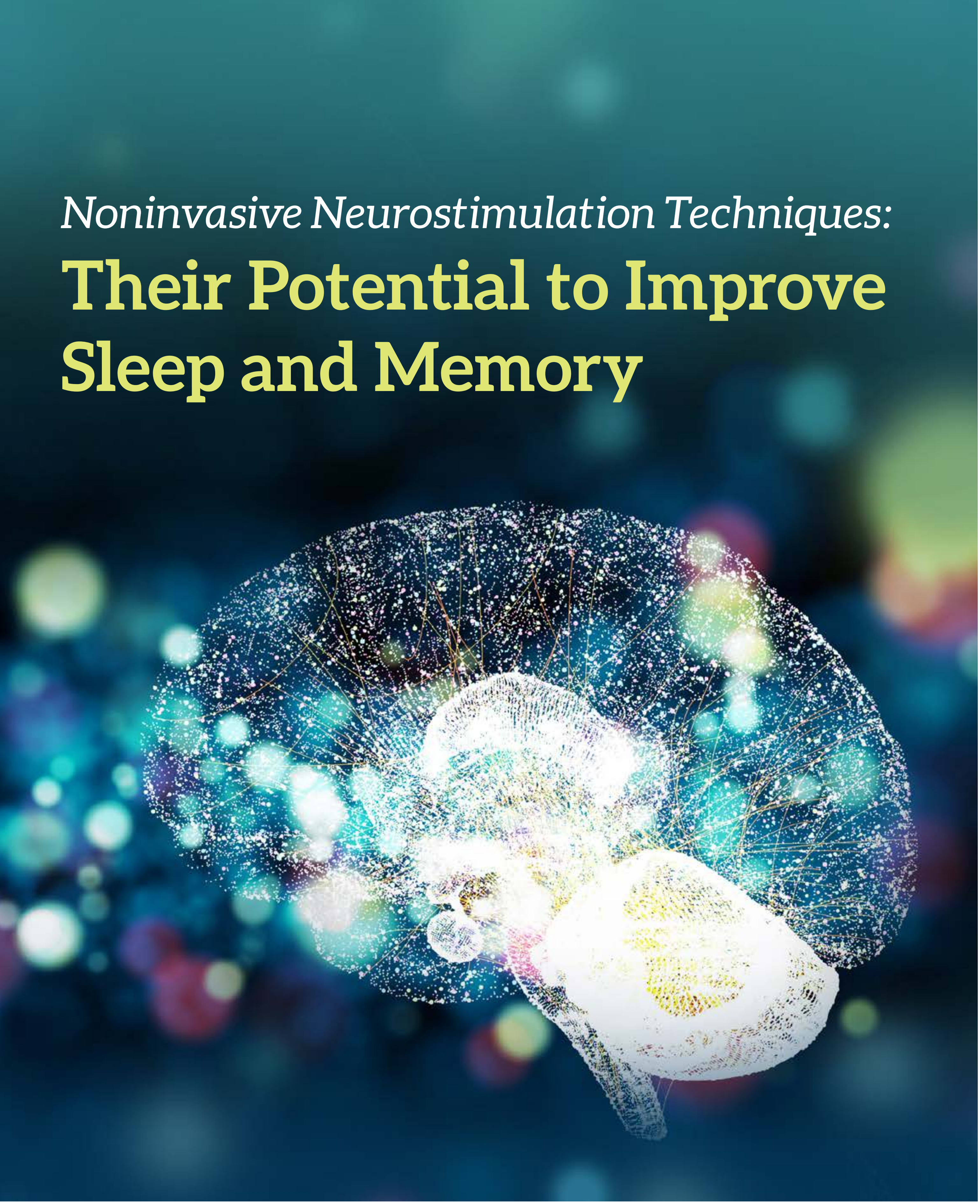
Noninvasive Neurostimulation Techniques: Their Potential to Improve Sleep and Memory



