Université de Montréal

Facteurs prédictifs de l'efficacité d'une intervention combinant entraînement cognitif et activités de loisirs (programme ENGAGE)

par
Kim Lasnier-Le Quang

Département de psychologie
Faculté des arts et des sciences

Essai présenté en vue de l'obtention du grade de doctorat en Psychologie (D.Psy)
Option Neuropsychologie clinique

Août 2023

Résumé

Objectif: Cette étude visait à déterminer l'influence des caractéristiques individuelles sur l'efficacité d'interventions combinant entraînement cognitif et activités de loisirs. **Méthode:** L'étude repose sur un essai contrôlé randomisé incluant 107 adultes âgés de 60 à 85 ans qui répondaient aux critères du déclin cognitif subjectif (DCS) ou du trouble neurocognitif léger (TNCL). Ils étaient assignés soit aux interventions ENGAGE-MUSIQUE (MUSIQUE) ou ENGAGE-ESPAGNOL (ESPAGNOL), qui combinaient entraînement cognitif et loisirs cognitivement stimulants, soit au programme ENGAGE-DISCOVERY (DISCOVERY), une condition de contrôle actif. Des modèles mixtes pour mesures répétées ont déterminé quelles variables prédisaient l'effet de l'intervention sur la performance en mémoire différée. Les variables évaluées étaient l'âge, le sexe attribué à la naissance (sexe), le nombre d'années de scolarité, le score à un questionnaire de réserve cognitive (QRC), les symptômes dépressifs, et le score initial à des tâches de flexibilité cognitive, d'inhibition et de mémoire épisodique. **Résultats:** Le sexe, le score au QRC et le score initial de flexibilité cognitive modéraient l'effet de l'intervention. Les femmes, les individus ayant un score plus élevé au QRC et ceux ayant un moindre score initial de flexibilité cognitive s'amélioraient plus à la suite des interventions MUSIQUE ou ESPAGNOL. Les individus ayant un meilleur score initial de flexibilité cognitive s'amélioraient davantage suivant DISCOVERY. **Conclusion:** Les effets d'interventions combinant entraînement cognitif et loisirs varient selon le sexe, le score à un questionnaire de réserve cognitive et le score initial de flexibilité cognitive. De telles informations pourraient servir à personnaliser les recommandations d'interventions cognitives en fonction des caractéristiques présentes chez les personnes âgées.

Mots clés: entraînement cognitif, intervention, loisirs, prédicteur, modérateur, réserve cognitive, fonctions exécutives, sexe, mémoire, personnes âgées, neuropsychologie clinique

Abstract

Objective: This study aimed to determine whether specific individual characteristics influenced the efficacy of interventions combining cognitive training and leisure activities. **Methods:** This study is based on a randomized controlled trial that included 107 older adults aged 60 to 85, who met the criteria for subjective cognitive decline (SCD) or mild cognitive impairment (MCI). Participants were assigned to either the ENGAGE-MUSIC (MUSIC) or ENGAGE-SPANISH (SPANISH) interventions, which combined cognitive training with stimulating leisure activities, or the active control condition ENGAGE-DISCOVERY (DISCOVERY). Mixed models for repeated measures were used to identify predictors of intervention effects on delayed memory performance. Factors examined as predictors included age, sex assigned at birth (sex), years of formal education, Cognitive Reserve Questionnaire (CRQ) scores, depressive symptoms, and baseline scores on cognitive flexibility, inhibition, and episodic memory tasks. **Results:** The results revealed that sex, CRQ scores, and baseline cognitive flexibility scores moderated intervention effects. Specifically, women, individuals with higher CRQ scores, and those with lower baseline cognitive flexibility performance exhibited greater improvements following the MUSIC or SPANISH interventions. Conversely, individuals with higher baseline cognitive flexibility performance demonstrated superior improvement from the DISCOVERY program. **Conclusion:** These findings underscore that intervention effects in combined cognitive training and leisure activities vary according to sex, CRQ scores, and baseline cognitive flexibility performance. Such insights could guide clinicians in recommending cognitive interventions for older adults, optimizing efficacy by aligning individual characteristics with program requirements.

Keywords: cognitive training, intervention, leisure, predictor, moderator, cognitive reserve, executive functions, sex, memory, older adults, clinical neuropsychology

Table des matières

Liste des tableaux

Liste des figures

Liste des abréviations

CCNA: Canadian Consortium on Neurodegeneration in Aging

CIMA-Q: Consortium for the Early Identification of Alzheimer's Disease

CR: Cognitive reserve

CRQ: Cognitive Reserve Questionnaire

GDS: Geriatric Depression Scale

IUGM: Institut universitaire de gériatrie de Montréal

MCI: Mild cognitive impairment

MMRM: Mixed Model for Repeated Measures

MoCA: Montreal Cognitive Assessment

RAVLT: Rey Auditory Verbal Learning Test

SCD: Subjective cognitive decline

TMT: Trail Making Test

Remerciements

Tout d’abord, je tiens à adresser mes sincères remerciements à ma directrice de recherche, Sylvie Belleville, pour ses conseils éclairés et sa grande disponibilité. Vos réflexions et vos commentaires avisés ont considérablement enrichi cet article et ont eu un impact indélébile sur mon développement. J’aspire à intégrer cette même rigueur, passion et ambition dans mes futures réalisations. Un immense merci s’adresse à Aline Moussard, qui, en plus de me guider dans la réalisation de cet article, m’a permis de plonger profondément dans les diverses dimensions de la recherche. Ton accompagnement bienveillant et ton travail au cœur du projet ENGAGE méritent une reconnaissance particulière.

