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Psychology: Cognitive, Emotional and Communicative Processes.

Multidomain and Music-based Interventions to Prevent Multidimensional Frailty in Ageing

Active aging: innovative and non-invasive non-pharmacological intervention programme for elderly homes (RSA) or community-dwelling individuals.

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Index

This thesis is based on the following papers:

1. **Lippolis, M.**, Lenti, R., Mantuano, P., De Luca, A., Pantaleo, A., Quaranta, N., Pilotto, A., Solfrizzi, V., Vuust, P. & Brattico, E. (2024). The MultiMusic Multidomain Intervention Including Choral Practice: A Study Protocol for BDNF Salivary Biomarkers, Audiometric and Neuropsychological Parameters. [Under review].
2. **Lippolis, M.**, Pantaleo, A., Mazzon, L., Diomede, R., Delussi, M., Seminerio, E., Quaranta, N., Pilotto, A., Solfrizzi, V., Vuust, P. & Brattico, E. (2026). Promoting Healthy Ageing through Choral Training: A 9-Month Multidomain Intervention (MultiMusic) Enhances Neural Processing Speed in Community-Dwelling Older Adults. [In submission].
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Chapter 1: Introduction

1.1. Ageing in the Framework of Multidimensional Frailty

Population ageing has emerged as one of the most significant demographic transformations shaping contemporary societies. As life expectancy continues to increase worldwide, a growing proportion of individuals experience age-related changes that may affect physical health, cognitive functioning, emotional well-being, and social participation. Research on ageing has traditionally devoted considerable attention to cognitive decline, particularly in relation to neurodegenerative disorders such as dementia and Alzheimer's disease (Harada et al., 2013; Livingston et al., 2020). While these changes are undeniably important, an exclusive focus on cognition risks oversimplifying the complexity of the ageing process. Indeed, ageing rarely involves isolated impairments in a single domain.

Rather, age-related changes often emerge from the interaction of multiple biological, psychological, and social factors that together shape trajectories of vulnerability and resilience in later life, with resilience defined as "the process of effectively negotiating, adapting to, or managing significant sources of stress or trauma" (Windle, 2011; Rowe & Kahn, 1997; Ferrucci et al., 2004). Among these, sensory decline represents an important contributor to vulnerability in later life, as it is a factor associated with accelerated cognitive decline and reduced functional independence (Livingston et al., 2020). It may limit access to environmental and social stimulation, increase cognitive load during communication, and contribute to social withdrawal and loneliness. Furthermore, reduced physical capacity, social isolation, and emotional factors may interact with cognitive changes, influencing both functional independence and overall quality of life (Clegg et al., 2013). For this reason, contemporary gerontology increasingly emphasizes the need to move beyond a strictly cognition-centered view of ageing and to adopt a broader perspective that considers the multidimensional determinants of health and functioning in later life

(Rowe & Kahn, 1997; WHO, 2015; Beard et al., 2016).

A further element contributing to the complexity of the ageing process is the marked heterogeneity that characterizes cognitive ageing trajectories. Older adults do not experience cognitive changes uniformly: while some individuals show significant decline in specific domains, others maintain relatively preserved cognitive functioning well into later life (Nyberg et al., 2012). In this context, the construct of cognitive reserve (i.e., the brain's capacity to maintain cognitive functioning despite age-related or pathological changes) has been introduced to explain why individuals differ in their ability to maintain cognitive functioning despite age-related neural changes (Stern, 2002; 2012). Such variability reflects the cumulative influence of genetic, environmental, lifestyle, and health-related factors across the lifespan, highlighting how ageing outcomes are shaped by dynamic interactions between risk and protective processes.

Within this perspective, the concept of multidimensional frailty has emerged as a key framework for understanding vulnerability in older adulthood. Frailty is no longer conceptualized solely as a physical syndrome but rather as a complex condition reflecting the cumulative burden of deficits across health status, daily functioning, cognition, nutrition, psycho-emotional aspects and socio-economic context (Fried et al., 2001; Rockwood & Mitnitski, 2007; Pilotto et al., 2008). Hence, multidimensional frailty can be understood as a state of increased vulnerability resulting from the reduced capacity of multiple physiological and functional systems to cope with internal and external stressors. It highlights how cognitive decline represents only one component of a broader process affecting the overall resilience of the ageing individual (as synthetized in Figure 1).

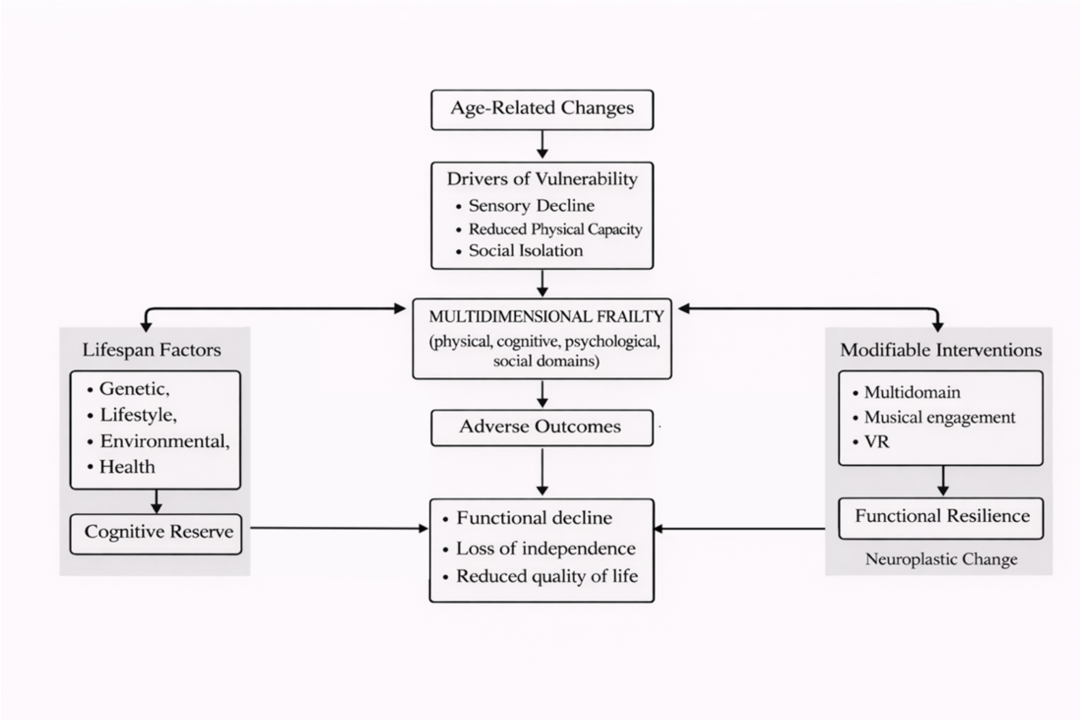

Figure 1. Conceptual schema linking age-related changes, multidimensional frailty, and modifiable intervention pathways object of the present thesis.

From a psychological point of view, multidimensional frailty can be understood not merely as the accumulation of deficits across domains, but as a progressive disruption in the integrated functioning of cognitive, affective, bodily, and social processes. Rather than reflecting isolated impairments, age-related vulnerability emerges from alterations in the dynamic coordination of these systems, which jointly support adaptive functioning in everyday life. This view is consistent with holistic and biopsychosocial models of health, which conceptualize the individual as a complex system in which biological, psychological, and environmental factors are continuously interacting (Engel, 1977). Cognitive processes, indeed, cannot be considered independently of emotional states, bodily conditions, and environmental context, as they are intrinsically interdependent. Contemporary approaches in cognitive neuroscience further support this perspective through embodied and integrative models of brain function. These models emphasize that cognition is grounded in bodily states and action-oriented processes, and that adaptive behavior emerges from the interaction between brain, body, and environment (Clark, 2008; Pessoa, 2008, review). From this standpoint, frailty may be interpreted as a reduced capacity to flexibly regulate and coordinate these interactions in response to internal and external demands.

Such a perspective shifts the focus from deficit-based models of ageing toward a process-oriented understanding of vulnerability and resilience. Besides being defined by decline, ageing trajectories can be understood in terms of the balance between dysregulation and adaptive capacity across multiple levels of functioning. This conceptualization is particularly relevant for intervention research, as it highlights the importance of experiences capable of engaging the individual as a whole system.

The expanded understanding of ageing-related vulnerability has stimulated growing interest in identifying modifiable factors capable of supporting resilience and functional adaptation in later life. In contemporary gerontology, health is increasingly understood not merely as the absence of disease but as the capacity to maintain functional ability and well-being despite age-related changes (WHO, 2015). Multidimensional frailty therefore reflects the progressive imbalance between accumulating vulnerabilities and the individual's capacity to maintain different kind of functioning. Consequently, identifying modifiable environmental and lifestyle factors capable of strengthening adaptive resources has become a central objective of ageing research.

For example, multidomain approaches have been proposed as strategies aimed at simultaneously stimulating multiple aspects of functioning (Ngandu et al., 2015; Deckers et al., 2015; Rosenberg et al., 2017; 2020) and likely contribute to mitigating the overall burden of frailty. At a biological level, the potential effectiveness of enriched and stimulating activities is often discussed in relation to neuroplasticity, namely the brain's capacity to adapt its structure and function in response to experience and environmental stimulation.

Among the various forms of environmental enrichment investigated in ageing research, musical engagement has attracted increasing attention due to its capacity to simultaneously recruit auditory, motor, cognitive, emotional, and social processes (Herholz & Zatorre, 2012; Altenmüller & Schlaug, 2015; Särkämö et al., 2014; Zendel et al., 2019; Pentikäinen et al., 2022). Considering all these aspects, the present thesis examines how multidomain and aesthetically enriched interventions, including both active and receptive forms of musical engagement, such as choir singing and immersive virtual reality experiences including music listening and watching natural landscapes, may contribute to reducing frailty and supporting overall well-being in ageing populations.

1.1.1 The Conceptual Evolution of Multidimensional Frailty

The concept of frailty has undergone significant evolution within gerontological research over the past several decades. Initially, frailty was broadly understood as a state of increased vulnerability associated with advanced age, often described in clinical terms as a general decline in physiological reserves and resistance to stressors. Early conceptualizations were largely grounded in biomedical perspectives and primarily focused on physical deterioration, reflecting the dominant orientation of geriatric medicine in the late twentieth century (Bergman et al., 2007).

The gerontological construct of frailty is significantly distinct from related concepts traditionally adopted in neurological and neuropsychological research, which have typically focused on domain-specific impairments, such as cognitive decline, brain pathology, or deficits in specific functional systems. While these approaches have provided fundamental insights into the mechanisms of ageing and disease, they have often addressed isolated domains rather than capturing the global and integrative nature of vulnerability in later life. In contrast, the concept of frailty introduces a broader, system-level perspective, emphasizing the cumulative and interactive nature of biological, cognitive, psychological, and social processes. This distinction is particularly relevant for nowadays intervention approaches, which aim to move beyond domain-specific frameworks and adopt a more integrative perspective on ageing, in which vulnerability and adaptive capacity are understood as emerging from the dynamic interplay of multiple dimensions of functioning.

One of the most influential attempts to operationalize frailty was the phenotypic model proposed by Fried and colleagues (2001), which defined frailty as a clinical syndrome characterized by a constellation of physical indicators including unintentional weight loss, muscle weakness, exhaustion, slow walking speed, and reduced levels of physical activity. According to this perspective, the presence of three or more of these criteria indicates frailty, while individuals presenting one or two criteria are classified as prefrail. The Fried phenotype provided an important step toward standardizing frailty assessment and has been widely used in epidemiological studies and clinical research. Nevertheless, its emphasis on physical manifestations has also been the subject of debate, as it captures only one dimension of the broader processes underlying ageing-related vulnerability.

In parallel with the phenotypic approach, alternative models emerged that conceptualized frailty as the result of the cumulative accumulation of health deficits across multiple physiological systems. The deficit accumulation model developed by Rockwood and Mitnitski (2007) proposed that frailty arises from the progressive aggregation of diverse health-related deficits, including diseases, symptoms, disabilities, and functional impairments. Here, frailty is quantified using the Frailty Index, which represents the proportion of deficits present in an individual relative to the total number of deficits assessed. This model shifted the focus from specific clinical symptoms to the broader notion of biological ageing as a process characterized by increasing systemic vulnerability. Also, it highlighted the dynamic and heterogeneous nature of ageing trajectories, suggesting that frailty reflects the cumulative impact of multiple interacting factors rather than a single pathological pathway.

Over time, growing evidence from gerontology, epidemiology, and social medicine has further expanded the conceptualization of frailty beyond strictly biomedical dimensions. Researchers increasingly recognized that ageing-related vulnerability cannot be fully understood without considering the interaction between physical health, cognitive functioning, psychological well-being, and social resources. In fact, cognitive impairment, depressive symptoms, social isolation, and reduced participation in daily activities have all been shown to contribute to increased vulnerability and adverse outcomes in later life (Clegg et al., 2013). This insight led to the development of multidimensional models of frailty, which conceptualize frailty as a complex condition emerging from the interplay of all these factors.

One influential multidimensional framework was proposed by Gobbens and colleagues (2010), who defined frailty as a dynamic state affecting an individual who experiences losses in one or more domains of human functioning which increases the risk of adverse outcomes such as disability, hospitalization, and mortality. This approach emphasized that frailty should not be interpreted solely as a medical condition but rather as a state reflecting reduced adaptive capacity across multiple systems.

Within clinical gerontology, these conceptual developments have also informed the creation of multidimensional assessment tools designed to capture the complexity of frailty in older populations. Among these instruments, the Multidimensional Prognostic Index (MPI; Pilotto et al., 2008) represents one of the most widely validated tools derived from Comprehensive Geriatric Assessment (CGA). The MPI integrates information from several domains, including functional status, cognitive functioning, nutritional status, comorbidity, medication use, and social support, to provide an overall prognostic score reflecting an individual's level of vulnerability. Some studies have demonstrated that the MPI is a robust predictor of mortality, hospitalization, and other adverse clinical outcomes in older adults (e.g., Sancarlo et al., 2012; Giantin et al., 2013; Pilotto et al., 2020, review).

More broadly, the progressive shift toward multidimensional perspectives reflects a fundamental transformation in the understanding of ageing within contemporary gerontology. Rather than viewing frailty as an inevitable consequence of biological decline, it is increasingly interpreted as a dynamic and potentially modifiable condition arising from complex interactions between physiological processes, lifestyle factors, and social environments. This interpretation has important implications for prevention and intervention strategies, as it suggests that targeting multiple domains of functioning may help mitigate vulnerability and promote resilience in later life.

1.1.1 Non-modifiable and Modifiable Determinants of Ageing Vulnerability

Ageing trajectories are shaped by the cumulative interaction of a wide range of determinants acting across the lifespan. Research in epidemiology, gerontology, and public health has increasingly emphasized that the risk of cognitive decline, disability, and frailty in later life reflects the combined influence of both non-modifiable and modifiable factors. Understanding how these determinants interact is essential for identifying potential targets for prevention and intervention.

Non-modifiable factors include biological and demographic characteristics that cannot be altered but significantly influence individual vulnerability to ageing-related conditions. Among these, age itself represents the strongest predictor of cognitive decline and dementia, reflecting the progressive accumulation of molecular, cellular, and systemic changes affecting multiple physiological systems. Genetic factors also play an important role, with specific alleles such as the apolipoprotein E ε4 (APOE-ε4) genotype being associated with increased risk of Alzheimer's disease and accelerated cognitive decline (Corder et al., 1993; Farrer et al., 1997). In addition, sex differences have been reported in the epidemiology of dementia and frailty, with women generally exhibiting higher prevalence rates in advanced age, likely reflecting complex interactions between biological, hormonal, and sociocultural factors (Mielke et al., 2014).

While non-modifiable determinants provide important insights into biological vulnerability, a growing body of research has demonstrated that a substantial proportion of cognitive decline and dementia risk may be attributable to modifiable environmental and lifestyle factors. Epidemiological research has identified several behavioral and health-related determinants associated with cognitive ageing, including physical inactivity, low educational attainment, social isolation, hearing loss, cardiovascular risk factors, and metabolic disorders (Norton et al., 2014; Deckers et al., 2015). These findings have contributed to the recognition that dementia and cognitive decline are not solely the result of inevitable biological ageing but are also influenced by potentially preventable exposures accumulated throughout the life course.

Many of these risk factors exert their effects through shared biological and psychosocial pathways, affecting multiple systems involved in cognitive and functional health. For example, vascular risk factors such as hypertension, diabetes, and obesity can contribute to cerebrovascular damage and neurodegeneration, while social isolation and reduced cognitive engagement may limit opportunities for neural stimulation (Fratiglioni, Paillard-Borg, & Winblad, 2004; Middleton & Yaffe, 2009). Some estimates suggest that a substantial proportion of dementia cases worldwide may be attributable to modifiable risk factors, highlighting the considerable potential for prevention strategies targeting lifestyle and environmental determinants (e.g., Norton et al., 2014). These findings have reinforced the importance of adopting a life-course perspective, according to which exposures occurring at different stages of life cumulatively influence vulnerability to cognitive decline and frailty. Life-course epidemiology emphasizes that early-life factors such as education may shape cognitive reserve, while midlife exposures and late-life determinants such as social isolation and physical inactivity may further influence trajectories of cognitive and functional ageing (Ben-Shlomo & Kuh, 2002).

1.1.3 The Role of Age-Related Hearing Loss in Multidimensional Frailty

Age-related hearing loss, commonly referred to as presbycusis, is among the most prevalent chronic conditions affecting older adults and represents one of the leading causes of sensory impairment in ageing populations. Epidemiological studies estimate that approximately one third of adults over the age of 65 and more than half of individuals over the age of 75 experience clinically significant hearing loss (Lin et al., 2011; Goman & Lin, 2016). Presbycusis is typically characterized by progressive bilateral sensorineural hearing impairment, primarily affecting high-frequency sounds and speech perception, particularly in noisy environments.

Age-related hearing loss arises from multiple structural and functional changes within the auditory system. Degenerative processes may involve the cochlea, including loss of hair cells, degeneration of the stria vascularis, and reductions in spiral ganglion neurons, which together contribute to decreased auditory sensitivity and impaired signal transmission along the auditory pathway (Schuknecht & Gacek, 1993; Gates & Mills, 2005). In addition to peripheral alterations, ageing is also associated with changes in central auditory processing, including reduced temporal resolution, impaired speech-in-noise perception, and altered cortical auditory responses (Humes et al., 2012; Anderson et al., 2013; Presacco et al., 2016; Peelle & Wingfield, 2016; Slade et al., 2020). These central changes suggest that presbycusis should not be interpreted solely as a peripheral sensory deficit but rather as a condition involving the broader auditory network.

A growing body of research indicates that hearing loss may have significant consequences beyond auditory perception, influencing cognitive performance, mobility, and social functioning. Longitudinal epidemiological studies have consistently shown that individuals with hearing impairment exhibit accelerated rates of cognitive decline and an increased risk of developing dementia compared with individuals with normal hearing (Lin et al., 2011; 2013; Gurgel et al., 2014; Deal et al., 2017). Several mechanisms have been proposed to explain this association. One proposed mechanism involves increased listening effort, whereby degraded auditory input requires greater allocation of cognitive resources for speech processing, thereby reducing the resources available for other cognitive operations (Pichora-Fuller et al., 2016). Another explanation involves sensory deprivation, whereby prolonged reductions in auditory input may contribute to structural and functional changes in cortical regions involved in auditory and cognitive processing (Peelle & Wingfield, 2016).

Beyond cognitive mechanisms, hearing loss may also influence broader aspects of daily functioning that are closely linked to vulnerability in older age. Difficulties in speech perception and communication can reduce participation in social activities and contribute to increased social isolation, which has been identified as an important risk factor for both cognitive decline and functional deterioration (Mick et al., 2014). In addition, hearing impairment has been associated with reduced physical activity levels and increased risk of falls, possibly due to alterations in spatial orientation (Viljanen et al., 2009).

Recent research has also explored the relationship between auditory dysfunction and frailty. In a population-based study, Sardone and colleagues (2020) reported that age-related central auditory processing disorder was significantly associated with cognitive frailty in older adults, suggesting that central auditory dysfunction may represent an early indicator of vulnerability affecting both sensory and cognitive systems. Taken together, audiological and epidemiological evidence indicates that age-related hearing loss should be considered a significant factor influencing health trajectories in later life. Hearing impairment may interact with multiple physiological and behavioral processes, influencing cognitive efficiency, social participation, and functional autonomy.

1.2 Neuroplasticity and Mechanisms of Brain Adaptation

Neuroplasticity refers to the capacity of the nervous system to modify its structural and functional organization in response to experience, environmental demands, and learning processes. Far from being limited to early developmental stages, plasticity remains a fundamental property of the adult brain. Through mechanisms such as synaptic remodeling, dendritic reorganization, and changes in synaptic efficacy, neural circuits are able to dynamically adapt to internal and external stimuli (Burke & Barnes, 2006; Kolb & Gibb, 2014).

A central feature of neuroplasticity is activity-dependent plasticity, whereby patterns of neuronal activity induce long-lasting modifications in synaptic strength and network organization. At the cellular level, these processes are primarily mediated by mechanisms such as long-term potentiation (LTP) and long-term depression (LTD), which regulate the strengthening or weakening of synaptic connections and are widely considered fundamental substrates of learning and memory (Citri & Malenka, 2008). LTP typically involves sustained increases in synaptic efficacy following high-frequency stimulation, whereas LTD results from prolonged low-frequency activity that decreases synaptic strength. These bidirectional processes allow neural circuits to dynamically encode experience by adjusting synaptic weights within distributed networks.

The induction of synaptic plasticity critically depends on the activation of glutamatergic NMDA receptors, which permit calcium influx into postsynaptic neurons when synaptic activity exceeds a specific threshold. The resulting increase in intracellular calcium concentration triggers a cascade of intracellular signaling pathways that regulate synaptic transmission and structural remodeling (Malenka & Bear, 2004). Calcium-dependent signaling cascades play a central role in regulating synaptic plasticity: increases in postsynaptic calcium concentration can activate kinase-dependent pathways that promote the phosphorylation of synaptic proteins and the insertion of AMPA receptors into the postsynaptic membrane, thereby strengthening synaptic transmission during long-term potentiation. Conversely, different patterns of calcium signaling may engage alternative pathways that facilitate AMPA receptor internalization, leading to synaptic weakening during long-term depression (Citri & Malenka, 2008).

Beyond functional modifications of synaptic transmission, plasticity also involves structural remodeling of neural circuits. Dendritic spines, small protrusions that host most excitatory synapses, are highly dynamic structures capable of changing their shape, density, and stability in response to neural activity and environmental stimulation. Activity-dependent remodeling of dendritic spines, together with processes such as synaptogenesis and synaptic pruning, contributes to the reorganization of neural networks and the consolidation of long-term memory traces (Holtmaat & Svoboda, 2009). These structural adaptations enable neural circuits to integrate new information while maintaining network stability.

Sustained forms of synaptic plasticity also involve the regulation of gene expression. Activity-dependent modulation of transcription factors such as CREB (cAMP response element-binding protein) plays a crucial role in stabilizing long-term synaptic changes by promoting the transcription of genes involved in synaptic growth and neuronal survival (Kandel, 2001). Through these mechanisms, transient patterns of neural activity can be translated into long-lasting molecular and structural changes within neural circuits. Among the molecular factors involved in these processes, neurotrophins play a particularly important role in modulating neuronal growth and synaptic function. One of the most extensively studied neurotrophins is brain-derived neurotrophic factor (BDNF), which is widely expressed throughout the central nervous system and critically involved in activity-dependent synaptic plasticity.

Experimental and translational research further suggests that cognitively, socially, and sensorily enriched environments can modulate neural plasticity and support adaptive brain responses across the lifespan (Kolb & Gibb, 2014). Understanding the biological mechanisms underlying these adaptive processes therefore represents an important step toward clarifying how behavioral stimulation and enriched environments may contribute to maintaining neural efficiency during ageing.

1.2.1 Neuroplasticity in the Ageing Brain

Ageing is accompanied by a wide range of structural, neurochemical, and functional changes in the brain. At the macroscopic level, neuroimaging studies have documented progressive reductions in grey matter volume and white matter integrity across several cortical and subcortical regions, with particularly marked effects in frontal and temporal areas supporting executive control, episodic memory, and processing speed (Raz et al., 2005; Fjell & Walhovd, 2010). These age-related changes are not spatially uniform: frontal regions, medial temporal structures, and association cortices tend to show greater vulnerability than primary sensory areas, although inter-individual variability is substantial. At the cellular level, ageing is also associated with alterations in synaptic structure and transmission, which may affect the efficiency of neural communication (Morrison & Baxter, 2012). Hence, brain ageing involves not only volumetric decline, but also widespread modifications in connectivity, signaling efficiency, and network dynamics.

These neural changes have often been interpreted as evidence of a gradual reduction in plastic potential. However, some evidence suggests that the ageing brain retains a significant capacity for experience-dependent adaptation, even if the mechanisms and expression of plasticity differ from those observed earlier in life (Burke & Barnes, 2006). Rather than reflecting a simple linear loss of function, ageing appears to involve both decline and reorganization, with preserved or newly recruited neural resources supporting performance when canonical systems become less efficient. In this sense, ageing-related neural change is increasingly understood as involving a dynamic balance between vulnerability and adaptation, rather than as a purely degenerative process (Grady, 2012).

Functional neuroimaging studies provide particularly strong support for this view. Older adults frequently show broader or alternative recruitment of neural networks during cognitive tasks, especially in situations requiring episodic memory, working memory, and executive control. For example, increased bilateral prefrontal activation has often been observed in older adults compared with younger adults, suggesting that additional neural resources may be engaged to support performance when task demands increase or when neural efficiency declines (Logan et al., 2002; Mattay et al., 2006;

Schneider-Garces et al., 2010). In some cases, such over-recruitment is associated with preserved or better performance, supporting a compensatory interpretation; in other cases, it may reflect reduced neural efficiency or dedifferentiation. This ambiguity has led to a more refined discussion in the literature about when increased activity should truly be interpreted as compensation.

Several neurocognitive models have been proposed to account for these age-related patterns of functional reorganization. The HAROLD model (Hemispheric Asymmetry Reduction in Older Adults) suggests that reduced hemispheric specialization in later life may reflect compensatory recruitment of bilateral neural resources during cognitive processing (Cabeza, 2002). The PASA model (Posterior–Anterior Shift in Ageing) describes a relative reduction in posterior activity accompanied by increased anterior, especially prefrontal, activation, interpreted as a shift toward top-down control processes that help sustain performance in the presence of posterior decline (Davis et al., 2008). The CRUNCH model (Compensation-Related Utilization of Neural Circuits Hypothesis) further proposes that older adults recruit additional neural resources already at lower levels of task demand, but that this compensatory capacity reaches a ceiling under high load, resulting in reduced performance when task demands exceed available resources (Reuter-Lorenz & Cappell, 2008).

Complementing these models, the Scaffolding Theory of Ageing and Cognition (STAC) proposes that the ageing brain can offset structural and functional decline by building and recruiting compensatory scaffolds, i.e., alternative neural circuits and processing strategies that support cognitive performance in the face of neural challenge (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). In this view, life experiences such as education, cognitively stimulating activities, and training opportunities may strengthen these scaffolds over time, thereby helping to preserve function despite ageing-related neural change. This idea provides an important bridge between neurocognitive models of compensation and intervention-based approaches aimed at promoting resilience in later life.

Belleville's work (e.g., Belleville et al., 2006; 2011; 2025) has also been important in showing, through cognitive intervention studies, that older adults and at-risk populations can still exhibit measurable neural reorganization in response to training. More recent work has emphasized that these models capture partly overlapping but distinct aspects of age-related neural adaptation. In particular, the distinction among maintenance, reserve, and compensation has become increasingly important in the cognitive neuroscience of ageing. In a major integrative account, Cabeza and colleagues (2018) argued that healthy cognitive ageing may be understood in terms of the interaction between preserved brain integrity (maintenance), accumulated adaptive resources (reserve), and task-related recruitment of additional neural processes (compensation).

Overall, the available literature suggests that ageing should not be interpreted simply as a process of neural loss, but as a condition in which decline, reorganization, and adaptation coexist. The ageing brain shows clear structural and neurochemical vulnerability, yet it also retains the capacity to recruit alternative neural resources, reorganize functional networks, and respond to stimulation and training. This residual plasticity provides the biological basis for interventions aimed at promoting cognitive and functional resilience in older adulthood.

1.2.2 Neuroplasticity and ERP components

Event-related potentials (ERPs) represent one of the most powerful electrophysiological approaches for investigating the temporal dynamics of neural processing and experience-dependent plasticity in the human brain. ERPs are derived from electroencephalographic (EEG) recordings and reflect time-locked postsynaptic potentials generated by synchronized activity of large neuronal populations, primarily within cortical pyramidal cells. Because of their millisecond temporal resolution, ERPs allow researchers to examine the sequential stages of sensory encoding, attentional selection, and cognitive evaluation that unfold following stimulus presentation (Kappenman & Luck, 2012; Luck, 2014). This temporal precision makes ERPs particularly suitable for detecting subtle changes in neural processing associated with learning, training, and environmental stimulation.

ERP components are typically characterized by their polarity, latency, and scalp distribution, and are often interpreted as reflecting specific stages of information processing. Early components, emerging within the first 100–200 ms after stimulus onset, are generally associated with sensory encoding and perceptual processing. In auditory paradigms, the P1–N1–P2 complex represents one of the most extensively studied markers of early cortical auditory processing (Näätänen & Picton, 1987; Crowley & Colrain, 2004; Wagner et al., 2017). The N1 component, typically peaking around 100 ms, is thought to originate primarily from generators within the auditory cortex of the superior temporal gyrus and reflects early stimulus detection and encoding of acoustic features (Näätänen & Picton, 1987).

Closely following the N1, the P2 component has attracted particular interest in studies of auditory learning and neuroplasticity. Unlike earlier sensory components that primarily reflect stimulus detection, P2 appears to be sensitive to perceptual learning and repeated sensory experience. Experimental studies have shown that auditory training can lead to increased P2 amplitudes, suggesting the strengthening or refinement of auditory cortical representations (Tremblay et al., 2001; 2014; Ross & Tremblay, 2009). These changes are often interpreted as reflecting plastic modifications in auditory cortical networks, potentially involving improved neural synchronization or more efficient neural coding of stimulus features.

Another important negative component associated with auditory processing is the mismatch negativity (MMN), which reflects automatic detection of deviations from expected auditory patterns. The MMN is typically elicited in oddball paradigms, i.e., when a deviant stimulus violates a regular sequence of standard stimuli and is thought to index the formation of short-term auditory sensory memory traces (Näätänen et al., 1978; 2007). Importantly, MMN amplitude and latency are sensitive to perceptual learning and auditory training, further supporting the use of ERP markers as indicators of experience-dependent plasticity within auditory cortical circuits (Näätänen et al., 1993; Tremblay et al., 1997).

Beyond early sensory processing, later ERP components are associated with higher-order cognitive functions. Among these, the N2 component, typically observed between 200 and 350 ms after stimulus onset, has been linked to processes such as conflict monitoring, stimulus discrimination, and attentional control (for a review, see Folstein & Van Petten, 2008). N2 responses are particularly prominent in tasks requiring target detection or response inhibition and are thought to involve neural generators in frontal and anterior cingulate regions involved in cognitive control.

The P3 component, particularly the P3b, is one of the most widely studied ERP markers of cognitive processing. The P3 typically emerges between 300 and 600 ms following stimulus presentation and is associated with stimulus evaluation, context updating, and working-memory-related processes (Donchin & Coles, 1988; Polich, 2007). Neurophysiological evidence suggests that P3 generation involves distributed neural networks including parietal, frontal, and hippocampal structures; moreover, P3 latency has often been interpreted as an electrophysiological index of cognitive processing speed, while amplitude is thought to reflect the allocation of attentional resources during task performance (Polich, 2007).

Crucially, ERP components should not be interpreted in isolation but rather as part of a dynamic cascade of neural processes. The temporal relationship between successive components provides important insights into the efficiency of neural processing across different stages of stimulus evaluation (Twomey et al., 2015; Kopp et al., 2020). The sensitivity of ERP measures to experience-dependent changes has made them a valuable tool for investigating neuroplasticity. A substantial body of research has demonstrated that perceptual learning, cognitive training, and repeated sensory stimulation can lead to measurable changes in ERP amplitude, latency, or scalp distribution (Tremblay et al., 2001; Shahin et al., 2003; Alain et al., 2010). Such modifications are often interpreted as reflecting improved neural efficiency and more selective recruitment of neural populations involved in task-relevant processing.

In the context of ageing, ERP studies have provided important insights into both decline and adaptation in neural processing. Age-related changes have been reported across multiple ERP components, including prolonged latencies and reduced amplitudes in early sensory responses as well as later cognitive components (Friedman, 2012). Meta-analytic evidence indicates that ageing is consistently associated with increased P300 latency, reflecting slower stimulus evaluation and reduced processing speed across the lifespan (van Dinteren et al., 2014). More recent work has also linked age-related changes in P3b amplitude to alterations in attentional resource allocation and cognitive decline (Porcaro et al., 2019). Similarly, age-related alterations have been reported in N1, N2, P2 and MMN responses, indicating that ageing affects multiple stages of neural processing, ranging from early sensory encoding to stimulus discrimination and higher-order functions (Amenedo & Díaz, 1998; Pekkonen, 2000; Getzmann et al., 2015; Chow et al., 2025).

