

Transcranial stimulation of the brain by magnetic fields

Dr. med. Oliver Seemann

Specialist in Psychiatry and Psychotherapy
Head of the Center for Transcranial Magnetic Stimulation Munich

Prof. Dr. med. Marcus Seemann

Professor of Neuroradiology and Nuclear Medicine, University of Tübingen

Over the last years a clear paradigm shift from chemistry to physics showed in neuroscience research. Particularly in brain research, it has been shown that new, above all, physical approaches can open up interesting perspectives and lead to better results. Various methods are used for stimulating the brain: electric current, acoustic and optical signals or magnetic fields. Many techniques are promising at first glance; however they often turn out to be awkward, sometimes harmful / dangerous, the efficiency can not be proven or long-term effects are missing. The most widely researched method for over 25 years is repetitive transcranial magnetic stimulation (rTMS). It could be shown that in healthy people effects a significant improvement in the quality of life can be accomplished. The latest developments make it possible to detach the rTMS from stationary use in practice and to use it in almost every location and in almost every activity. Due to the simple choice of different simulation programs, a versatile use of the mobile magnetic stimulator GLAD-X is possible: in an efficacy study conducted since 2017 with currently 173 evaluable healthy subjects, it has been shown that night sleep and its quality, daytime tranquility and well-being during the day can be improved, the cognitive speed and performance and efficiency of the power nappings (*fig. 1*). During the first practical use of the mobile magnetic stimulator, it was found that wrinkles around the forehead were (partially) smoothed by magnetic stimulation alone. In collaboration with stem cell researchers, the effect could be further increased in the clinical application.

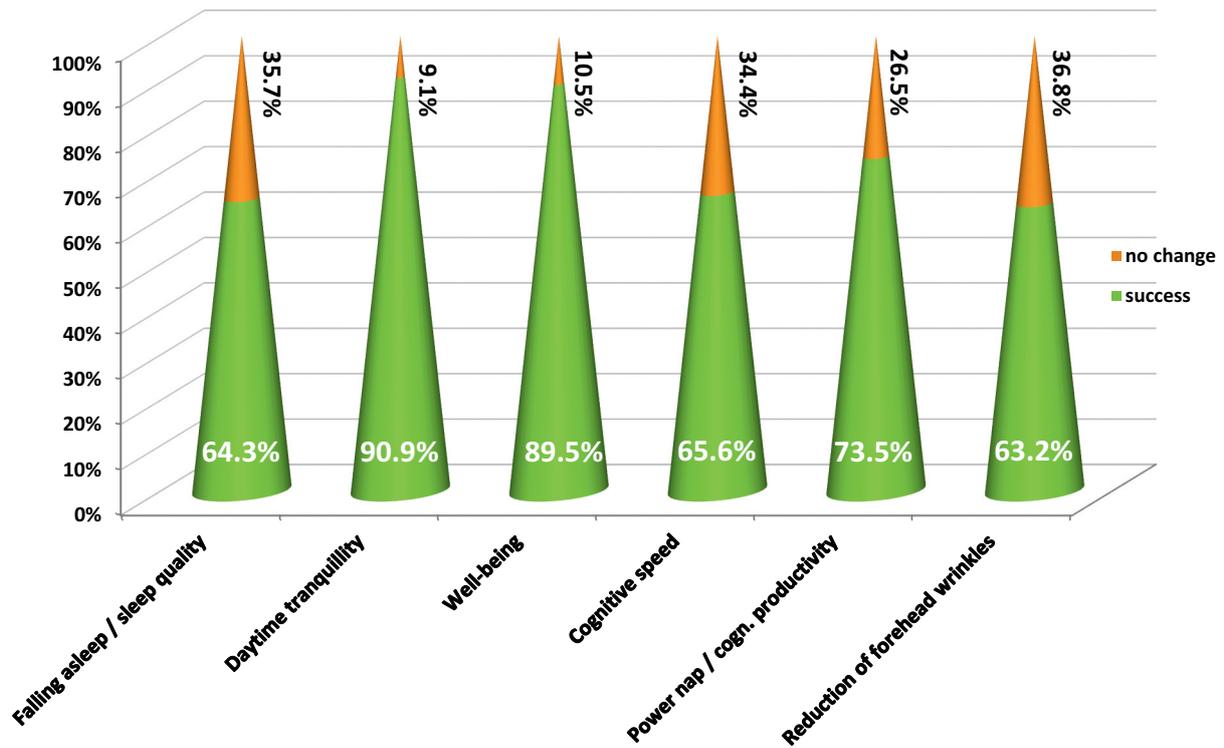


Fig. 1: Response to GLAD-X stimuli / efficacy study GLAD-X LS / intermediate analysis last updated on 11/20/2018