J’exprime également ma reconnaissance à Isaora Zefania Dialahy, dont l’expertise en statistiques a démystifié ce domaine complexe. Merci pour ton importante contribution et pour la patience dont tu as fait preuve dans tes explications. Mes remerciements se tournent également vers Annie Webb, dont la relecture attentive et efficace de l’anglais a grandement amélioré la qualité de ce travail. Mes remerciements s’étendent à l’équipe 10 du CCNV pour leur collaboration à ce projet. J’exprime également ma gratitude à mes collègues du Laboratoire Belleville, qui m’ont guidé, accompagné et diverti tout au long de mon parcours universitaire.

Aux personnes qui m’ont initié au domaine de la neuropsychologie en recherche et en clinique, merci d’avoir partagé votre passion et votre expérience avec moi. Je vous en suis infiniment reconnaissante.

Enfin, un immense merci à ma famille et mes amis. Votre soutien et vos encouragements constants me motivent dans tout ce que j’entreprends. À ceux et celles qui m’accompagnent en présence et en pensée, je partage cette réalisation avec vous.

Article

Predictors of Intervention Efficacy: Combining Cognitive Training and Leisure Activities (ENGAGE Program)

Author Names

Lasnier-Le Quang, Kim[1,2], Moussard, Aline[1], Dialahy, Isaora Zefania[1], Team 10 of the Canadian Consortium on Neurodegeneration in Aging (CCNA) and Belleville, Sylvie[1,2]

Affiliations

1. Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Québec, Canada

2. Département de Psychologie, Université de Montréal, Québec, Canada

Corresponding Author

Sylvie Belleville, Ph.D.

Centre de recherche de l'Institut universitaire de gériatrie de Montréal

4565 Queen Mary

Montréal H3W 1W5

Québec, Canada

Phone: 514-340-3540 ext. 4767

Fax: 514-340-3530

Email: sylvie.belleville@umontreal.ca

Abstract

Objective: This study aimed to determine whether specific individual characteristics influenced the efficacy of interventions combining cognitive training and leisure activities. **Methods:** This study is based on a randomized controlled trial that included 107 older adults aged 60 to 85, who met the criteria for subjective cognitive decline (SCD) or mild cognitive impairment (MCI). Participants were assigned to either the ENGAGE-MUSIC (MUSIC) or ENGAGE-SPANISH (SPANISH) interventions, which combined cognitive training with stimulating leisure activities, or the active control condition ENGAGE-DISCOVERY (DISCOVERY). Mixed models for repeated measures were used to identify predictors of intervention effects on delayed memory performance. Factors examined as predictors included age, sex assigned at birth (sex), years of formal education, Cognitive Reserve Questionnaire (CRQ) scores, depressive symptoms, and baseline scores on cognitive flexibility, inhibition, and episodic memory tasks. **Results:** The results revealed that sex, CRQ scores, and baseline cognitive flexibility scores moderated intervention effects. Specifically, women, individuals with higher CRQ scores, and those with lower baseline cognitive flexibility performance exhibited greater improvements following the MUSIC or SPANISH interventions. Conversely, individuals with higher baseline cognitive flexibility performance demonstrated superior improvement from the DISCOVERY program. **Conclusion:** These findings underscore that intervention effects in combined cognitive training and leisure activities vary according to sex, CRQ scores, and baseline cognitive flexibility performance. Such insights could guide clinicians in recommending cognitive interventions for older adults, optimizing efficacy by aligning individual characteristics with program requirements.

Keywords: cognitive training, intervention, leisure, predictor, moderator, cognitive reserve, executive functions, sex, memory, older adults, clinical neuropsychology

Introduction

Background

Cognitive training, which refers to structured programs designed to improve cognitive abilities through formal instruction and practice, is a potentially valuable tool to help maintain cognition and prevent dementia in older adults. Several reviews and meta-analyses support the efficacy of cognitive training (Lampit et al., 2014; Mewborn et al., 2017; Smart et al., 2017; Tse et al., 2023; Vaportzis, et al., 2019). However, significant variability exists in the individual response to cognitive training programs (Carlson et al., 2009; Langbaum et al., 2009; Marr et al., 2020; Rebok et al., 2014; Rosi et al., 2018; Traut, et al., 2021), possibly attributed to differences in cognitive, demographic, and psychological variables (Katz et al., 2021). This study aims to identify individual characteristics that predict the efficacy of cognitive interventions in older adults. This work holds considerable potential clinical implications, as it may reveal which older adults are more likely to benefit from cognitive interventions. Additionally, it could provide insights for studying intervention efficacy in a more nuanced manner. Such findings will offer guidance to clinicians in their recommendations and contribute to the personalization of cognitive interventions, improving their effectiveness at the individual level.