At the same time, ERP findings also indicate that the ageing brain retains a degree of functional plasticity. Training studies and repeated exposure paradigms have shown that older adults can exhibit measurable changes in ERP responses following sensory or cognitive stimulation, indicating that neural systems remain responsive to environmental input even in later life (e.g., Alain & Snyder, 2008; Ross & Tremblay, 2009). Because ERPs capture fine-grained temporal dynamics of neural activity, they provide a particularly sensitive approach for detecting these plastic adaptations, even when behavioral improvements are modest or not yet observable. For this reason, ERP measures represent an important methodological tool for investigating how neural processing adapts to experience and intervention.

1.3 Multidomain Interventions and Environmental Enrichment

In recent decades, increasing attention has been directed toward non-pharmacological strategies aimed at promoting healthy ageing and preventing functional decline. This shift reflects growing recognition that pharmacological approaches alone have shown limited effectiveness in preventing complex age-related conditions such as cognitive impairment, dementia, and frailty. At the same time, international health organizations have emphasized the importance of preventive strategies targeting modifiable determinants of health across the lifespan. In particular, the World Health Organization introduced the concept of healthy ageing, defined as "*the process of developing and maintaining the functional ability that enables well-being in older age*" (World Health Organization, 2015). Accordingly, recent global guidelines have highlighted the importance of addressing modifiable lifestyle factors, including physical activity, diet, cognitive engagement, and management of vascular risk factors, as key strategies for reducing the risk of cognitive decline and dementia (World Health Organization, 2019). These developments have contributed to a broader use of preventive approaches that address the multiple and interacting determinants of ageing-related vulnerability.

The roots of multidomain approaches can be traced to the concept of experience-dependent brain plasticity, originally articulated in the work of Donald Hebb. Hebb proposed that neural circuits are strengthened through repeated co-activation, summarized in the well-known principle that "neurons that fire together wire together" (Hebb, 1949), suggesting that environmental complexity and behavioral engagement could influence brain organization by promoting repeated activation of neural networks involved in perception, action, and learning. These ideas were subsequently explored in experimental neuroscience through the development of environmental enrichment paradigms in animal models. In these paradigms, animals are housed in environments that provide increased opportunities for sensory stimulation, exploration, social interaction, and physical activity compared with standard laboratory conditions. Seminal studies demonstrated that rodents raised in enriched environments exhibited substantial neuroanatomical changes, including increased cortical thickness and enhanced dendritic branching in several brain regions (Diamond, Krech, & Rosenzweig, 1964;

Greenough, West, & DeVoogd, 1978; Rosenzweig & Bennett, 1996). Later work further demonstrated that enriched environments could induce experience-dependent structural plasticity in the brain, including increased synaptic density and modifications in neural circuitry supporting learning and memory (Leggio et al., 2005).

Subsequent research expanded these findings by showing that environmental enrichment influences multiple biological mechanisms involved in neural plasticity. Animal studies have demonstrated that enriched environments can enhance hippocampal neurogenesis, facilitate synaptic plasticity, and improve performance in spatial learning and memory tasks (Kempermann, Kuhn, & Gage, 1997; van Praag, Kempermann, & Gage, 2000). In addition, enriched environments have been associated with increased expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), modulation of synaptic proteins, and structural remodeling of dendritic spines (Nithianantharajah & Hannan, 2006; Sale et al., 2014). Collectively, these findings provide compelling experimental evidence that environmental complexity and behavioral engagement can induce long-lasting modifications in neural structure and function. Experimental studies have shown that environmental enrichment can also influence brain structure and cognitive performance in adult and ageing animals, suggesting that neural systems retain a degree of experience-dependent adaptability throughout the lifespan (Nithianantharajah & Hannan, 2006).

The translation of these principles from animal models to human ageing research has contributed to the development of multidomain lifestyle interventions, which can be conceptualized as ecological analogues of environmental enrichment paradigms. Such interventions attempt to recreate key elements of enriched environments by combining multiple forms of stimulation within structured intervention programs. One of the most influential studies adopting this approach is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a large randomized controlled trial demonstrating that a two-year multidomain intervention combining diet, exercise, cognitive training, and vascular risk monitoring produced measurable improvements in cognitive performance among older adults at increased risk of dementia (Ngandu et al., 2015). The FINGER trial provided important proof-of-concept evidence that complex lifestyle interventions can influence cognitive trajectories in later life and has since served as a reference model for multidomain prevention strategies.

Subsequent multidomain trials have explored variations of this approach in different populations and healthcare contexts. The Multidomain Alzheimer Preventive Trial (MAPT) investigated the effects of combined cognitive training, physical activity, and nutritional supplementation in older adults with memory complaints (Andrieu et al., 2017), while the preDIVA trial examined whether intensive management of vascular risk factors delivered in primary care could reduce dementia incidence over a six-year period (Moll van Charante et al., 2016). Although the results of these studies have been heterogeneous, they have provided valuable insights into the complexity of implementing multidomain prevention strategies and have highlighted the importance of factors such as intervention duration, adherence, and participant risk profiles.

More recently, international collaborative initiatives have sought to expand multidomain prevention strategies across diverse populations. The World-Wide FINGER network represents a global effort to adapt multidomain interventions to different cultural and healthcare settings while maintaining a shared methodological framework (Kivipelto et al., 2020). In line with these international initiatives, the *InTempo* project (Sala et al., 2025), developed within the Italian Age-It (Ageing Well in an Ageing Society) program, aims to investigate the prevention of cognitive decline through large-scale, longitudinal and multidomain approaches. The project involves the recruitment of a large cohort of older adults across the national territory, who are followed over time to evaluate the impact of preventive interventions targeting multiple domains of functioning. Particular emphasis is placed on early identification of cognitive vulnerability and on the implementation of strategies aimed at reducing modifiable risk factors in real-world clinical and community settings, in close collaboration with general practitioners. This effort is particularly relevant in the Italian context, which is characterized by one of the oldest populations worldwide and a rapidly increasing prevalence of age-related conditions. The complexity of the Italian ageing scenario is further shaped by regional disparities in healthcare access, socio-economic variability, and differences in social support structures, all of which influence trajectories of vulnerability (ISTAT, 2025).

These initiatives reflect a growing consensus that complex lifestyle interventions targeting multiple determinants of health may represent one of the most promising avenues for delaying cognitive decline and supporting functional independence in ageing societies. The convergence of evidence from epidemiology, experimental neuroscience, and clinical trials suggests that simultaneous stimulation of multiple behavioral and environmental domains may represent an effective strategy for mitigating the accumulation of deficits that contributes to frailty.

1.3.1 Multidimensional Lifestyle Engagement in Ageing

While multidomain interventions aim to address multiple determinants of health simultaneously, an important question concerns the types of activities involved that may represent ecologically meaningful pathways through which multidomain stimulation can be implemented in real-life contexts.

Physical engagement represents a fundamental component of lifestyle-based strategies aimed at supporting brain and functional health in ageing. A large body of evidence indicates that regular physical activity exerts protective effects on both cognitive functioning and brain structure. Aerobic exercise interventions, for example, have been shown to increase hippocampal volume and improve spatial memory in older adults, suggesting that physical activity may promote experience-dependent plasticity even in later life (Erickson et al., 2011). Meta-analytic evidence further indicates that physical exercise can enhance executive functioning, processing speed, and attentional control in ageing populations (Colcombe & Kramer, 2003; Northey et al., 2018). These cognitive benefits are thought to arise from multiple interacting biological mechanisms, including increased cerebral perfusion, improved vascular health, modulation of inflammatory processes, and the upregulation of neurotrophic factors such as BDNF, which plays a central role in synaptic plasticity, neuronal survival, and learning processes (Cotman, Berchtold, & Christie, 2007). In addition to these neural mechanisms, regular physical engagement also contributes to maintaining mobility, balance, and respiratory efficiency, all of which are important components of functional independence.

Alongside physical activity, cognitive engagement has been widely recognized as another important determinant of healthy cognitive ageing. Activities that require sustained attention, learning, memory, and complex information processing may stimulate neural systems involved in executive control, working memory, and adaptive learning. Both experimental and observational studies suggest that engagement in intellectually stimulating activities, such as artistic practices, language learning, cultural participation, and complex leisure activities, may support cognitive functioning and contribute to delaying age-related cognitive decline (Valenzuela & Sachdev, 2006; Park & Bischof, 2013; Duffner et al., 2022; Yang et al., 2022; Wu et al., 2023). From a neurobiological perspective, cognitively demanding activities may promote the recruitment and strengthening of large-scale neural networks supporting attention, memory, and cognitive flexibility. Moreover, continuous engagement in complex tasks may foster adaptive neural efficiency by encouraging the flexible use of distributed brain networks, a process that may contribute to maintaining functional brain organization in ageing populations (Nyberg et al., 2012).

A third key dimension concerns social engagement, which has increasingly been recognized as an important determinant of health and well-being in later life. Epidemiological studies have shown that social isolation and loneliness are associated with increased risks of cognitive decline, dementia, depression, and mortality among older adults (Fratiglioni et al., 2000; Holt-Lunstad et al., 2015, review). Conversely, participation in socially stimulating activities, including volunteering, group learning, cultural participation, and community-based programs, has been linked to better cognitive functioning, improved psychological well-being, and reduced risk of functional decline. Several mechanisms have been proposed to explain these effects. Social interaction may provide opportunities for cognitively stimulating communication, promote emotional support and stress buffering, and encourage engagement in meaningful shared activities that reinforce motivation and behavioral activation (Haslam et al., 2014). In addition, social participation may facilitate the maintenance of identity, purpose, and belonging, psychological factors that are increasingly recognized as important contributors to successful ageing (Steptoe, Deaton & Stone, 2015).

Importantly, these three domains (physical, cognitive, and social engagement) rarely operate independently in everyday life. Many real-world activities involve the simultaneous activation of multiple behavioral systems, creating ecologically complex forms of stimulation that may amplify the benefits associated with single-domain interventions. For this reason, multidomain lifestyle programs increasingly aim to promote activities that integrate multiple forms of engagement within meaningful and intrinsically motivating experiences. Collective artistic practices represent a particularly illustrative example of such multidimensional stimulation, as they often combine cognitive effort, sensorimotor coordination, emotional expression, and social interaction.

1.3.2 Naturalistic and Quasi-Experimental Designs in Intervention Studies

Intervention research has traditionally relied on randomized controlled trials (RCTs) as the gold standard for establishing causal relationships, due to their ability to maximize internal validity through random allocation and experimental control. However, in many fields, including education and public health, interventions often take place within complex, real-world contexts where strict randomization is not always feasible, ethical, or desirable. In such cases, naturalistic and quasi-experimental designs represent a crucial methodological alternative. Naturalistic designs investigate interventions that occur within existing social or institutional settings, rather than being artificially implemented for research purposes. Closely related to this approach, natural experiments exploit naturally occurring variations in exposure to an intervention to approximate causal inference (Meyer, 1995; Dunning, 2012). These designs are particularly valuable for studying complex phenomena that unfold in everyday environments and involve multiple interacting components.

Quasi-experimental designs, more broadly, refer to studies in which participants are not randomly assigned to conditions but are instead allocated based on pre-existing structures or practical constraints. Although this lack of full randomization may introduce potential confounding factors, methodological models have demonstrated that causal inference can still be strengthened through appropriate design and analytical strategies. These include the use of longitudinal data, baseline measurements, repeated observations, and statistical control of relevant covariates (Shadish, Cook, & Campbell, 2002; Hernán & Robins, 2020).

Naturalistic and quasi-experimental approaches offer a key advantage over highly controlled experimental designs: they preserve ecological validity, allowing researchers to capture how interventions function in real-world conditions. This is particularly relevant when interventions are inherently complex, context-dependent, and socially embedded, as is often the case in educational, behavioral, and lifestyle-based programs (Craig et al., 2008; Skivington et al., 2021). In such contexts, attempting to isolate single components or impose strict experimental control may reduce the meaningfulness and effectiveness of the intervention itself. At the same time, it is increasingly recognized that the distinction between randomized and non-randomized designs is not always dichotomous. In real-world settings, elements of structured or constrained allocation may coexist with naturalistic conditions, resulting in hybrid designs that combine aspects of experimental and observational approaches. These designs allow for a more nuanced balance between internal validity and ecological validity, particularly when studying interventions that are already embedded in institutional or community practices.

Within this methodological landscape, quasi-experimental longitudinal designs are especially well-suited for capturing change over time and for examining both within-subject trajectories and between-group differences. By integrating repeated measures with theoretically informed covariates, such approaches can provide robust insights into intervention effects while maintaining sensitivity to individual variability and contextual influences. Overall, the increasing use of naturalistic and quasi-experimental designs reflects a broader shift in intervention research, moving from strictly controlled experimental paradigms toward approaches that better accommodate the complexity of real-world phenomena. This shift is particularly relevant for studies targeting multifactorial processes where ecological validity is essential for understanding how interventions operate in everyday life.

1.4 Music-Based Interventions and Neural Plasticity

Because of their inherently multimodal nature, musical activities have increasingly been investigated as promising tools for inducing experience-dependent neural plasticity and supporting cognitive and functional health across the lifespan (Fauvel et al., 2014). From a systems neuroscience perspective, music represents a particularly powerful model for studying experience-dependent plasticity because it does not rely on a single specialized neural module but instead recruits distributed networks spanning auditory, motor, limbic, cerebellar, and prefrontal systems. Neuroimaging and neurophysiological studies consistently demonstrate that musical engagement co-activates primary and secondary auditory cortices, premotor and motor regions, basal ganglia, cerebellum, limbic and paralimbic structures, and prefrontal areas involved in attention, prediction, reward processing, and working memory (Zatorre, Chen, & Penhune, 2007; Herholz & Zatorre, 2012; Koelsch, 2014). This broad recruitment profile has led several authors to conceptualize musical training as a model for investigating large-scale plasticity in the human brain. Reviews of the field have emphasized that repeated musical engagement can reshape both structural and functional brain organization through long-term coupling of sensory, motor, cognitive, and affective processes (Wan & Schlaug, 2010; Kraus & Chandrasekaran, 2010; Altenmüller & Schlaug, 2015; Criscuolo et al., 2022; Zaatar et al., 2024).

Within the literature on music-based interventions, a conceptual distinction is commonly made between active musical engagement and receptive musical engagement, as these two forms of interaction with music differ substantially in their sensorimotor demands, cognitive load, and social involvement and may therefore influence neural plasticity through partially distinct mechanisms. Active engagement refers to music production, such as singing, instrumental performance, rhythmic movement, or ensemble playing, and requires continuous integration between auditory perception and motor execution (Bangert et al., 2006; Zatorre, Chen & Penhune, 2007; Dalla Bella, Berkowska & Sowiński, 2015). By contrast, receptive engagement primarily involves music listening and relies more strongly on affective evaluation, mnemonic retrieval, and reward processing, although it can also recruit predictive and motor simulation processes (Janata, 2009; Trost et al., 2012; Koelsch, 2014; Vuust & Witek, 2014). Recent reviews in older adults have emphasized that these two modes of engagement should not be treated as interchangeable when interpreting cognitive, emotional, and neurobiological effects (Särkämö, 2018; Espinosa et al., 2025)

With respect to active musical engagement, converging evidence indicates that sustained musical training can induce both structural and functional reorganization in auditory–motor circuits. Early neuroimaging studies first demonstrated that professional musicians exhibit larger grey-matter volumes in auditory cortex, premotor areas, inferior frontal regions, and cerebellum relative to non-musicians (Gaser & Schlaug, 2003; Hyde et al., 2009). Subsequent neuroimaging work expanded these findings by showing that musical training is associated with structural adaptations in white-matter pathways supporting auditory–motor integration (Bengtsson et al., 2005; Halwani et al., 2011; Imfeld et al., 2009; Steele et al., 2013). Diffusion tensor imaging studies have reported structural adaptations in white-matter pathways supporting auditory–motor integration in musicians. In particular, enhanced connectivity has been observed in the arcuate fasciculus linking temporal and frontal regions, as well as in other fronto-temporal and interhemispheric tracts associated with auditory processing and sensorimotor coordination (e.g., Loui et al., 2011; Ellis et al., 2013; Moore et al., 2014; Oechslin et al., 2018; Acer et al., 2018). These structural modifications are widely interpreted as reflecting repeated coupling between auditory perception and motor execution during musical practice.

Evidence further suggests that musical experience is associated with structural differences not only in cortical regions but also in subcortical structures involved in reward processing, motor coordination, and memory formation. Morphometric analyses have linked cumulative musical training to structural variation in the superior temporal gyrus, putamen, hippocampus, amygdala, and thalamus (e.g., Vaquero et al., 2016). Importantly, the relationship between musical engagement and brain structure appears to extend into later life. In a structural neuroimaging study of older adults, Chaddock-Heyman et al. (2021) reported that individuals with musical training exhibited larger brain volumes in regions supporting executive functioning, emotional regulation, and episodic memory, including inferior frontal cortex, posterior cingulate cortex, insula, and parahippocampal regions. Similarly, observational studies have shown that lifetime musical activity in older adults is associated with better cognitive functioning and patterns of frontal–temporal brain organization consistent with the concept of cognitive reserve (e.g., Böttcher et al., 2022; Wolff et al., 2023, review).

More recent longitudinal neuroimaging research has begun to provide direct experimental evidence that musical training can induce plastic changes even when initiated in later life. In a randomized controlled intervention study combining behavioral assessment and structural MRI, Marie et al. (2023) followed healthy older adults participating in several months of structured musical training and observed increases in cerebellar grey-matter volume together with improvements in auditory working memory. In a related longitudinal resting-state fMRI study, Jünemann et al. (2023) reported training-related increases in functional connectivity between Heschl's gyrus and dorsal auditory-stream regions after extended piano training in older adults. Longer-term observational evidence further suggests that sustained musical practice may contribute to the maintenance of brain function in later life. In a four-year follow-up study, Wang et al. (2025) reported that older adults who continued instrumental training exhibited less decline in verbal working memory, better preservation of putamen volume, and increased cerebellar connectivity relative to individuals who discontinued training.

Complementary evidence comes from cross-sectional and observational studies examining lifetime musical engagement. For example, Liebscher et al. (2024) reported that older adults with a history of musical activity exhibited stronger resting-state connectivity between medial prefrontal cortex and distributed frontal and temporal regions associated with the default-mode network. Large cohort studies have likewise linked instrumental music practice with better working memory and executive functioning in later life, although effects appear somewhat smaller for singing alone (Vetere et al., 2024). Although such observational studies cannot establish causality, they support the hypothesis that long-term musical engagement may help preserve functional integration in large-scale brain networks that are vulnerable to ageing and neurodegenerative disease.

Mechanistically, the plasticity associated with active music making is increasingly interpreted within predictive processing and auditory–motor integration. During musical performance, the brain continuously generates predictions about pitch, timing, and timbre while comparing expected sensory consequences with incoming auditory feedback. This recurrent prediction–error loop recruits auditory cortex, premotor and supplementary motor areas, basal ganglia, cerebellum, and prefrontal regions involved in sequence learning and adaptive control (Patel, 2008; Pearce, 2018; Vuust et al., 2022). Such predictive sensorimotor coupling may contribute to strengthening neural pathways supporting temporal precision, cognitive control, and auditory discrimination. In this respect, choir singing provides a particularly illustrative example of multimodal engagement, as it integrates controlled breathing, vocal production, auditory monitoring, linguistic processing, and interpersonal synchronization within a socially meaningful activity (Pearce et al., 2016; Dichter et al., 2018; Fancourt & Perkins, 2018; Pentikäinen, 2023; Napadow et al., 2025).

Some parallels have often been drawn between musical training and physical exercise as models of experience-dependent neuroplasticity. Both activities involve repeated, structured practice that simultaneously engages multiple physiological and neural systems and has been shown to induce structural and functional adaptations in the brain. Extensive research in the field of exercise neuroscience has demonstrated that regular physical activity can promote neurogenesis, synaptic plasticity, and increased expression of neurotrophic factors contributing to improved cognitive performance and brain health across the lifespan (Cotman et al., 2007; Erickson et al., 2011; Hötting & Röder, 2013; Stillman et al., 2016). Similar mechanisms have been proposed in the context of musical training, where repeated sensorimotor practice, auditory feedback, and cognitive engagement may drive experience-dependent reorganization in distributed neural networks supporting perception, action, and cognition (Altenmüller & Schlaug, 2015). Hence, both physical exercise and musical training can be conceptualized as forms of enriched behavioral activity capable of stimulating large-scale neuroplastic processes, although they engage partially distinct neural systems and experiential domains (Brattico et al., 2021).

In contrast, receptive musical engagement refers to experiences in which individuals listen to music without actively producing it. Although listening requires less overt motor involvement than music making, it nonetheless recruits a wide network of neural systems associated with auditory perception, emotional processing, reward, and memory (Salimpoor et al., 2013; Zatorre & Salimpoor, 2013). Particularly noteworthy is the engagement of the mesolimbic dopaminergic reward system during emotionally powerful musical experiences. Early research using combined positron emission tomography and functional MRI, demonstrated that intensely pleasurable responses to music are associated with dopamine release in the nucleus accumbens and caudate nucleus, providing direct neurochemical evidence for the involvement of reward circuitry in music-evoked emotion (Salimpoor et al., 2011). Also, functional neuroimaging studies consistently demonstrate that music listening activates primary and secondary auditory cortices together with limbic and paralimbic regions including the amygdala, hippocampus, nucleus accumbens, insula, and medial prefrontal cortex (e.g., Koelsch, 2014; 2020; Trost, 2024; Fuentes-Sánchez, 2025).

Music listening is not merely a passive sensory event. Contemporary research suggests that attentive listening involves predictive, mnemonic, and evaluative processes that engage large-scale brain networks (Vuust & Witek, 2014; Pearce, 2018). Neuroimaging studies have shown that dynamic musical features such as timbre, rhythm, and harmony are associated with distributed patterns of brain activity during continuous music listening (Alluri et al., 2012). Complementary evidence from connectivity analyses indicates that extended music listening modulates large-scale brain networks, with functional connectivity patterns differing as a function of musical expertise and reflecting the integration of auditory, sensorimotor, and higher-order cognitive systems (Burunat et al., 2015; Alluri et al., 2017). These findings suggest that music perception engages large-scale functional networks whose organization reflects the integration of auditory, sensorimotor, and higher-order cognitive processes, rather than relying on isolated sensory responses.

Also, it can recruit networks involved in proprioception, emotional appraisal, attention, and higher-order cognitive evaluation and provoke neural adaptations (Reybrouck & Brattico, 2015; Reybrouck, Vuust & Brattico, 2018; 2021). Neuroimaging studies have also demonstrated that listening to personally meaningful or autobiographically relevant music can modulate large-scale functional connectivity. For example, increased synchronization between auditory cortex, hippocampus, and nodes of the default-mode network has been observed when individuals listen to familiar music, supporting autobiographical memory retrieval and self-referential processing (Janata, 2009; Jacobsen et al., 2015; King et al., 2019; Pereira et al., 2011).

Recent neuroimaging studies have further refined our understanding of music-evoked autobiographical memory in ageing. In an fMRI investigation including younger and older adults, Hennessy et al. (2025) showed that nostalgic music elicited stronger activation in the default-mode network, salience network, reward circuitry, and medial temporal regions relative to unfamiliar or non-nostalgic music. Functional connectivity analyses revealed enhanced coupling among posteromedial, insular, and limbic regions during nostalgic listening, suggesting that personally meaningful music may recruit large-scale systems involved in affective processing and autobiographical memory integration.

Electrophysiological evidence converges with these findings. Repeated exposure to musical stimuli has been shown to modify auditory cortical responses and mismatch-related activity, indicating experience-dependent plasticity even in listening contexts (Putkinen et al., 2013; Tervaniemi et al., 2014; Sihvonen et al., 2021). In ageing populations, receptive music interventions have been widely investigated for their potential to regulate mood, reduce stress, and facilitate memory retrieval. Listening to familiar or autobiographically meaningful music can activate relatively preserved emotional and mnemonic systems even in individuals with neurodegenerative disorders, suggesting that music listening may represent an accessible and powerful tool for engaging cognitive and affective processes in later life (Särkämö et al., 2014; Matziorinis & Koelsch, 2022).

Although active and receptive musical engagement differ in their behavioral demands, both forms of musical interaction may contribute to experience-dependent neural plasticity (Brattico et al., 2021). Active musical participation primarily emphasizes sensorimotor integration, motor learning, and executive control networks, whereas music listening predominantly recruits emotional, mnemonic, and reward-related circuits. These complementary mechanisms are highly relevant for the design of music-based interventions. Active approaches may be particularly effective for targets involving coordination, auditory–motor integration, and cognitive control, whereas receptive approaches may be especially useful for mood regulation, stress reduction, and autobiographical memory engagement.

1.4.1 Music Training and Developmental Trajectories

Music training represents a complex form of environmental enrichment that interacts with neurocognitive and socio-emotional development across the lifespan. Its effects are particularly relevant during childhood and adolescence, when brain plasticity and learning mechanisms are especially sensitive to structured experience.

A central issue in this field concerns the extent to which skills acquired through music training transfer beyond the musical domain. In this context, a distinction is commonly made between near transfer and far transfer (Miendlarzewska & Trost, 2014). Near transfer refers to improvements in abilities that are directly related to the trained domain, such as pitch discrimination, rhythm processing, and auditory or musical memory. These effects are widely documented and theoretically expected, as they rely on shared perceptual and neural mechanisms. By contrast, far transfer refers to improvements in more distal cognitive functions that are not inherently musical, including working memory, executive functions, language, and fluid intelligence. Evidence for far transfer remains more controversial, as it is often difficult to disentangle training-related effects from pre-existing individual differences.

Empirical research in developmental populations has consistently shown that music training is associated with enhanced performance in cognitive, perceptual and auditory domains, as well as in tasks requiring multisensory integration (Schellenberg, 2006; Jaschke et al., 2018; Swaminathan & Schellenberg, 2020). The MiddleMusic project, conducted in Bari from 2021 to 2024, provides a relevant example of this approach and consists in a longitudinal research program designed to investigate the impact of music training on cognitive, perceptual, emotional, and social development during preadolescence. The project focuses on students enrolled in Italian middle schools offering a structured music curriculum that integrates instrumental practice, music theory, and ensemble activities within the standard educational system (Lippolis et al., 2022). Participants are assessed using a multidimensional battery including cognitive, musical, and socio-emotional measures, allowing the investigation of both between-group differences (music vs. standard curriculum) and within-subject developmental trajectories over time. Importantly, the project also considers individual variability in musical engagement and practice intensity as key predictors, moving beyond binary distinctions between musicians and non-musicians (Lippolis et al., 2025a).

In a first, cross-sectional study, participation in structured instrumental training within school curricula has been associated with superior audiovisual working memory and fluid intelligence in preadolescents, even when controlling for baseline musical sophistication (Lippolis et al., 2022). However, the interpretation of such findings requires caution. Much of the literature relies on correlational or quasi-experimental designs, making it difficult to establish causality, as factors such as socioeconomic background, motivation, or initial cognitive abilities may influence both the likelihood of engaging in music training and developmental outcomes (Sala & Gobet, 2017; Schellenberg, 2019).

Within the same project, subsequent longitudinal and meta-analytic evidence have highlighted the importance of how music training is operationalized. In particular, measuring the intensity and continuity of musical engagement over time, rather than simply categorizing individuals as musicians or non-musicians, provides a more precise understanding of developmental effects. Evidence suggests that higher levels of sustained practice are associated with greater improvements in cognitive domains such as fluid intelligence, even after controlling for baseline abilities and environmental factors (Lippolis et al., 2025a; see Figure 2). These findings are consistent with theoretical accounts of experience-dependent neuroplasticity, whereby repeated and effortful engagement in structured activities leads to gradual changes in brain function and organization (Zatorre et al., 2012; Herholz & Zatorre, 2012).

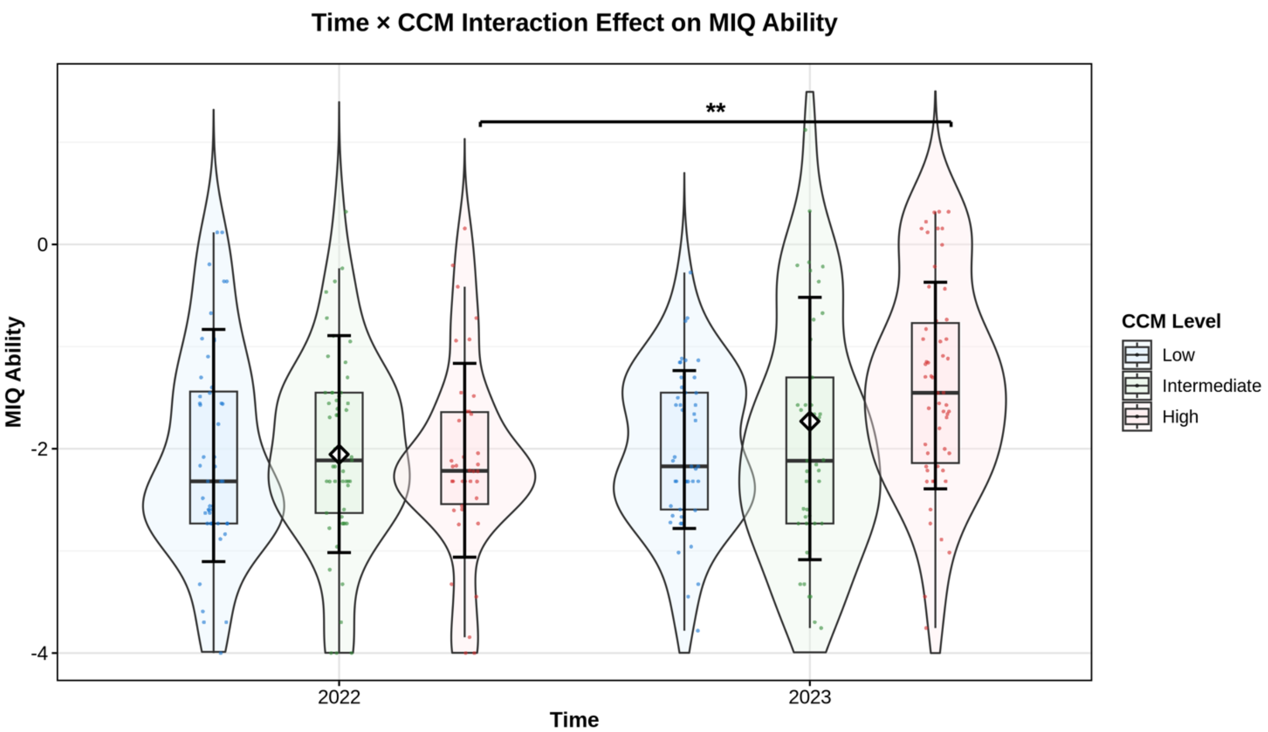

*Figure 2. Longitudinal results from the study by Lippolis et al. (2025a). Interaction between time and musical training intensity (CCM) on fluid intelligence (MIQ scores). Violin plots display the distribution of MIQ ability scores across two time points (2022, 2023) as a function of musical engagement intensity (low, intermediate, high), measured through the Concurrent Musical Activities (CCM) index. Results from mixed-effects modeling indicate a significant Time × CCM interaction (**p < .01), showing that participants with higher levels of sustained musical practice exhibit greater improvements in fluid intelligence over time compared to lower engagement groups.*

Beyond cognitive outcomes, music training during development was also linked to socio-emotional processes withing the same sample of participants. Musical activities, particularly those involving interpersonal coordination such as ensemble playing or group singing, require the integration of perception, action, and social interaction. In this context, higher levels of musical sophistication and engagement have been associated with greater empathy and prosocial tendencies in both Italian and Spanish preadolescents (Lippolis et al., 2025b). Longitudinal evidence further indicates that music training can enhance sensitivity to social reward, particularly in collective musical contexts, supporting its role in fostering interpersonal connection and social bonding (Lippolis et al., 2023).

Developmental changes were also evident in embodied and predictive aspects of musical experience. For instance, sensitivity to rhythmic complexity and the pleasurable urge to move to music (i.e., groove) were found to undergo significant refinement during early adolescence. This reflected the maturation of predictive processing and reward systems. Longitudinal evidence suggests that adult-like patterns of musical enjoyment, such as the preference for moderate levels of rhythmic complexity, emerge progressively during this stage and are linked to processes supporting learning, affect regulation, and social coordination (Lippolis et al., 2026).

Adolescence represents a particularly sensitive developmental window for these processes. During this stage, individuals increasingly engage with music as a means of emotional regulation, identity formation, and social affiliation. At the neural level, this period is characterized by substantial reorganization of reward-related systems, which may amplify the impact of musical experiences on affective and motivational processes (Foulkes & Blakemore, 2016; Penhune, 2020). Consistent with this view, higher levels of musical engagement have been associated with increased sensitivity to music-related reward across adolescence in a sample of Danish teens (Lippolis et al., 2024), as well as with stronger involvement in social and affective dimensions of musical experience.

