep is of shorter duration in space with respect

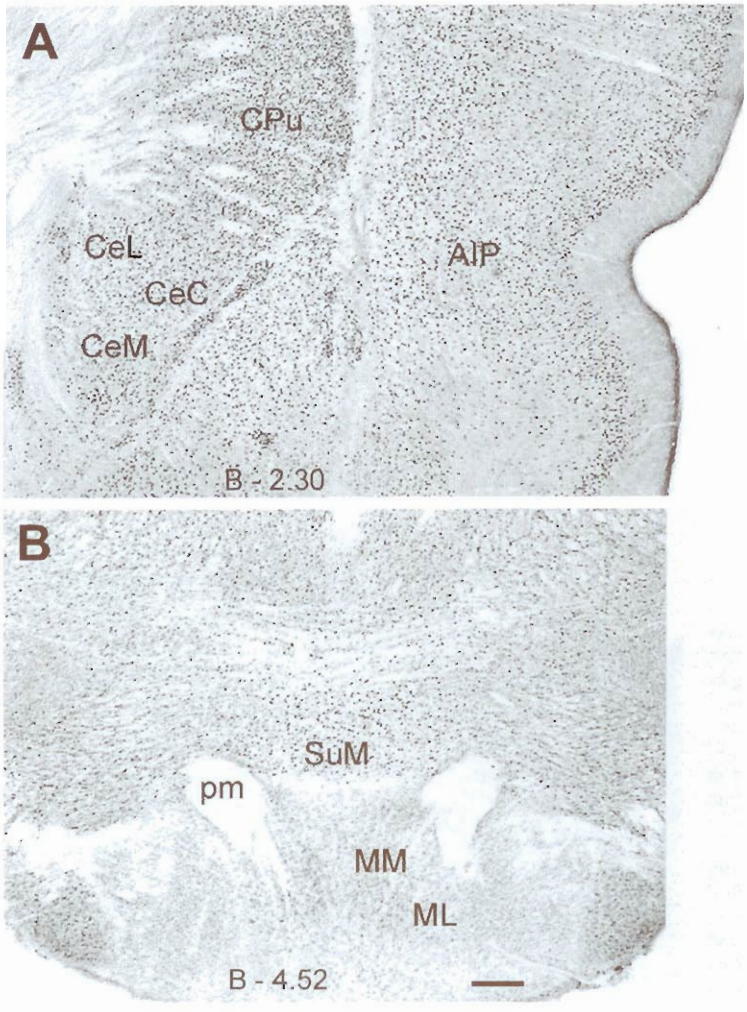

Fig. 5. – *In A, FRA immunoreactivity in most amygdaloid nuclei, such as central amygdaloid nucleus, lateral division (CeL), medial division (CeM, and capsular division (CeC). FRA labeling affects also caudate-putamen (CPu, striatum), as well as the agranular insular cortex, posterior area (AIP) of a NLP rat of the FLT group (R17) sacrificed at the re-entry (R + 1) (Bregma –2.30).*

In B the FRA immunoreactivity affects the supramammillary nucleus (SuM), the medial mammillary nucleus, lateral part (ML) and medial part (MM); pm corresponds to the principal mammillary tract (Bregma –4.52). Scale bar is 200 μm.

to controls (cf. 73). Crew members of the Neurolab mission were shown to experience also changes in sleep structure, in circadian phase and amplitude, with reduction of subjective sleep quality and decrement of neurobehavioral performance (43). Interestingly, after return to earth, REMS markedly increased, REMS latency significantly decreased, and SWS was reduced (43).

The increase of REMS on return from space flight may either represent a response specific to space flight or alternatively may depend on a delay of the sleep episode relative to the timing of sleep in space thus resulting in sleep on return being scheduled later in the circadian cycle, i.e. closer to the crest of REM sleep propensity rhythm (cf. 42).

To investigate the first hypothesis, sleep during and after space flight should be scheduled to nearly identical circadian phases. This requirement was neither met in the experiments by Dijk *et al.* (43), nor in those by Frost *et al.* (53), who postulated

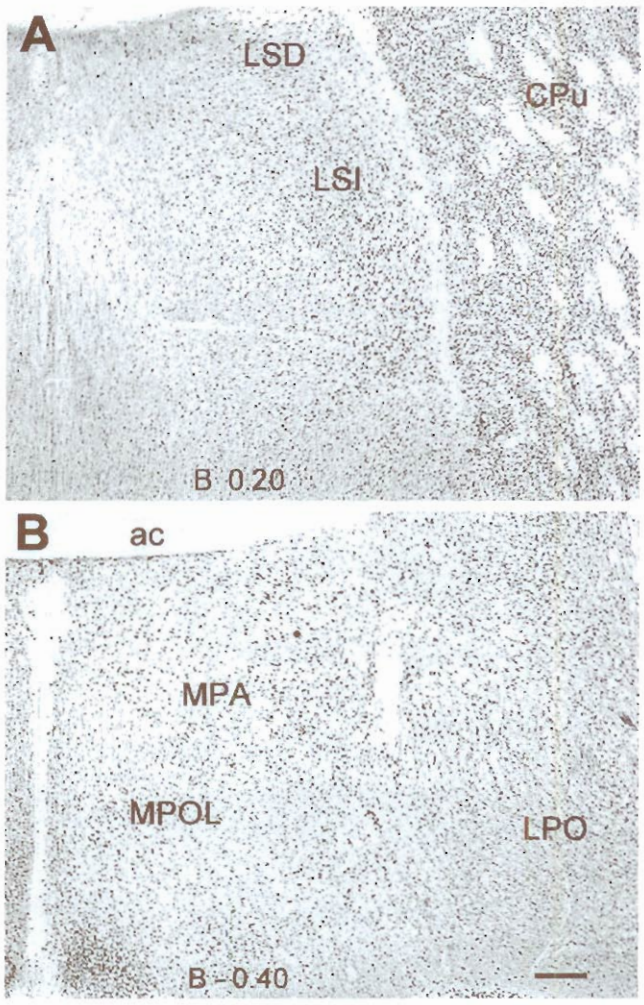

Fig. 6. – *Intense FRA immunoreactivity appears in the lateral septal nucleus, dorsal part (LSD) and intermediate part (LSI), as well as in the caudate putamen (striatum) (CPu) of a rat (R15) sacrificed at the re-entry (R + 1) (Bregma 0.20).*

The FRA immunoreactivity affects also the medial preoptic area (MPA), lateral part (MPOL), rather than the lateral preoptic area (LPO) of the same rat (Bregma -0.40); ac, anterior commissure. Scale bar is 200 μm.

that the post-flight REMS increase observed after long-duration Skylab missions was unlikely to be due to circadian rhythm changes. So far, sleep in space, as during the STS-90 Neurolab Mission, was polygraphically studied only in few subjects and for limited short periods of time (43).

Section 2. Fos immunostaining during the Neurolab mission.

All rats during the mission were sacrificed during their active period, when they were likely to be awake. AGC (control) rats also showed a pattern of Fos expression indicative of a state of wakefulness.

At *FD2*, the pattern of Fos immunostaining in FLT rats was similar to that in AGC rats and to that observed in rats after periods of *spontaneous-wakefulness* or short periods of sleep deprivation with moderate or high expression in all or most brain areas (18, 19, 23, 120, 121).

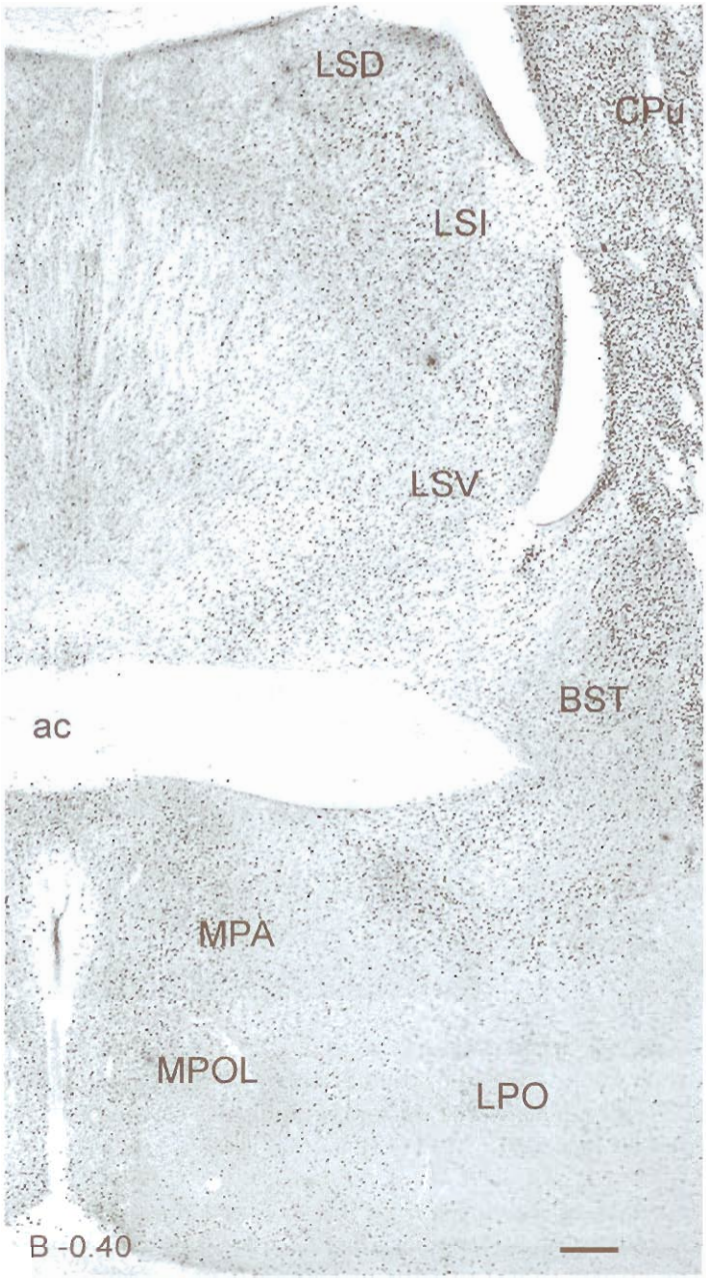

Fig. 7. – *FRA immunoreactivity occurring in several forebrain structures of a NLP rat of the FLT group (R17) sacrificed at R + 1.*

In particular, a prominent number of FRA positive cells was observed in the lateral septum, dorsal part (LSD), intermediate part (LSI), ventral part (LSV), the caudate-putamen (CPu), the bed nucleus of the stria terminalis (BST) and the medial preoptic area (MPA) (Bregma -0.40); ac, anterior commissure. MPOL, LPO, as in Figure 6. Scale bar is 200 μm.

The pattern of Fos immunostaining in FLT rats at *FD14* was also similar to that normally seen after a period of *spontaneous wakefulness* or rather of a short period of sleep loss as suggested by the moderately increased labeling in forebrain areas, including the cerebral cortex, the medial preoptic area of the hypothalamus and a decrease in the median preoptic nucleus with respect to the controls. No signs of long-term sleep deprivation were seen, like high Fos labeling in the medial preoptic area of the hypothalamus (19, 23), a structure which seems to play a major role in the regulation of sleep (165).