Sleep

Why we sleep is not completely clear yet, but it is clear that a brain without sleep for various reasons degenerates and becomes ill [1]. Since during sleep a number of sensory stimuli are eliminated or are perceived to be greatly diminished (especially environmental stimuli), it is understandable that the brain activity changes compared to the waking state. Brain activity during sleep is cyclic and repeats approximately every 90 minutes (*fig. 2*). During sleep phases with REM activity (Rapid Eye Movement) alternate with falling asleep and deep sleep phases. The REM phases account for about 20% of the total sleep duration and are the phases in which we dream.

During non-REM sleep, the nerve cells are in "bistable" energetic states of "highs" and "lows", with an approximate periodicity of one second. This results in slow waves (delta waves, frequency range 0.5-4 Hertz), which perform functional tasks of synchronization of other brain waves and the optimization of the energy level and thus overall induce sleep [2, 3].

Sleep regulation depends, on the one hand, on circadian rhythmic metabolic processes and, on the other hand, on the need for sleep as a consequence of the duration of the waking state. For example, a wakefulness of over 40 hours leads to a massive increase in delta waves during the subsequent sleep [4].

Sleep regulation depends, on the one hand, on circadian rhythmic metabolic processes and, on the other hand, on the need for sleep as a consequence of the duration of the waking state. For example, a wakefulness of over 40 hours leads to a massive increase in delta waves during the

subsequent sleep [4].

The quality of sleep depends significantly on the depth of sleep induced by delta waves [5, 6, 7, 8, 9]. These results are consistent with the finding that slow sleep waves have a regenerative effect [2]. Not surprisingly, experiencing stress while awake, and even expecting stress for the next day, can reduce delta activity during sleep and sleep quality [10].

Recognizing the importance of delta activity for sleep quality, several methods have been developed and explored to increase it. However, drugs which increase the slow waves via so-called GABAergic activation have no positive effects on memory [11] and can also have harmful effects (hangover) and side effects. Other methods that have the best possible natural effect on the brain are the physical methods with somatosensory stimuli, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (rTMS).

The rather complicated procedure of tDCS postulates an increase in delta activity when DC stimulation of nerve cells occurs at a frequency of 0.75 hertz [12]. It is supposed to also improve the hippocampus mediated memory functions. However, due to the strong signal interference of tDCS' DC stimulation with the much weaker brain waves, it is difficult to predict actual effectiveness on delta waves [13] and postulated results are mainly based on computer simulations [14].

Although somatosensory methods, in particular those with acoustic stimuli, are also intended to promote the delta activity during sleep [15, 16, 17, 18], the effect is detectable only during the application, ie without long-

