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Neural Dynamics of Audiovisual Entrainment: Comparative Effects of Cross-Lateralized and Bilateral Synchronous Stimulation on EEG Power and Multiscale Entropy

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Table of Contents

List of abbreviations

1. AVE - Audiovisual Entrainment
2. AVS - Audiovisual Stimulation
3. BWE - Brainwave Entrainment
4. LSM - Light and Sound Machines
5. CLS - Cross-Lateralized Stimulation
6. BSS - Bilateral Synchronous Stimulation
7. NIBS - Non-invasive Brain Stimulation
8. tDCS - Transcranial Direct Current Stimulation
9. rTMS - Repetitive Transcranial Magnetic Stimulation
10. LGN - Lateral Geniculate Nucleus
11. RVF - Right Visual Field
12. LVF - Left Visual Field
13. BB - Binaural Beats
14. MB - Monaural Beats
15. tACS - Transcranial Alternating Current Stimulation
16. tRNS - Transcranial Random Noise Stimulation
17. EC - Eyes Closed
18. EO - Eyes Open
19. EEG - Electroencephalography
20. iAPF - Individual Alpha Peak Frequency
21. HAM-D - Hamilton Rating Scale for Depression
22. SAD - Seasonal Affective Disorder
23. QIP - Performance Intelligence Quotient
24. WAIS-R - Wechsler Adult Intelligence Scale-Revised
25. RPM - Raven’s Progressive Matrices
26. SMR - Sensory Motor Rhythm
27. AD - Alzheimer’s Disease

Chapter one

Introduction:

Audiovisual Entrainment (AVE) is a non-pharmacological, rhythmic, stimulus-driven intervention that aligns the brain's electrical frequencies with externally presented audio and visual cues (Huang & Charyton, 2008). This synchronization is thought to influence various cognitive and emotional processes. Furthermore, to improve conceptual understanding, distinctions have been established between audiovisual entrainment and audiovisual stimulation (AVS) to clarify the usage contexts of these terms: AVE involves a controlled, consistent delivery of targeted frequencies, while AVS may include exposure to a range of frequencies, such as those experienced during television watching (Siever & Collura, 2017).

Technically, AVE is delivered through devices ranging from essential headphones and visual displays to more sophisticated systems like AVE-specific wearable glasses (Teng et al., 2011). These technologies highlight AVE's flexibility, simplicity, and portability, enabling its application in both traditional clinical environments and user-driven settings at home as it is findable in the market.

Economically, AVE offers a cost-effective solution for brain modulation. Unlike more noninvasive brain stimulation (NiBS) techniques requiring extensive setup and maintenance, AVE devices are standalone units that do not require ongoing consumables costs; such economic efficiency, combined with the broad applicational potential of AVE in therapeutic settings and cognitive research, positions it as a valuable tool in clinical and experimental neuroscience.

AVE could be categorized as a neuromodulatory technique. It may act through the entrainment of neural population to the delivered audio/visual frequency, a process utilized across various scientific disciplines. Entrainment, originally described as a biological phenomenon where an organism exhibits a frequency-resonant response to a sequence of stimuli, has also been found in neural populations in response to external stimulation (Johnson et al., 2020). AVE is characterized by its multifaceted aspects and can be implemented in numerous forms. The term "AVE" concisely encapsulates the essence of this technique; however, its representation varies across different studies. Despite these variations, the field of neuromodulation faces a significant challenge due to the absence of standardized protocols and consistent terminology for AVE.

AVE has also been referred to in literature as:

- Audiovisual Stimulation (AVS) (Brauchli et al., 1995; Hsiung & Hsieh, 2024a; Mansouri et al., 2022; Oppermann et al., 2023; H.-Y. Tang et al., 2014; H.-Y. J. Tang et al., 2016; Teplan et al., 2009; Timmermann et al., 1999)
- Brainwave Entrainment (BWE) (Aftanas et al., 2016; Frohlich et al., 2021; Huang & Charyton, 2008; Locke et al., 2020)
- Mind Machine (M. Hutchison, 1986; “Mind Machine,” 2024; *The Ultimate Guide To Brainwave Entrainment – SHIFT*, n.d.)
- Light and Sound Machines (LSM) (M. Hutchison, 1990; Siggins, n.d.)
- Light and Sound Stimulation (da Silva et al., 2015; M. Hutchison, 1990, 1990; Larkin, 2023)
- Audio Photic Stimulation (APS) (Budzynski et al., 1999; Leonard et al., 1999; Sanchez et al., 2012; H.-Y. Tang et al., 2014)
- Brain Wave Synchronizer (BWS) (“Brainwave Synchronizer,” n.d.; Morse, 1993)
- Haptic and Multimodal Rhythmic Stimuli (Bouwer et al., 2013; Whitmore et al., 2024)
- Multisensory Stimulation (Blanpain et al., 2024; Làdavas et al., 2022; Tajadura-Jiménez et al., 2012)

Audio and Visual Stimulation in History

The significance of audio and visual stimulation has been deeply entrenched in history. The impact of visual stimulation may have started with the discovery of fire when our ancestors perceived the alteration of consciousness by staring at a flaming burning fire (M. Hutchison, 1986). Knowledge about the effects of auditory stimulation and the effort to make instruments capable of producing beats has been dated to 5500–2350 BC (Liu, 2007).

In the Ancient Greek age, Apuleius (124-170 AD) fabricated a light stimulator with a pot. Ptolemy (100-170 AD) proclaimed that if you placed a spoke wheel by the sunlight and rotated it, the observer would see flickering lights and enter a euphoric state (*Theories of Vision from Al-Kindi to Kepler, Lindberg*, n.d.). In the late 19th and early 20th centuries, Pierre Janet, a French psychologist, observed that spinning a spoke wheel reduced symptoms of depression, tension, and hysteria (Bobon et al., 1982).

Auditory stimuli, particularly in the form of rhythmic pulses, play a significant role in various religious rituals, exemplified by the practices of Shamanism. This spiritual tradition, which focuses on establishing connections with the supernatural world, characteristically initiates its sacred ceremonies with drumming. The drumbeat precedes attaining a shamanic state of consciousness, a critical phase during which shamans should engage in healing, wellness, and communication with spiritual entities. The drum is perceived not merely as a musical instrument but as a transformative tool, metaphorically described as a horse that transports the shaman to other worlds (Harner, 1990).

In summary, compelling evidence suggests that ancient civilizations recognized the profound impact of visual and auditory stimuli on human consciousness. From the effects of gazing into a fire to the rhythmic drumming in shamanic rituals, these sensory experiences have shaped human interaction with the world. However, in contemporary society, the significance of such stimuli may need to be improved. This is attributed to the heightened threshold for sensory excitement, exacerbated by constant exposure to the intense and pervasive influences of modern multimedia devices. This evolution in sensory engagement reflects a significant shift in how humans perceive and respond to auditory and visual stimuli in the digital age.

AVE effects on brain regions

The pathway of the visual system

To grasp the operational effects of AVE, it is essential first to summarize how the brain receives and processes the stimuli this technique delivers. Unlike other noninvasive brain stimulation (NiBS) techniques, the stimuli do not reach the cerebral cortex from the scalp but rather navigate through multiple brain areas following the sensory pathways, engaging both the auditory and visual systems. Concerning the visual system, information travels from the initial contact with the eye to the higher processing stages in the brain. Converting light to an electrical signal happens in the retina through rods and cones, then is processed by intermediate neurons before the ganglion cells are reached. The signals navigate the optic nerve to the thalamus's lateral geniculate nucleus (LGN), which relays to the primary visual cortex (V1). Subsequent processing occurs in further cortical areas, each specialized for different visual functions.

This region is sensitive to visual features, such as orientation (Hubel & Wiesel, 1968) , and sends the processed signal to higher-order brain visual regions, such as V2, V3, V4, and the middle temporal area (Goldman-Rakic & Rakic, 1991). The visual system stream of information can be systematically classified into two principal pathways based on distinct functional roles: the ventral and dorsal pathways. The ventral pathway establishes a neural connection from the occipital lobe to the temporal lobe, facilitating object recognition, commonly called the "what" pathway. In contrast, the dorsal pathway connects the occipital lobe to the parietal lobe, enabling the spatial localization of objects, thus known as the "where" pathway. These pathways are

integral for processing complex visual information, as elucidated by Mishkin and Ungerleider (1982).
V4, for instance, has been introduced as an essential region for color perception(S. Zeki, 1998). Later, it was revealed that this is one of the critical nodes for perceiving complex features (Pasupathy & Connor, 2002). This is the first region of the ventral visual pathways, which processes object recognition. A further region that receives signals from the primary and secondary visual regions, which instead processes motion perception. In this area, direction-selective neurons that respond to a specific direction of motion (S. M. Zeki, 1974) and motion patterns (Stoner & Albright, 1992) are present.

In addition to these hierarchical cortical areas, the visual system includes a subcortical route extending from the lateral geniculate nucleus (LGN) to the superior colliculus. This pathway, highlighted in recent studies Grünert et al. (2021), is critical in mediating reflexive visual responses and orienting behaviors. The integration of cortical and subcortical pathways underscores the complexity and efficiency of the visual processing network, which is essential for interpreting and responding to the visual environment.

The pathway of the Auditory system

Compared to the visual system, the auditory system is complex and has not been studied or explored well (Tuckute et al., 2023). The frequency, intensity, and time are the physical parameters of sound. Sound waves of vibrating objects move through the air and enter the tympanic membrane or eardrum. The sound is mechanically propagated into the cochlea by the hammer, anvil, and stirrup. The cochlea has approximately 16,000 sensory receptors that encode the physical aspects of sound. The traveled waves pass through the basilar membrane, which organizes the high and low frequencies in frequency-specific or tonotopy. By the end, the sound is converted into electrical responses in auditory nerve fibers, a part of the 8th cranial nerve (vestibulocochlear) (Kelly, Johnson, Delgutte, & Cariani, 1996).
When the sound arrives in the brain, like the visual system, it goes through several

brain regions. Between those regions, there are two main pathways that the auditory system follows. First is the ascending auditory pathway, which pre-processes and carries the sensory input. Second is the descending auditory pathway, which modulates and controls the auditory inputs. These two pathways comprise various subcortical structures.
The dedicated region of the brain that processes sound is called the auditory cortex. It is situated inside the Sylvian fissure on the surface of the supratemporal plane and the upper banks of the superior temporal gyrus in each hemisphere. The auditory cortex comprises multiple structural (anatomical) brain areas with different roles in interpreting sound.
Anatomically, the auditory cortex includes Heschl's gyrus in the anterior-inferior and posterior-superior directions, along with the supratemporal plane and the upper bank of the superior temporal gyrus. (Kumar, Stephan, Warren, Friston, & Griffiths, 2007).

The components of AVE

The categorization of Audiovisual Entrainment (AVE) as a technique of the noninvasive brain stimulation (NiBS) techniques remains unclear. Nevertheless, AVE exhibits several standard parameters comparable to conventional NiBS methods, indicating potential parallels in their neuromodulatory impacts.

Various neuromodulation techniques, such as transcranial direct current stimulation (tDCS), employ multiple parameters influencing their functional mechanisms. In tDCS, aspects such as stimulation duration, the electric current's polarity, electrode size, and current intensity are critical. This setting dramatically determines whether the stimulation produces inhibitory or excitatory effects on neural circuits (Sreeraj et al., 2023). Notwithstanding initial research, the comprehensive effects of various AVE configurations on brain responses and clinical outcomes remain ambiguous. Preliminary findings, like those by Rosenfeld et al. (1997), illustrate possible applications of specific

AVE configurations while underscoring the necessity for additional research. Further comprehensive research are necessary to assess AVE's therapeutic potential and to refine its parameters for certain clinical requirements.

Similarly, the effectiveness of AVE in influencing neural activity is contingent upon several specific parameters. These parameters include the visual pulse's color and shape, the stimuli's frequency and phase, and the auditory pulse's pitch. Research exploring the modulation of psychiatric disorders by these parameters has shown that various settings can alter cortical activity effects to achieve precise therapeutic results (Fregni et al., 2021; Kekic et al., 2016; M.-F. Kuo et al., 2017).

Notwithstanding initial research, the comprehensive effects of various AVE configurations on brain responses and clinical outcomes remain ambiguous. Preliminary findings, like those by Rosenfeld et al., 1997, illustrate possible applications of specific AVE configurations while underscoring the necessity for additional research. Further comprehensive research is necessary to assess AVE's therapeutic potential and to refine its parameters for certain clinical requirements.

Intensity

The first essential element of the AVE treatment that requires modification prior to initiation is the intensity of the light and the sound volume, personalized for each participant. Customization is crucial because of the large variations in retinal sensitivity, pupil size (Unsworth et al., 2019), and the anatomy of eyelashes and eyelids among individuals, particularly those linked to ethnic origins (Unsworth et al., 2019). Moreover, auditory sensitivity is distinctly individual (Kidd et al., 2007), necessitating precise modulation of sound loudness to ensure an optimal and comfortable experience for every participant. The above factors are crucial, as failure to adapt them may result in diminished effectiveness, discomfort for the participant, and feelings of fatigue and aversion.

Color

Audiovisual Entrainment devices in the market typically incorporate lights of varying colors, as illustrated in Figure 1. A substantial body of research supports that color influences individual mood and behavior and elicits distinctly varied effects based on the specific hue (Babin et al., 2003; Kurt & Osueke, 2014; Kwallek et al., 1988). For instance, studies have documented how different colors can induce different psychological responses, ranging from calming effects with blue to stimulating effects with red (Birren, 2016; Greene et al., 1983; Itten & van Haagen, 1973).

Moreover, the interaction between color and brain function extends beyond subjective psychological effects to quantifiable changes in brain activity. Research Münch et al. (2014) has shown that various colors can distinctly influence brain wave patterns. This evidence implies that the selection of colors in AVE devices could be deliberately tailored to engage specific neural rhythms linked with desired psychological states.

These studies have important implications for the design and application of AVE devices. By understanding the nuanced effects of color on both psychological and neurophysiological levels, manufacturers can enhance the efficacy of AVE technologies. This approach allows for more personalized therapeutic options and opens new avenues for research into how visual stimuli interact with cognitive and emotional processing within the brain.

Figure 1 presenting the different color

Frequency

The frequency parameter is pivotal in noninvasive brain stimulation techniques, dramatically impacting neural outcomes. In the context of repetitive transcranial magnetic stimulation (rTMS), it has been documented that stimulation at a frequency of 1 Hz reduces cortical excitability, as demonstrated by Gerschlager et al. (2001). Conversely, higher frequencies have an excitatory effect on cortical areas (Fitzgerald et al., 2006). Similar variability in response based on frequency settings is observed in audiovisual entrainment (AVE). Research indicates that AVE stimulation within the theta frequency band (5 Hz) can enhance memory functions (Addante et al., 2021a). In contrast, stimulation in the beta frequency range appears to yield no significant improvements in cognitive performance (Roberts et al., 2018).

This differential impact underscores the critical role of precise frequency selection in aligning with specific neurophysiological targets. Frequency settings directly influence the synchronization of brain networks by modulating brain oscillations and facilitating activity coordination across various neural nodes (Hadjipapas et al., 2023). Therefore, the choice of frequency in AVE studies should be carefully considered and defined, drawing from an extensive review of the existing literature and the targeted therapeutic or cognitive outcomes. Such a strategic approach ensures that the selected frequencies are optimally aligned with the intended goals of the brain stimulation protocol.

Phase

As mentioned, the visual processing system is unique in its contralateral organization. More specifically, stimuli from the right visual field are exclusively processed by the left hemisphere of the brain, while stimuli in the left visual field enter the right hemisphere. Such an anatomical arrangement allows for selective, independent stimulation of each hemisphere. That is particularly valuable within neuromodulation techniques when one's goal is to target some areas or functions of the brain.

In the context of Audiovisual Entrainment (AVE), this neural architecture is exploited by stimulating the left visual field (LVF) and right visual field (RVF) with a phase offset, as illustrated in Figure 2. This method of stimulation results in differential brain responses, depending on the targeted hemisphere. Such hemisphere-specific stimulation can be particularly insightful for studies on understanding lateralized brain functions and their impact on cognitive and behavioral processes. Research by Henriksson et al. (2012), Liang et al. (2021), and Vanegas et al. (2013) supports the effectiveness of this approach, indicating that.

Targeted visual field stimulation can elicit distinct patterns of brain activity, offering a nuanced tool for investigating and manipulating brain dynamics.

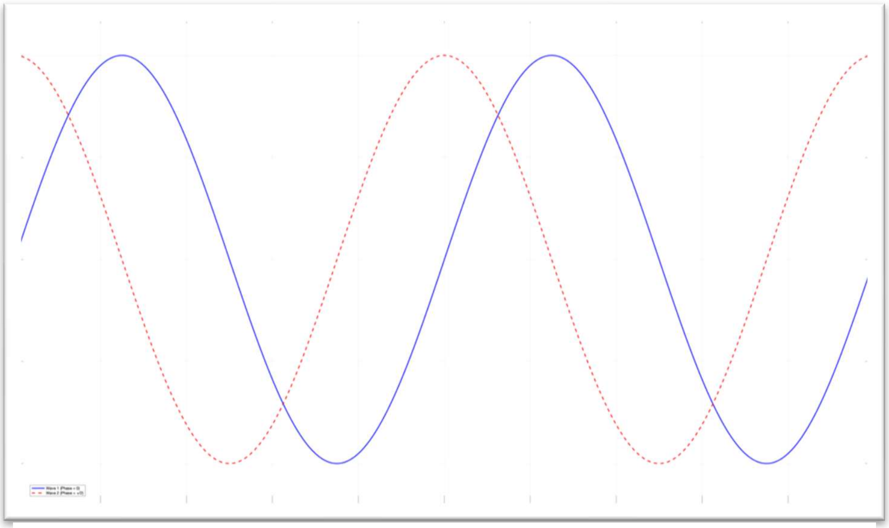


Figure 2 - two sinusoidal waves with different phases

The shape of the visual pulse

Flicker refers to the rapid oscillation of light intensity, akin to the repetitive switching of a light source between on and off states. The duration of each flicker and the temporal dynamics required to achieve the lowest and highest intensity peaks can vary considerably. These variations generate diverse waveform patterns, which can differ in frequency, amplitude, and shape. These patterns influence the perceptual and physiological responses elicited by the flicker. This variation is attributed to how different waveforms interact with the neural dynamics of the brain.

