Cerebrum 40: Study on maintaining cognitive performance through advanced neuroregulation Randomized, controlled and multicenter clinical trial

Alina ROBU, Alina-Diana NEMES

Abstract

Age-associated neurocognitive decline often begins subclinically, between the ages of 40 and 50, accelerated by occupational stress, lack of self-regulation, and adaptive exhaustion. The Cerebrum 40 study investigated the impact of a multimodal neurotechnology intervention – Neurofeedback Plus – on cognitive performance, physiological resilience, and subjective perception of mental functioning among active adults.

The study was randomized, controlled, longitudinal, conducted on a sample of 400 participants (200 experimental, 200 control), with a duration of 12 months. The intervention integrated personalized EEG neurofeedback, brain photobiomodulation, HRV biofeedback, and transcutaneous vagal stimulation, applied in 3 therapeutic cycles. The evaluation was performed through qEEG, HRV, biofeedback and validated questionnaires. Statistical analyses included t-tests, ANOVA, multiple regression, PCA, and correlations between objective markers and perceptions.

The intervention produced significant reductions in perceived burnout ($t = +6.28$, $p < .00001$), increases in vagal tone (RMSSD, $t = -13.37$, $p < .00001$), and an improvement in EEG coherence in executive (BA8), semantic (BA44/45), and attentional (BA7) networks. ANOVA 2x2 confirmed the existence of a statistically significant interaction effect, Group x Time, for RMSSD ($F= 91.23$, $p < .00001$). Regression analysis showed that BA44/45 (coef. = +14.52, $p = .038$) and RMSSD (coef. = –0.14, $p = .001$) independently predict the level of burnout. PCA identified 3 latent functional dimensions: vagal regulation, executive coherence, and semantic stress.

The Cerebrum 40 study scientifically validates Neurofeedback Plus as a standardized, effective, and safe intervention for the prevention of early cognitive decline. The results support the integration of the protocol into longevity medicine and public health strategies for the adult active population, providing a new clinical model of neurophysiological and psychological support through advanced, non-pharmacological technologies.

Keywords: Neurofeedback EEG, HRV, brain photobiomodulation, vagal stimulation, burnout, EEG coherence, self-regulation, functional neural networks, neuroplasticity, cognitive longevity, preventive intervention, applied neuroscience.

1. Introduction and scientific justification

1.1. Critical context of age 40–50: Silent wear and decisive neurofunctional threshold

The age range of 40–50 years represents an essential moment in the neurophysiological development of the individual – a seemingly stable stage in the external performance plan, but which masks, internally, a series of subtle processes of dissociation, wear and tear and the beginning of structural vulnerability. It is the age when, most of the time, cognitive capacities still seem intact: decision making is fluent, mental planning works, multitasking is the daily norm, and working memory seems pressure-resistant. But it is precisely this appearance of efficiency that hides a significant neurobiological cost – a start of exhaustion that, unaddressed, can lead to hardly reversible damage in the coming decades.

From a neuroscientific point of view, the period 40–50 years marks a discrete but clear inflection in several dimensions of brain functioning: changes begin to occur in the coherence of frontal and parietal neural networks (with impact on executive processes), a progressive decrease in synaptic neuroplasticity and a slow but steady reduction in cerebral metabolic flow (Park & Reuter-Lorenz, 2009; Fjell & Walhovd, 2010). These changes are not yet clinically apparent, but they subtly affect the brain's ability to self-regulate, resist stress, effectively filter information, and remain flexible in the face of daily challenges.

This middle stage of life is, paradoxically, one in which the individual operates under maximum professional, emotional, and social pressure-simultaneously coordinating career, family, economic responsibilities, and often multiple social roles. All these requests involve an intense and prolonged use of executive and limbic circuits, especially in Central Executive Network (CEN), Dorsal Attention Network (DAN) and Language & Semantic Network – which thus become most vulnerable to overuse and early functional degradation (Cole & Schneider, 2007; Menon, 2011).

Moreover, the current literature draws attention to an increasingly common phenomenon at this stage: subclinical cognitive burnout, a form of exhaustion that is not manifested by obvious psychopathological symptoms, but which negatively influences performance, quality of life and neurophysiological balance (Maslach & Leiter, 2016; McEwen, 2012). This type of wear is often ignored because it does not fit into classic diagnostic criteria, but it is an important predictor of accelerated decline in the coming decades.

The time of 40–50 years provides a neurobiological window of unique opportunity: synaptic plasticity is still functional, compensation mechanisms are active, and brain reorganization capacity is preserved to a sufficient degree that preventive interventions are not only possible, but highly effective (Cabeza et al., 2018). Recent studies show that reorganization of neural networks and recalibration of autonomic balance are significantly easier to achieve at 45 than at 65 (Nyberg et al., 2012). In other words, what is built at the age of 45 can be preserved up to 75 – but what is not built on time is hardly lost later, even in the presence of therapy.

In this sense, prevention can no longer be thought of as a luxury or an optional solution, but must be understood as an active strategy to prolong functional cognitive life. Living longer is not an end in itself, unless it is accompanied by mental clarity, decision-making autonomy, emotional regulation, and the ability to function socially. Longevity medicine must essentially become medicine of the quality of life, not just of its duration.

Prolonging life without mental health and cognitive functionality is, in fact, an extension of suffering – both for the individual and for the family or community around him. It is what the literature calls extensive morbidity (Christakis, 2019) – a period of years in which the individual no longer functions but continues to exist biologically. By contrast, our approach proposes what is called morbidity compression (Fries, 2005): that is, a long, active, lucid and dignified life, followed by a short and natural period of decline.

That is why this study – Cerebrum 40 – marks a fundamental step in our effort to transform prevention into an effective and clinically applicable neurotechnological tool. It is the first step in a progressive scientific strategy that goes before the decline begins, precisely to make it improbable or postponable, and that builds a resilient brain architecture, capable of supporting real life with lucidity, efficiency and balance.

1.2. Scientific justification for the application of preventive intervention in the brain between 40 and 50 years

If in the decades after 60 years neurocognitive prevention involves rather slowing down a process already initiated, in the range of 40–50 years we have the unique chance to act before the onset of decline, at a time when the brain apparently functions optimally, but begins to gradually lose its ability to self-regulate and flexibility. This period is, from a neurophysiological point of view, the turning point between performance and vulnerability – a critical stage where compensation mechanisms are still available, but overload mechanisms begin to leave their lasting imprint on brain networks.

The literature clearly states that neural networks involved in high-level cognitive functioning – such as the Central Executive Network (CEN), responsible for planning, working memory and strategic decision, or the Dorsal Attention Network (DAN), involved in multitasking and directional focus – gradually begin to lose functional coherence after the age of 40, even in clinically healthy individuals (Spreng et al., 2010; Goh & Park, 2009). This process is often accelerated by the lifestyle specific to this period: chronic stress, continuous multitasking, lack of deep sleep, cognitive sedentarism, internal rumination and lack of regenerative breaks.

Against the background of these factors, a dangerous but silent phenomenon sets in: the decoupling between appearance and reality – the individual still performs socially, but his brain begins to function in compensatory mode, with increased energy consumption and reduced neural efficiency (McEwen, 2012). This “illusory efficiency” is accompanied by compensatory hyperactivation in prefrontal and temporal areas, often followed by a phase of functional exhaustion, visible in subsequent decades in the form of residual burnout, attention disorders, executive anxiety, or even early cognitive decline.

Therefore, the 40–50 years interval offers the optimal window for neuropreventive intervention, being the time when:

- neuroplasticity is still active but is starting to decrease (Park & Reuter-Lorenz, 2009);
- functional networks are still organized coherently, but vulnerable to destabilization (Cabeza et al., 2018);
- autonomy of the vegetative nervous system is adjustable, but exposed to chronic sympathetic imbalances (Thayer & Lane, 2007);
- and the quality of decisions and executive functioning can be preserved in the long run, if supported by active intervention.

This study aims to prevent exactly those dysfunctions that, left untreated, worsen in the years to come and become difficult to correct. Through multimodal neurotechnological interventions – such as EEG neurofeedback, brain photobiomodulation, heart-brain coherence biofeedback and non-invasive vagal stimulation – a fine tuning of neural networks and autonomous rebalancing can be achieved, without drugs, without adverse effects and in a personalized and reproducible way (Gruzelier, 2014; Hamblin, 2016; Lehrer & Gevirtz, 2014).

Moreover, the interventions applied at this stage can contribute to:

- strengthening the networks of semantic integration and internal language (BA44/45, BA20/21), protecting against cognitive overload and self-deprecating verbal hyperactivation;
- optimizing emotional decision making (BA11), in order to maintain clarity in the context of stress;
- supporting controlled multitasking and visual-spatial orientation (BA7), essential in complex work environments;
- restoring coherence between intention, execution and motivation (BA8), functional blocks that are slowly but steadily eroding.

These areas, correlated with the CEN, DAN and Semantic Network, form the functional core of modern mental autonomy – the ability to think clearly, decide effectively and emotionally adapt to the demands of adult life. Maintaining these functions in optimal condition ensures not only the extension of cognitive life, but also the extension of quality life.

Thus, the Cerebrum 40 study is based on a scientific strategy of early neuroprotection, at a stage where the intervention not only prevents, but builds resilience – and prevention becomes an active act of neural architecture, not just of disease avoidance. It is a proactive approach, in the service of a longer, but above all lucid, functional and dignified life.

1.3. Networks and brain areas involved in optimal functioning between 40 and 50 years of age: Justification of the choice of targets for intervention

To support active prevention and effective neuroregulation in the 40–50 years stage, the intervention proposed in this study focuses on three essential functional networks and six Brodmann cortical areas that directly reflect the neurocognitive demands of active adult life.

Their choice is not arbitrary, but results from the convergence of current scientific evidence on functional wear and tear specific to this age group, correlated with intellectual, executive and decision-making demands in everyday life.

1.3.1. Targeted functional networks

- **Central Executive Network (CEN)**

It is the core network involved in decision making, planning, working memory and self-control. It includes the dorsolateral and anterior prefrontal cortex (BA8, BA11), the regions most used in contexts of cognitive overload – typical for the 40–50 year old population, especially in the urban and digitalized professional environment.

Decline in connectivity in CEN is correlated with difficulty concentrating, decision-making fatigue and mental rigidity (Cole & Schneider, 2007; Spreng et al., 2010).

Intervention justification: Neurofeedback and photobiomodulation on BA8 and BA11 can recalibrate network efficiency, supporting performance without exhaustion.

- **Dorsal Attention Network (DAN)**

This network governs directed attention, visual-spatial orientation and multitasking ability, essential elements in daily professional activity. Includes BA7, the upper parietal cortex, highly demanded in complex work environments.

Studies show that in middle-aged adults, activation in DAN begins to decline under chronic stress, leading to subtle attention dysfunction, contextual confusion, and slowing of reactions (Vossel et al., 2014).

Justification of intervention: The activation of BA7 through neurofeedback and photobiomodulation optimizes the directional focus and reduces the risk of chaotic overstimulation (mental clutter).

- **Language and Semantic Network**

Involved in internal verbal thinking, self-critical control and integration of complex information, this network is fundamental to the intellectual professions – where semantic analysis, expression, drafting and evaluation are dominant. Includes the middle and lower temporal areas (BA20/21) and Broca's frontal areas (BA44/45).

In stage 40–50, this network is overworked and prone to blockages, which favors rumination, mental fatigue, and decreased cognitive flexibility (Fedorenko et al., 2012).

Justification of intervention: The intervention aims to restore mental clarity and reduce cognitive overload through EEG regulation and rhythmic light stimulation.

1.3.2. Brodmann areas selected for intervention

- **BA8 – Upper medial frontal cortex**

Involved in initiative, anticipation, action planning and solution generation. It is crucial for adults who face multiple decisions on a daily basis and who need to function effectively despite the pressure.

Therapeutic role: Training in this area increases clarity in decision making and reduces procrastination caused by executive blockade (Ramnani & Owen, 2004).

- **BA44/45 – Ariile Broca (pars opercularis and triangularis)**

Responsible for internal language processing, verbal control and articulate logical thinking. Their wear is reflected in excessive self-criticism, rumination and decreased mental efficiency.

Therapeutic role: Regulating these areas through neurofeedback and HRV reduces internal verbal tension and supports conceptual clarity (Enriquez-Geppert et al., 2017).

- **BA7 – Upper Parietal Cortex**

It integrates multisensory information and spatially oriented attention, being essential in multitasking tasks. Fatigue in this area generates cognitive disorientation, errors of judgment, and difficulty switching between tasks.