In recent years, several reviews have investigated predictors impacting training responsiveness, focusing primarily on demographic and cognitive factors (Lampit et al., 2014; Ophey et al., 2020; Roheger et al., 2021). Many of these predictors have been interpreted within the framework of the *magnification* versus *compensation* perspective. The *magnification* perspective posits a heightened efficacy of interventions (i.e., higher learning potential) among individuals with superior initial performance, attributed to higher levels of neuroplasticity or cognitive resources (Lövdén et al., 2012; Schaie & Willis, 1986). Conversely, the *compensation* perspective suggests that those with lower initial performance will witness greater improvement, addressing their heightened need (Roheger, Kalbe, Corbett, Brooker, & Ballard, 2020a, 2020b). Many studies have reported data that aligns with the *compensation* view (Traut et al., 2021). For example, older age (Langbaum et al., 2009; Roheger et al., 2021), lower performance on tasks of memory (Langbaum et al., 2009; Roheger, Kalbe, Corbett, Brooker, & Ballard, 2020a, 2020b), or executive functioning (Carlson et al., 2008; Karbach & Verhaeghen, 2014; López-Higes et al., 2018; Zinke et al., 2014), as well as lower scores on cognitive reserve (CR) proxies (formal *education* or *CR questionnaires;* Mondini et al., 2016; Olazarán et al., 2004; Park et al., 2018) have all been associated with greater training gains following cognitive interventions. However, other studies have reported findings that are consistent with the *magnification* view. For example, some authors have reported larger intervention effects in older adults with higher scores on CR proxies (Langbaum et al., 2009; Legault et al., 2011; Roheger et al., 2019).

Non-cognitive variables may also impact intervention effects (Hess, 2014), even though they are often inadequately investigated (Rebok et al., 2013). The presence of depressive symptoms is an interesting factor to evaluate because depression has been associated with reduced cognitive resources (Gabryelewicz et al., 2007; Köhler et al., 2010; Sharifian et al., 2020) and lower activity engagement (Achterberg et al., 2003; Carretti, et al., 2011). Although results on the influence of depressive symptoms on cognitive training gains remain scarce, a few studies have failed to observe an association (Andrewes et al., 1996; Leahy et al., 2018; Royall, Palmer, Chiodo, & Polk, 2012). Sex is another intriguing factor, given its known impact on a range of biological, cognitive, and psychosocial dimensions (Beinhoff et al., 2008). Interestingly, several studies have reported a significant association between sex and cognitive outcomes. Moreover, evidence suggests that women benefit more from strategic cognitive interventions targeting memory enhancement compared to men (Aguirre et al., 2013; Bråthen et al., 2021; Rahe et al., 2015).

In conclusion, many studies have indicated that intervention efficacy may vary as a function of inter-individual differences. While there appears to be support for the *compensation* perspective, recent models suggest that the efficacy of cognitive interventions is dependent on the balance between the individual's available resources and the intervention's demands (Lövdén et al., 2012; Reuter-Lorenz & Park, 2014; Stine-Morrow et al., 2014). This implies that intervention efficacy may not solely depend on individual characteristics, but also on the alignment between these characteristics and the intervention's demands and content. Therefore, exploring the impact of individual characteristics on different types of interventions, as pursued in this study, holds significant interest.

The ENGAGE study

The ENGAGE study (Belleville, Moussard et al., 2019, 2023, in preparation) evaluated the efficacy of an intervention combining formal cognitive training and different cognitively stimulating leisure activities in older adults with subjective cognitive decline (SCD) or mild cognitive impairment (MCI). Individuals with SCD and MCI are an ideal population to study the impact of cognitive interventions, as they are at risk of cognitive decline, thus making the potential benefits substantial. Combining leisure activities with formal cognitive training represents an interesting approach for enhancing engagement and interest (Carlson et al., 2008; Park et al., 2014). Furthermore, participation in leisure activities alone has been associated with reduced age-related cognitive decline and positive effects on cognition (Park et al., 2014; Stine-Morrow et al., 2014). The ENGAGE study included three conditions: The ENGAGE-MUSIC (referred to here as MUSIC) and ENGAGE-SPANISH (referred to here as SPANISH) intervention conditions combined formal cognitive training with music or Spanish lessons, respectively. Music and Spanish lessons were selected as leisure activities due to their reported ability to maintain cognition (Hanna-Pladdy & Gajewski, 2012; Moussard et al., 2016; Craik et al., 2010). An active control condition (ENGAGE-DISCOVERY; referred to here as DISCOVERY) involved participants watching documentaries and engaging in group discussions as a leisure activity, which was assumed to be less cognitively stimulating than music and Spanish. They also received psychoeducation regarding the aging brain and lifestyle factors promoting healthy aging. The DISCOVERY condition did not involve formal cognitive training. When compared to the DISCOVERY condition, the MUSIC and SPANISH interventions have been found to improve attention but not delayed memory (Belleville et al., 2023, in preparation). The absence of an effect on memory was surprising, given previous findings that indicated memory efficacy for certain components integrated into the ENGAGE interventions (Belleville et al., 2018). However, an inter-individual variability in efficacy may have contributed to this absence of an effect on memory, which needs further exploration.