Sinusoidal waveforms, for instance, offer a smooth, continuous oscillation Figure 3 that might be less disruptive and more naturally integrated into the brain's rhythms in contrast, square waveforms create a more abrupt, discrete transition Figure 5 between light and dark , which can induce a stronger neural response, particularly by enhancing cortical excitability and generating a more pronounced steady-state visual evoked potential. Triangular waveforms balance these two, with a linear but sharper change Figure 4 in light intensity compared to sinusoidal waves. It has been shown that the signal's shape noticeably varies the entrainment's effects by up to 50% (Teng et al., 2011).

Beyond the primary effects of the waveform shape on entrainment, secondary parameters, often referred to as harmonic effects, also play a significant role. These effects are intricately linked to the fundamental waveform and arise from the overtones that each shape naturally produces. Harmonic effects can influence the complexity and the reach of entrainment across different brain regions, affecting both the efficacy and the stimulation experience (Teng et al., 2011).

Understanding the implications of these waveform characteristics is essential for optimizing flicker-based therapies and research protocols. It allows for designing more effective and tailored interventions to target specific neurological conditions or research objectives. For instance, choosing the appropriate waveform could enhance therapeutic outcomes in treatments for conditions like epilepsy, where precise control over neural rhythm modulation is crucial.

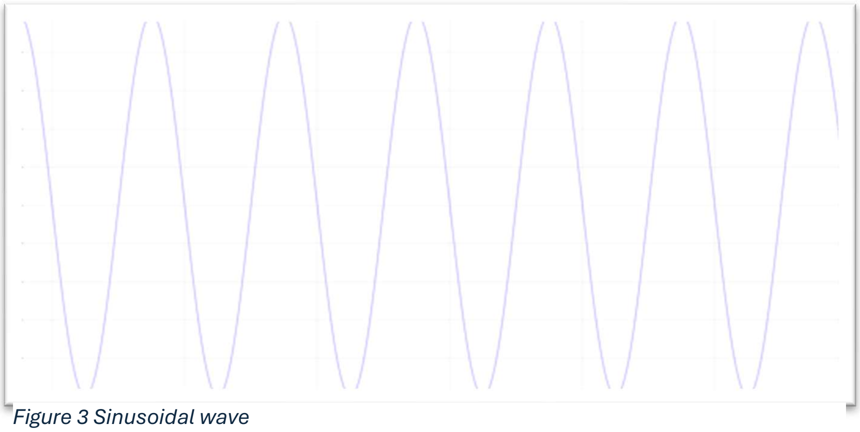


Figure 3 Sinusoidal wave

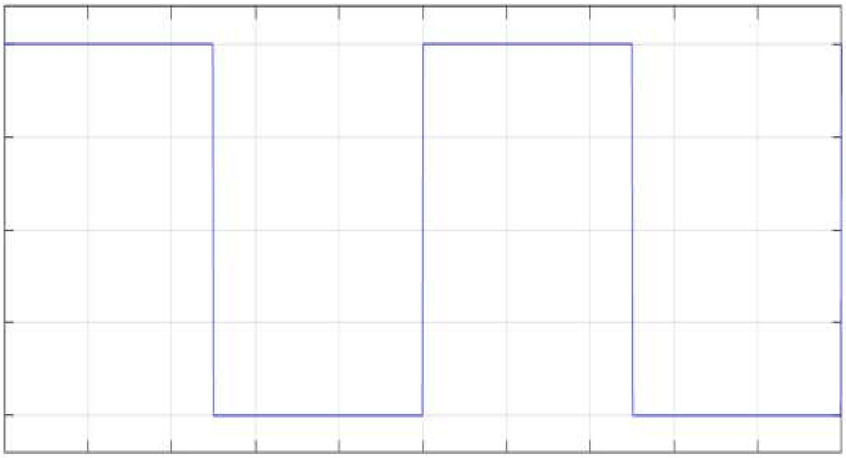


Figure 5 Square wave

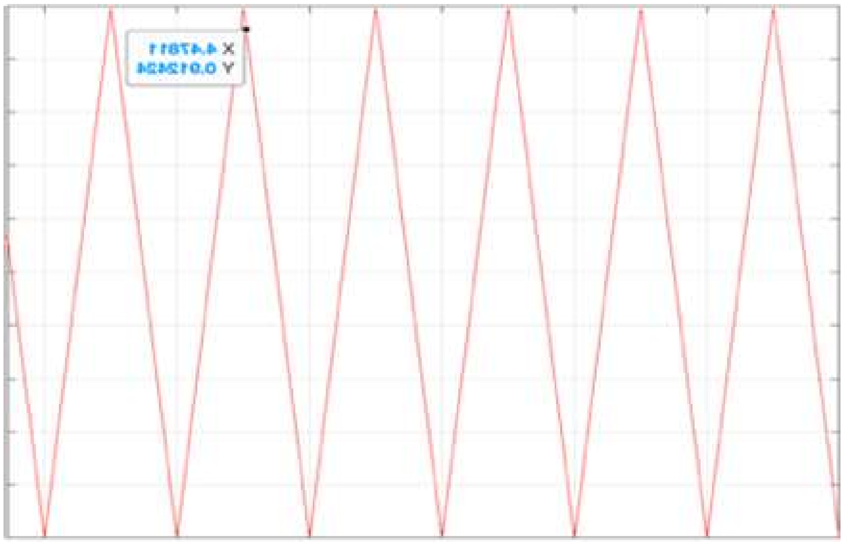


Figure 4 Triangle wave

The pitch of the auditory stimulus

Musical tones are primarily distinguished by pitch. This notion of pitch is essential for grasping auditory perception and has been the focus of scientific research for many years. Early research by Chatrian et al. (1960) explored how auditory clicks

presented to one ear can differ significantly in perception and brain response, setting the stage for subsequent investigations into auditory processing.
One seminal advancement in this field was introduced by (Oster, 1973) who investigated the phenomenon of auditory beat stimulation. This study showed that presenting two sinusoidal auditory waves at slightly different pitches to each ear led to distinct brain responses. This effect is known as binaural beats (BB), where each ear receives a different frequency, such as one ear receiving a tone at 200 Hz and the other at 210 Hz. The brain internally creates a perceptual third tone equal to the difference between the two frequencies. This internally generated beat is hypothesized to entrain brain activity, potentially increasing the amplitude of brain waves at the frequency of this beat. The beats with different pitches could be delivered spontaneously to both ears, introduced as monaural beats (MB), or each time to one of the ear binaural beats (BB).

Subsequent research has explored how these auditory stimuli influence cognitive functions and are reflected in changes observed through electroencephalography (EEG). Engelbregt et al. (2021) Reported that while the fundamental parameters of auditory beat stimulation (ABS), such as frequency and amplitude modulation, are similar, their cognitive effects and EEG manifestations can vary significantly. These differences can be attributed to how monaural and binaural beats interact with neural circuits involved in sound processing and cognitive control. Future research will likely continue to unravel these complex interactions, offering new avenues for theoretical insights and practical applications in neuropsychology and beyond.

How AVE could be presented

Audiovisual Entrainment (AVE) employs various approaches and modalities to stimulate brain activity, leveraging different configurations and parameters to achieve desired neurological effects. This stimulation methodology encompasses multiple factors, each capable of modifying the brain's response to AVE.

One significant variable in the AVE application is the choice between eyes-open (EO) and eyes-closed (EC) conditions. Research indicates that these conditions activate distinctly different neural networks. Research by Han et al. (2023) illustrates these differences, showing that brain network connectivity significantly shifts between EO and EC conditions. With EO, AVE tends to increase connectivity in networks related to external sensory processing and attentional engagement. At the same time, EC conditions reduce external sensory integration, leading to enhanced connectivity in networks related to introspection and self-referential thought. These findings suggest that AVE can be tailored more effectively by adjusting visual engagement (EO or EC), depending on whether the goal is to stimulate outward-focused attention or inward-focused relaxation.
Typically, AVE studies have utilized a conventional mode whereby visual stimuli are presented simultaneously to both eyes Figure 6. This approach ensures uniform stimulus delivery across the visual fields, providing a baseline for observing generalized brain responses to visual entrainment.

Figure 6 - delivering the light to both eyes and visual fields

In more specialized setups, stimuli can be directed separately to the right visual field (RVF) and left visual field (LVF), potentially even in different phases, as outlined in the phase section Bourne (2006). This method allows for the targeted stimulation of each brain hemisphere, as each visual field is primarily processed by the opposite cerebral hemisphere Figure 7, Figure 8. This arrangement can investigate lateralized brain functions or address hemispheric imbalances in clinical scenarios.

Figure 7 - delivering the light to both LVFs

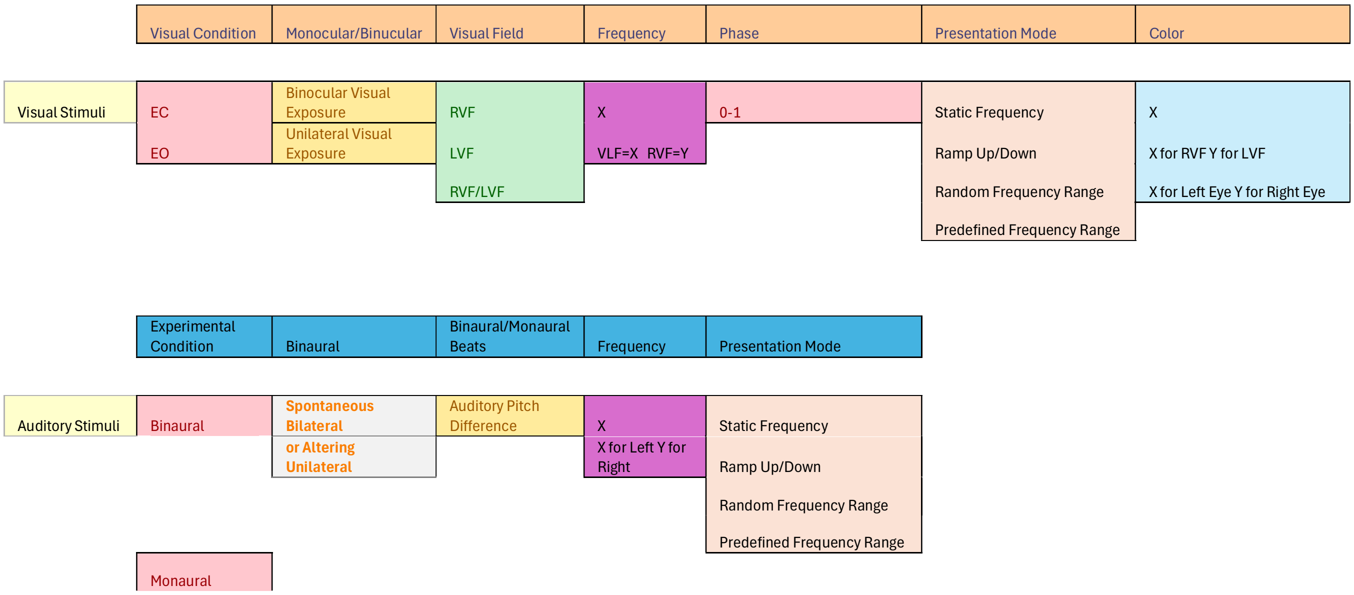
Figure 8 – delivering the light to both RVFs

Further variations include delivering flickering light to only one eye or adjusting the frequencies for LVF/RVF stimulation. These nuanced approaches enable researchers to explore the specific effects of unilateral versus bilateral visual input on neural activity and cognitive functions.

In addition to visual stimuli, auditory pulses in AVE can be presented in binaural or monaural forms. Binaural beats deliver auditory pulses at slightly different frequencies to each ear, producing a perceived beat frequency that arises from the differential in input. Conversely, monaural beats present a beat frequency directly. These auditory stimuli can be set at a fixed frequency, such as 10 Hz (as for transcranial alternative current stimulation (tACS)), or within a programmed range, like 13 to 18 Hz, mimicking parameters used in transcranial random noise stimulation (tRNS).

Alternatively, auditory stimuli can be administered randomly as introduced with white noise (H.-H. Kuo, 2018), which covers a broader frequency range. Depending on the frequency and randomness of the stimulation, such variability can induce different forms of brain plasticity or cognitive effects, potentially ramping up or down through different wavebands to elicit specific neural responses.

Each approach—visual or auditory, fixed or variable in frequency, eyes-open or eyes-closed—provides a unique toolset for manipulating neural activity through AVE. This versatility enhances the scope of research into brain function and Neurotherapy. It expands the potential clinical applications of AVE in treating neurological disorders, enhancing cognitive performance, or providing relaxation and stress relief. By tailoring the stimulation parameters, researchers and clinicians can optimize AVE methods to suit specific therapeutic goals or experimental needs, thereby advancing our understanding of the complex interactions between sensory stimuli and brain activity.



	Visual Condition	Monocular/Binucular	Visual Field	Frequency	Phase	Presentation Mode	Color
Visual Stimuli	EC	Binocular Visual Exposure	RVF	X	0-1	Static Frequency	X
	EO	Unilateral Visual Exposure	LVF	VLF=X RVF=Y		Ramp Up/Down	X for RVF Y for LVF
			RVF/LVF			Random Frequency Range	X for Left Eye Y for Right Eye
						Predefined Frequency Range	

	Experimental Condition	Binaural	Binaural/Monaural Beats	Frequency	Presentation Mode
Auditory Stimuli	Binaural	**Spontaneous Bilateral**	Auditory Pitch Difference	X	Static Frequency
		or Altering Unilateral		X for Left Y for Right	Ramp Up/Down
					Random Frequency Range
					Predefined Frequency Range
	Monaural				

Table 1 - Protocol Design Guide

Safety

There is a notable scarcity of comprehensive research examining the safety of audiovisual entrainment. To date, specific adverse effects have not been documented. Nevertheless, two conditions warrant consideration. Photosensitive epilepsy emerges as a primary concern within this context. Epidemiological data suggest that approximately 5% of individuals with epilepsy are susceptible to photic-induced seizures, with higher incidence rates observed among younger demographics and women (Martins da Silva & Leal, 2017). Consequently, this subgroup should be categorically excluded from AVE interventions to prevent the risk of seizures. In one of the studies in phase one the safety and feasibility of 40 Hz has been examined, including 2 patients with epilepsy. During a brief session no abnormal brain activity or discomfort has been reported by 40 Hz stimulation (Chan et al., 2022). However, further investigation is necessary regarding epilepsy, as another recent study has not only refrained from excluding it but has also successfully introduced audiovisual entrainment as a potential treatment for the condition (Blanpain et al., 2024).

Moreover, the implications of excessive AVE use have been studied in animal models, revealing significant neurobiological consequences. Research conducted by Mansouri et al. (2022) indicates that overexposure to AVE in rats increases neuronal density in the amygdala, which correlates with a marked decrease in social behavior. These findings underscore the need for regulated use and highlight AVE's potential to alter brain function adversely.

Considering these facts, it is imperative that future research rigorously explores the safety profile of AVE. This will not only delineate the boundaries of safe use but also ensure that AVE's therapeutic applications are both practical and safe for all user groups, especially those at risk of adverse effects.

Recent advances

The seminal discovery of audiovisual entrainment (AVE) occurred after electroencephalography (EEG) became available in the late 1920s. Initial research, notably by ADRIAN & MATTHEWS, 1934, demonstrated that brain rhythms could be modified through exposure to flickering lights at various frequencies. This foundational study is credited with pioneering the investigation of flickering light's effects on neural activity, catalyzing further research. Subsequent studies have rigorously examined the efficacy of this technique across different disorders.

EEG

The electroencephalogram (EEG) is a technique to monitor brain activity that stands out due to its cost-effectiveness and ability to record signals with high temporal resolution. This attribute makes it particularly useful for observing the effects of audiovisual entrainment (AVE). A pioneering study employing EEG in this domain utilized three protocols at 1 Hz and 12 Hz frequencies and a dynamic decrement from 12 to 1 Hz over 7.5 minutes (Brauchli et al., 1995). This resulted in the documentation of two extracted features. The alpha band power (8-12 Hz) considerably decreased across every intervention, while variations in the other bands were seen but not deemed significant. Dipole sources were computed, revealing variations across different bands. In the theta band (4-7.5 Hz) across all procedures, the dipole source shifted posteriorly and superiorly during stimulation. A leftward shift during protocol stimulation and a rightward and superior shift have been recorded, with more activity in the right hemisphere during beta band (12.5-20.5 Hz) stimulation (Brauchli et al., 1995). Variability in EEG responses to AVE has been noted, especially among individuals with different baseline alpha powers. This was observed after presenting 7.5 minutes of AVE in low, high, and combined intensities and variations. Alpha stimulation (10 Hz) and beta stimulation (22 Hz) enhance alpha power at both Cz and Pz but with varying effects in participants with high baseline alpha power. High baseline alpha power was associated with lower alpha entrainment and varied responses to stimulation. Beta stimulation's effects were influenced by both baseline alpha and beta power levels, with higher baseline beta and alpha power contributing to the observed effects. The presentation of stimuli at this frequency enhanced the power of other oscillatory bands (delta 1, 0.75–2 Hz; delta 2, 2–4 Hz; theta, 4–8 Hz; alpha, 8–12 Hz; beta 1, 12–21 Hz; and beta 2, 21–31 Hz), with effects persisting in the Beta 1 band up to 30 minutes post-stimulation (Timmermann et al., 1999).