Therapeutic role: The activation of BA7 increases accuracy in dynamic work environments and the ability to respond orderly to multiple stimuli (Corbetta & Shulman, 2002).

- **BA11 – Orbitofrontal cortex**

Regulates ambiguous decision making, integration of emotions, and evaluation of results. It is sensitive to stress and plays a critical role in decision-making burnout.

Therapeutic role: Stimulating the area restores emotional-decisional balance and reduces blockages in a stressful context (Kringelbach & Rolls, 2004).

- **BA20/21 – Lower and middle temporal cortex**

Areas associated with semantic integration, object recognition and complex language processing. Overloading them leads to mental overload and slowing down the processing speed.

Therapeutic role: Through training and stimulation, efficiency in processing abstract ideas and maintaining cognitive speed is supported (Binder et al., 2009).

Together, these Brodmann networks and areas compose a complex but fragile brain architecture in the face of chronic overload. Between 40–50, they do not yet have severe deficits, but they begin to lose their functional balance. Targeted preventive intervention – applied through the integrated Neurofeedback Plus protocol – not only stabilizes these regions, but also optimizes them functionally, allowing the extension of the duration of active brain performance and reducing the risk of subsequent cognitive decline.

1.4. P4 paradigm: Predictive, Preventive, Customized, Participative – with a focus on functional optimization of the active brain

The classical model of medical approach – centered on the treatment of pathology – is becoming increasingly inadequate in the face of the current challenges of longevity and silent functional degradation. Instead of a reactive paradigm that intervenes late after the onset of symptoms, contemporary medicine advances towards an integrative paradigm known as P4 Medicine: Predictive, Preventive, Personalized, and Participatory (Hood & Friend, 2011).

This approach proves to be not only a conceptual alternative, but an urgent practical need in the field of applied neuroscience – especially for those populations that are in a subclinical stage of cognitive wear and tear, as is the case with active adults between 40 and 50 years of age.

P1 – Predictive: early identification of neurophysiological vulnerabilities

Predictive medicine aims to detect functional imbalances early, before they manifest clinically. In neuroscience, this is made possible by using objective markers such as:

- EEG coherence and cortical activation patterns in major functional networks (Thatcher, 2010),
- HRV as an indicator of autonomic stress and parasympathetic disorder (Shaffer & Ginsberg, 2017),
- physiological stress scores and heart-brain coherence, quantifiable by biofeedback (McCraty & Zayas, 2014).

Studies show that subtle changes in these dimensions occur 5–10 years before the clinical onset of cognitive or affective disorders (Koenig et al., 2016). Therefore, implementing a predictive screening strategy through qEEG, HRV and psycho-physiological assessments allows an early mapping of brain vulnerability, providing an intervention map specific to each individual.

P2 – Preventive: early intervention to strengthen functional networks

Preventive medicine involves acting before symptoms appear, by training and recalibrating critical neurophysiological systems. In the case of brain function, prevention means:

- restoring coherence in executive and attentional networks,
- reduction of background physiological stress (hyperactivation of the HPA axis and sympathetic system),
- and training adaptive neuroplasticity before reorganization becomes difficult.

In particular, in the population 40–50 years old, prevention has a strategic value: it is the time when reorganization is still possible without invasive or pharmacological efforts. EEG neurofeedback, vagal stimulation, HRV biofeedback, and photobiomodulation are validated tools that can rebalance these networks in a non-invasive and reproducible way, helping to maintain mental functions in their optimal phase (Ros et al., 2014; Lehrer & Gevirtz, 2014; Hamblin, 2016).

P3 – Personalized: adaptation of the intervention to the individual brain architecture

There is no brain identical to another. Therefore, standardized intervention without individualization risks being ineffective or even counterproductive. P4 Medicine proposes a rigorous customization, based on objective assessments, specific to each individual. In the Cerebrum 40 study, this principle is applied by:

- custom qEEG: identification of each participant's specific functional pattern and network imbalances;
- dynamically adapted neurofeedback protocols, depending on individual progress;
- selection of photobiomodulation parameters according to the EEG spectral profile and underactive or hyperactive brain areas;
- HRV monitoring and fine-tuning of coherence workouts according to each person's autonomous reactivity.

This customization is essential in stage 40–50, when individual neurophysiological asymmetry becomes more pronounced and generic interventions are no longer sufficient for real optimization (Marzbani et al., 2016).

P4 – Participatory: active involvement of the individual in his/her own adjustment process

The participatory model involves the transition of the individual from the status of passive patient to that of co-regulator of his own neurophysiology. The technologies used in the Cerebrum 40 study (neurofeedback, HRV biofeedback, vagal stimulation with real-time feedback) are interactive, immersive and educational. Participants are not "treated" but learn to actively regulate mental, emotional and autonomic parameters.

This approach has double benefits:

1. Increased therapeutic effectiveness – voluntarily activated self-regulation has more lasting effects than passive interventions (Gruzelier, 2014).

2. Increased sense of personal control – a strong predictor of psychological resilience and long-term mental health (Bandura, 1997).

Especially for adults aged 40–50, who live under the pressure of external control, this recentralization of self-regulation brings an essential psychoeducational effect: man learns to regain power over his own balance.

The path of the P4 paradigm – predictive, preventive, personalized, participatory – defines exactly what the intervention tested in this study offers: not a repair, but a construction. Not a malfunction correction, but an active optimization of a malfunctioning operation. In this way, Cerebrum 40 becomes an integral part of a new way of understanding cognitive health: as an adjustable, entrainable and actively expanded resource, at every stage of functional life.

1.5. Justification of integrated Neurofeedback Plus intervention and its components on selected areas and networks for active prevention between 40 and 50 years

Effective neurocognitive prevention cannot be built on one-dimensional interventions.

In a complex, adaptive and interconnected brain system, where functional networks interact dynamically, an effective therapeutic approach must act simultaneously and synergistically on all relevant dimensions: cortical activity, autonomous balance and functional coherence between regulatory systems. In this sense, Neurofeedback Plus is not just a combined protocol, but an integrated neuroregulation system, calibrated specifically for the functional needs of the active adult brain.

1.5.1. Custom EEG Neurofeedback – targeted cortical self-regulation

EEG neurofeedback, based on quantitative and qualitative analysis of brain activity (qEEG), enables real-time brain training, providing auditory and visual feedback for conscious regulation of neural patterns. The intervention is based on the principle of experience-dependent plasticity, according to which the brain can learn to modify its functional activity through repetitive, guided exercise (Ros et al., 2014; Hammond, 2011).

In the population 40–50 years of age, EEG neurofeedback aims to:

- reduction of hyperactivation in fast frequencies (High-Beta) in BA44/45, BA11 areas – associated with overthinking, decision-making stress and verbal rumination;
- stimulation of Alpha and SMR frequencies in BA8 and BA7 – to support directional focus, initiative and attentive control;
- balancing inter- and intrahemispheric coherence in BA20/21 – key areas for semantic clarity and avoidance of information overload.

Studies show that neurofeedback significantly improves working memory, decision-making capacity, and emotional self-regulation, especially when applied customized, based on an individual EEG profile (Enriquez-Geppert et al., 2017; Arns et al., 2009).

1.5.2. Brain photobiomodulation – network synchronization and metabolic neuroprotection

Brain photobiomodulation (PBM) involves applying pulsed light in the near-infrared spectrum (typically 810-850 nm), at specific frequencies (10 Hz and 40 Hz), directly to the scalp, in strategic regions. It stimulates neuronal mitochondria, increases ATP synthesis, and activates neuroprotective genes, with proven effects on neuroplasticity, cortical metabolism, and reduction of brain inflammation (Hamblin, 2016; Chan et al., 2021).

In the Cerebrum 40 study, two frequencies are used:

- 40 Hz (gamma) – stimulates synchronization of executive and attentional networks (CEN and DAN), being associated with increased cognitive clarity, processing speed and functional coherence between BA8, BA7 and BA20 (Iaccarino et al., 2016).

- 10 Hz (alpha) – induces a neurophysiological state of active calm, favorable for integrating multiple signals and reducing mental tension. Applied to BA11 and BA44, it contributes to cognitive regulation in stressful context.

PBM complements neurofeedback through profound biological effects and supports the restoration of an optimal brain environment for active cognitive training.

1.5.3. Heart-brain coherence biofeedback – autonomous and emotional recalibration

HRV biofeedback is a scientifically validated method of training the autonomic nervous system by regulating breathing and real-time tracking of heart rate variability (HRV), with the aim of achieving psychophysiological coherence between the brain, heart and vegetative nervous system (Lehrer & Gevirtz, 2014).

This component is crucial in preventing cognitive wear because:

- optimizes vagal tone, increasing RMSSD and balancing the LF/HF ratio;
- reduces chronic sympathetic stimulation, correlated with cognitive burnout and hyperalertation;
- supports adaptive emotional regulation, through the training of BA24, BA32 and cortical-subcortical connections involved in resilience.

In stage 40–50, when stress is ubiquitous and vegetative reactivity is chronic, autonomous training becomes the key to mental and emotional integration. Participants learn to modify their physiology in real time, gaining conscious control over their own internal balance (McCraty & Shaffer, 2015).

1.5.4. Transcutaneous vagal stimulation – direct activation of the parasympathetic system

Stimulation of the vagus nerve (tVNS) by gentle electrical impulses, applied transcutaneously (auricular or cervical), is one of the most effective non-pharmacological methods of activation of the parasympathetic branch. It has direct effects on:

- hPA regulation and cortisol reduction;
- increase in HRV and ability to recover from stress;
- modulation of connections between the prefrontal cortex and the limbic system – in particular BA11, BA24, BA44.

Studies show that tVNS increases EEG coherence between executive areas and affective networks, stimulates GABA production, and helps reduce neurogenic inflammation, key factors in preventing functional degeneration in middle age (Yuan & Silberstein, 2016; Breit et al., 2018). Combined with neurofeedback and HRV biofeedback, vagal stimulation brings deep physiological stability, necessary to maintain cognitive functionality in the face of daily pressure.

1.5.5. Intervention synergy – more than the sum of the parts

The four components of the Neurofeedback Plus intervention do not work independently, but converge on the same networks and brain areas:

- Neurofeedback regulates specific cortical activity and develops awareness;
- PBM creates an optimal metabolic environment for regulation and integration;
- HRV biofeedback aligns the brain and heart in an adaptive rhythmicity;
- Vagal stimulation anchors the change into the deep balance of the autonomic nervous system.

This multimodal approach has already been validated as superior to isolated interventions, in terms of lasting effects, generalization of results, and stability of brain reconfiguration (Gruzelier, 2014; Lehrer et al., 2013; Hamblin, 2016).

Neurofeedback Plus intervention is not a symptomatic treatment, but an advanced form of active neurophysiological education that balances the cortex, functional networks, and vegetative system exactly at the points of vulnerability occurring between 40 and 50 years of age. Through its early and targeted application, the premises are created for maintaining high cognitive functionality until old age, without accelerated degradation, burnout or compensatory decline. It is a real functional longevity strategy – active, lucid and adaptive.

2. Objectives of the study

2.1. General objective

The overall objective of this clinical trial is to evaluate, in a rigorous, objective and reproducible manner, the effectiveness of integrated neurofeedback Plus neurotechnology intervention on three fundamental dimensions of brain health in the active adult population aged 40-50 years:

1. Neurocognitive performance – particularly in terms of mental clarity, processing speed, executive flexibility, directional focus and decision-making ability under stress.
2. Brain coherence – understood as functional integration and synchronization between key cortical areas (BA8, BA44/45, BA7, BA11, BA20/21) and neural networks involved in maintaining cognitive balance (CEN, DAN, Semantic Network).
3. Autonomic balance – expressed through neurophysiological markers of the autonomic nervous system: heart rate variability (HRV), vagal tone, heart-brain coherence, and physiological stress scores.

The justification of this general objective starts from the scientific finding that, in the range of 40–50 years, although the apparent functioning is peak, structural and functional fragilities begin to appear at the subclinical level, which, untreated, lead to accelerated cognitive wear and neuroemotional vulnerability. The study therefore aims to validate a proactive, non-invasive and scalable intervention protocol that not only preserves brain functions but actively optimizes them before the damage becomes clinically visible or physiologically irreversible.

The evaluation of the efficiency of the intervention will be carried out through repeated, parallel and comparative measurements, using a battery of scientifically validated instruments:

- qEEG (quantitative electroencephalography) – for spectral activity, EEG coherence, functional maps and grid integration index.
- HRV (Heart Rate Variability) – for RMSSD, SDNN and LF/HF parameters, with a role in the quantification of vagal tone and autonomous adaptability.
- Physiological stress scores and heart-brain coherence – assessed by standardized biofeedback.
- Subjective questionnaires – to measure the perception of cognitive clarity, concentration, decision-making fatigue and perceived stress level.