At *R + 1*, we also expected to find signs of active waking in FLT rats, with high levels of Fos expression in most forebrain structures since the animals were sacrificed in their active period. Surprisingly, FLT rats showed a much *decreased* Fos immunostaining in most forebrain structures with respect to controls. These observations suggest that at this time point, rats were actually *sleeping* before sacrifice, probably recovering from a previous period of sleep loss. As reported in a previous paper (cf. 128) moderate levels of Fos expression occurred at FD14 in some medullary and pontine reticular structures, which are known to project caudally to the spinal cord and rostrally to hypothalamic and non-specific thalamic nuclei. Similar results were also found at the reentry (R + 1). At this time point of the space flight an increase in Fos expression also affected several autonomic areas of the brain as shown in Section 4. Moderate levels of Fos expression were also observed at R + 1 in the noradrenergic locus coeruleus (LC) nucleus (cf. 122), a finding which was also confirmed in rats exposed to hypergravity, following centrifugation at 2G (48, 54, 87).

Rats sacrificed at *R + 13* were maintained in constant dim red light. Some rats showed very low levels of Fos expression indicative of a state of sleep (cf. also 129), while others showed higher levels. Since changes in the duration of the sleep and waking phases seem to be induced by dim light (178), we cannot exclude that some R + 13 rats were indeed sacrificed in their sleep phase.

Section 3. FRA immunostaining during the Neurolab mission.

For reasons indicated in the Results, we could not evaluate to changes in FRA expression which occurred in rats sacrificed at *FD2*.

At *FD14*, FRA expression was high in different neocortical and forebrain regions of FLT rats.

A very prominent difference between Fos and FRA expression in FLT rats was found at *R + 1*. At this time point, Fos expression strongly *decreased* with respect to controls (cf. also ref. 129), while FRA expression generally *increased*. In particular, FRA expression reached high levels in some areas of the neocortex and the limbic forebrain regions, the amygdala, lateral septum, the hippocampal formation and the caudate-putamen nucleus. Most of these areas, which are known to display prominent REMS related theta activity in rodents (83, 84, 118), showed an increase in c-fos expression after 4-8 days of total sleep deprivation in rats (21). Thus, while in the present experiments FLT rats sacrificed 24 hrs after landing, displayed a prominent *decrease in Fos expression* in several areas of the neocortex, indicative of a

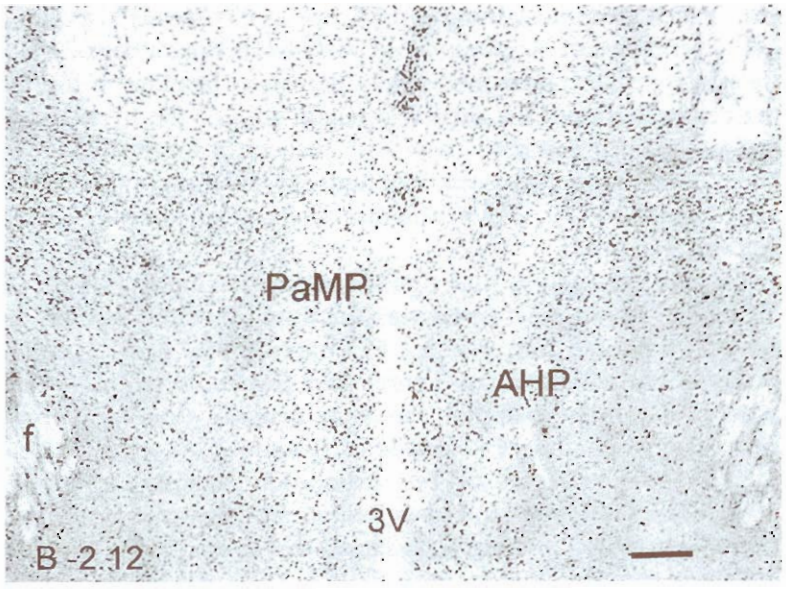

Fig. 8. – *Frontal section of the hypothalamus of the FLT rat (R17) sacrificed at R + 1 (Bregma -2.12).*

3V, third ventricle; PaMP, paraventricular hypothalamic nucleus, anterior magnocellular part; AHP, anterior hypothalamic area, posterior part; f, fornix. Scale bar is 200 µm.

state of SWS, *increased levels of FRA expression* affected in the same population of FLT rats several areas of the limbic system, which are indicative of a state of REMS (153, 153b). In addition to these findings previous experiments had shown that a moderate increase in Fos and FRA expression affected at the reentry (R + 1) pontomedullary reticular structures (cf. 128), which are likely to contribute to both the descending and the ascending manifestations of REMS (83, 123) characterized by postural atonia and the EEG desynchronization, namely the REM related theta activity which affected the limbic forebrain regions. Unfortunately due to our brainstem transection which passed through the pontomesencephalic tegmentum (Fig. 1), we could not study the effects of the space flight on the presumptive cholinergic pontine area, which is critically involved in the generation of REMS (cf. 96, 145). Interestingly, at the reentry FRA expression decreased in the anterodorsal thalamic nucleus, but increased in the paracentral thalamic nucleus and in a restricted area of the lateral *periaqueductal gray* in FLT with respect to control rats.

The different patterns of Fos and FRA expression particularly observed at R + 1 can in part at least be attributed to the different time course in the expression of the corresponding proteins. Fos persists only for a few hours (~6 hrs) in the brain tissue, thus reflecting phenomena occurring in the few hours before sacrifice, when the rats seem to be sleeping. FRA proteins persist for longer periods of time reflecting phenomena occurring several hours before and closer to landing, when rats certainly were awake. However, at variance with Fos and other FRAs, fra-2 mRNA was shown to increase in the cerebral cortex, after 4 hrs. of rebound sleep in the absence

cf *c-fos* mRNA (168). So, we cannot exclude that high FRA expression in sleeping animals at R + 1 may reflect an active recent induction rather than a delayed or continued expression.

Section 4. Evidence of stress, autonomic activation and sleep at the reentry (R + 1).

During the Neurolab mission the rat showed an inactivation period characterized by immobilization, which lasted for about 30 min after landing (cf. C.A. Fuller, personal communication). This represents a "freezing reaction" which is typical of stress (148).

A remarkable rebound of REMS can be elicited by appropriate *stressors*, such as *immobilization stress*, even if applied for short periods of time (39, 46, 97, 138) and, possibly, *acceleration stress*, as obtained also after exposure of rats to gravito-inertial force changes induced by means of a centrifuge (64, 154).

At the re-entry, the increase in gravity force and the related stress induce an activation of the autonomic system as shown by the increase in gene expression reported in autonomic areas of the brainstem [such as the lateral parabrachial nucleus (122) the nucleus of the tractus solitarius (NTS), and the area postrema (127)] and of the forebrain, such as the central nucleus of the amygdala (CeA) (127). Observations made in ground-based experiments have shown that stimulation of baroceptive afferents in the cat acute *encéphale isolé* preparation produced a pattern of SWS (10, 116). In the semichronic *encéphale isolé* the same stimulation also induced PGO waves, associated either with SWS (136) or REMS (51, 135). A pattern of SWS could also be induced by stimulation of either the NTS (94) or CeA (26, 161). There is now anatomical evidence that the NTS projects to the amygdala and other forebrain structures in the rat (140).

Here we found that Fos expression was quite low in the neocortex and most regions of the forebrain at R + 1, suggesting that these rats were asleep probably displaying a SWS before sacrifice (19, 121). Animals experienced also REMS, which was enhanced by the acceleration stress of reentry (see above), possibly associated with immobilization induced by the quick increase of gravity at the reentry (cf. 138). Signs of an increase in REMS could be the increased Fos and FRA expression at R + 1 observed in the medial vestibular nucleus (128). We previously suggested that this increase could be attributed not only to *labyrinthine* signals triggered by the persistent increase in gravity force, but also to *extralabyrinthine* signals related to REMS episodes occurring after landing (128, cf. also 126). In fact, vestibulo-ocular neurons of the medial vestibular nucleus have been shown to discharge during REMS (7), being triggered by the pontine waves typical of the PGO waves (105, cf. 124, 125).

Section 5. Role of amygdala at the reentry.

The amygdala is a component of the limbic system involved in the processing of emotions, particularly fear and anxiety (33, cf. for ref. 81). It is comprised of four subnuclei which are characterized by different afferent and efferent connections (164) and different sensitivity to various neuromodulators (143). The central nucle-

us of the amygdala (CeA) shows increased Fos expression following exposure to stress (35). It also represents the major source of output from the amygdala to basal forebrain, hypothalamus and brainstem. In our experiments the FRA expression which occurred at the reentry (R + 1) involved not only the central, but also the basolateral and lateral subdivisions of the amygdaloid complex (Fig. 2). It is of interest that different subnuclei of the amygdala, respond to different types of stressors (35).

CeA could also play a role in the control of sleep and waking (106, 107, 149), as supported by the existence of reciprocal connections with REMS generating areas in the brainstem (106, 148; cf. 81 for ref.) and with waking-inducing areas in the cholinergic basal forebrain (82). Inhibition or inactivation of CeA (166) decreased REMS. On the other hand, CeA stimulation increased REMS (159) and PGO frequency (in cats, 12) or amplitude (in rats, 37, 38) (cf. also 32). CeA stimulation also activates PGO wave-related parabrachial neurons (cf. 11b, 80, 142b, 150). In addition, these pontine neurons send afferents to the lateral geniculate nucleus (cf. 144), as well as to the medial vestibular nucleus (107, 132, 133) which contributes to the occurrence of both isolated ocular jerks and bursts of REM (cf. 125) (see Section 4). It is of interest that PGO waves are present both during waking, where they seem to represent a neural marker of alerting and during episodes of REMS, where they are related to bursts of REMs (cf. 106, 148, 149).

In our experiments, the increased Fos expression in CeA of FLT rats sacrificed at R + 1 may thus be related to REMS episodes. FRA expression also increased in CeA at R + 1. However, this increase may refer not only to the stress and autonomic activation of reentry, but also to the generation, regulation and expression of emotional states (143).

The possibility that sleep states can be related to learning periods has been discussed in previous review articles (159, 159b). In 1970, Pompeiano (124) hypothesized that endogenous signals possibly related to PGO waves typical of REMS exert a role in learning and memory. This possibility was further developed by Ullor and Datta (170), who postulated that these PGO waves contribute to long-term neural plasticity and long-term memory formation. There is in fact evidence that pontine waves increased the phosphorilation of c-AMP response element binding protein (CREB) and gene expression in several structures (hippocampus, hypothalamus) including the amygdala (142).

Section 6. FRA expression in brain structures projecting CRF fibers to the noradrenergic LC neurons at the reentry.