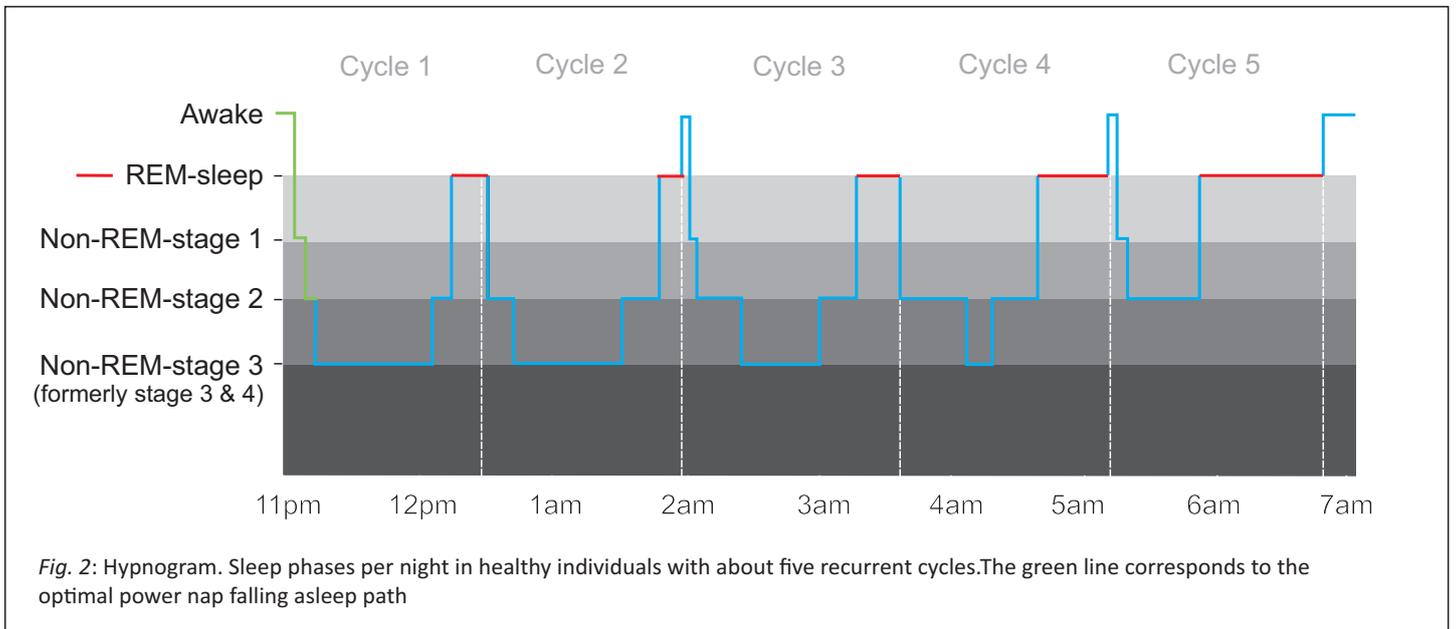


Fig. 2: Hypnogram. Sleep phases per night in healthy individuals with about five recurrent cycles. The green line corresponds to the optimal power nap falling asleep path

term effects and the (possibly) positive effect Memory is limited to linguistic functions.

Transcranial magnetic stimulation (rTMS) leads to the triggering of slow brainwaves during the non-REM phases, which are identical to those of the naturally occurring ones [19, 20]. Long-term effects of increased delta activity due to altered plasticity and network architecture are well known [21]. However, to date, a relatively high technical complexity has brought about these effects.

With the development of a mobile magnetic stimulator, a simple and continuous application of the rTMS at home is possible, whereby the sleep quality can be naturally improved in the long term. The recommended daily 30-minute bedtime treatment over several weeks obviously results in a favorable change in brain architecture that can be demonstrated beyond the application. The stimulation parameters of the mobile applicator provide excellent compatibility with convenient use.

Power napping

The so-called power napping has long been known as "afternoon nap". Especially in many Asian countries, it is widespread and integrated into everyday life.

Power napping targets non-REM sleep stages 1 and 2, which are achieved within the first 10 to 20 minutes of falling asleep. The return from these sleep stages to wakefulness is easy (fig. 2). If you sleep for more than about 25 minutes and then wake up, you will probably feel tired and dizzy because you have already been in (deep) sleep stage 3 (predominance of delta activity) [22].

The benefits of the short power nap are manifold, ranging from improving health to improving work performance [23] (fig. 3). In a large-scale study, it was shown that the risk of heart attack can be reduced by 37% within five years due to a reduction in stress and metabolic disorders [24]. Other health benefits include improving mood, promoting testosterone release and the immune system. Increased

sleep results in weight loss and increased potency.

The glymphatic system (neologism from glia and lymphatic system), which is practically active only during sleep, removes metabolites and soluble proteins from the brain. All neurodegenerative diseases such as Alzheimer's, Parkinson's, ALS, etc. are attributed to an accumulation of misfolded proteins in the brain [25]. A functioning glymphatic system, which presupposes a healthy and regular sleep, can therefore be regarded as protection against these diseases.

After power napping, there is an increase in attention and alertness. This increases productivity and the ability to develop problem-solving strategies in the workplace. By reducing stress [26] and improving job satisfaction, creativity increases and the rate of errors decreases [27].