EEG synchrony under audiovisual stimulation (AVS) by 4 and 20 Hz was investigated using Wavelet transform-derived instantaneous phases. Phase synchronization, measured by phase difference uniformity, increased significantly during AVS compared to non-stimulation across all cortex locations. The minor increases were in the frontal areas, while the central region maintained high synchronization levels similar to visual processing centers in the posterior cortex (Teplan et al., 2009).

In another study Oppermann et al. (2023), fourteen volunteers formed a study group that underwent 16 sessions of combined auditory-visual stimulation delivered via mobile phone over four weeks. The primary objective of these sessions was to enhance alpha peak activity. However, upon conducting a power analysis, the results did not indicate any significant changes in alpha peak activity. This outcome suggests that the intended modulatory effects of auditory-visual stimulation on alpha-peak activity may not be as readily achievable under the conditions tested in this study. Fourteen volunteers received 16 sessions of combined auditory-visual stimulation in patterns of alpha and beta bands (7.8, 8.8, 12.8, 13.4, 14.4, 18, 19, and 23 Hz) over four weeks.

In comparison, seven volunteers in the control group received auditory-only stimulation for two sessions. EEG recordings were taken at the beginning and end of the study to measure individual alpha peak frequencies (iAPF) and assess entrainment and resonance effects. Resting-state recordings (eyes open and eyes closed) during two lab sessions, one in week one and one in week four, were conducted for five minutes each before and after the stimulation session. Each stimulation session lasted approximately 16 minutes and consisted of three repetitions of the visual and auditory stimulation patterns. The study found no significant differences in individual alpha peak frequencies (iAPF) between week one and week four for the study and control groups. These first EEG studies suggested that AVE may interact with brain oscillatory behavior, which may be a proxy for treating diseases showing altered brain rhythms.

Depression

Depression is a global mental disorder with a prevalence of an estimated 5% of adults (World Health Organization, 2023). This condition extensively disrupts daily functioning, manifesting through various symptoms, including cognitive impairment, attention deficits, verbal and nonverbal learning, short-term and working memory, auditory and visual processing, problem-solving, processing speed, and motor skills (Lam et al., 2014). According to the 2021 EPICO Study, the societal cost of depressive disorders in Europe was estimated at approximately EUR 6145 million, with an average price per patient per year of EUR 3402 (Salvador-Carulla et al., 2011; Vieta et al., 2021). Based on 65 solid studies from 79 countries, the average treatment rate for this disease is 38.8% within 12 months, with significant differences between high-income countries (31.5%) and low-income countries (Mekonen et al., 2021).

To evaluate the efficacy of audiovisual entrainment (AVE), 16 participants underwent 20 sessions, each lasting 30 minutes per day (5 days per week) for four weeks. In treating depression, participants were subjected to 14 Hz stimulation, while the control group received relaxation music without any visual stimulation for five weeks. Significant outcomes include a reduction in depressive symptoms, positioning AVE as a promising non-pharmacological intervention (Cantor & Stevens, 2009). In another study with a closed-loop design, 15 participants underwent 52 sessions, each session 30 minutes. Based on the real-time EEG (real-time feedback) from the participants, the audiovisual stimuli presented in alpha (7.5-11.75 Hz) to induce relaxation and Beta (12-31 Hz) for cognitive enhancement and mood regulation. Significant reduction in depressive symptoms, with participants showing improvements in Hamilton Rating Scale for Depression (HAM-D) scores after the intervention was reported (Pino, 2017). Another study on depression indicated notable changes in depression measured by HAM-D. The study recruited 15 participants with anxiety and depressive symptoms and divided them into 8 for the experiment and 7 in the control group. Within 52 sessions (5 sessions per week), for 45 minutes online EEG feedback base (Pino, 2021).

Seasonal Affective Disorder

Seasonal affective disorder (SAD) is a type of depression that occurs after shifting to the primary winter months (Association, 2000). The prevalence is 6%, and according to the geographical location, the prevalence varies. This disorder is more seen in winter months (Melrose, 2015).

An investigation divided 74 affected participants into 16 in the control group and 58 who received two weeks of 20 Hz entrainment. The AVE group showed significantly reduced depression and anxiety symptoms. It also improved social interactions within family and work environments, enhancing happiness and energy levels. Moreover, there was a significant decrease in eating and appetite (Berg & Siever, 2009).

Insomnia

Insomnia, affecting up to 10% of the adult population in Europe, presents significant public health concerns (Ellis et al., 2023). Studies have demonstrated notable differences in the high-frequency EEG spectral power density of sleep among those with and without insomnia, suggesting neurophysiological disparities as potential underlying causes (Perlis et al., 2001; Wu et al., 2013). A recent study analyzing the EEG power spectrum of 1985 participants reproved this statement again (Kang et al., 2022). Different symptoms have been reported based on the period of the insomnia (Medic et al., 2017). Furthermore, all-cause mortality rates are heightened in men with chronic sleep disturbances (Medic et al., 2017).

Regarding therapeutic interventions, the use of an Audiovisual Stimulation (AVS) device over four weeks has been shown to yield significant improvements in insomnia symptoms and associated pain. The device operates through 30-minute sessions of light flickering (goggles) and sound pulsing (headphones), which gradually transition from alpha (8 Hz) to delta (1 Hz) frequencies, effectively entraining brainwaves towards a state of deep relaxation and sleep (H.-Y. Tang et al., 2014). A specific application of this technology in older adults over one month resulted in a significant decrease in insomnia severity, shifting from clinically moderate to sub-threshold (mild) insomnia (H.-Y. Tang et al., 2015). These findings highlight the potential of AVS as a non-pharmacological treatment option for insomnia, offering substantial benefits across different age groups.

Cognitive function

Thinking, reasoning, language, memory, problem-solving, decision-making, and attention constitute core aspects of human cognitive domains (Kiely, 2014). Impairments in these functions are called cognitive deficits, which can stem from various causes. While such deficits are not classified as a disorder, they may indicate an underlying condition.

Throughout various tasks or cognitive states, the brain modifies the ratio of the frequency bands. For example, during cognitive tasks such as problem-solving and concentration, the predominant wave observed is beta waves (13-30 Hz) (Berka et al., 2007). Alpha waves (8-12 Hz) are prevalent during relaxed states and light meditation (Klimesch, 1999a). The theta band (4-8 Hz) predominates during more profound relaxation or light sleep and is associated with creativity, intuition, and daydreaming (Hanslmayr et al., 2005). However, the brain state and the activated regions are more complex. These studies provided insights for the creation of AVE procedures.

Several studies have explored the effectiveness of AVE in addressing these cognitive impairments. Aiming to improve cognitive function, the research included 15 participants who completed 52 consecutive sessions, each lasting 30 minutes, conducted daily from Monday to Friday. The research presented AVE in frequencies: Delta (0.5-2.75 Hz), Theta (3.5-6.75 Hz), Alpha 1 (7.5-9.25 Hz), Alpha 2 (10-11.75 Hz), Beta 1 (13-16.75 Hz), Beta 2 (18-29.75 Hz), Gamma 1 (31-39.75 Hz), and Gamma 2 (41-49.75 Hz). A control group of 8 participants was assigned to a waitlist and engaged solely in self-help groups. Results indicated a considerable enhancement in cognitive function measured by the Performance Intelligence Quotient (QIP) (Pino, 2017). Another study with an RCT design and 15 participants, 7 for the treatment and 8 for the control group of depressed participants, measured the cognitive function by Cognitive functions by Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Raven's Progressive Matrices (RPM). After 52 sessions of giving AVE based on EEG online feedback in the frequency range of 0.5-49.75 Hz, the participants experienced significant improvements in cognitive functions. AVE is supposed to be a neurofeedback device compiled with EEG to monitor the brain state. A study examined the impact of audiovisual entrainment as neurofeedback on cognitive functioning in 18 psychiatric disorders. Participants completed 55 neurofeedback sessions and audiovisual entrainment treatments, recording brainwave activity. Results showed significant improvement in IQ scores for 16 out of 18 participants (Pino & Romano, 2022).

Memory

Memory is a pivotal mental process that encompasses the encoding, storage, and retrieval of information and plays a crucial role in learning and personal identity formation.
Research employing AVE to enhance memory functions has yielded promising results. Notably, theta band power (4-8 Hz) increases during memory-related activities (I. C. Hutchison & Rathore, 2015; Nyhus et al., 2019; Pearson & Wilbiks, 2021; Seger et al., 2023). It has been theorized that inducing theta band activity could improve memory abilities. Empirical studies with AVE have confirmed that theta induction (5.5 Hz) significantly improves memory, whereas inducing beta waves (14 Hz) does not yield significant differences (Addante et al., 2021b; Roberts et al., 2018). Additionally, stimulation in 3 minutes of 40-Hz has been examined, and equal to the beta stimulation, no significant change has been reported (Hsiung & Hsieh, 2024b).

Attention

Attention constitutes a critical aspect of cognitive functioning, encompassing the deliberate allocation of mental resources to specific objects, concepts, tasks, and particular elements within the environment. This cognitive process is essential for human consciousness and perception, facilitating information processing, decision-making, and communication while optimizing finite mental resources. Attention Deficit Hyperactivity Disorder (ADHD) represents a prevalent neuropsychiatric condition, with an incidence of 7.5% among children and adolescents (10% in boys and 5% in girls) (Ayano, Demelash, et al., 2023) and 3.10% in adults (Ayano, Tsegay, et al., 2023). The annual economic burden of ADHD in Europe is approximately 12,171€. This condition is associated with various comorbidities and adverse outcomes (Oberauer, 2019). Electroencephalogram (EEG) biomarkers for ADHD have revealed notably higher average delta (0-4 Hz) and theta (4-8 Hz) bands and lower beta (13-20 Hz) (Theta/Beta ratio) in the frontal regions (Barry et al., 2003; Kamida et al., 2016).

In an early investigation, thirty-four elementary school students had AVE treatment for seven weeks, each lasting around twenty minutes. The subjects underwent two distinct protocols. The initial eight sessions at low-alpha (7-9 Hz) given across 20 minutes are designed to facilitate relaxation. The remaining sessions for SMR (sensory motor rhythm) (12-15 Hz) and beta (15-19 Hz) will last 22 minutes each, and significant improvements in inattention and impulsivity will be reported (Joyce & Siever, 2000). In a subsequent study, school students participated in 30 sessions of AVE, lasting 20-30 minutes each, two or three times per week. The equal protocols employed initially ranged from 7-9 Hz to induce relaxation, followed by 13-18 Hz to increase brain arousal, resulting in marked improvements (Siever, 2008)

Unilateral spatial neglect is a disease that leads to significant complications. It involves the brain's failure to acknowledge or respond to stimuli on one (usually the left) side of the environment (Driver & Mattingley, 1998). AVE has been used as a therapeutic approach for this condition. Following ten daily training sessions, totaling four hours each over two weeks, results demonstrated improved visual exploration and a reduction in symptoms of neglect (Làdavas et al., 2022).

Pain

Chronic pain, a persistent and severe health issue, originates from various sources and affects approximately 27.5% of the global population (Zimmer et al., 2022). This condition significantly impacts multiple aspects of daily life. AVE has been employed to alleviate pain and its associated effects. Initial research in this field indicated significant reductions in medication use, suicidal thoughts, and stress, alongside increases in hope, self-esteem, and improvements in family dynamics (Boersma & Gagnon, 1992).

The pilot research involved nine participants independently engaged in a 30-minute AVS program each night at bedtime for one month. The results indicated that AVS may serve as a valuable intervention for enhancing and alleviating pain symptoms in persons with chronic pain (H.-Y. Tang et al., 2014). A more recent investigation recruited 28 participants. The result demonstrated a significant reduction in pain after administering 10 Hz AVE before sleep for 30 minutes over four weeks (Halpin et al., 2023).

Fibromyalgia is a disorder with a prevalence of 3.3% in the population. It is a multivariate in the symptoms. The leading indicators are musculoskeletal pain, fatigue, cognitive difficulties, and sleep disorders; their severity increases with aging. This disorder is more prevalent among women than men (Vincent et al., 2013).
A study evaluated the efficacy of three interventions for Fibromyalgia Syndrome. Forty-nine people with this disorder were randomized to the AVE, medicine, and nutrition groups. AVE was administered daily, three times for 30 minutes each, in the morning with Beta (12-30 Hz), in the afternoon with Alpha (8-12 Hz), and in the evening with Delta (0.5-4 Hz) and Theta (4-8 Hz) frequencies for one month. The AVE group exhibited substantial enhancement in all assessed variables (anxiety, pain, fatigue), but the medication group demonstrated more significant improvement (Berg, 2006).

Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative condition that compromises behavioral function and interferes with daily activities (McKhann et al., 2011). Among the 0.7%

of adults who have dementia, 60 to 80% progress to Alzheimer's disease, while the disorder is becoming prevalent worldwide (Javaid et al., 2021). This disorder not only hinders the individual from leading an everyday life but also manifests symptoms such as agitation, anxiety, and melancholy, imposing significant emotional and financial burdens on families due to caregiving, which leads to stress, burnout, and inadequate support (Rababa et al., 2023). The yearly personal expense of dementia was substantial, averaging $23,796 per individual in 2019. The increased cost places considerable pressure on families, especially in low- and middle-income countries, where a large share of care is unpaid and informal (Baert et al., 2022). Amyloid beta has been identified as a primary marker of Alzheimer's disease in these illnesses (Lue et al., 2017). The detected biomarkers of Alzheimer's in EEG findings included increasing amplitude of Delta and Theta (1-8 Hz) band and decreasing in Alpha (8-12 Hz) and Beta (8-30 Hz), mainly in occipital and parietooccipital areas (Jiao et al., 2023).

The studies in the mice model have shown promising results, and in the first studies, stimulation involved only 40-Hz light flicker (Without Auditory stimulation), causing a reduction of tau hyperphosphorylation, a significant decrease in Amyloid-β plaques in the hippocampus, and improvements in the circadian rhythm disturbances in AD mice (Manippa et al., 2022; Martorell et al., 2019; Yao et al., 2020). A randomized, placebo-controlled pilot trial recruited 15 persons with moderate probable Alzheimer's dementia to determine if similar effects would be observed in individuals. The results were inconclusive after three months of daily one-hour 40 Hz multi-sensory stimulation sessions. The initial effect of 40 Hz stimulation was shown in atrophy. Compared to the control group exposed to continual light and white noise, no substantial ventricular dilatation or hippocampus atrophy was observed, whereas the control group exhibited notable changes. The second finding indicated increased functional connectivity within the default mode network (DMN), whereas the control group demonstrated decreased connectivity. There has been a considerable improvement in cognitive function on the face-name association delayed recall test comparing the two groups. The final effect of AVE was on the regularity of disruptions in everyday activity patterns, which serves as a marker for

Alzheimer's disease. Substantial enhancement, as indicated by the Inter-daily Stability (IS) indicator, was observed during three months (Chan et al., 2022).

The current state of AVE

AVE has shown potential efficacy, highlighting its promise as a therapeutic intervention that merits further systematic and detailed investigation. While it is too early to affirm its effectiveness as a treatment, initial evidence indicates that AVE holds potential for a broader, systematic investigation.

The study of AVE is beyond traditional understandings of neural pathways and parameter settings. A prime example of this complexity is the fusion illusion, where the presentation of one visual flicker and two auditory pulses leads the brain to perceive two flickers, while the presentation of two visual flickers with one auditory pulse results in the perception of a single flicker (Andersen et al., 2004; Garner & Keller, 2022). Although explored, the integration of aural and visual stimuli still needs to be completed. Furthermore, the potential to integrate AVE with other sensory techniques, such as rhythmic tactile sensory stimulation, has not been fully explored, and new research avenues could be opened.

The current research landscape underscores the need to standardize AVE technology entirely to leverage its capabilities. The first step to standardization requires a thorough understanding of AVE devices' characteristics. The absence of standardized protocols for applying and replicating AVE studies poses a significant barrier to advancing the field. Overcoming these challenges is critical to enhancing the reliability and effectiveness of AVE applications.

Chapter Two

Introduction

Investigations into brain states and significant breakthroughs in that domain have facilitated novel methodologies for the enhancement and manipulation of cerebral function. This approach greatly benefited from EEG, enabling researchers to detect and analyze brain electrical activity, thereby uncovering patterns associated with psychological difficulties. For instance, neurological dysfunction in psychopathologies, such as depression, anxiety, and ADHD, exhibits distinct EEG patterns, indicating a neurological basis for these disorders (Barry et al., 2003; Charney, 2013; Kamida et al., 2016; Millan et al., 2015; Pérez-Edgar et al., 2013; Wang et al., 2017). Distinct EEG patterns are associated with cognitive functions like attention, memory, and problem-solving abilities (Cavanagh & Frank, 2014; Cohen, 2011; Fink & Benedek, 2014; Klimesch, 1999b). Furthermore, positive mental states, including well-being and life satisfaction, have unique EEG signatures (Aftanas et al., 2016; Davidson, 1998; Urry et al., 2004). This research highlights the significance of brain states in both the comprehension of mental health and the improvement of cognitive performance using neuromodulation techniques. The expanding research in this domain, especially concerning technologies such as AVE, aims to demonstrate the capacity to manipulate and augment brainwave activity, thus presenting promising opportunities for dealing with psychological disorders and enhancing cognitive productivity.