In flight rats sacrificed at R + 1, the reduced discharge of LC neurons which occurred during sleep (3, 71, cf. 5, 6, 49, 50, 72) was likely to be counteracted by excitatory influences due either to activation of macular labyrinth receptors (130, 131) following the increase in gravity force at the reentry, or to activation of autonomic afferents (46b) possibly related to stress (cf. 1, 14, 16, 162), a condition which increases the NE turnover in the forebrain (112). Noradrenergic LC cells receive a major glutamatergic excitatory input originating from the nucleus paragigantocellularis lateralis (PGi) (47, cf. 31, 173). The same neurons also receive corticotropin

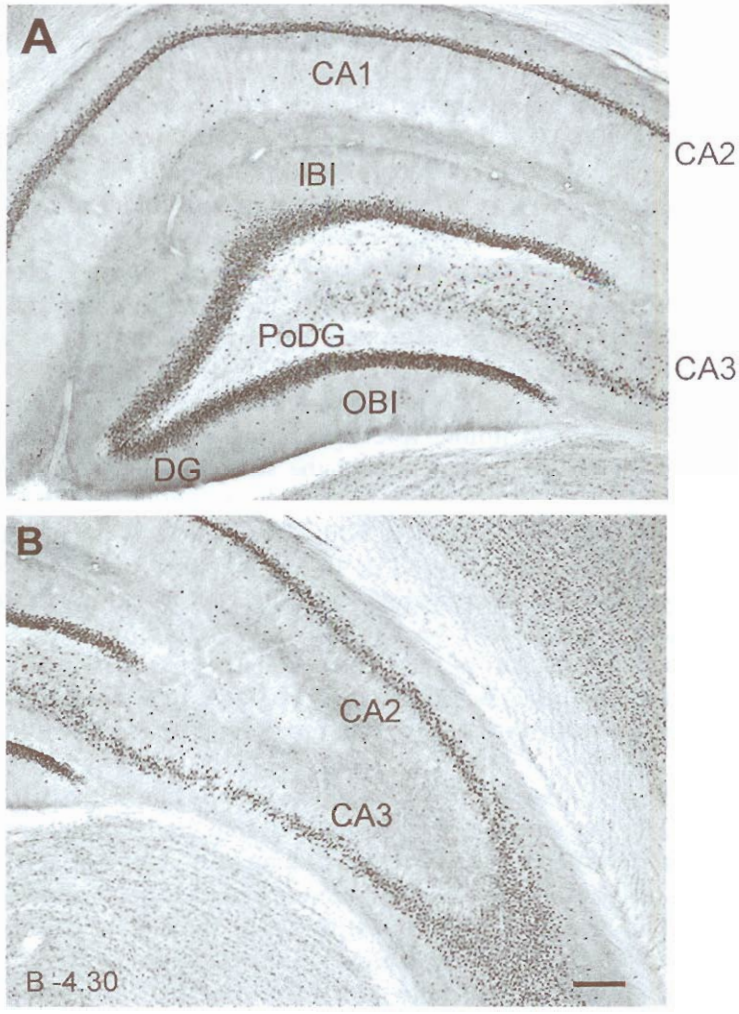

Fig. 9. – *FRA immunoreactivity in the medial (A) and lateral (B) aspect of the hippocampus (Bregma -4.30) of a NLP rat (R15) of the FLT group sacrificed 24 h after the reentry (R + 1).*

Notice the great number and high density of labeled cells in the DG, as well as in CA1, CA2 and CA3.
DG, dentate gyrus; CA1, CA2, CA3, field CA1, CA2, CA3 of the hippocampus; IBI, inner blade of dentate gyrus; OBI, outer blade of dentate gyrus; PoDG, polymorph layer dentate gyrus. Scale bar is 200 μm.

releasing factor (CRF) afferents (174-177). CRF is the neuropeptide promoting the synthesis and release of adrenocorticotropin hormone (ACTH) in the rat brain and its release increases during stress. CRF activates noradrenergic LC neurons during stress (cf. 27, 28, 173) and could then contribute to the increased FRA expression observed in LC neurons at R + 1 (122). The main brain regions sending CRF afferents to the LC are the PGi and CeA (91, 146, 147, 171-173, 176, 177, 180, 181; cf. 102 for ref.).

Interestingly, in our study FRA expression increased in the LC (122), PGi (31) and CeA (127) at the reentry. The PGi in the ventrolateral medulla projects also to autonomic areas of the spinal cord (171, 180). CeA as well as the medial amygdala (173, cf. 102 for ref.) may thus contribute to LC activation via release of CRF. Other

structures contributing CRF afferents to the noradrenergic LC neurons (cf. 91, 176, 177) and showing an increase in FRA expression at the reentry corresponded to the BSt, bed nucleus of the stria terminalis (Fig. 7), and also to hypothalamic structures such as the anterior hypothalamic area and the paraventricular nucleus (Fig. 8). The distribution of CRF receptors in several brain structures of rat has also been investigated (41, 134). An increase in Fos expression in the rat brain including both telencephalic and diencephalic structures was also found to occur after exposure of the rat to gravito-inertial changes obtained by a centrifuge (64). In our experiments FRA expression observed in the LC and all the structures which send to this structure CRF afferents occurred only at R + 1, i.e. when the gravity force increased from about 0 G to 1.5-1.6 G, before stabilizing to 1 G, but not at FD2, i.e. at launch, when the gravity force increased from 1 to 3 G, before stabilizing to ~0 G. It is of interest that single and repeated stress increase the expression of transcription factors in several stress-related limbic forebrain target regions, such as the central and medial amygdala, lateral bed nucleus of the stria terminalis, medial prefrontal cortex and lateral septum (104b). Repeated stress also increased the biosynthesis of norepinephrine (NE) in the LC (16, 68b, 101) as well as the synthesis and release of NE and tyrosine hydroxylase (TH) in the hippocampus (111, 112). We postulate that activation of the noradrenergic LC neurons at launch ensures a more prominent effect on target areas in response to a novel stressor represented by the reentry. This may account for part of the bigger increase in Fos and FRA expression at the reentry than at launch. The other reason could be represented by differences in the gravity signals occurring at these two time points of the space flight.

Section 7. Possible role of the hippocampus during the space flight.

The hippocampus exerts a critical role in learning and memory (7b) and is involved in the formation of spatial maps (99, 100, 160, 167). Such cognitive maps are plastic or modifiable as the animal acquires new information about the environment (7c). Changes in neuronal firing (88) and in gene expression (65, 66) have been shown in the rat hippocampus during spatial learning and as a result of a novel experience not directly related to stressfulness of that experience (115). Gravity-induced signals are thought to stabilize spatial maps (ref. in 89, 90). Changes in these signals are thus likely to affect hippocampal space maps and 'place' cell activity (cf. ref. 85, 182). In fact, hypergravity has been shown to affect hippocampal synaptic plasticity, as shown by the observed change in the long-term potentiation (LTP), the neuronal correlate of learning and memory (45, 169; cf also 34), which occurred after exposure of rodents to 4G (79), but not to 2G (61). There is also evidence that the LC neurons exert a prominent role in the regulation of cognitive performance (170b). Hypergravity may also modulate gene expression in the hippocampus of mice (40). Hippocampal CA1 'place' cells were recorded in rats navigating in a 3D-track in microgravity during the Neurolab mission by McNaughton *et al.* (89, 90). Place cell firing was abnormal on FD4 and it returned to normal on FD9. It was suggested that the 3D-navigation in microgravity leads to an inconsistency in the hip-

pocampal 'place' code, which may account for the disorientation experienced by astronauts during the first days of space flight (89, 90). A longer period of adaptation/experience seems to be necessary for the eventual formation of stable maps in microgravity than on the ground, possibly involving changes in the vestibular system and use of visual cues.

We found that Fos expression moderately increased in the hippocampal formation of Neurolab FLT rats at FD14 with respect to controls. The animals were sacrificed while awake and possibly exploring their 3D environment. This increase in hippocampal Fos expression may be due to a certain degree of sleep deprivation of FLT rats (see Section 2). However, Fos protein increases in CA1-3 after a short period of sleep deprivation (6 hrs; 19), while here we did not find any change in CA1 of FLT rats sacrificed at FD 14 with respect to controls. It would be of interest to see whether Fos expression changes in CA1 at FD14 when place cells show an abnormal pattern of firing (89, 90). The observation of no change in Fos expression in this area at FD14 can possibly be related to the fact that place cell firing returned to normal by FD9 (89, 90) [1].

Another observation against the hypothesis of FD14 rat suffering from sleep deprivation is that Fos protein increases after 6 and 24 hrs of sleep deprivation modestly and equally in both blades (cf. 19, 120). Here, we observed an increased Fos expression in the *upper* blade. We believe that this increase may be related to the rat novel 3D spatial experience. Recent work demonstrated that the upper blade shows equal expression of another plasticity related gene following exploration of a novel or a familiar environment, with respect to cage controls (15). The lower blade of the dentate gyrus instead is not activated after spatial behavioural experience (15). Anatomical observations support the higher responsiveness of the upper blade (15). One of these, is that the supramammillary (SuM) projections are twice as dense in the upper than in the lower blade (ref. in 15). Several studies have shown that neurons of the SuM region and adjacent structures like the medial mammillary nucleus are related to spatial training (149b) and possibly also to spatial learning and memory (2b, 91b, 154b). Both the SuM and adjacent region are profoundly connected with the hippocampal formation (93c, 179) and modulate the frequency of the hippocampal theta rhythm (87b, 169b). Interestingly FLT rats sacrificed at FD14 showed an increase in Fos expression also in the supramammillary nucleus. An additional finding in our experiments was that at the reentry FRA expression occurred in the rhinencephalon and striatum as shown either after microinjection of a GABA agonist in the periaqueductal gray of cat (ref.153, 153b) or after a long-term (4-8 days) period of total sleep deprivation (ref. 21). This finding could be attributed to the occurrence of episodes of REMS.

[1] It is worth to notice that unilateral labyrinthectomy (UL) produces in guinea pig an increase in the NE levels in the CA2 region but not in the CA1 region of the contralateral hippocampus (183). This effect can be attributed to asymmetric activity which affects the noradrenergic LC neurons after UL (17, 30).

Section 8. Evidence that noradrenergic LC neurons induce Fos and FRA expression in their target structures at the reentry.

The discharge of noradrenergic LC neurons increases: 1) during natural stimulation of macular labyrinth receptors (130, 131); 2) during wakefulness in the sleep-waking cycle (3, 71, cf. 5, 6, 50, 72), 3) during sleep deprivation (cf. 19, 21), and 4) during stress (1) (usually associated with autonomic activation (cf. Section 4). During waking, the increased activity of LC neurons is associated with an increase in Fos expression in this area (18, 121). Many other brain areas show an increase in Fos expression during waking (19, 121), which in part depends on the noradrenergic LC activity (20, cf. 24). Experimental anatomical studies have actually shown that most of these areas receive in the rat afferent projections from the LC (93b).

During the Neurolab mission, an increase in both Fos and FRA expression in the LC was seen particularly at the reentry (122). We think that this expression is driven by the reentry-associated stress and increased gravity and autonomic signals. Interestingly, in many forebrain areas Fos expression *decreased* in R + 1 FLT rats, while FRA expression showed moderate or *higher levels* with respect to controls. This increase in FRA expression affected not only several areas of the neocortex but also the limbic system and the hippocampus, as well as the amygdala and the striatum (caudate + putamen). This can be explained by the fact that FRA has a longer time course of expression than Fos and so it may act as an integrator of salient events happening in the previous hours (or days). In particular, as indicated above, these findings were related to stress of reentry, followed by a rebound of REMS (Section 4). Thus FRA expression may be in a more complex relationship with changes in neural activity than Fos.