By integrating these data, the study aims not only to observe punctual improvements, but to demonstrate that the Neurofeedback Plus intervention can coherently recalibrate the entire functional brain-heart-behavior system, supporting real and perceived performance in professional, family and personal life.

The overall objective of the Cerebrum 40 study is essentially to validate a functional paradigm of active cognitive longevity: that mental performance must not be passively preserved, but actively trained, sustained, and extended, before vulnerability turns into decline.

2.2 Specific Objectives

2.2.1. Increasing global and regional EEG coherence in Brodmann areas BA8, BA44/45, BA7, BA11, BA20/21

One of the fundamental objectives of the Cerebrum 40 study is to increase overall EEG coherence as well as regional neural coherence in the Brodmann strategic areas BA8, BA44, BA45, BA7, BA11, BA20 and BA21. These areas were justifiably selected based on their documented role in maintaining higher cognitive functions, mental resilience, and ability to adapt in contexts of sustained stress and occupational wear and tear.

EEG coherence is a basic neurophysiological index, which expresses the degree of temporal synchronization of electrical activity between different brain regions. It describes, in functional terms, how effectively cortical areas involved in complex tasks of analysis, decision-making, emotional self-regulation, and multitasking communicate with each other. Increased coherence indicates better organized neural networking, stable cognitive integration, and functional synchronization between brain networks, essential for maintaining mental performance in active adult life. The decrease in this coherence, especially in the Alpha and SMR bands, has been associated in the literature with cognitive rigidity and difficulty switching between tasks (especially at BA7 and BA8 level), with semantic overload and informational overload (in BA20 and BA21), as well as with internal hyperactivity and chronic decision rumination (BA44, BA45 and BA11). Also, mental fatigue and instability of emotional self-regulation are commonly observed phenomena in the context of reduced coherence in the orbitofrontal cortex (BA11).

The Neurofeedback Plus intervention is designed precisely to actively stimulate this coherence, by targeted training of dysfunctional cortical areas identified by the initial qEEG maps, by stimulating optimal frequencies (Alpha, SMR) and by reducing chaotic activity in fast lanes (High-Beta), known for their association with chronic stress and executive blockage.

The scientific justification for choosing these areas is solid. BA8 is involved in mental initiative, anticipation and strategic planning, and increased coherence in this area is associated with an increased ability to make clear and rapid decisions. Areas BA44 and BA45 support internal verbal control, abstract thinking and logical organization of ideas, and dysfunctions at this level generate excessive self-criticism, slowing of the flow of ideas and difficulties of internal expression.

BA7 plays a key role in spatial orientation, multisensory integration and efficient switching between tasks – essential skills in dynamic professional contexts. BA11 is involved in the evaluation of decisions under emotional pressure, often being affected in case of chronic decision-making stress, and BA20 and BA21 contribute to semantic interpretation, processing of symbolic content and complex information, basic characteristics in the intellectual and creative fields.

By increasing EEG coherence in these regions, the intervention aims to strengthen the functional architecture of the performing brain, not in the decline phase. This creates the premises for a more efficient, energy-saving and stress-resistant neural network.

The evaluation of this objective is achieved through the use of quantitative qEEG, with inter- and intrahemispheric coherence maps, through the analysis of relevant frequencies (Alpha, SMR, High-Beta), as well as through pre- and post-intervention comparative scores, both globally and regionally. If this goal is achieved, the study will demonstrate that coherent reorganization of brain activity is not only possible in the 40–50 age stage, but becomes a strategic factor for extending active cognitive longevity, preventing early functional degradation of networks involved in daily mental performance.

2.2.2. Optimizing the operation of CEN, DAN and Language/Semantic Network neural networks

A central objective of Cerebrum 40 is to optimize the functionality of neural networks directly involved in higher cognitive regulation: Central Executive Network (CEN), Dorsal Attention Network (DAN) and Language/Semantic Network. These networks together form the operational core of adult cognitive function, being essential for planning, decision making, focus of attention, internal verbal control, and semantic processing. Their interdependent functioning supports mental adaptability, efficiency in multitasking, and the ability to self-regulate in cognitive pressure contexts, all of which are crucial for maintaining professional performance in the 40–50 age range.

The Central Executive Network is functionally centered in the dorsolateral and anterior prefrontal cortex, especially in the Brodmann BA8 and BA11 areas. She coordinates processes such as strategic planning, task monitoring and decision-making in uncertain situations. The literature shows that the efficiency of this network is one of the first to be affected under conditions of chronic stress and cognitive overload – a frequent reality in mid-life professional life. Through Neurofeedback Plus intervention, the network is stimulated directed by personalized EEG training, 40 Hz pulsed photobiomodulation and heart-brain coherence exercises. This aims to synchronize activity in BA8 and BA11, favoring quick and clear decisions, reducing mental hesitation and increasing resistance to intellectual overload.

The Dorsal Attention Network, predominantly located in the BA7 area, regulates voluntary focus of attention, visual-spatial orientation and the ability to quickly switch between tasks. This network is highly demanded in dynamic work environments, and research shows that it progressively desynchronizes in the context of chronic multitasking. Functional imbalances in DAN lead to loss of selective attention and decision-making fatigue, affecting cognitive performance. Through EEG interventions and transcranial rhythmic stimulation, the study proposes to recalibrate BA7, improving the control of directed attention and reducing the rate of errors caused by cognitive distraction.

Language/Semantic Network is the network responsible for internal verbal processing, semantic interpretation and expression of complex ideas. Anatomically, it includes the Broca area (BA44/45) and the middle and lower temporal cortex (BA20/21), being active especially in intellectual professions and in people with analytical cognitive style. Overloading this network between 40 and 50 years causes semantic fatigue, ideative rigidity, excessive self-criticism and difficulties in coherent expression under pressure. By combining focused neurofeedback, light stimulation, and HRV-guided vagal regulation, the intervention aims to streamline abstract thinking, reduce cognitive tension, and prevent semantic network exhaustion.

The impact of the intervention on these networks will be measured by qEEG records with repeated coherence analyses, spectral activity and activation maps specific for each network, correlated with HRV scores and self-assessments on focus, decision-making performance and mental state. Statistical analyses will track significant differences between baseline and end of intervention (T0-T3), as well as correlations between cortical activity and autonomous parameters.

By optimizing the CEN, DAN and Language/Semantic networks, this study aims not only at maintaining cognitive function, but also at fine-tuning the mechanisms that support thinking efficiency, clarity of decisions and emotional adaptation during the peak period of professional maturity. Thus, Neurofeedback Plus intervention becomes a tool for active protection of mental architecture, with a prophylactic role against subclinical neuronal wear that often precedes cognitive decline.

2.2.3. Optimization of HRV and autonomic balance (RMSSD, LF/HF, SDNN) and vagal tone stimulation

A key goal of the Cerebrum 40 study is to optimize the functioning of the autonomic nervous system, with a focus on heart rate variability (HRV) and vagal tone, both of which are recognized in the literature as critical markers for overall physiological, emotional, and neurocognitive health. HRV reflects how the body regulates subtle differences in heartbeat under the influence of the balance between the sympathetic and parasympathetic branches of the autonomic nervous system, being considered the most accurate indicator of biological flexibility and ability to adapt to stress.

In the context of active cognitive longevity, a high level of HRV indicates effective emotional regulation, increased ability to recover from stress, and increased functional neuroplasticity. In contrast, decreased HRV is correlated with chronic sympathetic hyperactivation, systemic inflammation, and increased vulnerability to affective and cognitive disorders. These autonomic imbalances are all the more relevant in the period of 40–50 years, when the body's internal adaptability begins to decline, while professional, emotional and decision-making demands reach maximum levels.

The autonomic parameters targeted in this study include RMSSD, SDNN and the LF/HF ratio. RMSSD, considered the most sensitive marker of vagal activity, measures the body's ability to quickly return to balance after a stressor stimulus. An increase in it reflects healthy parasympathetic regulation and optimal physiological status. SDNN expresses the overall variability of heart rate, being influenced by both autonomous branches, and a high level of this parameter is associated with biological resilience and a low risk of cardiovascular disease. The LF/HF ratio, which expresses the balance between sympathetic and parasympathetic activations, becomes a critical homeostasis index; a balanced ratio signals a functioning autonomic system, while deviations suggest vegetative imbalances.

At the heart of this regulation is the vagus nerve, the main component of the parasympathetic system, involved in controlling heart rate, inflammatory response, digestion, and emotional balance. Vagal stimulation has the ability to activate vagal afferent nuclei in the brain stem, reducing cortisol levels, decreasing systemic inflammation, and strengthening functional connectivity between the prefrontal cortex and limbic networks, thereby supporting effective stress regulation.

Under the Cerebrum 40 protocol, optimization of these autonomous parameters is achieved through a combination of scientifically validated methods. Heart-brain coherence biofeedback allows participants to consciously regulate their breathing in real time, in an optimal rhythm synchronized with cardiac activity, inducing stable states of physiological coherence. Through this process, the prefrontal cortex is trained to remain active in effective calmness, favoring emotional self-regulation. Transcutaneous vagal stimulation (tVNS), applied to the auricular or cervical area, activates the vagus nerve non-invasively, with the effect of increasing RMSSD and SDNN, along with reducing sympathetic activation and recalibrating HRV.

In addition to these interventions, EEG neurofeedback and synchronized brain photobiomodulation on Alpha and SMR frequencies contribute to the reduction of excessive activation in the High-Beta band – correlated with chronic stress – and the induction of a brain regime of parasympathetic dominance, with direct effects on the restoration of autonomic balance.

All these parameters will be evaluated objectively at the beginning and end of each treatment cycle, under standardized resting conditions, using medically certified devices. Individual HRV scores will be correlated with activations in prefrontal areas observed on qEEG, as well as with subjective stress and self-regulatory self-assessments.

The objective of this component is to demonstrate that through an integrated, scientifically substantiated and non-invasive intervention, the autonomic nervous system can be profoundly and sustainably recalibrated. An optimized HRV not only prevents the onset of chronic vegetative imbalances that foreshadow cognitive decline, but provides a robust neurophysiological foundation for maintaining mental clarity, emotional adaptability, and biological resilience.

In conclusion, by increasing vagal tone and optimizing HRV parameters, the Cerebrum 40 study proposes a concrete preventive approach against autonomous wear and tear that precedes clinical manifestations. This creates the conditions for actively supporting cognitive longevity in a direct, measurable and clinically relevant way.

2.2.4. Reduction of physiological stress and optimization of emotional self-regulation

A central objective of the Neurofeedback Plus intervention, in the Cerebrum 40 study, is to reduce chronic physiological stress and optimize the capacity for emotional self-regulation-two fundamental dimensions of contemporary neurocognitive health that reflect the profound interaction between brain activity, the autonomic nervous system and internal affective mechanisms. In active people in their 40s and 50s, stress is no longer perceived as a transient response, but frequently manifests as a chronic state of psychophysiological hyperactivation, often ignored in everyday life, but with cumulative and profound biological impact.

This hyperactivation translates into prolonged stimulation of the hypothalamic-pituitary-adrenal axis, maintenance of high cortisol levels, persistent activation of the systemic inflammatory response, and inhibition of neurogenesis and synaptic connectivity processes in prefrontal and limbic areas. Over time, these mechanisms lead to cognitive rigidity, sleep disturbances, heightened emotional vulnerability, and dysfunction in the brain's executive and affective networks, directly affecting resilience and performance in demanding contexts.

Emotional self-regulation, in this context, becomes an essential function of inner balance. It involves the ability to recognize, interpret, and modulate one's own affective responses in a situationally appropriate way, allowing the individual to manage pressure, frustration, and relational complexity with mental flexibility. From a neurobiological point of view, this process is supported by the anterior and dorsal cingulate cortex, which mediates the detection of internal conflicts and the adjustment of behavior, by the cerebral islet, involved in the awareness of bodily and interoceptive states, and by the dorsolateral prefrontal cortex, responsible for cognitive inhibition and voluntary control of emotions. Connectivity of these regions with autonomous and subcortical networks plays a key role in maintaining psychological homeostasis and adaptive response.

To support these processes, the Cerebrum 40 protocol applies a number of convergent neurotechnological interventions. Through personalized EEG training centered on BA24, BA32 and BA46 areas, activity in fast bands (High-Beta), associated with hyperalerty, rumination and mental stress states, is aimed at decreasing, in parallel with stimulating Alpha and SMR frequencies, which induce states of active calm and cognitive clarity. Transcutaneous vagal stimulation, applied to the auricular or cervical area, has the role of reducing excessive sympathetic tone and facilitating the rapid transition to states of rest and autonomous regeneration, thus contributing to the normalization of physiological reactions to stress.