Among the various methods currently developed, non-invasive brain stimulation technologies demonstrate significant potential. Methods including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and neurofeedback aim to regulate the activity of cortical brain areas (Begemann et al., 2020; Brunoni et al., 2016; Rossi et al., 2021). Nonetheless, these approaches exhibit significant limits. Numerous procedures need clinical or hospital environments due to their complexity, expense, and requirement for qualified specialists (Antal & Paulus, 2013; Rossi et al., 2021; Tortella et al., 2015). Moreover, they primarily affect superficial regions of the brain, frequently neglecting deeper structures (Jamil & Nitsche, 2017; Koponen & Peterchev, 2020; Magnuson et al., 2023) vital for essential functions. This constraint underlines the need for more accessible economic technologies to effectively targets cortical and subcortical brain regions.

Neural oscillations are a feature of cerebral activity and can be precisely evaluated by EEG. Brainwaves can be broken down into delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low beta (12–18 Hz), high beta (18-30 Hz) and gamma (>30 Hz) frequencies, allowing researchers to correlate rhythmic patterns with mental and emotional states (Buzsaki, 2011). Their dominance signifies various brain states, ranging from deep sleep to heightened alertness (Borbély & Achermann, 1999; Sterman, 1996).

As previously stated in Chapter One, AVE is a non-invasive method that aligns brainwaves by synchronizing cerebral activity with rhythmic auditory and visual stimuli. Research indicates that AVE can modify brainwave patterns, enhance cognitive performance, and alleviate symptoms of various neurological and mental diseases. A significant benefit of AVE is its ability to pass through both cortical and subcortical regions, owing to the extensive interconnectivity of brain networks. This aspect distinguishes AVE from other brain modulation methods mainly targeting surface areas.

EEG is an optimal instrument for assessing the impacts of AVE as it provides superior temporal resolution which facilitating real-time monitoring of brainwave activity. This enables researchers to examine the effects of AVE on various cortical regions and frequency bands over time. In contrast to other imaging modalities, like functional magnetic resonance imaging (fMRI), EEG can decompose brainwave activity into precise frequency bands (Nunez & Srinivasan, 2006), elucidating the correlation between AVE stimulation and alterations in brain function.

Despite the growing interest in AVE, substantial gaps still need to be filled in our understanding of its capabilities. The influence of AVE on various frequencies and specific brain areas needs to be discovered. A significant portion of existing literature is confined to a limited frequency range, leaving unresolved fundamental problems regarding the response of broader and higher frequency ranges to neural activity. Moreover, the fact that AVE has several features which could modify the effects has not been considered. The advancement of AVE application for clinical and therapeutic objectives necessitates then the resolution of these deficiencies.

The objective of this study is to further understand AVE by examining its effects across a broader spectrum of frequencies and cerebral locations in two modes of stimulation. This investigation will utilize linear and nonlinear statistical approaches to ascertain whether various types of AVE elicit distinct brainwave patterns, as determined by EEG.

In this exploratory study, a linear approach, Power spectral density analysis, is employed to examine power distribution across frequency bands. Conversely, nonlinear entropy metrics will characterize the complexity and irregularity of brain wave signals. These two complementary methodologies comprehensively understand how AVE influences the brain’s activity. This will elucidate the mechanisms fundamental to AVE, which linear and nonlinear metrics, including PSD and entropy, may characterize. In addition, this study will examine alternate methods of administering AVE to ascertain if they have varying results that could inform advancements in brain modulation techniques.

Materials and Methods

Experimental Design

An inter-subject/within-subject approach was utilized to examine whether AVE-induced changes in brain activity transpired after stimulation, in addition to monitoring the modulation trend over time. Participants were subjected to different stimulation frequencies and categorized into two groups according to the presentation mode. EEG was employed in an open-loop configuration to examine the impact on cerebral wave patterns.

Participants

The sample size for this study were calculated with GPower 3.0, with an alpha level of .05, β = .9, and a medium effect size (.25), resulting in a N= 25. Twenty-six healthy volunteers of both genders (12 males and 14 females), aged 18 to 35 with a mean age of 27.5 years and a standard deviation of 4.5 years, participated to the study. Exclusion criteria were medical illnesses, substance abuse or dependency, usage of pharmaceuticals influencing the central nervous system, or any mental or neurological issues. The recruitment process was completed via the SONA system. Participants received CFU credits as compensation commensurate with the period of their participation in the experiment. Ethical approval for the project was secured from Bicocca University, Prot. N. RM-2022-591.

Instrumentation

The Entrainment device for this study is the Spectrum USB Eye Set, a product of Mind Alive company (approved with CSA, UL, and CE electrical certifications). The goggles have been tested to see if they make any electrical field that could contaminate the EEG signals. A 60-standard-channel cap with standard positions has been used to record the EEG (Eximia et al.).

Procedure

Participants were advised to ensure their scalp was clean and free of oils or hair products, to avoid caffeine and energy drinks, to maintain regular eating habits, and to stay hydrated. The steps of the experiment were clearly explained to reduce any anxiety and help participants feel relaxed during the procedure. Participants were seated in a comfortable, adjustable chair to minimize muscle tension and avoid physical fatigue during the experiment (Pivik et al., 1993).

Before placing the EEG cap, the mastoid areas and forehead were cleaned using NuPrep gel (Weaver Company, n.d.). After measuring the inion and nasion of each participant, the cap was positioned. Each electrode was cleaned through the electrodes according to its shape, which allowed it to be done. Reference electrodes were placed on the left mastoid, and the ground electrode was positioned on the left (Luck, 2014). Conductive gel (Electro-Cap et al., n.d.) was injected into the electrodes to ensure proper conductivity. Impedances at each electrode site were measured and tried to be kept below five kΩ, with a balance of less than one kΩ between them to avoid signal distortions (Teplan, 2002). The goggles' handles were removed and secured with a light elastic string to prevent any contact with the electrodes and avoid pressure on the mastoids. Data were acquired at a sampling rate of 1560 SPS.

Protocols

Each participant received AVE at several frequencies presented in a random order. The AVE frequencies were tuned to the average frequencies of conventional EEG brainwaves, including 2 Hz (Delta band's mean), 6 Hz (Theta band's mean), and 10 Hz (Alpha band's mean). Higher frequencies of 16 Hz, 25 Hz (Beta band), and 40 Hz (Gamma band) were also selected.

Before beginning the procedure, the light's intensity and the sound's volume were adjusted individually for each participant, as outlined in Chapter One. The adjustments were made to optimize the levels based on each participant's threshold, ensuring that the sound and light stimuli were not uncomfortable. The study involved eight main experimental conditions, all delivered randomly.

Resting state: Record the main pre-baseline with closed eyes for 5 minutes.
Resting state 2 min minutes pre-baseline
- 2 Hz AVE Stimulation, recording EEG, 10 minutes in EC condition
- Resting state 2 min minutes post-baseline

Resting state 2 min minutes pre-baseline
- 6 Hz AVE Stimulation, recording EEG, 10 minutes in EC condition

- Resting state 2 min minutes post-baseline

Resting state 2 min minutes pre-baseline

- 10 Hz AVE Stimulation, recording EEG, 10 minutes in EC condition
- Resting state 2 min minutes post-baseline

Resting state 2 min minutes pre-baseline

- 16 Hz AVE Stimulation, recording EEG, 10 minutes in EC condition
- Resting state 2 min minutes post-baseline

Resting state 2 min minutes pre-baseline

- 25 Hz AVE Stimulation, recording EEG, 10 minutes in EC condition
- Resting state 2 min minutes post-baseline

Resting state 2 min minutes pre-baseline

- 40 Hz AVE Stimulation, recording EEG, 10 minutes in EC condition
- Resting state 2 min minutes post-baseline

Resting state, Recording the main post-baseline with closed eyes, 5 minutes.

Participants were asked to keep their eyes open for 3 minutes following each block to avoid habituation and mitigate potential carryover effects from the previous protocol. They subsequently closed their eyes for two minutes before commencing the subsequent protocol's pre-baseline. The experimental procedures lasted 134 minutes, while the EEG setup lengthened the total session time to approximately 170 minutes per participant.

This study aimed to explore the effects of AVE delivered in conventional mode and investigate an innovative presentation style to discover the differences of their effects. Participants were divided into two groups of thirteen. For the initial group, AVE delivery included presenting the visual flickers into Right and left visual fields, and delivering alternation auditory pulses in binaural mode into audio channels, called Cross-Lateralized Stimulation (CLS). To achieve this aim a minor frequency variation of 0.2 Hz was implemented to divide the visual fields and auditory channels. For instance, when the protocol frequency was established at 10 Hz, the left visual field received 9.8 Hz, while the right visual field was 10.2 Hz, with a similar pattern observed in the auditory channels.

Moreover, the audio frequencies of 160 Hz for the left ear and 180 Hz for the right ear were intended to create binaural beats (Protocol 1). Group two underwent AVE in the traditional mode, with synchronized simultaneous entrainment of both auditory and visual fields, referred to as Bilateral Synchronous Stimulation (BSS) (Protocol 2).

	Visual Condition	Monocular/Binucular	Visual Field	Frequency	Phase	Presentation Mode	Color
Visual Stimuli	EC	Binocular Visual Exposure	RVF/LVF	2, 6, 10, 16, 25, 40 Hz VLF=-0.2 RVF=+0.2	Dynamic according to the frequency difference	0.2 Hz difference Ramp Up for 5 seconds	White same for both visual fields

	Experimental Condition	Audio Format	Binaural/Monaural Beats	Frequency	Presentation Mode
Auditory Stimuli	Binaural	**Altering Unilateral**	170 Hz, +-10 Hz difference	2, 6, 10, 16, 25, 40 Hz LE=-0.2 RE=+0.2	0.2 Hz difference Ramp Up for 5 seconds

Protocol 1 (Cross-Lateralized Stimulation (CLS))

	Visual Condition	Monocular/Binucular	Visual Field	Frequency	Phase	Presentation Mode	Color
Visual Stimuli	EC	Binocular Visual Exposure	integrated	2, 6, 10, 16, 25, 40 Hz	0	Ramp Up for 5 seconds	White same for both visual fields

	Experimental Condition	Audiod Format	Binaural/Monaural Beats	Frequency	Presentation Mode
Auditory Stimuli	Binaural	**Bilateral**	170 Hz	2, 6, 10, 16, 25, 40 Hz VLF=-0.2 RVF=+0.2	integrated Ramp Up for 5 seconds

Protocol 2 Bilateral Synchronous Stimulation (BSS)

RVL: Right Visual Field
LVF: Left Visual Field
EC: Eyes Closed
EO: Eyes Opened
LE: Left Ear
RE: Right Ear

Data analysis

For this study, the procedures were conducted by MATLAB (MathWorks, 2024), and the EEG lab extension was utilized for the preprocessing (Delorme & Makeig, 2004) and field trip for statistical analysis (Oostenveld et al., 2011). In addition, the neurokit2 toolbox in Python used for non-linear analysis (Makowski et al., 2021).

Pre-processing

EEGlab imported the acquired data. Channel locations were attached, including: 'Fp1','Fpz','Fp2','AF1','AFz','AF2','F7','F3','F1','Fz','F2','F4','F8','FT9','FT7','FC5','FC3','FC1','FCz','FC2','FC4','FC6','FT8','FT10','T7','C5','C3','C1','Cz','C2','C4','C6','T8','TP9','TP7','CP5','CP3','CP1','CPz','CP2','CP4','CP6','TP8','TP10','P9','P7','P3','P1','Pz','P2','P4','P8','P10','PO3','POz','PO4','O1','Oz','O2','Iz'.
The sample rate was downgraded to 512 SPS from 1450 SPS; the data was re-referenced into average reference. Artifact removal was first conducted manually. Independent component analysis (ICA) was undertaken to remove the artifacts from 1-20 Hz to minimize data loss. Once the ICA weight of artifacts in the 1-20 Hz range was recognized, the weight was removed from the main data, which included all the frequencies. By the end of preprocessing, the data were exported to .set files.

Time-frequency analysis

The power spectral density (PSD) was calculated via a Fast Fourier Transform (FFT) to assess the power distribution across each frequency band of the brainwaves. The Power PSD measures signal strength across frequency components, facilitating a comprehensive analysis of alterations in brainwave activity associated with AVE (Stoica & Moses, 2005). EEG data from 60 channels were analyzed over six frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), low beta (12-18 Hz), high beta (18-30 Hz), and Gamma (30-48 Hz) in AVE stimulation frequencies of 2, 6, 10, 16, 25, and 40 Hz.

Time-frequency analysis was crucial in this experiment since it allowed us to capture the dynamic variations in the power fluctuations of brain waves. The data were categorized into two epochs: prior to stimulation, and post to stimulation. This division will allow us to monitor the variations in brain wave activity in different conditions.

Multiscale Entropy

In addition to the time-frequency analysis, Multiscale entropy (MSE) was utilized to compute nonlinear changes. MSE is a statistical method that quantifies the complexity of time series data over multiple temporal scales (Costa et al., 2002). It extends the concept of traditional entropy measures by assessing the predictability and irregularity of a signal across various scales, thereby providing a comprehensive view of its dynamic behavior.

The computation of multiscale entropy begins with constructing coarse-grained time series at multiple scales. This involves transforming the original time series data, represented as $\{x_1, x_2, ..., x_N\}$, into several coarse-grained versions by averaging the data points within non-overlapping windows of increasing lengths denoted by τ. Each size corresponds to a scale factor τ, forming a new series $y(\tau)$ for each scale:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i \quad j = 1, 2, ..., \left\lfloor \frac{N}{\tau} \right\rfloor$$

Where τ is the scale factor, j indexes the coarse-grained time series.

Following the construction of the coarse-grained series for each scale, sample entropy (SampEn) is calculated for each series. SampEn is a measure of complexity that assesses the likelihood that s:

$$\text{SampEn}(m, r, N) = -\log\left(\frac{A}{B}\right)$$

- A represents the number of template vector pairs matching within a tolerance r for m+1 points.
- B represents the number of template vector pairs matching within r for m points.

The tolerance r is typically set as a percentage of the standard deviation of the original time series, and m is the length of sequences compared.
A recent study by Kosciessa et al. (2020) demonstrated that global similarity bounds that are typically used for computing multiscale analysis can bias the entropy estimates as the variance of EEG signals is not consistent across scales and tends to decrease with coarser scale analysis due to the influence of high-frequency components at finer scales. To counteract this issue, scale-specific similarity bounds were employed here, ensuring that the entropy calculation at each scale was adjusted to the changing signal variance. For each scale, the tolerance level was set to 0.5 times the standard deviation of the coarse-grained signals at that scale, and the embedded dimension of (m = 2) was used considering the recommendations of previous studies (Kosciessa et al., 2020; A. et al., 2008; Miskovic et al., 2016). To control for possible variability in MSE values from comparing samples with various durations, MSE was calculated on the first 70 seconds of Pre and post baseline of each frequency. The scales ranged from 1 to 20, corresponding to a scale window length between 1.9 to 39ms.

Statistical analysis

Due to the large dimensionality of the acquired data, a cluster-based permutation test was utilized to mitigate the issue of multiple comparisons associated with EEG data analysis. This method efficiently manages type I errors by assessing the importance of clusters of nearby temporal scales or electrodes instead of conducting separate comparisons for each pair (Maris & Oostenveld, 2007).

For the TFA, we conducted a cluster-based permutation test to identify significant differences between pre- and post-stimulation periods. The time-frequency data were extracted and organized by creating datasets for each experimental condition, where power spectral densities (PSD) were computed for frequencies ranging from delta to gamma bands. We selected relevant time points, comparing the pre-stimulation (baseline) and post-stimulation epochs.

To implement the cluster-based analysis, clusters were formed across electrodes and time points, applying a Monte Carlo method with a 500-permutation threshold. This method constructed a null distribution by shuffling conditions within subjects, allowing us to evaluate the significance of observed clusters against this distribution. Clusters with an effect size beyond the 95th percentile of the null distribution were marked as significant, providing insights into time-frequency dynamics and spatial organization across brain regions.

The entropy analysis data were further refined by categorizing and consolidating the scales into four groups, resulting in five measurement scales transitioning from finer to coarser temporal resolutions. This phase of dimensionality reduction was executed to enhance interpretation and visualization. Following previous research, the initial category of collapsed scales will be called "fine" scales, while the final group will be termed "coarse" scales (Kosciessa et al., 2020).

The MSE values of pre- and post-stimulation conditions were compared using a paired sample t-test. The clusters are delineated as continuous data points exhibiting a significant t-test, $p < .05$, two-tailed. The entrance criterion for a cluster was established at the same level as the significance threshold of the t-test. Consequently, a spatial constraint was established by forming a cluster including three adjacent electrodes. The importance of the resultant cluster-level statistics, the t-values aggregated across participants within each cluster, was assessed by comparing them to a distribution produced from permutation-based cluster-level statistics. To construct this permutation distribution, 500 iterations of Monte Carlo simulations were conducted. The final p-value for each cluster was calculated as the percentage of iterations in which the observed cluster-level statistic was surpassed. Clusters were deemed statistically significant if their probability values were below .05. Subsequent topographical plots illustrated the regional distribution of notable changes in entropy between situations.