Experimental studies have shown that Fos regulates in the LC the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme responsible for the synthesis of NE (52, 55, 56) and that the TH gene is a potential gene of Fos (13, 93). There is also evidence that not only c-fos but also FRA such as FRA 2 may, through the activating protein 1 (AP1) like site, regulate TH gene expression (140b). Thus a short-term (Fos) and also a long-term (FRA) regulation of TH expression may sustain an increased release of NE following activation of the LC neurons. This would finally lead to the induction of IEGs in several target structures, such as the hippocampus (2, 74, 76, 78, 111, 112) and the amygdala (36) (cf. 6 for ref.), which could then contribute to the occurrence of plastic events in these brainstem structures.

SUMMARY

1. Electrophysiological and behavioural observations have shown that changes in the sleep-waking activity occur in astronauts during the space flight. Experiments performed in ground-based experiments have previously shown that the immediate early gene (IEG) c-fos, a marker of neuronal activation, can be used as a molecular correlate of sleep and waking. However, while Fos expression peaks within 2-4 hours after the stimulus and returns to baseline within 6-8 hours, other IEGs as the

FRA proteins which are also synthetized soon after their induction, persist in the cell nuclei for longer periods of time, ranging from 1-2 days to weeks.

2. Both Fos and FRA expression were evaluated in several adult albino rats sacrificed at different time points of the space flight, i.e. either at FD2 and FD14, i.e. at launch and about two weeks after launch, respectively, or at R + 1 and R + 13, i.e. at the reentry and about two weeks after landing. The changes in Fos and FRA expression were then compared with those obtained in ground controls. These experiments demonstrate activation of several brain areas which varies during the different phases of the space flight. Due to their different time of persistence, Fos and FRA immunohistochemistry can provide only correlative observations. In particular, FRA expression has been quite helpful to identify the occurrence of short-lasting events such as those related either to *stress* or to *REM-sleep*, whose episodes last in the rat only a few min and could hardly be detected by using only Fos expression.

3. Evidence was presented indicating that at FD2 and FD14 Fos-labeled cells were observed in several brain areas in which Fos had been previously identified as being induced by *spontaneous or forced waking* in ground-based experiments. In contrast to these findings FLT rats sacrificed at R + 1 showed *low levels* of Fos immunostaining in the cerebral cortex (neocortex) and several forebrain structures such as the hypothalamus and thalamus. Some Fos staining was also present in limbic cortical areas, the septum, and the hippocampus. The main area of the forebrain of FLT rats sacrificed at R + 1, showing an increased expression of Fos, was the central nucleus of the amygdala (CeA) (cf. 127), as well as the noradrenergic locus coeruleus (LC) nucleus (cf. 122). At R + 13 Fos immunostaining was variable among FLT rats. However, none of these rats showed a significant number of Fos-positive cells in CeA.

4. Most of the rats studied for Fos expression were also tested for FRA expression. In particular, a scattered amount of FRA expression occurred at FD14 in different areas of the neocortex and in limbic forebrain regions (such as the cingulate, retrosplenial and entorhinal cortex). It included also the hippocampus, the lateral septum, the caudate/putamen, as well as some hypothalamic regions. At the reentry (R + 1) it was previously shown that a prominent increase in FRA expression occurred in the LC of FLT rats (cf. 122). This finding was associated with an increase in FRA expression which affected not only the nucleus paragigantocellularis lateralis of the medulla, which sends excitatory glutamatergic afferents to the LC (cf. 31 for ref.), but also structures which are known to produce corticotropin-releasing factor (CRF), a neuropeptide which activates the noradrenergic LC neurons during stress.

5. These findings which result from acceleration stress were followed by REMS episodes, which probably occurred after a long period of sleep deprivation following exposure to microgravity. It was previously shown that an increase in Fos and FRA expression occurred at the reentry in some pontine and medullary reticular structures (cf. 128), which are likely to be involved in both the descending (postural atonia) and the ascending manifestations of PS. These findings can be integrated by results of the present experiments showing that at the reentry high levels of FRA expression occurred in the hippocampus and the limbic system, i.e. in structures

which are involved in the generalized pattern of EEG desynchronization and the theta activity, typical of REMS (cf. 83, 84). A prominent increase in FRA expression also affected at the reentry some components of the amygdaloid complex, particularly the CeA, as well as some related structures, such as the lateral parabrachial nucleus (cf. 122) and the nucleus of the tractus solitarius (cf. 127). These structures are known to contribute to the PGO waves, which drive the oculomotor system either directly or through the medial vestibular nuclei (128, cf. also 126). Unfortunately due to our brainstem transections we were unable to evaluate the changes in gene expression which could affect the dorsolateral pontine structures during the occurrence of REMS episodes. Further experiments are thus required to investigate the role that these pontine structures exert in determining adaptive changes following exposure to microgravity after launch as well as readaptation to the terrestrial environment after landing.

Abbreviations.
ACTH adrenocorticotropin hormone
AGC asynchronous ground control group
AP1 activating protein 1
BSt bed nucleus of the stria terminalis
CA1, CA2, CA3 fields of the dorsal hippocampus
CeA central nucleus of the amygdala
CREB c-AMP-response element binding protein
CRF corticotropin releasing factor
EEG electroencephalogram
FLT flight group
FRA Fos related antigens
G gravity
IEGs immediate early genes
LC locus coeruleus
LL constant dim red-light
LD light-dark cycle
LDT laterodorsal tegmental nucleus
LP light pulse rats
LTP long term potentiation
MnPN median preoptic nucleus
NE norepinephrine
NLP no light pulse rats
NTS nucleus of the tractus solitarius
PAG periaqueductal gray
PGi nucleus paragigantocellularis
PGO ponto-geniculo-occipital waves
PPN pedunculopontine nucleus
PS paradoxical sleep
REM rapid eye movement
REMS rapid eye movement sleep
SCN suprachiasmatic nucleus
SLD sublaterodorsal nucleus
SuM supramammillary nucleus
SWS slow wave sleep
TH tyrosine hydroxylase
vlPOA ventrolateral preoptic area
3D three-dimensional

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REFERENCES

1. ABERCROMBIE, E.D. AND JACOBS, B.L. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and nonstressful stimuli. *J. Neurosci.*, **7**: 2837-2843, 1987.
2. ABERCROMBIE, E.D., KELLER, R.W. AND ZIGMOND, M.J. Characterization of hippocampal norepinephrine release as measured by microdialysis perfusion: pharmacological and behavioral studies. *Neuroscience*, **27**: 897-904, 1988.

2b. ARANDA, L., SANTIN, L.J., BEGEGA, A., AGUIRRE, J.A. AND ARIAS, J.L. Supramammillary and adjacent nuclei lesions impair spatial working memory and induce anxiolitic-like behavior. *Biobehavioural Brain Res.*, **167**: 156-164, 2006.

3. ASTON-JONES, G. AND BLOOM, F.E. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J. Neurosci.*, **1**: 876-886, 1981.
4. BASHEER, R., SHERIN, J.E., SAPER, C.B., MORGAN, J.I., MCCARLEY, R.W. AND SHIROMANI, P.J. Effects of sleep on wake-induced c-fos expression. *J. Neurosci.*, **17**: 9476-9750, 1997.
5. BERRIDGE, C.W. AND FOOTE, S.L. Effects of locus coeruleus activation on electroencephalographic activity in neocortex and hippocampus. *J. Neurosci.*, **17**: 3135-3145, 1991.
6. BERRIDGE, C.W. AND WATERHOUSE, B.D. The locus coeruleus noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res. Rev.*, **42**: 33-84, 2003.
7. BIZZI, E., POMPEIANO, O. AND SOMOGYI, I. Vestibular nuclei activity of single neurons during natural sleep and wakefulness. *Science*, **145**: 414-415, 1964.

7b. BLISS, T.V.P. AND COLLINGRIDGE, G.L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, **361**: 31-35, 1993.

7c. BLUM, K.J. AND ABBOTT, L.F. A model of spatial map formation in the hippocampus of the rats. *Neu.Comput.*, **8**: 85-93, 1996.

8. BOISSARD, R., FORT, P., GERVASONI, D., BARGAGLI, B. AND LUPPI, P.-H. Localization of the GABAergic and non-GABAergic neurons projecting to the sublatero-dorsal nucleus and potentially gating paradoxical sleep onset. *Eur. J. Neurosci.*, **18**: 1627-1639, 2003.
9. BOISSARD, R., GERVASONI, D., SCHMIDT, M.H., BARBAGLI, B., FORT, P. AND LUPPI, P.-H. The rat ponto-medullary network responsible for paradoxical sleep onset and maintainance: a combined microinjection and functional nauroanatomical study. *Eur. J. Neurosci.*, **16**: 1959-1973, 2002.
10. BONVALLET, M., DELL, P. AND HIEBEL, G. Tonus sympatique et activité électrique corticale. *EEG Clin. Neurophysiol.*, **6**: 119-144, 1954.
11. BRODAL, A. *Neurological Anatomy in Relation to Clinical Medicine*. Pp. 660-663. New York. Oxford, Oxford University Press, Third Ed., 1981.
11b. CALLAWAY, C.W., LYDIC, R., BAGHODOYAN, H.A. AND HOBSON, J.A. Pontogeniculooccipital waves: spontaneous visual system activity during rapid eye movement sleep. *Cell Mol. Neurobiol.*, **7**: 105-148, 1987.
12. CALVO, J.M., BADILLO, S., MORALES-RAMIREZ, M. AND PALACIOS-SALAS, P. The role of the temporal lobe amygdala in ponto-geniculo-occipital activity and organization in cats. *Brain Res.*, **403**:, 22-30, 1987.
13. CAMBI, F., FUNG, B. AND CHIKARAISHI, D. 5' Flanking DNA sequences direct cell-specific expression of rat tyrosine hydroxylase. *J. Neurochem.*, **53**: 1656-1659, 1989.
14. CECCARELLI, S., VILLAR, M.J., GOLDSTEIN, M. AND HOCKFELT, T. Expression of c-fos immunoreactivity in transmitter-characterized neurons after stress. *Proc. Natl. Acad. Sci. USA*, **86**: 6569-6573, 1989.
15. CHAWLA, M.K., GUZOWSKI, J.F., RAMIREZ-AMAYA, V., LIJA, P., HOFFMAN, K.L., MARRIOTT, L.K., WORLEY, P.F., MCNAUGHTON, B.L. AND BARNES, C.A. Sparce, environmentally selective expression of *Arc* RNA in the upper blade of the rodent fascia dentate by brief spatial experience. *Hippocampus*, **15**: 579-586, 2005.
16. CHEN, X. AND HERBERT, J. Regional changes in *c-fos* expression in the basal forebrain and brainstem during adaptation to repeated stress: correlations with cardiovascular, hypothermic and endocrine responses. *Neuroscience*, **64**: 675-685, 1995.
17. CIRELLI, C., POMPEIANO, M., D'ASCANIO, P., ARRIGHI, P. AND POMPEIANO, O. *c-fos* expression in the rat brain after unilateral labyrinthectomy and its relation to the uncompensated and compensated stages. *Neuroscience*, **70**: 515-546, 1996.
18. CIRELLI, C., POMPEIANO, M. AND TONONI, G. Fos-like immunoreactivity in the rat brain in spontaneous wakefulness and sleep. *Arch. Ital. Biol.*, **131**: 327-330, 1993.
19. CIRELLI, C., POMPEIANO, M. AND TONONI, G. Sleep deprivation and c-fos expression in the rat brain. *J. Sleep Res.*, **4**: 92-106, 1995.
20. CIRELLI, C., POMPEIANO, M. AND TONONI, G. Neuronal gene expression in the waking state: a role for the locus coeruleus. *Science* **274**: 1211-1215, 1996.
21. CIRELLI, C., SHAW, P.J. AND TONONI, G. Fos expression after prolonged REM sleep episodes following long-term sleep deprivation. *Sleep Res. Online*, **2** (Suppl. 1): 22, 1999.
22. CIRELLI, C. AND TONONI, G. Differences in gene expression between sleep and waking as revealed by mRNA differential display. *Mol. Brain Res.*, **56**: 293-305, 1998.
23. CIRELLI, C. AND TONONI, G. Gene expression in the brain across the sleep-waking cycle. *Brain Res.*, **885**: 303-321, 2000a.
24. CIRELLI, C. AND TONONI, G. Differential expression of plasticità-related genes in waking and sleep and their regulation by the noradrenergic system. *J. Neurosci.*, **20**: 9187-9194, 2000b.
25. CLAYTON, D.F. The genomic action potential. *Neurobiol. Learn. Mem.*, **74**: 185-216, 2000.