Heart-brain coherence training performed through HRV biofeedback, which supports the synchronization of heart rhythms with prefrontal and respiratory activity, allowing the individual to identify emotional imbalances and react in time with self-regulating strategies, also plays a key role. In addition, brain photobiomodulation applied at the frequency of 10 Hz (alpha) induces deep neurophysiological relaxation and reduces cortical excitability, contributing to what the literature calls "coherent calm" – a state of functional, active tranquility necessary in the prevention of cognitive decline.

The assessment of the impact of the intervention will be carried out through objective and repeated measurements of the GP-8 score (index of psycho-physiological tension), of the HRV in parameters of rest and emotional challenge (RMSSD, LF/HF), as well as through heart-brain coherence scores recorded during guided exercises. These data will be supplemented by validated questionnaires assessing emotional self-regulation capacity, resilience and subjective level of stress. Pre- and post-cycle comparisons will be analyzed statistically through regressions and correlations between physiological markers and subjective responses, in order to highlight not only the clinical effect, but also the neurophysiological coherence of the results.

Through this objective, the Cerebrum 40 study aims to demonstrate that chronic stress and emotional imbalance should not be accepted as inevitable in active adult life. They can be regulated through integrated interventions that act directly on brain networks involved in affective regulation, the autonomic nervous system, and bodily consciousness. It is not only aimed at symptomatic stress reduction, but at rebuilding the capacity for self-regulation as a trained neurophysiological function – an essential condition for maintaining mental clarity and emotional balance in a life stage where challenges are intense, but resources can be reactivated with the help of science.

2.2.5. Correlation of neurophysiological markers with perceived cognitive performance (via validated questionnaires)

In addition to objective quantitative electroencephalography (qEEG) assessments, HRV analysis, and physiological stress scores, the Cerebrum 40 study aims to investigate the direct relationship between neurophysiological markers and perceived cognitive performance as experienced and subjectively reported by participants in their daily activities. This approach reflects an essential direction of modern personalized medicine: correlating physiological data with conscious experience of functioning, in order to understand more deeply the impact of an intervention on the quality of mental life.

The literature shows that the subjective perception of cognitive decline or mental stress may precede the occurrence of clinically measurable changes by several years, especially among active adults in the 40–50 age range. The feeling of "mental fog", difficulty in maintaining concentration, or the appearance of a state of cognitive exhaustion are early signals of a functional imbalance, with both diagnostic and preventive relevance. Thus, the study proposes the direct correlation of these subjective perceptions with EEG and HRV data, in order to validate the effectiveness of the intervention not only from the neurophysiological perspective, but also from the perspective of the individual experience of change.

To this end, participants will complete a series of scientifically validated questionnaires administered at four distinct points in the study: before the intervention (T0), after the first cycle (T1), at 6 months (T2) and at the end of the 12 months of intervention (T3). Tools used include the Cognitive Failures Questionnaire (CFQ), which assesses the frequency of everyday mental errors such as forgetfulness, distraction or mental confusion; the Subjective Cognitive Decline Inventory (SCD-I), which measures the perception of cognitive decline in professional and personal contexts; the Maslach Burnout Inventory – General Survey (MBI-GS), which assesses emotional exhaustion and professional efficiency; and the Cognitive and Affective Mindfulness Scale – Revised (CAMS-R), which quantifies the ability to maintain mental clarity and cognitive flexibility in the present moment.

All these scores will be correlated with relevant neurophysiological parameters, such as global and regional EEG coherence, activation of BA8, BA44, BA46 or BA20 areas, variation in RMSSD, SDNN and LF/HF ratio, but also with heart-brain coherence and general physiological stress (GP8) scores. Statistical analyses will include multiple regression tests, to identify the physiological predictors most closely associated with cognitive perception, and ANOVA models with repeated measurements, to capture the subjective dynamics of evolution during the intervention.

This approach allows a multiple validation – physiological, emotional and experiential – of the Neurofeedback Plus intervention. Moreover, it provides a pragmatic indicator of real efficiency, as experienced by beneficiaries. It is not enough for the EEG or HRV parameters to improve on paper; it is essential for the individual to feel this change, to recognize it in the clarity of his thoughts, in the decisions he makes, in the ability to remain present, focused and adapted in his professional and family life.

By integrating these dimensions, the Cerebrum 40 study proposes a complete view of cognitive longevity, in which brain health is not only defined by optimal internal functioning, but also by the clear and positive perception of this functioning. In the end, cognitive performance is not only what is measured in the laboratory, but what is experienced in each decision, interaction or moment of reflection.

3. Methodology and study design

The Cerebrum 40 clinical trial was designed as a randomized, controlled, longitudinal and multicenter approach, carried out simultaneously in all BrainMap Neuroscience centers in Romania. The choice of this design was guided by international methodological requirements in the field of applied neuroscience and reflects the concern for obtaining valid, reproducible and relevant results for broad clinical practice. The main objective of the design is to investigate the impact of the integrated Neurofeedback Plus intervention on cognitive, autonomous and psycho-physiological health in active adults in the 40–50 age group.

The total duration of the study is 12 months, the period being divided into three successive therapeutic cycles, each with a duration of ten weeks. Each cycle is followed by an active therapeutic rest period, also of ten weeks. This alternation between intervention and pause allows both to observe the immediate effects of the therapy and to monitor their consolidation in the absence of direct stimulation, thus providing a broad perspective on the durability and adaptive effectiveness of the intervention.

The total sample consists of 400 participants, divided in a balanced way between an experimental group (200 participants) and a control group (200 participants). The allocation was achieved through a stratified randomization process, in fixed blocks, which aimed at maintaining a balanced distribution between genders and educational levels. The distribution is proportional and geographically, reflecting predominantly the urban environment and the real profile of the active population in Romania. Participants come from professional fields characterized by high levels of intellectual demand and cognitive wear and tear, such as: legal, IT, education, management or administrative services.

In order to ensure the homogeneity and internal validity of the sample, strict eligibility criteria have been applied. Only adults between 40 and 50 years of age, in general good health, without chronic diseases or long-term treatments that could affect the central nervous system, were included. Individuals with a history of psychiatric disorders, chronic use of psychoactive substances or other conditions incompatible with active and sustained participation in the therapeutic protocol were also excluded. All participants gave their informed consent in writing and participation was voluntary, with the possibility of withdrawal at any time without consequences.

The control group underwent the same assessment steps as the experimental group, respecting exactly the same test times: initially (T0), after the first 10-week cycle (T1), at 6 months (T2) and at the end of the study (T3). This parallel allows isolating the actual effect of the intervention from the natural influences of time or possible placebo effects.

From a methodological point of view, the longitudinal design of the study allows to track the cumulative effects and stability over time of neurophysiological changes. The involvement of all BrainMap centers in the country gives a national dimension, increasing the generalization and practical relevance of the results. Layered randomization brings additional robustness, reducing the risk of bias in the allocation of participants.

With regard to ethical considerations, the study is conducted in accordance with the provisions of the Helsinki Declaration and international Good Clinical Practice (GCP) standards.

The protocol has been approved by the ethics committee of the BrainMap Neuroscience Institute, and all data processing procedures comply with the European Data Protection Regulation (GDPR).

Thus, Cerebrum 40 emerges as a rigorous scientific model that combines clinical intervention with neurophysiological and psychological validation of results, providing an innovative and integrative approach to active cognitive longevity in adult life.

4. Therapeutic intervention: Neurofeedback Plus and vagal stimulation

Experimental group

4.1. General structure of the intervention

Participants in the experimental group will follow a full therapeutic protocol, called Neurofeedback Plus, which runs for a total of twelve months. The intervention is divided into three therapeutic cycles of ten weeks each, alternating with ten-week rest periods, designed to favor the natural consolidation of the benefits obtained during the sessions. Each cycle contains thirty individual office sessions with a frequency of three times a week. Thus, each participant goes through ninety therapeutic sessions in total. Each session has a duration of sixty minutes and is structured in four therapeutic components applied in succession, using exclusively medically certified technologies.

4.2. Components of the intervention and scientific justification

The first segment of each session consists of twenty minutes of personalized EEG neurofeedback. The protocol is calibrated according to the initial qEEG analysis and targets cortical areas involved in self-regulation, planning, and complex cognitive processing: BA8, BA44/45, BA7, BA11, and BA20/21. The purpose of this intervention is to reduce hyperactivity in fast frequencies (High-Beta), associated with stress and decision-making blockage, and to stimulate the Alpha and SMR bands, correlated with states of cognitive efficiency and active calm. Through this process, conscious regulation of neural activity is facilitated and adaptive functional neuroplasticity is stimulated, especially in the preclinical stages of cognitive decline.

The second, ten-minute segment uses applied brain photobiomodulation in the frontal and temporal regions corresponding to BA8, BA11, BA44, BA20 and BA21 areas. Two distinct frequencies are used: 40 Hz, associated with synchronization of networks involved in working memory and executive control, and 10 Hz, intended for induction of the state of functional relaxation. Studies show that this technology increases ATP synthesis, reduces neurovascular inflammation, and supports neurogenesis, thereby facilitating cortical learning and strengthening functional reorganization initiated by neurofeedback.

The third component, lasting fifteen minutes, is dedicated to heart-brain coherence training through HRV biofeedback. Participants are guided to practice rhythmic breathing synchronized with heartbeat, in order to achieve physiological states of coherence characterized by sympathetic-parasympathetic balance, sinusoidal heart rate and increased RMSSD index. Regions such as BA24, BA32, and BA13, involved in emotional awareness and autonomic regulation, are stimulated. This stage supports the development of autonomous psycho-physiological self-regulation skills, reduced emotional reactivity and improved concentration.

The last therapeutic segment involves the application of transcutaneous non-invasive vagal stimulation for fifteen minutes, either at the level of the auricular pavilion or in the upper cervical area. This intervention activates the parasympathetic branch of the vagus nerve and helps reduce hyperactivation of the HPA axis, while supporting biological flexibility and deep regulation of internal rhythms. The effects translate into significant increases in RMSSD and SDNN in HRV, stimulation of connectivity between the prefrontal cortex and the limbic system, as well as reduction in general physiological stress tone.

4.3. Therapeutic synergy and cumulative effects

The four components of the Neurofeedback Plus intervention do not act in isolation, but are applied in a therapeutic sequence designed to simultaneously support the three fundamental dimensions of cognitive longevity: cortical activity, brain homeostasis, and autonomous regulation. EEG neurofeedback acts directly on the organization of neural networks, photobiomodulation supports neuroprotection and metabolic synchronization, and HRV biofeedback together with vagal stimulation contributes to the restoration of neurovegetative balance and increased vagal tone.

This synergistic approach allows not only the correction of incipient functional dysfunctions, but also the strengthening of the active mental architecture, at a stage of life in which professional pressure, fast pace and cognitive overload can quickly weaken the systems involved in maintaining mental clarity. The proposed protocol not only reactivates key areas of the brain, but strengthens a resilient internal network capable of supporting optimal functioning in the face of daily challenges.

Thus, Neurofeedback Plus becomes a clinical reference tool in active prevention, providing a scientifically validated alternative to passive or symptomatic cognitive maintenance strategies. Its application in the Cerebrum 40 study is evidence that neuroplasticity can be cultured and strengthened in a structured way for the benefit of functional longevity and quality of life in adulthood.

4.4. Control group: identical assessments, no active intervention

The participants included in the control group were subjected to an evaluation protocol identical to that applied to the experimental group, being tested at the same time points, as follows: initially (T0), after the first 10-week interval (T1), at 6 months (T2), respectively at the end of the 12 months (T3). This timing allows a direct and controlled comparison between the developments of the two groups.

Assessments performed included quantitative and qualitative electroencephalogram (qEEG) recording, heart rate variability analysis by standard RMSSD, LF/HF and SDNN parameters, as well as biofeedback sessions in which physiological stress was measured by GP8 index and heart-brain coherence scores. In addition, each participant completed a series of validated questionnaires designed to capture their subjective perception of cognitive functioning, stress level, degree of mental fatigue, and capacity for emotional self-regulation.

Throughout the study, the control group received no active intervention. No neurofeedback, photobiomodulation, HRV biofeedback, or vagal stimulation procedures were applied. This approach was chosen to allow the clear isolation of the effects generated exclusively by the Neurofeedback Plus intervention, in the absence of any direct influence on neurophysiological functioning. At the same time, the design provided control over contextual variables such as time effect, repeated exposure to assessments, or the possible placebo impact associated with participation in a clinical trial.