Result

Time-Frequency Analysis

Based on the results comparing the pre-baseline and post-baseline EEG data of participants subjected to cross-lateralized stimulation at different frequencies (2 Hz, 6 Hz, 10 Hz, 16 Hz, 25 Hz, and 40 Hz), significant clusters were identified in different frequency bands using cluster-based permutation analysis. Positive clusters indicate a decrease in power spectral density (PSD) post-stimulation, as it has been subtracted from the pre-baseline. Conversely, negative clusters indicate an increase in PSD post-stimulation. Below is a summary of the significant findings of the 70 seconds of Pre-baseline and post-baseline:

2 Hz Stimulation

- **Low Beta Band**: Two significant clusters were observed early in the session (p = 0.008, p = 0.026) Positive in left Central.
- **High Beta Band**: A significant cluster was detected close to the end of the session (p = 0.030) Positive in left anterior.
- **Gamma Band**: Three significant clusters were found, one in the middle (p = 0.010), one early (p = 0.036), and one at the end of the session (p = 0.040) positive in left anterior.

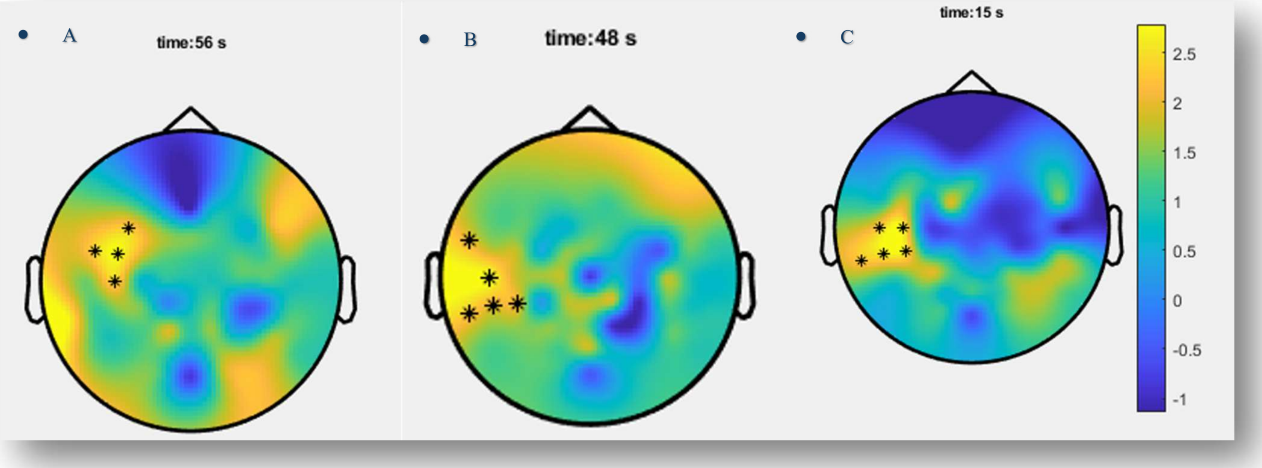


Figure 9 The significant clusters in different times points and regions related to 2 Hz CLS

A) High Beta

B) Low Beta

C) Gamma

6 Hz Stimulation

- **High Beta Band**: One significant cluster was observed in the middle of the session (p = 0.002) positive in left Centro-parietal region

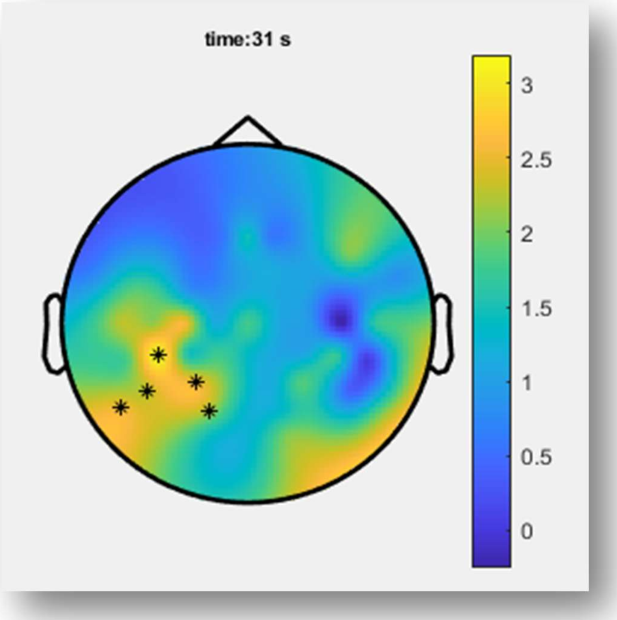


Figure 10 The significant cluster in 31 seconds, related to 6 Hz CLS

10 Hz Stimulation

- **High Beta Band**: A significant cluster appeared in the middle of the session ($p = 0.040$) Positive in right Centro-frontal regions

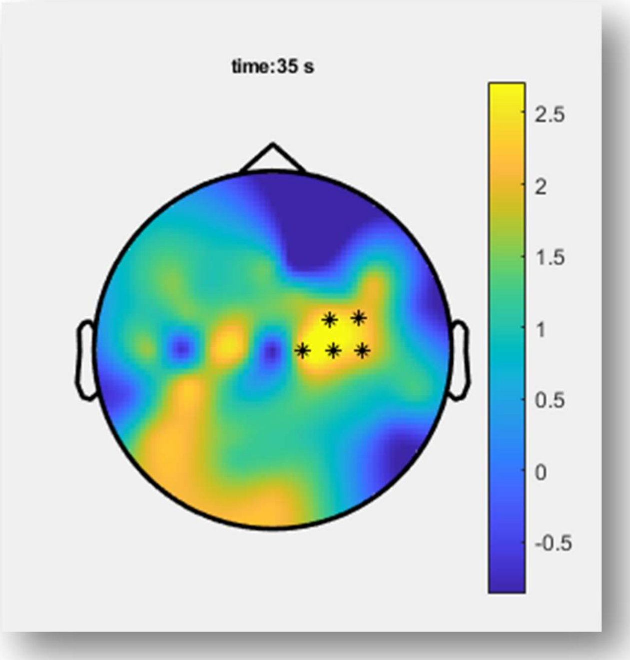


Figure 11 The significance cluster related to 10 Hz CLS

16 Hz Stimulation

- **High Beta Band**: A significant cluster was observed early in the session (p = 0.030) Positive in right posterior temporal and parietal regions
- **Gamma Band**: A significant cluster appeared very early in the session (p = 0.028) Positive in left posterior parietal and temporal regions

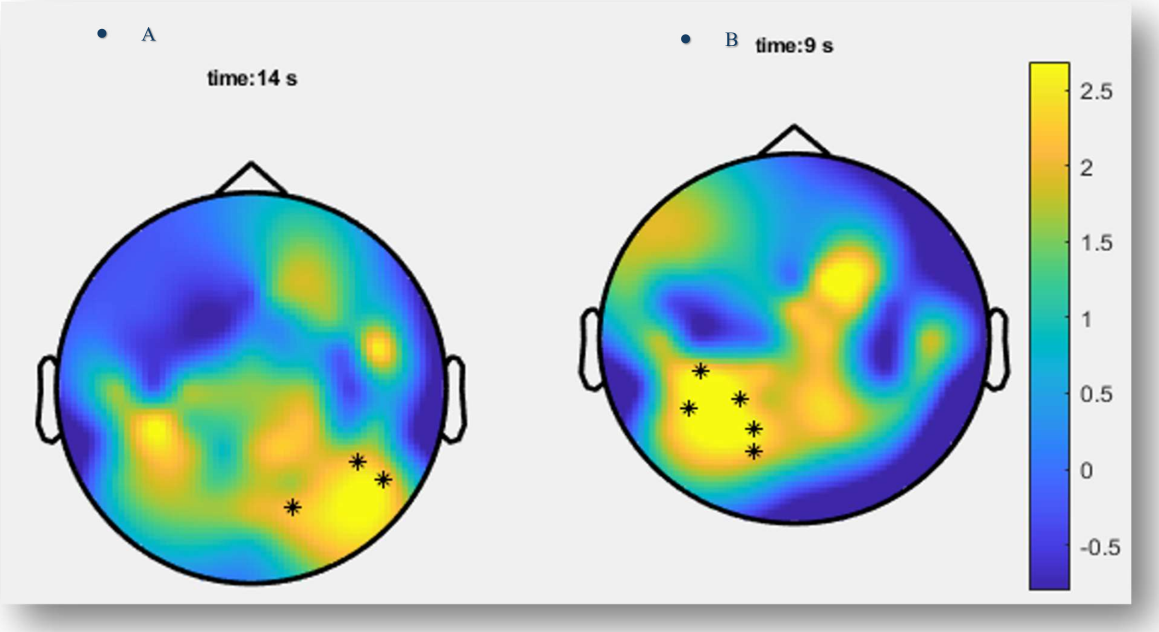


Figure 12 The significant clusters in different times points and regions related to 16 Hz CLS

A) High beta

B) Gamma

25 Hz Stimulation

- No significant clusters were observed across any frequency bands.

40 Hz Stimulation

- **Low Beta Band**: One significant cluster occurred in the middle of the session (p = 0.018) Positive **left posterior parietal** and **temporal regions**
- **High Beta Band**: Another significant cluster was found in the middle (p = 0.002) Positive in **left posterior temporal** and **parietal regions**

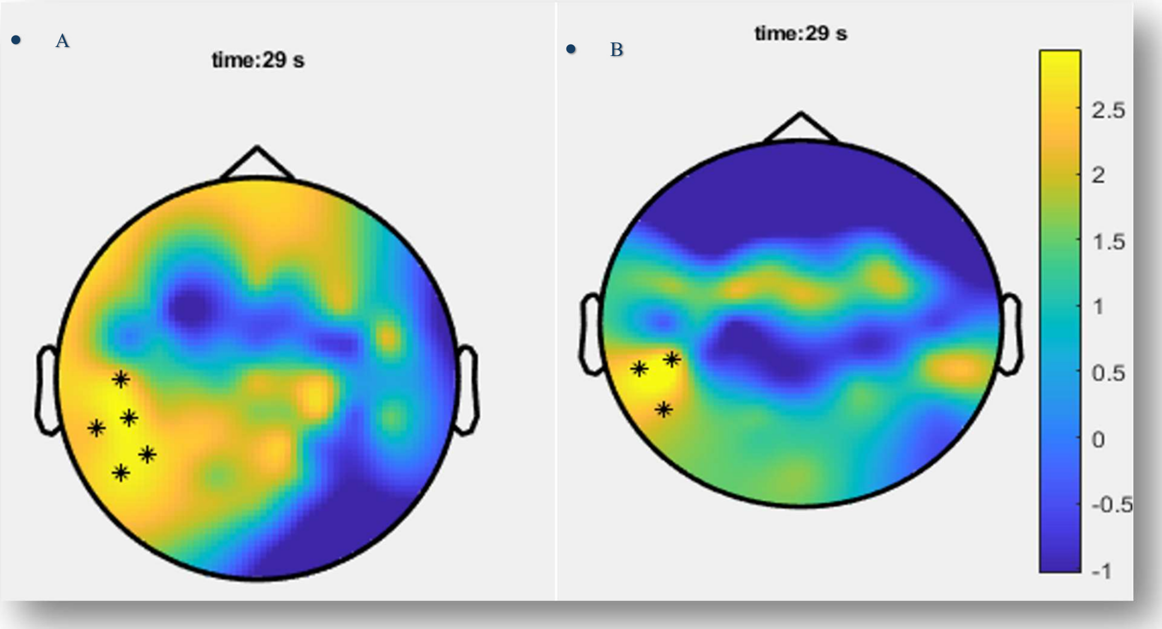


Figure 13 The significant clusters in different times points and regions related to 40 Hz CLS

A) High Beta

B) Gamma

These results of CLS stimulation mode demonstrated how different stimulation frequencies induced significant changes in various EEG bands, particularly in the beta and gamma ranges.

Based on the second group's EEG data, which involved bilateral synchronous stimulation, here are the significant findings across different frequency bands using cluster-based permutation analysis:

2 Hz Stimulation

- **Alpha Band**: Two significant clusters were observed early in the session (p = 0.006, p = 0.032) Positive left frontal and fronto-central areas and right frontal regions
- **Gamma Band**: Three significant clusters appeared, two close to the end of the session (p = 0.020, p = 0.020) and one at the end (p = 0.046) Positive in right frontal and fronto-temporal areas

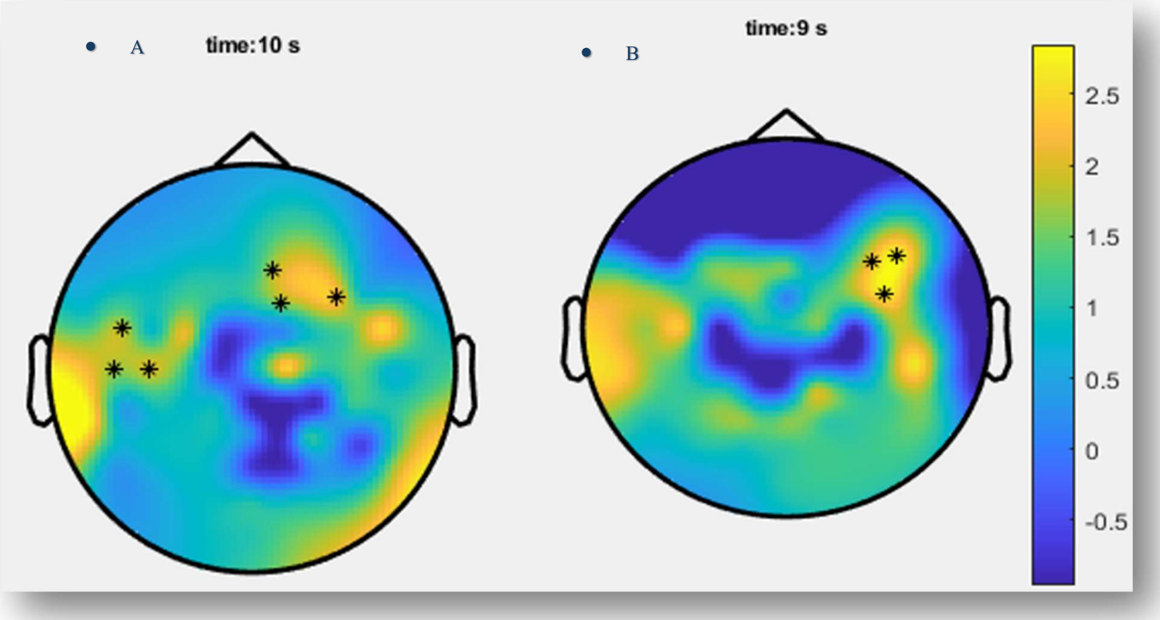


Figure 14 The significant clusters in different times points and regions related to 2 Hz BSS

A) Alpha

B) Gamma

6 Hz Stimulation

- **High Beta Band**: One significant cluster was detected early in the session (p = 0.040) Positive in **left centrofrontal region**, spread slightly across the midline and extending laterally to right frontal
- **Gamma Band**: Five significant clusters were observed, with three early in the session (p = 0.004, p = 0.008, p = 0.010), one in the middle (p = 0.018), and one more early (p = 0.040) Positive in **right frontal region**, slightly to the side

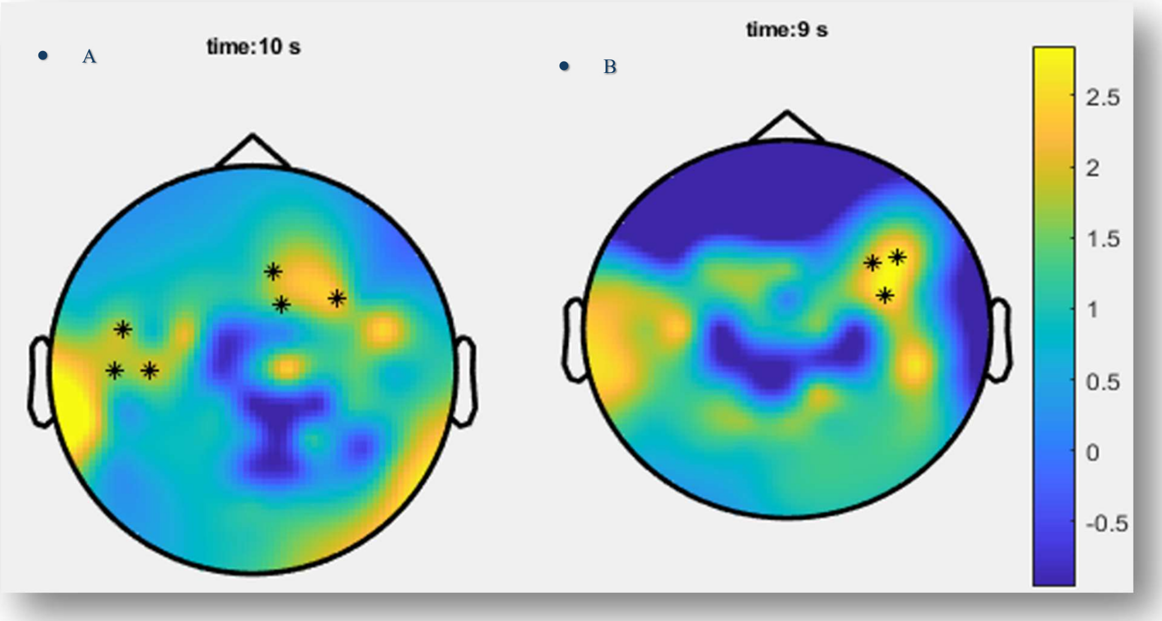


Figure 15 The significant clusters in different times points and regions related to 6 Hz BSS.