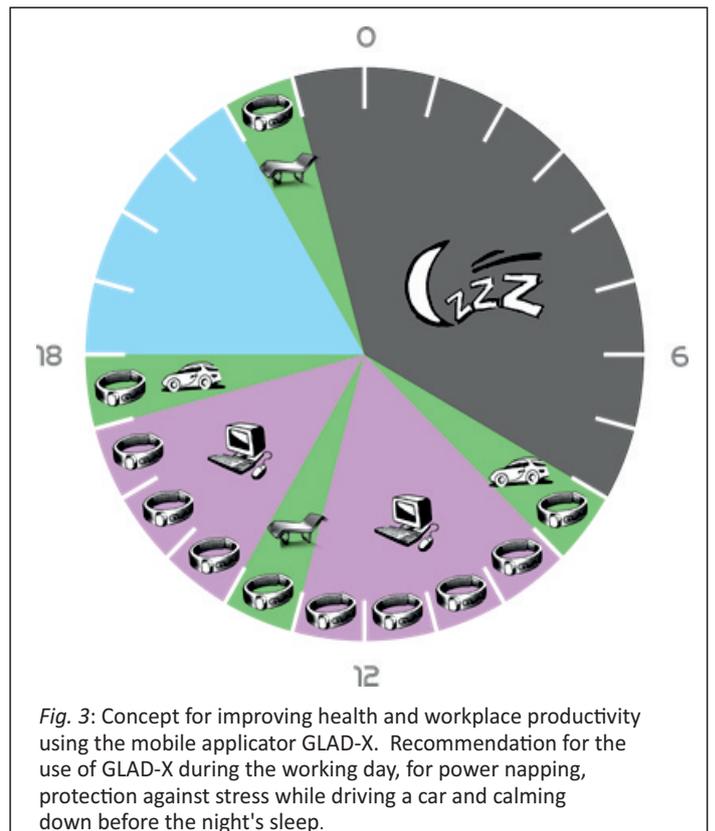


Fig. 3: Concept for improving health and workplace productivity using the mobile applicator GLAD-X. Recommendation for the use of GLAD-X during the working day, for power napping, protection against stress while driving a car and calming down before the night's sleep.

51% of employees feel they are less productive due to stress during work [28]. The increased attention results in a reduction of accidents in the workplace and in-duty strokes, thus reducing absenteeism at the workplace.

In contrast to stimulants like coffee or taurine, this natural stimulation method does not cause any mental crashes as soon as the effect wears off.

The safe and effective method of rTMS helps to promote sleep, especially delta activity [23, 24]. With the help of the easy-to-use mobile applicator for 10 to 20 minutes, falling asleep can be accelerated and the time to reach non-REM phases 1 or 2 shortened, thus increasing the efficiency of power nappings [29]. This also applies to people who have difficulty falling asleep during the day. The optimal period for the nap is between 1 and 2 pm and should be carried out while lying down [30].

Energizing, Emotional Intelligence

During the daily activity the brain tries to keep the activation state of the brain waves in a healthy balance. In the normal state the so-called alpha-activity (8-12 hertz) (*fig. 4*) predominates in the active brain, which makes us feel awake, active and balanced.

In conditions with excess rapid beta activity (12-25 Hertz), the organism is over-excited. This happens, for example, while driving, whereby the stress leads to a hyperarousal. As a natural consequence, the organism tries to escape external stimuli in order to reduce the stimulation for the brain and thus come to rest. The healthy response to too-rapid brain activity is thus fatigue and withdrawal as protection against stimulus flooding [31].

In phases with increased occurrence of slow theta and delta waves, the equilibrium is also disturbed. In order to reach the equilibrium state, the organism tries to counteract, to obtain as many stimuli as possible, so that the brain activity is increased again in the direction of the normal state [31]. The emotional response is restlessness, nervousness, irritability and the search for external stimuli.

To avoid counter-regulatory measures with negative emotional effects and performance deficits, it is desirable to maintain the system in a natural balance.

GLAD-X offers the option to provide the brain with natural alpha frequencies to permanently promote a balanced and healthy state of activation of the brain as well as maintaining emotional balance and performance (*fig. 5*).

Concentration, Attention, Intellectual Intelligence

In order to express intellectual abilities, at least 5 anatomical structures in the brain must be coordinated (Formatio reticularis, hippocampus, amygdala, frontal basal cortex, corpus geniculatum). These structures must work synchronously and in balance.