This literature suggests that music training contributes to shaping a multidimensional profile of cognitive, emotional, and social capacities through mechanisms that are dynamic, context-dependent, and sensitive to individual differences. From a lifespan perspective, these developmental processes may have long-term implications. Early and sustained engagement with music may contribute to the formation of cognitive and socio-emotional resources that remain available along life, potentially supporting cognitive and emotional resilience and providing a developmental foundation for interventions in adulthood.

1.5 Aesthetic Engagement and Well-Being

Over the past two decades, increasing attention has been directed toward the role of aesthetic experiences in shaping emotional and psychological functioning. Research in neuroaesthetics has sought to understand how the brain perceives, evaluates, and emotionally responds to aesthetically meaningful stimuli, including visual artworks, music, architecture, and natural environments (Chatterjee & Vartanian, 2014; Skov & Nadal, 2020). Rather than being confined to a single sensory modality, aesthetic experience is generally understood as emerging from the interaction of perceptual analysis, emotional appraisal, cognitive interpretation, and value-based evaluation processes that together give rise to subjective experiences such as beauty, fascination, and aesthetic appreciation.

Theoretical models of aesthetic processing emphasize that aesthetic experience arises from the dynamic interaction between stimulus properties and characteristics of the perceiver. Some influential models conceptualize aesthetic appreciation as a multistage process involving perceptual analysis, implicit memory integration, cognitive mastering, and evaluative judgment, while subsequent developments have placed greater emphasis on contextual interpretation, affective engagement, and meaning-making as central components of aesthetic response (Leder et al., 2004; Pelowski et al., 2017; 2025). Then, aesthetic experience can be understood as a complex psychological state in which perceptual, affective, and cognitive processes converge.

Neuroscientific investigations indicate that aesthetic experiences recruit distributed brain systems extending beyond primary sensory cortices. Functional neuroimaging studies indicate that aesthetically preferred stimuli are consistently associated with activity in valuation-related regions such as the orbitofrontal cortex and ventromedial prefrontal cortex, areas implicated in the representation of subjective value and hedonic appraisal across sensory modalities (Kawabata & Zeki, 2004; Ishizu & Zeki, 2011; Brown et al., 2011, review; Brattico et al., 2025). Particularly engaging aesthetic experiences have also been associated with activity in components of the default mode network, including medial prefrontal cortex and posterior cingulate cortex, suggesting that aesthetic appreciation may involve autobiographical memory, self-referential cognition, and reflective meaning-making rather than mere sensory preference (Vessel et al., 2012; 2019; 2023). These findings support the view that aesthetic experience reflects an integrative brain state in which perceptual processing, emotional appraisal, valuation, and reflective cognition interact.

Another important aspect of aesthetic experience concerns its embodied and affective dimensions. Aesthetic responses are frequently accompanied by emotional reactions and bodily responses, including autonomic changes, chills, and feelings of awe or fascination, reflecting the integration of sensory processing with limbic and interoceptive systems involved in emotional awareness and valuation (Brattico & Pearce, 2013). In this sense, aesthetic experience is not only a matter of perceptual judgment, but also a mode of emotionally charged engagement through which sensory perception, bodily feeling, and meaning-making converge.

Music provides a particularly informative domain for understanding aesthetic engagement. Because musical stimuli unfold over time and simultaneously engage perceptual, predictive, emotional, mnemonic, and evaluative processes, they offer a powerful model for investigating the temporal and affective dynamics of aesthetic experience. Electrophysiological evidence indicates that aesthetic judgments of music can be dissociated from non-aesthetic structural judgments and are associated with late ERP components reflecting higher-order evaluative processing (Brattico et al., 2010). Functional neuroimaging studies further indicate that neural responses associated with perceived emotional expression in music can be dissociated from those underlying aesthetic liking, indicating that emotional and reward-related processes rely on overlapping but partially distinct neural systems (Brattico et al., 2016).

Musical aesthetic experience has been theorized as unfolding through temporally ordered interactions among perceptual, emotional, and evaluative stages (Brattico, Bogert, & Jacobsen, 2013). It arises from the interaction between bottom-up sensory processes and top-down interpretative mechanisms, with the former reflecting the neural progression of sensory pleasure and the latter involving conceptual, contextual, and individual factors shaping musical enjoyment (Brattico, 2015), within a broader framework emphasizing the integration of perceptual, affective, and reward-related systems in aesthetic responses to music (Brattico, 2019). Naturalistic paradigms have shown that timbral, tonal, and rhythmic features dynamically modulate distributed auditory, limbic, and frontal activity during extended music listening (Alluri et al., 2012; Brattico & Alluri, 2021), and that dynamic functional connectivity during naturalistic listening is further shaped by musical expertise, with musicians showing stronger sensorimotor-cognitive integration and non-musicians greater reliance on emotion- and engagement-related network states (Dai et al., 2025). Recent work has linked musical beautiful passages to orbitofrontal engagement within a naturalistic free-listening context (Brattico et al., 2025).

Individual variability in music-induced pleasure has also been linked to variability in structural brain connectivity. Stronger white-matter connectivity between auditory cortices and reward-related regions, particularly pathways linking the superior temporal gyrus with medial prefrontal areas, has been associated with greater sensitivity to musical reward, suggesting that the intensity of aesthetic responses to music depends in part on the integrity of auditory–reward pathways (Sachs et al., 2016). Together, such findings are important because they move beyond highly simplified laboratory paradigms and suggest that aesthetically meaningful music listening in everyday contexts may recruit broad neural systems involved in sensory processing, affective evaluation, and cognitive integration. Therefore, these models are particularly relevant for health and well-being, as they imply that music does not influence listeners only through simple hedonic pleasure, and they also provide a neurobiological basis for the idea that aesthetic engagement with music can differentially support positive emotional experience across individuals.

In fact, aesthetic engagement with music has been proposed to support psychological resilience not only by eliciting pleasure, but also by facilitating emotional processing, reflective self-engagement, and meaning-related cognition (Taruffi & Koelsch, 2022). Emerging work has also suggested that musical aesthetic experiences may have translational relevance for emotional health and mental well-being, including in applied and therapeutic contexts (e.g., Pradeep et al., 2026). In this sense, music is particularly important within neuroaesthetics because it provides one of the clearest examples of how aesthetic experience may extend beyond appreciation per se and contribute to broader domains of psychological functioning.

More generally, much of the strongest evidence linking aesthetic and artistic engagement to health outcomes derives from the broader fields of arts-and-health and cultural engagement research, which include observational studies, intervention studies, and large-scale evidence syntheses on artistic participation and health (Fancourt & Finn, 2019). In particular, the World Health Organization scoping review synthesized more than 3,000 studies and concluded that engagement in the arts may contribute to health promotion, disease prevention, and the management of mental and physical health conditions across the lifespan, although the strength of evidence varies across domains and study designs (Fancourt & Finn, 2019). This broader perspective situates neuroaesthetic research within a translational perspective in which aesthetic experiences are understood not only as objects of basic neuroscience, but also as potentially meaningful contributors to health and well-being.

Additional evidence syntheses suggest that participation in artistic and cultural activities may be associated with reductions in symptoms of anxiety and depression, improvements in quality of life, and broader enhancements in psychological well-being (Daykin et al., 2018). Population-based and longitudinal studies have further shown that cultural engagement in later life is associated with better mental and social well-being, lower risk of incident depression, and even lower subsequent mortality risk after adjustment for major socioeconomic and health-related covariates (Cuypers et al., 2012; Fancourt & Steptoe, 2019; Tymoszuk et al., 2019). Overall, these findings suggest that aesthetic and cultural engagement may represent a meaningful pathway through which enriching experiences support psychological vitality and quality of life, particularly in ageing populations.

These health-related effects are plausibly linked to the capacity of aesthetic experiences to recruit neural systems involved in reward processing, emotional regulation, attention, and self-referential meaning-making. Aesthetic emotions such as awe, fascination, and beauty have been argued to support psychological flourishing by eliciting positive affect, attentional engagement, and reflective forms of cognition that can contribute to emotional regulation and well-being (Wang, 2024). Reviews of the literature further suggest that aesthetic experiences may promote emotional awareness, reduce stress, and support positive affective states through interactions between perceptual and emotional brain systems (Mastandrea et al., 2019).

Among the various forms of aesthetically engaging stimuli, natural environments have attracted particular attention within environmental psychology and health research. Natural landscapes are characterized by perceptual properties such as visual coherence, moderate complexity, and soft fascination, which may facilitate attentional recovery and emotional regulation. According to Attention

Restoration Theory, natural environments support recovery of directed attention by engaging involuntary attentional processes, thereby allowing depleted cognitive resources to replenish after sustained mental effort (Kaplan & Kaplan, 1989; Kaplan, 1995). Complementarily, Stress Reduction Theory proposes that exposure to natural scenes can evoke rapid affective responses that promote physiological relaxation and stress recovery (Ulrich et al., 1991).

Recent neuroscientific work has begun to identify neural mechanisms underlying these restorative effects. Exposure to natural environments has been associated with reduced activation in the subgenual prefrontal cortex, a region implicated in rumination and negative affect, suggesting that natural scenes may influence neural systems involved in affective regulation (Bratman et al., 2015). More specifically, dynamic and aesthetically appealing natural landscape stimuli have been associated with neural responses in networks involved in perceptual analysis and affective evaluation, supporting the idea that aesthetic responses to natural environments may contribute to emotional well-being rather than merely visual preference (Isik & Vessel, 2021).

Importantly, restorative responses to nature do not necessarily require direct immersion in outdoor environments. Visual exposure to natural scenes through photographs, videos, or other mediated representations has also been shown to elicit restorative cognitive and emotional effects (Berto, 2005; Stevenson et al., 2018). This point is especially relevant for intervention research because it suggests that aesthetically meaningful environmental content can be delivered even when direct access to natural settings is limited.

Advances in immersive technologies have further expanded these possibilities. Virtual reality allows the creation of multisensory environments that simulate natural landscapes and other aesthetically engaging stimuli with a high degree of perceptual realism. Emerging evidence suggests that immersive virtual environments can promote relaxation, reduce stress, and enhance emotional well-being, including in ageing populations (Anderson et al., 2017; Chirico & Gaggioli, 2019; White et al., 2018). Exposure to natural or aesthetically meaningful environments through VR has therefore been explored as a promising tool for psychological restoration and mood regulation, particularly when direct access to natural settings is limited (Browning et al., 2020; Mattila et al., 2020). By enabling the delivery of enriched sensory environments in accessible formats, immersive technologies offer novel opportunities to investigate how aesthetic experiences may influence emotional states, cognitive processes, and well-being, while also supporting the development of ecologically valid interventions that can be implemented within community contexts.

1.6 Objectives of the present thesis

The present thesis investigates the potential contribution of enriched and aesthetically meaningful experiences to the promotion of healthy ageing and the prevention of frailty. As ageing is increasingly understood as a multidimensional process involving interacting biological, cognitive, psychological, and social changes, non-pharmacological and lifestyle-based interventions have gained increasing attention as potential strategies for supporting resilience and maintaining functional capacity in later life.

In particular, multidomain forms of environmental enrichment have been proposed as promising approaches for mitigating vulnerability associated with ageing trajectories. Among these, musical engagement and exposure to aesthetically meaningful environments constitute complex forms of stimulation capable of simultaneously recruiting perceptual, motor, affective, cognitive, and social processes. Then, it has been assumed that such experiences may influence both neural plasticity and psychological well-being.

Building on this assumption, the present thesis explores how enriched and aesthetically engaging experiences may contribute to supporting adaptive processes in ageing populations. The work focuses primarily on healthy ageing and early stages of vulnerability, considered here as a potential threshold condition within preventive strategies aimed at limiting the progression toward more severe forms of cognitive and functional decline, consistent with a continuum view of ageing that situates early cognitive vulnerability along a graded trajectory rather than as a discrete entity. From this perspective, variability in cognitive functioning, such as that captured through screening measures, can be understood as reflecting different positions along this continuum, rather than distinct diagnostic categories. Studying both cognitively healthy older adults and individuals exhibiting early signs of cognitive vulnerability may therefore provide complementary insights into the mechanisms through which environmental and experiential factors influence resilience and trajectories of multidimensional frailty.

Particular attention is devoted to interventions that can be implemented in ecologically meaningful and community-based contexts, framing two complementary lines of investigation, the first centred on music-based multidomain interventions and their role in promoting experience-dependent neuroplasticity in ageing. Among the musical interventions, choral singing represents a particularly promising activity because it naturally integrates auditory perception, vocal-motor coordination, attentional control, linguistic processing, emotional expression, and interpersonal synchronization. In the intervention examined in this thesis, choir practice constitutes the central activity within a broader multidomain program that also includes complementary forms of stimulation targeting additional domains relevant for healthy ageing. This structure reflects the rationale that combining musical engagement with other forms of cognitive, social, and lifestyle stimulation may enhance the potential for experience-dependent plasticity and functional resilience in later life. To address this objective, the thesis presents both a methodological protocol for investigating biological markers associated with music-based multidomain interventions and an empirical study examining longitudinal changes following sustained participation in a choir-based program.

The second line of investigation explores the role of aesthetically enriched environments in influencing emotional well-being. In particular, the thesis examines the potential of immersive virtual reality environments incorporating music and natural landscapes as tools for delivering aesthetically engaging experiences capable of promoting psychological restoration and positive emotional states.

Accordingly, the main objectives of the present thesis are:

1. To develop and describe a multidomain music-based intervention protocol (MultiMusic) designed to investigate the potential effects of a choir-centered enrichment program on neurobiological, audiometric, and cognitive parameters in older adults, including the exploration of neurotrophic biomarkers such as brain-derived neurotrophic factor (BDNF).
2. To investigate the effects of long-term participation in a choir-based multidomain intervention on a broad range of outcomes related to healthy ageing, including musical abilities, cognitive performance, auditory processing, neurophysiological indices, psychological well-being and multidimensional frailty.
3. To explore the potential effects of immersive aesthetically enriched environments delivered through virtual reality on mood and psychological well-being in older adults with cognitive decline.

By combining the development of a multidomain music-based intervention with empirical investigations of neurophysiological, cognitive, audiometric, and psychological outcomes, alongside exploratory research on immersive aesthetic environments, this thesis aims to advance current understanding of how enriched and ecologically implementable experiences may support adaptive processes in ageing and help mitigate frailty.

Chapter 2: Multidomain Music-Based Interventions and Neuroplasticity in Ageing

The studies presented in this chapter are part of the MultiMusic project, an interdisciplinary initiative developed and implemented in the metropolitan area of Bari, and especially in the Libertà district, a densely populated urban area characterized by socio-economic and cultural disadvantage. The project was embedded within the local community and designed to operate in ecologically valid, real-world settings, with the aim of reaching older adults in contexts where access to structured health-promotion activities is often limited. This territorial grounding represents a core feature of the project, allowing the intervention to be delivered within existing social infrastructures and to engage participants in a familiar and socially meaningful environment.

MultiMusic was conceived as a collaborative effort across a wide network of institutions and stakeholders, reflecting the multidimensional nature of the intervention. The project involved the Department of Education, Psychology, and Communication (For.Psi.Com) at the University of Bari, the Department of Pharmacy–Drug Sciences, and the Geriatrics and Otolaryngology Units of the Bari Polyclinic Hospital, ensuring the integration of psychological, neurocognitive, audiological, and clinical expertise. In parallel, strong partnerships were established with third-sector organizations operating within the local area, including ANAS Puglia, the Centro Servizi per le Famiglie Libertà, and the association MusicaInGioco, which played a crucial role in participant recruitment, community engagement, and the practical implementation of the intervention.

The chapter brings together two complementary studies reflecting the core objectives of the project across different levels of investigation. The first study presents the intervention protocol, developed in preparation for a larger randomized controlled trial (RCT). In this context, particular attention is devoted to the assessment of brain-derived neurotrophic factor (BDNF) through salivary sampling, as a non-invasive and scalable biomarker with emerging potential for capturing experience-dependent plasticity in ecological settings. The second study adopts a longitudinal and multidimensional perspective, assessing cognitive, neurophysiological, and psychosocial outcomes over time in order to characterize intervention-related changes across domains. Together, these studies provide a multilevel and translational account of intervention effects, bridging methodological feasibility, biomolecular innovation, and longitudinal evidence, contributing to a more comprehensive understanding of how complex, community-based interventions may support adaptive ageing, particularly in socially vulnerable contexts.

2.1 The MultiMusic Multidomain Intervention Including Choral Practice: A Study Protocol for BDNF Salivary Biomarkers, Audiometric and Neuropsychological Parameters

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Abstract

Background: Brain-Derived Neurotrophic Factor (BDNF) is pivotal for neuroplasticity and overall brain health, particularly in response to sensory, cognitive, and motor stimuli—such as those elicited by music and sports. Despite encouraging evidence from cross-sectional studies, there is a notable gap in longitudinal research assessing how multimodal interventions might enhance BDNF levels in older adults.

Primary aim: To determine whether a 9-month multidomain intervention—including choral practice along with physical, intellectual, and manual activities—can improve neuroplasticity by increasing salivary BDNF levels and reducing multidimensional frailty (assessed via the Multidimensional Prognostic Index, MPI) in the ageing population. Secondary aim: To investigate the relationship between changes in BDNF levels and outcomes across perceptual, cognitive, audiometric, and psychosocial domains.

Methods: Up to 150 elderly participants will be randomly allocated to one of three groups. The experimental group will participate in a 9-month multidomain program that includes choir practice, manual and physical music-based activities. The active control group will engage in physical, intellectual and manual activities, but not in music, over the same period. The passive control group will participate only in sporadic (non-musical) activities or no activities. Assessments—including salivary BDNF measurements, comprehensive geriatric evaluations, neuropsychological testing, audiometric, and neurophysiological measures—will be conducted at baseline and at the end of the intervention. Participants' daily activity engagement will be documented using diaries.

Expected Outcomes/Implications: We anticipate that the experimental group will show significant increases in salivary BDNF levels along with measurable improvements in neuropsychological performance, audiometric thresholds, and a reduction in frailty. This study aims to provide evidence on the potential of choral and multidomain activity to enhance neuroplasticity and to test non-invasive, saliva-based BDNF assessments as markers of neuroprotection in older adults.

Trial Registration: This study is registered on ClinicalTrials.gov under the identifier NCT06767410 (registration date: 09/01/2025).

Keywords: BDNF, ageing, multidomain intervention, music training, neuroplasticity

Background

An "enriched environment" for a successful ageing

Ageing is a stage of life characterized by psychological and physiological decline, either in healthy or pathological conditions. While 'crystallized' skills (i.e., abilities learned throughout life like autobiographical memories and vocabulary), tend to remain stable, a decline is observed in fluid abilities, like executive functions (Binder et al., 2016). In the brain, ageing is reflected by typical morphologic and functional changes, such as brain matter shrinkage and loss of synaptic strength, that have been related to the ageing process (Taki et al., 2011; Morrison & Baxter, 2012). Few studies suggest that those neuronal changes may be related to the decrease of serum and salivary biomarkers of synaptic plasticity, such as the brain-derived neurotrophic factor (BDNF), a neurotrophin plays a role in maintaining brain function levels over the course of life (e.g., Driscoll et al., 2012; Mizoguchi et al., 2020).

Although irreversible, however, the decline process related to ageing may be slowed down; acting on modifiable risk factors (e.g., sedentariness, obesity, poor social skills, little cognitive stimulation etc.)

may help prevent neurodegenerative diseases (Nazam et al., 2021). Older people can, indeed, engage in various compensatory and adaptive processes to maintain cognitive function. This adaptive process, known as “scaffolding” (Park and Reuter-Lorenz, 2009; 2014), helps individuals cope with neural decline thanks to experience-dependent plasticity, which can be enhanced through cognitive training, continuous social or intellectual engagement, learning new skills, and regular physical exercise. This is possible as experience-dependent neuroplasticity, which is most evident during childhood development, has been demonstrated to persist into adulthood and during ageing (Boyke et al., 2008; Lövdén et al., 2010; Zatorre et al., 2012).

A “successful ageing” occurs when elderly experience a high physical, psychological, and social functioning in absence of major diseases (Rowe & Kahn, 1997). On the contrary, when vulnerable and at risk, they are considered as “frails” (Italian National Institute of Health, 2023). Multidimensional frailty (Pilotto et al., 2020) raises the risk of adverse health outcomes, i.e., falls, hospitalization, institutionalization etc. (Clegg et al., 2013). Multidimensional frailty is closely related to quality of ageing, as they are influenced by common factors and have a mutual impact. In fact, both rely on the domains of health and daily living activities, physical and cognitive operation, social participation and engagement (Urtamo, Jyväkorpi & Strandberg, 2019; Veronese et al., 2022). Consequently, these multiple domains need to be targeted with a multifaceted approach to intervention.

Some authors addressed the concept of “enriched environment” as a strategy to foster neuroprotection in ageing (e.g., Mora, 2013; McDonald et al., 2018; Miranda et al. 2019) with the aim promote active and healthy ageing, for rehabilitation or to prevent neurodegenerative diseases. Such a notion stems from the first animal studies conducted during the last century, where experimental settings were designed to enhance cognitive, social and motor ability and to potentiate learning and memory (Hebb, 1947; Rosenzweig et al., 1962; Diamond et al., 1964). In a broader sense, an enriched environment for humans implies the set-up of contexts and conditions that foster personal development, social, emotional and cognitive enhancement, and general well-being.

One type of intervention akin to an enriched environment is the multi-domain intervention, which can be used to support healthy ageing and reverse multidimensional frailty (Schneider & Yvon, 2013; Murukesu et al., 2020). Multi-domain intervention is commonly defined as a therapeutic or preventive strategy involving two or more domains (e.g., diet, physical activity, cognitive training etc.) to address complex or multifactorial problems. Thus far, it has been found to be particularly effective for healthy elderly (Rosenberg et al., 2018; 2020), able to induce brain changes in individuals at risk of developing Alzheimer's disease (Perus et al., 2022) and to prevent frailty (Huang et al., 2023). Furthermore, the FINGER study by Ngandu et al. (2015) showed that a multidomain intervention can improve and maintain cognitive functioning in at-risk elderly people from the general population.

It is broadly known that engaging in challenging cognitive, physical and social activities can be a trigger for neuroplasticity and prevent multidimensional frailty and cognitive decline (Draganski et al., 2004; Glass et al., 2006; Cotman, Berchtold & Christie, 2007; Gerstorf et al., 2016; Pickersgill et al., 2022). Hence, the simultaneous combination of such a variety of stimuli may be considered a medium to prevent neurodegenerative diseases, despite transfer studies on the topic still being few and inconsistent (Binder et al., 2016). Some evidence on the effects of an intervention combining different domains on serum BDNF levels is recently emerging. For example, an exploratory study by Moon et al., (2022) evaluated the impact of two different 24-week multidomain interventions including physical exercise, dieting and cognitive training, and found an increase in both serum BDNF levels and global cortical thickness for the multidomain group. However, the relationship between multidomain intervention and BDNF levels needs to be explored much more in depth, especially when considering the effects of a multidomain intervention including music training.

Brain-derived neurotrophic factor: Main roles and clinical implications

BDNF is a protein belonging to the neurotrophin family: a group of closely related proteins responsible for the survival, development, and function of neurons in both central and peripheral nervous systems, CNS and PNS (Reichardt, 2006). In the CNS, BDNF is mainly synthesised in regions that participate in perceptual, emotional and memory functions, namely the sensory cortices, hippocampus, frontal cortex, amygdala, hypothalamus, striatum, midbrain and hindbrain (Palasz et al., 2020; Lipsky & Marini, 2007; Suri et al., 2013). In the PNS, it is synthesised in non-neuronal cells, including T- and B-lymphocytes, monocytes (Wang et al., 2021), vascular endothelial cells (Meuchel et al., 2011), smooth and skeletal muscle cells (Matthews et al.,2009), adipocytes (Chaldakov et al., 2009), lacrimal glands (Ghinelli et al.,2003), and in the salivary glands of rats and humans (Saruta et al., 2010; Saruta et al., 2012). BDNF is stored primarily in a bound state within platelets in the blood, liver, and spleen (Walsh et al., 2020).

Discovered in 1982 (Adachi et al., 2014), BDNF plays a central role in many physiological processes including the establishment, strengthening, and maintenance of synaptic plasticity throughout life. Although its level increases during post-natal development, BDNF remains highly expressed in the adult brain and is involved in the regulation of both excitatory and inhibitory synaptic transmission, mainly by modulating in activity-dependent plasticity processes such as learning, and memory (Webster et al., 2006; Karpova, 2014; Kojima et al., 2017; Edelmann & Leßmann, 2018). Recent research has highlighted that the role of BDNF is not limited to brain development and ageing but is also crucial in pathological conditions such as depression, anxiety and neurodegenerative diseases. This has led to a surge of interest in BDNF as pharmacological agent and/or target over the past few decades (Colucci-D'Amato et al., 2020; Gao et al., 2022).

The BDNF gene is located on chromosome 11 and contains 9 promoters that can initiate transcription of 24 transcripts, each containing an alternative 5′ noncoding exon spliced to a 3′ coding exon that comprises the entire open reading frame for the BDNF protein (Palasz et al., 2020). Similarly, to other proteins, the synthesis of BDNF is a sequential process involving the formation of multiple precursor isoforms. A range of factors, including hypoxia, stress, epileptic seizures and ischemia, have been observed to increase BDNF expression (Brigadski & Leßmann, 2020). The preproBDNF precursor (32-35 kDa) is synthesized and folded in the endoplasmic reticulum, then translocated to the Golgi apparatus where the proregulatory sequence is cleaved to form proBDNF (28-32 kDa). ProBDNF can be converted in the trans-Golgi network into mBDNF (13 kDa) by the subtilisin-kexin family of endoproteases, such as furin, or into intracellular vesicles by convertases (Foltran & Diaz, 2016). Extracellular cleavage of proBDNF is mediated by plasmin and matrix metalloproteinases 2 and 9 (MMP2 and MMP9) (Liu et al., 2005; Mizoguchi et al., 2011; Kowiański et al., 2018).

BDNF functions as a paracrine and autocrine factor at both pre-synaptic and post-synaptic target sites. The proBDNF and mBDNF isoforms exhibit activity and stimulate opposing effects through interaction with the p75 neurotrophin receptor (p75NTR) and the TrkB receptor, respectively. These interactions stimulate signalling pathways involved in brain development, synaptic plasticity and protection or regeneration after damage. The balance between proBDNF and mBDNF differs depending on the stage of brain development and the region of the brain. During developmental stages, there is a more significant presence of proBDNF, while mBDNF is predominant in adulthood (Colucci-D'Amato et al., 2020).

A multitude of factors, including age, gender, body mass index (BMI) and gene polymorphism, may exert an influence on the levels of BDNF in brain, peripheral tissues, and blood. This also applies to environmental and hormonal factors such as caloric restriction (Mattson et al., 2003), estrogen levels (Scharfman & Maclusky, 2005) and environmental enrichment (van Praag et al., 2000). The single nucleotide polymorphism rs6265 o G196A located in the BDNF gene promoter, is responsible for a change in the amino acid sequence at codon 66 (Val66Met), resulting in a deficit in BDNF release and a reduction in the efficiency of BDNF-TrkB signaling, which is responsible for memory and LTP (Egan et al., 2003; Hariri et al., 2003; Zhao et al., 2018).

Reduced levels of BDNF have been linked to brain disorders such as Alzheimer's, depression, and schizophrenia, as well as to the physiological ageing process, which highlight its potential role in these conditions (Durany et al., 2001; Shimizu et al., 2003; Karege et al., 2005; Peng et al., 2005; Palomino et al., 2006), although some aspects are still controversial (Laske et al., 2006; Komulainen et al., 2008; Angelucci et al., 2009; Nettiksimmons et al., 2014).Considering the evidence reviewed above, a number of external interventions might boost BDNF expression. As a result, such interventions may represent viable treatment options for cognitive impairments associated with low BDNF levels age-related.

Music Training: A Powerful Catalyst for Brain Health

After a few decades of research, music training, intended as active music making with instruments or voice, is now recognised as a putative non-pharmacological intervention for structurally and functionally inducing neuroplastic processes in childhood, adulthood and ageing (Zatorre, Chen, & Penhune, 2007; Herholz & Zatorre, 2012; Olszewska et al., 2020), making it a useful tool for both prevention and rehabilitation (Hyde et al., 2009; Seinfeld et al., 2013; Bergman-Nutley et al., 2014; Bidelman et al., 2014; Seither Preisler et al., 2014; Schlaug, 2015; Degé et al., 2018; MacAulay et al., 2019; Bugos et al., 2022; Lu et al., 2022; Lippolis et al., 2023; Marie et al., 2023; Schneider et al., 2023). In younger adults, music training results in functional changes such as significant modifications in synaptic strength across cortical networks, affecting various stages of the sensorimotor and auditory pathways as well as higher-order cognition areas (Lappe et al., 2008; Schlaug et al., 2009; Zuk et al., 2014; for a meta-analysis of neuroimaging studies, cf. Criscuolo et al., 2022). For older adults, long-term musical experience throughout life has been shown to act as a protective factor, as it leads to have an enhanced brain volume and cognitive functions in later life (White-Schwoch et al., 2013; Bidelman & Alain, 2015; Sihvonen et al., 2017; Chaddock-Heyman et al., 2021).

Besides duration, intensity of music training (i.e., actual time spent in musical practice) was shown to play a role. A study using diffusion tensor imaging showed enhanced structural connectivity in regions connecting visual, auditory, and motor areas due to the amount of individual musical practice (Ellis et al., 2013). Other studies, both on children and adults, which used intensity to define the music training variable, showed brain changes and increased abilities for those having a higher amount of practice, such as intellectual and verbal abilities (Loui et al., 2019), working memory (Bergman-Nutley et al., 2014), motor and auditory skills (Jabusch et al., 2009; Schlaug et al., 2009; Schneider et al., 2023) and fluid intelligence (Lippolis et al., in preparation). In older adults, intensity of musical practice also leads to an increased processing speed and visuospatial ability (Okely et al., 2023), phonological verbal fluency and reaction time (Wang et al., 2023). In particular, to be highly engaged in choral practice produces improvements in cognitive flexibility, phonemic fluency and sense of social integration (Pentikäinen et al., 2021; 2023).

For elderly, not only instrumental and choral training are beneficial from a cognitive point of view, but also for psychosocial well-being (Johnson et al., 2013; Coulton et al., 2015; Bugos et al., 2016; Biasutti & Mangiacotti, 2019; Pentikäinen et al., 2021; 2023; Zanto et al., 2023). This happens as musical activities help connecting with others, boosting self-esteem and reducing feelings of isolation and loneliness (Varvarigou et al., 2012). Additionally, these activities influence hormone levels, such as cortisol, and affect the autonomic nervous system by decreasing stress-related activation (de Witte et al., 2020).

The positive long-term effects of reiterated music listening and physical activities on BDNF are already known thanks to studies conducted on animals and humans (Chikahisa et al., 2006; Soya et al., 2007; Erickson et al., 2011; Forti et al., 2015; Xing et al., 2016; Schega et al, 2016; Nair et al., 2021), although, for both the evidence on physical activity is much more extensive than on music listening (cf. Brattico et al., 2021). The long-term effects have been studied in neuronal assemblies of animal models: repetitive and intensive electric stimulation induces long-term potentiation (LTP) mediated by NMDA glutamate receptors, leading to an increase of BDNF levels and to strengthening neuronal circuits at the synaptic level. Based on this, it is conceivable that repeated musical training could have similar effects at the cellular level in humans (Brattico et al., 2021). Supportive evidence of this hypothesis comes from a study by Minutillo et al. (2020): higher BDNF plasma levels were found in musicians' brains as compared with non-musicians, providing a neurochemical explanation to the increased brain plasticity found in musicians by many neuroimaging studies (cf. Criscuolo et al., 2022). The picture becomes even more complex when considering the BDNF gene, which regulates the baseline levels of BDNF in humans.

Bonetti et al., (2023) demonstrated that music-derived plasticity in the auditory cortex (as reflected in enhanced brain MMN responses) was obtained only in Val/Val musicians as compared to non-musicians, whereas Met musicians did not differ from non-musicians in their auditory-cortex responses. However, this initial evidence in humans of a relation between music-derived plasticity and BDNF levels is confined to observational cross-sectional studies. To date, no longitudinal studies investigating the effects of music training on changes in BDNF levels.