26. CLEMENTE, C.D. AND STERMAN, M.B. Cortical synchronization and sleep patterns in acute restrained and chronic behaving cats induced by basal forebrain stimulation. *Electroenceph. Clin. Neurophysiol.*, **24** (Suppl.): 172-187, 1963.
27. CURTIS, A.L., FLORIN-LECHNER, S.M., PAVCOVICH, L.A. AND VALENTINO, R.J. Activation of the locus coeruleus noradrenergic system by intracoerulear microinfusion of corticotropin-releasing factr: effects on discharge rate, cortical norepinephrine levels and cortical electroencephalographic activity. *J. Pharmacol. Exp. Ther.*, **281**: 163-172, 1997.
28. CURTIS, A.L., GRIGORADIS, D., PAGE, M.E., RIVER, J. AND VALENTINO, R.J. Pharmacological comparison of two corticotropin-releasing factor antagonists: *in vivo* and *in vitro* studies. *J. Pharmacol. Exp. Ther.*, **268**: 359-365, 1994.
29. CZEISLER, C.A., CHIASERA, A.J. AND DUFFY, J.F. Research on sleep, circadian rhythms and aging: applications to manned spaceflight. *Exp. Gerontol.*, **26**: 217-232, 1991.
30. D'ASCANIO, P., ARRIGHI, P. AND POMPEIANO, O. The locus coeruleus and Fos-protein expression in vestibular compensation. *Neurol. Psych. Brain Res.*, **5**: 171-180, 1998.
31. D'ASCANIO, P., CENTINI, C., POMPEIANO, M., POMPEIANO, O. AND BALABAN, E. Fos and FRA protein expression in rat nucleus paragigantocellularis lateralis during different space flight conditions. *Brain Res. Bull.*, **59**: 65-74, 2002.
32. DATTA, S., SIWEK, D.F., PATTERSON, E.H. AND CIPOLLONI, P.B. Localization of pontine PGO wave generation sites and their anatomical projections in the rat. *Synapse*, **30**: 409-423, 1998.
33. DAVIS, M. Are different parts of the extended amygdala involved in fear versus anxiety? *Biol. Psychiatry*, **44**: 1239-1247, 1998.
34. DAVIS, S., BUTCHER, S.P. AND MORRISON, R.G. The NMDA receptor antagonist D-2-amino-5-phosphonopentanoate (D-AP5) impairs spatial learning and LTP in vivo at intracerebral concentrations comparable to those that block LTP in vitro. *J. Neurosci.*, **12**: 21-34, 1992.
35. DAYAS, C.V. AND DAY, T.A. Opposing roles for medial and central amygdala in the initiation of noradrenergic cell responses to a psychological stressor. *Eur. J. Neurosci.*, **15**: 1712-1718, 2001.
36. DE BOCK, F., KURZ, J., AZAD, S.C., PARSONS, C.G., HAPFELMEIER, G., ZIEGLGÄNSBERGER, W. AND RAMMES, G. α_2-Adrenoceptor activation inhibits LTP and LTD in the baselateral amygdala: involvement of Gi/o-protein-mediated modulation of Ca^{2+}-channels and inwardly rectifying K^+-channels in LTD. *Eur. J. Neurosci.*, **17**: 1411-1424, 2003.
37. DEBOER, T., ROSS, R.J., MORRISON, A.R. AND SANFORD, L.D. Electrical stimulation of the amygdala increases the amplitude of elicited ponto-geniculo-occipital waves. *Physiol. Behav.*, **66**: 119-124, 1999.
38. DEBOER, T., SANFORD, L.D., ROSS, R.J. AND MORRISON, A.R. Effects of electrical stimulation of the amygdala on ponto-geniculo-occipital waves in rats. *Brain Res.*, **793**: 305-310, 1998.
39. DEL C., GONZALES, M.M., DEBILLY, G., VALATX, J-L. AND JOUVET, M. Sleep increase after immobilization stress: role of the noradrenergic locus coeruleus system in the rat. *Neurosci. Lett.*, **202**: 5-8, 1995.
40. DEL SIGNORE, A., MANDILLO, S., RIZZO, A., DI, MAURO, E., MELE, A., NEGRI, R., OLIVERIO, A. AND PAGGI, P. Hippocampal gene expression is modulated by hypergravity. *Eur. J. Neurosci.*, **19**: 667-677, 2004.
41. DE SOUZA, E.B., INSEL, T.R., PERRIN, M.H., RIVIER, J., VALE, W.W. AND KUHAR, M.J. Corticotropin-releasing factor receptors are widely distributed within the rat central nervous system: an autoradiographic study. *J. Neurosci.*, **5**: 3189-3203, 1985.

42. DIJK, D.-J. AND CZEISLER, C.A. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves and sleep spindle activity in humans. *J. Neurosci.*, **15**: 3526-3538, 1995.
43. DIJK, D.-J., NERI, D.F., WYATT, J.K., RONDA, J.M., RIEL, E., RITZ-DE, CECCO, A., HUGHES, R.J., WILIOTT, A.R., PRISK, G.K., WEST, J.B. AND CZEISLER, C.A. Sleep, performance, circadian rhythms AND light-dark cycles during two space shuttle flights. *Am. J. Physiol. Regulatory Integrative Comp. Physiol.*, **281**: R 1647-R 1664, 2001.
44. DINGES, D.F., PACK, F., WILLIAMS, K., GILLEN, K.A., POWELL, J.W., OTT, G.E., APTOWICZ, C. AND PACK, A.I. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*, **20**: 267-277, 1997.
45. DOYERE, V. AND LAROCHE, S. Linear relationship between the maintenance of hippocampal long-term potentiation and retention of an associative memory. *Hippocampus*, **2**: 39-48, 1992.
46. DUARTE, PALMA, B., SUCHECKI, D. AND TIFIK, S. Differential effects of acute cold and footshock on the sleep of rats. *Brain Res.*, **861**: 97-104, 2000.
46b. ELAM, M., THOREO, T. AND SWENSSON, T.H. Locus coeruleus neurons and sympathetic nerves. Activation of visceral afferents. *Brain Res.*, **375**: 117-125, 1986.
47. ENNIS, M. AND ASTON-JONES, G. A potent excitatory input to the nucleus locus coeruleus from the ventrolateral medulla. *Neurosci. Lett.*, **71**: 299-305, 1986.
48. FIDELINA, O.V. AND KRASNOV, I.B. Expression of the immediate-early gene c-Fos in the brain of the rats exposed to repeated 2G influence. *J. Gravit. Physiol.*, **11**: 35-36, 2004.
49. FOOTE, S.L., ASTON-JONES, G. AND BLOOM, F.E. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proc. Natl. Acad. Sci. USA*, **77**: 3033-3037, 1980.
50. FOOTE, S.L., BLOOM, F.E. AND ASTON-JONES, G. Nucleus locus coeruleus: New evidence of anatomical and physiological specificity. *Physiol. Rev.*, **63**: 844-914, 1983.
51. FOUTZ, A.S., TERNAUX, J.P. AND PUIZILLOUT, J.J. Les stades de sommeil de la preparation "encéphale isolé". II. Phases paradoxales. Leur déclenchement par la stimulation des afferences baroceptives. *EEG Clin. Neurophysiol.*, **37**: 577-588, 1974.
52. FRITSCHY, J.-M., FRONDOZA, C.G. AND GRZANNA, R. Differential effects of reserpine on brainstem catecholaminergic neurons revealed by Fos protein immunohistochemistry. *Brain Res.*, **562**: 48-56, 1991.
53. FROST, J.D., SHUMATE, W.H., SALAMY, J.G. AND BOOHER, C.R. Experiment M133. Sleep monitoring on skylab. Pp. 113-126. In: JOHSTON, R.S. AND DIETLEIN, L.F. (Eds.), *Biomedical Results from Stylab*. NASA Washington, D.C., 1977.
54. FULLER, P.M., JONES, T.A., JONES, S.M. AND FULLER, C.A. Evidence for macular gravity receptor modulation of hypothalamic, limbic and autonomic nuclei. *Neuroscience*, **129**: 461-471, 2004.
55. FULLER, C.A., MURAKAMI, D.M., HOBAN-HIGGING, T.M., FULLER, P.M., ROBINSON, E.L., HSIUNG-TANG, J. The effects of spaceflight on the rat circadian timing system. Pp. 233-241. In: BUCKEY, J.C. JR. AND HOMICK, J.L. (Eds.), *The Neurolab Spacelab Mission: Neuroscience Research in Space*. NASA SP-535, NASA, London B. Johnson Space Center, Houston, Texas, 2003.
56. GIZANG-GINSBERG, E. AND ZIFF, E.B. Nerve growth factor regulates tyrosine hydroxylase gene transcription through a nucleoprotein complex that contains c-Fos. *Genes Dev.*, **4**: 477-491, 1990.
57. GONG, H., MCGINTY, D., GUZMAN-MARIN, R., CHEW, K.-T., STEWART, D. AND SZYMUSIAK, R. Activation of c-fos in GABAergic neurones in the preoptic area during sleep and in response to sleep deprivation. *J. Physiol., Lond.*, **556**: 935-946, 2004.