In particular, the beta (12 to 25 hertz) and gamma activity

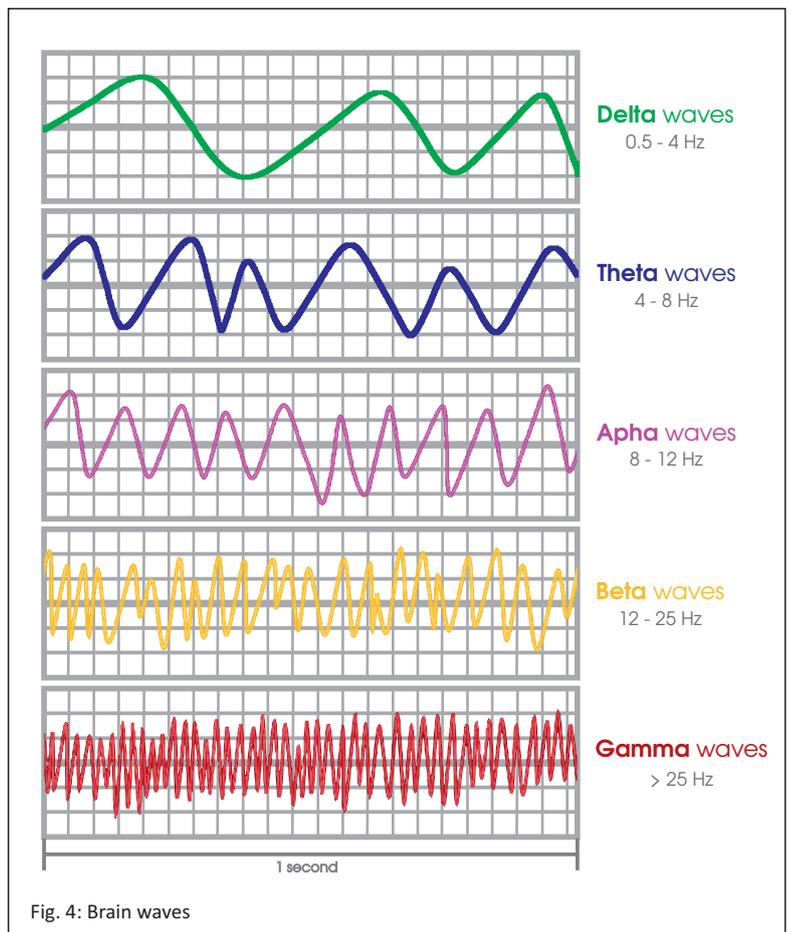


Fig. 4: Brain waves

(over 25 hertz) are considered to be of great importance [32, 33, 34]. It is postulated that GLAD-X facilitates the synchronization and balancing of these brain structures by stimulating pulsed magnetic fields on both sides, thus promoting concentration, attention, and intelligence, which could be demonstrated in an efficacy study [35] (*fig. 1*).

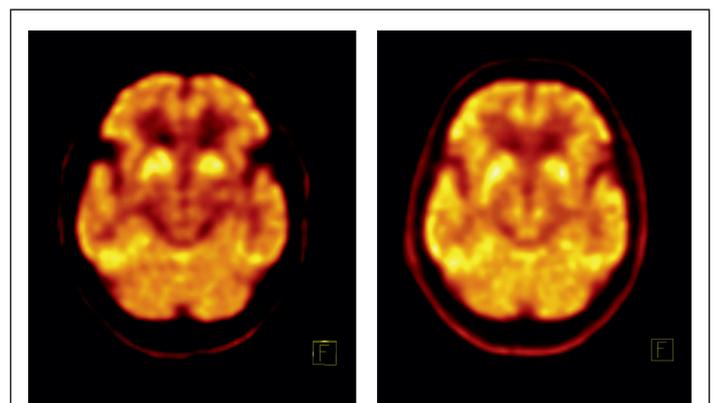


Fig. 5: PET-scans before/after magnetic stimulation (GLAD-X): increase in metabolism in the basal ganglia and the cerebral cortex

Meditation and Spiritual Intelligence

Spiritual intelligence is an inner wisdom that is guided by compassion and leads to serenity. This form of intelligence is superior to the emotional and intellectual.

Meditation teachers, religious leaders, spiritual masters and gurus as well as martial artists should have a particularly high spiritual intelligence quotient and thus have a

higher consciousness.

Brain physiologically, the basis for this is a special frequency of brain waves in the gamma region, especially 40 hertz [36, 37]. This frequency is intended to promote the synchronization of neuronal activity. The so-called "binding problem" describes the hitherto unexplained phenomenon that different sensory impressions (for example, color, contour, contrast, movement) are deposited at different parts of the brain but are perceived simultaneously by the brain, ie in the subjective present. There are many indications that such synchronization processes are transmitted by means of electromagnetic waves [38, 39], which is also supported by studies with magnetoencephalographic examinations[40].

The mobile applicator GLAD-X provides this frequency and has the advantage of a bihemispheric stimulation over the conventional rTMS, facilitating the synchronization of the two hemispheres of the brain (fig. 5).

It thus promotes the qualities and feelings associated with spiritual intelligence: compassion, kindness, sense of purpose in life, gladness, love and joy, summit experiences, spontaneity, visions, inspirations, flow feelings, mindfulness, self-esteem, better sensory perception and memory.

Relaxation / well-being

Feeling good is the opposite of negative stress (distress). In the case of distress there is a dysbalance in the neural network of gladness with over-excitement in some areas (amygdala) and lower-excitation in others (hippocampus, frontal-brain). Similarly, both halves of the brain are poorly connected and synchronized.

