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DOTTORATO DI RICERCA IN NEUROSCIENZE APPLICATE XXXVIII° CICLO BIS

TESI DI DOTTORATO

"The MultiMusic multidomain intervention including choral practice in community-dwelling older people"

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Abstract (English)

Population aging is associated with cognitive, sensory, functional, and psychosocial changes that contribute to the development of multidimensional frailty. In the absence of effective pharmacological treatments for age-related cognitive and functional decline, non-pharmacological, multidomain interventions represent a priority strategy for promoting neuroplasticity, resilience, and healthy aging. Within this framework, active musical engagement, and in particular choir singing, constitutes an ecological intervention capable of integrating cognitive, auditory, motor, emotional, and social stimulation.

This PhD thesis describes the design of a randomized controlled study protocol with the results of a non-randomized feasibility study based on the MultiMusic program, a multidimensional choir-centered intervention for community-dwelling older adults without prior formal musical training.

The nine-month feasibility study involved 54 older adults assigned to a choir group, an active control group (non-musical recreational activities), and a passive control group. Assessments conducted at baseline and follow-up included measures of cognitive functioning, psychological well-being, multidimensional frailty, music perception, audiometric thresholds, and auditory evoked potentials.

Overall, the MultiMusic program showed good feasibility and high acceptability. Longitudinal analyses revealed an increase in cognitive reserve and, in parallel, a specific reduction in N2-P3 inter-peak latency in the choir group, suggesting greater efficiency in auditory-cognitive processing. Additionally, exploratory within-group analyses showed a reduction in multidimensional frailty among choir participants and individuals with higher overall activity engagement, while greater engagement was associated with higher psychological well-being at follow-up.

Overall, the findings support the MultiMusic program as a feasible, sustainable, and ecologically grounded multidomain intervention, and provide a solid foundation for the development of future randomized controlled trials with larger samples.

Abstract (Italian)

L'invecchiamento della popolazione è associato a cambiamenti cognitivi, sensoriali, funzionali e psicosociali che contribuiscono allo sviluppo di una fragilità multidimensionale. In assenza di terapie farmacologiche efficaci per contrastare il declino cognitivo e funzionale legato all'età, gli interventi non farmacologici e multidominio rappresentano una strategia prioritaria per promuovere neuroplasticità, resilienza e invecchiamento sano. In questo contesto, la pratica corale costituisce un intervento ecologico in grado di integrare stimolazione cognitiva, uditiva, motoria ed interazione sociale. Tuttavia, le evidenze sulla sua fattibilità e sui correlati neurofisiologici negli anziani residenti in comunità sono ancora limitate.

La presente tesi di Dottorato descrive la progettazione di un protocollo di studio randomizzato controllato e presenta i risultati di uno studio di fattibilità non randomizzato basato sul programma MultiMusic, un intervento multidimensionale incentrato sulla pratica corale, rivolto ad anziani residenti in comunità privi di precedente formazione musicale.

Lo studio di fattibilità, della durata di nove mesi, ha coinvolto 54 anziani suddivisi in gruppo coro, gruppo di controllo attivo (attività ricreative non musicali) e gruppo di controllo passivo. Le valutazioni, effettuate al basale e al follow-up, hanno incluso misure di funzionamento cognitivo, benessere psicologico, fragilità multidimensionale, percezione musicale, misure audiometriche e potenziali evocati uditivi.

Il programma ha mostrato buona fattibilità ed elevata adesione. Le analisi longitudinali hanno evidenziato un miglioramento nella riserva cognitiva e, parallelamente, una riduzione specifica della latenza interpicco N2-P3 nel gruppo del coro, suggerendo una maggiore efficienza nell'elaborazione uditivo-cognitiva. Inoltre, le analisi esplorative hanno mostrato una riduzione della fragilità multidimensionale nel gruppo corale e nei partecipanti con maggiore coinvolgimento complessivo, mentre livelli più elevati di engagement risultavano associati a punteggi più alti di benessere psicologico al follow-up.

Nel complesso, i risultati supportano il programma MultiMusic come intervento multidimensionale sostenibile ed ecologicamente valido, e forniscono una solida base per lo sviluppo di futuri studi controllati randomizzati su campioni più ampi.

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Preface

Population ageing is one of the most significant demographic transitions of the 21st century. According to the World Health Organization (WHO) the proportion of people aged 60 years and older is increasing faster than any other age group worldwide, with the global population of older adults expected to double by 2050. This demographic shift is occurring across both high-income and low- and middle-income countries and reflects major achievements in public health, medical care, and living conditions (World Health Organization 2015).

However, increased longevity does not necessarily translate into extended periods of good health. Evidence indicates that gains in life expectancy are frequently accompanied by disproportionate increases in morbidity, functional decline, disability, and heightened vulnerability (Sierra 2019). Therefore, population ageing poses complex public health challenges. There is a clear need to move beyond a narrow focus on disease prevention and treatment toward comprehensive models of healthy ageing that emphasize functional ability and intrinsic capacity across the life course (Beard et al. 2016; Rudnicka et al. 2020). Addressing the challenges of an aging population requires coordinated policy action that goes beyond healthcare and extends to social services and urban planning (Khan et al. 2024). As highlighted by Gianfredi et al. (Gianfredi et al. 2025) the success of this transformation ultimately hinges on implementing integrated health policies and multidisciplinary care models that can translate increased longevity into meaningful improvements in quality of life.

Within this context, a growing attention has been directed toward non-pharmacological, lifestyle-based interventions aimed at sustaining functional ability and resilience in later life (Ngandu et al. 2015; World Health Organization 2019). In particular, lifestyle-based approaches involving physical activity, cognitive stimulation, and social engagement are consistently associated with better brain health and cognitive outcomes in older age (Colcombe and Kramer 2003; Hertzog et al. 2008). These approaches are formalized within multidomain intervention models, which recognize that age-related vulnerability stems from the interaction of cognitive, sensory, physical, and psychosocial factors.

Within this framework, music has emerged as a particularly promising form of enrichment, as musical engagement simultaneously involves auditory, cognitive, motor, emotional, and social processes (Kraus and Chandrasekaran 2010; Herholz and Zatorre 2012). Among music-based activities, choral singing represents a particularly valuable intervention from an ecological perspective, as it integrates auditory-motor coordination, cognitive demands, respiratory training, and structured social interaction in a group setting.

Although community-based and neurophysiological studies suggest cognitive, emotional, and neural benefits of choir participation in older adults (Pentikäinen et al. 2021, 2023, 2022; Moisseinen et al. 2025), longitudinal multidomain investigations combining cognitive, audiometric, and neurophysiological outcomes remain limited.

This doctoral thesis fits into this context, focusing on *MultiMusic*, a multidomain intervention centred on choral practice and designed for older adults living in communities without prior musical training. Based on theoretical models of enriched environments, multidimensional frailty, and experience-dependent neuroplasticity, this work adopts an integrated assessment framework that includes cognitive, audiological, psychosocial, and neurophysiological measures.

Specifically, this thesis presents the development and methodological rationale of a randomized controlled study protocol investigating a multidomain music intervention (Chapter II) and the results of a non-randomized feasibility study conducted in an ecologically valid community setting (Chapter III).

The chapters are drawn from manuscripts developed during the doctoral period. Chapter II is based on the manuscript "*The MultiMusic multidomain intervention including choral practice in community-dwelling older adults: a study protocol for salivary biomarkers of brain-derived neurotrophic factor (BDNF), audiometric, and neuropsychological parameters*", submitted to Heliyon and currently under peer review. Chapter III is based on a manuscript currently under preparation. The original manuscripts have been substantially adapted to ensure consistency with the structure, objectives, and integrative narrative of this thesis.

Chapter I - Background

1.1 Biological and functional changes in older age

Ageing is a multifactorial process marked by physiological damage and heightened disease risk throughout life (Silva et al. 2023; Z. Li et al. 2021).

Biologically, ageing reflects failing cellular maintenance systems driven by hallmarks including genomic instability, epigenetic changes, mitochondrial dysfunction, proteostasis loss, stem cell exhaustion, and altered intercellular communication (Maldonado et al. 2023; López-Otín et al. 2013). Genomic instability and telomere shortening promote mutations accumulation and increase the risk of chronic diseases (López-Gil et al. 2023; Martemucci et al. 2022). Age- related changes in epigenetic mechanisms (DNA methylation, histone modifications) alter gene expression without changing the DNA sequence and contributing to the so-called epigenetic clock (López-Gil et al. 2023). Mitochondrial function declines, with reduced ATP production and increased reactive oxygen species (ROS) generation, amplifying oxidative stress (Maldonado et al. 2023). Cells progressively lose proteostasis, resulting in the accumulation of damaged or misfolded proteins characteristic of many neurodegenerative disorders (Martemucci et al. 2022). Concurrently, stem cell exhaustion reduces regenerative capacity in several tissues (Morganti and Ito 2021; Granic et al. 2023). These processes are shaped by both genetic background and environmental influences, as endogenous and exogenous stressors converge on regulatory pathways that progressively compromise cellular homeostasis (Warraich et al. 2020).

These changes cause decline across multiple bodily systems, including musculoskeletal, sensory, cognitive, cardiovascular, and neurophysiological functions, leading to frailty in in older adults (Alsararatee 2025). In the cardiovascular system, ageing leads to arterial stiffening, fibrosis, and impaired cardiac function, resulting in increased cardiovascular disease risk (Wood et al. 2025; Fajemiroye et al. 2018). The respiratory system undergoes parallel age-related alterations, including reduced alveolar surface area, decreased lung tissue elasticity, and weakening of respiratory muscles, leading to diminished ventilatory efficiency (Janssens et al. 1999). Sympathetic-parasympathetic imbalance favors sympathetic overactivity, impairing baroreflex sensitivity and promoting inflammaging via reduced parasympathetic anti-inflammatory effects (Errico et al. 2025). Skeletal muscle mass decreases 0.64-0.98% yearly after age 75, while strength decreases 2.5-4% annually(Mitchell et al. 2012). Grip strength peaks in early adulthood and weakens progressively, predicting mortality (Metter et al. 2002). Age-related impairments in hearing, balance, smell, and voice are also prevalent in older adults, associated with reduced quality of life and disability (Sable-

Morita et al. 2023; Assi et al. 2023). Among sensory modalities, age-related hearing loss represents one of the most pervasive and impactful conditions in later life, affecting approximately one third of adults over 65 years of age and up to two thirds of those over 70 (Frank R. Lin et al. 2011) and is a leading modifiable risk factor for cognitive decline (Livingston et al. 2024). Degraded auditory input increases listening effort and cognitive resource use, while communication difficulties reduce social participation (Peelle and Wingfield 2016; Mick et al. 2014). Hearing loss is also associated with cortical atrophy and altered connectivity in auditory and frontal regions (F. R. Lin et al. 2014; Peelle and Wingfield 2016; Uchida et al. 2019).

From a cognitive perspective, later adulthood is characterized by changes in processing speed, attentional control, and working memory, which impair efficiency in daily activities and reduce independence (Harada et al. 2013; Park and Festini 2017). However, cognitive ageing follows heterogeneous trajectories. While some older adults experience decline leading to cognitive impairment or dementia, others maintain preserved cognitive functioning into advanced age. This variability reflects the influence of factors across the lifespan, including lifestyle, socioeconomic conditions, social participation, and health status. Older adults who remain mentally, socially, and physically active show greater resilience to cognitive decline (Colcombe and Kramer 2003; Hertzog et al. 2008), whereas reduced stimulation and social withdrawal accelerate deterioration. Cognitive aging is thus conceptualized as a modifiable process, and research emphasizes identifying protective factors and developing non-pharmacological interventions to preserve cognitive functioning in later life, aligned with preventive approaches to healthy aging (Ngandu et al. 2015; World Health Organization 2019).

1.2 Multidimensional frailty

Frailty is increasingly recognized as a multidimensional clinical syndrome characterized by a decreased physiological reserves and increased vulnerability to stressors, arising from cumulative decline and dysregulation across multiple interrelated systems (physical, medical, cognitive, psychological, and social) (Pilotto et al. 2020; Clegg et al. 2013; De Biasio et al. 2020). This multidimensional perspective aligns with modern views of aging that emphasize heterogeneity, resilience, and the dynamic interplay between biological and environmental factors.

Epidemiological and clinical evidence consistently shows that multidimensional frailty is common in older adults and strongly predicts a wide range of negative outcomes, including falls, disability, hospitalization, institutionalization, poor quality of life, and mortality in community, hospital, and intensive care settings (Clegg et al. 2013; De Biasio et al. 2020; Chu et al. 2021; Vermeiren et al. 2016). Meta-analyses indicate that individuals who are pre-frail or frail have a disability, hospitalisation, fall, fracture and death risk that is approximately 1.6 to 2.8 times greater than that of robust older adults (Vermeiren et al. 2016; Chu et al. 2021).