58. GRAEBER, R.C. Sleep in space. Pp. 59-60. In: ROUSSEL, B. et JOUVET, M. (Eds.), *Actes du 27eme seminaire du GRD le sommeil et ses implications militaries*. Lyon, A.C.E.M.L., 1988.
59. GRASSI-ZUCCONI, G., GIUDITTA, A., MANDILE, P., CHEN, S., VESCIA, S. AND BENTIVOGLIO, M. c-Fos spontaneous expression during wakefulness is reversed during sleep in neuronal subsets of the rat cortex. *J. Physiol., Lond.*, **88**: 91-93, 1994.
60. GRASSI-ZUCCONI, G., MENEGAZZI, M., CARCERERI, DE PRATI, A., BASSETTI, A., MONTAGNOSI, P., MANDILE, P., COSI, C. AND BENTIVOGLIO, M. c-fos mRNA is spontaneously induced in the rat brain during the activity period of the circadian cycle. *Eur. J. Neurosci.*, **5**: 1071-1078, 1993.
61. GUINAN, M.J., HOROWITZ, J.M. AND FULLER, C.A. Effects of hyperdynamic fields in input-output relationships and long-term potentiation in the rat hippocampus. *J. Gravity Physiol.*, **5**: 31-40, 1988.
62. GUNDEL, A., NALISHITI, V., REUCHER, E., VEJVODA, M. AND ZULLEY, J. Sleep and circadian rhythm during a short space mission. *Clin Investing.*, **71**: 718-724, 1993.
63. GUNDEL, A., POLYAKOV, V.V. AND ZULLEY, J. The alteration of human sleep and circadian rhythms during spaceflight. *J. Sleep Res.*, **6**: 1-8, 1997.
64. GUSTAVE, DIT DUFLO, S., GESTREAU, C. AND LACOUR, M. Fos expression in the rat brain after exposure to gravito-inertial force changes. *Brain Res.*, **861**: 333-344, 2000.
65. GUZOWSKI, J.F., SETLOW, B., WAGNER, E.K. AND MCGAVGH, J.L. Experience-dependent gene expression in the rat hippocampus after spatial learning: A comparison of the immediate-early genes *Arc*, *c-fos* AND *zif 268*. *J. Neuroscience*, **21**: 5089-5098, 2001.
66. GUZOWSKI, J.F., TIMLIN, J.A., ROYSAM, B., MCNAUGHTON, B.L., WORLEY, P.F. AND BARNES, C.A. Mapping behaviorally relevant neural circuits with immediate-early gene expression. *Curr. Opin. Neurobiol.*, **15**: 599-606, 2005.
67. GVILIA, I., TURNER, A., MCGINTY, D. AND SZYMUSIAK, R. Preoptic area neurons and the homeostatic regulation of rapid eye movement sleep. *J. Neurosci.*, **26**: 3037-3044, 2006.
68. HARRISON, Y. AND HORNE, J.A. The impact of sleep deprivation on decision making: a review. *J. Exp. Psychol. Appl.*, **6**: 236-249, 2000.
68b. HERBERT, M.A., SEROVA, L.I. AND SABBAN, E.L. Single and repeated immobilization stress, differentially trigger induction and phosphorilation of several transcription factors and mitogen-activated protein kinases in the rat locus coeruleus. *J. Neurochemistry*, **95**: 484-498, 2005.
69. HERDEGEN, T. AND LEAH, J.D. Inducible and constitutive transcription factors in the mammalian nervous system: control of gene expression by Jun, Fox and Krox, and CREB/ATF proteins. *Brain Res. Rev.*, **28**: 370-490, 1998.
70. HERRERA, D.G. AND ROBERTSON, H.A. Activation of c-fos in the brain. *Progr. Neurobiol.*, **50**: 83-107, 1996.
71. HOBSON, J.A., MCCARLEY, R.W. AND WYZINSKI, P.W. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science*, **189**: 55-58, 1975.
72. HOBSON, J.A. AND STERIADE, M. Neuronal basis of behavioral state control. Pp. 701-823. In: BLOOM, F.E. (Ed.), *Intrinsic Regulatory System of the Brain*. Section I. *The Nervous System*. Vol. IV. Amer. Physiol. Soc., Bethesda, MD, 1986.
73. HOBSON, J.A., STICKGOLD, R., PACE-SCHOTT, E.F. AND LESLIE, K.R. Sleep and vestibular adaptation: implications for function in microgravity. *J. Vest. Res.*, **8**: 81-94, 1998.
74. HOPKINS, W.F. AND JOHNSTON, D. Frequency-dependent noradrenergic modulation of long-term potentiation in the hippocampus. *Science*, **226**: 350-352, 1984.
75. HORNE, J.A. *Why we Sleep. The Functions of Sleep in Humans and other Mammals*. Oxford, Oxford University Press, 1988.

76. HUANG, Y.-Y. AND KANDEL, E.R. Modulation of both the early and the late phase of mossy fiber LTP by the activation of beta-adrenergic receptors. *Neuron*, **16**: 611-617, 1996.
77. HUGHES, P. AND DRAGUNOW, M. Induction of immediate-early genes and the control of neurotransmitter-regulated gene expression within the nervous system. *Pharmachol. Rev.*, **47**: 133-178, 1995.
78. INVONE, P.M. AND DUNN, A.J. Tyrosine hydroxylase activation in mesocortical 3, 4.dihydroxyphenylethylamine neurons following foot-shock. *J. Neurochem.*, **47**: 837-844, 1986.
79. ISHII, M., TOMIZAWA, K., MATSUSHITA, M. AND MATSUI, H. Exposure of mouse to high gravitational forces induces long-term potentiation in the hippocampus. *Acta Med. Okayama*, **58**: 143-149, 2004.
80. JEANNEROD, M. AND KIMONO, S. Décharge unitaire de la formation réticulare pontique et activité phasique ponto-géniculo-occipitale chez le chat sous reserpine. *Brain Res.*, **12**: 112-128, 1969.
81. JHA, S.K., ROSS, R.J. AND MORRISON, A.R. Sleep-related neurons in the central nucleus of the amygdala of rats and their modulation by the dorsal raphe nucleus. *Physiol. Behav.*, **86**: 415-426, 2005.
82. JOLKKONEN, E., MIETTINEN, R., PIKKARAINEN, M. AND PITKANEN, A. Projection from the amygdaloid complex in the magnocellular cholinergic basal forebrain in rat. *Neuroscience*, **111**: 133-149, 2002.
83. JOUVET, M. Recherches sur les structures nerveuses et les mechanisms responsables des différentes phases du sommeil physiologique. *Arch. Ital. Biol.*, **100**: 125-206, 1962a.
84. JOUVET, M. Sur l'existence d'un système hypnique ponto-limbique. Ses rapports avec l'activité onirique. Pp. 297-329. In: PASSOUANT P. (Ed.), *Symposium sur la Physiologie de l'Hippocampe*. CNRS, Paris, 1992b.
85. JUNG, M.W. AND MCNAUGHTON, B.L. Spatial selectivity of unit activity in the hippocampal granular layer. *Hippocampus*, **3**: 165-182, 1993.
86. KANAS, N. Psychological and interpersonal issues in space. Am. J. Psychiatry, **144**: 703-709, 1987.
87. KAUFMAN, G.D., ANDERSON, J.H. AND BEITZ, A.J. Fos-defined activity in rat brainstem following centripetal acceleration. *J. Neurosci.*, **12**: 4489-4500, 1992.
87b. KIRK, I.J. Frequency modulation of hippocampal theta by the supramammillary nucleus and the hypothalamo-hippocampal interactions: mechanisms and functional implications. *Neurosci. Biobehav. Rev.*, **22**: 291-302, 1998.
88. KNIERIM, J.J., KUDRIMOTI, H.S. AND MCNAUGHTON, B.L. Place cells, head direction cells and the learning of landmark stability. *J. Neurosci.*, **15**: 1648-1659, 1995.
89. KNIERIM, J.J., MCNAUGHTON, B.L. AND POE, G.R. Three-demensional spatial selectivity of hippocampal neurons during space flight. *Nat. Neurosci.*, **3**: 209-210, 2000.
90. KNIERIM, J.J., POE, G.R. AND MCNAUGHTON, B.L. Ensemble neural coding of place in zero-G. Pp. 63-68. In: BUCKEY, J.C., JR. AND HOMICK, J.L. (Eds.), *The Neurolab, Spacelab Mission: Neuroscience Research in Space*. NASA SP 535, NASA, Lindon B. Johnson Space Center, Houston, Texas, 2003.
91b. KOCSIS, B. The effect of descending theta rhythmic input from the septohypocampal system on firing in the supramammillary nucleus. *Brain Res.*, **1086**: 92-97, 2006.
91. LECHNER, S.M. AND VALENTINO, R.J. Glucocorticoid receptor-immunoreactivity in corticotrophin releasing factor afferents to the locus coeruleus. *Brain Res.*, **816**: 17-28, 1999.
92. LEDOUX, L., SASTRE, J.P., BUDA, C., LUPPI, P.-H. AND JOUVET, M. Alterations in c-fos expression after different experimental procedures of sleep deprivation in the cat. *Brain Res.*, **735**: 108-118, 1996.

93. LEWIS, E.J., HARRINGTON, C.A. AND CHIKARAISHI, D. Transcriptional regulation of the tyrosine hydroxilase gene by glucocorticoid and cyclic AMP. *Proc. Natl. Acad. Sci. USA.*, **84**: 3550-3554, 1987.

93b. LUPPI, P.-H., ASTON-JONES, G., AKAOKA, H., CHOUVET, G. AND JOUVET, M. Afferent projections to, the rat locus coeruleus demonstrated by retrograde and anterograde tracing with cholera-toxin B subunit and *phaseolus vulgaris* leucoagglutinin. *Neuroscience*, **65**: 119-160, 1995.

93c. MAGLOCZKY, Z., ACSADY, L. AND FREUND, T.F. Principal cells are the postsynaptic targets of supramammillary afferents in the hippocampus of the rat. *Hippocampus,* **4**: 322-334, 1994.

94. MAGNES, J., MORUZZI, G. AND POMPEIANO, O. Synchronization of the EEG produced by low-frequency electrical stimulation of the region of the solitary tract. *Arch. Ital. Biol.*, **99**: 33-67, 1961.

95. MALLIS, M.M. AND DE ROSHIA, C.W. Circadian rhythms, sleep and performance in space. *Aviation, Space and Environmental Medicine*, **76**: No 6, Section II, B94-B 107, 2005.

96. MALONEY, K.J., MAINVILLE, L. AND JONES, B.E. Differential c-Fos expression in cholinergic, monoaminergic and GABAergic cell groups of the pontomesencephalic tegmentum after paradoxical sleep deprivation and recovery. *J. Neurosci.*, **19**: 3057-3072, 1999.

97. MARINESCO, S., BONNET, C. AND CESPUGLIO, R. Influence of stress duration on the sleep rebound induced by immobilization in the rat: a possible role for corticosterone. *Neuroscience*, **92**: 921-933, 1999.

98. MCCLUNG, C.A., ULERY, P.G., PERROTTI, L.I., ZACHARIOU, V., BERTON, O. AND NESTLER, E.J. Δ Fos B: a molecular switch for long-term adaptation in the brain. *Mol. Brain Res.*, **132**: 146-154, 2004.

99. MCDANIEL, W.F., COMPTON, D.M. AND SMITH, S.R. Spatial learning following posterior parietal or hippocampal lesions. *Neuroreport*, **5**: 1713-1717, 1994.

100. MCNAUGHTON, B.L., CHEN, L.L. AND MARKUS, E.J. "Dead reckoning", landmark learning and the sense of direction: a neurophysiological and computational hypothesis. *J. Cogn. Neurosci.*, **3**: 190-202, 1991.

101. MELIA, N.R., RYABININ, A.E., SCHROEDER, R., BLOOM, F.E. AND WILSON, M.C. Induction and habituation of immediate early gene expression in rat brain by acute and repeated restraint stress. *J. Neurosci.,* **14**: 5929-5938, 1994.