The neural network for gladness consists of at least seven anatomical structures (ventral tegmentum, amygdala, nucleus accumbens, orbitofrontal cortex, anterior cingulus, precuneus, hypothalamus). To be glad, all seven must be active at the same time and in balance.

One of the most important sources of regeneration processes is the thalamus, which "cleanses" the brain system - mainly while asleep - at a frequency of 4 Hertz (equivalent to garbage collection in computer jargon, removing unneeded data fragments) [41]. The child's brain also shows more activity with frequencies around 4 hertz, promoting the learning process [42]. In the shamanistic tradition, this frequency is used in drum rituals to induce a healing trance.

In clinical observation with GLAD-X, it has indeed been shown that the frequency of 4 Hertz initiates and supports the feeling of gladness and well-being, and thus serves not only the well-being, but also the regeneration.

Beauty

By increasing feelings of happiness and relaxation as well as a supposed improved blood circulation of the skin, the charisma can improve, wrinkles on the skin can be reduced and thus the attractiveness be increased. GLAD-X is already used in cosmetics in combination with stem cell injections to increase the efficacy of stem cells by suggesting that stem cells survive longer through magnetic fields and are easier to divide and differentiate [43]. As the hair follicle cells are also stimulated, the hair root can be strengthened and hair growth promoted. In particular, the use of GLAD-X at bedtime promotes night sleep, which may lead to weight loss [44].

Synopsis

The use of pulsed magnetic fields to stimulate the brain is a method from high-tech research, whose enormous potential and performance has been proven by numerous studies. It allows for a positive impact on various aspects of quality of life and intellectual ability. For companies, there is a significant return on investment in the form of increased productivity and less absenteeism in the workplace.

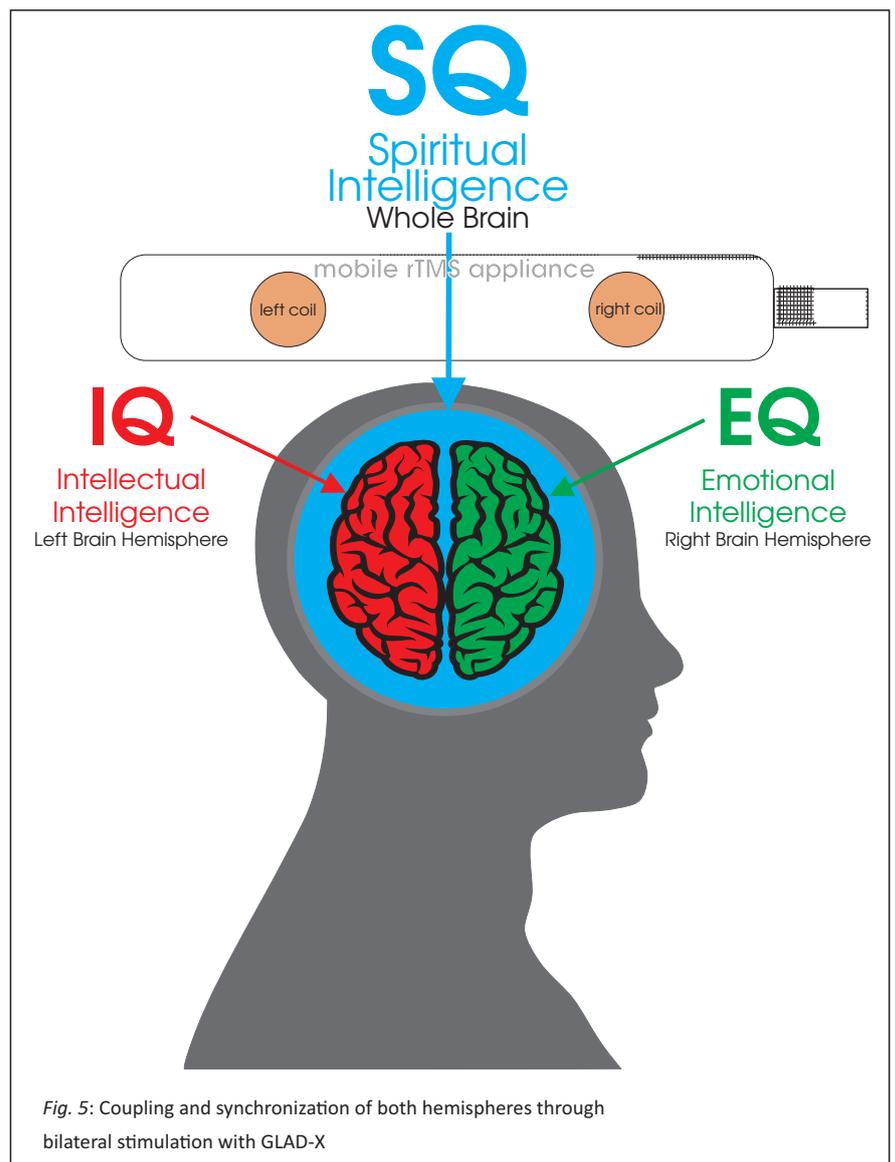


Fig. 5: Coupling and synchronization of both hemispheres through bilateral stimulation with GLAD-X