How do we measure BDNF? A glance back at literature

The potential of BDNF as a biomarker in the diagnosis and evaluation of treatment outcomes for various diseases, including those associated with the ageing process, is currently under wide investigation. Therefore, the availability of kits that permit the accurate and reproducible assaying of BDNF is paramount. The concentration of BDNF varies throughout lifespan, with generally higher levels observed during childhood compared to adulthood. However, BDNF levels tend to be higher in early adulthood (Webster et al., 2006), with a gradual decrease observed over time. Lommatzch and colleagues (2005) stratified average plasma levels of BDNF according to age group. In young adults, approximately 100 pg/ml was found (n = 45; age range 20–33 years). In middle age, the average plasma BDNF level was approximately 80 pg/ml (n = 59, age 34-47 years). In the elderly, the average plasma BDNF level was approximately 50 pg/ml (n = 36, age 48-60 years). Furthermore, a study of 5,104 adults aged 65-97 years demonstrated an average serum BDNF level of 21 ng/ml (SD = 5.4 ng/ml), exhibiting a decline of approximately 0.1 ng/ml for each additional year of age (Shimada et al., 2014). BDNF can permeate the blood-brain barrier in both directions, thereby exhibiting a bidirectional correlation between peripheral and cerebral BDNF levels (Ikenouchi et al., 2023).

The quantification of BDNF in whole blood, plasma and serum can be performed with an enzyme immunoassay (ELISA). It is recommended that serum is used as the preferred sample, as BDNF is approximately 100-fold higher than in plasma. Furthermore, plasma concentration is influenced by the handling of blood samples due to the presence of platelets, which store BDNF and can secrete it. Indeed, during the process of blood collection, the stress (or the damage) generated by the needle may cause platelet degranulation with the consequent secretion of BDNF. Additionally, the time taken by the operator to separate the plasma, or changes in ambient temperature, may also induce platelet degranulation and a significant release of BDNF into the plasma fraction.

Additionally, the release of BDNF from platelets may be influenced by individual factors, such as age, disease, or drug treatment. Consequently, the quantification of BDNF from plasma is susceptible to variations in sample preparation procedures and is challenging to reproduce among different operators (Polacchini et al., 2015). The strict adherence to standard operating procedures is therefore required for reliable plasma determinations. Similarly, the measurements of BDNF in whole blood samples is challenging. In fact, although results comparable to those obtained in serum can be obtained, the preparation of blood samples involves a methodological step of cell lysis, which introduces an additional variable (Elfving et al., 2010). In general, the process of blood sampling in certain patient groups, such as children and the elderly, can be perceived as stressful and time-consuming. Therefore, the development of a less invasive procedure for the determination of BDNF concentration would be advantageous.

A potentially viable alternative is salivary BDNF. Saliva sampling offers several advantages. Firstly, it is a minimally invasive procedure that allows a reasonable amount of sample to be collected, also multiple times. Secondly, although it is preferable for the procedure to be rigorously performed by experienced personnel, it may be performed also independently, making it accessible to a wider range of patients, including children and elderly people (Pandit et al., 2024) In support of this approach, whole saliva is a complex mixture of secretions from salivary glands and blood components that pass through intercellular spaces by transcellular or paracellular diffusion into saliva. Consequently, many substances present in blood are also present in saliva, including epidermal growth factor, nerve growth factor and insulin growth factor (Jasim et al., 2018; Kagami et al., 2000). Recent studies have demonstrated the presence of BDNF in human saliva using immunoblotting and enzymatic digestion (Mandel et al., 2009; Mandel et al., 2011). Then another main topic of the study will be to take advantage of the available methodological approach for detecting salivary BDNF (Mandel et al., 2011) in the population under study.

Rationale and aims of the study

Ageing is a delicate phase of life, with important physical, cognitive and functional changes. In Italy, there is a high prevalence of secondary ageing, due to poor prevention and poor early intervention on modifiable risk factors (Guastafierro et al., 2020). However, with the lengthening of human life span, old age is now seen not only from the perspective of decline. It is instead considered a stage of life worthy of being kept active and meaningful. Therefore, an increasing number of programmes are being implemented for the psycho-physical well-being of people even in later life (Poscia et al., 2017; Barbabella et al., 2022).

With the present study, we aim to examine the effectiveness of a non-pharmacological and multi-domain intervention including participation in choir for musically naïve healthy elderly, while adapting the methodological approach for extracting BDNF from saliva to our sample. Salivary BDNF was selected as our primary neuroplasticity biomarker for music training interventions. For our purposes, it is an optimal biomarker of central neuroplastic processes induced by auditory and physical stimulation due to its unique role in activity-dependent plasticity within auditory and sensorimotor neural circuits (Gómez-Pinilla et al., 2007; Sly et al., 2012; Vermehren-Schmaedick et al., 2015; Pisani et al., 2023).

Hence, BDNF's direct, synapse-specific modulation of neural networks makes it a perfect marker to detect functional, adaptive changes in the nervous system. In contrast, a marker such as Insulin-like Growth Factor-1 (IGF-1), which was found to be unrelated to exercise intensity compared to BDNF (Habibian & Valinejad, 2017), better serves to broadly support neural growth and metabolic processes (Dyer et al., 2016). Likewise, Nerve Growth Factor (NGF) is primarily linked to peripheral and cholinergic neuron survival (Levi-Montalcini, 1987; Korsching, 1993), thus it does not directly contribute to the rapid synaptic modifications that underlie experience-dependent plasticity, while the Vascular Endothelial Growth Factor (VEGF) mainly promotes angiogenesis and vascular support (Senger et al., 1983; Ferrara & Henzel, 1989). Compared to other similar markers, the activity-dependent release of BDNF mirrors the dynamic perceptual, cognitive and physical demands of music training, making it a more directly relevant indicator of training-induced neuroplasticity.

Based on this compelling evidence, our main objective is to test whether a reiterated, intensive participation in several motor, manual, intellectual and musical activities can enhance BDNF levels in older adults, along with neuropsychological and neurophysiological outcomes including risk of multidimensional frailty. Our idea is that continuity and assiduity in attending enriching contexts, from both cognitive, social and physical point of view, can promote neuroplasticity and contrast multidimensional frailty in ageing, and that this is linked to perceptual, cognitive and socio-psychological well-being.

Research hypothesis

We intend to exhibit for the first time that a multi-domain intervention including choir can counteract cognitive and perceptual-auditory decline and frailty in ageing, supported by BDNF-related neuroplastic processes. Specifically, we hypothesize to find significantly increased BDNF levels over time in the intervention group, hand in hand with cognitive and perceptual improvement (measured with performance tests and questionnaires) with respect to a control group carrying out only sporadic activities. In the case of the individuals scoring higher in multidimensional frailty, we identify an improvement in the slowing of cognitive and perceptual decline over the course of time.

Methods

The trial is registered in Clinicaltrials.gov public registry under the ID NCT06767410 (registration date: 09/01/2025). We adopted rigorous research protocols to ensure the validity of the results. For the sake of brevity and clarity, we summarized in Table 1 the most relevant information and details inspired by WHO guidelines (World Health Assembly, 2022). The study, including the BDNF sample collection procedures, has already been approved by the institutional review board of the department of Education, Psychology and Communication of the University of Bari (reference number: ET-23-27). A unique ID will be created for each participant to ensure the anonymity of data. Moreover, due to the wide range of measurements envisaged for a comprehensive evaluation of participants, an interdisciplinary collaboration was setup between the Department of Education, Psychology, Communication and the Department of Pharmacology at the University of Bari, as well as with the Otolaryngology and Geriatrics Units of the Policlinic consortium hospital of the University of Bari.

Table 1. Information about the study

Data category	Information
Approving entity	Ethics Committee of the department of Education, Psychology and Communication of the University of Bari
Reference number	ET-23-27
Source of monetary support	This research was supported by EU funding within the MUR PNRR A novel public-private alliance to generate socioeconomic, biomedical and technological solutions for an inclusive Italian ageing society (project n. PE00000015, AGE-IT).
Primary sponsor	University of Bari
Contact for queries	Prof. Elvira Brattico: elvira.brattico@uniba.it
Title	A MultiMusic multi-domain intervention for the prevention of multidimensional frailty in healthy ageing
Countries of recruitment	Italy
Problems studied	Counteract and prevention of cognitive decline
Intervention (s)	Group 1: multi-domain intervention combining continuous musical, manual and physical music-based activities
	Group 2: multi-domain intervention combining continuous manual, physical and intellectual activities but no music Group 3: non-musical sporadic activities or no activity
Time of measurement	9 months + another measurement foreseen in 8/12 months
Inclusion criteria of participants	Age ≥ 65
	Living independently
	No previous formal musical experience
	No severe cognitive and functional impairments
Study design	Current non-randomized feasibility study with subsequent RCT implementation
Expected first enrolment date	November 2023 (psychological and neurophysiological/audiometric measurements) Jan 2026
Target sample size	Minimum of 144 up to 150
Recruitment status	Anticipated
Expected end of study	Dec 2027
Potential risks	Procedures are non-invasive and ensure a total absence of risk
Primary outcomes	Difference in BDNF levels over time between the groups (i.e., those who participate regularly in group activities, including choir, will increase their BDNF levels compared to those who engage in non-musical activities or engage only sporadically or not at all, in relation to individual frailty scores)
Secondary outcomes	Correlation between higher BDNF levels with better cognitive performance and perceptual abilities, as well as a positive link between BDNF and physical activity, and mediation effects of music contributing to improved psychological well-being through the increase of BDNF levels.

Design and timeline

The present study will take place in Bari, Southern Italy. A pilot non-randomized feasibility pilot study of the multi-domain intervention on a small sample is currently underway, with a randomized controlled trial (RCT) planned for subsequent implementation which will maintain the same features apart from random assignment of participants to the three groups. The RCT study employs a pre-post research design on the effects of a multi-domain intervention and includes an active group and a control group. The first group carries out a repeated, regular series of various musical, physical and manual activities, while the second one engages in no musical activities and the third group does not undertake any activity. Each participant is tested 9 months after the first measurement. In addition, another measurement time is planned after a further 8-12 months. The study design is summarized in Figure 1.

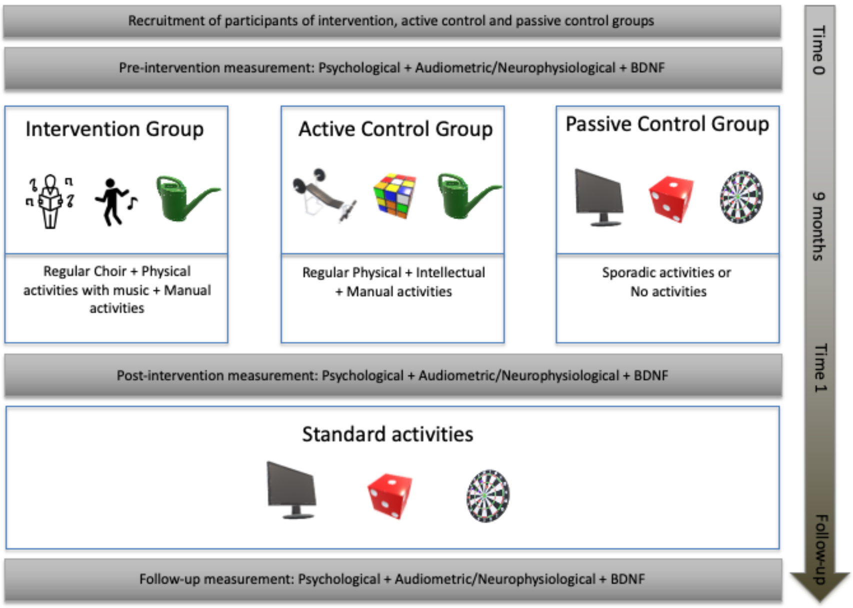

Figure 1. Study design.

For the pilot feasibility study, participants from the two active groups freely choose which activities they want to attend. They have been being recruited since November 2023 through some district service centers for elderly people located both in the metropolitan and suburban areas. Also, for the RCT, we will reach elderly participants via district service centers, but we will randomly assign them to the three groups. Participants are included in the study if they are 65 or older, live independently, have no continuing and extensive musical experience and do not have severe cognitive or functional deficits.

Intervention

The choral training protocol will replicate the one previously implemented in the feasibility study. At the beginning of each meeting, the teacher starts with body percussion exercises carried out playfully and designed to strengthen body awareness, memory, motor coordination and concentration. Subsequently, respiration exercises and explanations of the functioning of organs impaired in the phonation process are proposed, in order to raise awareness on the use of vocal and respiratory apparatus. This is followed by progressive vocalizations, adapted to the textures of the various vocal sections (basses, tenors, altos, sopranos and treble voices) and, finally, the repertoire is studied, starting with participants' cultural background, **i.e.,** music from popular culture, then gradually enriched it with more complex, multi-voice and more articulate pieces. Songs are also performed with the participation of soloists and also in the form of duets and trios, in dialogue with the choir, to stimulate creativity and improvisation. Simple musical and rhythmic reading exercises are also provided, being participants totally naïve in musical instruction.

As here we deal with a multidomain intervention, participants are engaged in different structured activities according to their group assignment (Tables 2a and 2b).

Table 2a. List of activities

Category	Activity	Frequency	Intensity
Physical	Music-based activities and Gymnastics	Twice a week	1 hour/class
Musical	Choir	Once a week	2 hours/class
Manual	Horticulture	Twice a week	1 hour/class
Intellectual	Mental gymnastics	Twice a week	1 hour/class

Table 2b. Combination of activities among the three groups of participants

Intervention Group	Activities
Multidomain with choir	Musical + Physical with music + Manual
Programs without choir	Physical + Intellectual + Manual
Sporadic non-musical activity / No activity	-

The experimental group will engage in choir practice (as described above), music-based physical activities, and manual activities (horticulture). The active control group participates in standard physical exercise (gentle gymnastics), mental gymnastics and horticulture, while the passive control group receives no intervention. Specifically, beyond the choir practice, the experimental group's activities include:

1. Music-based Physical Activities, incorporating rhythmic movements, dance elements, and musical games designed to enhance physical coordination, balance, and motor skills (2 × 1 hour/week).
2. Manual Activities, involving standardized gardening projects that promote fine motor skills through structured, rewarding tasks (2 × 1 hour/week).

The active control group will receive:

1. Physical Activity: Standard gentle gymnastics sessions (2 × 1 hour/week), focusing on flexibility, balance, and light resistance exercises.
2. Intellectual Activity: Mental gymnastics sessions (2 × 1 hour/week), involving standardized cognitive training exercises targeting attention, memory, problem-solving, and executive functions.
3. Manual Activity: Sessions identical to those in the experimental group (2 × 1 hour/week).

Hence, the only difference between groups is that physical and intellectual activities in the experimental group are based on music, being dance and choir whereas in the active control group do not contain any musical component. Choir sessions are conducted once per week for two hours to accommodate the necessary warm-up, body percussion, and vocal training components, while other activities are scheduled twice weekly for one hour each due to their sustained demanding nature. This different time distribution maintains equivalent weekly engagement (2 hours) and overall intensity across all activities.

Procedures and measurements

Saliva collection and BDNF extraction

Prior to sample collection, participants sign informed consent forms to perform sample collection. They were instructed to abstain from eating, drinking, or brushing their teeth for two hours before the collection, as well as from consuming alcoholic beverages for 24 hours; this, in order to avoid any alteration or contamination of the samples. Right before saliva collection, each participant rinsed their mouth with distilled water in order to remove debris and moisturize the oral mucosa. Following a period of ten minutes, samples were collected via passive autonomous salivation. This approach was adopted in order to prevent the potential for non-specific binding of proteins present in the samples by cotton within the collection devices (ex. Salivettes). This phenomenon can result in a reduction in the concentration of these proteins including BDNF (Mandel et al., 2011). Approximately 1 mL of saliva was collected from each participant in a pre-cooled Eppendorf tube; a protease inhibitor cocktail (v/v 1:500 PMSF, Sigma Aldrich, St. Louis, MO, USA) was added right after collection.

Behavioral measurements

Besides BDNF sample collection, participants underwent a range of behavioral measurements (summarized in Table 3) to assess various domains. Cognitive functions, including visual and sustained attention, task switching, visuoconstructive skills, naming, memory, working memory, calculation, language, fluency, abstraction, and orientation, were evaluated using the Montreal Cognitive Assessment (MoCA) by Nasreddine et al. (2005). Each section includes specific tasks, such as word recall, solving logical problems, drawing figures, and naming objects.

Table 3. Behavioral assessment. List of the standardized tests and questionnaires used for assessing psychological functions of the elderly participants.

Area	Construct	Test	Type	Reference
Cognitive	Cognitive functioning	MoCA	Paper-and-pencil, researcher-administered	Nasreddine et al. (2005)
	Cognitive reserve	CRIq	Paper-and-pencil, researcher-administered	Nucci, Mapelli & Mondini (2012)
	Fluid intelligence	MIQ	Computerized, self-administered	Condon & Revelle (2014); Chan & Kosinski (2015)
Motor	Physical Activity	GPAQ	Paper-and-pencil, researcher-administered	Armstrong & Bull (2006)
Geriatric	Multidimensional Frailty	Selfy-MPI	Computerized, self-administered	Pilotto et al. (2019)
Psychosocial	Well-being	Flourishing Scale	Paper-and-pencil, self-administered	Diener et al. (2010)
Perceptive	Melody Discrimination	MDT	Computerized, self-administered	Harrison et al. (2017)
	Mistuning Perception	MPT	Computerized, self-administered	Larrouy-Maestri et al. (2019)
	Rhythm Ability	RAT	Computerized, self-administered	MacGregor et al. (2024)
	Emotion Discrimination	EDT	Computerized, self-administered	MacGregor & Müllensiefen (2019)

Cognitive reserve was measured with the Cognitive Reserve Index Questionnaire (CRIq) developed by Nucci, Mapelli & Mondini (2012), based on factors such as education level, professional career, and engagement in intellectual and social activities. Physical activity was monitored using the Global Physical Activity Questionnaire (GPAQ) by Armstrong & Bull (2006), which measures the frequency and duration of physical activities in different areas of life, including work, daily walking and recreational activities.

New computerized adaptive tests were used to assess both fluid intelligence (Matrix Reasoning, Condon & Revelle 2014; Chan & Kosinski, 2015) and musical abilities. Specifically, the perceptive tests used were created by the LongGold group: the Melody Discrimination Test (MDT; Harrison et al., 2017), the Rhythm Ability Test (RAT; MacGregor et al., 2024), the Mistuning Perception Test (MPT; Larrouy-Maestri et al., 2019) and the Emotion Discrimination Test (EDT; MacGregor & Müllensiefen, 2019).

In the Matrix Reasoning task (MIQ) participants identify the missing shape in a 3x3 array of geometric shapes, similarly to Raven's Progressive Matrices. The Melody Discrimination Test (MDT) is a three-alternative forced-choice test where participants identify the "odd" melody out of three, based on similarity judgments. In the Rhythm Ability Test (RAT), participants select the image that matches the rhythm they hear, with increasing difficulty and sounds of varying pitches. In the Mistuning Perception Test (MPT): participants distinguish between in-tune and out-of-tune musical excerpts, using a two-alternative forced choice format. In the Emotion Discrimination Test (EDT), participants identify the emotion expressed in a melody (anger, happiness, sadness, or tenderness) by comparing two musical fragments, again in a two-alternative forced-choice format.

For the sake of accuracy in results, attendance of any extra-musical activity and/or individual intensity of choral practice were also assessed. Socio-psychological prosperity was measured using the Flourishing Scale by Diener et al. (2010), while multidimensional frailty was assessed with the Selfy-MPI (Pilotto et al., 2019).

The Selfy-MPI is a self-administered instrument here used in its digital version via the Portable-MPI app (downloadable from the following webpage: https://multiplat-age.it/index.php/it/strumenti) and is based on several dimensions:

1. Functional status and independence, measured respectively by ADLs (Activities of Daily Living) and IADLs (Instrumental Activities of Daily Living), the first one measuring the ability to perform basic daily activities, such as dressing and eating, while the second one assesses more complex activities that require a certain level of independence, such as shopping and managing finances.
2. Mobility, assessed through the MOB, a series of self-assessment questions concerning the ability to move independently.
3. Cognitive condition, measure with brief test assessing temporal and spatial orientation, short-term memory ability, calculation, language and attention.

4. Nutritional status, assessed with MNA (Mini Nutritional Assessment), including information on anthropometric measures (body mass index and weight loss), neuropsychological problems, recent psychological stress, mobility, and decline in food intake.
5. Comorbidity, i.e., assessment of the number and severity of chronic diseases using the CIRS (Cumulative Illness Rating Scale).
6. Medication use, through the Anatomical Therapeutic Chemical Classification code system (ATC classification), where the participant has to state the number of drugs taken regularly to detect the presence of poly pharmacotherapy.
7. Living situation, through questions asking if the participant is living alone or with family members, at home or in RSA.

After the completion of all the sessions an automatic score is computed. Values between 0 and .33 indicate low prognostic frail risk; values between .34 and .66 indicate moderate prognostic frail risk; values between .67 and 1.00 indicate severe prognostic frail risk. The psychological measurements are taking place in the presence of researchers and qualified psychologists, in those leisure centers collaborating in the research with a duration of about 1.30 hours per participant. Participants are tested individually or in small groups, often in pairs, alternating between computerized and paper-based tests and allowing for a more efficient use of time and resources. Additionally, participants were given careful instructions before beginning the tasks, as many were unfamiliar with technology, ensuring they were able to complete the computerized procedure independently.

Audiometric measurements

Tone and speech audiometric measurements are also taken (i.e., liminal tonal audiometric test and speech audiometry), including a matrix sentence test to assess patients' speech comprehension under noise conditions, and assessments of ABR and P300 auditory cortical potentials. The audiometric and neurophysiological measurements, as well as the BDNF sample collection, take place at the

Otolaryngology Unit, lasting approximately 30 minutes per participant.

Liminal tonal audiometric test is used to determine the hearing threshold, **i.e.,** the minimum acoustic intensity perceivable by the test subject at the different frequencies of the tonal field. The speech audiometry assesses and establishes verbal intelligibility, **i.e.,** the recognition of words as a sound stimulus with meaning by sending the vocal material (phonemes, logotomes, words, sentences) to the patient in a silent booth.

The Matrix Sentence test is an adaptive test assessing the patient's verbal comprehension under noise conditions, simulating the difficult listening conditions one may find oneself in in everyday life. The patient is asked to repeat 5-word sentences that are presented to him/her together with a disturbing noise (called ‘competition noise’). Likewise, the perceptive computerized tests here used, this task is adaptive as that after each response the software automatically makes the next sentence ‘easier’ or ‘harder’ to understand. In this way, the test tends towards a precise volume of words and a precise volume of noise for which the patient will understand approximately 50% of the words presented. The result is a value known as the Signal Reception Threshold (SRT), which reflects the difference between the word volume and the signal volume at which the test reaches convergence.

The auditory evoked potentials of the brainstem are evoked by means of an acoustic stimulus (click) of short duration (100 μs) presented independently to each ear through earphones with foam ear tips at a level of 90 dBnHL at a rate of 11.0/s. Filters were set at 100 and 3000 Hz. The resulting tracing,characterized by five waves, represents the activity of the auditory pathway between the most distal part of the auditory nerve and the inferior quadrigeminal tubercle. Finally, P300 auditory cortical potentials are measured as part of the auditory assessment. Using the same electrode montage as used in ABR, burst stimuli were used, 50-ms tones presented at a rate of 1.1/s to the right ear through an insert phone. For each condition, the standard stimulus was presented with 80% probability and the target stimuli was presented randomly with 20% probability.

Current status of the study

We have completed a preliminary feasibility study employing a quasi-experimental design. This initial phase allowed us to assess and refine our multidomain intervention approach—including choral practice, music-based physical activities, and manual activities—as well as to optimize our procedures for collecting BDNF samples.

Key insights from the feasibility study include the importance of achieving a well-balanced sample in terms of group sizes and gender distribution. Such balance is crucial to enhancing the internal validity of our comparisons between the experimental group (engaged in music-based and other activities) and the control groups (active and passive), thereby minimizing potential confounding influences. For instance, the literature suggests that BDNF expression may differ between males and females due to hormonal influences (see Chan & Ye, 2017); hence, balancing gender proportions ensures that observed effects are more reliably attributable to the intervention itself rather than to underlying demographic differences.

In preparation for the upcoming RCT, we are now finalizing protocols to ensure that all relevant demographic factors—including health conditions and regular medication use—are carefully monitored. This meticulous approach in the feasibility phase informs our strategies for the RCT, aiming to enhance the robustness and generalizability of conclusions regarding the impact of the intervention on BDNF levels and associated neuroplastic processes.

Analysis

Analysis of BDNF levels

We conducted an initial preliminary assessment to verify the availability of commercial ELISA kits with a detection range compatible with the expected salivary concentration of BDNF (median = 618 pg/mL). However, this evaluation did not yield positive results. In the absence of commercially available ELISA kits that are specifically validated for measuring BDNF in saliva, several studies have attempted to adapt ELISA kits that are validated for plasma and serum for quantifying salivary BDNF. However, the significantly lower levels of BDNF in saliva compared to circulating concentrations mean that these kits cannot detect values above their minimum sensitivity threshold. Similarly, our attempts to use commercially available kits were unsuccessful.

Mandel and colleagues (2011) developed a sandwich ELISA protocol optimised for the measurement of BDNF in saliva. We therefore adopted the proposed methodology; however, due to the discontinuation of the anti-BDNF mouse monoclonal antibody (35928.11, Calbiochem®), it was not possible to replicate the original protocol faithfully. We are currently looking for an alternative antibody, as preliminary experiments using the anti-BDNF antibody SAB1402127 (Sigma-Aldrich) produced unsatisfactory results. Should this approach prove ineffective, alternative quantitative methods will be considered.

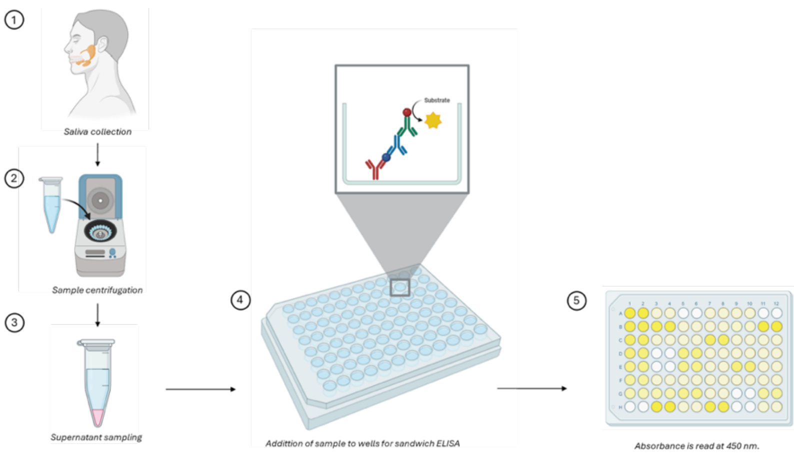

Figure 2. Schematic representation of the experimental protocol: (1-3) The saliva sample will be acquired, processed and stored as described (4) The sample will be added to a microtiter plate that has an antibody specific for BDNF immobilized on the bottom. The analyte present in the sample will bind to the antibody. A second antibody, conjugated to an enzyme, will bind to the analyte captured by the first

antibody. Subsequently, a substrate for the enzyme will be added. The reaction between the enzyme and the substrate generates a colorimetric signal, which is proportional to the amount of analyte present in the sample. (5) The absorbance is then measured using a spectrophotometer, and the results are compared with a standard sample in order to quantify the analyte (Image was created with Biorender free version).

Power analysis

We calculated that a minimum of n = participants per cohort was needed through an a priori sample size analysis using G*power software (version 3.1.9.2, available online for free). We performed a F test for 'ANOVA: Fixed effect, omnibus, one-way' to determine the required sample size for each of the three groups based on α, power, and effect size. Based on our power analysis, assuming an effect size of 0.3, the subsequent fully powered study would require a total of 144 participants (48 per group). The critical value for significance testing would be $F(2, 141) = 3.06$, $\alpha = .05$ (see Table 4 and Figure 3).

*Table 4. A Priori Power Analysis. Power size analysis conducted with G*Power*

					User Defined		
N_1	**N_2**	**N_3**	**Critical F**	**df**	**Effect Size**	**Power**	**α**
48	48	48	3.06	2	0.30	0.90	0.05

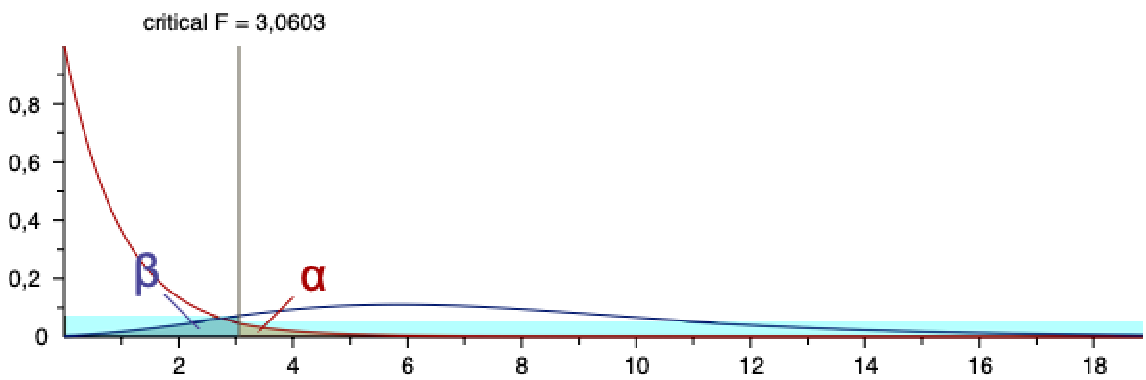

Figure 3. Power analysis.

Statistical analysis

To evaluate differences in BDNF levels and other measurements between elderly individuals who participate regularly in group activities, such as choir and other activities, versus those who engage sporadically in non-musical activities, we will conduct comprehensive statistical analysis by means of Jamovi software as well as R Studio. Specifically, given the pre-post design and the complexity of our study, we will use mixed-effects models to analyze the data. These models will account for both fixed effects, such as group membership, age, frailty score, and time, as well as random effects to capture individual variability. We will also include residential areas (urban vs. suburban) as a random effect to explore its potential influence on the outcomes. Mixed-effects models will be also used to examine how changes over time interact for each group with the different variables, including the effects of physical activity patterns, acoustic awareness, level of socio-psychological prosperity and multidimensional frailty. Mediation analyses will be also computed to deepen how the regular participation in group activities influence the outcomes of interest, thus supporting the direction of causal relationships. This comprehensive approach will allow us to see if and how all these variables are interrelated, and to assess the impact of regular versus sporadic activities, while also considering how perceptual levels and lifestyle may affect BDNF levels and related outcomes in relation to individual frailty conditions.

Dissemination

Results of this research will be presented at national and international conferences focusing on geriatry or music research and published in a peer-reviewed journal.

Data monitoring and management

A data monitoring committee is not considered as necessary because the study is of minimal risk. The behavioral and audiologic data from the digital questionnaires will be stored in an encrypted folder and the paper-and-pencil tests and questionnaires will be preserved in a locked cabinet and entered in an electronic file also stored in an encrypted folder. All saliva samples were kept on ice during the procedure and then centrifuged at 4000 rpm for 15 minutes at 4°C; the supernatant is then aliquoted and stored at -80°C until the assay is performed. The access to these data will be permitted to the research members only. Any adverse events will be reported by filling in the appropriate form. The data that support the findings of this study will be openly available on Zenodo repository.

Expected outcomes

Based on our study design and previous literature, we expect to find significant results with regard to both the primary and secondary outcomes, with a special attention on BDNF being a measure under-investigated in the literature. Other primary and secondary outcomes related to cognition, auditory functions and multidimensional frailty are mentioned but will be treated in more detail in the future reports of this study.

The primary outcome on which we concentrate here is the BDNF level in the saliva. Overall, we expect that the multidomain intervention including choral practice will yield the highest increase in BDNF levels, given its multimodal stimulation of sensory, motor, and cognitive networks. The multidomain intervention without musical components is also anticipated to elevate BDNF, although potentially to a lesser degree, while the passive group is expected to show minimal or no significant changes in BDNF levels. These effects will be stronger when including aspects of individual multidimensional frailty as a control variable. Previous research suggests that regular engagement in social and physically stimulating activities can lead to higher BDNF levels, particularly in elderly populations, where BDNF is associated with neuroplasticity and cognitive function. It should be noted that the referenced data pertains to BDNF levels in the circulation, rather than in saliva.

To date, no studies have been conducted that provide definitive evidence on the fluctuations of this protein within saliva over the course of an individual's lifetime. Additionally, there is a lack of literature that suggests a correlation between salivary BDNF and circulating BDNF. We hypothesize that the groups with regular participation will show a significant increase in BDNF levels over time compared to the sporadic activity group, reflecting the positive impact on brain health of sustained social and cognitive engagement. Also, we foresee the multidomain intervention as able in contrasting frailty aspects in ageing or at least in keeping them stable over time, i.e., with no further deterioration in participants' conditions.

Additional primary outcomes not related to BDNF focus on cognitive functions. First, based on previous research linking enriched environments to brain changes, we expect an improvement in general cognitive abilities in both active groups, assessed through behavioral tests. Second, we foresee an improvement for the choir group in near and far perceptual skills (assessed through musical, audiometric and auditory evoked potential tests) and hearing-related cognitive skills. In individuals of the intervention group, improvement is intended as decreased decline in the perceptuo-cognitive skills as opposed to controls. A concrete example of the expected changes in hearing-related cognitive skills is the speech-in-noise ability, which involves both basic auditory processing as well as higher-level cognitive functions. Indeed, choral singing seems to be particularly effective in improving speech perception in noise, especially through enhanced pitch discrimination, supporting the idea that even brief participation in a choir can be a valuable intervention to counter age-related hearing decline (Dubinsky et al., 2019).