The present study assessed whether age, sex assigned at birth (referred to here as sex), years of formal education, CR questionnaire scores, depressive symptoms, baseline executive functioning, and baseline episodic memory moderated the effect of the ENGAGE intervention—comprising diverse leisure-based cognitive intervention programs—on delayed memory. The selected variables have shown a moderating effect in the existing literature and could offer clinicians valuable insights for recommending cognitive interventions. To the best of our knowledge, this is the first study to investigate predictors of memory change following a leisure-based cognitive intervention in older adults.

The variables, including age, formal education, sex, cognitive reserve, depressive symptoms, baseline memory, and executive functioning, were hypothesized to interact with the intervention effects. Women were expected to experience more pronounced benefits compared to men from the MUSIC and/or SPANISH interventions, as they involve strategic memory training. In the case of depressive symptoms, the scarcity of literature led to the absence of specific directional hypotheses. However, an important hypothesis was that the role of these individual variables would differ for the MUSIC, SPANISH, and DISCOVERY programs because they vary in terms of cognitive demand and content.

Methodology

Experimental design

This research is part of the ENGAGE study, which is a double-blind randomized controlled preference trial using a comprehensive cohort design to measure the effects of a cognitive intervention known as the ENGAGE program (Belleville et al., 2019, 2023, in preparation). The intervention program combined leisure activities with formal cognitive training. The design of the main study was published by Belleville et al. (2019) and registered with the US National Institutes of Health clinical trials registry (ClinicalTrials.gov identifier NCT03271190). Participants were randomized to either the intervention conditions (MUSIC or SPANISH) or the active control condition (DISCOVERY). However, before randomization, participants were given the option to exclude the music or Spanish leisure activities based on their preference. For participants randomized to the intervention condition who did not exclude an activity, a second independent randomization assigned them to the MUSIC or SPANISH intervention. Recognizing that certain individuals may strongly dislike one of the two leisure activities, a preference trial design was used to enhance randomization acceptance and reduce selective dropout (Craig et al., 2008). The study was conducted across two sites: Montreal (Institut universitaire de gériatrie de Montréal, IUGM) and Toronto (Centre for Memory and Aging, Baycrest Health Sciences).

The three programs (MUSIC, SPANISH, and DISCOVERY) were administered over the course of 24 sessions spanning four months. Assessments were carried out at three time points: baseline (PRE; within eight weeks preceding the intervention), at the four-month follow-up (POST; within four weeks following the intervention), as well as 24 months after the initial evaluation (F24; within two years +/- 3 months after PRE). Only the PRE and POST measures will be presented here. The ENGAGE study received approval from the research ethics boards of the Jewish General Hospital in Montreal, and the Baycrest Health Sciences Center in Toronto.

Participants

This study is part of the Canadian Consortium on Neurodegeneration in Aging (CCNA), and most participants were included in the CCNA Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) cohort (Chertkow et al., 2019). A subset of participants was also part of the Consortium for the Early Identification of Alzheimer's Disease (CIMA-Q; Belleville, LeBlanc et al., 2019). Recruitment was executed through pamphlets, newspapers, magazine advertisements, as well as in community centers. At baseline, participants ranged in age from 60 to 85 years and lived independently in the community. They met the criteria for SCD or early MCI (Jessen, Wolfsgruber, et al., 2014; Petersen et al., 2001). They answered positively to the questions: "Do you feel your memory is declining" and "Does this worry you?" (Jessen, Amariglio, et al., 2014). They exhibited minimal or no cognitive deficits as measured by: a score higher than the education-adjusted score on Story A of the logical memory task from the Wechsler Memory Scale-III (WMS-III; Elwood, 1991; Wechsler, 1997) based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria (≥ 9 for 16+ years of education; ≥ 5 for 8–15 years of education; ≥ 3 for 0–7 years of education; Chapman et al., 2016), a score above 20 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), and a score higher than 4 on the delayed recall of the Consortium to Establish a Registry for Alzheimer's Disease's (CERAD) word list task. Their clinical Dementia Rating score (CDR) was below 1.0 (Morris, 1997). In addition, they demonstrated normal or corrected visual and auditory abilities, were proficient in French or English, were available for the intervention period and follow-up visits, possessed an internet connection at home and were able to provide contact details for an available informant.

Exclusion criteria were: (1) the presence of a disease or injury affecting the central nervous system; (2) a clinical diagnosis of major depression, anxiety or other psychiatric illnesses that may interfere with participation in the intervention; (3) inability to undergo an MRI scan due to medical conditions or intolerance; (4) being a musician, having more than five years of formal musical training, or possessing more than 10 years of choir experience; (5) speaking Spanish or having taken Spanish lessons for more than five years (excluding in high school); having lived in a Spanish-speaking country or being currently enrolled in Spanish lessons; (6) concurrent involvement in another research project; (7) prior participation in a cognitive intervention centered on learning of memory strategies.