Beyond physical impairment, greater frailty is linked to poorer mental health, unhealthy lifestyles, cognitive deficits, and structural brain changes, underscoring its systemic nature (Jiang et al. 2023). Longitudinal cohort studies show that frailty is a dynamic and reversible syndrome, characterized by frequent bidirectional transitions between states of robustness, pre-frailty, and frailty that correlate with significant changes in mortality risk and health-related quality of life outcomes (Romero-Ortuno et al. 2021; S. Wang et al. 2026).

Multidimensional approaches to frailty recognize distinct profiles of frailty, including physical, cognitive, psychological, and social frailty. Network and cohort studies show that mobility and balance impairments, depressive symptoms, social vulnerability, and cognitive decline often form central nodes within frailty networks and that their co-occurrence greatly amplifies the risk of adverse outcomes compared to physical frailty alone (Liang Feng et al. 2017; Panza et al. 2018; Y. Lee et al. 2022). In particular, the concept of cognitive frailty, i.e., the coexistence of physical frailty and cognitive decline in the absence of overt dementia, has attracted increasing attention as a transient and potentially modifiable state linking frailty to cognitive decline in older age (Panza et al. 2018; Ponvel et al. 2025).

Several multidimensional tools have been developed to operationalize this complexity, including the Multidimensional Prognostic Index, the Tilburg Frailty Indicator, and multidomain frailty indices, which integrate physical, medical, cognitive, psychological, social, and environmental domains (Vermeiren et al. 2016; Zamora-Sánchez et al. 2022; Pilotto et al. 2019). Using these tools, heterogeneity in aging trajectories can be captured more accurately than chronological age alone and clinically meaningful prognostic information can be provided in multiple care settings.

Both conceptually and practically, recognizing frailty as a bio-psycho-social syndrome provides a solid rational basis for comprehensive geriatric assessment and multidomain interventions that simultaneously target mobility, comorbidities, nutrition, cognition, mood, sensory function, and social support, rather than in isolation (Pilotto et al. 2020; Hoogendijk et al. 2019). Emerging interventional studies suggest that such multidomain approaches may modify trajectories of physical vulnerability and cognitive decline, particularly in prefrail individuals and in those with cognitive frailty, supporting a preventive and resilience-oriented model of care (Panza et al. 2018; Ponvel et al. 2025).

1.3 Non-pharmacological interventions and multidomain approaches

In the absence of disease-modifying pharmacological treatments capable of reliably preventing or halting age-related cognitive decline, research has increasingly focused on non-pharmacological, lifestyle-based strategies for dementia risk reduction. Extensive observational and interventional research suggests that elevated levels of physical activity, cognitive engagement, adherence to a healthy diet, and active social participation are correlated with enhanced cognitive performance and a reduced risk of dementia in later life (Colcombe and Kramer 2003; Whitty et al. 2020; Dominguez et al. 2021). Importantly, many of these factors are potentially modifiable even in older age, providing a strong rationale for preventive approaches targeting behaviour and lifestyle rather than disease pathology alone (Coley et al. 2022; Walsh et al. 2022).

Over the past decade, these findings have been translated into multidomain intervention models, which explicitly recognise that late-life vulnerability arises from the joint effects of cognitive, sensory, physical, vascular, and psychosocial factors rather than from isolated impairments (Grande et al. 2020; Coley et al. 2022; Deckers et al. 2024). The landmark Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) provided the first large-scale randomized evidence for this framework, demonstrating that a two-year intervention combining nutritional guidance, structured physical exercise, cognitive training, and intensive vascular risk monitoring yielded small but significant benefits in global cognition, executive function, memory, and processing speed in at-risk older adults (Rosenberg et al. 2018; Ngandu et al. 2015). Notably, these improvements were largely independent of baseline age, sex, education, socioeconomic status, and cardiovascular risk, indicating broad applicability across diverse aging populations (Rosenberg et al. 2018). Greater adherence to the various lifestyle components was correlated with enhanced cognitive gains, highlighting the importance of sufficient intensity and sustained behavioral engagement (Ngandu et al. 2022).

Subsequent FINGER-inspired trials conducted in different cultural and clinical contexts have further supported the multidomain approach while highlighting important sources of heterogeneity. The GOIZ ZAINDU feasibility trial in Southern Europe reported high adherence and a reduced risk of decline in executive function and processing speed (Tainta et al. 2024), whereas FINGER-NL expanded the multidomain framework to include sleep counselling, stress management, and social activities, aiming to clarify long-term effects in a large Dutch cohort (Deckers et al. 2024). Scalable delivery formats have also been explored: a large Australian randomized trial demonstrated that a fully remote, personalized, internet-delivered multidomain intervention targeting physical activity, diet, cognitive activity, and mood produced significantly better global cognition than information-only control over three years (Brodaty et al. 2025).

Systematic reviews and meta-analyses converge on the conclusion that both single-domain and multidomain lifestyle interventions can preserve or improve cognitive functioning in older adults without dementia, with combined physical and cognitive training and broader multidomain programs among the most effective strategies (Gavelin et al. 2021; Whitty et al. 2020; Coley et al. 2022). In cognitively unimpaired older adults, network meta-analyses indicate small but significant benefits of interventions combining exercise, cognitive training, diet, and health education compared with usual care (Mendes et al. 2025), whereas in individuals with mild cognitive impairment, multimodal programs tend to outperform single-component approaches across multiple cognitive domains (Chan et al. 2025).

Conceptually, multidomain lifestyle interventions are closely aligned with the World Health Organization's healthy ageing and intrinsic capacity frameworks, which emphasise maintaining functional ability by supporting neuromusculoskeletal, cognitive, psychological, sensory, and vitality domains across the life course (World Health Organization 2015). This perspective overlaps substantially with models of multidimensional frailty, which conceptualise vulnerability as the cumulative burden of deficits across physical, cognitive, psychological, functional, and social domains (Rockwood and Mitnitski 2007; Pilotto et al. 2020). From this standpoint, the goal of multidomain interventions extends beyond cognition per se, encompassing functional independence, emotional well-being, social participation, and quality of life outcomes that are deeply intertwined with cognitive resilience in older age (Grande et al. 2020; Deckers et al. 2024).

Despite this promising evidence, results across trials are not uniformly positive, and effect sizes are generally modest. Heterogeneity in target populations, intervention composition, intensity, duration, and outcome measures complicates direct comparisons and may partly explain mixed findings (Coley et al. 2022; Whitty et al. 2020; Deckers et al. 2024). Moreover, adherence can be demanding, and the adoption of multiple lifestyle changes may be less feasible in individuals with greater frailty or fewer resources, raising important implementation and equity considerations (Chan et al. 2025; Walsh et al. 2022). Identifying intervention formats that are ecologically valid, socially embedded, and intrinsically motivating therefore remains a key challenge for the field.

1.4 Neuroplasticity, cognitive reserve, neurophysiological and biological markers

The effectiveness of multidomain non-pharmacological interventions in older adults depends on the persistence of experience-dependent neuroplasticity and interindividual differences in cognitive reserve and maintenance of brain function. Neuroplasticity refers to the nervous system's ability to reorganize its structure, function, and connectivity in response to intrinsic and extrinsic stimuli throughout life. Although neuroplasticity processes are most pronounced during early development, converging evidence from animal and human studies demonstrates that significant neural reorganization continues throughout adulthood and into older age, particularly under conditions of environmental enrichment (Parambath et al. 2025; Cutuli et al. 2022)

In animal models, long-term environmental enrichment, even when initiated in mid- or late life, enhances hippocampal neurogenesis, improves learning and memory, and attenuates markers of age-related degeneration, indicating that sustained behavioral activity can augment plastic potential beyond the developmental period (Parambath et al. 2025; Cutuli et al. 2022; Birch and Kelly 2019).

At the systems level, these plastic mechanisms underlie contemporary models of cognitive resilience. Cognitive reserve refers to the ability to maintain cognitive performance despite age-related or pathological brain changes, reflecting interindividual differences in the efficiency, flexibility, and adaptability of neural resource recruitment (Stern 2002; Stern et al. 2019). Reserve is shaped by life experiences such as education, occupational complexity, intellectual engagement, and social participation, and supports the recruitment of alternative or compensatory networks when structural or functional decline occurs (Cabeza et al. 2018; Oosterhuis et al. 2023). Closely related constructs include brain reserve, which emphasizes structural aspects (e.g., synaptic density, brain volume), and brain maintenance, which refers to the relative preservation of youthful brain structure and function in old age (Cabeza et al. 2018; Stern et al. 2019). Together, these mechanisms help explain the marked interindividual variability observed in cognitive aging trajectories.

From a methodological perspective, the effects of experience-dependent neuroplasticity and reserve enhancement may not be fully captured by behavioral measures alone, particularly in preventive interventions targeting older adults without cognitive deficits or with mild deficits. Meta-analyses of combined physical and cognitive training and cognitive stimulation show small-to-moderate cognitive gains, often domain-specific, suggesting that early neural adaptations may precede or exceed measurable behavioral change (Gómez-Soria et al. 2023; Nguyen et al. 2019). Consequently, growing emphasis is placed on neurophysiological and iological markers that can index latent changes in processing efficiency.

A key biological mediator linking environmental enrichment, neuroplasticity, and reserve is brain-derived neurotrophic factor (BDNF). BDNF is the most widely distributed neurotrophins in the adult brain and plays a central role in neuronal survival, synaptogenesis, dendritic remodeling, neurogenesis, and the induction and maintenance of long-term potentiation (Colucci-D’Amato et al. 2020; Numakawa et al. 2018). BDNF is synthesized as the precursor proBDNF and undergoes proteolytic cleavage to produce mature BDNF (mBDNF), with these two forms exerting opposite biological effects through distinct receptor systems(Mitrovic et al. 2025). ProBDNF activates p75NTR signaling pathways that promote neuronal apoptosis and synaptic weakening(Teng et al. 2005), while mature BDNF activates TrkB receptors, stimulating neuronal survival, synaptic strengthening, and dendritic spine maturation (Benarroch 2015). BDNF expression is highly activity-dependent and can be modulated by sensory, cognitive, and physical stimulation. Enriched environments and exercise reliably regulate BDNF in the hippocampus and cortex and are proposed to mediate experience-dependent plasticity and cognitive benefits in both healthy and neurodegenerative conditions (Colucci-D'Amato et al. 2020; Numakawa et al. 2018; Cutuli et al. 2022) Conversely, chronic stress, neurodegenerative pathology, and inactivity are associated with reduced BDNF signaling (Gao et al. 2022; Numakawa and Kajihara 2024). The Val66Met polymorphism further modulates these effects, influencing activity-dependent BDNF secretion and potentially contributing to individual differences in neuroplasticity and cognitive vulnerability (Kailainathan et al. 2016).

Electroencephalography (EEG) and event-related potentials (ERPs) provide sensitive, non-invasive measures of sensory and cognitive processing and are widely used to characterize age-related change, early cognitive decline, and intervention effects. Indeed, aging produces measurable changes in ERP components, characterized by delayed latencies and altered amplitudes across cognitive processes. Kropotov et al. (Kropotov et al. 2016) found that cognitive control ERP component latencies increased with age, with early components showing 8 ms delays per decade and late components showing 20 ms delays per decade. E. Paitel et al. (Paitel et al. 2021) identified that reduced amplitude and delayed latency patterns are evident in later ERP components during complex tasks, particularly in pathological aging. Differences in P3a and P3b components between young and elderly groups were showed by Porcaro et al. (Porcaro et al. 2019), reflecting aging's impact on attention and cognitive processing. Recent randomized trials demonstrate that multidomain interventions can enhance ERP markers of memory and attention in older adults with subjective cognitive decline, even when standard neuropsychological tests show limited improvement(Cheng et al. 2024) highlighting that ERPs as more sensitive indices of intervention-related brain plasticity than traditional cognitive assessments (Cheng et al. 2024; Hong et al. 2021).

1.5 Music training as a multidimensional model of neural, cognitive, and biological plasticity

Musical training represents one of the most comprehensive models for studying experience-dependent brain plasticity across the lifespan, as it involve extensive and highly interconnected neural networks along with higher-order cognitive and emotional processes (Herholz and Zatorre 2012; Pantev and Herholz 2011). This multimodal and structured nature makes musical training particularly effective in inducing behavioral, functional, and structural changes in the brain on time scales ranging from a few days to years (Herholz and Zatorre 2012) and has therefore been conceptualized as a powerful and ecologically valid form of environmental enrichment, often described as “aerobics for the brain”.