A) Gamma

B) High Beta

10 Hz Stimulation

- **Gamma Band**: A significant cluster was observed early in the session (p = 0.032) Positive **posterior midline region**, close to the **occipital area**

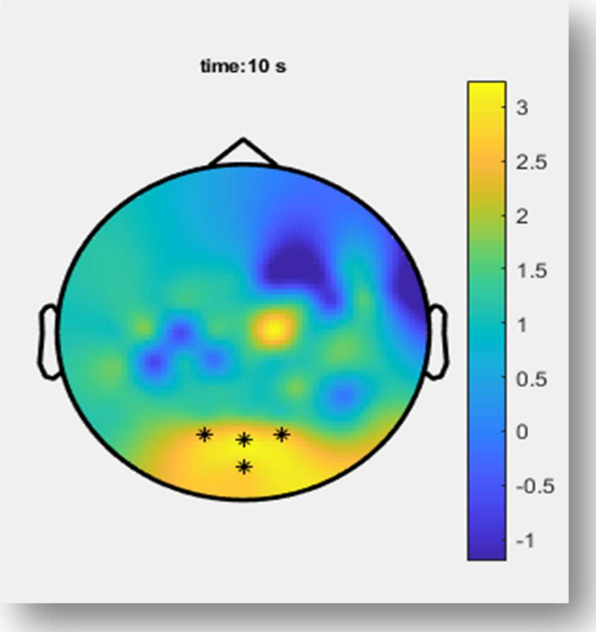


Figure 16 The significant cluster related to 10 Hz BSS in Gamma band

16 Hz Stimulation

- **Alpha Band**: One significant cluster was observed early in the session (p = 0.030) **left posterior region**, covering areas associated with **parietal** and **occipital** regions
- **Gamma Band**: Three early clusters were detected (p = 0.002, p = 0.006, p = 0.010) Positive in **central region of the scalp** near the **vertex** but slightly extending towards the **parietal** area

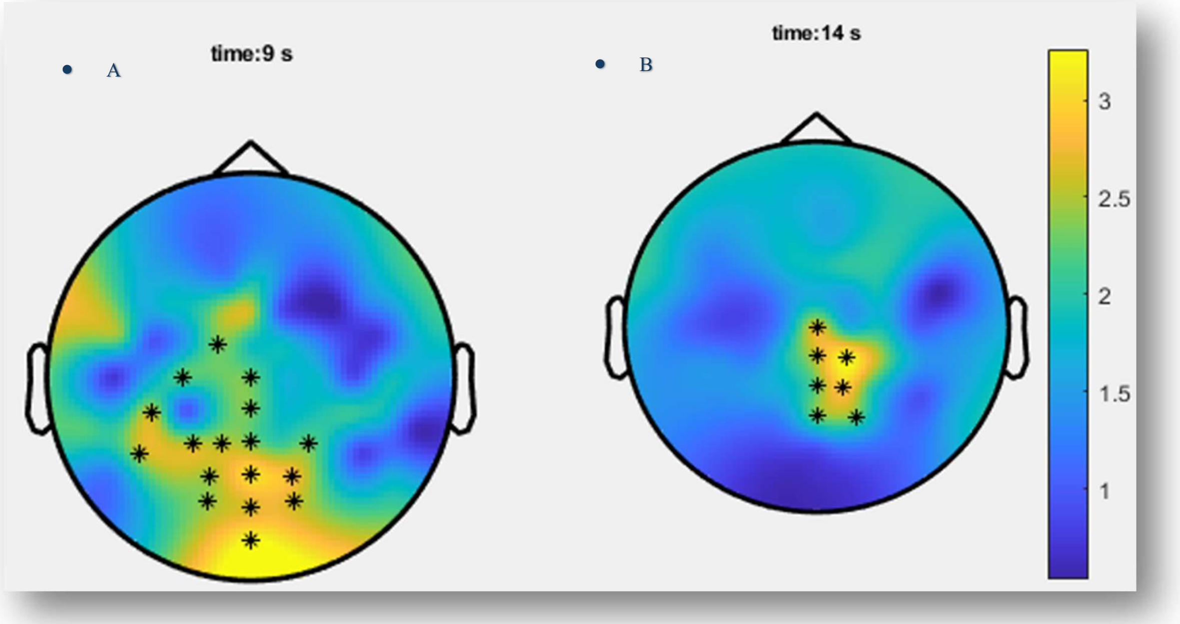


Figure 17 The significant clusters in different times points and regions related to 16 Hz BSS

A)Gamma

B) Alpha

25 Hz Stimulation

- **Gamma Band**: A significant cluster was observed at the beginning of the session (p = 0.048) Positive in approximately located in the left posterior region of the scalp, which might correspond to the parieto-occipital area

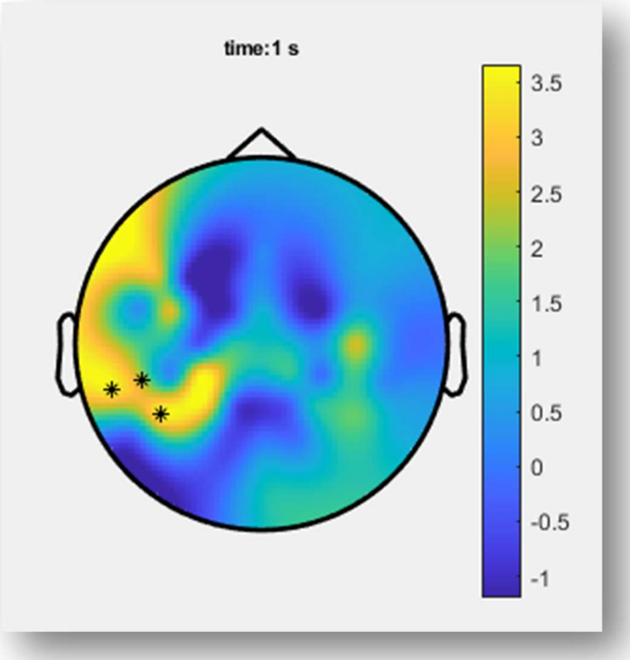


Figure 18 The significant cluster related to 25 Hz BSS.

40 Hz Stimulation

- No significant clusters were observed across all frequency bands.

These findings highlight that for bilateral synchronous stimulation, significant effects were most prominent in the Gamma band across most of the stimulation frequencies. Significant effects the Alpha band High Beta bands were also observed but less frequently.

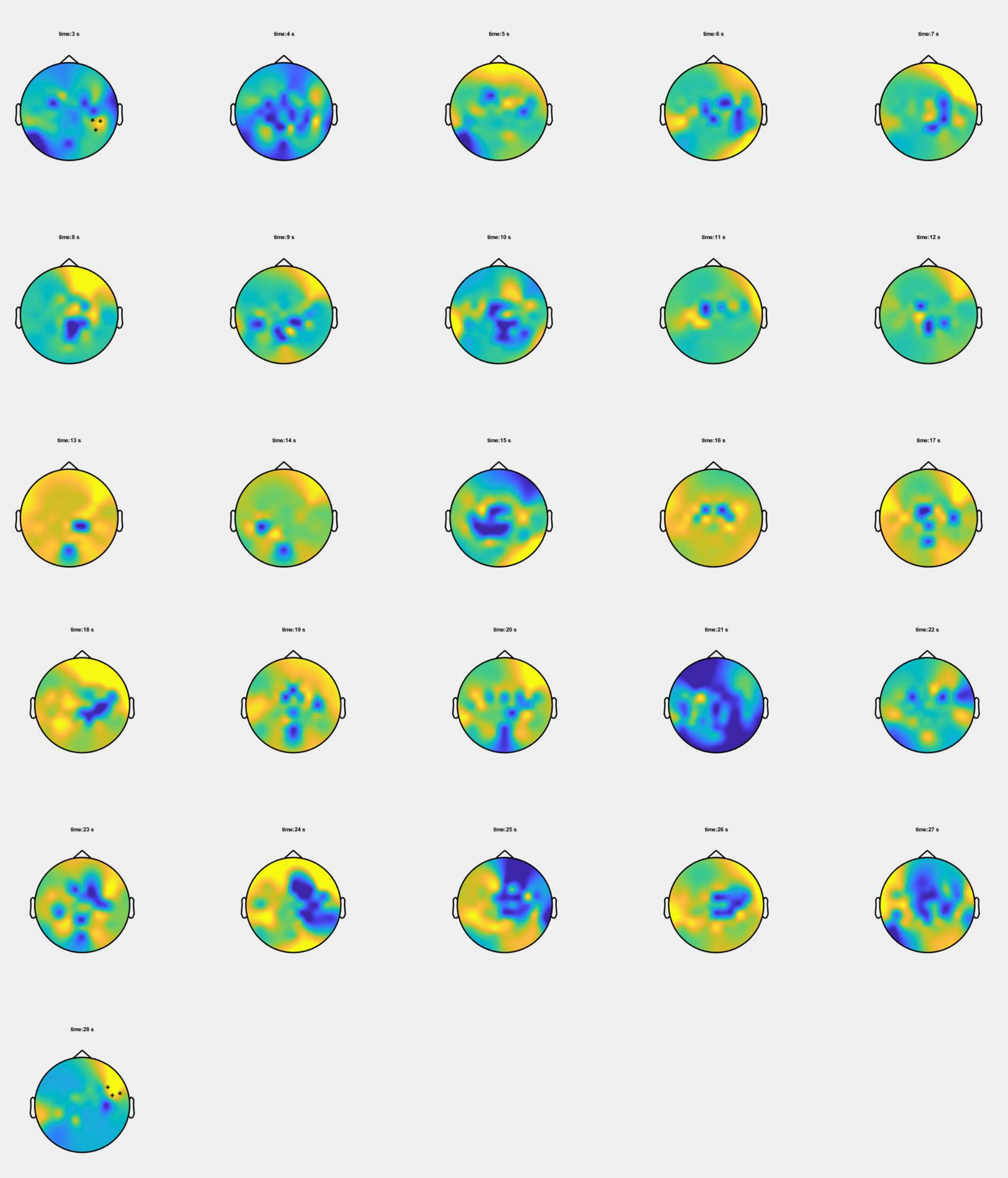


Figure 19 An overview of dynamics changes, time 1 to 26 where there is no significant differences until second 26

Multiscale Entropy (MSE) Results

Figures x and y illustrate the heat map of the MSE value differences across various scales and channel locations, derived from subtracting the pre-stimulation values from the post-stimulation values. The visual examination of these statistics indicates a general downward trend in the data, with most channel locations marked in blue signifying less entropy. Furthermore, coarser scales (>10) seem to be more influenced by the stimulus than finer scales.

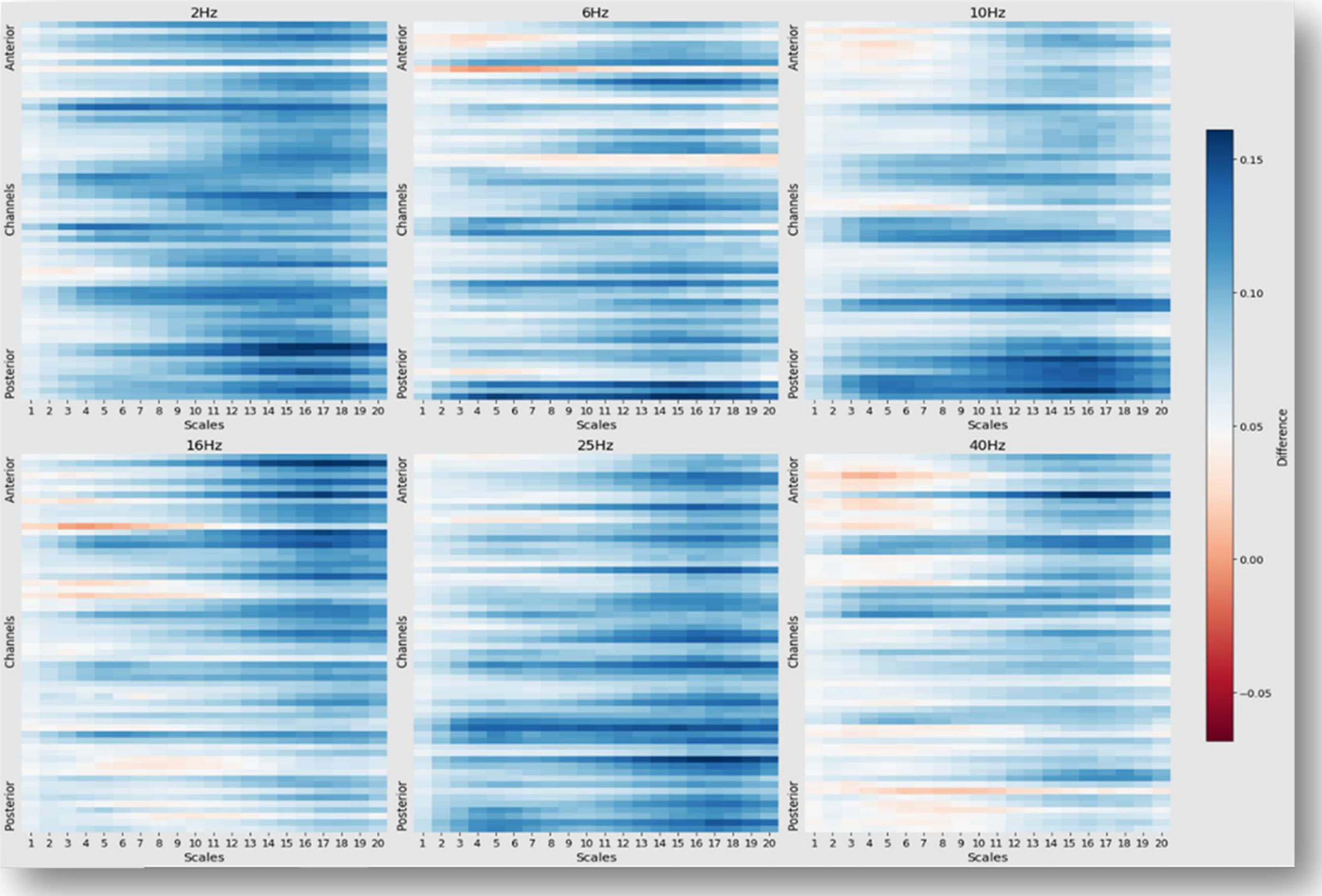


Figure 20 BSS condition heat map of MSE value differences across various scales and channel locations for each stimulation frequency. MSE differences are calculated by subtracting the post-stimulation MSE from the pre stimulation MSEs.

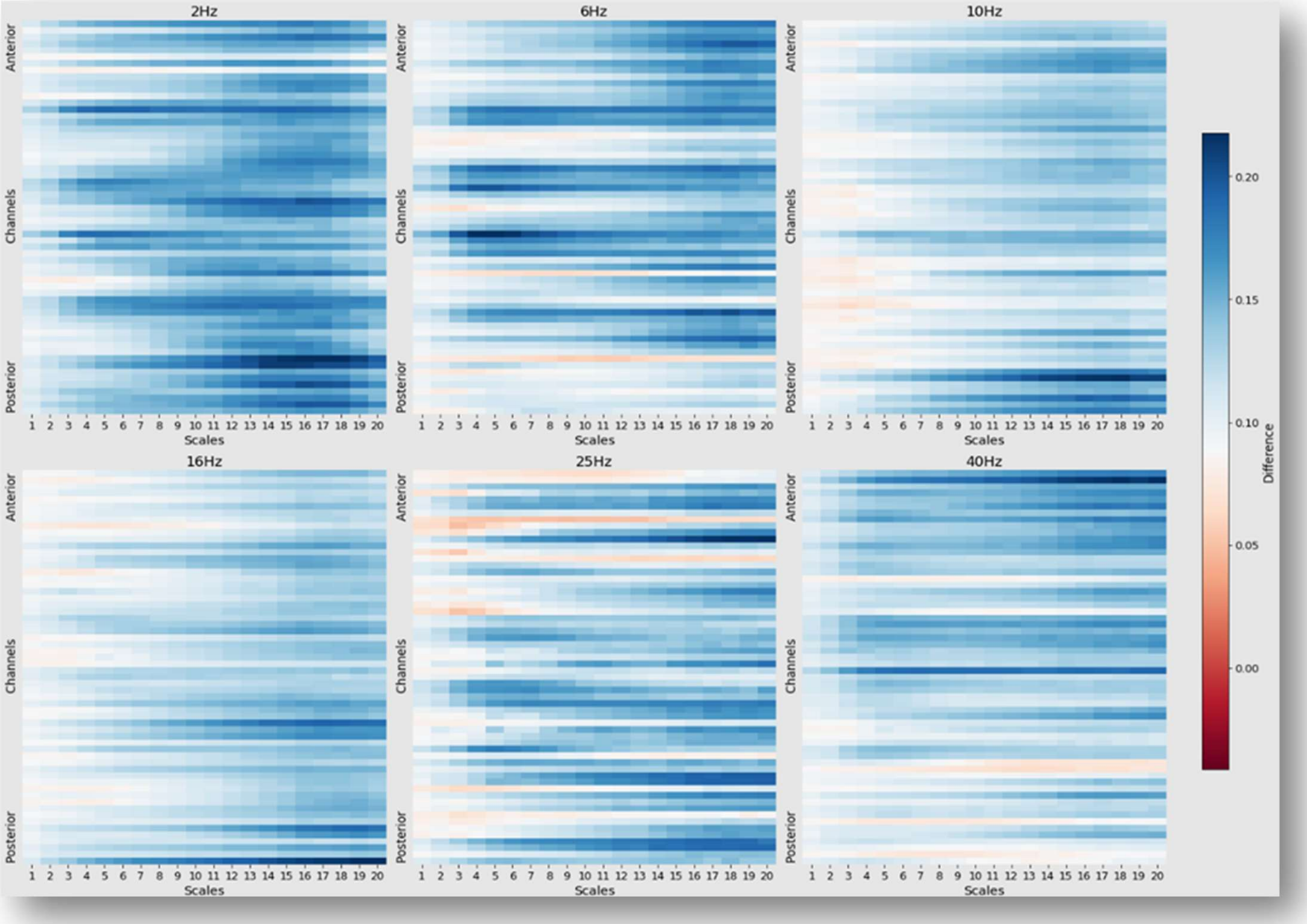


Figure 21 CLS condition heat map of MSE value differences across various scales and channel locations for each stimulation frequency. MSE differences are calculated by subtracting the post-stimulation MSE from the pre stimulation MSEs.