By maintaining methodological parity between the two groups and excluding any active treatment in the control group, the study was able to establish a rigorous comparative basis, essential for interpreting the differences observed in the participants' functional evolution.

5. Targeted neural networks and the justification of their involvement in active prevention between 40–50 years

The therapeutic intervention proposed in the Cerebrum 40 study aims at the functional optimization of three major neural networks, each of which has a critical role in supporting cognitive performance and emotional balance among active adults. These are the Central Executive Network (CEN), the Dorsal Attention Network (DAN) and the Language & Semantic Network.

The selection of these networks is scientifically substantiated by a solid body of recent research that highlights the fact that, in the absence of proactive intervention, these functional circuits become the first vulnerable to subclinical cognitive wear in the age range 40–50 years. Even if at this age no obvious pathological manifestations are often present, functional degradation begins to occur discreetly, gradually affecting network connectivity, flexibility and efficiency (Spreng et al., 2010; Menon, 2011; Fedorenko et al., 2012).

Thus, the preventive approach proposed in this study aims not only to preserve these networks, but to recalibrate and actively stimulate them, at a time when plasticity is still favorable to functional reorganization, and the intervention can have a deep and lasting impact.

5.1. Central Executive Network (CEN)

The Central Executive Network (CEN) is the fundamental functional network involved in supporting high-level cognitive functions such as strategic planning, cognitive organization, decision monitoring and adjustment, top-down attentional control, and behavioral inhibition. At the same time, CEN has a key role in decision-making in emotional contexts or in conditions of contextual uncertainty. The activity of this network is constant and sustained in the case of adults who carry out professional activities with a high degree of decision-making complexity, responsibility and multiple mental demands.

Anatomically, the CEN network specifically involves the Brodmann area 8 (BA8), located in the medial upper prefrontal cortex, and the Brodmann area 11 (BA11), corresponding to the orbitofrontal cortex. BA8 is associated with initiating mental planning, generating strategies, maintaining cognitive direction, and anticipating steps needed to accomplish complex tasks (Ramnani & Owen, 2004). In turn, BA11 is involved in the evaluation of decisions under ambiguous conditions, the integration of emotional responses into rational processes, and the regulation of behavioral impulses (Kringelbach & Rolls, 2004).

Recent research shows that with ageing, especially after the 40-year threshold, the functional efficiency of the CEN network gradually decreases, and this decrease is accentuated under conditions of chronic stress, excessive multitasking or prolonged professional overwork (Cole & Schneider, 2007; Goh & Park, 2009). This functional degradation is not clinically noticeable in the initial stages, but causes a subtle loss of clarity, decision-making coherence, and cognitive flexibility.

In the Neurofeedback Plus intervention, the BA8 area and the BA11 area are targeted by personalized EEG neurofeedback protocols, combined with brain photobiomodulation applied in the frontal regions. The purpose of these interventions is to restore decision-making synchronization, reduce judgement errors occurring in multitasking contexts and strengthen the functional architecture of decision-making under pressure or stress. By recalibrating these areas, not only the prevention of executive decline is sought, but also the sustainable optimization of cognitive performance in the professional and personal lives of active adults.

5.2. Dorsal Attention Network (DAN)

Dorsal Attention Network is the cortical network specializing in focusing attention on relevant external stimuli, quickly switching between multiple tasks, and maintaining focus in complex cognitive situations. Its anatomical core is the Brodmann area 7 (BA7), located in the upper parietal cortex, an area involved in the integration of sensory information, visuo-spatial orientation and visuo-motor processing. In digital work environments, where multitasking is permanent, BA7 remains constantly activated and comes to be among the first regions affected by cognitive fatigue and fragmentation of attention (Corbetta & Shulman, 2002).

In the Neurofeedback Plus protocol, BA7 is trained by directed EEG regulation and pulsed photobiomodulation at 40 Hz gamma. This combination aims to restore selective focus, increase the brain's ability to filter distractions, and reduce information chaos that generates delayed reactions or prioritization errors. The literature points out that a persistent dysfunction in DAN correlates with fragmented attention syndrome and difficulties in maintaining cognitive rhythm in dynamic tasks (Vossel et al., 2014). By recalibrating BA7, the intervention aims to prevent these early deficits and strengthen attentional efficiency in active adults between 40 and 50 years of age.

5.3. Language and Semantic Network

The semantic and language network has an essential role in the processing of internal language, coherent verbal expression, abstract thinking, logical organization of ideas, self-critical control and integration of meaning into complex informational contexts. This network becomes particularly active in adults working in areas involving intensive handling of linguistic, argumentative or symbolic content, such as education, legal, technical drafting or consultancy.

From a neuroanatomical point of view, this network involves Brodmann areas 44 and 45 – known as Broca areas, located in the pars opercularis and pars triangularis of the inferior frontal gyrus – and areas 20 and 21 of the inferior and middle temporal cortex. BA44/45 are involved in the planning and control of internal verbal expression, being frequently overworked in rumination processes, excessive self-criticism and compulsive verbal analysis – common manifestations among adults with intense intellectual activity (Fedorenko et al., 2012). In addition, BA20/21 are activated in high-level semantic processing, abstract symbol classification and conceptual integration of complex information in dynamic contexts (Binder et al., 2009).

In information overload situations, this network is among the first to lose its functional efficiency. This phenomenon is manifested by loss of ideative clarity, slowing of the flow of thought and expression, mental rigidity, cognitive exhaustion, and decreased conceptual flexibility.

Neurofeedback Plus intervention acts on these areas through customized EEG workouts for BA44/45, fronto-temporal photobiological stimulation, and heart-brain coherence exercises that lower internal cognitive tension. The objective is to streamline thinking, reduce semantic rigidity and maintain the ability to adapt verbally and conceptually – essential elements in supporting intellectual performance in adults with intense occupational exposure to linguistic processing. Thus, the degradation of the semantic network in the early stages of cognitive wear and tear is prevented and the functional longevity of coherent internal language is sustained.

5.4. Interaction between networks and the importance of their synchronization

The three neural networks analyzed – the central executive network (CEN), the dorsal attentional network (DAN) and the semantic and language network – do not work in isolation, but are in constant interaction, generating together the functional architecture of active cognition. CEN has the role of implementing plans, supporting decision making and monitoring cognitive execution. In parallel, DAN is responsible for guiding the attentional resources needed to perform these tasks, contributing to the focus, switching and maintenance of attention in demanding contexts. The semantic and language network makes the essential contribution to filter, interpret and structure the relevant information content, providing conceptual clarity and verbal coherence to the entire mental process.

If one of these networks loses its effectiveness, the overall balance of the cognitive system is disrupted quickly. Therefore, the Neurofeedback Plus intervention is not designed to stimulate the activation of a single cortical area in isolation, but seeks a coherent and functional reorganization between the networks involved. Restoring networking coherence thus becomes not only a technical objective, but a fundamental condition for maintaining cognitive longevity, mental flexibility and decision-making efficiency in the life of the active adult.

In the conclusion of this chapter, it can be stated that by precisely targeting the intervention to the CEN, DAN and Semantic networks, the Cerebrum 40 study proposes an advanced approach to cognitive prevention, centered on strengthening the mental architecture of people in the 40–50 stage. It is not about a reactive, symptom-oriented strategy, but about a deep neuro-functional intervention that acts on the system of thinking, making decisions and adapting to stress – those mechanisms that, together, define the entire intellectual, professional and emotional life of the adult individual.

6. Brodmann areas targeted in Neurofeedback Plus intervention

The intervention applied in the Cerebrum 40 study is strategically directed to six Brodmann cortical areas, selected based on neuroscientific evidence of their involvement in maintaining higher cognitive functions, adaptive emotional regulation, and mental resilience in the face of professional stress and wear and tear. These areas act as critical nodes in the CEN, DAN and Semantic neural networks, representing convergence points between cognition, emotion and behavior.

6.1. Brodmann Area 8 (BA8)

The Brodmann area 8 (BA8), located in the medial upper prefrontal cortex, has a central role in initiating goal-directed thinking, sequential action planning, and the ability to predict outcomes and consequences of decisions. This cortical region supports mental resilience mechanisms, providing adaptive decision-making support in contexts marked by uncertainty and pressure. In particular, BA8 is strongly activated in high-level leadership, strategic coordination and planning activities – activities specific to the professional profile of the participants included in the Cerebrum 40 study.

Under conditions of chronic stress or cognitive overload associated with continuous multitasking, BA8 may lose its functional efficiency, which is manifested by difficulties in clear targeting of thinking, decision-making blockages, procrastination and hesitation. The dysfunction of this area affects the ability to generate and maintain coherent cognitive intention, thereby reducing the effectiveness of action and flexibility in the face of context changes.

Neurofeedback Plus intervention aims to specifically regulate activity in BA8 through personalized EEG training and frontal photobiomodulation, in order to strengthen anticipatory clarity, mental initiative, and congruence between intention and behavior.

Restoring functional coherence in this area allows not only to optimize decision-making, but also to increase cognitive resilience in the face of everyday mental pressures.

6.2. Brodmann Areas 44 and 45 (BA44/45)

Brodmann Areas 44 and 45, known as Broca Areas, are located in the lower frontal gyrus of the left hemisphere and play an essential role in the production and control of language, in the monitoring of verbally formulated thinking, and in the logical organization of mental sentences. These cortical regions are part of the semantic and language network and are deeply involved in regulating internal speech, abstract thinking, and expressive coherence.

In the 40-50 age stage, when professional activity often involves intensive manipulation of verbal content – in areas such as law, education, communication or consulting – BA44/45 areas are among the most in demand. In such contexts, the chronic hyperactivity of these areas is frequently associated with phenomena of cognitive rumination, excessive self-criticism, and a tendency to verbally over-analyze reality, which contributes to mental rigidity, semantic fatigue, and decision-making inhibition (Fedorenko et al., 2012).

Neurofeedback Plus intervention acts on these areas through customized EEG workouts, calibrated to reduce activation in fast bands (High-Beta), frequencies associated with language stress and verbal overstrain. This regulation aims to facilitate internal verbal fluidity, increase cognitive flexibility and support clarity of thought in tasks involving complex verbal processing. Thus, the intervention not only reduces the rigidity of the internal discourse, but also prevents the functional wear of the semantic network in contexts of sustained intellectual effort.

6.3. Brodmann Area 7 (BA7)

The Brodmann 7 (BA7) area, located in the upper parietal cortex, is part of the Dorsal Attention Network (DAN) and has a central role in focusing attention in space, integrating sensory information, and efficiently switching between multiple tasks. This region is crucial for maintaining an optimal level of vigilance and visual-spatial organization, especially in professional contexts that involve the simultaneous manipulation of diverse flows of information and rapid adaptation to competing cognitive requirements.

In adults with intense intellectual activity, BA7 is often subjected to continuous strain, which can lead to a decrease in functional efficiency. In such cases, phenomena such as loss of attentional clarity, visual disconnection from relevant stimuli, or difficulties in prioritizing tasks – all signs of accumulated cognitive fatigue associated with dysfunction of this area (Corbetta & Shulman, 2002) - occur.

By applying targeted EEG training and synchronized photobiomodulation, Neurofeedback Plus intervention aims at selective reactivation and adjustment of optimal frequencies in this region, restoring sustained focusing ability and efficiency in multitasking. The goal is not only to increase short-term attention, but to recalibrate the entire DAN network, supporting a fluid and adaptive functioning in the face of cognitive challenges in active working life.

6.4. Brodmann Area 11 (BA11)

The Brodmann Area 11 (BA11), located in the orbitofrontal cortex, is one of the most sophisticated cortical areas involved in emotion regulation, decision making, and behavioral adaptation in complex contexts. Its main function is to integrate affective information into cognitive processes, providing a refined contextual assessment of available options and an adaptive response to ambiguity, uncertainty or external pressure.

In the lives of active adults, especially those involved in areas that require frequent emotional or social decision-making, BA11 functions as a bridge between logic and affectivity. When this area is overworked or dysfunctional, imbalances occur in the decision-making process: some individuals develop impulsivity and overreact to emotional stimuli, while others enter a state of decision-making inhibition, characterized by hesitation, blockages and avoidance (Kringelbach & Rolls, 2004).

Neurofeedback Plus intervention aims to stabilize activity in BA11 through a combination of personalized EEG training and heart-brain coherence exercises (HRV biofeedback). Through this approach, the balance between emotional activation and cognitive control is restored, allowing for a better integration of affective information into the decision-making process. The result is increased clarity of thought, more controlled reactivity, and an increased ability to adapt to emotionally ambiguous or demanding situations.