Research consistently demonstrates that musicians exhibit distinct neural characteristics compared to non-musicians, with converging evidence for both structural and functional adaptations across sensorimotor, auditory, and limbic regions (Criscuolo et al. 2022). Structurally, musicians show greater cortical thickness in frontal and parietal areas, enhanced fractal dimensionality and sulcal depth in regions such as the left fusiform gyrus (Liu et al. 2025), and increased gray-matter volume in auditory–motor cortices and cerebellum that can be maintained into older age (Yamashita et al. 2021). Long-term and even shorter-term training across the lifespan is associated with increased white-matter integrity and enhanced interhemispheric connectivity within auditory–motor networks, reinforcing the notion that musical practice is a powerful model of experience-dependent plasticity (Q. Li et al. 2018; Criscuolo et al. 2022).

Functionally, musicians display stronger resting-state and task-related coupling among auditory, motor, and multisensory cortices, with increased connectivity within perceptual–motor networks and insula-based salience and control networks, suggesting more efficient integration of sensory inputs with precisely timed motor commands (Luo et al. 2012; Zamorano et al. 2017). These neural adaptations are paralleled by behavioral advantages in auditory and multisensory processing, including superior frequency and gap discrimination, speech perception, and audiovisual integration, as well as enhanced working memory and visuospatial abilities compared with non-musicians (Grassi et al. 2017; Román-Caballero et al. 2018).

In older adults specifically, observational and interventional work shows that lifelong or newly initiated musical practice is associated with better speech-in-noise perception, organization despite normal age-related atrophy (Grassi et al. 2017; Román-Caballero et al. 2018). 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. 2024; Zendel et al. 2019), and long-term interventions in musically naïve participants lead to a solid 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 and Schlaug 2015).

Electrophysiological studies provide converging evidence that music education induces experience-dependent neuroplastic changes throughout life. Using auditory and visual oddball paradigms, George and Coch (George and Coch 2011) showed that individuals with long-term musical training exhibit shorter P300 latencies and larger P300 amplitudes compared to non-musicians, consistent with enhanced efficiency of attentional and working memory-related processes associated with musical training.

In older adults, Bidelman et al. (Bidelman and Alain 2015) showed that musical experience is associated with greater temporal precision of both subcortical and cortical auditory responses accompanied by superior speech recognition abilities, indicating that musical training promotes the preservation of central auditory processing mechanisms that would otherwise be vulnerable to aging.

Bugos et al. (Jennifer A. Bugos et al. 2022) reported that a short music training course for older adults is associated with an increase in auditory-evoked theta oscillatory activity. Theta band activity has been linked to auditory segmentation, attentional engagement, and encoding-related processes. Importantly, these training-related changes were maintained in a three-month follow-up assessment, suggesting that modulation of cortical auditory dynamics may persist beyond the immediate intervention period.

From a molecular perspective, although still limited, evidence suggests that musical activities may influence biological pathways related to plasticity, including stress and neurotrophin regulation systems such as the BDNF. Angelucci et al. (Angelucci et al. 2007) conducted a controlled study exposing young adult mice to music with slow rhythm (6 hours/day at 50-60 dB) for 21 consecutive days, finding significantly increased BDNF levels specifically in the hippocampus, with no corresponding changes in nerve growth factor. Subsequently, Brattico et al. (Brattico et al. 2021) noted that animal models consistently demonstrate that musical stimulation can upregulate BDNF expression in a manner comparable to physical exercise. More recently, exposure to tonal music for 14 days in mice has been shown to increase BDNF, TrkB, CREB, PI3K–AKT and MAPK pathway components in hippocampus and prefrontal cortex, along with more neurons, dendritic spines, and synaptic proteins (SYP, PSD95)(J. Wang et al. 2023). In parallel, a systematic review of 15 studies reported that both receptive and active music-based interventions upregulate genes related to neuroprotection and synaptic plasticity, enhance peripheral neurotrophic factors (including BDNF), alter hormonal profiles, and reduce stress, while long-term musical training is associated with neurogenetic alterations in pathways linked to music perception/production, neurogenesis, and neurotransmission (Kunikullaya U et al. 2025). However, to date, no randomized longitudinal study has directly examined changes in BDNF levels following structured music training in older adults, representing an important gap in the literature.

Chapter II -Development of the MultiMusic multidomain intervention and methodological framework for a future randomized controlled trial

Building on the conceptual framework presented in Chapter I, this chapter describes the development of the MultiMusic multidomain intervention and the methodological choices underlying the planned study design. At the time of writing, the randomized controlled trial (RCT) has not been conducted; the present thesis therefore reports findings exclusively from a non-randomized feasibility study implemented as a preparatory phase.

2.1. Rational and aims of the study

Non-pharmacological, multidomain interventions have gained relevance as strategies to promote healthy aging, preserve functional resilience, and delay adverse aging trajectories, particularly through their ability to stimulate neuroplasticity and protect against age-related decline (James et al. 2024; Salzman et al. 2022; Chan et al. 2025). Lifestyle-based approaches involving physical activity, cognitive stimulation, and nutritional interventions are consistently associated with better brain health and functional outcomes (Fourteau et al. 2020; García-Llorente et al. 2024). 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 (Dedeyne et al. 2017). Such interventions are particularly well suited to addressing the complexity of age-related decline, as they act simultaneously on multiple affected functions producing superior improvements across multiple cognitive domains compared to single-domain interventions or usual care (Chan et al. 2025).

Within this framework, music has emerged as a particularly promising form of enrichment, as musical engagement simultaneously involves auditory, cognitive, motor, emotional, and social processes (Kraus and Chandrasekaran 2010; Herholz and Zatorre 2012). Among music-based activities, choral singing represents a particularly valuable intervention from an ecological perspective, as it integrates auditory-motor coordination, cognitive demands, respiratory training, and structured social interaction in a group setting. 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, 2024) However, 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 aging trajectories.

Based on these considerations, the MultiMusic intervention protocol was developed to examine whether participation in a multidomain program including choral practice is associated with changes over time in biological, cognitive, audiological, and neurophysiological domains, as well as to explore relationships between behavioral and neurophysiological measures.

Accordingly, a non-randomized feasibility phase was conducted to evaluate recruitment, adherence, retention, intervention acceptability, and the applicability of a multidimensional assessment battery in a real-world community setting, while also allowing exploratory analyses of baseline profiles and longitudinal trends to inform the design and hypotheses of the subsequent RCT (Orsmond and Cohn 2015). Specifically, the feasibility phase was designed to assess whether a multidomain program including choral practice could achieve satisfactory engagement and adherence, and to explore potential trends in cognitive, auditory-cognitive, measures relative to comparison conditions. Neurophysiological markers were included to examine their sensitivity in capturing intervention-related modulation. The results of this feasibility phase are presented and discussed in the Chapter III.

2.2 RCT and feasibility study protocol

The MultiMusic protocol was developed with the aim of evaluating the effects of a multidomain intervention, on cognitive, audiological, neurophysiological, and biological outcomes in community-dwelling older adults. The protocol of the upcoming randomize controlled trial (RCT) has been prospectively registered in the ClinicalTrials.gov public registry (ID: NCT06767410; registration date: January 9, 2025) and was developed followed internationally recognized methodological standards to ensure scientific rigor and transparency. The main features of the planned RCT design are summarized in, ***Appendix A***, in accordance with relevant World Health Organization guidelines (World Health Assembly, 2022).

An a priori power analysis was conducted to inform sample size planning for the subsequent RCT; detailed calculations are provided in ***Appendix B.***

The protocol was tested through a non-randomized feasibility phase designed to evaluate recruitment strategies, adherence, intervention acceptability, and the applicability of the multidimensional assessment battery in a real-world community setting. With the exception of participant randomisation, the feasibility phase retains the core elements of the RCT protocol, including intervention content, duration, and assessment procedures.

Ethical approval for the study, including all procedures related to salivary Brain-Derived Neurotrophic Factor (BDNF) collection, was obtained from the Institutional Review Board of the Department of Education, Psychology, and Communication of the University of Bari (reference number: ET-23-27). All procedures were conducted in accordance with ethical standards for research involving human participants. To ensure data protection and confidentiality, each participant was assigned a unique anonymized identification code.

2.3 Study design and setting

The study adopts a longitudinal pre–post design and includes three study arms: a multidomain intervention group (*choir* group), an active control group, and a passive control group. The intervention group engages in a structured program combining choral practice, music-based physical activities, and manual activities. The active control group participates in non-musical physical, cognitive, and manual activities, while the passive control group does not take part in any structured intervention. This design allows differentiation between music-specific effects, general activity-related effects, and the absence of intervention.

Participants are assessed at baseline and after approximately nine months of participation. An additional follow-up assessment is planned after a further 12 months to explore the stability of intervention-related effects over time. The overall study design is summarized in *Figure 2.1*.

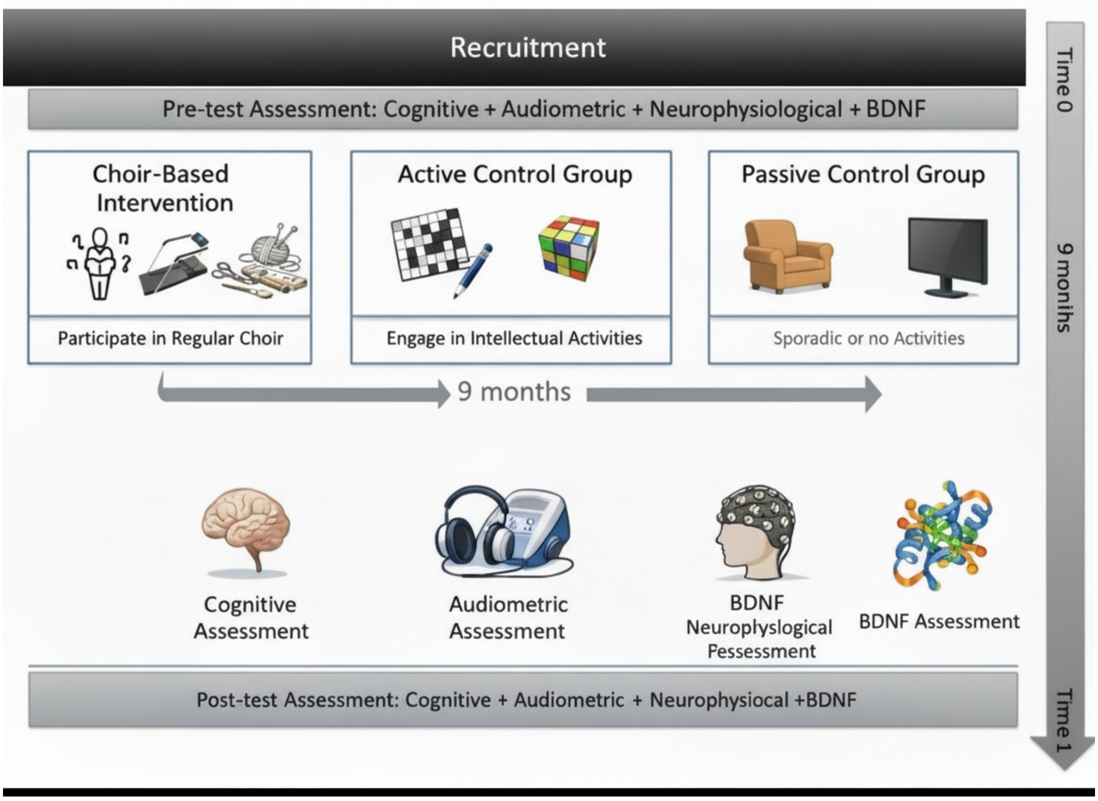

Figure 2.1. Study design with three groups (Choir group, active and passive control groups) and assessments at baseline and after the intervention

2.4 Eligible participants

Participants are community-dwelling older adults recruited through district service centers and Universities of the Third Age located in both metropolitan and suburban areas of Bari (Southern Italy). Inclusion criteria comprise age 65 years or older, independent living, absence of prior formal musical training, and adequate cognitive and functional abilities to participate in group activities and complete 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.

Exclusion criteria include severe cognitive impairment, major neurological or psychiatric disorders, and medical conditions that could interfere with participation in the intervention or completion of the assessment procedures. Participants presenting otological conditions other than age-related hearing loss were also excluded.

2.5 Outcome selection and multidimensional assessment strategy

Consistent with multidimensional models of aging and frailty, the assessment battery incorporates cognitive, audiological, psychosocial, neurophysiological, and biological measures to characterize functional resilience and experience-dependent adaptation (Clegg et al., 2013; Pilotto et al., 2020).

Behavioral and neuropsychological measures are included to assess cognitive functioning and everyday-related abilities relevant to autonomy and quality of life. Audiological assessments are incorporated to characterize peripheral hearing and speech perception, which contribute to listening effort and social participation in aging. Neurophysiological measures of auditory processing are selected to index sensory-cognitive efficiency and neural timing, providing markers potentially sensitive to training-related plasticity.

Finally, a non-invasive biological marker is included to complement functional and neurophysiological outcomes and to explore plasticity-related processes at a molecular level. Overall, the assessment strategy is designed to balance methodological sensitivity with feasibility and acceptability in a community-based context, ensuring suitability for repeated administration across the feasibility phase and the subsequent randomized controlled trial.