Intervention

The MUSIC, SPANISH, and DISCOVERY programs followed the same structure in terms of number and duration of classes, hours of homework, and the ratio of formal class to leisure activity. All programs were offered in groups of two to nine individuals (generally between five and seven) and lasted approximately two hours each. Over the course of four months, a total of 24 training sessions were delivered, with two sessions per week during the first eight weeks, and one session per week during the following eight weeks. The programs comprised 17 hours of formal classes (cognitive training or psychoeducation) and 31 hours of leisure activities. Each week, participants also completed two hours of homework to practice and apply what they had learned into their daily lives, thus enhancing the likelihood of transfer. Due to the COVID-19 pandemic, 20 participants (seven from MUSIC and 13 from SPANISH) received seven to nine sessions of the intervention through Zoom.

MUSIC and SPANISH

The MUSIC and SPANISH intervention programs combined formal cognitive training with the practice of leisure activities that were cognitively demanding. Cognitive training sessions were administered by research professionals, while leisure sessions were conducted by professional music or Spanish teachers. The cognitive training component remained consistent across the MUSIC and SPANISH programs, encompassing psychoeducation on cognitive aging as well as memory and attention training. Memory training was based on the MEMO program (Belleville et al., 2006, 2018) as well as the Memory and Aging Program (Troyer, 2001). Participants learned internal (e.g., mental imagery, spaced retrieval) and external (e.g., use of media, organizational strategies) strategies to maximize their memory. Attentional training included computerized exercises focusing on attentional control and dual tasking (Bherer et al., 2005; Gagnon & Belleville, 2012). The practice of leisure activities comprised 27 hours of learning Spanish or music and four hours of exercises with attention-demanding video games. The leisure sessions were comparable to classes offered in the community. Formal cognitive training sessions and leisure activity sessions were alternated to facilitate the application of strategies learned in the respective activities. Weekly homework assignments consisted in the application of memory strategies through Spanish or music exercises, along with practicing attentional strategies while playing selected video games.

DISCOVERY

The DISCOVERY program was used as an active control condition. The program was designed to be less cognitively demanding than the MUSIC and SPANISH interventions while still being motivating and enjoyable. The formal classes consisted of psychoeducation on cognitive processes, cognitive aging, and lifestyle tips to promote healthy aging. In terms of leisure activities, participants engaged in watching documentaries, participating in discussions, and playing video games. As this was a control condition, the video games were chosen for their entertainment value, without deliberately engaging cognitive processes, such as attentional control or processing speed. For homework, participants were tasked with completing exercises aligned with the psychoeducation sessions and playing the designated video games at home.

Measures

Outcome measure

The primary outcome was a composite score for delayed memory, given its established sensitivity to cognitive interventions in a previous study (Belleville et al., 2006). Two tasks were used to derive the composite score: the delayed recall of the Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996), and the CIMA-Q Face-name association task (Belleville, LeBlanc et al., 2019). The RAVLT is composed of five learning trials involving a list of 15 unrelated words (List A). Subsequently, participants learn and recollect an interference list (List B), followed by an immediate recall of List A. The delayed recall of List A is done after a 20-minute interval. The face-name association task requires participants to memorize nine face and first-name associations, with immediate and 20-minute delayed recall assessments for each name. The composite score was calculated by merging the delayed recall from both tasks. For each participant, task, and time point, the score obtained was converted into a z-score (score – reference mean / reference SD), using the mean baseline score of the group as a reference. Z-scores for both tasks were averaged to obtain the delayed memory composite score.

Predictor variables

The predictor variables examined in this study encompassed demographic factors, such as age (years), sex assigned at birth (here, whether they were women or men) and number of years of formal education. Additionally, the participant's score on the Cognitive Reserve Questionnaire (CRQ; Rami et al., 2011) was considered. This questionnaire evaluates the participant's education level as well as engagement in cultural, professional, intellectual, and social activities throughout their lifetime (maximum score of 30). Depressive symptoms were also evaluated using the Geriatric Depression Scale (GDS; Scogin et al., 2000). For the cognitive assessment, we used completion time in the Trail Making Test (TMT) conditions B - A (Sánchez-Cubillo et al., 2009) as well as completion time in the Delis-Kaplan Executive Function System color-word interference test's inhibition condition (D-KEFS Inhibition; Delis et al., 2004) to measure baseline cognitive flexibility and inhibition, respectively. Episodic memory at baseline was assessed through the delayed recall of the Logical Memory subtest (Story A) from the WMS-III (Wechsler, 1997). To ensure uniformity in interpretation, cognitive variables were reversed in cases where it was deemed necessary so that higher scores consistently indicated enhanced performance.

Further details on the materials and methods are available in the study protocol (Belleville, Moussard et al., 2019).

Statistical analyses

Demographic characteristics

To initiate the analysis, one-way ANOVA and chi-squares were used to compare the three groups (MUSIC, SPANISH, and DISCOVERY) in terms of demographic variables, baseline cognitive scores and other predictor variables.

Variable selection

To assess predictors, stepwise multiple regression analyses were first used to select the predictor variables suitable for inclusion in the Mixed Models for Repeated Measures (MMRM). This process involved examining the variables that reliably predicted the delayed memory composite score at POST. Only the variables identified as significant predictors ($p < 0.005$) in this preliminary regression analysis were included in the MMRM presented below.