By consequence, as secondary outcomes we expect to find significant correlation between BDNF levels and cognitive function, particularly in areas such as memory, fluid intelligence and attention. Considering the primary outcomes, we expect, of course, this relationship to be also linked to perceptual abilities. This analysis will be complemented with data coming from the neurophysiological assessment. For example, both latency and frequency of the P300 response, which reflects cognitive processes such as working memory and sensory discrimination, will be analyzed to assess the participants' auditory processing abilities and cognitive function.

Moreover, we await a positive correlation between higher BDNF levels and physical activity, which is a well-known modulator of BDNF expression. Mediation analyses will show whether the increase of BDNF levels can mediate psychological well-being. In fact, we speculate that regular participation in group activities, especially those with a social component like choir, is likely to enhance socio-psychological well-being thanks to increased positive social interactions and stress reduction.

Further exploratory outcomes may involve the effects of control variables such as the area of residence, cognitive reserve and frailty level. We hypothesize urban environments might offer more opportunities for social interaction and engagement in activities, potentially leading to higher BDNF levels. The same applies to high levels of cognitive reserve and low levels of frailty, which we expect to facilitate a more active life in elderly people.

Discussion

This ongoing study aims to evaluate the effects of a multidomain non-pharmacological intervention, including choral music training, on the BDNF levels, and on audiometric and neuropsychological measures in a sample of healthy older adults, assessed also for their multidimensional frailty. Changes in BDNF levels will then be correlated with a number of measures of cognitive, perceptual functioning and psychosocial well-being, to better understand the role of BDNF as a mediator in brain plasticity processes, especially in response to interventions aimed at boosting the cognitive and the social spheres. Moreover, the challenge of our project is to detect these changes in the elderly population, when neuroplasticity tends to be reduced, as a prevention strategy for multidimensional frailty.

In recent years, the idea that stimulating different domains affects brain plasticity and connectivity, especially in ageing, has become increasingly evident (Nyberg et al., 2012; Bamidis et al., 2014; Lee et al., 2023). Indeed, some studies already showed that programmes combining both physical and cognitive activities can slow cognitive decline and reduce the risk of dementia more effectively than interventions focused on only one domain (e.g., Ngandu et al., 2015; Rosenberg et al., 2020). However, real studies investigating the effects of the multi-domain intervention on BDNF levels are currently scarce (with the exception, e.g., of Moon et al., 2022) and addressing this lack is one of the main objectives of this study.

Also, and more specifically, this study would fill the gap of the current absence of pre-post studies investigating the effects of music training on BDNF. Although our design includes only three time points and does not allow for a full temporal series analysis, we believe that even a pre-post intervention—with a follow-up session—can substantially contribute to filling this gap by providing valuable preliminary evidence of the effects of musical training on BDNF levels. This design serves as an important step towards more comprehensive, long-term investigations in future studies. In fact, a number of studies have been conducted so far only on the effects of physical activity on BDNF (e.g., Seifert et al., 2010; Schmolesky et al., 2013; Yeh et al., 2015; Martínez-Díaz et al., 2020) but there is no long-term evidence that music training can increase BDNF levels over time. However, it can be inferred as not only physical activity, but also repeated listening to music leads to higher levels of BDNF (Brattico et al., 2021).

Music training has unique characteristics that allow the simultaneous stimulation of several domains (i.e., perceptual-sensory, cognitive, motor, social, emotional etc.) (Herholz & Zatorre, 2012). Indeed, the reiterated practice of movements is accompanied by auditory feedback, which allows in turn to regulate the following movement (Zatorre et al., 2007). Interestingly, this also applies to choral training between the sound produced by the voice and the motor work of the larynx (Dichter et al., 2018). So that, similarly to sport, playing an instrument and singing activate the body, to the extent that they can provoke changes in the brain. For example, in music players bimanual coordination allows a better connection between the hemispheres (Jäncke et al., 2000; Burunat et al., 2015). This is why the motor domain is considered a ‘’near skill‘’ to music training (Bangert & Altenmüller, 2003) and why playing an instrument can be considered on a par with physical activity (Rodrigues et al., 2010; Wan & Schlaug, 2010).

In the present study, we hypothesize that the musical component enhances BDNF release by engaging sensorimotor circuits in ways that go beyond those elicited by standard physical, manual, or intellectual activities. Musical activities, such as choir practice and music-based physical exercises, not only integrate auditory feedback with precise motor control but also create a unique sensorimotor loop that may promote rapid synaptic modifications underlying experience-dependent plasticity. Given BDNF's unique role in activity-dependent plasticity within auditory and sensorimotor neural circuits (Gómez-Pinilla et al., 2007; Sly et al., 2012; Vermehren-Schmaedick et al., 2015; Pisani et al., 2023), music training's capacity to affect BDNF levels appears especially promising compared to non-musical interventions, as it uniquely combines multisensory integration with precise motor control demands.

In addition to the physiological measures, in this study we are also carrying out perceptual, cognitive and audiologic assessments, as they are very interconnected domains and are also linked to the BDNF. Perceptual skills are crucial for keeping aware of one's surroundings. Especially the loss of hearing, affecting two thirds of the elderly population, has been linked to the progressive reduction of brain volume and subsequent cognitive deterioration (Lin et al., 2011; Peelle et al., 2011; Eckert et al., 2012). Without proper perceptual functioning, stimuli from the environment cannot be processed correctly and this has inevitable, negative implications for the brain. Functional changes in the brain in response to auditory signals are also found to reduce hearing in noisy environments (Campbell & Sharma, 2013), a function associated with cognitive processes (e.g., executive functions) susceptible to neurodegeneration.

As music training is known to be an activity that benefits the auditory system and enhances abilities like auditory discrimination, attention and memorization (Kraus & Chandrasekaran, 2010; Besson et al., 2011; Moreno & Bidelman, 2014; Habibi et al., 2018; Alain et al., 2019) as well as speech-in-noise perception (Zendel et al., 2017; Dubinsky et al., 2019) it is able to keep perceptual and cognitive functions well trained. For all these reasons, we believe that the implementation of choral training, stimulating the memorisation of sounds, intonation seeking, involvement of the body and synchronization with others, both melodically and rhythmically, is a key addition in a non-pharmacological intervention. Although the far transfer of music training is still a debated topic (see, e.g., Sala & Gobet 2017; Schellenberg & Lima, 2024), it is fair to assume that the multimodality of music training can be a resource for the strengthening of a variety of skills.

Thanks to its full cognitive, motor and sensory involvement, we think choir training to be able to contribute to neuroplasticity and go beyond musical abilities, reducing the risk of several impairments and diseases in ageing. Maintaining a good level of neuroplasticity, in turn, makes one capable of being adaptable and keep learning. Also, the social dimension of choir should not be underestimated. While many studies on multidomain interventions focus on home-based methods and neglect the social aspect (e.g., Belleville e al., 2020; Moon et al., 2022), choral training offers a cohesive group experience. This, as seen in previous studies (e.g., Pentikäinen et al., 2021; 2023), leads to an increase in social well-being. Such evidence, together with the strong relationship existing between BDNF and stress (see, e.g., Notaras & van den Buuse, 2020), makes it conceivable that engaging in music may lead to well-being through the increase of BDNF levels, which positive feeds back into psychosocial outcomes. We infer, indeed, that participating in choral training can give an all-round sense of fulfillment, despite the hardships of old age. The results will, further, support the adoption of an active lifestyle, such as participation in choral activities, both in healthy ageing and in neurological conditions (Brancantisano et al., 2019), for contrasting the functional and cognitive decline.

In our study, we set up an observational period of 9 months as a fair period to detect differences between the groups, based on previous literature. Previous studies, in fact, were able to show changes in BDNF levels after a similar amount of time, even if as a result of a different type of training (Seifert et al., 2010; Yeh et al., 2015; Moon et al., 2022). For music training, some studies showed improvements in older adults after 4-6 months, in cognitive functions (Bugos et al., 2007), as well as mood and quality of life (Seinfeld et al., 2013). Also, a few studies already showed that elderly undergoing more intensive music musical activities show improvements in cognitive abilities (Guo et al., 2020; Okely et al., 2023), but more research is needed on this particular topic.

The procedures for analyzing salivary BDNF levels are subject to several limitations as well. Although saliva is an easily collected sample, it is a highly complex matrix that is influenced by numerous factors, including the circadian rhythm of secretion, diet and medication. In order to minimize these variables, we ensured that the sample will be collected at the same daily time range (14:00 p.m. to 17:00 p.m.) and provided careful instructions to the participants on the behavior to adopt prior to sample collection.

In sum, we propose a study protocol for investigating the effects of a multidomain intervention based on choir practice on the older population which implements a robust methodology and a pre-post design. Results will inform health professionals in designing appropriate multidomain interventions for supporting BDNF-mediated neuroprotective processes by means of easy-to-implement, engaging, emotional, and social musical activities such as choir singing.

2.2 Promoting Healthy Ageing through Choral Training: A 9-Month Multidomain Intervention (MultiMusic) Enhances Neural Processing Speed in Community-Dwelling Older Adults

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Abstract

Background

Older adulthood is often accompanied by declines in auditory processing and cognitive functioning, increasing the risk of reduced autonomy and quality of life. Multidomain lifestyle interventions have shown potential to counteract these changes, and choir-based activities represent a promising approach by simultaneously engaging auditory, cognitive, physical, and social domains. However, evidence regarding their feasibility and neurophysiological impact in community-dwelling older adults, particularly those without formal musical training, remains scarce.

Methods

This 9-month quasi-experimental feasibility study involved 54 community-dwelling older adults (mean age = 72.9 years) with no formal musical background. Participants self-selected into a choir-based intervention group, an active control group engaging in non-musical leisure activities, or a passive control group; however, some participants in the control groups were selected from the waiting list for the choir. Assessments were conducted at baseline and follow-up and included measures of global cognition, cognitive reserve, psychological well-being (Flourishing Scale), multidimensional frailty (Selfy-MPI), music perception, pure-tone audiometry, and auditory evoked potentials recorded using a standardized clinical oddball paradigm.

Results

The choir-based intervention was feasible in a community setting. At the neurophysiological level, choir participation was associated with a bilateral, significant shortening of the N2–P3 inter-peak latency, indicating faster auditory–cortical processing. Additionally, through explorative analyses multidimensional frailty, as assessed by the Selfy-MPI, showed a significant reduction in individuals engaging in a higher number of activities, irrespective of group allocation. Similarly, psychological well-being revealed a decrease in flourishing scores in the passive control group relative to the choir group. No changes were observed in audiometric thresholds or music perception measures.

Conclusion

Choir-based multidomain participation is a feasible intervention for community-dwelling older adults without formal musical training and is associated with selective benefits in cognitive reserve, psychological well-being, auditory–cortical processing speed, and multidimensional frailty. These findings provide a foundation for a larger randomized controlled trial aimed at clarifying the cognitive, psychosocial, and neural mechanisms underlying choir-based interventions in ageing.

Trial Registration

The upcoming trial has been prospectively registered on ClinicalTrials.gov (ID: NCT06767410; registration date: January 9, 2025).

Introduction

Ageing is a complex and multidimensional process characterized by biological, psychological, and social changes across the life span. In later adulthood, declines in processing speed, attentional control, and working memory often compromise everyday functioning and independence (Harada et al., 2013; Park & Festini, 2017). Importantly, cognitive ageing trajectories are highly heterogeneous: while some individuals preserve cognitive functioning into advanced age, others experience accelerated decline leading to mild cognitive impairment (MCI) or dementia. This variability highlights the need to identify protective factors and interventions capable of extending healthy cognitive ageing.

Among the most pervasive contributors to late-life vulnerability is sensory decline, particularly age-related hearing loss. Affecting nearly one third of adults over 65 and up to two thirds over 70 (Lin et al., 2011), hearing loss has been identified as a leading modifiable risk factor for dementia (Livingston et al., 2020). Beyond reduced audibility, degraded auditory input increases cognitive load on attentional and memory systems (Peelle & Wingfield, 2016) and promotes social withdrawal, thereby reducing engagement in cognitively stimulating activities (Mick et al., 2014). Neuroimaging evidence further links hearing loss to atrophy in auditory and prefrontal regions (Lin et al., 2014; Uchida et al., 2018), supporting the concept of a "cognitive ear," whereby sensory degradation contributes silently to cognitive vulnerability in ageing (Sardone et al., 2019).

In response, growing attention has shifted toward non-pharmacological strategies to promote healthy and active ageing. Lifestyle-based approaches involving physical activity, cognitive stimulation, and social engagement are consistently associated with better brain health (Colcombe & Kramer, 2003; Hertzog et al., 2008; Kelly et al., 2014). These approaches have been formalized within multidomain intervention models, which acknowledge that age-related vulnerability emerges from the interaction of cognitive, sensory, physical, and psychosocial factors. Large-scale trials provide compelling evidence for this framework: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrated that multidomain programs can slow cognitive decline and reduce dementia risk, particularly in cognitively intact individuals or those at the MCI stage, when neuroplastic potential remains substantial (Ngandu et al., 2015; Rosenberg et al., 2020; Perus et al., 2022). This evidence has informed international initiatives, including WHO guidelines, which identify multidomain lifestyle interventions as central to dementia prevention (WHO, 2019).

This perspective aligns closely with the construct of multidimensional frailty, which conceptualizes vulnerability as the cumulative burden of deficits across multiple domains rather than a purely physical condition (Rockwood & Mitnitski, 2007; Pilotto et al., 2008, 2009). Multidomain interventions are therefore particularly well suited to address the complexity of ageing-related decline and to support cognitive reserve, defined as the capacity to maintain cognitive performance through flexible recruitment of neural resources in the face of brain ageing (Stern, 2002; 2012; Barulli & Stern, 2013).

Within this framework, music has emerged as a particularly promising form of enrichment. Music engagement simultaneously recruits auditory perception, attention, working memory, motor coordination, emotion regulation, and social interaction (Kraus & Chandrasekaran, 2010; Herholz & Zatorre, 2012), leading it to be described as "aerobics for the brain." Converging evidence from developmental, cross-sectional, and longitudinal studies shows that musical training induces structural and functional brain adaptations, including changes in auditory and motor cortices and more efficient sound encoding (Gaser & Schlaug, 2003; Hyde et al., 2009; Habibi et al., 2016; Schlaug, 2015). A large meta-analysis further documented consistent differences in auditory, sensorimotor, interoceptive, and limbic regions between musicians and non-musicians (Criscuolo et al., 2022).

In older adults, music represents a feasible and socially rewarding activity that may overcome adherence limitations observed in other training programs (Davidson & Faulkner, 2010; Creech et al., 2013). Musical engagement has been associated not only with improved auditory skills but also with benefits in executive control, memory, and speech-in-noise perception (Bugos et al., 2007; Bialystok & DePape, 2009; Särkämö et al., 2014; Zendel & Alain, 2012; Slater et al., 2015). Crucially, randomized controlled trials (RCT) provide causal support for these associations: structured musical training has been shown to enhance cognitive and auditory functioning in healthy older adults (James et al., 2014; James et al., 2020), and long-term interventions in musically naïve participants lead to robust acquisition of musical skills with implications for cognitive and psychosocial outcomes (Losch et al., 2024). Together, these RCTs motivate the investigation of music-based interventions in later adulthood, consistent with models of experience-dependent learning and neuroplasticity proposed in the music neuroscience literature (Altenmüller & Schlaug, 2015).

Electrophysiological evidence further substantiates music as a model of neural plasticity in ageing. EEG studies show that musically trained individuals exhibit more precise auditory encoding, greater temporal precision, and resistance to age-related neural slowing (Parbery-Clark et al., 2011; Bidelman et al., 2015; Sanju & Kumar, 2016; Pentikäinen et al., 2022; Bonetti et al., 2024). In oddball paradigms, event-related potentials such as the N2 and P3 index successive stages of auditory–cognitive processing, including stimulus evaluation and attentional updating (Polich, 2007). Ageing is typically associated with delayed latencies, reduced amplitudes, and reduced inter-peak intervals, reflecting reduced processing efficiency (Cheng et al., 2019; Shubhadarshan & Gaiwale, 2024), whereas musical engagement has been shown to modulate these markers, highlighting their sensitivity to experience-dependent plasticity (Brown et al., 2017; Okhrei et al., 2018; Hajimohammadi & Heidari, 2024).

Within the spectrum of music-based activities, choral singing represents a particularly ecologically valid intervention, integrating auditory–motor coordination, cognitive demands, respiratory training, emotional regulation, and structured social interaction. Community-based and neurophysiological studies report cognitive, emotional, and neural benefits of choir participation in older adults, including enhanced auditory encoding and structural connectivity (Pentikäinen et al., 2021, 2022, 2023; Moisseinen et al., 2024, 2025; Särkämö et al., 2025). Nevertheless, longitudinal studies examining choir participation within a multidomain intervention framework and integrating cognitive, audiometric, and neurophysiological outcomes remain scarce, limiting mechanistic understanding of how choir-based multidomain interventions influence ageing trajectories.

Aims of the study

The protocol of this study is described in Lippolis et al. (2024). The present feasibility study had two overarching objectives. First, to evaluate the practicality of delivering a choir-centered multidomain intervention in community settings, focusing on recruitment and retention, participant adherence, and the implementation of a comprehensive measurement battery in preparation for a subsequent randomized controlled trial (RCT). Second, to explore the longitudinal effects of the intervention on cognitive and neurophysiological functioning in community-dwelling older adults. The program was designed to integrate musical, cognitive, physical, and social stimulation, consistent with evidence that multidomain approaches provide the strongest preventive benefits in ageing. By embedding choir participation as the central activity, we aimed to determine whether group singing can foster measurable improvements in cognition and auditory–cortical processing compared with both active and passive control conditions.

Hypothesis

Based on prior evidence linking multidomain interventions and musical engagement to cognitive and neural plasticity, we hypothesized that choir-based training would yield selective longitudinal benefits, outperforming both engagement in alternative non-musical activities and the absence of structured activity. Specifically, we expected improvements in musical abilities, cognitive functioning and concomitant changes in auditory evoked potentials (AEP). Given previous findings of enhanced P2, N2, and P3 responses in musically trained individuals (e.g., Sanju & Kumar, 2016; Brown et al., 2017; Okhrei et al., 2018), we anticipated that choir participation would attenuate age-related slowing in these components (i.e., increased amplitudes and shortened latencies), whereas control groups would show stability or decline.

Moreover, besides absolute peak latencies and amplitudes, we predicted changes in the interpeak measures, as these indices capture the efficiency of information transfer between successive processing stages. Previous research has shown that musical training enhances temporal precision and neural synchrony across auditory–cognitive pathways, reflected in faster or more reliable latencies and reduced temporal variability in auditory evoked responses (Zendel & Alain, 2014; Kraus & Strait, 2015; Liang et al., 2016; Meha-Bettison et al., 2018; Sorati & Behne, 2019). Such evidence makes interpeak dynamics a plausible and sensitive marker of training-induced plasticity.

More broadly, we predicted that embedding choir participation within a multidomain framework would provide synergistic cognitive, motor, and social stimulation, translating into measurable gains in cognitive reserve. At the psychosocial level, we further hypothesized that choir-based participation would be associated with improvements in psychological well-being, as indexed by higher flourishing, and that higher engagement in structured activities would be inversely associated with multidimensional frailty.

In addition to the outcome-related hypothesis, this study was designed as a feasibility investigation to inform a subsequent RCT. Indicators of feasibility included successful recruitment, adherence to choir activities, retention across the 9-months study period and tolerability of the assessment protocol, in line with established recommendations for feasibility studies (e.g., Orsmond & Cohn, 2015; Eldridge et al., 2016). These indicators were evaluated descriptively through participation rates, attrition patterns and completion of the whole assessment.

Methods

This feasibility study was conducted in preparation for a larger randomized controlled trial (RCT), which will replicate the design with an expanded sample size. The upcoming trial has already been prospectively registered on ClinicalTrials.gov (ID: NCT06767410, registration date: January 9, 2025). Ethical approval was granted by the Ethics Committee of the Department of Education, Psychology, and Communication at the University of Bari (reference number: ET-23-27). To safeguard participants' identity, each subject was assigned a unique anonymized ID. Given the broad range of assessments required for a comprehensive evaluation, the study was carried out within an interdisciplinary framework, involving collaboration between the Department of Education, Psychology, and Communication, the Department of Pharmacology, and the Otolaryngology and Geriatrics Units of the Polyclinic consortium hospital of Bari.

Design

The study was conducted in Bari, Southern Italy, and follows a quasi-experimental pre–post design with three arms: a choir-based multi-domain intervention group *"MultiMusic"*, an active control group, and a passive control group (**Figure 1**). Participants were assessed at baseline (T0) and after 9 months (T1). Recruitments and assessments began in November 2023 through local Universities of the Third Age (U3A) and district leisure centers for older adults in both metropolitan and suburban areas of Bari and ended in April 2025. Some participants in the control groups were selected from the waiting list for the choir, rather than being randomly allocated. Although this design may entail baseline imbalances and limits causal inference, it enables the evaluation of the intervention under ecologically valid, community-based conditions. Baseline variables were assessed and statistically controlled to mitigate potential confounding effects.

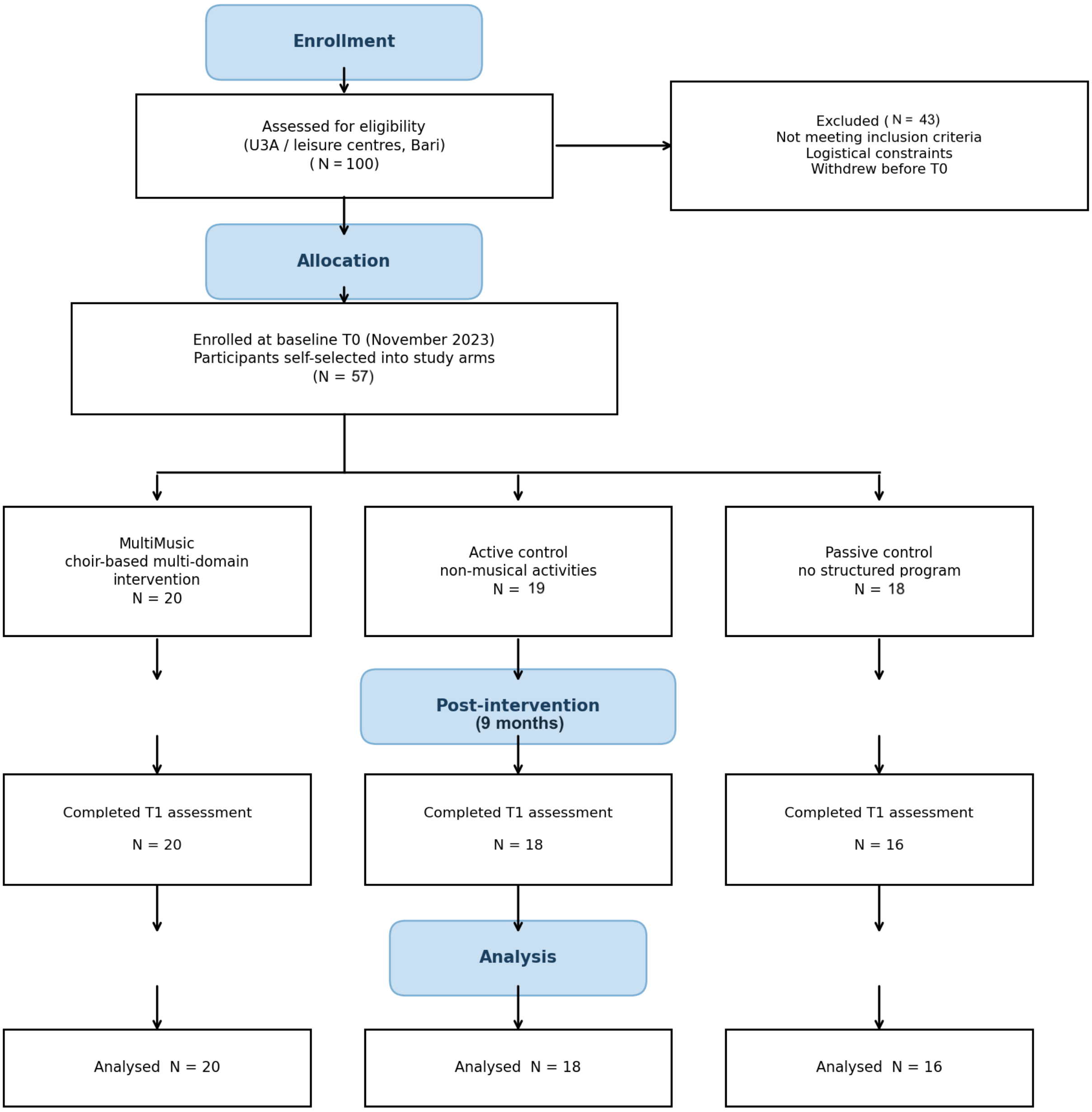

Figure 1. Study design and assessment protocol. As part of this feasibility study, participants self-selected in one of three conditions: a choir-based multi-domain intervention (MultiMusic) group, an active control group (engaged in non-musical activities), or a passive control group (no structured activity). Assessments were conducted at baseline (T0) and after 9 months (T1), covering cognitive, audiometric, and neurophysiological domains.

Participants

Eligibility

Participants were recruited from community-based settings in Bari (Southern Italy) and were eligible for inclusion if they were aged 65 years or older, lived independently in the community, had no extensive prior musical training, and did not present severe cognitive or functional impairments that could interfere with participation in group-based activities or completion of the assessment protocol. Additional eligibility criteria included normal hearing or symmetrical hearing loss, defined as an interaural threshold difference of ≤15 dB at any tested frequency; mild to moderate–severe hearing loss, as determined by the four-frequency pure-tone average (PTA; 500, 1000, 2000, and 4000 Hz) calculated across both ears; and the absence of audiological conditions other than presbycusis.

Descriptives

Tables 1a and 1b contain the general sample descriptives. About 100 participants were initially enrolled in the study. However, nearly half of them discontinued participation due to logistical constraints, i.e., they resided in a municipality located farther from the assessment site and could not reliably travel to the hospital-based evaluations. Among those without major logistical barriers, 59 participants remained eligible to continue the study; of these, three withdrew due to health-related reasons and two were excluded from the dataset following the detection of otosclerosis. Hence, the final sample comprised 54 participants (M_{age}: 72.91; SD = 5.40; 77.7% females) who completed both baseline (T0) and follow-up (T1) assessments, representing those living closer to the assessment center or experiencing fewer logistical barriers to attendance.

Table 1a. General sample descriptives for age and gender

	Gender	**N**	**Mean**	**SD**	**Minimum**	**Maximum**
Age	**female**	42	73.2	5.83	64.6	87.5
	male	12	71.8	3.38	66.2	78.7

Table 1b. General sample descriptives for cognitive functioning (MoCa), cognitive reserve (CRI-q) and fluid intelligence (MIQ) at T0

	Mean	**SD**	**Minimum**	**Maximum**
MoCa	21.74	3.70	14.00	30.00

CRI-q	107.20	23.2	70.00	163.00
MIQ	-2.60	1.26	-4.00	1.39

Participants demonstrated a broad range of cognitive functioning on the MoCA (M = 21.74, SD = 3.70), spanning values typically associated with both normal ageing and mild cognitive impairment. Importantly, Bosco et al. (2017) have shown that Italian older adults generally obtain lower MoCA scores compared to the original validation sample by Nasreddine et al. (2005), with optimal cut-off scores being reduced when distinguishing between normal cognition, probable cognitive impairment, and Alzheimer's disease. Thus, the mean level observed in our sample should not be interpreted as uniformly pathological, but rather as reflecting the expected variability within an Italian elderly population.

Intervention

Participants self-selected into three groups. The group participating in the choir-based *MultiMusic* intervention (N = 20; M_{age} = 72.1; SD = 4.67) was engaged for two hours a week in choral training starting from November 2023. For the sake of clarity and brevity, this group is hereafter referred simply as Choir. At the beginning of each meeting, the teacher started with body percussion exercises carried out playfully and designed to strengthen body awareness, memory, motor coordination and concentration. Subsequently, respiration exercises and explanations of the functioning of organs impaired in the phonation process were proposed, in order to raise awareness on the use of vocal and respiratory apparatus. This was followed by progressive vocalizations, adapted to the textures of the various vocal sections (basses, tenors, altos, sopranos and treble voices) and, finally, the repertoire is studied, starting with participants' cultural background, i.e. music from popular culture, then gradually enriched it with more complex, multi-voice and more articulate pieces. Songs were also performed with the participation of soloists and also in the form of duets and trios, in dialogue with the choir, to stimulate creativity and improvisation. Moments of very simple musical and rhythmic reading exercises are also provided, being participants totally lacking musical instruction.

As here we deal with a multidomain intervention, participants were also engaged in various other non-musical activities targeting complementary functional domains. A comprehensive overview of all activities, including their frequency and intensity, is provided in Table 2a, while Table 2b summarizes the distribution and combination of activities across participants. Activities can be grouped into the following macro-categories:

1. Physical activities: this category includes gymnastics, group dancing, sports (e.g., swimming), postural exercise (pilates or body harmony).
2. Musical activities: choir and body percussion.
3. Manual activities: horticulture, handicraft, tailoring, cooking.
4. Arts/Intellectual activities: theater, mental gymnastics, reading, learning programs (such as history, languages etc.).

Participants in the active control group (N = 18; M_{age} = 74.4; SD = 6.89) engaged in a comparable schedule of non-musical activities, drawn from the same pool of physical, manual, and intellectual programs (e.g., gymnastics, dancing, handicraft, theater etc.), combined according to individual preference and availability. The passive control group (N = 16; M_{age} = 71.0; SD = 3.93) did not take part in any structured program.

Table 2a. List of activities carried out by the participants

Category	Activity	Frequency	Intensity
Physical	Group dance	Once a week	1 hour/class
	Gymnastics	1-3 times a week	1 hour/class
	Postural exercise	Twice a week	1 hour/class
	Sports	1-3 times a week	1 hour/class
Musical	Choir	Once a week	2 hours/class
Manual	Tailoring	Once a week	1 hour/class
	Handcraft	Once a week	1 hour/class
Intellectual	Theatre	Once a week	1 hour/class

	Learning programs	Three times a week	1 hour/class
	Mental gymnastics	Once a week	1 hour/class

Table 2b. Distribution of activities among participants

	Activities	N° Participants
Multidomain with choir	Musical activities + Physical activities	7
	Musical activities + Intellectual activities	1
	Musical activities + Manual activities	1
	Musical activities + Physical activities + Intellectual Activities	4
	Musical activities + Physical activities + Manual activities	5
	Musical activities + Intellectual activities + Manual activities	0
	Musical activities + Physical activities + Intellectual activities + Manual activities	2
Programs without choir	Physical activities	3
	Intellectual activities	10
	Manual activities	1
	Physical activities + Intellectual activities	3
	Physical activities + Manual activities	0
	Intellectual activities + Manual activities	0
	Physical activities + Intellectual activities + Manual activities	1
Sporadic non-musical activity / No activity	-	16
Total		54

Procedures

Participants underwent a comprehensive set of cognitive, musical, audiometric, and neurophysiological assessments. As part of the protocol, participants also provided saliva samples for Brain-Derived Neurotrophic Factor (BDNF) measurement as specified in the registered RCT protocol; ClinicalTrials.gov Identifier: NCT06767410 (for details, see Lippolis et al., 2024). However, these data are not included in the present analyses due to ongoing collection and processing. Data collection took place in district leisure centers seniors and at the Otolaryngology Unit of the Bari University Hospital.

Behavioral and cognitive testing sessions were conducted in the presence of trained researchers and psychologists. Each session lasted approximately 90 minutes per participant and was administered either individually or in small groups (often in pairs). Computerized and paper-based tests were alternated to optimize time and minimize fatigue. Because many participants were not accustomed to technology, researchers provided detailed instructions before computerized tasks, ensuring participants could complete them independently.

Audiometric, neurophysiological, and biological measurements were conducted at the Otolaryngology Unit. Pure-tone audiometry was performed in a sound-attenuated booth, while neurophysiological recordings and BDNF sampling were carried out in dedicated clinical testing rooms. Each session lasted about 40 minutes per participant. Attendance at extra-musical activities and the individual intensity of choir practice were also monitored throughout the intervention using attendance records collected during scheduled activities.

Materials

Primary outcomes

a) Cognitive tests

Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) was chosen as a reliable and common tool to evaluate general cognitive functioning in elderly population, also longitudinally (Cooley et al., 2015; Malek-Ahmadi et al., 2018; Luo et al., 2022; Aiello et al, 2024). MoCa evaluated multiple domains, including attention, task switching, visuoconstructive abilities, naming, memory, WM, calculation, language, fluency, abstraction, and orientation. Subtests included word recall, figure drawing, and object naming.