2.6 The MultiMusic multidomain intervention

Each choir session follows a standardized structure. Sessions typically began with body percussion exercises conducted in a playful and interactive manner, aimed at enhancing body awareness, attention, motor coordination, and short-term memory. These activities also serve as a warm-up and group engagement phase. Subsequently, breathing exercises and basic vocal education are introduced, including simple explanations of vocal and respiratory mechanisms involved in phonation. This phase is intended to promote awareness of the vocal apparatus and to facilitate safe and effective voice use among participants. The core musical component consists of progressive vocalizations adapt to the different vocal sections (basses, tenors, altos, sopranos, and treble voices), followed by rehearsal of the choir repertoire. Repertoire selection is grounded in participants' cultural background, initially emphasizing familiar music from popular traditions and gradually incorporating more complex polyphonic and structured pieces over time. Rehearsals also include moments of creative musical interaction, such as solo, duet, and trio performances in dialogue with the full choir, to encourage improvisation, expressive engagement, and active participation. Given the absence of prior formal musical training among participants, brief and simplified musical and rhythmic reading exercises are introduced when appropriate, focusing on accessibility rather than technical proficiency.

As the study is conceived as a multidomain intervention, participants are also involved in a range of non-musical activities targeting complementary functional domains.

A comprehensive overview of all activities, including their frequency and intensity, is provided in ***Table 2.1***. For analytical and descriptive purposes, activities are grouped into four macro-categories:

- Physical activities, including group dance, gymnastics, postural exercises (e.g., Pilates or body harmony), and recreational sports (e.g., swimming);
- Musical activities, comprising choir participation and body percussion;
- Manual activities, such as horticulture, handicraft, tailoring, and cooking;
- Intellectual and artistic activities, including theater, mental gymnastics, reading, and structured learning programs (e.g., history or language courses).

Participants in the active control group engage in a schedule of non-musical activities comparable in frequency and intensity to those of the intervention group. Activities are selected from the same pool of physical, manual, and intellectual programs (e.g., gymnastics, dance, handicraft, theater) and are combined based on individual preferences and availability, reflecting naturalistic engagement patterns.

Participants allocated to the passive control group do not engage in any structured or organized activities during the observation period.

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 2.1. List of activities carried out by the participants

2.7 Procedures

Saliva collection

Participants are instructed to refrain from eating, drinking, or brushing their teeth for two hours prior to sample collection, and to abstain from consuming alcoholic beverages for 24 hours, to prevent any alteration or contamination of the samples. Immediately before saliva collection, each participant rinses their mouth with distilled water to remove debris and moisturize the oral mucosa. After a ten-minute interval, saliva is collected through passive autonomous salivation. This method is selected to avoid the potential non-specific binding of proteins present in the samples by cotton in the collection devices (e.g., Salivettes), which can reduce measurable protein concentrations, including BDNF (Mandel et al. 2011). Approximately 1 ml of saliva is collected from each participant in a pre-cooled Eppendorf tube, and immediately after collection, a cocktail of protease inhibitors (v/v 1:500 PMSF, Sigma Aldrich, St. Louis, MO, USA) is added. The detailed analytical protocol is reported in ***Appendix C.***

Behavioral and musical measurements

The assessment protocol includes a comprehensive set of behavioral measurements aimed at evaluating multiple cognitive, psychological, and functional domains (summarized in ***Table 2.2*****).**

Cognitive measures

MoCA: The Montreal Cognitive Assessment (Nasreddine et al. 2005) is used 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). MoCA assess multiple domains, includying memory, executive functioning, attention, language, visuospatial, and orientation. Subtests therefore includes tasks such as trail-making, cube and clock drawing, animal naming, digit span, serial 7s, phonemic fluency, sentence repetition, abstraction similarities, five-word immediate and delayed recall, and orientation question. The total score range from 0 to 30, with higher scores reflecting better performance; a cut-off score of <26 is commonly used to indicate possible cognitive impairment, and one extra point is added for individuals with ≤12 years of formal education to account for educational effects on performance.

MIQ: The Matrix Reasoning(Condon and Revelle 2014) is a computerized adaptive measure of fluid intelligence, structured as a series of 3×3 geometric patterns with one item missing. Participants are required to 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. The MIQ has been employed in developmental studies with children, demonstrating sensitivity to inter-individual differences in abstract reasoning (Lippolis et al. 2022; Müllensiefen et al. 2022). In the present study, its application is extended 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.

CRIq: The Cognitive Reserve Index Questionnaire (Nucci et al. 2012) 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. The CRI-q collects information across three domains: CRI-Education (measuring formal and informal educational experiences), CRI-Working Activity (assessing occupational complexity and cognitive demands), and CRI-Leisure Time (capturing intellectual and social engagement activities). Each domain generates a separate subscore, which are then combined to produce a total CRIq score that reflects an individual's overall cognitive reserve level. The questionnaire has been extensively applied in aging research, including Italian populations, and has demonstrated consistent associations with performance in memory, attention, and executive functioning (Maiovis et al. 2016; Marselli et al. 2024; Ozakbas et al. 2021).

Physical activity

GPAQ: The Global Physical Activity Questionnaire (GPAQ) is a 16-item World Health Organization tool to monitor physical activity (Armstrong and Bull 2006) 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. assesses physical activity across three domains: work-related activities (including household tasks). For each domain, the questionnaire captures frequency (days/week) and duration (minutes or hours/day) of moderate- and vigorous-intensity activities performed for at least 10 consecutive minutes.

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 rate 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 are summed to yield a total flourishing score ranging from 8 to 56, with higher values indicating greater psychological flourishing and overall well-being.

Multidimensional frailty

Selfy-MPI: The Self-administered Multidimensional Prognostic Index (Pilotto et al. 2019), integrates information across multiple domains, including functional independence (Activities of Daily Living and Instrumental Activities of Daily Living), mobility (MOB self-report), cognitive status, nutritional status (Mini Nutritional Assessment), comorbidity burden (Cumulative Illness Rating Scale), medication use (Anatomical Therapeutic Chemical classification), and living situation.

For each domain, responses are converted into three risk levels: 0 (no problems, low risk), 0.5 (minor problems, moderate risk), and 1 (major problems, high risk) . The domain scores are summed and divided by the total number of domains to generate a continuous composite score ranging from 0 to 1. Scores between 0.00 and 0.33 indicate low frailty risk, values between 0.34 and 0.66 indicate moderate frailty risk, and values between 0.67 and 1.00 indicate severe frailty risk. The Self-MPI is administered in its digital form via the Portable-MPI application, which automatically computes the final score and immediately provides frailty risk stratification, facilitating rapid use in community and non-specialist settings

Musical abilities

The following LongGold computerized, adaptive perceptual tasks are employed in the study.

MDT: The Melody Discrimination Test (MDT) is is an adaptive psychometric task that uses a three-alternative forced-choice (3-AFC) paradigm to assess individuals’ melodic discrimination abilities (Harrison et al. 2017) . In each trial, participants hear three short melodies presented sequentially and are instructed to identify the “odd” melody out of the three, where two melodies are identical in their interval structure and one contains a pitch or contour change. This format parallels other 3-AFC music-perception tasks in which listeners choose the deviant melodic pattern from among three alternatives, while the position of the deviant pattern is randomized across trials to minimize response bias. Task difficulty in the MDT is manipulated adaptively by varying structural parameters of the stimuli, such as the length of the melodies and the size of the interval changes, thereby increasing cognitive load and perceptual demands at higher difficulty levels.

MPT: The Mistuning Perception Test (MPT) is a two-alternative forced-choice (2-AFC) experimental tool designed to assess listeners’ ability to detect vocal pitch deviations in musical excerpt (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 generated 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.

RAT: The Rhythm Ability Test (MacGregor et al., 2022) is used to assess rhythmic abilities. The RAT is an adaptive task in which participants match auditory rhythmic patterns composed of high- and low-pitched tones to corresponding visual representations. 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).

EDT: The Emotion Discrimination Test, is a two-alternative forced-choice task designed to assess participants' ability to recognize emotions in short musical excerpts through acoustic and structural features (MacGregor and Müllensiefen 2019). The test evaluates emotion recognition across four primary emotions: anger, happiness, sadness, and tenderness, with item difficulty varying based on acoustic characteristics**.** 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.

Area	Construct	Test	Type
Cognitive	Cognitive functioning	MoCA	Paper-and-pencil, researcher-administered
	Cognitive reserve	CRIq	Paper-and-pencil, researcher-administered
	Fluid intelligence	MIQ	Computerized, self-administered
Motor	Physical activity	GPAQ	Paper-and-pencil, researcher-administered
Geriatric	Multidimensional frailty	Selfy-MPI	Computerized, self-administered
Psychosocial	Well-being	Flourishing Scale	Paper-and-pencil, self-administered
Perceptive	Melody discrimination	MDT	Computerized, self-administered
	Mistuning perception	MPT	Computerized, self-administered
	Rhythm ability	RAT	Computerized, self-administered
	Emotion discrimination	EDT	Computerized, self-administered

Table 2.2. Behavioral assessment.

List of the standardized tests and questionnaires used for assessing behavioral functions of the elderly participants

Audiological and neurophysiological measurements

Audiological assessment

Prior to audiological testing, otoscopy is performed to examine the external auditory canal and tympanic membrane and to rule out any potential pathological conditions in all participants.

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

Speech perception in quiet is evaluated through speech audiometry according to standard clinical procedures.Speech Reception Threshold (SRT) is measured separately for each ear using standardized lists of disyllabic, phonetically balanced words and is defined as the lowest presentation level (dB HL) at which the participant correctly repeated 50% of the presented items and is used as an estimate of the minimum intensity required for reliable speech perception (Hamid and Brookler 2006).

Speech intelligibility is 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 are presented at a fixed level above each participant's SRT, typically around 40 dB sensation level. Participants are 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 perception in noise is assessed using the Italian Matrix Sentence Test (ITAMatrix) (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". 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, the ITAMatrix is administered via the Oldenburg Measurement Applications software (HörTech GmbH, Oldenburg, Germany). Speech and noise stimuli are 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 are digitally reproduced from the software's internal library.

Neurophysiological assessment

Auditory Brainstem Responses (ABR) are recorded to assess the integrity and temporal precision of the auditory pathway from the auditory nerve to the midbrain. BR waveforms consist of a series of peaks reflecting successive neural generators along the auditory pathway: 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 and Hamilton 1976; Melcher and Kiang 1996).

ABR is recorded using the Interacoustics Eclipse EP25 system. Disposable surface electrodes are placed according to a standard montage, with reference electrodes positioned on the right (M1) and left (M2) mastoids, the active electrode placed on the upper forehead (Fz), and the ground electrode(Gnd) positioned on the lower forehead, slightly lateral to the midline. Monaural acoustic stimulation is delivered through insert earphones (Ear Tone ABR). Click stimuli are presented at an intensity of 90 dB nHL with a stimulation rate of 27.7 clicks per second. The analysis time window is set to 10 ms. For each ear, two recordings are obtained, with a minimum of 2,000 artifact-free sweeps averaged per trace. Band-pass filtering is applied between 100 and 3000 Hz. Recordings were conducted while participants lay supine on a stretcher and are instructed to relax and minimize movement. Absolute latencies of Waves I, III, and V are extracted, along with interpeak latencies (I–III, I-V, and III-V).

Auditory cortical event-related potentials are recorded as part of the same assessment session to capture higher-order auditory-cognitive processing. P300 AEP are recorded monaurally using the same electrodes montage ad for ABR, with the exception that the active electrode is moved to the vertex (Cz), to optimize cortical potential detection. Interelectrode impedances are maintained below 5 kΩ. The ER-3A insert earphones are used to provide auditory stimuli. An oddball paradigm is 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 last 700 milliseconds and from 1 Hz to 20Hz. Participants are 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. Throughout the procedure, participants remain in a supine position, with eyes open, and are instructed to minimize eye movements, blinking, swallowing, and other sources of artifacts.

Oddball-elicited AEP components included the P2 (150-220 ms), reflecting early sensory–attentional encoding; N2 (200-350 ms), associated with novelty detection and cognitive control; and P3 (300-600 ms), a large positive deflection related to attentional resource allocation and context updating. Extracted measures comprised absolute latencies (ms) of P2, N2, and P3 from stimulus onset, component amplitudes (μV) relative to baseline or adjacent troughs, and interpeak intervals (e.g., P2-N2, N2-P3), providing indices of cortical processing speed and transmission efficiency.

In addition, interpeak latency measures (IpL) (e.g., P2-N2, N2-P3) are computed to provide indices of cortical processing speed and neural transmission efficiency. In the present protocol, particular analytical emphasis is placed on the P300 component due to its established sensitivity to cognitive aging, attentional modulation, and auditory training effects, while ABR measures are included primarily as physiological control.