List of references

1. Cirelli C, Tononi G. Is sleep essential? *PLoS Biology*, 6(8):e216, 2008.
2. Cirelli C, Tononi G. Sleep function and synaptic homeostasis. *Sleep Medicine Reviews*, 10(1):49–62, 2006.
3. Cirelli C, Tononi G. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron*, 81(1):12–34, 2014.
4. Borbély A. A two-process model of sleep regulation. *Human Neurobiology*, 1(3):195–204, 1982.
5. Hauner KK, Howard JD, Zelano C, Gottfried JA. Stimulus-specific enhancement of fear extinction during slow-wave sleep. *Nature Neuroscience*, 16(11):1553–5, 2013.
6. Keklund G and Åkerstedt T. Objective components of individual differences in subjective sleep quality. *Journal of Sleep Research*, 6(4):217–220, 1997.
7. Åkerstedt T, Hume K, Minors D, Waterhouse J. Good sleep — its timing and physiological sleep characteristics. *Journal of Sleep Research*, 6(6):221–229, 1997.
8. Hoch CC, Reynolds CF, Kupfer DJ, Berman SR, Houck PR, Stack JA. Empirical note: self-report versus recorded sleep in healthy seniors. *Psychophysiology*, 24(3):293–299, 1987.
9. Kryger MH, Steljes D, Pouliot Z, Neufeld H, Odynski T. Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. *Sleep*, 14(5):399–407, 1991.
10. Kecklund G, Åkerstedt T. Apprehension of the subsequent working day is associated with a low amount of slow wave sleep. *Biological Psychology*, 66(2):169–176, 2004.
11. Feld GB, Wilhelm I, Ma Y, Groch S, Binkofski F, Mölle M, and Born J. Slow wave sleep induced by GABA agonist tiagabine fails to benefit memory consolidation. *Sleep*, 36(9):1317–26, 2013.
12. Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature*, 444(7119):610–613, 2006.
13. Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, Rothwell JC, Lemon RN, Frackowiak RS. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *European Journal of Neuroscience*, 22(2):495–504, 2013.
14. Kunze T, Hunold A, Haueisen J, Jirsa V, Spiegler A. Transcranial direct current stimulation changes resting state functional connectivity: a large-scale brain network modeling study. *Neuroimage*, 140: 174–87, 2016.
15. Ngo HV, Miedema A, Faude I, Martinetz T, Mölle M, Born J. Driving sleep slow oscillations by auditory closed-loop stimulation—a self-limiting process. *The Journal of Neuroscience*, 35(17):6630–6638, 2015.
16. Papalambros NA, Santostasi G, Malkani RG, Braun R, Weintraub S, Paller KA, Zee PC. Acoustic enhancement of sleep slow oscillations and concomitant memory improvement in older adults. *Frontiers in Human Neuroscience*, 11(March):1–14, 2017.
17. Santostasi G, Malkani R, Riedner BA, Bellesi M, Tononi G, Paller KA, Zee PC. Phase-locked loop for precisely timed acoustic stimulation during sleep. *Journal of Neuroscience Methods*, 1–14, 2015.
18. Leminen MM, Virkkala J, Saure E, Paajanen T, Phyllis C Zee, Santostasi G. Enhanced memory consolidation via automatic sound stimulation during non-REM sleep. *Sleep*, 40(3):1–10, 2017.
19. Massimini M, Ferrarelli F, Esser SK, Riedner BA, Huber R, Murphy M, Peterson MJ, Tononi G. Triggering sleep slow waves by transcranial magnetic stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, 104(20):8496–8501, 2007.
20. Bellesi M, Riedner BA, Garcia-Molina G, Cirelli C, Tononi G. Enhancement of sleep slow waves: underlying mechanisms and practical consequences. *Frontiers in Systems Neuroscience*, 8(October):1–17, 2014.
21. Assenza G, Pellegrino G, Tombini M, Di Pino G, Di Lazzaro V. Wakefulness delta waves increase after cortical plasticity induction. *Clin Neurophysiol*, 126(6):1221–1227, 2015.
22. Hilditch C, Centofanti S, Dorrian J, Banks S. A 30-Minute, but Not a 10-Minute Nighttime Nap is Associated with Sleep Inertia. *Sleep*. 39(3): 675–685, 2016.
23. Santos-Silva R, Jankavski C, Lorenzi-Filho G. The experience of a Power Nap Center in the largest city of Brazil. *Sleep Sci*, 9(3):151–152, 2016.
24. Naska A, Oikonomou E, Trichopoulou A, Psaltopoulou T, Trichopoulos D. Siesta in Healthy Adults and Coronary Mortality in the General Population. *Arch Intern Med*, 167(3):296–301, 2007.
25. Jessen N A , Munk A S, Lundgaard I, Nedergaard N. The Glymphatic System: A Beginner's Guide. *Neurochemical research* 40(12): 2583–2599, 2015.
26. Oriyama S, Miyakoshi Y, Kobayashi T. Effects of two 15-min naps on the subjective sleepiness, fatigue and heart rate variability of night shift nurses. *Ind Health*, 52(1):25–35, 2014.
27. Mednick, S C et al. The restorative effects of naps on perceptual deterioration. *Nature Neuroscience*, 5:677–81, 2002.
28. Officevibe. www.officevibe.com, 2018.
29. Hayashi M, Motoyoshi N, Hori T. Recuperative power of a short daytime nap with or without stage 2 sleep. Hayashi M1, Motoyoshi N, Hori T. *Sleep*, 28(7):829–36,