102. MICHAUD, D.S., MCLEAN, J., KEITH, S.E., FERRAROTTO, C., HAYLEY, S., KHAN, S.A., ANISMAN, H. AND MERALI, Z. Differential impact of audiogenic stressors on Lewis and Fisher rats: behavioral, neurochemical and endocrine variations. *Neuropsychopharmachology*, **28**: 1068-1081, 2003.

103. MONK, T.H., BUYSSE, D.J., BILLY, B.D., KENNEDY, K.S. AND WILLRICH, L.M. Sleep and circadian rhythms in four orbiting astronauts. *J. Biol. Rhythms*, **13**: 18-201, 1998.

104. MORGAN, J.I. AND CURRAN, T. Stimulus-transcription coupling in the nervous system: involvement of inducible proto-oncogenes fos and jun. *Annu. Rev. Neurosci.*, **14**: 421-451, 1991.

104b. MORILAK, D.A., BARRERA, G., ECHEVARRIA, D.J., GARCIA, A.S., HERNANDEZ, A., MA, S., PETRE, C.O. Role of brain norepinephrine in the behavioral response to stress. *Progr. Neuro-Psychopharm. Biol. Psychiatry,* **29**: 1214-1224, 2005.

105. MORRISON, A.R. AND POMPEIANO, O. Vestibular influences during sleep. IV Functional relations between vestibular nuclei and lateral geniculate nucleus during desynchronized sleep. *Arch. Ital. Biol.*, **104**: 425-458, 1966.

106. MORRISON, A.R., SANFORD, L.D. AND ROSS, R.J. Initiation of rapid eye movement sleep beyond the brainstem. Pp. 51-68. In: MALLICK, B.N. AND INOUE, S. (Eds.), *Rapid Eye Movement Sleep*. Norosa Publ. House, New Delhi, 1999.

107. MORRISON, A.R., SANFORD, L.D. AND ROSS, R.J. The amygdala: a critical modulator of sensory influence on sleep. *Biol. Signals Recept.*, **9**: 283-296, 2000.
108. NESTLER, E.J. Molecular mechanisms of drug addition. *J. Neurosci.*, **12**: 2439-2450, 1992.
109. NESTLER, E.J., KELZ, M.B. AND CHEN, J. ΔfosB: a molecular mediator of long-term neural and behavioral plasticity. *Brain Res.*, **835**: 10-17, 1999.
110. NICOGOSSIAN, A.E. AND PARKER, J.F. *Space physiology and medicine*. Pp. 160-162. Washington DC, NASA Scientific and Technical Information Branch, 1982.
111. NISENBRAUM, L.K. AND ABERCROMBIE, E.D. Enhanced tyrosine hydroxylation in hippocampus of chronically stressed rats upon exposure to a novel stressor. *J. Neurochem.*, **58**: 276-281, 1992.
112. NISENBRAUM, L.K., ZIGMOND, M.J., SVED, A.F. AND ABERCROMBIE, E.D. Prior exposure to chronic stress results in enhanced synthesis and release of hippocampal norepinephrine in response to a novel stressor. *J. Neurosci.*, **11**: 1478-1484, 1991.
113. NOVAK, C.M. AND NUNEZ, A.A. Daily rhythms in Fos activity in the rat ventrolateral preoptic area and midline thalamic nuclei. *Am. J. Physiol.*, **275**: R1620-R1626, 1998.
114. O'HARA, B.F., WATSON, F.L., ANDRETIC, R., WILER, S.W., YOUNG, K.A., BITTING, L., HELLER, H.C. AND KILDUFF, T.S. Daily variation of CNS gene expression in nocturnal vs. diurnal rodents and in the developing rat brain. *Mol. Brain Res.*, **48**: 73-86, 1997.
115. PACE, T.W.W., GAYLORD, R., TOPCZEWSKI, F., GIROTTI, M., RUBIN, B. AND SPENCER, R.L. Immediate-early gene induction in hippocampus and cortex as a result of novel experience is not directly related to stressfulness of that experience. *Eur. J. Neurosci.*, **22**: 1679-1690, 2005.
116. PADEL, Y. AND DELL, P. Effects bulbaires et réticulaires des stimulations endormantés du tronc vago-aortique. *J. Physiol., Paris*, **57**: 269-270, 1965.
117. PAXINOS, G. AND WATSON, C. *The Rat Brain in Stereotaxic Coordinates. 4th ed.* San Diego, CA, Academic Press, 1998.
118. PEDEMONTE, M., BARRENECHEA, C., NUMEZ, A., GAMBINI, J.P. AND GARCIA-AUSTT, E. Membrane and circuit properties of lateral septum neurons: relationships with hippocampal rhythms. *Brain Res.*, **800**: 145-153, 1998.
119. POMPEIANO, M., CIRELLI, C., RONCA-TESTONI, S. AND TONONI, G. NGFI-A expression in the rat brain after sleep deprivation. *Mol. Brain Res.*, **46**: 143-153, 1997.
120. POMPEIANO, M., CIRELLI, C. AND TONONI, G. Effects of sleep deprivation on fos-like immunoreactivity in the rat brain. *Arch. Ital. Biol.*, **130**: 325-335, 1992.
121. POMPEIANO, M., CIRELLI, C. AND TONONI, G. Immediate-early genes in spontaneous wakefulness and sleep: expression of c-fos and NGFI-A mRNA and protein. *J. Sleep Res.*, **3**: 80-96, 1994.
122. POMPEIANO, M., D'ASCANIO, P., CENTINI, C., POMPEIANO, O. AND BALABAN, E. Short-term (Fos) and long-term (FRA) protein expression in rat locus coeruleus neurons during the Neurolab Mission: contribution of altered gravitational fields, stress and other factors. *Neuroscience*, **115**: 111-123, 2002.
123. POMPEIANO, O. The neurophysiological mechanisms of postural and motor events during desynchronized sleep. *Res. Publ. Ass. Nerv. Ment. Dis.*, **45**: 351-423, 1967.
124. POMPEIANO, O. *Mechanisms of sensorimotor integration during sleep*. In: STELLAR, E. AND SPRAGUE, J.M. (Eds.), *Progress in Physiological Psychology*. New York, London Academic Press, **3**: 1-179, 1970.
125. POMPEIANO, O. Vestibular influences during sleep. Pp. 583-622. In: KORNHUBER, H.H. (Ed.), *Handbook of Sensory Physiology*. Vol VI/1. *Vestibular System*. Part 1. *Basic Mechanisms*. Springer Verlag, Heidelberg, 1974.
126. POMPEIANO, O. Contribution of REM sleep to Fos and FRA expression in the vestibular

nuclei of rat leading to vestibular adaptation during the STS-90 Neurolab Mission. *Arch. Ital. Biol.*, **145**: 55-85, 2007.

127. POMPEIANO, O., D'ASCANIO, P., BALABAN, E., CENTINI, C. AND POMPEIANO, M. Gene expression in autonomic areas of the medulla and the central nucleus of the amygdala in rats during and after space flight. *Neuroscience*, **124**: 53-69, 2004.
128. POMPEIANO, O., D'ASCANIO, P., CENTINI, C., POMPEIANO, M. AND BALABAN, E. Gene expression in rat vestibular and reticular structures during and after space flight. *Neuroscience*, **114**: 135-155, 2002.
129. POMPEIANO, O., D'ASCANIO, P., CENTINI, C., POMPEIANO, M., CIRELLI, C. AND TONONI, G. Gene expression in the rat brain during space flight. Pp. 27-37. In: BUCKEY, JR., J.C. AND HOMICK, J.L. (Eds.), *The Neurolab, Spacelab Mission: Neuroscience Research in Space*. NASA SP 535. NASA, Lindon B. Johnson Space Center, Houston, Texas, 2003.
130. POMPEIANO, O. AND HOSHINO, K. Tonic inhibition of dorsal pontine neurons during the postural atonia produced by an anticholinesterase in the decerebrate cat. *Arch. Ital. Biol.*, **114**: 310-340, 1976.
131. POMPEIANO, O., MANZONI, D., BARNES, C.D., STAMPACCHIA, G. AND D'ASCANIO, P. Responses of locus coeruleus and subcoeruleus neurons to sinusoidal stimulation of labyrinth receptors. *Neuroscience*, **35**: 227-248, 1990.
132. POMPEIANO, O. AND MORRISON, A.R. Vestibular influences during sleep. I. Abolition of the rapid eye movements during desynchronized sleep following vestibular lesions. *Arch. Ital. Biol.*, **103**: 569-595, 1965.
133. POMPEIANO, O. AND MORRISON, A.R. Vestibular input to the lateral geniculate nucleus during desynchronized sleep. *Pflügers Arch.*, **290**: 272-274, 1966.
134. POTTER, E., SUTTON, G., DONALDSON, C., CHEN, R., PERRIN, M. AND LEWIS, K. Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. *Proc. Nat. Acad. Sci. USA*, **91**: 8777-8781, 1994.
135. PUIZILLOUT, J.J. Déclenchement réflexe de sommeil paradoxal par la stimulation des troncs vago-aortiques. Faits et hypothèses. *Rev. EEG Neurophysiol.*, **6**: 5-16, 1976.
136. PUIZILLOUT, J.J., TERNAUX, J.P., FOUTZ, A.S. AND FERNANDEZ, G. Les stades de sommeil de la préparation "encéphale isolé" I. Déclenchement des pointes ponto-geniculo-occipitales et du sommeil phasique à ondes lentes. Rôle des noyaux du raphé. *EEG Clin. Neurophysiol.*, **37**: 561-576, 1974.
137. QUADENS, O. AND GREEN, H. Eye movements during sleep in weightlessness. *Science*, **225**: 221-222, 1984.
138. RAMPIN, C., CESPUGLIO, R., CHASTRETTE, N. AND JOUVET, M. Immobilization stress induces a paradoxical sleep rebound in rat. *Neurosci. Lett.*, **126**: 113-118, 1991.
139. RECHTSCHAFFEN, A., BERGMANN, B.M., GILLILAND, M.A. AND BAUER, K. Effects of method, duration AND sleep stage on rebounds from sleep deprivation in the rat. *Sleep*, **22**: 11-31, 1999.
140. RICARDO, J.A. AND KOH, E.T. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala AND other forebrain structures in the rat. *Brain Res.*, **153**: 1-26, 1978.

140b. SABBAN, E.L. AND KVETNANSKY, R. Stress-triggered activation of gene-espression in, catecholaminergic systems: dynamics of transcriptional events. *Trends Neurosci.*, **24**: 91-98, 2001.

141. SAGAR, S.M., SHARP, F.R. AND CURRAN, T. Expression of c-fos protein in brain metabolic mapping at the cellular level. *Science*, **240**: 1328-1331, 1988.
142. SAHA, S. AND DATTA, S. Two-way active avoidance training-specific increases in phosphorylated cAMP response element-binding protein in the dorsal hippocampus, amygdala AND hypothalamus. *Eur. J. Neurosci.*, **21**. 3403-3414, 2005.

142b. SAITO, H., SAKAI, H. AND JOUVET, M. Discharge pattern of the nucleus parabrachialis, lateralis neurons of the cat during sleep and waking. *Brain Res.*, **134**: 59-72, 1977.

143. SAJDYK, T.J., SHEKHAR, A. AND GEHLERT, D.R. Interaction between NPY and CRF in the amygdala to regulate emotionality. *Neuropeptides*, **38**: 225-234, 2004.