Mixed Models for Repeated Measures (MMRM)

Subsequently, MMRM were used to determine the variables that predicted change in the delayed memory composite score between the PRE and POST assessments, as a function of the Group (3; Intervention: MUSIC, SPANISH, and Active control: DISCOVERY). Models were estimated with the lme4 package of R.4.2.1, with a standard 5% significance level two-sided alpha ($p < 0.005$). Selected predictors were defined as fixed main effects in the models, with an individual intercept representing the effect of the DISCOVERY control condition. Thus, the effect was assessed against DISCOVERY, the active control condition. Individual models were computed for each predictor selected from the stepwise multiple regression analyses. For each model, the Time x Group x Predictor interaction indicated whether the Time x Group interaction varied according to the level of the predictor variable.

When significant Time x Group x Predictor interaction effects were found, Group comparisons were computed for fixed interaction effects. These comparisons aimed to evaluate changes in delayed memory between groups (MUSIC, SPANISH, and DISCOVERY) according to different levels of predictor variables. Change in memory performance was defined as the difference between the PRE to POST slopes (Engle, 1984) for each group (MUSIC, SPANISH, and DISCOVERY). For the sake of concision, only results from models with significant three-way (Time x Group x Predictor) interactions are presented.

Results

Demographic characteristics

In total, 107 participants were included in the present study. Table 1 details the characteristics of the participants at baseline according to their group. No significant differences were found between the groups in demographic variables, questionnaire scores, or baseline cognitive abilities.

Table 1

Baseline Participant Characteristics as a Function of Group

	MUSIC *n = 29*	SPANISH *n = 41*	DISCOVERY *n = 37*	F or chi-square[a]	p
Age (years) – M *(SD)*	70.64 *(5.13)*	71.01 *(5.89)*	71.11 *(5.55)*	.062	.940
Sex - % women (n women)	51.35 *(19)*	60.98 (*25)*	81.08 *(30)*	3933	.140
Years of formal education – M *(SD)*	14.96 *(3.37)*	14.63 *(3.53)*	15.81 *(3.20)*	1.226	.298
MoCA – M *(SD)*	26.34 *(2.73)*	25.68 *(2.94)*	26.38 *(2.33)*	.816	.445
CRQ[b]– M *(SD)*	18.24 *(3.94)*	16.89 *(3.48)*	17.82 *(3.84)*	1.141	.324
GDS– M *(SD)*	4.34 *(4.328)*	4.34 *(3.071)*	5.92 *(4.781)*	1.813	.168
TMT[c]– M *(SD)*	54.61 *(47.59)*	45.86 *(39.18)*	43.06 *(21.18)*	.824	.442
D-KEFS Inhibition[d] – M *(SD)*	60.90 *(13.86)*	61.77 *(14.76)*	62.30 *(17.04)*	.068	.934
Logical memory[e] – M *(SD)*	13.52 *(5.17)*	12.90 *(4.04)*	15.05 *(4.11)*	2.400	.096

Note. Sex = Sex assigned at birth; MoCA = Montreal Cognitive Assessment; *CRQ* = Cognitive Reserve Questionnaire; GDS = Geriatric Depression Scale; TMT = Trail Making Test completion time - condition B – A; D-KEFS Inhibition = Inhibition condition completion time of the Delis-Kaplan Executive Function System color-word interference test. Lower scores for the TMT and D-KEFS Inhibition indicate better performance. Higher scores indicate better performance on all other tests.

[a] df = 2, [b] n = 94, [c] n = 100 , [d] n = 106, [e] n = 106.

Preliminary analyses

Five variables were identified in the stepwise analysis (Appendix A) as predictors of the delayed memory composite score at POST and were therefore included in the MMRM. These variables were sex assigned at birth (here women vs. men), score on the CRQ, and baseline cognitive flexibility (TMT), inhibition (D-KEFS Inhibition), and episodic memory (logical memory).

Mixed Models for Repeated Measures (MMRM)

Significant Time x Group x Predictor interaction effects were obtained for the models that included sex, CRQ score, and baseline cognitive flexibility as predictors. The effects of each variable are described below as well as slope comparisons between the groups.

For the group comparisons, we compared *men* vs. *women,* and *higher* vs. *average* vs. *lower* scores on the CRQ and the TMT. *Higher* was defined as scores that were more than 1 standard deviation above the mean *(+1 SD)* and *lower* was defined as scores that were less than 1 standard deviation below the mean *(-1 SD)*. *Average* refers to scores in the middle range (between -1 and +1 standard deviation of the mean, inclusively). Appendix B presents estimates of the fixed effects on the delayed memory composite scores for all models. Detailed results of the group comparisons are presented in Appendix C.