Matrix Reasoning (MIQ; Condon & Revelle, 2014). The MIQ is a computerized adaptive measure of fluid intelligence, structured as a series of 3×3 geometric patterns with one item missing. Participants must identify the correct piece to complete the matrix, in a task design reminiscent of Raven's Progressive Matrices. Its adaptive algorithm adjusts task difficulty in real time according to participant performance, thereby enhancing both efficiency and precision. To date, the MIQ has been successfully employed in developmental studies with children, showing strong sensitivity to inter-individual differences in abstract reasoning (Lippolis et al., 2022; Müllensiefen, Elvers, & Frieler, 2022). In the present feasibility study, we extend its application to older adults, aiming to test its validity and responsiveness in the context of age-related changes in fluid intelligence, where adaptive tools may offer advantages in reducing fatigue and measurement error.

b) Audiometric Measures

Otoscopy was performed in all participants to examine the external auditory canal and tympanic membrane and to rule out any potential pathological conditions. Pure-tone and speech audiometry were performed using the Madsen® Astera2 audiometer (GN Otometrics), in accordance with European (IEC 60645-1) and international (ISO 389-1) standards, within a sound-treated booth.

Pure-Tone Audiometry

Air conduction (AC) thresholds were measured using insert earphones at frequencies ranging from 250 to 8000 Hz. Bone conduction (BC) thresholds were assessed using a bone vibrator placed on the mastoid for frequencies between 500 and 4000 Hz. The pure-tone average (PTA) was calculated as the mean threshold at 500, 1000, 2000, and 4000 Hz for each ear, reflecting sensitivity in the speech-relevant frequency range.

Speech Audiometry

Speech audiometry was conducted following standard clinical procedures. Speech Reception Threshold (SRT) was measured separately for each ear using standardized lists of disyllabic, phonetically balanced words and was defined as the lowest presentation level (dB HL) at which the participant correctly repeated 50% of the presented items and was used as an estimate of the minimum intensity required for reliable speech perception (Hamid and Brookler 2006). Speech intelligibility was assessed using the Word Recognition Score (WRS), defined as the percentage of correctly repeated monosyllabic words presented at suprathreshold intensity levels (Hamid 2006). Standardized monosyllabic, phonetically balanced word lists were presented at a fixed level above each participant's SRT, typically around 40 dB sensation level. Participants were asked to repeat each word they perceived aloud, and their responses were rated as correct or incorrect to obtain a percentage score. WRS offers an indicator of speech recognition performance beyond thresholds in guaranteed audibility and adds value to threshold-based measures by defining speech comprehension beyond pure-tone sensitivity.

Speech-in-noise

Matrix Sentence Test (speech-in-noise; Kollmeier & Wesselkamp,1997; Puglisi et al., 2015). It consists of syntactically fixed, but semantically unpredictable five-word sentences generated from a 50-word matrix (10 names, 10 verbs, 10 numerals, 10 adjectives, 10 nouns), e.g., "Andrea eats many useful chairs.The purpose of the Matrix Test is to find the signal/noise ratio (SNR) that allows the patient to understand 50% of the words (SRT, Speech Recognition Threshold). The test uses an adaptive procedure that adjusts the speech level while keeping the background noise fixed, enabling accurate estimation of the SRT with a precision of approximately 1 dB. Normative data in normal-hearing listeners report mean SRT of –6.7 ± 0.7 dB SNR (open-set) and –7.4 ± 0.7 dB SNR (closed-set). Puglisi et al., 2015). In the present study, speech intelligibility in noise was measured using the Oldenburg Measurement Applications software (HörTech GmbH, Oldenburg, Germany). Speech and noise stimuli were presented in free-field conditions through a loudspeaker positioned at 0° azimuth with respect to the listener, with a background noise fixed at 65 dB SPL; All audio stimuli were digitally reproduced from the software's internal library.

c) Neurophysiological Measures

Auditory Brainstem Response (ABR) evaluates hearing function and auditory pathway integrity by recording waves generated along the brainstem. Wave I originates from the auditory nerve and represents spiral ganglion cell activity; Wave II is generated by globular cells of the cochlear nucleus; Wave III reflects activity from spherical cells of the cochlear nucleus; and Waves IV and V arise from central brainstem structures, including the lateral lemniscus, inferior colliculus, and medial superior olive (Starr & Hamilton, 1976; Melcher & Kiang, 1996).

ABR was recorded using the Interacoustics Eclipse EP25 system. Four disposable surface electrodes were applied: reference electrodes were placed on the right (M1) and left (M2) mastoids, the active electrode on the upper forehead (Fz), and the ground electrode on the lower forehead, slightly right of the midline (Gnd). Acoustic stimuli were delivered monaurally through earphones (Ear Tone ABR). A click stimulus at 90 dB nHL was presented at a rate of 27.7 clicks per second. The recording window was set to 10 milliseconds. Each participant underwent two trials per ear, with an average of 2,000 responses recorded for each. High-pass and low-pass filters were set at 100 Hz and 3,000 Hz, respectively. Recordings were conducted while participants lay supine on a stretcher and were instructed to relax and remain as still as possible. The absolute latencies of waves I, III, and V were measured, as well as the interpeak latencies I–III, I–V, and III–V.

P300 Auditory evoked potential (AEP): P300 AEPwere recorded monaurally using the same electrodes montage and for ABR, with the exception that the active electrode was moved to the vertex (Cz), to optimize cortical potential detection. Interelectrode impedances were maintained below 5 kΩ. The ER-3A insert earphones were used to provide auditory stimuli. An oddball paradigm was employed, using a 1KHz tone burst as standard stimulus and 2KHz tone burst as target stimulus, with a 20% target probability and 80% standard probability. During the test, each stimulus window lasted 700 milliseconds and from 1 Hz to 20Hz. Participants were instructed to listen to a series of identical auditory stimuli, interspersed randomly with a rare auditory stimulus, and to maintain a mental count of how many rare stimuli they had heard. Participants maintained a supine position throughout the procedure, remaining awake with their eyes open and were instructed to minimize movement, blinking, and swallowing. Oddball-elicited AEP were examined focusing on the P2, N2, and P3 components. The P2 component (150–220 ms) was defined as an early positive deflection indexing sensory–attentional encoding. The N2 component (200–350 ms) was identified as a negative peak associated with novelty detection and cognitive control, whereas the P3 component (300–600 ms) was characterized as a large positive deflection reflecting attentional resource allocation and context updating.

For each component, absolute peak latencies (in milliseconds) were extracted as the time from stimulus onset to the maximum or minimum peak. Component amplitudes (in microvolts) were quantified relative to baseline or, when appropriate, to the preceding trough (Figure 2). In addition to component-specific measures, inter-peak temporal intervals between successive components (e.g., P2–N2 and N2–P3) were calculated to index processing speed and the efficiency of cortical information transmission across successive stages of auditory–cognitive processing. Inter-peak latencies (IPLs) were considered alongside absolute peak latencies to capture not only isolated responses but also their temporal relationships. The P300 was prioritized in the analyses given its established sensitivity to cognitive ageing, attentional modulation, and auditory training effects, while ABR served as a physiological control.

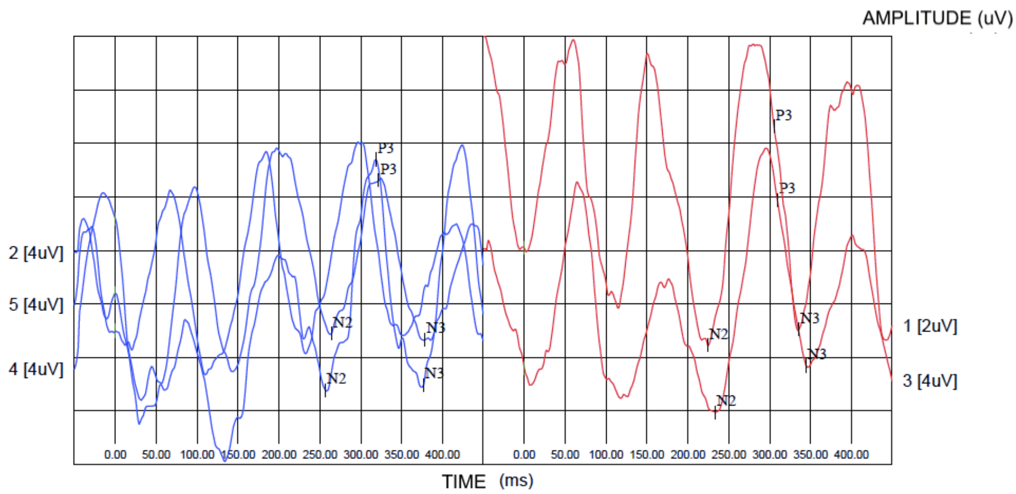

Figure 2. Example waveform of auditory event-related potentials recorded with the clinical system used in the present study, illustrating late cortical components in an oddball paradigm.

d) Multidimensional frailty

Multidimensional frailty was assessed using the Selfy-MPI (Pilotto et al., 2019) via the Portable-MPI app, a digital self-administered version of the Multidimensional Prognostic Index designed to capture frailty as a cumulative vulnerability across multiple domains. The instrument integrates information on functional autonomy in activities of daily living and instrumental activities of daily living (ADLs/IADLs), mobility, cognitive functioning, nutritional status, comorbidity burden, medication use/polypharmacy, and living situation/social context. Responses across domains are combined to compute a single composite frailty score, providing an overall index of multidimensional frailty, with higher scores indicating greater vulnerability.

e) Socio-psychological well-being

The Flourishing Scale (Diener et al., 2010) is an 8-item self-report questionnaire designed to capture key aspects of eudaimonic well-being. The scale evaluates multiple domains of positive psychological functioning, including purpose and meaning in life, quality of interpersonal relationships, self-esteem, competence, optimism, and engagement with life. Participants rated their agreement with each statement (e.g., *"I lead a purposeful and meaningful life"*) on a 7-point Likert scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). Item scores were summed to yield a total flourishing score ranging from 8 to 56, with higher values indicating greater psychological flourishing and overall well-being. In the present study, the total score was used as a continuous measure to assess longitudinal changes in psychological well-being across groups.

Secondary outcomes

a) Musical abilities

The following LongGold computerized, adaptive perceptual tasks were employed for this study:

Melody Discrimination Test (MDT). The MDT is an adaptive three-alternative forced-choice (3-AFC) paradigm designed to measure melodic discrimination (Harrison et al., 2017). On each trial, participants hear three versions of the same melody: two are identical in interval structure (lures), while one contains a single altered note (the "odd" version). The task is to identify the odd melody by comparing the three versions and selecting the one that does not belong to the most similar pair. Task difficulty is manipulated by varying the length of the melodies, thereby increasing cognitive load. In the present study, the MDT included 18 items.

Mistuning Perception Test (MPT). The MPT follows a two-alternative forced-choice (2-AFC) format where each trial presents two renditions of the same pop-music excerpt, one in tune and the other deliberately pitch-shifted (Larrouy-Maestri et al., 2019). The stimuli consist of short segments (6–12 s) with a vocal line accompanied by instrumentation. The "out-of-tune" versions are produced by applying a constant pitch shift to the voice, while the accompaniment remains unaltered. Participants are required to decide which of the two excerpts contains the mistuned vocal line.

Rhythm Ability Test (RAT). The RAT is an adaptive assessment of rhythmic perception and reproduction (MacGregor et al., 2022). Participants listen to rhythmic sequences consisting of high- and low-pitched tones and must select the image that best represents the heard pattern. Visual representations display rows of colored squares, with high tones at the top row and low tones at the bottom. The test increases in complexity across trials, with sequences expanding from 4 to 16 elements (quarter, eighth, and sixteenth notes).

Emotion Discrimination Test (EDT). The EDT is an adaptive task using a two-alternative forced-choice (2-AFC) format to evaluate recognition of musical emotions (MacGregor & Müllensiefen, 2019). For each trial, two variations of the same melody are presented, and participants must choose which one conveys a target emotion (anger, happiness, sadness, or tenderness). Item difficulty varies according to differences in acoustic and structural features across excerpts. For example, anger is typically conveyed by loud amplitude, fast tempo, and high roughness; happiness by fast tempo and high amplitude but lower roughness; sadness by slow tempo and low intensity; and tenderness by acoustic qualities similar to sadness but with subtle expressive cues.

b) Physical activity

Physical activity levels were assessed using the Global Physical Activity Questionnaire (GPAQ), developed by Armstrong and Bull (2006) for the World Health Organization (WHO). The GPAQ is a standardized self-report instrument designed to capture habitual physical activity across multiple domains of daily life, allowing a comprehensive characterization of overall activity patterns in adult and older populations. Specifically, the questionnaire assesses physical activity performed in work-related contexts, transport-related activity (i.e., walking or cycling to and from places), and recreational physical activity, as well as sedentary behavior.

Other measures

Cognitive Reserve Index Questionnaire (CRI-q; Nucci, Mapelli & Mondini, 2012). The CRI-q is one of the most used tools for quantifying cognitive reserve (Nogueira et al., 2022), defined as the reserve of mental resources accrued throughout life. It collects information across three domains, i.e., education, occupational attainment, and social/intellectual engagement, to generate a composite index. The instrument has been applied in numerous ageing studies across populations, including Italian population, to examine protective factors against cognitive decline, showing valid associations with performance on memory, attention, and executive tasks (Caffo et al., 2016; Maiovis et al., 2016; Ozakbas et al., 2021; Cao et al., 2022; Marselli et al., 2024).

Although cognitive reserve was initially listed as a primary outcome in the trial registration, in the final analytic plan it was treated as a baseline control variable rather than a longitudinal outcome. This decision was made on theoretical grounds, because CRI-q reflects accumulated lifetime cognitive reserve rather than a short-term intervention-sensitive endpoint.

Statistical Analysis

All analyses were conducted in R (version 4.3., R Core Team, 2025) using the packages *lme4* 1.1-35, *lmerTest* 3.1-3, *emmeans* 1.9-5, *cocor* 1.4-2, *car* 3.1-2, and *performance* 0.10-4. Baseline normality and variance homogeneity were assessed with Shapiro–Wilk and Levene's tests. Full output and results can be found in the Supplementary Information.

Baseline analyses

A cluster analysis of baseline variables was first conducted to inform domain definition. Specifically, a hierarchical cluster analysis was performed using a correlation-based dissimilarity measure. The distance between subjects was defined as $1-|r|$, where r is the Pearson correlation coefficient computed across the set of variables. This distance metric groups subjects who exhibit similar profiles across variables, regardless of the direction of the correlation. Complete linkage was used as the agglomeration method, and only subjects with complete data on all clustering variables were included (listwise deletion; n = 95).

Audiometric measures clustered with perfect purity (7/7 variables), confirming their coherence as a single domain. Neurophysiological measures formed three clusters, separating absolute peak latencies (P2, N2, P3 bilaterally), inter-peak latencies (IPLs; P2–N2 and N2–P3), and inter-peak amplitudes (IPAs; P2–N2 and N2–P3), while cognitive and musical tasks clustered together, reflecting their strong empirical association.

Based on this structure and theoretical considerations, four operational domains were defined for subsequent analyses: (i) cognitive (MoCA, MIQ, CRI-q), (ii) musical (MDT, MPT, EDT, RAT), (iii) audiometric (pure-tone and speech thresholds, intelligibility, and speech reception in noise), and (iv) neurophysiological, subdivided into latency (absolute latencies and IPLs) and IPAs. Although cognitive and musical variables clustered together, they were analyzed separately given their distinct conceptual targets. For neurophysiology, a parsimonious latency–amplitude subdivision was adopted to avoid peak-specific fragmentation driven by methodological covariance rather than functional distinctions.

For conceptual and statistical coherence, Selfy-MPI and Flourishing scores were excluded from the cluster-based domain structure. As global, integrative outcome constructs indexing multidimensional frailty and psychological well-being, respectively, they were treated as downstream outcomes and analyzed separately using targeted longitudinal models consistent with the multidomain framework.

Baseline group differences across domains were assessed using one-way ANOVAs (Choir, Active Control, Passive Control). Pairwise baseline and T1 correlations within and across domains were computed using Pearson's or Spearman's coefficients, as appropriate. Audiometric scores were directionally aligned so that higher values consistently reflected better performance prior to computing composites (PTA and SRT scores multiplied by −1; intelligibility unchanged). For bilateral audiometric and neurophysiological measures, differences between correlation coefficients were tested using Zou's method (2007). Multiple comparisons were controlled within and across domains using the Benjamini–Hochberg FDR procedure ($\alpha = 0.05$).

Longitudinal analyses

Longitudinal effects were examined using hierarchical linear mixed-effects models (maximum likelihood estimation), with model building guided by step-up comparisons based on likelihood-ratio tests and information criteria (AIC, BIC). Dependent variables included domain-specific outcomes: cognitive outcomes (MoCA and MIQ), musical tasks (MDT, MPT, EDT, RAT), audiometric measures (SRT, PTA, intelligibility, Matrix Test), neurophysiological AEP measures (P3 latency and amplitude), multidimensional frailty (Selfy-MPI), and psychological well-being (Flourishing Scale).

Domain-specific baseline covariates were derived at T0 using principal component analysis (PCA) conducted separately within each domain. For the cognitive domain, the PCA included MoCA, MIQ, and CRI-q, with CRI-q contributing only to the derivation of the baseline cognitive component and not treated as a longitudinal outcome. Variables were z-standardized, PCA was fitted on complete cases, and component scores were computed for all participants, with projection used in cases of partial missingness. Leading PCs were retained based on explained variance and interpretability and entered as baseline covariates. The domain-level PC scores were derived independently from the hierarchical cluster analysis described above: whereas clustering operated on the original observed variables to identify subject subgroups, PCA operated on domain-specific variable sets to reduce collinearity and produce summary scores.

Models included fixed effects of Time, Group, and, when applicable, Side (right/left), with participant-specific random intercepts. Activity intensity and baseline ability were included as covariates to control for individual differences and additional training exposure. Fixed effects and interaction terms (Time × Group, Time × Side, Group × Side, and Time × Group × Side) were entered hierarchically and retained only when supported by a significant likelihood-ratio test ($p < .05$) and a ≥2-point reduction in both AIC and BIC. When significant Time × Group interactions were observed, baseline outcome values were additionally included to adjust for initial between-group differences.

For Selfy-MPI and Flourishing Scale an additional mixed model was set up. Besides testing Group as the main between-subject factor, the activity level (i.e., number of structured activities) was tested in a parallel model to further assess the role of engagement. For descriptive purposes, participants were categorized into four activity-count groups (0, 1, 2, ≥3 activities). For inferential analyses, activity engagement was dichotomized into Low (0–1 activities) and High (≥2 activities), reflecting a distinction between minimal and cumulative multidomain engagement. Estimated marginal means and post-hoc contrasts were obtained using Kenward–Roger degrees of freedom, with Bonferroni correction for multiple comparisons.

Results

Baseline results

At T0, Levene's test of homogeneity of variance showed no significant heteroscedasticity for the measures tested. Seven measures survived the Benjamini–Hozchberg correction applied to the one-way ANOVA. The Choir scored lower than both control groups on CRI-q (pFDR < .001), MoCA (pFDR = .019), and MIQ (pFDR = .029), indicating poorer cognitive reserve and global cognition. In the musical domain, the Choir showed lower rhythmic aptitude on RAT (pFDR = .018). Electrophysiologically, the Choir showed longer left-hemisphere P2 latency (pFDR < .05; higher latency = worse) and higher N2–P3 IPL values bilaterally (right: pFDR < .001; left: pFDR < .01). No audiometric measures survived FDR correction (Figure 3).

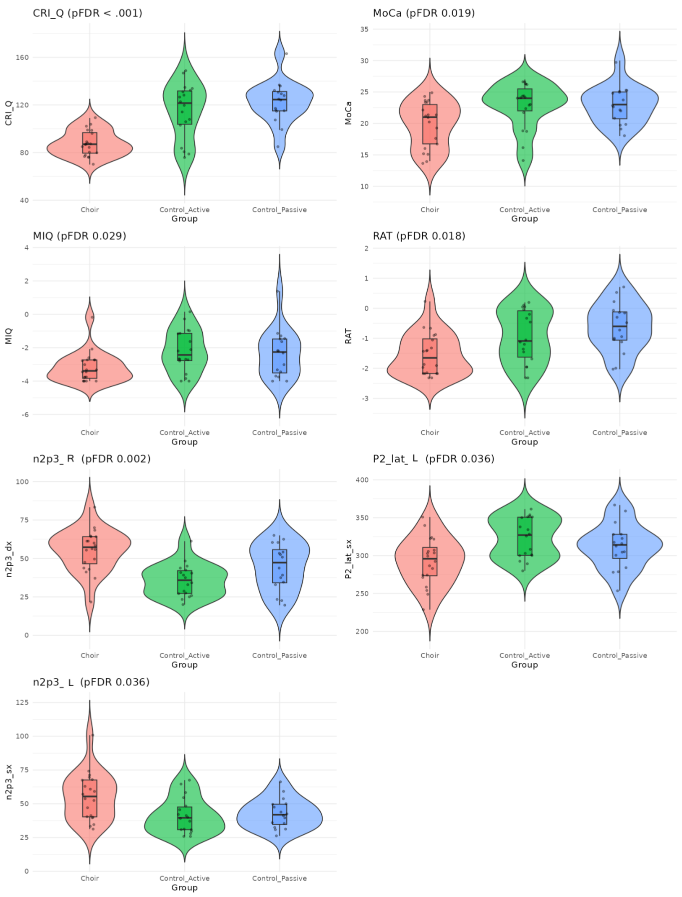

Figure 3. Baseline group comparisons (T0) on cognitive, musical, and neurophysiological measures that survived Benjamini–Hochberg FDR correction. Violin plots display the distribution, median, and interquartile range for each group (Choir, Active Control, Passive Control). These results highlight baseline disadvantages in the Choir group across cognitive reserve, global cognition, musical rhythm aptitude, and specific electrophysiological latency indices.

Descriptive statistics indicated no significant baseline differences between groups in Selfy-MPI scores (Kruskal–Wallis test, p = 0.072), confirming comparable levels of multidimensional frailty at study entry. Flourishing Scale's baseline scores did not differ significantly among the three groups (Kruskal–Wallis test, p = 0.407).

Correlation results

Shapiro–Wilk tests indicated non-normality for multiple variables, so we used Spearman correlations whenever at least one variable in a pair violated normality ($p < .05$). Widespread correlations were observed among tests within the same domains. Regarding inter-domain correlations, musical tests related to audiometric measures primarily via MDT, with significant positive links to PTA left, PTA right, SRT left, and SRT right. A positive trend just above the FDR threshold was also observed for Matrix, as well as for Intelligibility thresholds of both sides. EDT and RAT did not yield FDR-significant associations with any of the audiometric measures.

Significant correlations also emerged between cognitive and musical measures, including CRI-q with RAT, MoCA with MDT, MIQ with RAT, MoCA with MPT, MoCA with RAT and MIQ with MDT. In contrast, associations between cognitive and audiometric measures showed positive trends but did not remain significant after FDR correction in this analysis. MIQ correlated with the right N2 neurophysiological amplitude index, while several neurophysiological amplitude measures were associated with neurophysiological latency indices. As for the Zou's test, the largest asymmetry was observed for N2 amplitude with MIQ, where the right-side correlation exceeded the left and the Zou 95% CI excluded zero (significant), whereas other sizeable differences did not reach significance.

At T1, intra-domain coherence was largely preserved relative to T0, with audiometric variables remaining the most strongly intercorrelated (rs = 0.49–0.96) and cognitive and musical domains showing moderate internal associations. However, the inter-domain pattern shifted notably: the musical–audiometric links observed at T0 (MDT with PTA and SRT) did not survive FDR correction at T1, nor did the cognitive–musical associations (e.g., MoCA/MIQ with MDT/RAT). Instead, MIQ emerged as a new cross-domain bridge between cognitive and audiometric measures (rs = 0.40–0.45). Neurophysiological amplitude and IPL sub-domains remained internally correlated, but again showed no significant cross-domain links after FDR correction. Unlike T0, no significant bilateral asymmetries were detected at T1 (Zou's method, all $p > 0.40$).

Flourishing scores showed no significant correlations with cognitive, musical, audiometric, or neurophysiological measures after within-domain FDR correction at T0 nor T1. While at baseline correlations between outcome measures did not survive correction, at T1, higher frailty was associated with lower cognitive functioning (MoCA, MIQ, CRI-q) and with slower auditory–cortical processing indexed by P2–N2 inter-peak latency.

Longitudinal results - Groups

Significant longitudinal effects were found only for the Neurophysiological (latency) domains. Longitudinal trends were also found for MIQ, Selfy-MPI and Flourishing Scale.

The linear mixed-effects model revealed a significant Time × Group interaction for the N2–P3 inter-peak latency ($F(2, 377.56) = 33.42$, $p < .001$). Post hoc comparisons (Kenward–Roger correction, Bonferroni-adjusted) showed that only the choir group exhibited a significant reduction from T0 to T1 (−21.12 ms, SE = 1.84, t = −11.50, $p < .001$). In contrast, no significant longitudinal change was observed in the active control group (−0.92 ms, SE = 1.98, p = 1.000) or in the passive control group (−3.92 ms, SE = 2.05, p = .172). At baseline (T0), groups did not significantly differ. At T1, however, the choir group showed significantly shorter N2–P3 inter-peak latencies compared to both the active (−14.72 ms, $p < .001$) and passive control groups (−13.43 ms, $p < .001$), while the two control groups did not differ from each other (p = 1.000) (Figure 4a, 4b).

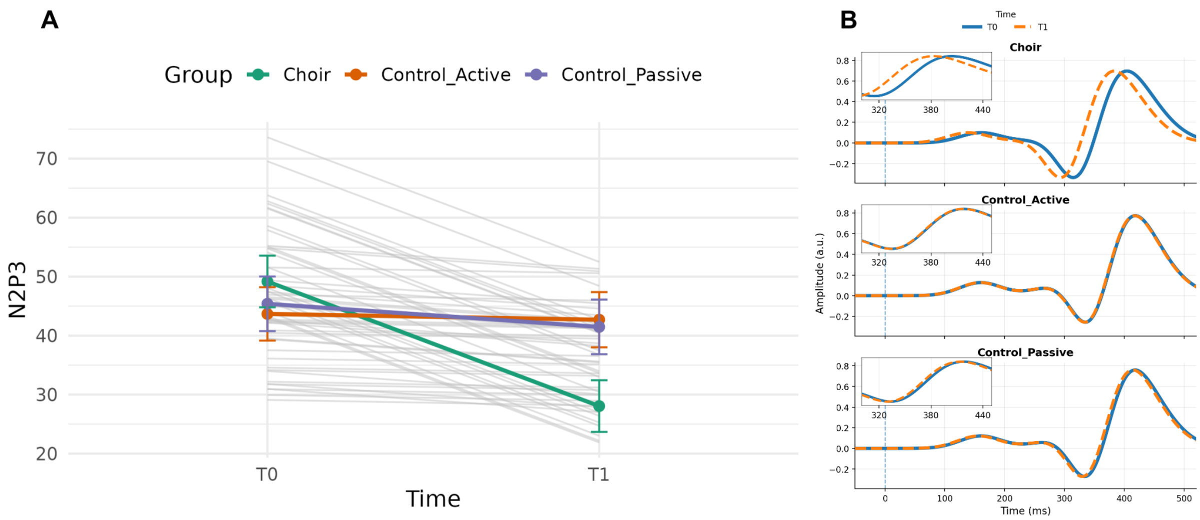

Figure4. Longitudinal changes in N2–P3 inter-peak latency (IPL). (A) Spaghetti plot of individual fitted values derived from the linear mixed-effects model. Thin grey lines represent subject-specific trajectories, while colored points and lines indicate estimated marginal means (± SE) at T0 and T1. A significant reduction in N2–P3 IPL was observed only in the Choir group (p < .001), with no longitudinal change in the active or passive control groups. (B) Group-averaged auditory evoked potentials (AEPs) illustrating the N2–P3 IPL by group

and hemisphere. The shorter IPL at T1 reflects a faster N2→P3 transition in the Choir group.

For P2 latency, the linear mixed-effects model revealed no significant effects of Time or Group, and no evidence of differential longitudinal changes across groups (all ps > .54). For N2 latency, a significant Time × Group interaction emerged ($F(2, 159) = 3.84$, $p = .023$). However, post hoc within-group comparisons did not show significant longitudinal changes in any group (all ps ≥ .066). No significant interactions were found for P3 latency and P2-N2 IPL.

For MIQ, the interaction Time x Group was significant, $F(2, 108) = 4.06$, $p = .020$. Post hoc comparisons indicated a marginal improvement in the Choir group ($\Delta = +0.42$, $p = .056$), whereas no significant changes were observed in the control groups. No significant interaction effects were found for MoCa.

In the mixed-effects models examining longitudinal changes in Selfy-MPI and Flourishing, the Time × Group interaction was not significant, indicating that overall changes across groups did not differ statistically. However, exploratory within-group contrasts were conducted to characterize longitudinal trends. These contrasts showed a modest reduction in frailty in the Choir group ($\Delta = -0.036$, $p = .049$), whereas no significant changes were observed in the Active ($p = .682$) or Passive control groups ($p = .124$) (Figure 5). For Flourishing Scale, pairwise comparisons showed between-group differences at T1, where the difference between the Choir and Passive Control groups approached significance ($\Delta = 3.56$, $p = .054$). Contrasts are summarized in Table 3.

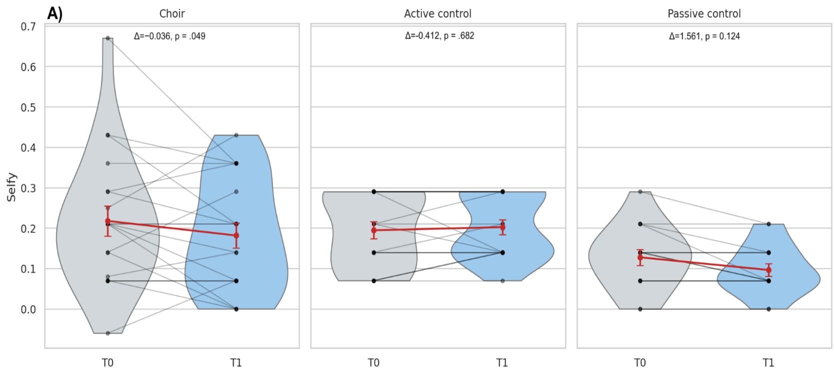

Figure 5. Multidimensional frailty (Selfy-MPI) at baseline and follow-up by study group. Violin plots show the distribution of Selfy-MPI scores at T0 and T1 in the Choir, Active control, and Passive control groups. Individual participant trajectories are overlaid as connecting lines between repeated measurements, and red points with error bars represent group means ± SE. Exploratory within-group contrasts showed a significant reduction in frailty in the Choir group (Δ=−0.036, p = .049), with no significant change in the Active control (p = .682) or Passive control groups (p = .124).

Table 3. Post- hoc Group contrasts N2-P3 IPL, MIQ, Selfy-MPI, and Flourishing

Outcome	Contrast type	Comparison	Δ	SE	df	t	p
N2-P3 IPL	Within-group	Choir, T1 - T0	-21.12	1.84	377	-11.50	< .001
N2-P3 IPL	Within-group	Control_Active, T1-T0	-0.918	1.98	387	0.465	1.0000
N2-P3 IPL	Within-group	Control_Passive, T1-T0	-3.917	2.05	377	-1.907	0.1717
MIQ	Within-group	Choir, T1 - T0	0.424	0.217	58.3	1.952	.056.
MIQ	Within-group	Control_Active, T1-T0	-0.377	0.229	58.3	-1.644	0.1056
MIQ	Within-group	Control_Passive, T1-T0	0.357	0.243	58.3	1.470	0.1468
Selfy-MPI	Within-group	Choir, T1 - T0	-0.036	0.0179	58.3	2.011	.049*
Selfy-MPI	Within-group	Control_Active, T1 - T0	-0.0077	0.0189	58.3	-0.412	0.6817
Selfy-MPI	Within-group	Control_Passive, T1 - T0	0.03125	0.0200	58.3	1.561	0.1239

*Note. Δ values represent estimated post hoc contrasts from linear mixed-effects models. Within-group change scores are expressed as T1 - T0 where applicable. Positive values for between-group differences indicate higher scores in the first group listed. Bonferroni-adjusted p values are reported where applicable. Asterisks indicate significance level: ***: p<0.001; **: 0.001≤p<0.01; *: 0.01≤p<0.05; .: 0.05≤p<0.1; (no symbol): p≥0.1.*

Longitudinal results – Level of engagement

The analyses based on activity engagement indicated that a significant reduction in frailty was observed only among participants with high levels of activity engagement (Δ = −0.036, p = .034), whereas no change emerged in the low-engagement group (p = .641) (Figure 6a).