The outcomes of cluster-based permutation tests exclusively encompassed positive clusters, indicating that entropy was diminished solely after stimulation, with no significant increases observed. A notable effect for BSS was detected at 2, 6, 10, and 25 Hz, whereas 16 and 40 Hz were not significant.

At 2Hz BSS, a significant drop in brain entropy was found across all scales (p = 0.004). Figure 5 illustrates the topographical representation of MSE variations across diverse sizes and locales. The effects were predominantly lateral at finer scales, however at coarser scales, both central and lateral regions were more impacted.

At 6Hz NS, the effects were restricted both in time and space. A notable drop (p = 0.04) in MSE was seen exclusively at a medium scale (13 to 17) and solely in anterior regions (figure 6, A).

Alpha BSS at 10Hz markedly diminished entropy across all scales (p= 0.004). Figure 7 illustrates that posterior regions were more engaged in these alterations. No substantial change was seen at 16Hz following stimulation at any size. After the BSS at 25Hz, entropy decreased at fine scales (p = 0.02). This alteration was noted in the posterior regions, as illustrated in Figure 6, B. Ultimately, BSS at 40Hz did not significantly influence the MSE values at any scale.

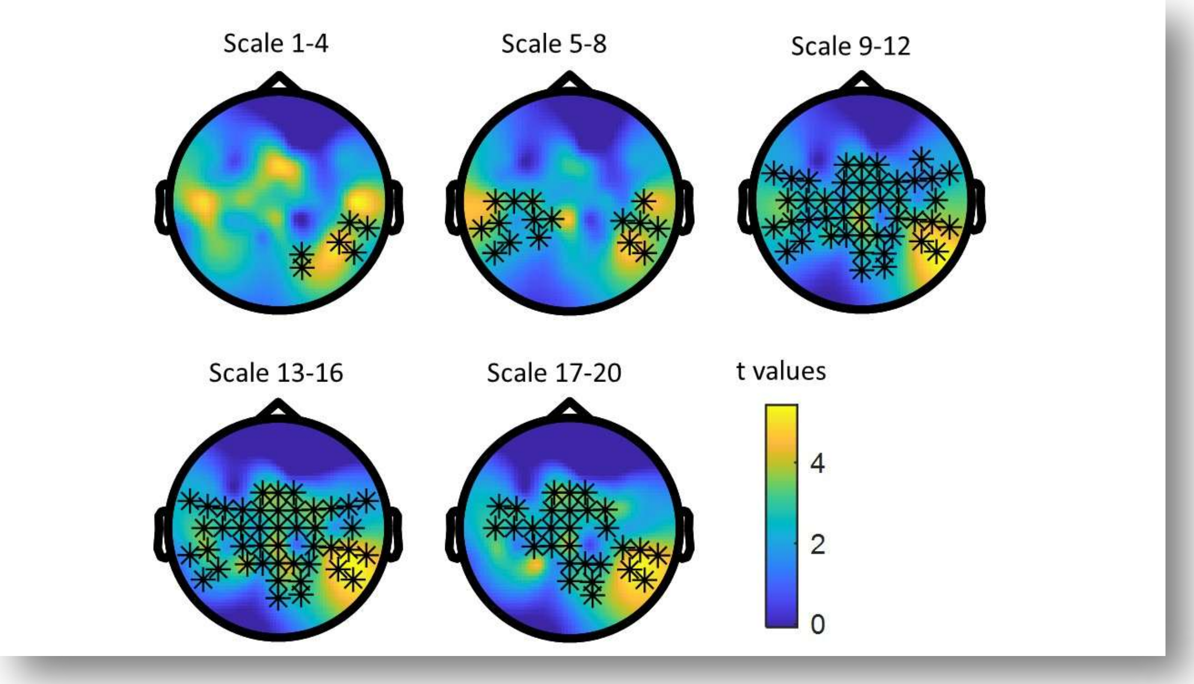


Figure 22 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 2Hz NS

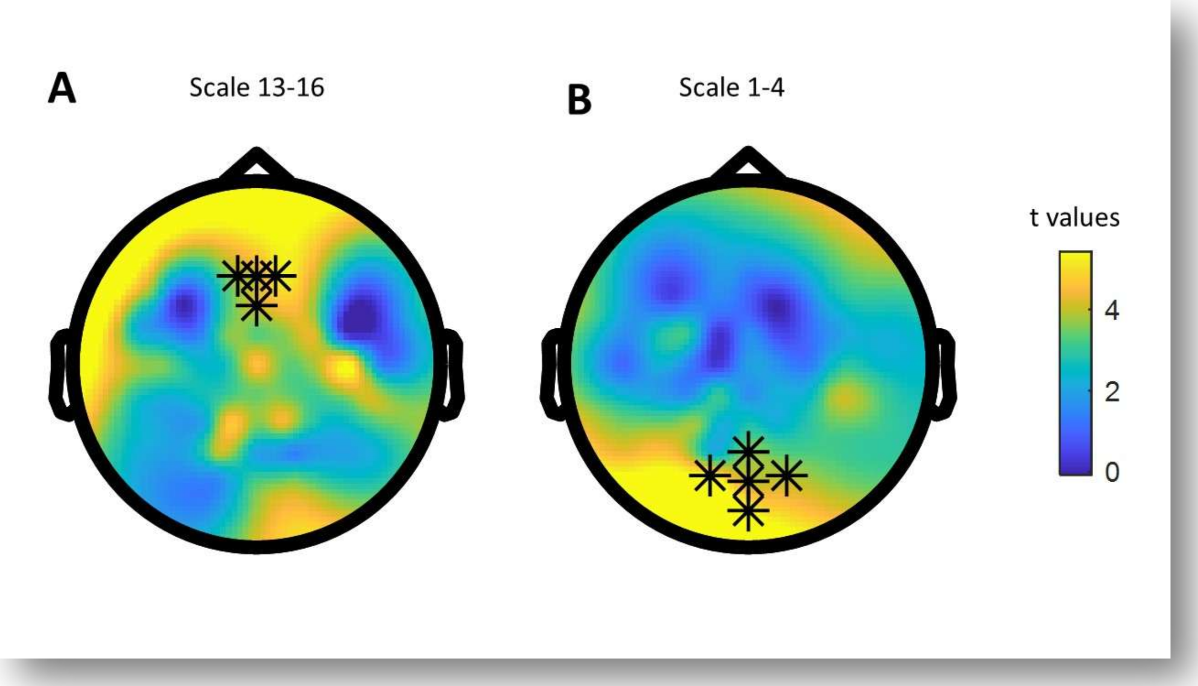


Figure 23 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 6Hz BSS (A) and 25Hz BSS (B)

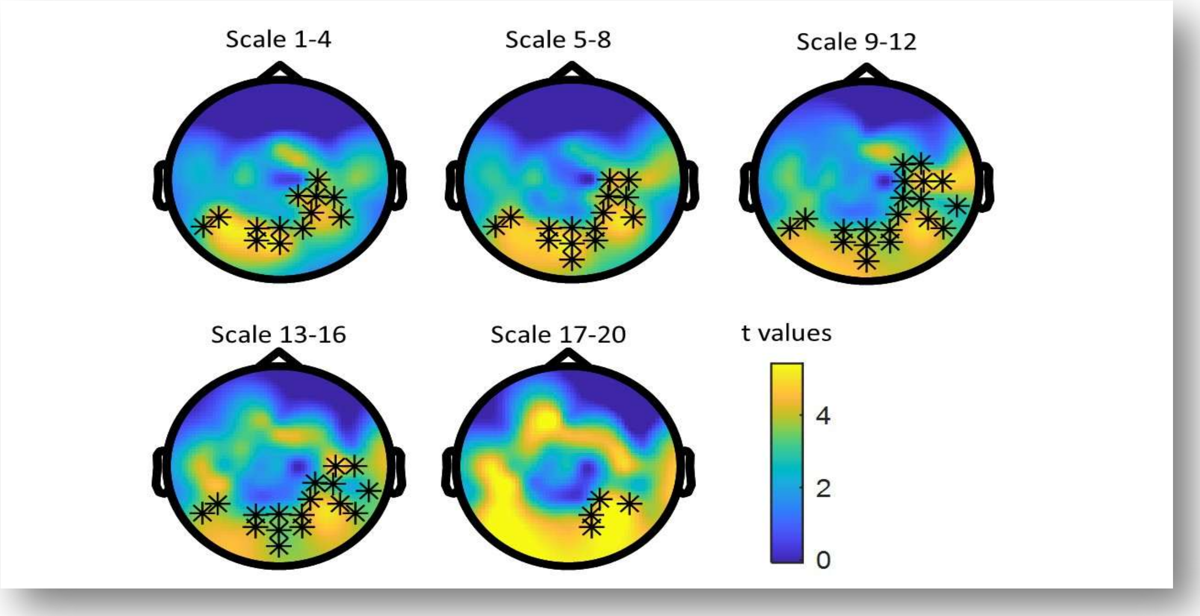


Figure 24 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 10Hz

The other protocol, CLS, showed significant effects at all the stimulation frequencies except for 40Hz condition. Interestingly, fine scales were not affected at any frequency stimulation except in a local manner at 2Hz. Delta CLS at 2Hz showed significant reduction in MSE across all the scales (p = 0.006). As shown in figure 8for finer scales the effects were more local and at the lateral sites but for more coarse scales central and posterior areas are involved too. At 6Hz, CLS reduced the entropy across medium and coarse scales (p = 0.01). The effects were observed more at the centro-lateral and anterior locations, especially at coarse scales (figure 9). MSE diminished at 10Hz CLS across coarse scales (p = 0.006) with more effects at central and lateral areas (figure 10). After 16Hz CLS entropy changed across the last two coarse scales (p =0.008). Figure 11 shows that the effects were more lateral, but also central areas were involved at coarse scales. The 25Hz CLS reduced MSE across coarse scales (p =0.002) with the effects confined to central regions (figure 12). Finally, similar to BSS no significant effects were observed at 40Hz gamma frequency for the CLS.

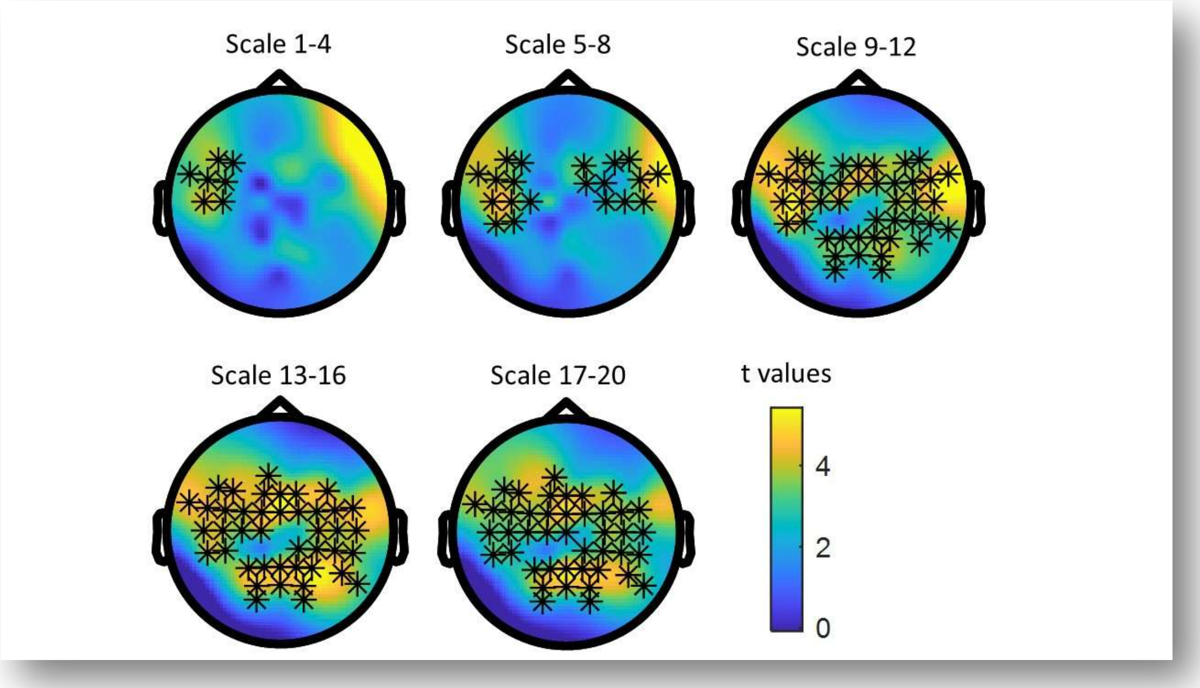


Figure 25 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 2Hz CLS.

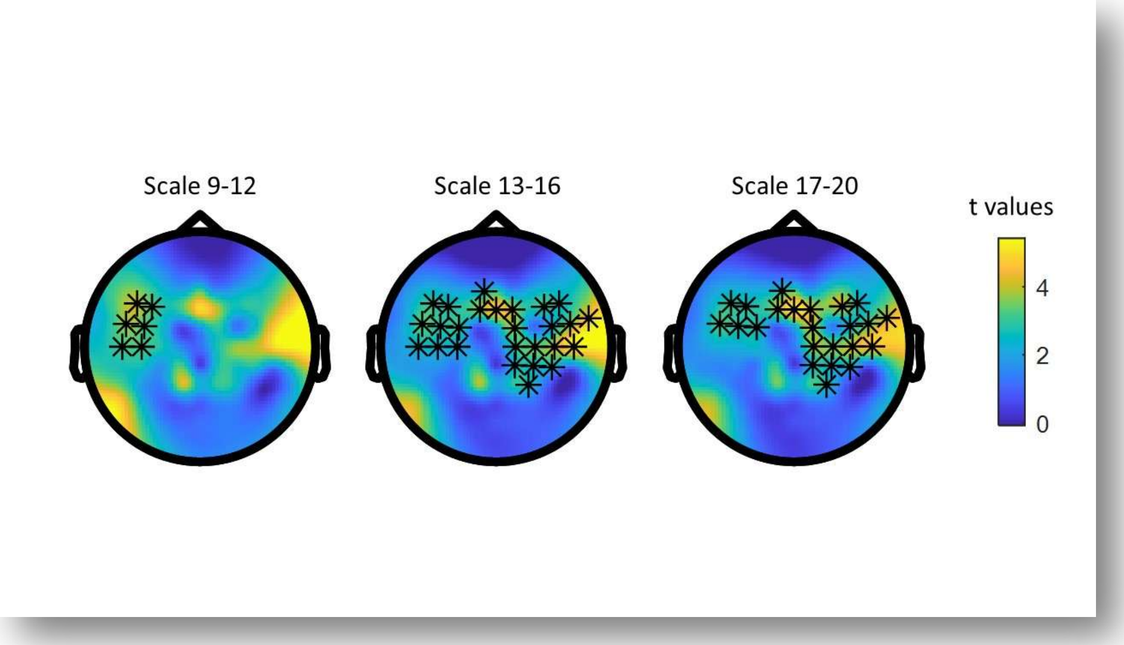


Figure 26 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 6Hz CLS.

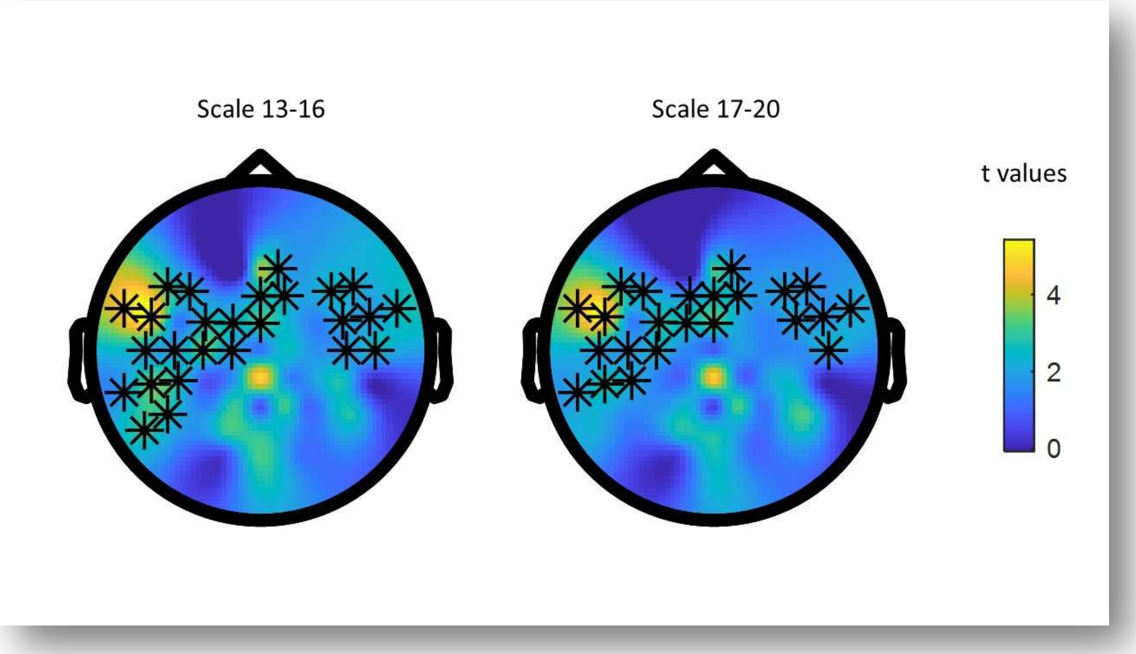


Figure 27 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 10Hz CLS.