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Aging and neurodegenerative conditions (e.g., Alzheimer's disease) are associated with changes in sleep features such as slow-wave sleep (SWS), slow oscillations (SOs) and spindles, and changes in these sleep features have been associated with impaired memory and cognition.[1-8] Some recent research indicates that administering noninvasive brain stimulation (e.g., transcranial magnetic stimulation and transcranial ultrasound stimulation) can enhance SWS, SOs and spindles.[1] These techniques can also improve certain aspects of memory in older adults and in adults with mild cognitive impairment.[9,10]

Effects of Aging on Sleep

With aging, an individual's brain volume shrinks, particularly in the frontal cortex, which is responsible for cognitive functions such as attention, working memory (i.e., the ability to remember and use information while performing an activity) and social-emotional evaluation of stimuli. Gray matter (i.e., the cortex of the brain) also thins with aging. These changes are thought to occur because neurons shrink in volume; the number of dendrites (i.e., extensions from the neuronal body that convey an impulse from the axon of another neuron into the neuronal body) decrease; myelin (a fatty substance surrounding axons) deteriorates; and the number of connections (i.e., synapses) between brain cells also decreases, which can affect learning and memory.[11]

In addition, as people age, sleep becomes more fragmented, and sleep duration becomes shorter. The amount of SWS and slow-wave activity also reduces with aging, whereas the amount of non-rapid eye movement in sleep stage 1 and stage 2 (NREM1 and NREM2, respectively) increases. The characteristics of sleep features such as SOs and sleep spindles also change with aging.[2] SOs (i.e., a type of slow-wave activity with an electroencephalogram (EEG) frequency of <1 cycle/second or Hz) are generated by the thalamocortical system and have a lower density and amplitude in older adults than in younger individuals. SOs also have a depolarizing phase (i.e., "upstate"), which reflects neuronal activation, followed by a hyperpolarization phase (i.e., "downstate"), which reflects neuronal inhibition. Sleep spindles (i.e., intermittent short bursts of activity with a frequency of 12–15 Hz during NREM2 sleep) are generated by neurons in the thalamic reticular nucleus and synchronized by thalamocortical interactions. With aging, sleep spindles tend to reduce in density, duration, amplitude and frequency.

Electricity Treatments

Scientists have long been interested in using electricity to treat brain disorders. In 1804, Giovanni Aldini reported his experience using what is now called transcranial direct current stimulation.[12] In his self-experiment, he used a voltaic pile to deliver the electrical current. (A voltaic pile consists of several elements, each of which contains a copper disk, which releases electrons, covered by an electrolyte — e.g., salt water-soaked felt — that is then covered by a zinc disc, which accepts electrons.) A rod extended from the pile's top disk to Aldini's head. Thus, a weak electrical current traveled from the voltaic pile to his brain. Aldini described feeling a strong shock against the inner surface of his skull, which increased as he moved the rod from ear to ear, and he experienced insomnia for several days thereafter.

In 2000, Nitsche and Paulus[13] reported their experience in applying a weak, direct current (DC) through the scalp to noninvasively modulate the activity of neurons in the motor cortex of live humans. They found that cerebral neuronal activity could be selectively increased or decreased, depending on whether an anodal electrical current (i.e., the flow of positive ions starts at the anode) or a cathodal electrical current (i.e., the flow of ions starts at the cathode) was applied; anodal stimulation enhances excitability, whereas cathodal stimulation decreases it. For either stimulation method, the neuronal activity lasted a few minutes after the stimulation.

Since the Nitsche and Paulus study, various modalities (e.g., electric current, magnetic field, sound waves) have been used to alter the electrical activity of the brain. Examples of transcranial electrical stimulation (TES) are transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial magnetic stimulation (TMS) and transcranial ultrasound stimulation (TUS/tFUS).

Transcranial Direct Current (tDCS)

An anodal current is usually used in tDCS. Many direct current systems use sponge electrodes that are soaked in a saline solution before being applied to the head. More recently, EEG electrodes with conductive gel have been used. The active electrode (usually the anode) is placed over the target region, and the inactive electrode (usually the cathode) is placed opposite it. The current is applied for 10 to 40 minutes, depending on the activation desired, and the current applied can range from 1 milliamp to 4 milliamps.