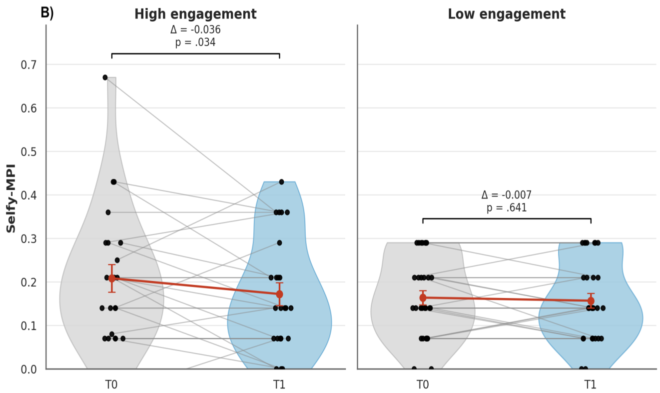

Figure 6a. Selfy-MPI scores at baseline (T0) and post-intervention (T1) by activity engagement level. Violins depict score distributions, black dots indicate individual participants, grey lines connect repeated measures, and red points with error bars represent estimated means ± standard error. Post hoc comparisons showed a significant decrease in the High engagement group, whereas no significant change emerged in the Low engagement group.

Between-group comparisons at T1 revealed significantly higher flourishing scores in the high engagement group compared to the low engagement group (Δ = 3.16, p = .008) (Figure 6b). Contrasts are summarized in Table 4.

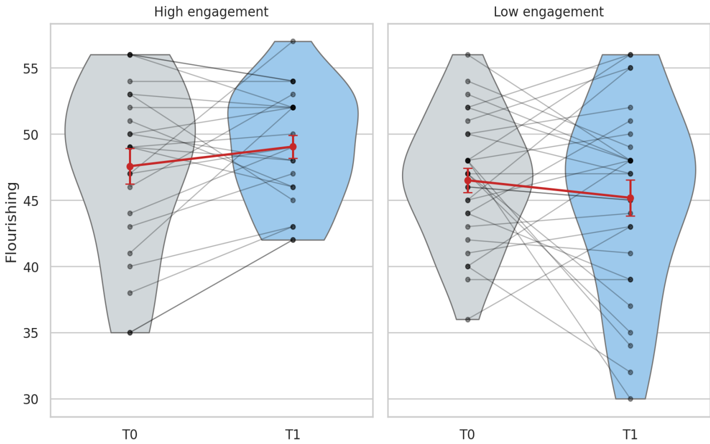

Figure 6b. Psychological well-being (Flourishing Scale) at baseline and follow-up by activity engagement level. Violin plots show the distribution of Flourishing Scale scores at T0 and T1 in participants with high versus low activity engagement. Individual participant trajectories are overlaid as connecting lines between repeated measurements, and red points with error bars represent group means ± SE. participants with high activity engagement showed significantly higher flourishing scores than those with low engagement at T1 (Δ=3.16, p = .008), whereas no difference was observed at baseline (p = .814).

Table 4. Post- hoc Engagement contrasts N2-P3 IPL, MIQ, Selfy-MPI, and Flourishing

Outcome	Contrast type	Comparison	Δ	SE	df	t	p
Selfy-MPI	Within-group	High engagement, T1 - T0	-0.0362	0.0167	57.2	-2.169	.034*
Selfy-MPI	Within-group	Low engagement, T1 - T0	-0.0070	0.0149	57.2	-0.468	.641
Flourishing Scale	Between-group	High - Low engagement T0	0.274	1.16	107	0.236	0.8142
Flourishing Scale	Between-group	High - Low engagement T1	3.160	1.16	107	2.720	.008**

*Note. Δ values represent estimated post hoc contrasts from linear mixed-effects models. Within-group and between-group change scores are expressed as T1 - T0 where applicable. Positive values for between-group differences indicate higher scores in the first group listed. Bonferroni-adjusted p values are reported where applicable. Asterisks indicate significance level: ***: p<0.001; **: 0.001≤p<0.01; *: 0.01≤p<0.05;.: 0.05≤p<0.1; (no symbol): p≥0.1.*

Discussion

This feasibility study tested a choir-centered, community-delivered multidomain program ("MultiMusic") of 9 months in healthy older adults and examined longitudinal change in cognition, multi-dimensional frailty, musical ability, psychological well-being, audiometric measures and auditory–cortical evoked potentials (AEP). The strongest and most consistent longitudinal change was found in N2-P3 interpeak latency (IPL) only for the Choir group.

Feasibility Outcomes

In line with the predefined feasibility objectives, the present study provides encouraging evidence regarding the feasibility of implementing a choir-based multidomain intervention in community-dwelling older adults. Recruitment was successful, indicating substantial interest and willingness to engage in structured musical and leisure activities within this population. Adherence to choir participation was high among those enrolled, supporting the acceptability of choir singing as a sustained group-based activity over an extended period. Importantly, retention across the 9-month study period was strongly influenced by logistical rather than motivational factors: participants residing closer to the assessment facilities showed high completion rates, whereas attrition primarily reflected difficulties associated with travel to hospital-based assessments.

This pattern suggests that dropout was not driven by lack of engagement with the intervention itself, but rather by structural barriers. Finally, the tolerability of the cognitive, audiometric, and neurophysiological assessments was generally good among participants who completed the post session testing, supporting the practicality of the multimodal assessment battery. Together, these findings indicate that the core elements of the intervention (i.e., recruitment, adherence, and acceptability) met feasibility benchmarks, while also highlighting specific logistical constraints that should be addressed in a future randomized controlled trial (RCT).

Baseline characteristics and correlations

Baseline analyses indicated that choir participants exhibited a less favorable cognitive and neurophysiological profile than controls, with lower CRI-q, MoCA, and MIQ scores and longer bilateral N2–P3 inter-peak latencies, despite comparable peripheral hearing, pointing to central cognitive–neural rather than sensory differences. This finding could be interpreted as reflecting baseline differences linked to the socio-cultural characteristics of the choir group, recruited within the Libertà district of Bari, an area characterized by socioeconomic disadvantage. On the contrary, control groups originated from more advantaged districts within the same metropolitan area. Correlation analyses showed coherent within- and cross-domain clustering: melodic discrimination (MDT) correlated with audiometric thresholds, consistent with links between pitch processing and fine-grained auditory resolution (Parbery-Clark et al., 2011; Grassi et al., 2017), whereas weaker EDT and RAT associations suggest greater reliance on higher-order cognition.

In fact, musical and cognitive measures were tightly coupled: cognitive reserve and fluid reasoning related to rhythmic aptitude, and global cognition to multiple music tasks, supporting the role of executive resources in musical ability (Criscuolo et al., 2019). Fluid reasoning also correlated with right-hemisphere N2 amplitude, and amplitude–latency couplings indicated integrated auditory–cognitive cascades (Polich, 2007; Alain et al., 2018), with lateralization patterns consistent with prior ageing research (Divenyi & Haupt, 1997; Alain et al., 2014; Bidelman & Alain, 2015).

Neurophysiological evidence

Neurophysiological data were acquired using a standardized clinical AEP setup (Cz reference, low impedances <5 kΩ, ER-3A insert earphones, auditory oddball paradigm). Although less spatially dense than high-density EEG, such configurations are optimized for reliability and reproducibility and are widely used in both research and clinical contexts. Comparable protocols have established normative

P300 values in older adults (Cóser et al., 2010; Didoné et al., 2016), validated cortical AEPs for objective auditory assessment (Van Dun et al., 2015), and demonstrated high test–retest stability even in biometric applications (Seha & Hatzinakos, 2018), supporting the robustness of the present approach.

The N2-P3 IPL has been shown to be particularly sensitive to cognitive status in older adults, including MCI populations (Papaliagkas et al., 2008, 2011), and indexes the temporal coupling between successive processing stages, i.e., from novelty detection and conflict monitoring (N2) to higher-order cognitive evaluation and context updating (P3; Polich, 2007; Sur & Sinha, 2009; Picton, 2011; Luck, 2014). Age-related slowing of this cascade is well documented (Gaál et al., 2007; Kropotov et al., 2016; Tarawneh et al., 2021), making IPLs particularly informative markers of ageing-related neural inefficiency.

Although direct evidence on training-induced modulation of N2–P3 IPL remains limited, converging work indicates that auditory–cognitive training enhances neural timing and synchrony at both cortical and subcortical levels in older adults (Anderson & Kraus, 2013; Skoe & Kraus, 2024; Fisher et al., 2025). Importantly, N2–P3 IPL captures the efficiency of information transfer between perceptual–attentional and cognitive updating stages, whereas P3 latency reflects the cumulative duration of earlier sensory and cognitive processes (Pihlaja et al., 2023). The selective IPL shortening observed here therefore suggests an acceleration of higher-order cognitive integration rather than global sensory speeding.

N2 and P3 are generated by partially distinct but interacting networks, including medial frontal (ACC/pre-SMA) and posterior parietal–temporal regions, respectively (Halgren et al., 1998; Folstein & Van Petten, 2008). Efficient communication between these regions depends on fronto-parietal connectivity and theta-band synchrony supporting cognitive control and memory updating (Sauseng et al., 2010; Cavanagh & Frank, 2014). Ageing is associated with reduced conduction velocity and weakened theta coherence across these networks (Cummins & Finnigan, 2007; Andrews-Hanna et al., 2007). The choir-specific N2–P3 IPL reduction, together with behavioral gains, may therefore reflect strengthened fronto-parietal coupling and improved temporal coordination within auditory–cognitive circuits.

Absolute peak latencies did not show a consistent training-related modulation. P2 and P3 latencies were unaffected, and although N2 latency yielded a significant Time × Group interaction, post hoc comparisons revealed no significant within-group longitudinal changes, with a pattern not consistent with the hypothesized facilitation. Likewise, the earlier P2–N2 inter-peak interval did not change significantly. Given that the N2–P2 interval primarily reflects early cortical discrimination and perceptual encoding within auditory regions (Näätänen & Picton, 1987; Crowley & Colrain, 2004), and that P2 modulation has been more closely associated with stimulus-specific auditory learning than higher-order executive integration (Tremblay et al., 2001; Alain et al., 2010), the absence of effects at these stages suggests that the intervention did not globally accelerate early sensory processing. Rather, plasticity appears to have selectively targeted later integrative stages, as indexed by the N2–P3 interval.

The lack of robust single-peak modulation is consistent with prior reports highlighting variability in P2, N2, and P3 effects depending on task demands, recording parameters, and heterogeneity in ageing cohorts (Luck, 2014; Alain et al., 2014; Kropotov et al., 2016). This variability parallels the broader literature on music-related auditory plasticity, where cortical ERP changes are frequently observed but differ in magnitude and direction (Sanju & Kumar, 2016; Brown et al., 2013; Okhrei et al., 2018), and where large-scale evidence suggests limited generalization to early subcortical encoding (Whiteford et al., 2025).

Consistent with this interpretation, no longitudinal changes were observed in pure-tone thresholds or speech-in-noise performance. Given the slow rate of age-related threshold decline (≈1 dB/year from age 60; Lee et al., 2005), the absence of peripheral changes is expected. Prior work similarly shows that short- to medium-term musical interventions preferentially induce central neurophysiological modulation, without concomitant improvements in audiometric thresholds or speech-in-noise scores (Grassi et al., 2017; Fleming et al., 2019; Hennessy et al., 2022; Feng et al., 2020). When behavioral gains in challenging listening conditions do emerge, they are more consistently mediated by central mechanisms such as auditory working memory, attentional control, and cortical recruitment (Zendel et al., 2019; Guo et al., 2021; Neves et al., 2023).

Overall, the choir-specific shortening of N2–P3 IPL in the absence of peripheral hearing changes identifies this interval as a sensitive marker of central auditory–cognitive plasticity. This finding aligns with evidence that musical engagement sharpens neural timing and mitigates age-related slowing (Parbery-Clark et al., 2011; Bidelman et al., 2015; Lu et al., 2022; Bonetti et al., 2024) and with reports linking P300 timing to responsiveness to auditory–cognitive training (Ferguson & Henshaw, 2015; Skoe & Kraus, 2024; Pearson et al., 2025). Importantly, converging evidence from the language domain shows that music training is associated with enhanced processing speed and cognitive control in both auditory and visual modalities, particularly in bilingual musicians, supporting shared temporal and executive mechanisms across music and language (Bugos et al., 2026).

The observed gains in this community-based cohort, despite baseline cognitive and neural disadvantages in the choir group, are consistent with the broader literature. Contextual factors are known to shape cognitive trajectories and vulnerability to age-related disorders, plausibly accounting for the lower initial performance observed in the choir group. Crucially, longitudinal mixed-effects models adjusted for baseline outcome levels, reducing the likelihood that observed changes merely reflect regression to the mean and supporting the interpretation of genuine longitudinal improvement. These findings align with growing evidence that cognitively and socially enriching activities can engage compensatory mechanisms in populations at elevated risk of decline.

Multidimensional Frailty

At baseline, groups did not differ in Selfy-MPI scores, supporting the interpretation of subsequent changes as longitudinal modulation rather than pre-existing imbalance. At T1, higher frailty was associated with poorer cognitive performance and slower auditory–cortical processing, consistent with evidence that frailty predicts accelerated decline in global cognition and executive function and shares neurobiological substrates with cognitive vulnerability (Zhang et al., 2025; Skalska et al., 2025; Carcelén-Fraile et al., 2025). Within the Comprehensive Geriatric Assessment (CGA)–based framework underlying the SELFY-MPI, frailty is conceptualized as a loss of harmonic interaction among interdependent biological, functional, cognitive, and psychosocial domains, leading to reduced homeostatic stability (Pilotto et al., 2019, 2020). The observed cognitive and neurophysiological associations are therefore coherent with a multisystem view in which central nervous system efficiency represents one embedded component of the broader frailty architecture.

Although the longitudinal mixed model did not reveal a significant Time × Group interaction, exploratory contrasts suggested lower frailty among participants exposed to richer multidomain engagement and higher cumulative activity levels. While interpreted cautiously, this pattern is theoretically consistent with the multidimensional structure of the MPI, which parallels the rationale of multidomain preventive strategies targeting mobility, cognition, and social participation simultaneously. Accordingly, multidomain interventions show superior effects on frailty trajectories compared with single-component approaches (de Souto Barreto et al., 2018; Yu et al., 2020), in line with large prevention frameworks such as FINGER, AGELESS, and SUPERBRAIN (Ngandu et al., 2015; Rosenberg et al., 2018; Deckers et al., 2024; Ponvel et al., 2025; Ong et al., 2025; Moon et al., 2025). The dose–response trend further accords with longitudinal evidence that sustained social and cognitive engagement reduces progression toward frailty (Rogers & Fancourt, 2020; Goto & Yamatsu, 2025), reinforcing the conceptualization of frailty as a dynamic and potentially modifiable multisystem condition (Pilotto et al., 2022).

Interestingly, the neurophysiological findings observed in the present study may provide a biologically plausible mechanism underlying the frailty patterns. The reduction in N2–P3 IPL observed in the choir group suggests faster auditory–cortical processing and improved neural efficiency. Event-related potentials such as the P300 are widely considered markers of attentional allocation and cognitive processing speed in ageing populations and have been proposed as neurophysiological indicators of cognitive vulnerability and cognitive frailty in older adults (Pavarini et al., 2018; Tanaka et al., 2024). Because cognitive processing speed and executive control contribute to several domains included in multidimensional frailty frameworks such as the MPI, improvements in neural processing efficiency may plausibly support broader resilience against frailty-related decline.

Physicological well-being

The Flourishing Scale primarily captures eudaimonic dimensions (i.e., purpose, meaning, relational connectedness, and perceived contribution) rather than cognitive efficiency per se. Indeed, in early-stage dementia, flourishing relates more strongly to quality of life, mood, and self-efficacy than to measurable cognitive impairment (Clarke et al., 2025).

Longitudinal mixed-effects models showed no significant main effects or Time × Group interaction, indicating overall stability of global well-being across the intervention period. This pattern aligns with meta-analytic evidence that behavioral interventions in generally healthy older adults produce small and heterogeneous effects on well-being, with stronger shifts typically observed in clinically distressed populations (Weiss et al., 2016). Notwithstanding the absence of omnibus longitudinal effects, planned contrasts revealed higher flourishing at follow-up in the Choir group relative to the Passive Control group. This selective difference suggests that structured, socially embedded engagement may confer modest psychosocial advantages compared to inactivity, while diverse forms of active participation yield broadly comparable well-being levels. Consistent with this interpretation, choir-based interventions have been shown to reduce loneliness and enhance social integration even when cognitive or physical indices remain unchanged (Pentikäinen et al., 2021; Johnson et al., 2020). Together, these findings indicate that multidomain engagement may not substantially elevate global flourishing in already well-functioning older adults over a medium-duration period, but may help buffer against psychosocial stagnation associated with disengagement.

Strengths and limitations

Strengths include the ecologically valid, choir-centered design; the multidomain assessment spanning cognition and auditory neurophysiology; and the formal outcome-level comparison demonstrating the dominance of the N2–P3 effect. Limitations concern the non-randomized allocation with baseline imbalances (addressed statistically but not fully eliminated), attrition that may bias generalizability, and substantial variability in the activities undertaken both within the choir's multidomain program and across control groups. Such heterogeneity, combined with the relatively short time between the two assessment points, may have diluted some effects that could emerge more clearly in a longer and more standardized trial. Our electrophysiology used a clinical AEP setup optimized for translational use; high-density EEG/MEG could refine source-level inferences in future work.

Clinical implications and future directions

Clinically, these findings position choir-based multidomain engagement as a scalable, socially embedded strategy to support cognitive efficiency in later life, particularly reasoning-related functions and reserve-linked behaviors, while enhancing the temporal coordination of auditory–cortical processing. The selective shortening of the N2–P3 interval suggests that such engagement strengthens network-level integration between conflict monitoring and cognitive updating rather than uniformly accelerating early sensory stages, consistent with models proposing that musical training refines temporal prediction and attentional dynamics, thereby reducing neural processing costs (Parbery-Clark et al., 2011; Bidelman et al., 2015; Lu et al., 2022; Zhang et al., 2025). Converging neuroimaging evidence indicates that lifelong musical engagement is associated with preserved functional connectivity, cerebellar and auditory structural adaptations, and compensatory prefrontal and reward-system recruitment, all of which may contribute to resilience against age-related decline (Marie et al., 2023; Zhang & Tremblay, 2025; Ma et al., 2025; Espinosa et al., 2025).

The MultiMusic intervention occupies an intermediate position between primary and secondary prevention, targeting community-dwelling older adults without dementia but with potential early vulnerability profiles. Its activity-based multidomain structure converges with large-scale lifestyle prevention programs that have demonstrated the feasibility and efficacy of coordinated cognitive, physical, and social stimulation in modifying age-related trajectories. Yet, it differs from conventional multicomponent programs by embedding coordinated cognitive, sensorimotor, emotional, and social stimulation within a single meaningful activity. Choral singing simultaneously recruits auditory perception, vocal–motor synchronization, executive control, memory, and structured social interaction, i.e., processes central to both cognitive reserve and psychosocial well-being (Pentikäinen et al., 2021; Moisseinen et al., 2024; Raja et al., 2025). In preventive samples with largely intact baseline cognition, electrophysiological indices such as N2–P3 provide sensitive markers of functional adaptation that may precede detectable behavioral change, overcoming ceiling effects common in standard neuropsychological testing (Kujala & Näätänen, 2010).

From a public health perspective, community choirs represent low-cost, non-pharmacological interventions implementable within existing cultural and senior infrastructures, without reliance on specialist medical settings. Economic evaluations suggest that community singing and multidomain lifestyle programs can achieve favorable cost-effectiveness profiles while improving mental health–related quality of life and reducing psychosocial risk factors such as loneliness (Melis et al., 2008; Coulton et al., 2015; Hoang et al., 2022). By engaging individuals who are not yet patients but may already exhibit early frailty or cognitive vulnerability, stimulating activities and programs may contribute to maintaining intrinsic capacity and slowing multidimensional decline (Liang et al., 2024;

Sánchez-Sánchez et al., 2022). Building on this feasibility study, the forthcoming RCT should mitigate baseline imbalances, extend follow-up duration to assess persistence of effects, and increase sample size to enable stratified analyses by hearing and cognitive status. Given emerging longitudinal evidence for sustained cognitive and neural benefits of late-life musical engagement (Zendel et al., 2019; Marie et al., 2023; Wang et al., 2025; Moisseinen et al., 2025), a sufficiently powered RCT is warranted to determine efficacy, mechanisms, and boundaries of effect.

Chapter 3: Technological and Aesthetic Extensions of Multisensory Enrichment in Cognitive Decline

This chapter presents a complementary line of intervention research addressing cognitive vulnerability through a technology-mediated multisensory approach. In contrast to the community-based and longer-term intervention framework described in the previous chapter, the work presented here explores the potential of a brief immersive experience as a form of enriched stimulation that may be applicable across different stages of cognitive decline. In this sense, the chapter broadens the translational scope of the thesis by considering whether supportive and meaningful interventions can also be developed in formats that are more targeted, flexible, and potentially adaptable to individuals with more heterogeneous clinical profiles.

The study included in this chapter should be understood as an initial exploratory step rather than as a definitive efficacy trial. Its relevance lies in testing the feasibility and clinical meaningfulness of an immersive intervention model that may complement more extended and socially embedded programs, particularly in populations for whom sustained participation in complex activities may be less accessible. The chapter therefore introduces a different but converging strategy within the broader context of non-pharmacological interventions in ageing: one aimed at examining the potential of brief, structured, and emotionally engaging multisensory experiences to support well-being and adaptive functioning in conditions of cognitive vulnerability.

3.1 Proof-of-Concept Study on the Use of Virtual Reality with Evocative and Aesthetic Content for Elderly Individuals with Cognitive Decline

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Abstract

Recent technological advances have introduced novel therapeutic interventions for Alzheimer's disease (AD). This study introduces a novel virtual reality (VR) intervention consisting of aesthetically pleasing and relaxing immersive videos paired with evocative music for patients with or without cognitive decline. The goal of this intervention is to improve the mood, evoke autobiographical memories in, and enhance the overall well-being of elderly individuals, across stages of cognitive decline (from absent to severe). Twenty-one elderly participants (5 cognitively healthy, 13 with a mild cognitive decline, 2 with a moderate decline, and 1 with a severe decline) were exposed to immersive 360- degree videos depicting both familiar and unfamiliar, pleasant and calming environments, accompanied by emotionally evocative, pleasant, and soothing music. The results demonstrated high levels of immersion and predominantly positive emotional responses, with several participants reporting autobiographical memory recall triggered by the VR stimulation. Statistical analysis revealed a significant improvement in mood over time, regardless of cognitive status, supporting the effectiveness of the intervention. While there were some side effects of fatigue or transient anxiety, the experience was generally perceived as engaging and meaningful. This feasibility study adds to the acceptability and potential clinical utility of VR interventions and provides a justification for future larger trials aimed at the integration of immersive technologies into cognitive rehabilitation interventions for individuals at different stages of cognitive decline.

Keywords: virtual reality; mild cognitive impairment; cognitive rehabilitation; music therapy; autobiographical memory; multisensory stimulation; feasibility study

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by a significant cognitive decline, emotional disturbances, and impaired social interactions. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), AD falls under the category of Major Neurocognitive Disorders and is defined by a decline from a previous level of performance in one or more cognitive domains that interferes with independence in everyday activities (American Psychiatric Association, 2013). As one of the leading causes of dis- ability in older adults, it presents substantial challenges for patients, caregivers, and healthcare systems worldwide (Alzheimer's Association, 2023). Strategies for AD prevention, aimed at risk factor identification and reduction, or early intervention, aimed at addressing behavioral symptoms, could enhance the quality of life of impaired subjects by mitigating its pathological impact.

For the planning of early interventions, it is crucial to identify the prodromal stages of AD. Mild cognitive impairment (MCI), a condition associated with an elevated risk of AD progression, which shows measurable deficits in different cognitive domains but does not significantly impair daily activities (Petersen et al., 1999) could represent a critical therapeutic window for interventions aimed at slowing cognitive decline and enhancing psychosocial well-being. For MCI, an estimated 10–15% per year conversion rate has been reported in clinical settings, while community-based studies report lower rates, ranging from 3.8% to 6.3% annually. Moreover, long-term studies reveal that approximately 80% of patients with MCI convert to AD over a six-year follow-up interval (Jack et al., 2018). Recent progress in AD has made evident how this disease could be considered a continuous process of neurodegeneration rather than a series of distinct stages, beginning with asymptomatic phases, progressing through MCI, and culminating in full-blown dementia (Aisen et al., 2017). This poses challenges in precisely evaluating individuals to assess their condition and their specific risk factors for progression (Parnetti et al., 2019; Porsteinsson et al., 2021). Figure 1 illustrates the escalating severity associated with each stage of the AD continuum.

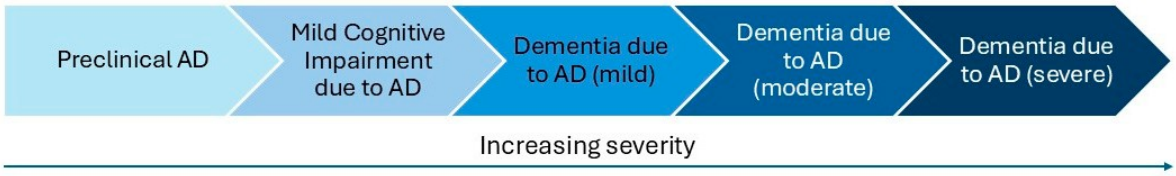

Figure 1. The Alzheimer's continuum, showing the progression from preclinical stages to severe dementia, with an increasing severity of cognitive and functional decline across distinct stages of the disease. Modified from Parnetti, Chipi, Salvadori, D'Andrea, and Eusebi [6].

Accurate staging is critical for implementing early, targeted interventions that can delay or prevent irreversible neuronal damage and cognitive decline. This highlights the need for advanced diagnostic tools capable of identifying the AD pathology in its earliest stages to maximize the potential benefits of therapeutic strategies.

Current treatments for AD and MCI mainly include pharmacological interventions, including acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and NMDA receptor antagonists (memantine), which manage symptoms rather than halt disease progression (Cummings et al., 2019). In July 2023, Lecanemab was approved by the FDA; it is a monoclonal antibody targeting amyloid-beta aggregates, which represents a milestone as one of the first medications for the Alzheimer's pathology (U.S. Food and Drug Administration, 2023). Lecanemab binds to soluble amyloid-beta protofibrils, halting cognitive deterioration in early AD. In the Clarity AD phase-three trial, it significantly delayed clinical decline over 18 months, also showing improvement in cognitive and functional endpoints (van Dyck et al., 2023). However, risks such as amyloid-related imaging abnormalities (ARIAs) highlight the need for careful patient monitoring. While approved in the US, Lecanemab is not yet available in Italy, with EMA approval pending (El País, 2024).

Therefore, non-pharmacological interventions, such as cognitive stimulation, physical activity, and diet modifications, have been shown to have potential in retarding cognitive impairment while improving overall well-being (Ngandu et al., 2015). In addition, complementary therapies, such as music therapy, art therapy, and mindfulness-based therapies, are gaining recognition for their ability to manage behavioral symptoms, reduce anxiety, and enhance the quality of life in both MCI and AD populations (Jung et al., 2020). For instance, a systematic review of 15 studies investigating the impact of music therapy on AD patients showed significant improvements in cognitive abilities and daily living activities (Wang et al., 2020). Another systematic re- view and meta-analysis also implied that non-pharmacological therapies, including music therapy, positively impacted activities of daily living (ADLs), behavioral and psychological symptoms of dementia (BPSDs), cognition, and quality of life in individuals with moderate- to-severe dementia (Livingston et al., 2014). Furthermore, music therapy alone was shown to significantly enhance both cognitive function and quality of life in subjects with AD (Bleibel et al., 2023).

Such evidence highlights the need to include these non-pharmacological interventions in treatment plans; in fact, by integrating both pharmacological and non-pharmacological approaches, patient outcomes can be best optimized on a multimodal basis by addressing both the cognitive as well as emotional deficits of AD.

Emerging technologies like virtual reality (VR) hold much potential in the treatment of both MCI and AD. Offering the presentation of immersive, simulated environments that can engage cognitive and emotional processes, VR can be considered a suitable technological framework to address the challenges associated with MCI and early AD (Manera et al., 2016; Appel et al., 2020). The recent literature provides evidence supporting the efficacy of VR interventions in this context. For example, Kim et al. (2019), introduced the positive impact of VR on cognitive function for MCI subjects, also impacting daily living activities and neuropsychiatric symptoms, highlighting its potential as a tool for cognitive rehabilitation. Furthermore, Zhu et al. (2021) investigated the effects of dual-task interventions in individuals with MCI, combining motor and VR- based cognitive training, reporting enhanced executive function and gait performance.

Very recently, Yang et al. (2025) conducted a meta-analysis of 18 randomized controlled trials conducted with VR interventions on MCI patients (722 participants were included), demonstrating significant improvements in cognitive functions among older adults with MCI compared to control groups. The effect sizes reported included a Standardized Mean Difference (SMD) of 0.20 (95% CI: 0.02–0.38) for memory, 0.25 (95% CI: 0.06–0.45) for attention and information-processing speed, and 0.22 (95% CI: 0.02–0.42) for executive functions, indicating small to moderate improvements in these cognitive domains. Many of these scenarios included soundscapes, such as ambient environmental sounds like birdsong or flowing water, or music tailored to enhance relaxation and engagement. Additionally, VR has been used for dual-task exercises that combine cognitive challenges with motor activities, such as navigating virtual pathways or interacting with objects within the virtual space (Manera et al., 2016; Kim et al., 2019). These findings emphasize the potential of VR as a therapeutic tool for mitigating cognitive decline and improving the quality of life in individuals with MCI and early

AD. At the same time, the scarcity of applications of VR for early AD compared to MCI, as well as the high costs of devices and the need for multiple sessions, highlight significant challenges to its accessibility and feasibility for long-term AD treatment. This underscores the need for implementing novel methodologies that are both cost- and time-effective, paving the way for more sustainable and widely applicable interventions.

In addition to the outcome-based results, it is important to consider the possible effectiveness of VR interventions on age-related cognitive and motor decline. VR provides optimal stimulation through multisensory access within digital worlds that can also pro- mote the cognitive functions of memory and executive control. In particular, Kim et al. (2024) advanced a compelling argument for some of the older adults' motor issues: internal models and visuomotor predictions are poorly managed within the framework of reactive, feedback-driven strategies. VR has unique advantages in this respect, as it can provide manipulable environments that are safe, yet meaningful, and within which users may practice anticipatory actions in a variety of contexts. VR interventions do not only focus on the acquisition of new motor skills. They also enhance the cognitive components of planning, attention, and decision-making. Moreover, VR is more effective than traditional tasks, since real-world scenarios aid in enhanced emotional engagement and presence, which are vital resources for those with diminished cognitive and emotional reserves. At the same time, it is relevant to consider the accumulating evidence on the impact of beauty in dementia, namely the positive outcomes in terms of improved mood and quality of life thanks to music- and art-based interventions (Deshmukh et al., 2018; Matrone & Brattico, 2015). Here, we build on previous studies with VR as well as music- and art-based interventions to evaluate the acceptability of a VR-based intervention with novel aesthetic and mnestic features for individuals with various levels of cognitive decline, from absence to MCI and to AD.

More specifically, here we wanted to assess whether personalized, emotionally evocative, and aesthetically engaging 360-degree videos combined with music can improve transient mood, evoke autobiographical memories, and enhance overall well-being in this population. The audio–video VR stimulation is rooted in research demonstrating the significant role of multi-sensory experiences in enhancing cognitive and emotional outcomes in ageing populations (de Dieuleveult et al., 2017). Positive aesthetic experiences, such as engaging with visually and aurally pleasing stimuli, have been shown to promote emotional well-being, reduce stress, and foster a sense of tranquility (Brancatisano et al., 2020; Fancourt & Finn, 2019; Brattico & Varankaitè, 2019; Reybrouck, Vuust, P. & Brattico, 2021). Music, in particular, has a unique ability to evoke autobiographical memories, even in individuals with significant cognitive impairments, by stimulating neural pathways associated with memory and emotion (Lippolis et al., 2023; Campo & Brattico, 2023; Matziorinis & Koelsh, 2022).

The rationale for this specific VR intervention builds upon previous music–neuroaesthetic findings, leveraging the synergistic effects of immersive environments and evocative music to stimulate cognitive processes and elicit positive emotional responses. By integrating familiar landscapes and culturally relevant music, the intervention seeks to evoke memories, enhance mood, and provide a calming and meaningful experience tailored to the needs of individuals with AD or MCI.

Materials and Methods

Participants

Twenty-one elderly participants (4 males and 17 females) with a mean age of 75.09 ± 9.22 years (range: 65–93) were included in the study. Participants included cognitively healthy elderly individuals and individuals exhibiting cognitive impairments compatible with an AD profile, as assessed by their MoCA scores. Specifically, four participants scored within the normal cognitive range (MoCA scores: 26–30), thirteen participants presented with mild cognitive impairment (MoCA scores: 18–25), three participants exhibited moderate cognitive impairment (MoCA scores: 10–17), and one participant showed severe cognitive impairment (MoCA score below 10). These classifications align with the Alzheimer's continuum framework, which describes a progression of cognitive decline consistent with an AD-related pathology. The mean MoCA score was 21.33 ± 5.34 (range: 5–27). Individual clinical and neuropsychological profiles are detailed in Table 1.