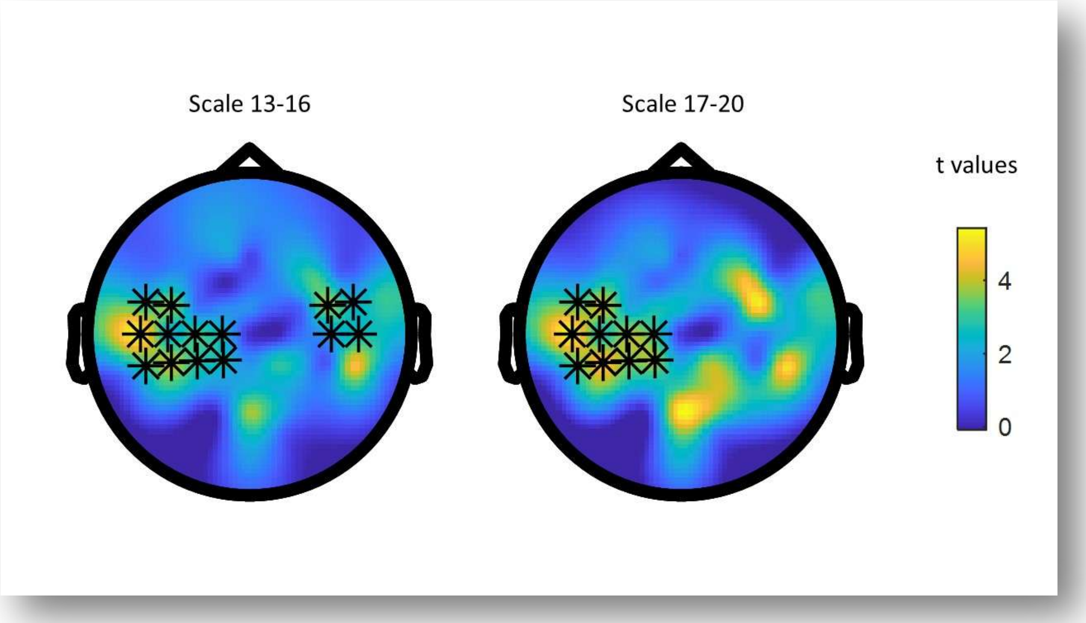


Figure 28 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 16Hz CLS.

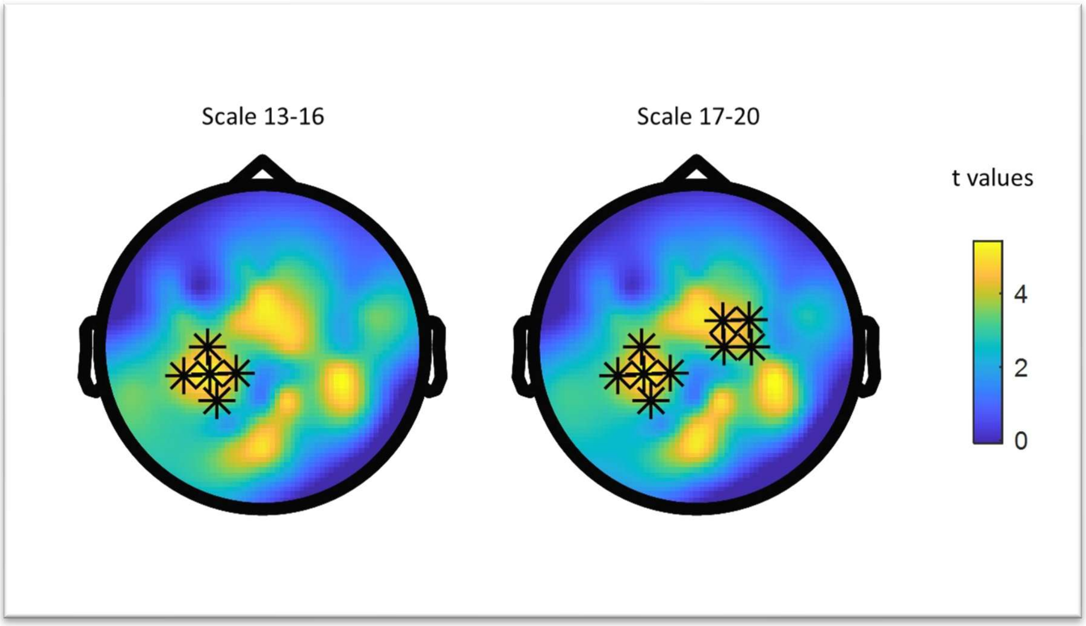


Figure 29 Topographic maps of MSE changes across different scales resulting from subtracting post-stimulation MSEs from pre-stimulation MSEs for 25Hz CLS.

Statistical Summary

In summary, these findings indicate that both BSS and CLS protocols induced significant frequency-specific alterations in neural activity and entropy across different scales and brain regions. Notably, cross-lateralized stimulation (CLS) led to consistent reductions in MSE across medium and coarse scales, affecting central and lateral areas, particularly at lower frequencies. In contrast, bilateral synchronous stimulation (BSS) showed significant entropy reductions primarily at finer scales and posterior regions. High-frequency stimulation (25 Hz and 40 Hz) was less impactful across both protocols, with no significant changes at 40 Hz. Overall, these results suggest that lower frequencies, particularly 2 Hz and 6 Hz, yield more prominent and spatially extensive effects in both power spectral and entropy measures, highlighting frequency-dependent and protocol-specific neural responses to AVE stimulation.

Conclusion

This experiment explored the nuanced effects of AVE on brainwave activity, focusing on two distinct stimulation protocols: Bilateral Synchronous Stimulation (BSS) and Cross-Lateralized Stimulation (CLS). Employing EEG analysis with both linear and nonlinear metrics, this study provided a comprehensive assessment of how different AVE protocols impact neural responses across a range of frequencies. Findings from the time-frequency and multiscale entropy analyses revealed that both protocols influenced brain activity, albeit with distinctive spatial and frequency-specific patterns that underscore AVE’s versatility and potential for targeted neuromodulation.

The results indicated that AVE stimulation frequencies in the lower range, particularly 2 Hz and 6 Hz, produced the most notable effects. BSS produced 17 positive clusters, with marked reductions in beta and gamma activity, and entropy reductions at finer scales primarily in posterior brain regions. This suggests that BSS may be effective for localized neural modulation, potentially making it suitable for applications requiring focused brain engagement within specific regions.

Conversely, the novel CLS protocol, which introduced slight frequency and phase variations across hemispheres, demonstrated broader effects across brain regions. CLS yielded 12 positive clusters with substantial reductions in entropy at medium and coarse scales, affecting central and lateral areas more widely and consistently than BSS. This pattern of response highlights CLS's capacity to engage wider neural networks, which may hold particular promise for interventions targeting large-scale neural circuits or hemispheric imbalances. The broader spatial impact of CLS suggests it may be advantageous in applications seeking to modulate brain areas related to holistic cognitive functions, such as attention and emotional regulation, where a broader neural influence is beneficial.

The differential impacts of BSS and CLS emphasize that protocol-specific modifications in AVE can result in varied neural responses, affirming the importance of customized parameter settings to achieve optimal neuromodulatory outcomes. Both protocols showed potential for targeted brain modulation but presented unique effects depending on frequency and spatial distribution, which has important implications for therapeutic applications. For example, the observed reduction in high beta and gamma activity across protocols aligns with research linking these bands to neuropsychiatric conditions, such as anxiety (Oathes et al., 2008), schizophrenia (Uhlhaas & Singer, 2010), and autism spectrum disorder (ASD) (Orekhova et al., 2007), suggesting that tailored AVE protocols may provide therapeutic benefit in managing symptoms associated with these disorders.

Despite the study's interesting findings, there are some limitations to consider. First, even though this study used statistical analysis and a robust experimental design, individual differences in brain responses to AVE continue to be a significant constraint. For example, baseline cognitive status, age, sex, and cortical excitability levels were not thoroughly examined and might have had an impact on the results Furthermore, not every external element that could affect the results was taken into account, including participant-specific variables like stress or exhaustion and environmental factors like lighting and noise. Furthermore, only brain activity before and after stimulation was examined; as a result, the duration of AVE effects is unknown, and its long-term mechanism of action is not well understood.

Additionally, there are inherent limitations in the study's approach. Despite being statistically adequate, the sample size might not be typical of larger groups, which restricts how broadly the results can be applied. A sham condition, for instance with fixed light, has not been collected to control for placebo effects. Even with preprocessing measures, residual artifacts may have affected the results since EEG is naturally sensitive to noise and artifacts, even if it offers great temporal resolution. Lastly, alternative potentially useful frequencies and configurations were not investigated because the study concentrated on two presentation modalities (BSS and CLS) and particular AVE frequencies. These drawbacks emphasize the necessity of more study to fill in these knowledge gaps and improve AVE techniques for optimal clinical and experimental use.

While the study support the efficacy of AVE as a neuromodulatory method, it also points to the need for further exploration into protocol variations. Future studies would benefit from integrating shorter protocols, introducing rest breaks, and addressing individual variability to improve reproducibility and generalizability. Addressing these factors will refine AVE's effectiveness and further delineate the specific mechanisms underlying its impact on brain activity.

In conclusion, the findings from Chapter Two validate AVE's effectiveness in modulating brain activity and emphasize the protocol-specific neural outcomes that arise from variations in AVE delivery. This research establishes a foundation for developing targeted AVE interventions tailored to specific neural and cognitive objectives, advancing the potential of AVE as a versatile tool for both research and therapeutic purposes.

Chapter 3

Discussion

Audiovisual Entrainment (AVE) is a non-pharmacological, stimulus-driven intervention that synchronizes the brain's electrical activity with externally delivered auditory and visual cues, promoting targeted brainwave modulation. Delivered through devices ranging from basic visual and audio setups to sophisticated wearable systems, AVE offers a flexible and accessible approach to influencing cognitive and emotional processes. Its specificity in frequency selection enables applications in therapeutic and experimental settings for conditions such as depression, insomnia, and cognitive deficits. However, despite its potential, AVE research is hindered by variability in methodologies and a need for standardized protocols, highlighting the need for further refinement to maximize its therapeutic impact.

This study presented the first attempt to systematically standardize AVE parameters, addressing the variability that has limited previous applications. We introduce detailed considerations of how AVE parameters such as frequency, phase, color, intensity, and visual waveform shape can influence its mechanisms of action. These factors can affect AVE's impact on brain function, providing a pathway toward a more controlled and replicable approach to AVE research.

Additionally, this study pioneers the examination of a broader range of frequencies than has been previously explored, revealing nuanced effects of AVE across different brainwave states. Our results suggest that lower frequencies produce broader effects across brain regions, underscoring the importance of careful frequency selection. By clearly defining these parameters and settings, we aim to create a foundation for more reliable AVE applications in clinical and research contexts, enabling more precise targeting of neural processes.

We also investigated two distinct presentation modes for the first time: CLS showed more targeted and controlled engagement with specific brain regions. BSS demonstrated broader activation patterns in MSE, making each approach suited for therapeutic applications. These innovative additions not only expand the understanding of AVE's effects across frequency bands but also highlight the importance of presentation mode in tailoring AVE's application for specific therapeutic goals. These findings lay critical groundwork for developing targeted AVE protocols that optimize its neuromodulatory potential.

Beyond the standardization of parameters and settings, AVE's integration possibilities with other neuromodulation techniques, such as NiBS and even tactile stimulation, are excellent. These added dimensions offer further avenues for enhancing AVE's efficacy, allowing it to interact with different sensory systems and target diverse brain regions. This study not only establishes foundational standards for AVE parameters but also opens the door to exploring these integrations, which could amplify AVE's impact on cognitive and therapeutic outcomes.

The rhythmic presentation that forms the basis of audiovisual entrainment (AVE) presents several opportunities for integration with other neuromodulation techniques, potentially enhancing its effectiveness. Among the most studied are rTMS and tACS, which rely on rhythmic stimulation. Combining these techniques with AVE could yield a more robust brain response. AVE operates through the eyes and ears, engaging multiple brain regions before reaching the cortex, whereas rTMS and tACS are transcranial techniques directly targeting the cortex. This complementary interaction is thus both meaningful and promising.

Additionally, AVE's versatility lies in its capacity to incorporate tactile stimulation. While AVE typically engages the auditory and visual senses, adding a third modality, tactile stimulation, offers intriguing possibilities. The somatosensory system has distinct neural pathways, and several brain regions are involved in processing tactile information, making this a compelling area for further exploration. How AVE can be presented could be another challenge for AVE.

Generalizing data from current or comparable studies is challenging due to the influence of several variables on responses. Although prior studies yield promising results concerning the brainwave activity-modulating efficacy of AVE, several critical aspects of this technique remain unexamined, including individual differences, environment variables, data computation, and mode of presentation affecting responsiveness to AVE. A better understanding of these aspects may change expectations for AVE and additional refining.

Similar to other NIBS procedures, such as rTMS and tDCS, AVE can rely on the individual's baseline brain activity and cortical excitability levels. Silvanto and Pascual-Leone, 2008, indicated that variability in individual excitability influences responses to neuromodulation, a characteristic that would also apply to AVE interventions. Various factors, including genetic impacts that modulate cortical plasticity in response to rTMS, may contribute to variations in responsiveness to AVE-based experiments (Cheeran et al., 2008).

Age is a significant determinant that affects neuroplasticity. Overall, responses are more robust in younger individuals, as observed by Freitas, Farzan, and Pascual-Leone (2013). The age-dependent plasticity may manifest in AVE, indicating that younger individuals could derive more advantages than their older counterparts. Documented individual differences related to these factors have been shown to influence neuroplastic responses, as indicated by Kuo et al., 2006; hence, it is anticipated that AVE will also be similarly affected by sex and hormone influences. Other parameters, including baseline cognitive status, brain anatomy, and neurotransmitter systems, equally influenced the outcomes of neuromodulation techniques used by tDCS and rTMS, likely affect to AVE reactions (Luber & Lisanby, 2014; Nitsche & Paulus, 2011; Opitz et al., 2015).

An EEG reference signifies the point of comparison for all electrode data, serving as the foundation for interpreting electrical brain activity. The choice of reference utilized can significantly influence the recorded signals and may substantially impact on the interpretation of brain dynamics, particularly in complex tasks such as AVE.

The average reference in EEG is the standard method in which the electrical activity at each electrode is compared to the mean signal from all electrodes on the scalp. This method mitigates the influence of individual electrodes, facilitating a more equitable and comprehensive perspective on cerebral activity (Dien, 1998; Nunez & Srinivasan, 2006). Within the framework of AVE, this is a common methodology employed in effect computation, as AVE typically impacts numerous brain regions concurrently.

As mentioned in Chapter one, AVE influences extensive areas of the brain, therefore using the average reference may unintentionally reduce or obscure effects throughout the whole brain, as activity is averaged globally. This may mask the broader impact of AVE, making the specific effects significantly more difficult to identify.

Another referring technique, Linked Ears Reference, is more localized and enables enhanced attention on certain brain regions. Nonetheless, it possesses limitations: the influence of residual brain activity or noise at the reference sites the ears or mastoids can be conveyed onto the signal (Luck, 2014; Nunez & Srinivasan, 2006). The employment of a Cz reference, with the central electrode at the vertex designated as the reference point, may also introduce biases, as it presupposes that Cz is neutral or exhibits low brain activity. This may result in distortions, especially in midline structures, and may overlook significant signals emanating from the Cz location.

Although referencing like Current Source Density (CSD) provide a more nuanced enhancement of spatial resolution and mitigate the influence of distant regions, a more definitive understanding of the localized effects of AVE would be achieved by concentrating on cortical sources (Kayser & Tenke, 2015). This approach mitigates the constraints of both average and localized references, facilitating the elucidation of more precise neuronal processes that alternative referencing approaches may conceal.

Comprehending individual variability computational feature extractions are essential for progressing AVE research and enhancing its overall effectiveness. Although existing evidence indicates that AVE affects brainwave modulation, additional research is necessary to elucidate the specific processes via which these parameters interact with AVE, facilitating more accurate and targeted results. This research, alongside others, illustrates that AVE can proficiently regulate brainwaves. Nevertheless, the accuracy and reproducibility of these findings necessitate further examination to improve the precision of the results. Notwithstanding these constraints, both our research and the current literature validate AVE's capacity to affect brain activity.

Given the distinct patterns observed in both linear and nonlinear analyses, along with the adjustable parameters of AVE, future research has great potential to uncover the mechanisms underlying AVE's effects across different presentation modes. Further studies could help clarify how each AVE mode aligns with specific neural and cognitive outcomes. This understanding could guide the development of targeted protocols optimized for treating particular disorders. Expanding research in this area may provide valuable insights into the suitability of various AVE configurations for managing specific psychological or neurological conditions, ultimately advancing its therapeutic applications.

The results of this study indicate that AVE has substantial potential as a neuromodulatory tool, with measurable impacts on brainwave activity through both linear and nonlinear analyses. Moreover, AVE's flexibility in terms of presentation modes suggests a broad scope for further exploration, highlighting its adaptability for various applications. AVE stands out due to its accessibility as an easy-to-use, home-based technology that requires no specialized administration, making it particularly promising for widespread use. Given these unique features and its demonstrated effectiveness, AVE merits continued research to fully understand and optimize its potential for therapeutic and cognitive enhancement purposes.

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