Transcranial Alternating Current Stimulation (tACS)

Transcranial alternating current stimulation is applied similarly to transcranial direct current stimulation, except a small pulsed alternating current is delivered through electrodes on the head. Sponge electrodes or EEG electrodes with conductive gel are used. The current applied ranges from 0.2–1 milliamp at a frequency of 0.1–640 Hz.

Transcranial Random Noise Stimulation (tRNS)

In 2008, German researchers Terney and colleagues[14] were the first team to apply tRNS in humans. In this technique, the same equipment is used as for tACS. However, the alternating current applied to the scalp has a random amplitude and frequency (range 0.1–640 Hz). After stimulation, cortical excitability can last up to 60 minutes. However, this excitatory effect only occurs at the higher frequencies. How tRNS affects brain

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activity is unknown. An interesting finding is that reversing electrode polarities in tRNS does not interfere with increased cortical excitability (i.e., tRNS-induced cortical excitability appears to be independent of current flow direction).[15]

Transcranial Magnetic Stimulation (TMS)

In TMS, brief pulses of currents are emitted through a stimulating coil held over a person's scalp at the target brain region. Two types of TMS exist: repetitive TMS and single-pulse TMS. The current flow (lasting <0.001 second) generates a rapidly changing magnetic field around the coil. The currents stimulate neurons on the areas on the cortex close to the stimulation. The stimulatory effects can travel to neurons just below the surface of the brain and to distant locations that are connected to certain networks. The poststimulatory effects last longer with repetitive TMS than with single pulse TMS.

Transcranial Ultrasound Stimulation (TUS/tFUS)

In transcranial ultrasound stimulation, ultrasound waves are used to induce electrical changes in the brain. Brain regions beneath the transducer (i.e., the device that delivers the ultrasound waves) are activated. In a technique called focused ultrasound, the ultrasound waves are delivered as a continuous wave. However, a drawback of focused ultrasound is the potential danger of brain heating as well as the generation of unintended secondary stimulation. In a more recently developed technique called transcranial pulse stimulation,[16] single ultrashort (3 μs) ultrasound pulses with typical energy levels of 0.2–0.3 mJ/mm2 and pulse frequencies of 1–5 Hz are administered to the scalp. The shorter pulses and lower energy levels avoid the drawbacks of focused ultrasound. Scientists are not sure how ultrasound activates neurons in the brain. A possibility is that the mechanical effect of the waves on a neuron's surface impacts the release of neurotransmitters (e.g., serotonin, gamma-aminobutyric acid) that alter neuronal activation.[16]

Improving Memory Consolidation

Some research indicates that applying TES during sleep modulates memory consolidation.[17] For example, Cellini and colleagues[18] applied short-duration, repetitive TES during sleep to examine the consolidation of declarative memory (i.e., the ability to remember facts) in healthy young- to middle-aged individuals. The stimulation was delivered at regular intervals (4 seconds at 0.75 Hz oscillating current) during NREM sleep. They found that this stimulation technique, compared to sham treatment (i.e., no stimulation) enhanced memory performance immediately after sleep and 48 hours later. The stimulation also increased the proportion of time spent in non-rapid eye movement sleep stage 3 (NREM3) sleep and increased the overall rate of SOs during NREM2/NREM3 sleep.

Improved memory with noninvasive brain stimulation has been noted in the elderly, as well. For example, in adults with mild cognitive impairment who were, on average, 71 years old, Ladenbauer and colleagues[10] applied a slow-oscillatory transcranial direct current (so-tDCS) during a daytime nap to modulate sleep neuronal activity and sleep-related memory consolidation. They found that the stimulation significantly increased the overall SOs and spindle power, amplified the spindle power during the SO upstate, and resulted in stronger synchronization between SO and spindle power fluctuations in EEG recordings. They further found that visual declarative memory (e.g., the ability to remember the sequence of images in a presentation) improved with the stimulation compared to without the stimulation.

In an animal study, French researcher Lendai and colleagues[19] treated rats with the serotonin-depleting drug parachlorophenylalanine. As a consequence, the animals had frequent arousals and insomnia associated with the loss of serotonin levels. After applying TES to these animals, the duration and number of rapid eye movement (REM) sleep periods increased and the brain's serotonin activity increased, which may have improved sleep.