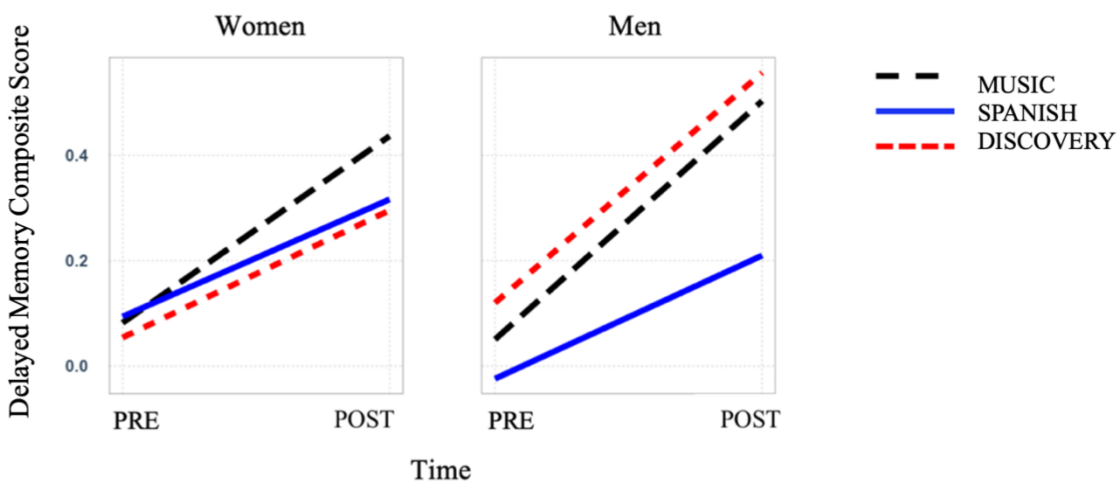
Effects of Sex

A significant Time x Group x Predictor interaction effect was obtained in the model that included sex as a predictor for the SPANISH group ($p < .001$), whereas no such effect was observed for the MUSIC group.

For *women*, there was a greater improvement following the MUSIC intervention compared to the DISCOVERY program ($|\Delta\beta| = .113$, $\chi 2 = .212$, $p = .040$), as well as after MUSIC in contrast to SPANISH (|Δβ| = .132, χ2 = 5.735, p = .017). For *men*, there was a greater improvement after the DISCOVERY program compared to the SPANISH intervention |(|Δβ| = .203, χ2 = 13.502, p < .001). The improvement was also greater for participants in the MUSIC group than those in the SPANISH group (Δβ| = .219, χ2 = 15.702, p < .001). These results are shown in Figure 1.

Figure 1

Delayed Memory Composite Score from PRE to POST for the Three Groups as a Function of Sex



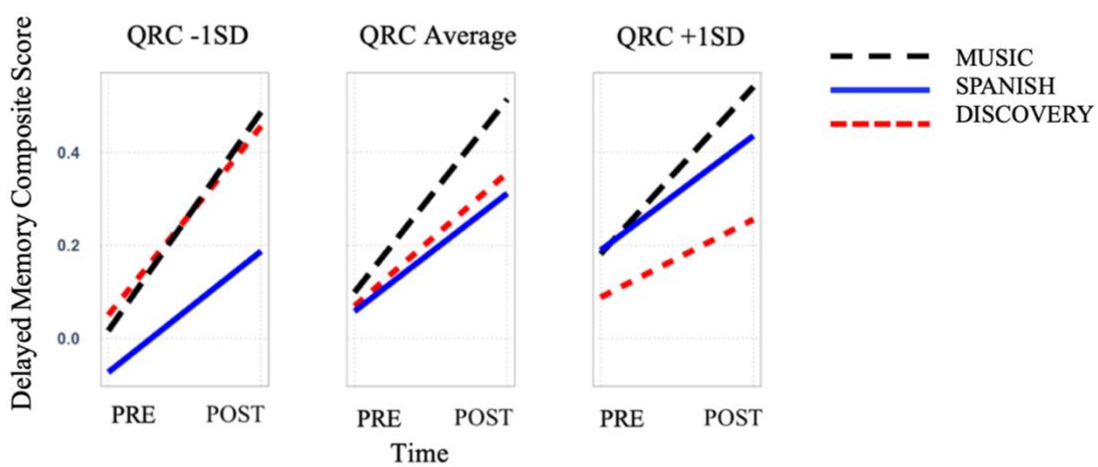
Effects of the Cognitive Reserve Questionnaire (CRQ)

A significant Time x Group x Predictor interaction was obtained for the models that included the CRQ as a predictor for the MUSIC (p = .030) and SPANISH (p < .001) groups.

Among individuals with *lower* CRQ scores, there was a greater improvement in the DISCOVERY group compared to the SPANISH group (|Δβ| = .171, χ2 = 27.421, p < .001). The improvement was also greater for MUSIC than SPANISH (|Δβ| = .221, χ2 = 45.926, p < .001). For those with *average* CRQ scores, a greater increase in memory performance was associated with the MUSIC intervention compared to the DISCOVERY program (|Δβ| = .117, χ2 = 12.754, p < .001), and a more considerable improvement was noted for the MUSIC intervention compared to the SPANISH intervention (|Δβ| = .170, χ2 = 27.290, p < .001). Individuals with *higher* CRQ scores displayed a larger increase in delayed memory in the MUSIC group compared to DISCOVERY (|Δβ| = .183, χ2 = 31.385, p < .001). Additionally, a more pronounced improvement was observed for the MUSIC intervention compared to the SPANISH intervention (|Δβ| = .120, χ2 = 13.477, p < .001). These results are shown in Figure 2.