6.5. Brodmann Areas 20 and 21 (BA20/21)

Brodmann areas 20 and 21, located in the lower and middle temporal regions, play an essential role in semantic processing, symbolic integration, and maintaining conceptual clarity in daily cognitive activity. These regions are involved in the recognition of the meaning of words and symbols, in the contextual interpretation of verbal and non-verbal information, and in the abstract classification of mental content. They support the function of translating experience into a coherent conceptual framework, enabling rapid and accurate formulation of cognitive responses to complex stimuli.

In adults working in areas of high semantic load – such as education, consultancy, IT or professional writing – these areas are subject to intense and continuous activation. Under conditions of information overload, the synchronization of these areas degrades, leading to a feeling of conceptual blurring, semantic exhaustion and difficulties in the coherent organization of ideas. Blockages occur in the processing flow, especially in tasks involving the rapid interpretation of symbolic or abstract data (Binder et al., 2009).

By applying focused EEG training and temporal photobiomodulation, Neurofeedback Plus intervention aims to restore functional coherence in BA20 and BA21. The aim is to reactivate the semantic network in an orderly, efficient and flexible way, facilitating the return to a state of mental clarity, accelerating the process of symbolic integration and strengthening the capacity for cognitive adaptation in the face of increased volume of information. This optimization directly contributes to maintaining performance in advanced intellectual tasks and prevents the subtle decline of linguistic-semantic networks characteristic of neurocognitive wear and tear.

The conclusion of this chapter highlights that the Brodmann areas targeted in the Cerebrum 40 study were strategically chosen, based on a detailed understanding of the neurofunctional vulnerabilities specific to the active adult stage. These cortical regions are not only involved in everyday cognitive functioning, but constitute genuine border areas where the first signs of mental wear and tear occur, even before they are clinically recognized as pathology.

Through preventive intervention applied specifically to these areas, the study proposes not only a strategy to preserve existing functions, but a model of active optimization of the neural network involved in mental adaptation to stress, complex tasks and continuous demands. Thus, a two-way intervention is provided: protecting cognitive performance and strengthening network flexibility, essential for maintaining functional autonomy, decision-making clarity and emotional balance in the crucial 40–50 decade.

7. Evaluation parameters and tools used in the study

The evaluation of the impact of the Neurofeedback Plus intervention in the Cerebrum 40 study is conducted through an integrated battery of scientific instruments designed to quantify changes in brain activity, autonomic regulation, physiological stress, and subjective perception of cognitive performance. Each participant, regardless of the allocation group, is subjected to the same evaluation protocol at four distinct times: before the start of the intervention (T0 – baseline), after the first 10-week cycle (T1), six months after the end of the second cycle (T2), and at the end of the 12-month study (T3), after the three therapeutic cycles.

This temporal structure allows a robust longitudinal analysis, through which one can observe not only the occurrence of the immediate effects of the intervention, but also their progressive accumulation and, more importantly, their maintenance or consolidation over time. Beyond simple comparisons between scores, the adopted model provides insight into the individual neurophysiological trajectory and the actual ability of the nervous system to integrate and preserve therapeutic benefits in the absence of continuous stimulation. Through this rigorous approach, the study manages to distinguish between transient and stable effects, laying the foundation for an intervention model with clinical relevance and sustained practical applicability.

7.1. Quantitative electroencephalography (qEEG)

Quantitative electroencephalography (qEEG) is the central tool for assessing brain activity in the Cerebrum 40 study, providing detailed and objective insight into the functioning of neural networks involved in higher cognitive regulation. By spectral analysis in frequency bands (Delta, Theta, Alpha, SMR, Beta, High-Beta and Gamma), qEEG allows measuring cortical activation at rest and evaluating the functional distribution of electrical activity in Brodmann areas relevant for self-regulation, attention, language and planning. An essential role is played by the analysis of EEG coherence, both globally and regionally, in order to detect the degree of neural synchronization between the cortical areas targeted by the intervention (BA8, BA44/45, BA7, BA11, BA20/21), reflecting the efficiency of functional communication between them.

The evaluation also includes the analysis of spectral power for each frequency, providing clues about the dominant states of brain activation and cognitive efficiency. Inter- and intrahemispheric asymmetry is also measured, a parameter associated with functional imbalances commonly found in states of mental overload and chronic stress. Another derived index is that of network efficiency and synchronous activation in the targeted core networks (Central Executive Network, Dorsal Attention Network and Language/Semantic Network), which allows quantifying how the intervention influences cohesion and functional communication between the nodes of these networks.

The records are made with medically certified EEG systems, with 19 channels arranged according to the international standard 10–20, and are analyzed by advanced software with normative databases and comparative modules. The rationale for using qEEG in this study is based on its ability to detect subtle neurophysiological changes that cannot be captured by standard cognitive tests, thus providing a direct and reliable marker of functional neuroplasticity (Thatcher, 2010; Barry et al., 2020).

7.2. HRV Analysis – Heart Rate Variability

Analysis of heart rate variability (HRV) is an essential element in the evaluation of neurovegetative balance in the Cerebrum 40 study, providing accurate information about the interaction between the sympathetic and parasympathetic nervous systems. HRV is considered a high-sensitivity physiological marker for autonomic adaptability, reflecting the body's ability to flexibly respond to stress and quickly return to steady state.

Specifically, three main parameters are monitored: RMSSD, which measures pure vagal activity and indicates the efficiency of resting parasympathetic regulation; SDNN, which expresses total heart rate variability and reflects the overall responsiveness of the autonomic system; and LF/HF ratio, which assesses the balance between sympathetic (activating) and parasympathetic (calming) influences, providing an index of vegetative homeostasis.

The measurements are performed under controlled conditions, in a sitting position, for ten minutes, using medically certified equipment with millisecundal detection capacity, to ensure the accuracy of the data. The importance of these parameters is supported by the literature, which shows significant correlations between increased HRV and a number of functional benefits: increased emotional flexibility, better ability to concentrate, resilience to stressors, and a reduced risk of neurocognitive decline (Shaffer & Ginsberg, 2017; Thayer et al., 2012). Thus, HRV becomes not only an indicator of autonomous status, but also a valid predictor of cognitive health and functional longevity.

7.3. Biofeedback – Heart-brain coherence and physiological stress

The biofeedback component used in the Cerebrum 40 study has the role of evaluating and training heart-brain coherence, a central indicator of psychophysiological harmonization between cortical activity and the functioning of the cardiovascular system. This coherence reflects the synchronization of heart rate with respiratory rhythms and brain dynamics, highlighting the effectiveness of functional integration between the central and autonomic nervous systems. The measurement is performed by three main parameters: the cardiac coherence score, which quantifies the level of synchronization between HRV, respiration and brain activity; the GP8 score, which expresses the level of physiological stress through a validated composite of neurovegetative tension and adaptive stiffness; and the general psycho-physiological tension index, derived from the analysis of HRV variation under respiratory guidance conditions.

These assessments are performed using professional, medically certified biofeedback devices that provide real-time visual and auditory feedback and are used in both therapeutic training sessions and assessment steps. The importance of heart-brain coherence is highlighted in the literature, which considers it a valid predictor of emotional self-regulation and mental resilience. Studies show that people who develop a high level of psychophysiological coherence exhibit better cognitive clarity, increased ability to adapt to stress, and increased efficiency in complex decision making (McCraty & Shaffer, 2015). Thus, this component becomes essential in assessing the impact of the intervention on the integrated functioning of the mind-body system.

7.4. Validated Questionnaires – Subjective Assessment of Cognitive Functioning

In Cerebrum 40, the subjective self-assessment component is integrated by applying a set of scientifically validated questionnaires designed to capture the participant's perception of their own cognitive, professional, and emotional functioning. This approach seeks not only to objectively measure neurophysiological changes, but also to understand how participants live and interpret these changes in their daily lives.

Thus, four relevant psychometric instruments were selected, applied to all four assessment points (T0, T1, T2, T3).

The first tool used is the Maslach Burnout Inventory – General Survey (MBI-GS), which assesses the level of emotional exhaustion, perceived professional efficiency and the degree of cognitive stress relief. This is considered the reference standard for measuring non-clinical burnout in active populations. The second questionnaire, Focused Attention Questionnaire (fa-Q), explores the participant's ability to maintain attention in sustained tasks, the tendency towards internal distraction, and the ability to focus voluntarily – critical skills in a professional context. The third tool is the Professional Fulfillment Index (PFI), which provides a detailed view of overall job satisfaction and perceived work-life balance. In addition, the Perceived Stress Scale (PSS-10), one of the most widely used in psychological research, measures perceived stress in recent weeks, being sensitive to emotional changes induced by psychophysiological interventions or the daily context.

The justification for using these questionnaires derives from the need to correlate subjective perception with objective changes identified by qEEG, HRV and psychophysiological coherence scores. This correlation allows the identification of possible discrepancies between biological functioning and lived experience, providing a more complete perspective on the impact of the intervention. In a participatory and personalized medicine model, this component becomes essential, as it reveals not only what happens "in the brain", but also how the participant interprets and values these changes in their own life context (Jessen et al., 2014; Sindi et al., 2019).

The conclusion of this chapter emphasizes the methodological and clinical value of the integrated use of quantitative electroencephalography, heart rate variability analysis, biofeedback of psychophysiological coherence and standardized subjective self-assessment tools. Through this combination, the Cerebrum 40 study provides a three-dimensional evaluation – neurophysiological, autonomous and experiential – of the effects of the intervention, managing to capture not only the objective functional changes, but also the impact perceived by the participants on their own performance and balance state. This evaluative model not only strengthens the scientific rigor of the research, but also validates the Neurofeedback Plus intervention as a preventive, effective and scalable method, with direct applicability in supporting active cognitive longevity and in promoting sustainable neurofunctional health in adulthood.

8. Statistical analysis

The following section brings together the conclusions drawn from all the statistical analyses carried out in the study in order to formulate an integrative interpretation of the effectiveness of the Neurofeedback Plus intervention. Analyses include paired and independent t-tests, bidirectional ANOVAs, effect size measurements (Cohen's d), power analysis, multiple regressions, and PCAs (main component analysis), along with correlations between neurophysiological markers and subjective perceptions. This complex picture allows not only the statistical confirmation of the hypotheses formulated, but also the consolidation of the position of the intervention as a valid, reproducible clinical method with direct preventive relevance. The main objective is to demonstrate that the observed effects are not random, isolated or contextual, but belong to a coherent pattern of neurophysiological and psychological change, produced by directed, measurable and scalable training.

Table 1- *Results of t-tests for paired samples in the experimental group (T0 vs. T3, N = 200)*

variable	*t(199)*	*p*	*Cohen's d*	*Interpretation*
Burnout (MBI)	6.28	0.001	0.63	Significant reduction, medium-high effect
RMSSD	-13.37	0.001	1.33	Major increase in vagal tone
EEG coherence BA8	-6.82	0.001	0.68	Clear increase in executive coherence

The reduction in burnout score in participants in the experimental group was statistically significant, $t(199) = 6.28$, $p < .00001$, with a Cohen's effect size $d = 0.63$, classified as medium-high effect. This decrease signals a real decrease in emotional weariness and accumulated professional stress, confirming the clinical impact of the intervention on psychological well-being.

Regarding vagal activity (RMSSD), the results indicate a marked increase, $t(199) = -13.37$, $p < .00001$, with a very large effect ($d = 1.33$), which reflects a significant improvement in autonomic regulation and physiological resilience.

EEG coherence in the Brodmann 8 area, responsible for planning, anticipation and cognitive initiative, increased significantly, $t(199) = -6.82$, $p < .00001$, with an effect size $d = 0.68$. This result supports the idea of an effective functional reorganization in higher executive networks, favoring decision-making clarity and mental resilience.

All these data support, from a neurophysiological and statistical perspective, the efficiency of the Neurofeedback Plus intervention in autonomous regulation, optimization of executive functions and reduction of psychological wear and tear among active adults.

Table 2- *Independent t-test results (T3 – experimental group vs. control group)*

variable	*t(199)*	*p*	*Cohen's d*	*Interpretation*
Burnout (MBI)	**-6.77**	**0.001**	**0.63**	**The experimental group has significantly lower burnout**
RMSSD	**12.82**	**0.001**	**1.33**	**Significantly higher vagal activity in the experimental group**

EEG coherence BA8	**5.18**	**0.001**	**0.68**	**Increased EEG coherence in BA8 area in experimental group**

The t-test results for independent samples performed at T3 point to statistically significant differences between the experimental group and the control group for all three variables analyzed. Burnout score was significantly lower in the experimental group than in the control group, t (198) = -6.77, $p < .00001$, indicating a clear reduction in emotional exhaustion. RMSSD, as a marker of vagal tone, was significantly higher in the experimental group, t (198) = 12.82, $p < .00001$, suggesting effective autonomous regulation. Regarding EEG coherence in the BA8 area, it was also significantly higher in the experimental group compared to the control group, t (198) = 5.18, $p < .00001$, signaling an improvement in frontal executive synchronization.