2.8 Data monitoring and management

A data monitoring committee is considered unnecessary due to the minimal risk associated with the study. Behavioral and audiologic data obtained from digital questionnaires are securely stored in an encrypted folder, while paper-and-pencil tests and questionnaires are kept in a locked cabinet and subsequently entered into an electronic file, also stored in an encrypted folder. All saliva samples are maintained on ice during the procedure, followed by centrifugation at 4000 rpm for 15 minutes at 4°C; the supernatant is then aliquoted and stored at -80°C until assay execution. Access to these data is restricted to research team members only. Data supporting the findings of the study will be made openly available in the Zenodo repository.

Appendix

A. Study registration and protocol characteristics

Data category	Information
Approving entity	Ethics Committee of the Department of Education, Psychology and Communication, University of Bari
Ethics reference number	ET-23-27
Source of monetary support	EU funding (MUR PNRR – Project PE00000015, AGE-IT: A novel public–private alliance to generate socioeconomic, biomedical and technological solutions for an inclusive Italian aging society)
Primary sponsor	University of Bari
Contact for queries	Prof. Elvira Brattico (elvira.brattico@uniba.it)
Study title	A MultiMusic multi-domain intervention for the prevention of multidimensional frailty in healthy aging
Countries of recruitment	Italy
Problems studied	Prevention and counteraction of cognitive decline and multidimensional frailty
Interventions	Group 1: Multidomain intervention including continuous musical (choir), manual and music-based physical activities Group 2: Multidomain intervention including continuous manual, physical and intellectual activities without music Group 3: Non-musical sporadic activities or no intervention
Time of measurement	9-month intervention with an additional follow-up assessment at 8–12 months
Inclusion criteria	Age ≥ 65 years; living independently; no previous formal musical experience; absence of severe cognitive or functional impairments
Study design	Non-randomized feasibility study with subsequent randomized controlled trial (RCT)

Target sample size	Minimum of 144 participants, up to 150
Potential risks	Non-invasive procedures; no foreseeable risks
Primary outcome	Between-group differences in salivary BDNF levels over time in relation to multidimensional frailty
Secondary outcomes	Associations between BDNF levels and cognitive performance, perceptual abilities, physical activity; mediation effects of musical activities on psychological well-being through BDNF modulation

B. Power analysis

An a priori power analysis was conducted to inform sample size planning for the subsequent randomized controlled trial. Sample size estimation was performed 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 planned fully powered study would require a total sample of 144 participants (48 per group). The critical value for significance testing would be F (2, 141) = 3.06, α = .05 (see Table 2.3 and Figure 2.3)

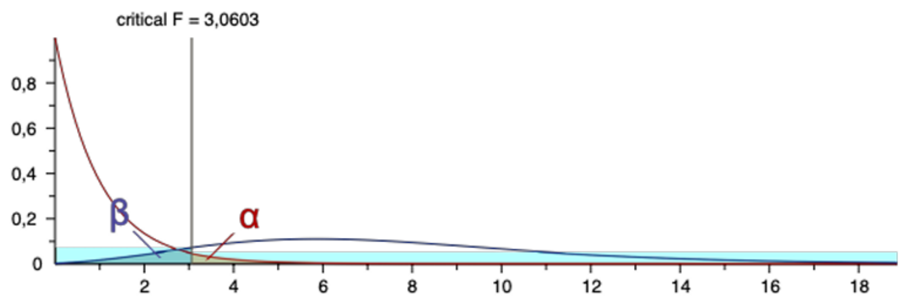

Figure 2.2. Power analysis

N_1	N_2	N_3	Critical F	Df	Effect size (f)	Power	Α
48	48	48	3.06	2	0.30	0.90	0.05

Table 2.3. A priori power analysis conducted with G*Power

C. Analysis of BDNF levels

For the extraction and quantification of Brain-Derived Neurotrophic Factor (BDNF), established methodological approaches are adopted. Rather than employing commercial ELISA kits, which show limited applicability and variable reliability when applied to salivary samples (Vrijen et al., 2017), the present protocol implements a sandwich ELISA procedure adapted from the method developed by Mandel et al. (2011), specifically optimized for the detection of BDNF in saliva. According to the original study, this method has a reported detection limit of 62.5 pg/mL, with intra-assay and inter-assay coefficients of variation of 4.2% and 8.2%, respectively, although it yields lower BDNF concentrations than those typically observed in serum. The optimized procedure is designed to ensure a detection range suitable for the expected concentrations of BDNF in salivary sample (see ***Figure 2.3***). Statistical analysis will be performed using GraphPad Prism v8.4 software. The concentration of BDNF (pg/ml) in each sample will be calculated in accordance with a standard curve. The data will be expressed as means ± standard error of the mean (SEM).

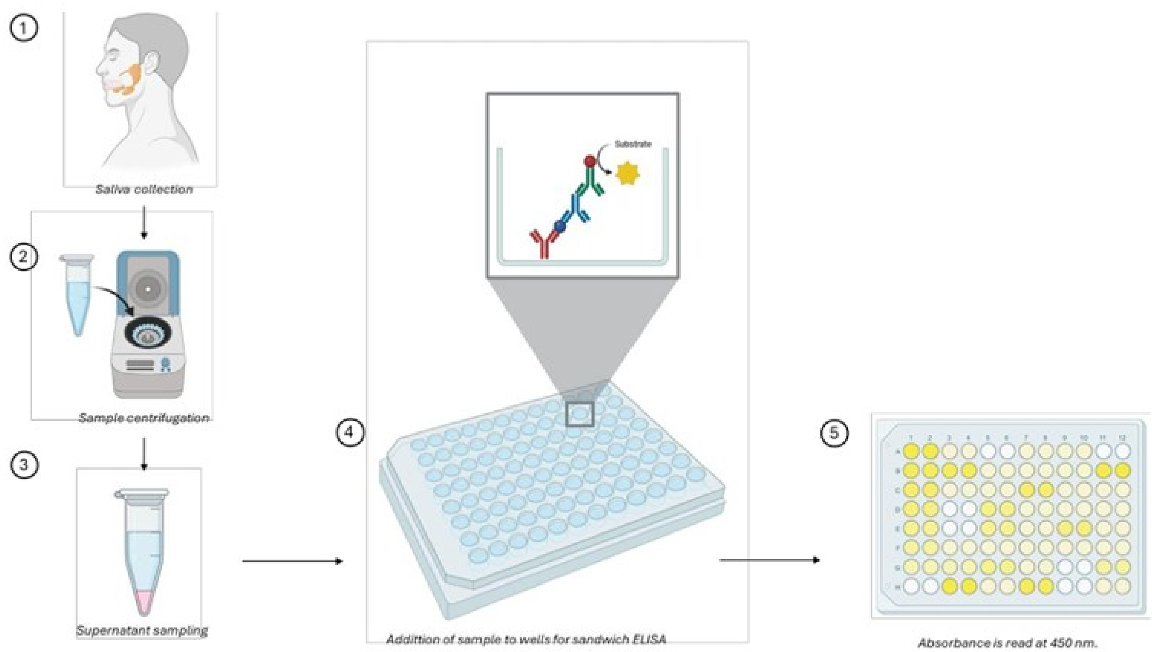

Figure 2.3 Schematic representation of the experimental protocol

(Steps 1–3) Saliva samples are collected, processed, and stored as described. (Step 4) Samples are added to a microtiter plate coated with an antibody specific for brain-derived neurotrophic factor (BDNF) immobilized on the well surface. BDNF present in the sample binds to the immobilized antibody. A second enzyme-conjugated antibody is then added, which binds to the captured analyte. Subsequently, an appropriate substrate is introduced. The enzymatic reaction generates a colorimetric signal proportional to

the amount of BDNF present in the sample. (Step 5) Absorbance is measured using a spectrophotometer, and values are compared with a standard curve to quantify BDNF concentration. ***.*** *Image created using Biorender (free version).*

Chapter III -The MultiMusic multidomain intervention including choral practice in community-dwelling older people: A feasibility study with exploratory cognitive, audiological and neurophysiological outcomes

3.1 Implementation of the MultiMusic protocol

All intervention components, assessment procedures, outcome measures, and timing followed the predefined randomized controlled trial (RCT) protocol, with the sole exception of participant allocation, which was not randomized in this phase.

Participants self-selected into one of three conditions: a choir-based multidomain intervention group (choir group), an active control group engaging in non-musical activities, or a passive control group. This allocation strategy was adopted to evaluate recruitment feasibility, adherence, intervention acceptability, and the applicability of the multidimensional assessment battery under ecologically valid, community-based conditions. No modifications were introduced to the content, intensity, or duration of the intervention or to the assessment protocol during the feasibility phase. The results of this study were therefore used to inform the implementation and optimization of the subsequent fully powered RCT.

It should be noted, however, that self-selection into groups may have introduced baseline differences across conditions. Since participants were not randomly assigned, pre-existing differences in cognitive, neurophysiological, and sociodemographic characteristics cannot be excluded and may act as potential confounders. Selection bias is a recognised limitation in community-based intervention trials, where volunteer participants tend to differ systematically from the general population in ways that may affect both baseline performance and intervention response (Coley et al. 2021). Furthermore, participants were recruited between November 2023 and April 2025 from different neighborhoods within the Bari metropolitan area. Neighborhood socioeconomic status has been shown to independently predict both cognitive function and the rate of cognitive decline in older adults(Rosso et al. 2016; Yang et al. 2024). These contextual factors may therefore confound between-group comparisons and should be considered when interpreting the findings. Baseline differences between groups are described in the Results section and were analytically addressed through baseline adjustment in the mixed-effects models.

Behavioral and cognitive assessments were conducted within collaborating community and leisure centers, 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. Given participants' limited familiarity with digital technology, researchers provided detailed instructions before computerized tasks while ensuring independent task completion.

Audiological and neurophysiological assessments were carried out at the Otolaryngology Unit of the University Hospital of Bari, using standardized clinical equipment and protocols. In line with the predefined RCT protocol, saliva samples were also collected for the quantification of brain-derived neurotrophic factor (BDNF). Sample laboratory processing and analyses are currently ongoing and are therefore not reported. 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.

3.2 Participants

Participants were recruited according to the inclusion and exclusion criteria defined in Chapter II. Approximately 100 participants were initially enrolled in the study, of whom 59 completed the comprehensive baseline assessment, which included audiological and neurophysiological evaluations conducted in the hospital setting. Following baseline, three participants withdrew due to health-related reasons and two were excluded after a diagnosis of otosclerosis. 54 participants completed the follow-up assessment (T_1) approximately nine months later. Participants who did not complete the full assessment phases at baseline most frequently came from suburban or rural areas further away from the Bari metropolitan area. Abandonment was therefore largely associated with logistical constraints related to hospital assessments, indicating that transportation represents a significant obstacle for this elderly population.

3.3. Statistical Analysis

Data preparation and Baseline 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.

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 amplitude measures, 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 amplitude (N2 and P3 amplitudes). 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 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 inferential 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 cognitive outcomes (MoCA, MIQ, CRI-q), 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 T_0 using principal component analysis (PCA) conducted separately within each domain. 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.

3.4 Results

Sample Characteristics

The final sample comprised 54 participants who completed both baseline (T_0) and follow-up (T_1) assessments. The mean age was 72.91 years (*SD = 5.40; range= 64.6-87.5)*. Females represented 77.7% of the sample (*n = 42*), while males accounted for 22.3% (*n = 12*). Twenty participants (*Choir group:* M_{age}*: 72.1 years* ± *4.67*) were involved in multi-domain programmes including choral training combined with other activities (physical, intellectual and/or manual). Eighteen participants (*Active control group: M_{age}: 74.4 years ± 6.89*) participated in structured non-musical programs that included physical, intellectual, and/or manual activities. The sixteen remaining participants (*Passive control group: M_{age}: 71.0 years ± 3.93*) only occasionally participated in non-musical activities or didn't participate in any structured program during the study period. Age distribution by gender and group is reported in ***Table 3.1a***, while activity combinations are reported in ***Table 3.1b***. In the choir group, the most frequent combination was musical + physical activities (n = 7), followed by musical + physical + manual (n = 5) and musical + physical + intellectual (n = 4); two participants engaged in all four activity domains, whereas combinations involving only one additional domain (intellectual or manual activities) were less common (n = 1 each). Within the active control group, intellectual activities were the most common (n = 10), followed by physical activities only (n = 3), combined physical + intellectual activities (n = 3), manual activities only (n = 1), and the combination of all three non-musical domains (n = 1).