144. SAKAI, K. Some anatomical and physiological properties of ponto-mesencephalic tegmental neurons with special reference to the PGO waves and postural atonia during paradoxical sleep in the cat. Pp. 427-447. In: HOBSON, J.A. AND BRAZIER, M.A.B. (Eds.), *The Reticular Formation Revisited. IBRO Monograph Series*. Vol. 6. Raven Press., New York, 1980.

145. SAKAI, K., SASTRE, J.-P., KANAMORI, N. AND JOUVET, M. State-specific neurons in the ponto-medullary reticular formation with special reference to the postural atonia during paradoxical sleep in the cat. Pp. 405-429. In: POMPEIANO, O. AND AJMONE MARSAN, C. (Eds.), *Brain Mechanisms of Perceptual Awareness and Purposeful Behavior*. Raven Press, New York, 1981.

146. SAKANAKA, M., SHIBASAKI, T. AND LEDERIS, K. Distribution and efferent projections of corticotrophin-releasing factor-like immunoreactivity in the rat amygdaloid complex. *Brain Res.*, **382**: 213-238, 1986.

147. SAKANAKA, M., SHIBASAKI, T. AND LEDERIS, K. Corticotropin-releasing factor-like immunoreactivity in the rat brain as revealed by a modified cobalt-glucose oxide-diaminobenzidine method. *J. Comp. Neurol.*, **260**: 256-298, 1987.

148. SANFORD, L.D., SILVESTRI, A.J., ROSS, R.J. AND MORRISON, A.R. Influence of fear conditioning on elicited ponto-geniculo-occipital waves and rapid eye movement sleep. *Arch. Ital Biol.*, **139**: 169-183, 2001.

149. SANFORD, L.D., TEJANI-BUTT, S.M., ROSS, R.J. AND MORRISON, A.R. Amygdaloid control of alerting and behavioral arousal in rats: involvement of serotonergic mechanisms. *Arch. Ital. Biol.*, **134**: 81-99, 1995.

149b. SANTIN, L.J., AGUIRRE, J.A., RUBIO, S., BEGEGA, A., MIRANDO, R. AND ARIAS, J.L. c-Fos expression in supramammillary and medial mammillary nuclei following spatial reference AND working memory tasks. *Physiol. Behav.*, **78**: 733-739, 2003.

150. SAITO, SAKAI K. and JOUVET M. Discharge patterns of the nucleus parabrachialis lateralis neurons of the cat during sleep and waking. *Brain Res.*, **134**: 59-72, 1977.

151. SANTY, P.A., KAPANKA, H., DAVIS, J.R. AND STEWART, D.F. Analysis of sleep on shuttle missions. *Aviat. Space Environ. Med.*, **59**: 1094-1097, 1988.

152. SASTRE, J.P., BUDA, C., KITAHAMA, K. AND JOUVET, M. Importance of the ventrolateral region of the periaqueductal gray and adjacent tegmentum in the control of paradoxical sleep as studied by muscimol microinjection in the cat. *Neuroscience*, **74**: 415-426, 1996.

153. SASTRE, J.-P., BUDA, C., LIN, J.-S. AND JOUVET, M. C-fos striato – septo-hippocampal., targets of paradoxical sleep. *Sleep*, **21** (Suppl): 14, 1998.

153b. SASTRE, J.P., BUDA, C., LIN, J.S. AND JOUVET, M. Differential c-fos expression in the, rhinencephalon and striatum after enhanced sleep-wake states in the cat. *Eur-J. Neurosci.*, **12**: 1397-1410, 2000.

154. SHAHED, A.R., SON, M., LEE, J.C. AND WERCHAN, P.M. Expression of c-fos, c-Jun and HSP70 mRNA in rat brain following high acceleration stress. *J. Grav. Physiol.*, **3**: 49-56, 1996.

154b. SHAHIDI, S., MOTAMEDI, F. AND NAGHDI, N. Effects of reversible inactivation of the supramammillary nucleus on spatial learning and memory in rats. *Brain Res.*, **1026**: 267-274, 2004.

155. SHARP, F.R., SAGAR, S.M., HICKS, K., LOWENSTEIN, D. AND HISANAGA, V. c-fos and other mRNA, Fos and Fos-related antigen induction by hypertonic saline and stress. *J. Neurosci.*, **11**: 2321-2331, 1991.

156. SHENG, M. AND GREENBERG, M.E. The regulation and function of c-fos and other immediate early genes in the nervous system. *Neuron*, **4**: 477-485, 1990.
157. SHERIN, J.E., SHIROMANI, P.J., MCCARLEY, R.W. AND SAPER, C.B. Activation of ventrolateral preoptic neurons during sleep. *Science*, **271**: 216-219, 1996.
158. SIEGEL, J.M. Brainstem mechanisms generating REM sleep. Pp. 1-28. In: KRYGER, M.K., ROTH, T. AND DEMENT, W.C. (Eds.), *Principles and practice of sleep medicine*. (Soc. Edition) Saunders, New York, 2000.
159. SMITH, C. Sleep states and learning: a review of the animal literature. *Neurosci. Biobehav. Rev.*, **9**: 157-168, 1995.
160b. SMITH, C. AND LAPP, L. Increases in number of REMS and REM density in humans following an intensive learning period. *Sleep*, **14**: 325-330, 1991.
160. SMITH, P.F. Vestibular-hippocampal interactions. *Hippocampus*, **7**: 465-471, 1997.
161. STERMAN, M.B. AND CLEMENTE, C.D. Forebrain inhibitory mechanisms: cortical synchronization induced by basal forebrain stimulation. *Exp. Neurol.*, **6**: 91-102, 1962.
162. STONE, E.A. AND ZANG Y. Adrenoceptor antagonists block c-fos response to stress in the mouse brain. *Brain Res.*, **694**: 279-286, 1995.
163. SWANSON, L.W. *Brain Maps: Structure of the Rat Brain*. Elsevier Sci. Publ., Amsterdam, New York, p. 240, 1992.
164. SWANSON, L.W. AND PETROVICH, G.D. What is the amygdala? *TINS*, **21**: 323-331, 1998.
165. SZYMUSIAK, R. Magnocellular nuclei of the basal forebrain: substrates of sleep and arousal regulation. *Sleep*, **18**: 478-500, 1995.
166. TANG, X., YANG, L., LIU, X. AND SANFORD, L.D. Influence of tetrodotoxin inactivation of the central nucleus of the amygdala on sleep and arousal. *Sleep*, **28**: 923-930, 2005.
167. TAUBE, J.S., GOODRIDGE, J.P., GOLOB, E.J., DUDCHENKO, P.A. AND STACKMAN, R.W. Processing the head direction signal: a review and commentary. *Brain Res. Bull.*, **40**: 477-486, 1996.
168. TERAO, A., GRECO, M.A., DAVIS, R.W., HELLER, H.C. AND KILDUFF, T.S. Region-specific changes in immediate early gene expression in response to sleep deprivation and recovery sleep in the mouse brain. *Neuroscience*, **120**: 1115-1124, 2003.
169. TEYLER, T.J. Comparative aspects of hippocampal and neocortical long-term potentiation. J. *Neurosci. Meth.*, **28**: 101-108, 1989.
169b. THINSCHMIDT, J.S., KINNEY, G.G. AND KOCSIS, B. The supramammillary nucleus: is it, necessary for the mediation of hippocampal theta rhythm? *Neuroscience*, **67**: 301-312, 1995.
170. ULLOR, J. AND DATTA, S. Spatio-temporal activation of cyclic AMP response element-binding protein, activity-regulated cytoskeletal-associated protein and brain-derived nerve growth factor: a mechanism for pontine-wave generator activation-dependent two-way active-avoidance memory processing in the rat. *J. Neurochemistry*, **95**: 418-428, 2005.
170b USHER, M., COHEN, J.D., SERVAN-SCHREIBER, D., RAJKOWSKI, J. AND ASTON-JONES, G. The, role of locus coeruleus in the regulation of cognitive performance. *Science*, **283**: 549-554, 1999.
171. VALENTINO, R.J., CHEN, S., ZHU, Y. AND ASTON-JONES, G. Evidence for divergent projections of corticotropin-releasing hormone neurons of Barringhton's nucleus to the locus coeruleus and spinal cord. *Brain Res.*, **732**: 1-15, 1996.
172. VALENTINO, R.J., PAGE, M.E., VAN, BOCKSTAELE, E. AND ASTON-JONES, G. Corticotropin-releasing factor innervation of the locus coeruleus region: distribution of fibers and sources of input. *Neuroscience*, **48**: 689-705, 1992.
173. VALENTINO, R.J., RUDOY, C., SAUNDERS, A., LIU, X.-B. AND VAN BOCKSTAELE, E.J. Corticotropin-releasing factor is preferentially colocalized with excitatory rather than

inhibitory amino acids in axon terminals in the peri-locus coeruleus region. *Neuroscience*, **106**: 375-384, 2001.

174. VAN BOCKSTAELE, E.J., CHAN, J. AND PIECKEL, V.M. Input from central nucleus of the amygdala efferents to pericoerulear dendrites, some of which contain tyrosine hydroxylase immunoreactivity. *J. Neurosci. Res.*, **45**: 289-302, 1996.
175. VAN BOSKSTAELE, E.J., COLAGO, E.E.O. AND VALENTINO, R.J. Corticotropin-releasing factor containing axon terminals synapse onto catecholamine dendrites and may presynaptically modulate other afferents in the rostral pole of the nucleus locus coeruleus in the rat brain. *J. Comp. Neurol.*, **364**: 523-534, 1996.
176. VAN BOSKSTAELE, E.J., COLAGO, E.E.O. AND VALENTINO, R.J. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites substrate for the coordination of emotional and cognitive limbs of the stress response. *J. Neuroendocrinol.*, **10**: 743-757, 1998.
177. VAN BOCKSTAELE, E.J., PEOPLES, J. AND VALENTINO, R.J. Differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. *Biol. Psychiatry*, **46**: 1352-1363, 1999.
178. VAN GOOL, W.A., WITTING, W. AND MIRMIRAN, M. Age-related changes in circadian sleep-wakefulness rhythms in male rats isolated from time cues. *Brain Res.*, **413**: 384-387, 1987.
179. VERTES, R.P., PHA-L analysis of projections from the supramammillary nucleus in the rat. *J. Comp. Neurol.*, **326**: 595-622, 1992.
180. VINCENT, S.R. AND SATOH, K. Corticotropin-releasing factor (CRF) immunoreactivity in the dorsolateral pontine tegmentum: further studies on the micturition reflex system. *Brain Res.*, **308**: 387-391, 1984.
181. WALLACE, D.M., MAGNUSON, D.J. AND GRAY, T.S. Organization of amygdaloid projections to brainstem dopaminergic, noradrenergic AND adrenergic cell groups in the rat. *Brain Res. Bull.*, **28**: 447-454, 1992.
182. WILSON, M.A. AND MCNAUGHTON, B.L. Dynamics of hippocampal ensemble code for space. *Science*, **261**: 1055-1058, 1993.
183. ZHENG, Y., SMITH, P.F. AND DARLINGTON, C.L. Noradrenaline and serotonin levels in the guinea pig hippocampus following unilateral vestibular deafferentation. *Brain Res.*, **836**: 199-202, 1999.