Participants were recruited through the Centro Servizi per le Famiglie "Libertà" in Bari and through acquaintances. All the recruited participants were of Italian nationality and were born and currently residing in the region of Puglia, Southern Italy. All participants or their caregivers provided informed consent after being instructed as to the study's purpose and procedures.

All experimental procedures complied with the Declaration of Helsinki—Ethical Principles for Medical Research and were approved by the Ethics Committee at the Department of Education, Psychology, Communication of the University of Bari (ET-24-18-R1).

Table 1. Demographic, clinical, and neuropsychological characteristics of the study participants. The table includes participant gender, age, and cognitive performance scores measured using the Montreal Cognitive Assessment (MoCA).

Participant	**Gender**	**Age**	**MoCa**
1	Male	68	24
2	Male	75	22
3	Female	70	21
4	Female	71	21
5	Female	71	17
6	Female	70	24
7	Female	68	21
8	Female	90	5
9	Male	71	27
10	Male	79	26
11	Female	65	22
12	Female	71	24
13	Female	69	19
14	Female	69	26
15	Female	70	21
16	Female	87	11
17	Female	89	20
18	Female	92	26
19	Female	93	25
20	Female	65	27
21	Female	74	19

Neuropsychological and Behavioral Examination

Self-assessments of mood were recorded before and after each video presentation through simple questions, and the responses were noted each time. Following each video session, participants completed a custom-made questionnaire designed to assess their experience. The questionnaire included items from the Slater–Usoh–Steed (SUS) presence scale (Usoh et al., 2000), which measures the sense of presence on a scale from 0 (no presence at all) to 7 (a strong feeling of being physically present in the environment), and the Visual Analogue Scale (VAS) (Heller et al., 2016) for an evaluation of mood before (at arrival), during, and after the VR stimulation. Moreover, additional semi-structured questions developed by the research team were included to explore specific aspects of satisfaction and mood regulation during the VR experience, as well as any memory recollection triggered by the videos.

The eligibility of the participants was determined using MoCA (Montreal Cognitive Assessment), a brief cognitive screening tool with high sensitivity and specificity for detecting MCI (Chertkow et al., 2011; Nasreddine et al., 2005).

Video recordings of each participant's session were collected during the administration of the experimental procedure to support further qualitative analysis and ensure accurate documentation of individual responses.

Additionally, we measured physiological and autonomic observations, like respiratory rate and heart rate variability, which will be analyzed in a separate paper.

VR Stimulation and Procedure

This work included the administration of four 360-degree videos, each lasting up to 5 min, delivered through VR. Video administration was performed using the Oculus Quest 2, a standalone virtual reality headset equipped with a high-resolution display (1832 × 1920 pixels per eye), a refresh rate of up to 120

Hz, and a wide field of view to enhance immersion. The device's lightweight design and built-in tracking system enabled participants to interact with the virtual environment comfortably, without requiring additional external sensors (Figure 2). The videos, which were selected by the team of authors to provide contrasting yet equally immersive and emotionally engaging experiences, included two familiar scenarios and two non-familiar scenarios.

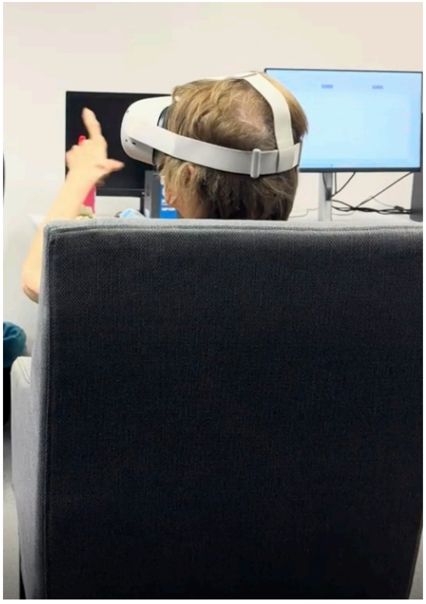

Figure 2. Example of the virtual reality (VR) experimental setup.

The familiar scenarios consisted of relaxing beach landscapes in Sardinia, created using footage from a YouTube video (https://www.youtube.com/watch?v=6yAHk_0sv0Q; accessed on 8 July 2024). Given the high presence of coastal environments in this area and the value of their cultural context on local inhabitants, we considered the beach scenarios as "familiar". Although the selected VR videos specifically depicted Sardinian beaches, this choice is due to the limited availability of high-quality 360-degree footage of locations in Puglia. Sardinian beaches were nevertheless deemed appropriate as a depiction for familiar landscapes, given their strong visual and cultural resemblance to the coastal environments to which the participants are or were regularly exposed. These videos were looped to depict calm, uninterrupted seaside environments without external interferences or people, aiming to evoke memories of Southern Italian beaches where the participants were born and live.

The non-familiar scenarios included a serene park in Japan, sourced from a YouTube video (https://www.youtube.com/watch?v=uaJdWd_n1lg; accessed on 8 July 2024), and a mesmerizing aurora borealis display, sourced from another YouTube video (https://www.youtube.com/watch?v=cg_jfip4pSQ; accessed on 8 July 2024). These videos were paired with corresponding music: traditional Italian folk or melodic pop songs for the familiar scenarios, and non-familiar folk songs for the non-familiar scenario (Figure 3).

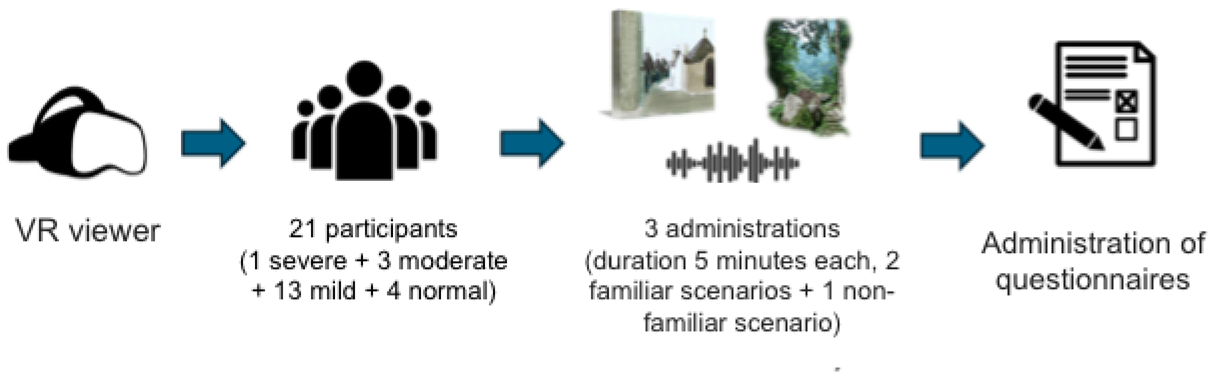

Figure 3. Schematic representation of the experimental paradigm. Participants (n = 21; 3 with moderate and 1 with severe dementia due to AD) engaged in three virtual reality (VR) sessions using an Oculus Quest 2 VR viewer. Each session lasted 5 min and included exposure to two familiar scenarios (e.g., Italian beaches) and one non-familiar scenario (e.g., the aurora borealis or a Japanese park), accompanied by corresponding music. After each session, participants completed questionnaires to evaluate their experiences and emotional responses.

The selection of the songs was guided by an evaluation process conducted by a group of 4 musicians with expertise in musicology. The evaluation was based on a pool of 30 songs categorized into three groups: Italian lyric songs, Italian folk songs, and foreign compositions. The evaluation process considered several key dimensions for each song. Familiarity was assessed using a 5-point scale, where 1 indicated very low familiarity (the participant did not know the song at all) and 5 indicated very high familiarity (the participant knew the song well or found it reminiscent of similar genres or melodies). Arousal was also rated on a 5-point scale, with 1 representing very low arousal (the song elicited calmness and relaxation) and 5 representing very high arousal (the song evoked energy and excitement).

Additionally, pleasantness was measured on a 5-point scale, where 1 indicated very low pleasantness (the song was not enjoyable) and 5 indicated very high pleasantness (the song was highly enjoyable and evoked positive feelings).

The songs that were rated as the most relaxing and least activating were selected for the study to ensure they aligned with the calming and immersive goals of the VR intervention. The selected songs included "Non ho l'età" sung by G. Cinquetti; "Il cielo in una stanza" sung by G. Paoli; "Sogna fiore mio" performed by Lucilla Galeazzi, Marco Beasley, L'Arpeggiata, and Christina Pluhar and composed by Ambrogio Sparagna; and "Vulesse addeventare nu Brigante" sung by Carlo D'Angiò and produced by Musicanova for the familiar scenarios; and "Finnish Chant" and "Japanese Sonata" for the non-familiar scenarios. A full list of the evaluated songs is provided in Supplementary Table S1.

Each participant was shown the two familiar scenarios and one of the two non-familiar scenarios paired with familiar or unfamiliar music (randomly assigned to the videos from among the selected songs), with the order of presentation randomized as follows: one familiar scenario, followed by the other familiar scenario, and finally a non-familiar scenario.

Statistical Analysis

To explore the relationship between mood changes and cognitive status, one linear mixed-effects model was performed using Jamovi (version 2.6) (The jamovi project. Jamovi, 2024). Participants were divided into two groups based on the median MoCA score of the sample (median = 22): a low-MoCA group with moderate to severe cognitive decline (scores 0–21) and a high-MoCA group with absent to mild cognitive decline (scores 22–26). The model was specified as

$$\text{VAS\_score} \sim 1 + \text{Time} + \text{MoCA Scores} + \text{Time} \times \text{MoCA Scores} + (1 \mid \text{ID})$$

The model aimed to evaluate overall differences in mood between the two groups and to investigate mood changes over time (pre-, mid-, and post-exposure) and how these changes interacted with cognitive status. In this model, VAS mood scores served as the dependent variable, with Time (three repeated measures), MoCA group (low-MoCA scores and high-MoCA scores), and their interaction (Time × MoCA scores) included as fixed effects. Participant ID was modeled as a random intercept to account for within-subject variability across repeated measures. Model residuals were assumed to follow a Gaussian distribution. Degrees of freedom were estimated using the Satterthwaite method, and Wald confidence intervals were calculated. The model converged successfully using the bobyqa optimizer, with a total of 63 observations from 21 participants.

Results

Behavioral Data

The following section provides a comprehensive overview of the results obtained from the SUS presence scale and the VAS. Nineteen participants reported a high level of immersion in the VR environment, with most perceiving the surroundings as highly realistic. According to the SUS questionnaire, which measures the sense of presence on a scale from 0 (no presence at all) to 7 (a strong feeling of being physically present in the environment), scores ranged from 0 to 7, with a mean score of 6.05 ± 1.60. Notably, one participant was unable to answer the SUS immersion item due to the severity of their cognitive condition, while another participant responded with a score of 0, indicating no sense of presence in the virtual environment. From a qualitative perspective, about half of the participants described the environment as resembling a documentary or an external visual space, whereas the other half reported the sensation of having personally visited the location.

Regarding mood changes as measured by the VAS, most participants showed stable or improved emotional states following the VR experience. Specifically, 11 out of 21 participants exhibited an improvement in mood (i.e., a lower VAS score after the experience compared to before), 9 participants maintained a stable mood throughout the session, and only 1 participant reported a slight worsening of mood (an increase from 1 to 3 on the VAS). It is important to note that on the VAS scale, lower values indicate a more positive mood (0 = extremely happy, 5 = extremely sad). The participant, who expressed a negative change in mood, attributed this change to the type of landscapes presented, describing them as isolated and reminiscent of once-lived in spaces that now appeared abandoned. This was, however, an exception, because the vast majority of participants had tranquility as the most prominent sensation: apart from this one participant who reported a feeling of desolation, all the others felt a sense of calmness during the VR experience.

Regarding side effects, most participants did not report any adverse reactions. However, two participants experienced mild anxiety, likely triggered by aversive memories or recent news events evoked by the VR scenario, as indicated by their VAS responses. One participant reported mental fatigue, which was attributed to the weight of the VR headset. Additionally, four participants described the headset as physically uncomfortable due to its weight. These observations point to potential limitations related to the physical burden of the Oculus headset, which should be carefully considered in future studies, particularly in terms of comfort and accessibility for older adults.

Regarding memory recall, 13 participants reported recollections of past events from their childhood or adolescence, often related to time spent with family members or visits to places resembling those shown in the VR scenarios. Two participants recalled more recent positive experiences, also connected to similar environments depicted in the virtual scenes. The remaining participants did not report any memory recall during the experience. Notably, one participant with moderate cognitive impairment, despite reporting feelings of anxiety and sadness, recalled a specific episode from the past while viewing the Tokyo park scenario, since it resembled a garden where she and her mother used to play with her children. In terms of feedback, six participants expressed a desire to explore more scenarios, three wished to move around or interact with the environment, and four suggested improvements to make the VR headset lighter and more comfortable. Three participants also expressed a preference for a greater variety of music.

The participant diagnosed with Alzheimer's disease, who obtained a MoCA score of 5, exhibited notable difficulties in responding to the open-ended questions included in the post-experience questionnaires. While this participant was able to provide responses related to mood, a more comprehensive understanding of the engagement with the VR experience was derived from the video recordings. Qualitative analysis of the footage revealed a high level of involvement: the participant appeared emotionally engaged and was observed singing along during the virtual scenarios, pointing at parts of the scene, and commenting about the beauty of what was observed. However, due to discomfort caused by the weight of the headset and a minor engagement (less singing and commenting) during the non-familiar scenario, the session had to be interrupted ahead of time.

Statistical Results

The linear mixed-effects model revealed a significant overall fit (Likelihood Ratio Test: $\chi2(6) = 16.13$, $p = 0.013$), with a marginal R2 of 0.229, indicating that the fixed effects accounted for 22.9% of the variance in mood scores. Omnibus tests showed a significant main effect of Time ($F(2, 63) = 6.44$, $p = 0.003$), as well as a significant main effect of the MoCA group ($F(1, 63) = 4.31$, $p = 0.042$). However, the Time × MoCA interaction was not significant ($F(2, 63) = 0.55$, $p = 0.581$), suggesting that mood improved over time similarly in both cognitive groups.

Post hoc analyses revealed a significant decrease in mood scores from pre- to mid- exposure ($\beta = –0.56$, $p = 0.007$) and from pre- to post-exposure ($\beta = –0.67$, $p = 0.001$), indicating an overall improvement in mood (Figure 3). Additionally, participants in the high-MoCA group reported significantly more positive mood scores overall (β = 0.34, p = 0.042). No significant interaction effects were observed between Time and MoCA group.

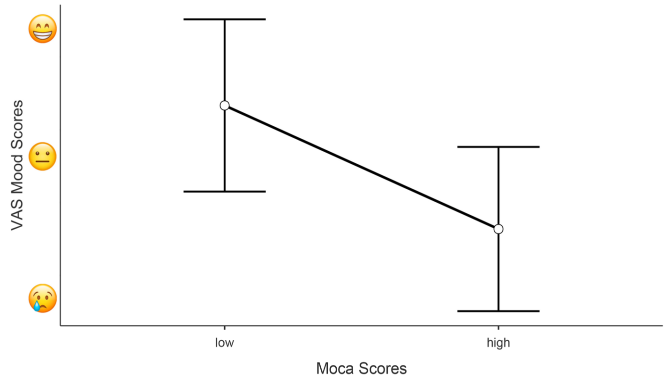

Figure 4. Mood scores by MoCA cognitive group. Boxplots show the distribution of overall mood scores (VAS averaged across the three time points) for participants with a low (MoCA ≤ 21) and high (MoCA ≥ 22) cognitive performance. The low-MoCA group showed significantly more positive mood scores overall compared to the high-MoCA group (p = 0.042).

Estimated marginal means showed a consistent decline in mood scores across the three time points (Figure 4), confirming a general trend of mood improvement: pre (M = 1.51, SE = 0.14), mid (M = 0.95, SE = 0.14), and post (M = 0.85, SE = 0.14). All statistical analyses are provided in Supplementary Table S2.

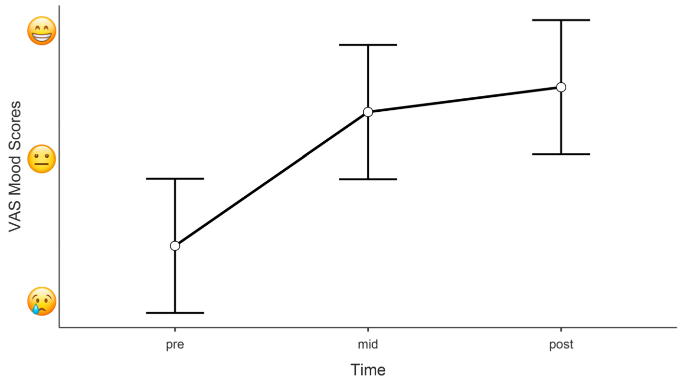

Figure 5. Mood changes over time across all participants. Estimated marginal means and standard errors of VAS mood scores at three time points: pre-, mid-, and post-video exposure. A significant improvement in mood was observed over time, with mood scores decreasing from pre (M = 1.51) to mid (M = 0.95) and post (M = 0.85) exposure (p < 0.01). Lower scores indicate a more positive mood.

Discussion

Here, we present a proof-of-concept study on the potential benefits of immersive VR- based interventions for individuals with different stages of cognitive decline, from absent to severe (including individuals with a clinical profile compatible with MCI or dementia). The results suggest that combining immersive virtual environments with emotionally evocative music can promote positive mood changes, trigger autobiographical memories, and offer a calming and engaging experience for most participants.

Statistically, mood significantly improved over the course of the intervention, with a clear reduction in negative affect from the pre- to mid- and post-video assessments. Specifically, participants reported lower mood disturbance scores after the VR experience, suggesting a progressive improvement in emotional state. Interestingly, this positive effect was observed regardless of cognitive status, although participants with lower MoCA scores (indicating greater impairment) exhibited even lower VAS scores overall—indicating a stronger emotional benefit in this subgroup. Previous studies have highlighted the potential of VR therapies in MCI and early AD for improving cognitive and physical functions (Yi et al., 2022). Additionally, the integration of music therapy within virtual environments has shown promise in alleviating the psychological and cognitive symptoms of AD (Byrns et al., 2020; Manera et al., 2015).

Our findings build upon previous research by integrating VR and music into a multi- sensory therapeutic intervention. This novel, multimodal approach shows promise in enhancing both emotional and cognitive outcomes. Notably, several participants with moderate cognitive impairment, as indicated by lower MoCA scores, were able to engage meaningfully with the experience. Many of them recalled emotionally salient autobiographical memories, often from childhood or adolescence, despite occasional feelings of anxiety or sadness. Even the participant with severe Alzheimer's disease showed signs of emotional involvement—such as singing along during the VR session—although they experienced challenges in verbal communication and required an early termination of the session due to the weight of the headset. These observations highlight the potential of immersive environments to foster emotional and cognitive engagement, even in individuals at more advanced stages of neurodegeneration (Chirico et al., 2020). Personalized and culturally relevant stimuli played a central role in eliciting these responses, emphasizing the importance of tailoring interventions to individual needs. Moreover, the aesthetically pleasing design of the VR scenarios contributed significantly to the intervention's overall appeal and effectiveness, enhancing user satisfaction and emotional resonance (Chatterjee & Vartanian, 2014). While minor side effects such as mental fatigue or discomfort were noted, they underscore the necessity of optimizing the device design and content customization to improve usability and the participants' experience.

Overall, our findings underline the importance of further research to advance VR- based interventions. Future studies should investigate how integrating culturally sensitive and individually tailored content can amplify the therapeutic benefits of VR. Additionally, exploring long-term impacts, scalability, and the integration of VR with other therapeutic modalities could pave the way for more robust applications in diverse clinical contexts.

The current study has several limitations. Firstly, the characteristics of the sample (elderly individuals with mild to moderate cognitive decline, with only one diagnosed AD patient) limit the generalizability of the findings to the broader AD population. Secondly, the short-term nature of the intervention precludes conclusions about its long-term effects on mood, cognition, or quality of life. Moreover, the lack of a control group makes it difficult to determine whether the observed effects can be attributed solely to the VR intervention. The variability in participants' familiarity and comfort with technology, as well as the subjectivity of the questionnaire ratings, may have also influenced the outcomes. Finally, another limitation concerns the practical aspects of the VR system itself. The weight of the Oculus Quest 2 device may have caused discomfort during prolonged sessions, particularly for older participants, potentially impacting their overall experience. Additionally, the relatively high cost of VR equipment may limit its accessibility and scalability in broader clinical applications.

However, it is important to note that this is a first proof-of-concept study, and these limitations are more pertinent to intervention studies, which are beyond the scope of the current research. Instead, the specific methodological limitations associated with proof-of- concept studies should be considered. Additionally, the absence of objective physiological metrics to assess engagement and stress levels during VR exposure is often considered a limitation. However, in this study, we collected physiological data, including respiratory frequency and heart rate variability, alongside subjective assessments, which will be used in a subsequent study to verify the feasibility and applicability of this novel VR approach, now that the protocol has been illustrated and proved tolerable even for individuals with dementia (Park et al., 2019).

Conclusions

The positive results of this proof-of-concept study provide a solid foundation for the design and implementation of larger-scale randomized controlled trials (RCTs) to validate the preliminary findings. Future RCTs should aim to assess the efficacy of VR interventions in improving cognitive and emotional outcomes in AD populations, with a particular focus on long-term effects. Building on the promising outcomes observed, further research could also explore the integration of VR with other non-pharmacological approaches, such as cognitive training or physical exercise, to potentially enhance its therapeutic impact. These next steps will contribute to establishing VR as an accessible and effective tool for cognitive rehabilitation in neurodegenerative conditions.

An important issue related to VR immersions using the Oculus device is its high cost and relatively bulky design, which may reduce its accessibility for widespread use. This limitation could be addressed in future studies by adopting VR visors compatible with mobile phones. These devices are not only more affordable but also portable and easier to use, making them more accessible for patients and their caregivers. As current VR technology allows the translation of Oculus-programmed scenarios to smartphone- compatible formats, this approach could facilitate the testing of this paradigm and other similar interventions in diverse settings, including home environments, thereby increasing its feasibility and practicality.

In our study, we utilized existing videos and music, adopting them to the cultural background of our participants and enhancing their aesthetic and evocative impact. The findings confirmed the validity of this approach. In future, the VR content could be fully tailored to the cultural and individual differences of the participants to further optimize the intervention's effectiveness and accessibility. For example, VR scenarios could be adapted to reflect familiar landscapes or cultural landmarks relevant to specific populations, such as local parks, iconic monuments, or traditional environments. Additionally, incorporating language customization and culturally specific auditory cues (e.g., traditional music or ambient sounds) could enhance the user experience. Personalizing content based on individual preferences, such as serene natural scenes for relaxation or interactive tasks for cognitive stimulation, might further improve engagement and therapeutic outcomes (Pardini et al., 2022). In summary, while this study underscores the promise of VR as a complementary therapeutic tool for improving emotional well-being in AD patients, it is noteworthy that even participants with lower MoCA scores, indicative of moderate dementia, and one participant with diagnosed AD, demonstrated positive outcomes.

Despite challenges such as transient anxiety and sadness, all our participants recalled meaningful autobiographical memories, suggesting the potential of VR aesthetic immersions to evoke emotional and cognitive engagement even in the most advanced stages of cognitive decline. Quantitative analyses further support this observation: mood scores showed a significant improvement over time, with reductions in negative affect from pre- to mid-VR exposure and from pre- to post-VR, indicating a progressive enhancement in emotional well-being across the session. Interestingly, participants with lower MoCA scores seemed to have even more pronounced mood improvements, suggesting that those with a greater cognitive impairment may derive a particular benefit from this kind of intervention. The aesthetic quality of the VR experience, characterized by its immersive and visually engaging content, contributed to its overall effectiveness and user satisfaction, encouraging one to further expand the applications of VR for mood and cognitive rehabilitation in dementia.

Discussion

The studies included in this thesis examined whether participation in music-based multidomain activities and exposure to immersive aesthetic environments may influence neural, cognitive, and psychological processes that are relevant for ageing trajectories and the development of frailty. According to contemporary gerontological perspectives, frailty is increasingly understood as a multidimensional condition rather than as a purely physical syndrome. Moreover, multidomain interventions have emerged as promising strategies for addressing the complex determinants of ageing vulnerability by simultaneously targeting several domains such as cognition, physical activity, nutrition, and social engagement. However, the potential contribution of structured musical activities within multidomain intervention frameworks has so far received relatively limited empirical investigation. Together, the studies of the present thesis explored how multidomain forms of engagement and enriched environments may contribute to supporting adaptive functioning and potentially mitigating processes associated with frailty in later life.

The studies included in this thesis examined populations situated at different points along the ageing continuum. The first two investigations focused on community-dwelling older adults without diagnosed impairment, representing a context of healthy or pre-frailty ageing. The third exploratory study examined older individuals exhibiting varying levels of cognitive functioning, as assessed through cognitive screening measures (MoCA). Although these populations differ in their level of vulnerability, they can be understood within a common continuum of ageing processes rather than as categorically distinct states. Contemporary perspectives on health increasingly conceptualize it not merely as the absence of disease, but as the capacity to maintain functional ability, psychological well-being, and adaptive engagement with the environment across the lifespan (World Health Organization, 2015). Furthermore, variability in cognitive performance can be interpreted as part of a dynamic trajectory of ageing in which biological, cognitive, and psychosocial resources interact to determine individual resilience or vulnerability.

The research presented in this thesis adopts a life-course perspective on ageing that considers both healthy ageing and early cognitive vulnerability as relevant contexts for identifying environmental and experiential factors capable of supporting resilience and delaying trajectories of multidimensional frailty. The work presented in Section 2.1 described the methodological design of the MultiMusic multidomain intervention, which integrates neurobiological, audiometric, neurophysiological, cognitive, and psychosocial measures in the investigation of choir-centered enrichment programs. By combining molecular indicators such as brain-derived neurotrophic factor (BDNF) with neurophysiological and behavioral measures, the protocol provides a structured approach for examining how musical activities, combined with different type of activities, may influence neural plasticity and functional outcomes in ageing populations. Biological markers such as BDNF have been associated with synaptic plasticity and learning processes and have increasingly been considered promising indicators of experience-dependent neural adaptation in intervention research (e.g., Cotman et al., 2007; Erickson et al., 2011; de Sousa Fernandes et al., 2020, review; Zou & Hao., 2024, review). The protocol therefore contributes to methodological efforts aimed at integrating biological and neurophysiological markers within multidomain lifestyle-based intervention studies targeting mechanisms potentially relevant to the prevention of frailty and decline.

The empirical investigation described in Section 2.2 examined the effects of sustained participation in a choir-based multidomain intervention. The findings indicated that a 9-month engagement in choral practice was associated with changes in neurophysiological indices of auditory processing together with improvements in psychological well-being and multidimensional frailty indicators. These results are consistent with the idea that multidomain interventions including musical activities represent particularly complex forms of engagement capable of simultaneously recruiting and act on multiple systems. In fact, musical participation has been shown to involve distributed networks including auditory, motor, limbic, and frontal regions supporting perception, prediction, emotional processing, and cognitive control (Zatorre et al., 2007; Herholz & Zatorre, 2012; Koelsch, 2014; Vuust et al., 2022).

In the context of ageing, activities such as choir singing may therefore provide ecologically meaningful forms of stimulation that combine cognitive effort, sensorimotor coordination, emotional expression, and social interaction within a single experience. In addition to neural mechanisms, group-based musical engagement may also influence psychological and social dimensions that are closely related to trajectories of frailty in later life. Participation in choir singing has been associated with improvements in mood, social connectedness, and overall well-being among older adults (Johnson, 2013; 2017; 2020). Because multidimensional frailty involves not only biological decline but also psychosocial vulnerability, activities capable of fostering social participation and emotional engagement may play an important role in supporting resilience across multiple domains of functioning.

A complementary perspective is provided by the exploratory study described in Section 3.1, which examined the potential effects of immersive virtual reality environments incorporating music and natural landscapes. The findings suggested that exposure to aesthetically enriched environments may positively influence mood and psychological well-being in individuals experiencing cognitive vulnerability. These results are consistent with research indicating that aesthetically engaging stimuli can activate neural systems involved in emotional appraisal, reward processing, and self-referential cognition (Vessel et al., 2012; 2019; 2023). In addition, exposure to natural environments has been associated with emotional restoration and reductions in stress-related neural activity (Ulrich et al., 1991; Bratman et al., 2015). Immersive technologies such as virtual reality therefore offer new opportunities for delivering emotionally meaningful sensory experiences that may support psychological well-being, particularly when direct access to natural environments or cultural activities is limited.

The present findings can also be interpreted in terms of flourishing, a multidimensional construct that includes emotional well-being, psychological functioning, and social integration (Keyes, 2002; Huppert & So, 2013). This perspective shifts the focus from the reduction of deficits to the capacity to maintain engagement, meaning, and participation in life despite age-related challenges. Enriched experiences such as musical engagement and immersive environments may support flourishing by promoting emotional engagement, social connection, and adaptive functioning. Importantly, flourishing does not require the absence of vulnerability, but rather reflects the ability to sustain positive functioning in its presence (VanderWeele, 2017). The effects observed in this thesis can therefore be interpreted not only as reductions in frailty-related vulnerability, but also as indications of enhanced capacity for positive adaptation.

At the same time, several limitations should be considered when interpreting the findings presented in this thesis. Some of the studies relied on relatively small samples or exploratory designs, and the complexity of multidomain interventions makes it difficult to isolate the contribution of individual components. In addition, ageing trajectories are highly heterogeneous, and responses to enrichment-based activities may vary substantially across individuals. Future research will be necessary to further clarify the mechanisms through which enriched experiences influence neural and psychological functioning across the ageing process. Larger and randomized studies will be essential to determine the long-term impact of music-based and aesthetically enriched interventions on cognitive health, functional independence, and trajectories of multidimensional frailty.

Overall, the studies included in this thesis suggest that enriched experiences combining sensory, cognitive, emotional, and social stimulation may represent promising approaches for supporting adaptive processes in ageing. Music-based engagement and aesthetically immersive environments can be understood as complementary forms of experiential enrichment capable of stimulating multiple neural and psychological systems simultaneously. Within the multidimensional context of frailty, such experiences may contribute to strengthening resilience, as they reflect the integrative nature of everyday human activities.

Conclusion

Population ageing represents one of the most significant demographic transformations of contemporary societies and poses new challenges for promoting functional ability, psychological well-being, and to counteract the negative effects of cognitive decline and loneliness in later life. In current perspectives, ageing is increasingly understood as a dynamic process in which multiple factors interact to shape trajectories of vulnerability and adaptation. Addressing frailty therefore requires approaches that move beyond purely biomedical models and consider the broader environmental and experiential contexts in which ageing unfolds. Stimulating activities, social participation, and access to stimulating environments may represent important resources for maintaining engagement and supporting adaptive functioning across the ageing trajectory. Rather than focusing exclusively on the treatment of disease, contemporary perspectives on ageing emphasize the importance of creating conditions that allow individuals to remain active participants in meaningful experiences.

Among the many forms of environmental engagement available in later life, artistic activities and aesthetic contents offer particularly rich opportunities for multidimensional stimulation. Music, for example, simultaneously engages perceptual, motor, affective, and social processes, while aesthetic encounters with natural or artistic environments can evoke emotional responses, attentional restoration, and reflective experiences. Such activities may therefore contribute to supporting adaptive capacities that are relevant for ageing populations.

These considerations can be further interpreted within a psychological perspective that emphasizes the role of behavior, experience, and meaning-making processes in shaping ageing trajectories. In fact, nowadays approaches increasingly highlight the importance of promoting adaptive psychological functioning, including engagement, emotional regulation, and perceived meaning in everyday activities instead of focusing exclusively on risk reduction. In this context, large-scale collaborative initiatives such as the World-Wide FINGERS network have emphasized multidomain strategies combining lifestyle, cognitive, and social interventions to address the complex determinants of ageing-related vulnerability (Ngandu et al., 2015; Kivipelto et al., 2020). Such interventions can be understood as targeting not only cognitive and physical health, but also motivational, affective, and self-regulatory processes that sustain long-term engagement.

Therefore, the concept of multidimensional frailty can be meaningfully extended beyond its traditional gerontological framing and reinterpreted within a psychological, mind–body perspective. In this view, frailty reflects not only the accumulation of deficits, but a reduced capacity to integrate cognitive, emotional, bodily, and social processes in adaptive interaction with the environment. This perspective has important implications for intervention research, as it highlights the value of experiences that engage the individual as an integrated system. Cultural participation and access to aesthetically enriched environments acquire particular relevance, as they provide opportunities for emotionally meaningful and intrinsically motivating experiences. Community-based initiatives incorporating artistic and aesthetic engagement may therefore contribute to supporting well-being not only through stimulation, but also by fostering psychological processes such as interest, enjoyment, social connectedness, and sense of purpose. In this sense, integrating experiential and meaning-related dimensions into multidomain intervention frameworks may represent a valuable direction for promoting adaptive functioning and well-being in later life.

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