Cognitive and reserve-related measures showed substantial inter-individual variability in the sample (***Table 3.2***). MoCA scores ranged from 14 to 30 (M = 21.74, SD = 3.70); CRI-q scores ranged from 70 to 163 (M = 107.20, SD = 23.20); and MIQ scores ranged from −4.00 to 1.39 (M = −2.60, SD = 1.26). Compared with both control groups, the choir group showed markedly lower scores on MoCA (M = 19.85, SD = 3.63), CRI-q (M = 87.65, SD = 10.73), and MIQ (M = −3.18, SD = 0.92). Similar differences were observed in the School subscale of the CRI-q, with lower scores in the choir group (M = 106.45, SD = 17.42) relative to the active Control (M = 122.06, SD = 17.69) and passive Control groups (M = 121.31, SD = 12.46).

Baseline audiometric characteristics are reported in ***Table 3.3***. Mean PTA were comparable between ears across the sample, with right-ear mean values ranging approximately from 25 to 28 dB HL and left-ear values from 24 to 28 dB HL. Speech reception thresholds (SRT) showed a similar pattern, with mean values ranging from 31 to 35 dB HL for both right and left ears.

Word recognition scores (WRS) showed overlapping distributions across ears, with mean values ranging approximately from 91% to 96% for the right ear and from 91% to 97% for the left ear. Speech-in-noise performance assessed with the Matrix test also showed comparable distributions across participants.

	Active control group (n=18)	***Choir group (n=20)***	***Passive control group (n=16)***

	Age Mean ± SD		
Gender			
Female	75.8 ± 7.46 (*n* = 13)	71.8 ± 4.71 (*n* = 17)	71.2 ± 4.53 (*n* = 12)
Male	70.9 ± 3.63 (*n* = 5)	73.9 ± 4.92 (*n* = 3)	70.3 ± 0.99 (*n* = 4)
Total	74.4 ± 6.89	72.1 ± 4.67	71.0 ± 3.93

Table 3.1a. Age distribution by gender and group

	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

Table 3.1b. Distribution of activities among participants

		MoCA	*CRI-q*	*MIQ*
Group	***N***	***Mean (SD)***		

Choir	20	19.85 (3.63)	87.65 (10.73)	−3.18 (0.92)
Active Control	18	22.78 (3.66)	115.39 (23.13)	−2.18 (1.27)
Passive Control	16	22.94 (3.00)	122.44 (17.63)	−2.35 (1.43)
Total	54	21.74 (3.70)	107.20 (23.20)	−2.60 (1.26)

Table 3.2. Baseline descriptive statistics for cognitive functioning (MoCA), cognitive reserve (CRI-q), and fluid intelligence (MIQ) across groups

	Active control group (n=18)	*Choir group (n=20)*	*Passive control group (n=16)*
	Mean ± SD		
Measure (T_0)			
PTA right (dB HL)	28.46 ± 10.96	26.34 ± 9.11	25.77 ± 8.13
PTA left (dB HL)	28.19 ± 11.16	24.29 ± 8.91	24.80 ± 7.50
SRT right (dB HL)	34.89 ± 9.36	31.55 ± 8.13	31.19 ± 9.20
SRT left (dB HL)	35.00 ± 9.32	30.65 ± 7.67	31.25 ± 8.58
WRS right (%)	91.11 ± 19.37	96.00 ± 11.42	93.75 ± 14.55
WRS left (%)	91.11 ± 17.11	96.50 ± 11.37	93.75 ± 14.08
Matrix test (SNR)	−1.69 ± 1.98	−1.93 ± 2.06	−2.34 ± 1.36

Table 3.3. Baseline audiometric characteristics (T_0).

Note. PTA = pure-tone average; SRT = speech reception threshold; WRS = word recognition score. Higher PTA and SRT values indicate poorer auditory sensitivity, whereas higher WRS values indicate better speech recognition; lower Matrix scores indicate better speech-in-noise performance.

Baseline group differences (T0) Levene's tests indicated no variance inhomogeneity. After Benjamini–Hochberg correction, omnibus group effects were significant for CRI-q ($p_{FDR} < 0.001$), MoCA ($p_{FDR} = 0.019$), and MIQ ($p_{FDR} = 0.029$), RAT ($p_{FDR} = 0.018$), left-hemisphere P2 latency ($p_{FDR} < 0.05$), and N2–P3 inter-peak latency (right $p_{FDR} < 0.001$; left $p_{FDR} < 0.01$). No audiometric measures survived FDR correction (***Figure 3.2***).

No statistically significant baseline group differences were found for multidimensional frailty (Selfy-MPI; Kruskal-Wallis, $p = 0.072$) or psychological well-being (Flourishing Scale; $p = 0.407$).

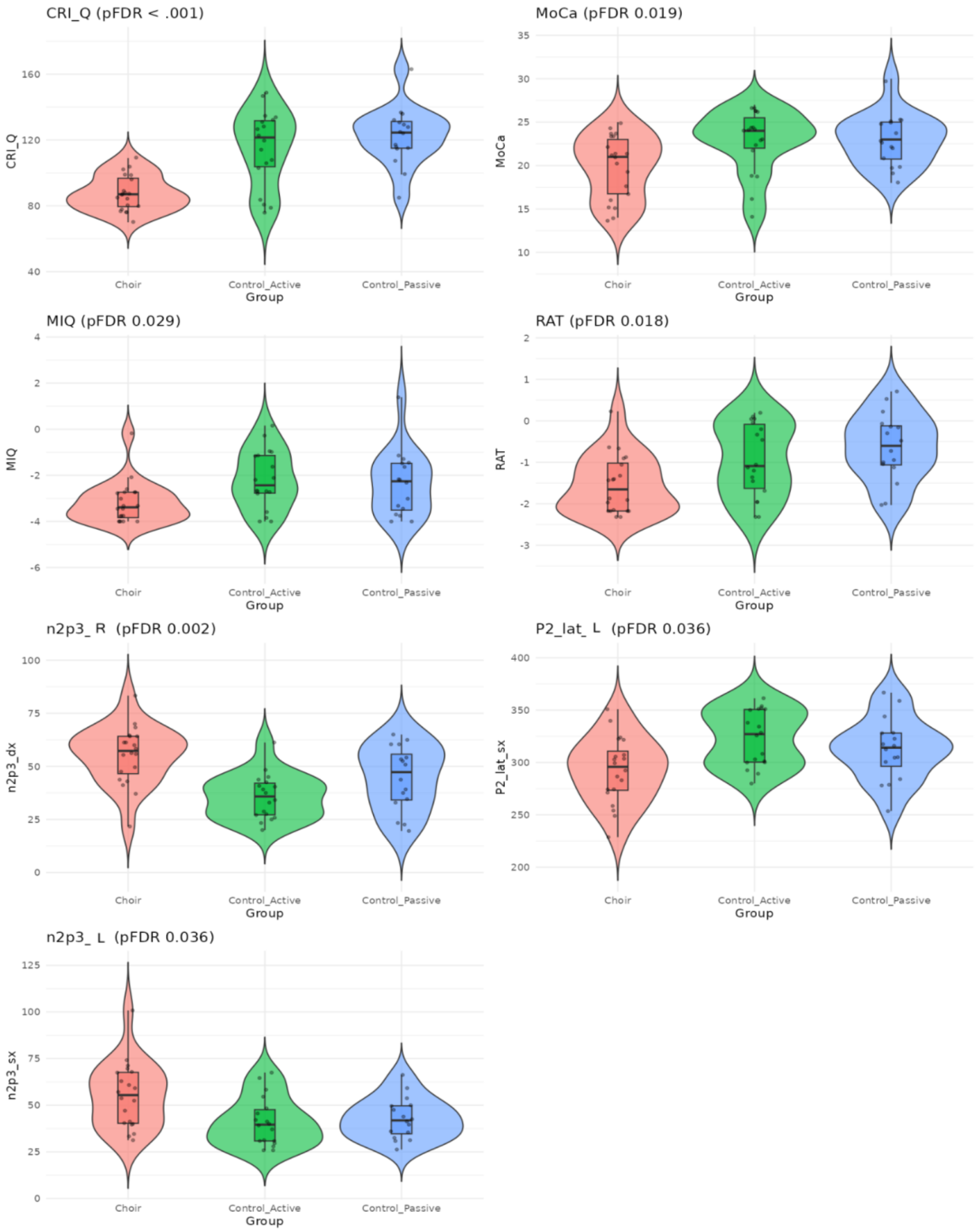

Figure 3.2. Violin plots display distributions (median, IQR) for Choir, Active Control, and Passive Control, highlighting baseline disadvantages in the Choir group for cognitive reserve, global cognition, rhythmic aptitude, and selected electrophysiological latency indices.

Baseline (T_0) and Follow-up (T_1) Correlational Analyses

Shapiro-Wilk tests indicated non-normality for multiple variables. Accordingly, Spearman's rank correlations were used whenever at least one variable in a pair violated normality assumptions ($p < 0.05$).

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 T_1, intra-domain coherence was largely preserved relative to baseline, with audiometric variables remaining the most strongly intercorrelated (r_s = 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 (r_s = 0.40–0.45). Within the neurophysiological domain, amplitude and inter-peak latency (IPL) measures remained internally correlated. However, no significant cross-domain associations survived FDR correction at follow-up.

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 Changes

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

Cognitive results

For MIQ, a significant Time × Group interaction was found, $F(2, 108) = 4.06$, $p = 0.020$. Post hoc comparisons indicated a marginal improvement in the Choir group ($\Delta = +0.42$, $p = 0.056$), whereas no significant changes were observed in the control groups.

For CRI-q, the Time × Group interaction was significant, $F(2, 98) = 15.62$, $p < 0.001$. The Choir group increased from T0 to T1 ($\Delta = +8.10$, $p = .009$), while both the Active ($\Delta = -6.94$, $p = 0.031$) and Passive control groups ($\Delta = -11.56$, $p = 0.001$) declined. At T1, the Choir group scored significantly higher than both control groups (Active: $p = 0.049$; Passive: $p = 0.010$). No significant interaction effects were found for MoCa (***Figure 3.3)***

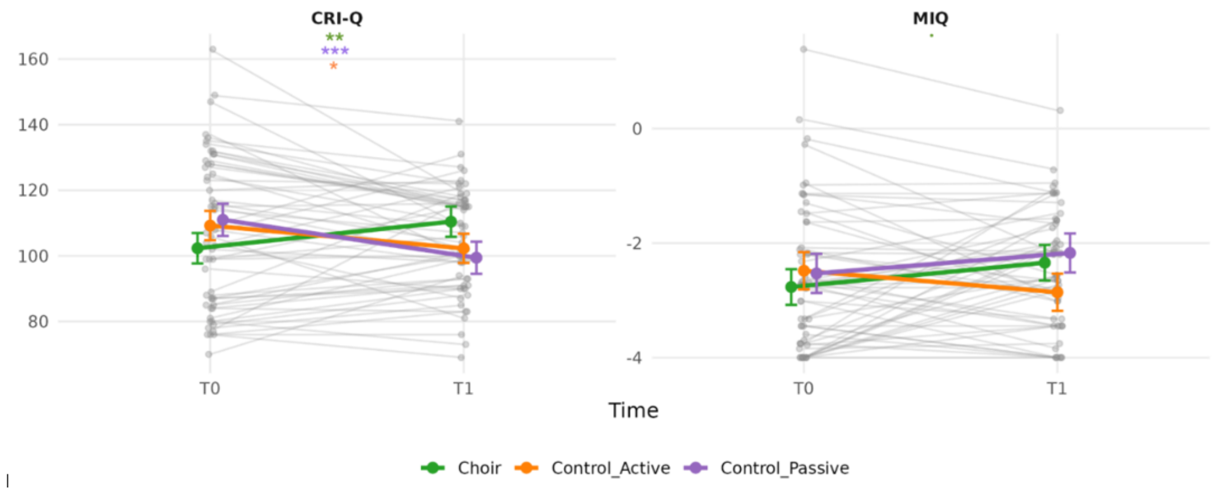

Figure 3.3 Model-informed mean trajectories (EMMs) for Matrix Reasoning (MIQ) and Cognitive Reserve Index Questionnaire (CRI-q), adjusted for baseline covariates.

*For MIQ, only the Choir group showed a marginal improvement over time (p = .056). The Time × Group interaction was retained given its a priori theoretical relevance and improvement in AIC, despite not being supported by BIC. For CRI-q, a significant Time × Group interaction emerged (p < .001), with the Choir group increasing over time while both control groups declined. 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.*

Neurophysiological results

In the neurophysiological domain, the linear mixed-effects model revealed a significant Time × Group interaction for the N2-P3 inter-peak latency ($F(2, 377.56) = 33.42$, $p < 0.001$). Post hoc comparisons (Kenward-Roger correction, Bonferroni-adjusted) showed that only the choir group exhibited a significant reduction from T_0 to T_1 (−21.12 ms, SE = 1.84, $t = -11.50$, $p < 0.001$). 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, $p = 0.172$). 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, $p < 0.001$) and passive control groups (−13.43 ms, $p < 0.001$), while the two control groups did not differ from each other ($p = 1.000$) (***Figure 3.4a, 3.4b***).