83(3):207-13, 2010.

31. Hegerl U, Hensch T. The vigilance regulation model of affective disorders and ADHD. *Neurosci Biobehav Rev*, 44:45-57, 2014.

32. Rosen A, Reiner M. Right frontal gamma and beta band enhancement while solving a spatial puzzle with insight. *Int J Psychophysiol*, 122:50-55, dec 2017.

33. Lundqvist M, Rose J, Herman P, Brincat SL, Buschman TJ, Miller EK. Gamma and Beta Bursts Underlie Working Memory. *Neuron*, 6;90(1):152-164, apr 2016.

34. Montefusco-Siegmund R, Leonard TK, Hoffman KL. Hippocampal gamma-band Synchrony and pupillary responses index memory during visual search. *Hippocampus*, 27(4):425-434, apr 2017.

35. Seemann O, k.u.k. Datentechnik GmbH. Observational Study transcranial magnetic stimulation with GLAD-X. *Intermediate evaluation last updated on 11/20/2018*. Publication is prepared.

36. Singer W. Striving for coherence. *Nature*, 397:391-393, 1999.

37. Crick F, Koch C. Towards a neurobiological theory of consciousness. *Seminars in the neurosciences*, 2:263-275, 1990.

38. Morgan HM, Muthukumaraswamy SD, Hibbs CS, Shapiro KL, Bracewell RM, Singh KD, Linden DE. Feature integration in visual working memory: parietal gamma activity is related to cognitive coordination. *J*

Neurophysiol, 106(6):3185-94, 2011.

39. Ross B, Fujioka T. 40-Hz oscillations underlying perceptual binding in young and older adults. *Psychophysiology*, 53(7):974-90, 2016.

40. Hagiwara K, Okamoto T, Shigeto H, Ogata K, Somehara Y, Matsushita T, Kira J, Tobimatsu S. Oscillatory gamma synchronization binds the primary and secondary somatosensory areas in humans. *Neuroimage*, 51(1):412-20, 2010.

41. Roy A, Svensson FP, Mazeh A, Kocsis B. Prefrontal-hippocampal coupling by theta rhythm and by 2-5 Hz oscillation in the delta band: The role of the nucleus reuniens of the thalamus. *Brain Struct Funct*, 222(6):2819-2830, 2017.

42. Bauch EM, Bunzeck N, Hinrichs H, Schmitt FC, Voges J, Heinze HJ, Zaehle T. Theta oscillations underlie retrieval success effects in the nucleus accumbens and anterior thalamus: Evidence from human intracranial recordings. *Neurobiol Learn Mem*, 155:104-112, 2018

43. Liu H, Han XH, Chen H, Zheng CX, Yang Y, Huang XL. Repetitive magnetic stimulation promotes neural stem cells proliferation by upregulating MiR-106b in vitro. *J Huazhong Univ Sci Technolog Med Sci*, 35(5):766-772, 2015.

44. Theorell-Haglöw J, Lindberg E. Sleep Duration and Obesity in Adults: What Are the Connections? *Curr Obes Rep*, 5(3):333-43, 2016.