Spindling and SOs are involved in memory consolidation, and decreases in these sleep features are associated with impaired memory.[1,3] Findings of increased spindling, SOs and improved memory with noninvasive brain stimulation are encouraging. Transcranial electrical stimulation could potentially be used to improve sleep in people with neurocognitive disorders or, when changes in spindling or SOs are detected, the technique could be used to strengthen these features to delay (or prevent) the onset of neurocognitive disorders. However, the extent transcranial brain stimulation improves sleep, cognition and memory remains unclear, and scientists continue to investigate TES techniques to learn exactly how they exert their effect and how to best utilize them as a treatment for impaired cognition and sleep.

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References

1. Grimaldi D, Papalambros NA, Zee PC, et al. Neurostimulation techniques to enhance sleep and improve cognition in aging. Neurobiology of Disease. 2020;141:104865.

2. Gorgoni M, Lauri G, Truglia I, et al. Parietal fast sleep spindle density decrease in Alzheimer's disease and amnesic mild cognitive impairment. Neural Plasticity. 2016;2016:8376108.
3. Ju Y, Ooms, SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-beta levels. Brain. 2017;140:2104-2111.
4. Mander B, Rao V, Lu B, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. Nature Neuroscience. 2013;16:357-364.
5. Mander B, Marks SM, Vogel JW, et al. Beta-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. Nature Neuroscience. 2015;18:1051-1057.
6. Varga A, Wohlleber ME, Gimenez S, et al. Reduced slow-wave sleep is associated with high cerebrospinal fluid Abeta42 levels in cognitively normal elderly. Sleep. 2016;39:2041-2048.
7. Cordone S, Annarumma L, Rossini PM, et al. Sleep and beta-amyloid deposition in alzheimer disease: insights on mechanisms and possible innovative treatments. Frontiers in Pharmacology. 2019;10:695.
8. Dube J, Lafortune M, Bedetti C, et al. Cortical thinning explains changes in sleep slow waves during adulthood. Journal of Neuroscience. 2015;35:7795-7807.
9. Malkani RG, Zee PC. Brain stimulation for improving sleep and memory. Sleep Medicine Clinics. 2020;15:101-115.
10. Ladenbauer J, Ladenbauer J, Kulzow N, et al. Promoting sleep oscillations and their functional coupling by transcranial stimulation enhances memory consolidation in mild cognitive impairment. Journal Neuroscience. 2017;37:7111-7124.
11. Peters R. Ageing and the brain. Postgraduate Medical lJournal. 2006;82(964):84-88.
12. Aldini G. Essai theorique et experimental sur le galvanisme, avec une serie d'experiences faites devant des commissaires de l'Institut National de France, et en divers amphitheatres anatomiques de Londres. [Theoretical and experimental test on galvanism, with a series of experiments made in front of commissioners of the National Institute of France, and in various anatomical amphitheaters of London]. Paris: Fournier Fils; 1804. In French.
13. Nitsche M, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. Journal of Physiology. 2000;527:633-639.
14. Terney D, Chaieb L, Moliadze V, et al. Increasing human brain excitability by transcranial high-frequency random noise stimulation. Journal of Neuroscience. 2008;28:14147-14155.
15. Paulus W. Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods. Neuropsychological Rehabilitation.21:602-617.
16. Beisteiner R, Matt E, Fan C, et al. Transcranial pulse stimulation with ultrasound in Alzheimer's disease—a new navigated focal brain therapy. Advanced Science (Weinh). 2020;7:1902583.
17. Rasch B, Born J. About sleep's role in memory. Physiological Reviews. 2013;93:6811-6766.
18. Cellini N, Shimizu RE, Connolly PM, et al. Short duration repetitive transcranial electrical stimulation during sleep enhances declarative memory of facts. Frontiers in Human Neuroscience. 2019;13:123.
19. Lendais I. CF, Laude D, et al. Effect of transcranial electrical stimulation on sleep in rats. Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales [Reports of the Sessions of the Biological Society and its Subsidiaries]. 1989;183:329-336. In French.