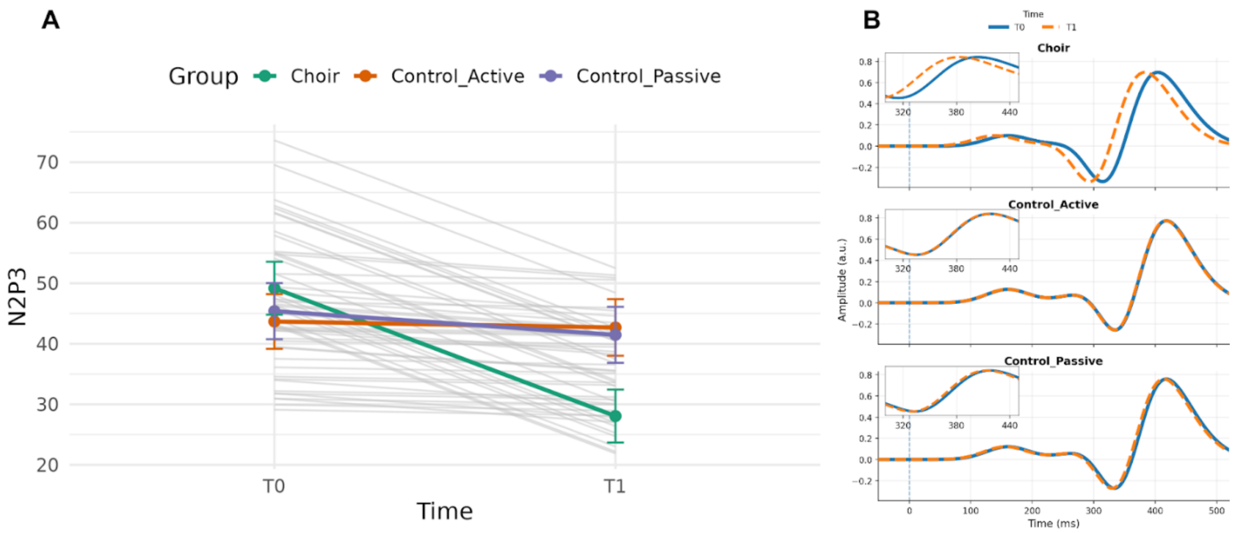

Figure 3.4 ***Longitudinal changes in N2–P3 inter-peak latency (IPL).***

*(**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 T_0 and T1. A significant reduction in N2–P3 IPL was observed only in the Choir group ($p < 0.001$), 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 > 0.54). For N2 latency, a significant Time × Group interaction emerged ($F(2, 159) = 3.84$, $p = 0.023$). However, post hoc within-group comparisons did not show significant longitudinal changes in any group (all ps ≥ 0.066). No significant interactions were found for P3 latency and P2N2 IPL.

Selfy-MPI and Flourishing Scale

In all mixed models, interaction effects were not significant, indicating that no robust differential group trajectories were detected for these outcomes. In line with CONSORT guidelines for pilot and feasibility trials, which discourage formal hypothesis testing for effectiveness and recommend treating any clinical outcome analyses as strictly exploratory (Eldridge et al. 2016), the following within-group contrasts should be interpreted with caution and not as evidence of efficacy(Eldridge et al. 2016).

Exploratory within-group contrasts revealed a significant reduction in frailty (Selfy-MPI) in the Choir group For Selfy-MPI ($\Delta = -0.036$, $p = 0.049$), whereas no significant changes were observed in the Active ($p = 0.682$) or Passive control groups ($p = 0.124$). Similarly, a significant reduction in frailty was observed only among participants with high activity engagement ($\Delta = -0.036$, $p = .034$), while no change emerged in the low-engagement group ($p = .641$) (***Figure 3.6***).

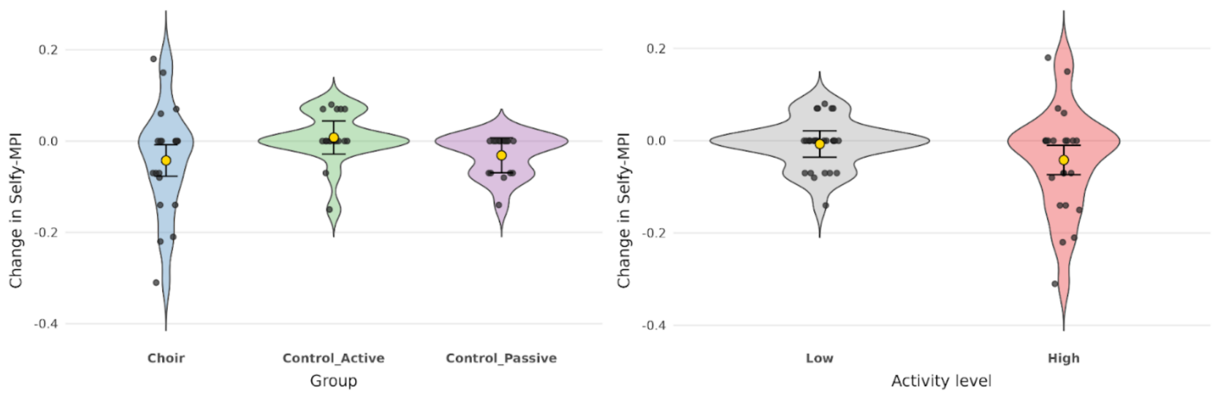

Figure 3.6. Estimated individual change scores (T_1–T_0) in multidimensional frailty (Selfy-MPI), shown separately by experimental group (left panel) and by activity level (right panel).

Although the Time × Group and Time × Activity interactions were not significant in the mixed-effects models, planned within-group contrasts indicated a significant reduction in frailty in the Choir group ($\Delta = -0.036$, $p = 0.049$) and among participants with high activity engagement ($\Delta = -0.036$, $p = 0.034$). No significant changes were observed in the control groups or in the low-engagement group.

For Flourishing Scale, pairwise comparisons showed between-group differences at T1, where the difference between the Choir and Passive Control groups approached significance ($\Delta = 3.56$, $p = 0.054$). However, 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 = 0.008) (***Figure 3.7***)

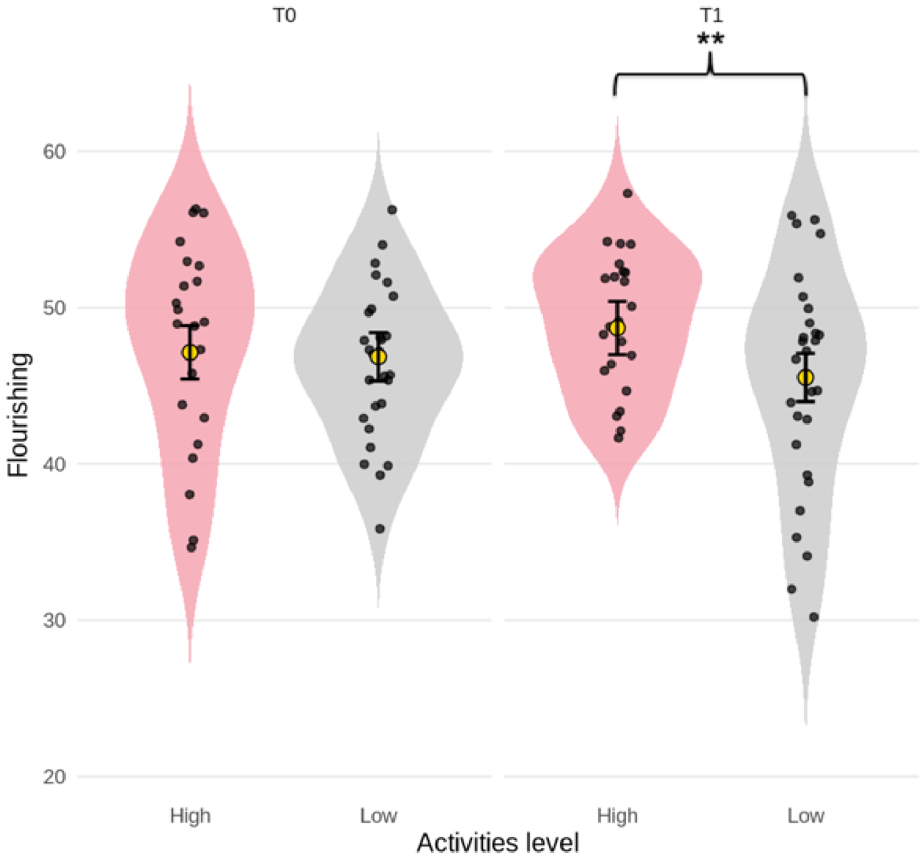

Figure 3.7. Distribution of psychological well-being (Flourishing) by activity level (high vs low) at baseline (T_0) and follow-up (T_1).

Violin plots display individual scores with estimated marginal means (± SE) adjusted for baseline flourishing. No differences between activity levels were observed at T_0 ($p = 0.814$). At T_1, the High engagement group showed significantly higher flourishing compared to the Low engagement group ($\Delta = 3.16$, $p = 0.008$).

3.5 Discussion

This present study showed that the MultiMusic multidomain intervention can be sustained and implemented in a real-world community setting involving community-dwelling older adults.

Feasibility outcomes

In line with current recommendations for complex interventions in the early stages in older populations, feasibility was assessed in terms of recruitment, retention, adherence, and correct administration of a comprehensive multidimensional assessment battery under ecologically valid conditions (Orsmond and Cohn 2015).

Recruitment through local senior universities and recreation centers proved effective, and retention during the nine-month intervention period was high. The content, intensity, and duration of the intervention were provided as originally planned, with no need for protocol modifications, supporting its acceptability and procedural robustness within a real-world community context.

The main feasibility constraint related to logistical barriers associated with hospital-based audiological and neurophysiological assessments: participants living farther from the assessment site were more likely to discontinue the study, pointing to travel demands and transportation difficulties as major deterrents; Conversely, retention was high among participants living in closer proximity, underscoring the importance of minimizing logistical burden in future implementations. This pattern aligns with previous evidence indicating that logistical barriers negatively affects recruitment and retention of older adults and community-based multidomain trials (Forsat et al. 2020).

The mixed community-clinic model adopted in this study, which combines community-based behavioral testing with hospital-based audiological and neurophysiological assessments, has been successfully implemented in other early-stage multidomain and arts/music-based interventions in older adults (Clifford et al. 2021; Moon et al. 2021). Therefore, the successful administration of an extensive multidimensional assessment battery without excessive fatigue or adverse events confirms its tolerability.

Baseline group characteristics and correlations

Participants demonstrated a broad range of cognitive performance, spanning values typically associated with both normal aging and mild cognitive impairment. As reported by Bosco et al. (Bosco et al. 2017) Italian older adults generally obtain lower MoCA scores than those reported in the original validation sample by Nasreddine et al.(Nasreddine et al. 2005) with correspondingly adjusted cut-offs; Accordingly, the mean level observed in the present sample should not be interpreted as uniformly pathological, but rather as reflecting the expected variability within an Italian elderly population.

Within this overall cognitive profile, participants who self-selected into the choir showed lower baseline scores on global cognition, cognitive reserve, and fluid reasoning compared to control participants, alongside longer N2-P3 inter-peak latencies, despite comparable peripheral hearing. Such differences may reflect socio-cultural disparities, as choir participants were recruited from a socioeconomically disadvantaged neighbourhood, whereas control groups originated from more advantaged districts within the same metropolitan area. Socioeconomic environment is known to shape cognitive trajectories and vulnerability to age-related disorders, plausibly accounting for the lower initial performance observed in the choir group. Importantly, longitudinal mixed-effects models accounted for baseline outcome levels, thereby mitigating the likelihood that subsequent changes reflect regression to the mean. Therefore, improvements observed over time in the choir group assume interpretative relevance, as they represent adaptive intra-individual change emerging from a comparatively less favourable starting condition rather than the maintenance of a pre-existing advantage.

Correlation analyses revealed a consistent pattern of associations within and across domains, with a particularly strong coupling between musical and cognitive measures. Cognitive reserve and fluid reasoning were significantly associated with rhythmic aptitude, while global cognition was correlated with performance on multiple musical tasks, supporting the role of executive resources in musical ability (Criscuolo et al. 2019). Conversely, melodic discrimination (MDT) was primarily correlated with audiometric thresholds, consistent with links between pitch processing and fine-grained auditory resolution (Grassi et al. 2017; Parbery-Clark et al. 2011), suggesting a functional differentiation within the musical domain, whereby some components are more closely linked to peripheral auditory sensitivity, while others depend more on higher-order cognitive mechanisms.