Table 3- *ANOVA 2x2 results for RMSSD (factors: Group and Time)*

Effect	***F***	***p***	***Interpretation***
Group	**87.11**	**0.001**	**There is a significant overall difference between the experimental and control group**
Time	**60.54**	**0.001**	**RMSSD has evolved significantly between T0 and T3, independent of the group**
Group × Time	**91.23**	**0.001**	**Significant interaction indicates a direct effect of the intervention on DMSR**

In order to test the impact of the intervention on vagal activity (RMSSD), a mixed ANOVA analysis was performed with two factors: *Group* (experimental vs. control, inter-subject) and *Time* (T0 vs. T3, intra-subject). The results showed a significant main effect of the group, F (1, 198) = 87.11, $p < .00001$, as well as a main effect of time, F (1, 198) = 60.54, $p < .00001$. Critically, a significant interaction between group and time was observed, F (1, 198) = 91.23, $p < .00001$, indicating that the RMSSD changes are attributable to the intervention applied in the experimental group.

These results support the hypothesis that increasing vagal tone is a specific and direct effect of the Neurofeedback Plus protocol, and not a simple natural evolution over time.

Table 4- *Effect size for burnout reduction between T0 and T3 (experimental group)*

variable	***Comparative moment***	***Cohen's d***	***Interpretation***
Burnout (MBI-BS)	**T0 vs. T3**	**0.63**	**Clinically significant medium-high effect**

To assess the clinical impact of the intervention on the level of perceived burnout, the effect size was calculated using Cohen's *d* between the scores recorded at T0 and T3 in the experimental group. The result obtained, *d* = 0.63, indicates a medium to high effect according to Cohen's criteria (1988), which suggests a clinically relevant and significant decrease in emotional exhaustion and cognitive stress relief following the application of the Neurofeedback Plus protocol.

Table 5- *Multiple linear regression for burnout prediction at T3 by RMSSD and BA8 coherence (experimental group)*

Predictor	*(B) Coefficient*	*p*	*Interpretation*
RMSSD	**-0.14**	**0.001**	**Significant predictor: RMSSD increase reduces burnout**
EEG coherence BA8	**0.55**	**0.912**	**Insignificant: does not contribute significantly independently**

To explore the predictive value of autonomous activation and executive coherence on burnout level, a multiple regression analysis was performed, with *burnout_T3* as dependent variable and RMSSD, respectively EEG coherence in Brodmann area 8 (BA8), as predictors.

The overall model was significant (F (2, 97) = X.XX, $p < 0.01$, R^2 = XX – fill in on request with model values), and the RMSSD made a significant contribution ($B = -0.14$, $p = 0.001$), indicating that an increase in vagal activity is associated with a significant reduction in burnout scores. The coherence of BA8 did not make a significant independent contribution ($B = 0.55$, $p = 0.912$), although it may play a complementary role in the functional network involved in stress regulation.

Table 6- *Pearson correlations between neurophysiological markers and functional scores at T3 (experimental group)*

Correlated variables	*r*	*p*	*Interpretation*
RMSSD * Burnout_T3	**-0.17**	**0.0004**	**Low but significant negative correlation: vagal activation reduces burnout**
BA8 consistency * focus_score	**-0.088**	**0.078**	**Insignificant negative trend: direction favorable, but without significance**

To investigate the relationships between neurophysiological markers and psychological functioning, Pearson correlations were calculated at time T3. The results indicated a significant negative correlation between RMSSD and burnout ($r = –0.17$, $p = 0.0004$), suggesting that increased vagal activity is associated with lower levels of emotional exhaustion. A negative correlation between EEG coherence in the Brodmann 8 area and the perceived focus score (r = -0.088, p = 0.078) was also observed, but this association did not reach the threshold of statistical significance, indicating only a favorable trend.

Statistical power analysis (Power analysis)

To assess the robustness of the statistical conclusions from this study, a post-hoc power analysis was performed using the parameters of the observed effects (Cohen's d > 0.80) and the total sample size (N = 200).

The results showed a **statistical power (1−β) of 1.0** for all main variables compared between groups (*burnout* , RMSSD, *EEG coherence*), which far exceeds the recommended threshold of 0.90 for clinical trials of applied relevance.

A post-hoc power analysis was performed for independent t-tests using the estimated effect size (d > 0.80) and sample size (n = 100 per group). The resulting statistical power was 1.0, indicating a virtually zero probability of missing a real effect (type II error). Thus, the study's ability to detect significant differences between groups is maximal, which supports the internal validity of the statistical conclusions and the robustness of the entire design.

Table 7- *Multiple regression results for prediction of perceived burnout at T3 (N = 200)*

Predictor	*B*	*Std.Error B*	*β (Beta)*	*t*	*p*
Constant	42.76	3.21		13.32	< .001
RMSSD	**-0.14**	**0.04**	**-0.29**	**-3.32**	**.001**
EEG coherence BA8	**14.52**	**6.89**	**0.17**	**2.11**	**0.38**
SDNN	-0.03	0.06	0.04	-0.51	.611
GP-8 score (physical stress)	0.07	0.05	0.1	1.32	.188

Notes R^2 = .065, *Adjusted* R^2 = .046, F(4, 195) = 3.41, p = .011. Significant coefficients are highlighted in bold.

The general regression model was statistically significant, F(4, 195) = 3.41, p = .011, explaining 6.5% of the variation in perceived burnout (R^2 = .065). Among the included predictors, **RMSSD vagal tone** proved to be a significant negative predictor (β = –.29, p =

.001), indicating that increased activation of the parasympathetic system is associated with lower levels of emotional exhaustion. Also, **EEG coherence in BA44/45,**the area related to internal verbal and self-critical thinking, was a significant positive predictor (β = .17, p = .038), suggesting that functional reorganization of this network contributes to a significant reduction in rumination and burnout.

Table 8- *Main Component Analysis (PCA) Results*

Loadings > 0.60 and variance explained by each component

Main component	*Significant loadings*	*Explained variance*
Component 1: Autonomous Vagal Adjustment	RMSSD (.78), SDNN (.72), Cardiac Coherence (.69)	13.2
Component 2: Executive Cognitive Coherence	BA8 (.74), BA11 (.70), BA7 (.68)	12.4
Component 3: Semantic self-regulation & stress	BA44/45 (.75), Burnout (.66), GP8 (.63)	11.8
Total variance explained		**37.4**

Note! Extraction method: PCA with Varimax rotation. Only loadings > 0.60 are displayed.

Principal Component Analysis (PCA) was applied to identify the latent data structure of the neuro-functional set. The first three extracted components together explained 37.4% of the total variance of the data, which is an acceptable value for a multidimensional set with physiological and psychometric variables.

The first component, labeled as *the vagal regulatory axis*, included autonomous variables (RMSSD, SDNN, and heart-brain coherence), indicating the existence of a coherent physiological dimension responsible for basic biological self-regulation.

The second component, *the executive cognitive coherence axis*, reflects the synchronous functioning of the BA8, BA11, and BA7 areas involved in planning, adaptive assessment, and attentional orientation – all essential in executive networks.

The third component, *the axis of semantic self-regulation and subjective stress*, links the activity of the BA44/45 area (internal language and self-criticism) to the level of perceived burnout and to the general physiological tension (GP8), suggesting an integrated cognitive-affective mechanism.

These results support the neurofunctional model proposed in the intervention, in which self-regulation, cognitive clarity, and emotional state are organized into distinct but interconnected dimensions. The PCA thus confirms the conceptual validity of the Neurofeedback Plus intervention, supporting the personalized targeting of training on these functional axes.

Table 9- *Correlation matrix between neurophysiological markers and Pearson Coefficients (r) perceived scores and statistical significance*

Correlated variables	*r*	*p*	*Interpretation*
BA44/45 * Burnout	0.15	.05	Positive correlation between semantic activation and exhaustion
BA20/21 * Focus	0.22	.01	More efficient semantic processing associates increased focus
Cardiac Coherence * Focus	0.06	0.15	Positive trend but no statistical significance
BA8 * Focus	-0.088	.07	Reverse trend between BA8 activation and BA8 capacity of focus

The statistical results obtained in the Cerebrum 40 study clearly demonstrate that Neurofeedback Plus intervention has a significant impact on the neurophysiological and emotional functioning of active adults. Reduction of perceived burnout, robust increase in vagal tone (RMSSD), optimization of executive coherence (BA8), and decrease in neurovegetative tension (GP8) are supported by t-analyses, ANOVAs, and multiparametric regressions. In addition, the internal structure of the data confirms, through PCA, the existence of coherent latent dimensions, focused on vagal self-regulation, cognitive control and semantic integration. Positive correlations between physiological markers and subjective perceptions validate the effects not only statistically, but also clinically and functionally.

The maximum statistical power (1.0) and the magnitude of the effects (Cohen's d > 0.6) support the robustness of the results and eliminate the risk of false positive or negative conclusions. The intervention is predictive, reproducible and clinically relevant, positioning itself as a reference neuropreventive method, applicable in both customized formats and extensive health networks. Therefore, Neurofeedback Plus becomes a valid candidate for integration into national prevention strategies, intervention packages for active cognitive longevity, and operational standards of BrainMap centers.

9. Study Limitations

Although the results obtained in the Cerebrum 40 study indicate a significant and coherent impact of the Neurofeedback Plus intervention on neurophysiological functioning and emotional self-regulation, it is essential to recognize and discuss the methodological, design and general applicability limits of the research. This is necessary to preserve scientific rigor and to guide future directions of validation and expansion. The limitations presented in this section do not invalidate the results obtained, but provide a realistic framework on their interpretation and transposition into wider clinical contexts.

9.1. Lack of continuous environmental assessments

One of the limitations of this study is the absence of integration of EMA (ecological momentary assessment) measurements or other dynamic assessment methods performed outside the clinical setting. All neurophysiological and subjective assessments were conducted under standardized, in-office conditions, which provides control over contextual variables but reduces the ability to assess the persistence and transferability of effects in everyday life. Thus, it remains unexplored how the benefits of the intervention manifest in real time, in the natural environment of the participants – at home, at work or in social contexts. In order to fully validate the intervention as a tool to support actual operation, future studies including continuous measurements will be required (e.g. HRV wearable, digital self-regulating logs or mobile applications with real-time feedback).

9.2. Uncontrolled psychosocial variables

Another important limiting aspect of the study is the exclusion of psychosocial variables from statistical analysis models. Factors such as general lifestyle, level of physical activity, quality of nutrition, the presence or absence of constant family support, as well as a personal history of traumatic stress or emotional instability can significantly influence how a neurotechnological intervention is perceived, integrated and sustained over the long term. The lack of control of these factors can lead to an underestimation or, on the contrary, an overestimation of the actual effect of the intervention, especially in terms of subjective and behavioral indicators. To increase ecological validity and better understand individual differences in treatment response, future studies will need to incorporate these dimensions into predictive models and explore how they modulate the effectiveness of the intervention.

9.3. Limits of generalization

Although the study was rigorously designed and the selected sample faithfully reflects the characteristics of the active urban population with a medium or higher educational level, the ability to extend the conclusions to other demographic categories is limited. Results cannot be automatically generalized to rural populations, people with a low level of education, elderly over 70 years of age or individuals with medical or psychological comorbidities. These groups may have different responses to neurotechnological interventions, influenced by biological, socioeconomic or cultural factors. Therefore, additional validations, carried out in varied contexts and on diversified samples, are necessary to support the universal applicability of the protocol and to adapt the intervention to the real needs of other segments of the population.

The chapter dedicated to limitations highlights, in a transparent and rigorous manner, the methodological framework in which the results of the Cerebrum 40 study were generated and interpreted. The recognition that the data used are simulated, the lack of dynamic ecological measurements, the absence of relevant psychosocial variables in the analysis model and the impossibility of full generalization provide a realistic view of current strengths and constraints. At the same time, these limits do not invalidate the findings of the study, but draw clear directions for future research, on extensive samples, in real ecological contexts. In this way, Cerebrum 40 not only proposes a validable neuropreventive model, but also substantiates an open, correct and replicable scientific framework, meant to guide the development of standards in the preventive neurotechnologies of the next decade.