Fluid reasoning also correlated with right-hemisphere N2 amplitude, and amplitude–latency couplings indicated integrated auditory-cognitive cascades(Polich 2007) , with lateralization patterns consistent with prior research (Divenyi and Haupt 1997; Bidelman and Alain 2015).

Longitudinal changes

Building upon this baseline functional architecture, longitudinal findings indicated domain-specific adaptations associated with sustained choir participation within the multidomain program.

For fluid reasoning (MIQ) the choir group showed a trend toward improvement across the intervention period, whereas no meaningful change was observed in the control groups. Although the within-group improvement reached only marginal significance, the interaction effect suggests a divergence in trajectories that may reflect emerging gains in higher-order reasoning processes following sustained musical engagement.

A clearer and more pronounced longitudinal pattern was identified for cognitive reserve (CRI-q). Despite beginning from a comparatively lower baseline, choir participants demonstrated a progressive increase over time, while both the active and passive control groups showed declines, resulting in marked group differences at follow-up. A growing body of researches show that musical engagement and enriched lifestyle activities can support reserve-related mechanisms, particularly in individuals starting from less advantageous cognitive baselines (Román-Caballero et al. 2018; Mansens et al. 2018). Randomized and longitudinal work in older adults has documented working memory (WM) and executive and auditory benefits after instrument or piano training (Seinfeld et al. 2013; Degé and Kerkovius 2018; J. A. Bugos et al. 2007), also measured through electroencephalography (EEG) (Lu et al. 2022; Jennifer A. Bugos et al. 2022). Choir-based interventions may extend these benefits by integrating cognitive stimulation into a socially cohesive and motivating environment, which are known mediators of adherence and transfer (Creech et al. 2013; Tamplin et al. 2020). Very recent work points to cognitive and emotional benefits of choral participation across adulthood (Pentikäinen et al. 2021; Moisseinen et al. 2024, 2025) and functional neuroplasticity after singing-based rehabilitation in clinical populations (Martínez-Molina et al. 2025).

Complementary to the behavioral findings, neurophysiological measures were included to examine potential training-related modulation of auditory-cognitive processing dynamics. Responses were acquired using a clinical setup with Cz as the active site, low impedances (< 5 kΩ), ER-3A insert earphones, and a standard auditory oddball paradigm. Although less spatially dense than EEG, such configurations are optimized for reproducibility and widely applied in both research and clinical contexts. Previous studies using comparable systems have established their reliability across adult populations: P300 latencies in elderly cohorts have been characterized with clinical protocols (Cóser et al. 2010), normative reference values in adults have been documented with insert-earphone oddball paradigms (Didoné et al. 2016), cortical AEPs have been validated for objective hearing-threshold estimation in clinical practice (Van Dun et al. 2015), and even biometric recognition studies have demonstrated the stability of transient cortical responses obtained with clinical-grade equipment(Seha and Hatzinakos 2018).

The most robust neurophysiological effect was a bilateral, choir-specific shortening of the N2–P3 inter-peak latency (IPL). This measure has been shown to be particularly sensitive to cognitive status in older adults, including MCI populations((Papaliagkas et al. 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 (Polich 2007; Sur and Sinha 2009; Luck 2014). Age-related slowing of this cascade is well documented (Kropotov et al. 2016; Tarawneh et al. 2021) making IPLs particularly informative markers of aging-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 and Kraus 2013; Skoe and 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 and Van Petten 2008). Efficient communication between these regions depends on fronto-parietal connectivity and theta-band synchrony supporting cognitive control and memory updating (Cavanagh and Frank 2014; Sauseng et al. 2005). Aging is associated with reduced conduction velocity and weakened theta coherence across these networks (Cummins and 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 and Picton 1987; Crowley and 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 aging cohorts (Kropotov et al. 2016; Luck 2014; Alain et al. 2014). 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 and 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;(F.-S. 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 (Hennessy et al. 2021; Fleming et al. 2019; Grassi et al. 2017). In choir-specific randomized controlled trials, neurophysiological modulation has been reported in the absence of measurable improvements in speech-in-noise performance following short-term interventions (Hennessy et al. 2021), while longer-duration choir studies have shown modest protection against cognitive decline without clear concomitant biomarker changes over comparable time frames (Lei Feng et al. 2020). More broadly, both longitudinal and meta-analytic evidence suggests that gains in challenging listening conditions, when present, are more consistently linked to central mediators such as auditory working memory, attentional control, and cortical recruitment rather than to changes in absolute auditory sensitivity (Guo et al. 2021; Neves et al. 2022).

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 and Alain 2015; Bonetti et al. 2024) and with reports that P300 timing relates to speech-in-noise performance and improves after auditory-cognitive training (Ferguson and Henshaw 2015; Skoe and 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 (Jennifer A. Bugos et al. 2025) .

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 model did not detect a robust differential trajectory across groups, exploratory analyses suggested lower frailty among choir participants and among individuals exposed to richer multidomain engagement and higher cumulative activity levels.

While interpreted cautiously, this pattern aligns with prior evidence indicating that music-based and multidomain interventions may contribute to maintaining or improving frailty-related outcomes in community-dwelling older adults, particularly when combined with physical activity (Sun et al. 2021). Choir participation integrates physical effort, cognitive stimulation, emotional expression, and structured social interaction, components that conceptually overlap with community-based strategies recommended for preventing or delaying frailty (Rogers and Fancourt 2020; Raja et al. 2025).

More broadly, multidomain interventions have demonstrated 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; Moon et al. 2025).The observed dose-response trend accords with longitudinal evidence showing that sustained social and cognitive engagement reduces progression toward frailty, whereas inactivity increases vulnerability (Rogers and Fancourt 2020; Goto and Yamatsu 2025). Collectively, these findings reinforce the conceptualization of frailty as a dynamic and potentially modifiable multisystem condition(Pilotto et al. 2022).

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) .

Across the intervention period, global levels of flourishing remained largely stable. This pattern aligns with meta-analytic evidence indicating that behavioral interventions in generally healthy older adults tend to produce small and heterogeneous effects on well-being, with more pronounced improvements 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.

3.6 Strengths, limitations and future directions

The main strengths of this study include the implementation of the intervention in the real world and the use of a multidomain assessment framework encompassing cognitive, audiological, and neurophysiological outcomes. The application of longitudinal mixed-effects models supports the analysis of within- and between-group changes over time, while accounting for individual variability in repeated measures. Additionally, evaluating the intervention in a cohort starting from lower cognitive reserve and cognitive performance than controls, provides an ecologically meaningful view of potential benefits in a more vulnerable population.

Nevertheless, as a feasibility study, the design limits causal inference and external validity. Non-random group allocation generated baseline imbalances that, while statistically adjusted, may still leave residual confounding; Exposure to the activity was heterogeneous both within the choir's multidomain program and among the control groups, complicating the attribution of effects to choral practice itself and warranting dose-response and mediation analyses in the definitive trial. Moreover, the nine-month duration may have been insufficient to elicit changes in slower-moving outcomes, and the clinical AEP setup, while reproducible, limited spatial resolution, precluding source-level and network analyses.

Overall, the study establishes procedural feasibility and identifies a coherent pattern of central auditory-cognitive adaptation that warrants confirmatory testing. The planned randomized controlled trial will address these limitations through concealed randomization and stratification, predefined activity modules with adherence monitoring for dose-response modelling, an extended duration, and enhanced neurophysiological assessment; it will also incorporate biological markers (e.g., BDNF) to clarify mechanisms underlying experience-dependent plasticity and functional adaptation.

Chapter IV: Final Considerations

The MultiMusic intervention was designed to operate between primary (reducing risk before clinical impairment) and secondary prevention (addressing early, subclinical changes), targeting community-dwelling older adults without dementia and without formal musical training, who may present early or subclinical vulnerability profiles.

Conceptually, MultiMusic aligns with large multidomain lifestyle interventions such as FINGER and its World-Wide FINGERS adaptations, as well as AGELESS, SUPERBRAIN and related initiatives (Ngandu et al. 2015; Rosenberg et al. 2018; Deckers et al. 2024; Ponvel et al. 2025; Ong et al. 2025; Moon et al. 2025). These studies share the hypothesis that cognitive and functional aging is modifiable through coordinated changes in lifestyle and vascular risk and that addressing multiple risk factors simultaneously yields greater benefits than single-domain programs. Typically, they employ a component-based structure combining cognitive training, physical exercise, nutritional counseling, vascular/metabolic risk management, and often psychosocial support, delivered over 6–36 months with substantial adherence demands (Ngandu et al. 2015; Moon et al. 2021; Deckers et al. 2024; Ponvel et al. 2025). The results indicate small but significant cognitive and functional benefits, particularly in at-risk subgroups, while single-domain interventions often show more limited effects (Ngandu et al. 2015; Lisko et al. 2020; Ponvel et al. 2025; Liang et al. 2024; Crocker et al. 2024).

MultiMusic adopts an activity-focused multidomain strategy, where complex stimulation arises naturally from sustained participation in a single meaningful activity: choral singing. Choir participation intrinsically integrates auditory perception, vocal–motor coordination, respiratory and postural control, executive monitoring, memory processes, emotional regulation, and structured social interaction that support cognition and well-being in aging (Pentikäinen et al. 2021; Moisseinen et al. 2024; Raja et al. 2025). Given the centrality of auditory processing, temporal integration, and attentional control within choir singing, neurophysiological measures capturing auditory–cognitive dynamics represent particularly appropriate indicators of intervention-related adaptation in this contex.

Accordingly, the event-related potential (ERP) findings from MultiMusic provide particularly valuable insights into these processes. . When working with preventive populations who demonstrate largely normal baseline cognitive function, standard behavioral assessments often encounter ceiling effects that limit the detection of meaningful change (Kujala and Näätänen 2010). In contrast, ERP components such as mismatch negativity and P3 offer sensitive indices of auditory discrimination, attentional resource allocation, and cognitive updating processes, which are directly and repeatedly engaged during choir participation(Bidelman and Alain 2015). Controlled trials examining multidomain interventions in individuals with subjective cognitive concerns have similarly documented intervention-related modulations in ERP markers even in the absence of significant behavioral improvements, supporting the utility of ERPs as complementary indicators of early-stage, subclinical neuroplastic change (Kujala and Näätänen 2010; Bidelman and Alain 2015).

Whitin this context, outcomes associated with participation in MultiMusic are consistent with patterns of experience-dependent plasticity in later life (Román-Caballero et al. 2018; Bidelman and Alain 2015). Current theories of cognitive aging suggest these neural modifications reflect enhanced information processing efficiency and improved network coordination, rather than mere performance gains (Zendel and Alain 2014). Converging evidence from cognitive and musical training indicates that interventions can produce changes in brain activation patterns, neural connectivity, and neurochemical processes even when behavioral improvements are minimal or confined to specific cognitive domains(Román-Caballero et al. 2018; Bidelman and Alain 2015). This suggests that neural adaptation mechanisms may operate independently of, or in advance of, measurable changes in overt performance.

From a clinical and public health perspective, this activity-based structure represents a key strength of the MultiMusic approach. Community choirs are low-cost, non-pharmacological interventions that can be implemented within existing senior centers, cultural associations, and social venues, engaging large numbers of older adults without requiring specialist medical infrastructure. Community singing programs have been shown to be at least marginally more cost-effective than normal recreational activities, while producing significant improvements in mental health-related quality of life, anxiety, and depressive symptoms (Coulton et al. 2015). More broadly, economic evaluations of multidomain and community-based prevention programs indicate that interventions delivered outside clinical environments can achieve favorable cost-effectiveness profiles, providing meaningful health gains at relatively modest cost and helping to relieve pressure on health systems in aging societies (Melis et al. 2008; Coulton et al. 2015).

Choir-based multidomain programs are also well positioned to reach older adults who are not yet patients but may already show early vulnerability profiles among whom multidomain interventions have been shown to enhance intrinsic capacity and slow deterioration in frailty and cognition (Liang et al. 2024; Sánchez-Sánchez et al. 2022). Indeed, participation in a choir directly targets social frailty and loneliness, recognized risk factors for adverse outcomes, by providing regular, meaningful social engagement around a shared cultural activity that promotes belonging, purpose, and motivation while avoiding the stigma sometimes associated with explicitly therapeutic programs (Hoang et al. 2022; Pentikäinen et al. 2021; Johnson et al. 2020).

Overall, the findings support choir-based multidomain interventions as promising tools to induce early indicators of functional adaptation across cognitive, neural, and psychosocial domains, consistent with contemporary preventive models of aging. By integrating multidomain stimulation into a culturally meaningful, low-cost, adaptable group activity that promotes sustained participation, social connection, and intrinsic motivation, MultiMusic complements existing multidomain and precision-prevention strategies, offering a scalable avenue to support intrinsic capacity and stabilize functional trajectories in aging populations (Ngandu et al. 2015; Rosenberg et al. 2019; Deckers et al. 2024; Kivipelto et al. 2020; Matton et al. 2025).

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