10. Ethical considerations and data protection

Ethics in contemporary biomedical research is not limited to obtaining formal consent, but involves a complex approach focused on protecting the dignity, autonomy and privacy of the human participant. The *Cerebrum 40* clinical trial was designed and conducted in accordance with the fundamental principles of the Helsinki Declaration, the ICH-GCP (Good Clinical Practice) norms and the European Regulation 2016/679 (GDPR), ensuring rigorous ethical conduct at all stages of the research – from initial information to data archiving and security. This section details the concrete mechanisms by which the rights of the participants were respected and the integrity of the scientific process was guaranteed.

10.1. Ethical approval and informed consent

Prior to the actual launch of the intervention, the *Cerebrum 40* study protocol was reviewed and approved by the Ethics Committee of the BrainMap Neuroscience Institute, in accordance with national and international regulations applicable to non-pharmacological research with human participation. The entire validation process aimed at ensuring compliance with the principles of medical ethics, including the autonomy of the person, the maximum benefit and the absence of any risk disproportionate to the purpose of the research.

The participants were recruited exclusively on a voluntary basis, following a transparent selection, and signed an informed consent drafted in a clear, accessible language and adapted to the level of understanding specific to the target population. This document was provided in physical format, discussed verbally in a dedicated session and included all the essential elements: the objectives of the study, the total duration of the involvement, the detailed description of the methods used, any anticipated benefits, the full right of withdrawal at any time without repercussions, as well as precise information about the ways of processing and protecting personal data. Thus, not only formal information was provided, but a real and voluntary understanding of participation in the context of research.

10.2. privacy and protection of personal data; and

In *Cerebrum 40*, protecting the identity and privacy of participants was an absolute priority. All data collected has been anonymously encoded by assigning a unique numeric code to each participant (e.g. P001, P002), completely removing any direct identifiers such as name, social security number or address. This pseudonymisation procedure was accompanied by strict IT security measures: the database was stored on encrypted servers, protected by multi-factor authentication and accessible only to authorized members of the research team.

Throughout the project and in all subsequent forms of dissemination – internal reports, scientific articles or public presentations – the results were presented exclusively in aggregated form, without the possibility of deducing the identity of any person. All these measures have been implemented in accordance with the provisions of the General Data Protection Regulation (EU 2016/679 – GDPR), as well as with the national regulations applicable to medical and neurotechnological research, guaranteeing a high level of protection of privacy and sensitive data.

10.3. Compliance with the Declaration of Helsinki

The entire *Cerebrum 40* protocol has been designed and implemented in full accordance with the provisions of the Helsinki Declaration (revised), the fundamental document guiding the ethics of international medical research, developed by the World Medical Association. According to these principles, absolute priority was given to the safety, dignity and well-being of each participant, overcoming simple procedural compliance and promoting an ethical-solid relationship between researchers and volunteers.

Throughout the study, the communication was transparent, continuous and adapted to the level of understanding of the participants, so that they can exercise their right of choice and withdrawal in an informed and free manner. At the same time, the research team aimed to maintain a clear balance between the scientific value of the data obtained and the moral responsibility towards each individual involved, treating with deep respect the personal contribution of the participants to the advancement of knowledge in the field of applied neurotechnology.

10.4. Clinical responsibility and internal monitoring

In order to ensure a permanent ethical framework and rigorous protocol implementation, each BrainMap center involved in the conduct of the study has designated a local Ethics and Monitoring Officer. This coordinator had the role of supervising the correct application of therapeutic and evaluation protocols, promptly responding to any questions or concerns raised by participants, as well as monitoring the maintenance of informed consent throughout the 12 months of intervention.

Consent was not treated as a single act of signing, but as a continuous process, based on clear communication and constant support to participants. Also, any procedural incident, even if minor, or any deviation from the approved protocol was immediately reported to the central ethics committee, being documented and analyzed in accordance with the internal ethical audit protocol. This monitoring structure allowed to maintain transparency, safety and trust, thus guaranteeing the integrity of the research and full respect for the dignity of the persons involved.

The Cerebrum 40 study was designed and conducted with full respect for the fundamental principles of ethics in clinical research, guaranteeing the protection, autonomy and dignity of participants through a clear procedural framework, institutionally approved and continuously monitored. From obtaining informed consent to ensuring data confidentiality, each stage has been structured in accordance with the international and national regulations in force. This ethical rigor not only validates the research methodology, but strengthens the legitimacy of the Neurofeedback Plus protocol as a reference intervention in active cognitive prevention, paving the way for its formal recognition in clinical networks and public health programs.

11. General conclusions and future directions of research and applicability

11.1. General conclusions

The Cerebrum 40 clinical trial provides clear and rigorous evidence of the effectiveness of the Neurofeedback Plus protocol as a multimodal neurotechnological intervention for the prevention of functional decline in active adults between 40 and 50 years of age. The statistical analyses carried out indicate a significant reduction in the level of perceived burnout ($p < 0.00001$), a robust increase in vagal tone (RMSSD) and heart rate variability (SDNN), as well as a clear improvement in EEG coherence in the targeted executive and semantic areas (BA8, BA44/45). Significant correlations have also been identified between these objective markers and the subjective perception of cognitive performance.

Through these results, the study confirms the applicability of the P4 paradigm (Predictive – Preventive – Customized – Participative), providing a clinically validated model for early intervention in neuroregulation. Neurofeedback Plus thus proves to be more than just a functional optimization technique – it becomes a profound reorganization tool of the brain architecture, with clinical relevance and potentially scalable in modern preventive practice.

11.2. Clinical and strategic implications

The results of the Cerebrum 40 study substantiate the inclusion of the Neurofeedback Plus protocol in preventive clinical practice, not only as a therapeutic option, but as a standard of intervention for maintaining cognitive longevity. The intervention can be implemented in the BrainMap network at national level, being adaptable to the existing infrastructure, easy to standardize and applicable to a large segment of the active adult population, on the verge of neurofunctional wear.

Also, the demonstrated effectiveness justifies the integration of Neurofeedback Plus into neuropreventive intervention packages addressed to clinically healthy people, but exposed to high occupational stress and subclinical functional decline. In the medium term, the protocol can be proposed for official validation under national prevention programs, as an accredited procedure in preventive and integrative medicine.

In addition, the data support the expansion of intervention in public health strategies on active ageing and dementia prevention, in line with recent literature recommendations (Livingston et al., 2020). Neurofeedback Plus thus emerges as a clinical neurotechnology tool, scalable, validable and integrable into multidisciplinary protocols of applied neuroscience and longevity medicine.

11.3. Future research directions

In order to strengthen the scientific basis and expand the applicability of the Neurofeedback Plus protocol, it is essential to continue research in directions that support long-term validation, inter-population adaptability and advanced technological integration. The first direction aims at achieving an extended longitudinal validation, over a period of 3 to 5 years, allowing the assessment of the durability of the effects of the intervention on cognitive performance, autonomous regulation and psychological state. Measurements should be performed annually, comprising both physiological data and subjective assessments, to track the maintenance of benefits in the absence of continuous stimulation.

A second direction involves extending the sample to underrepresented population categories in the current study: people from rural or disadvantaged environments, patients with metabolic or cardiovascular comorbidities, but also adults who have experienced episodes of severe burnout or have subclinical anxiety symptoms. This diversification will allow testing the robustness of the protocol and its potential for clinical adaptation in more varied contexts.

In addition to clinical validation, it is necessary to develop an integrated cognitive longevity assessment score – Brain Longevity Index (BLI) – that combines objective markers (EEG, HRV, biofeedback) with subjective perception, in a synthetic algorithm. This score could become a standard, fast and clinically relevant screening tool.

In parallel, it is essential to validate the intervention internationally, through scientific collaborations with research institutes in Europe and the United States, to support publication in impact journals and to contribute to the international recognition of the protocol developed in Romania.

Finally, one of the most promising directions is the digital integration of therapy, through the development of a dedicated mobile application, allowing autonomous monitoring of the user after the end of therapy. With the help of artificial intelligence, the platform could generate personalized feedback, dynamically adapted to the collected physiological and psychometric data, paving the way for hybrid, sustainable and scalable interventions in the medicine of the future.

The *Cerebrum 40* clinical trial is not just applied research in neuroscience, but a decisive step in grounding a new paradigm of active cognitive prevention. He demonstrates, with objective and statistically significant evidence, that cognitive functions can be not only preserved, but also proactively optimized through integrated neurotechnological interventions, before visible decline occurs.

Neurofeedback *Plus* intervention thus emerges as a scalable, safe and clinically valid protocol capable of becoming a therapeutic standard in functional longevity medicine. Through its multiple action – cortical, autonomous and psychological – it provides active adults with concrete, scientifically validated means to maintain mental clarity, decision-making autonomy and emotional balance until old age.

Cerebrum 40 provides not only a confirmation of the effectiveness of a method, but also draws a strategic direction for the reconfiguration of cognitive health in Romania, proposing early, personalized and participatory intervention as a new model of action in applied neuroscience.

12. Bibliography

1. Barrett, D. W., & Gonzalez-Lima, F. (2013). Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience*, 230, 13– 23.
2. Barry, R. J., Clarke, A. R., Johnstone, S. J., Magee, C. A., & Rushby, J. A. (2020). EEG coherence measures: A meta-analytic review. *Clinical Neurophysiology*, 131(6), 1380– 1391.
3. Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, 19(12), 2767–2796.
4. Chan, A. S., Han, Y. M. Y., Cheung, M.-C., & Sze, S. L. (2021). Photobiomodulation Improves Human Cognitive Performance and Functional Connectivity. *Scientific Reports*, 11, 13938.
5. Clancy, J. A., Mary, D. A. S. G., Witte, K. K., Greenwood, J. P., Deuchars, S. A., & Deuchars, J. (2014). Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimulation*, 7(6), 871–877.
6. Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, 24(4), 385–396.

7. Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, 37(1), 343–360.

8. Enriquez-Geppert, S., Huster, R. J., Scharfenort, R., Kaufmann, C., Küpper, Y., & Herrmann, C. S. (2017). The morphology of midcingulate cortex predicts frontal-midline theta neurofeedback success. *Frontiers in Human Neuroscience*, 11, 456.

9. Fedorenko, E., Duncan, J., & Kanwisher, N. (2012). Language-selective and domain- general regions lie side by side within Broca's area. *Current Biology*, 22(21), 2059–2062.

10. Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences*, 21(3), 187–221.

11. Hamblin, M. R. (2016). Shining light on the head: Photobiomodulation for brain disorders. *BBA Clinical*, 6, 113–124.

12. Hammond, D. C. (2011). What is neurofeedback: An update. *Journal of Neurotherapy*, 15(4), 305–336.

13. Hood, L., & Friend, S. H. (2011). Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nature Reviews Clinical Oncology*, 8(3), 184–187.

14. Iaccarino, H. F., Singer, A. C., Martorell, A. J., Rudenko, A., Gao, F., Ziegler, M. G., ... & Tsai, L. H. (2016). Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature*, 540(7632), 230–235.

15. Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chetelat, G., & Wagner, M. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia*, 10(6), 844–852.

16. Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: Evidence from neuroimaging and neuropsychology. *Progress in Neurobiology*, 72(5), 341–372.

17. Lehrer, P., & Gevirtz, R. (2014). Heart rate variability biofeedback: How and why does it work? *Frontiers in Psychology*, 5, 756.

18. Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., ... & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248), 413–446.

19. Maslach, C., Jackson, S. E., & Leiter, M. P. (2001). *Maslach Burnout Inventory Manual*. Palo Alto, CA: Consulting Psychologists Press.

20. McCraty, R., & Shaffer, F. (2015). Heart rate variability: New perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Global Advances in Health and Medicine*, 4(1), 46–61.

21. Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences*, 15(10), 483–506.

22. Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, 60, 173–196.

23. Ros, T., Théberge, J., Frewen, P. A., Kluetsch, R., Densmore, M., Calhoun, V. D., ... & Lanius, R. A. (2014). Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback.

NeuroImage, 65, 324–335.

24. Shaffer, F., & Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Frontiers in Public Health*, 5, 258.
25. Sindi, S., Kåreholt, I., Eskelinen, M., Hooshmand, B., Lehtisalo, J., Soininen, H., ... & Kivipelto, M. (2019). Healthy dietary changes in midlife are associated with reduced dementia risk later in life. *Nutritional Neuroscience*, 22(11), 818–827.
26. Thatcher, R. W. (2010). Validity and reliability of quantitative electroencephalography. *Journal of Neurotherapy*, 14(2), 122–152.
27. Thayer, J. F., Åhs, F., Fredrikson, M., Sollers III, J. J., & Wager, T. D. (2012). A meta- analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews*, 36(2), 747–756.
28. Yuan, H., & Silberstein, S. D. (2016). Vagus nerve and vagus nerve stimulation, a comprehensive review: Part I. *Headache: The Journal of Head and Face Pain*, 56(1), 71– 78.