Figure 2

Delayed Memory Composite Score from PRE to POST for the Three Groups as a Function of Score on the Cognitive Reserve Questionnaire (CRQ)



Effects of Baseline Cognitive Flexibility

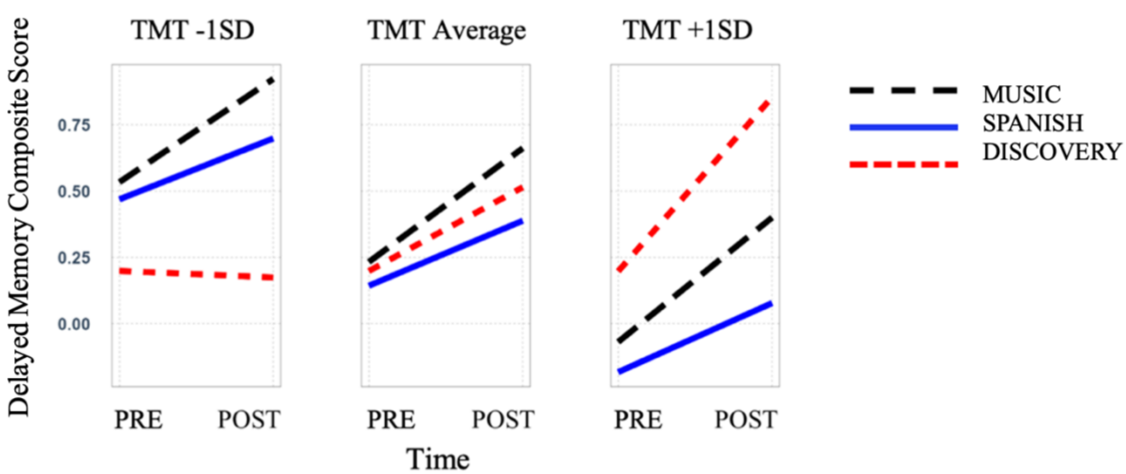
A significant Time x Group x Predictor interaction effect was obtained in the models that included baseline cognitive flexibility performance as a predictor for the MUSIC (p < .001) and SPANISH (p < .001) groups.

For individuals with *lower* baseline cognitive flexibility performance, there was a greater improvement for the MUSIC and SPANISH groups as compared to the DISCOVERY group, which exhibited no notable improvement in memory performance, as shown in Figure 1 (|Δβ| = .398, χ2

= 58.025, $p < .001$ and $|\Delta\beta| = .237$, $\chi 2 = 20.626$, $p < .001$, for the comparison with MUSIC and SPANISH, respectively). Furthermore, a more pronounced improvement was evident for the MUSIC intervention in contrast to the SPANISH intervention ($|\Delta\beta| = .161$, $\chi 2 = 9.461$, $p = 0.002$). Among individuals with *average* baseline cognitive flexibility performance, a more significant improvement was noted after the MUSIC intervention compared to the SPANISH intervention ($|\Delta\beta| = .186$, $\chi 2 = 12.668$, $p < .001$). For individuals with *higher* baseline cognitive flexibility performance, a larger increase was found for the DISCOVERY group compared to the MUSIC and SPANISH groups ($|\Delta\beta| = .221$, $\chi 2 = 17.900$, $p < .001$ and $|\Delta\beta| = .432$, $\chi 2 = 68.451$, $p < .001$ for the comparison with MUSIC and SPANISH, respectively). Moreover, a greater improvement was observed for the MUSIC intervention compared to the SPANISH intervention ($|\Delta\beta| = .211$, $\chi 2 = 16.343$, $p < .001$). These results are shown in Figure 3.

Figure 3

Delayed Memory Composite Score from PRE to POST for the Three Groups as a Function of Baseline Cognitive Flexibility Performance (TMT)



Discussion

Previous literature reports notable inter-individual variability in the efficacy of cognitive interventions in older adults. This present study aimed to investigate whether individual characteristics contributed to differences in efficacy for three different leisure-based cognitive programs: MUSIC, SPANISH, and DISCOVERY. Our results show that intervention effects on delayed memory vary according to sex, CR, and baseline cognitive flexibility. However, age, years of formal education, depressive symptoms, and baseline measures of inhibition or episodic memory did not moderate intervention effects. Importantly, when comparing the effects of the three types of intervention, we found that optimal programs for memory improvement differ according to individual variables. Women, individuals with more robust CR, and those with lower baseline cognitive flexibility exhibited greater improvements following the MUSIC or SPANISH interventions. Conversely, individuals with higher baseline cognitive flexibility showed more improvement after participating in the DISCOVERY program. The main findings and their implications are discussed below.

First, our results indicate that different interventions are most efficient for different subgroups of older adults. Notably, women benefitted more from the MUSIC intervention than all other conditions, whereas men benefitted most from the DISCOVERY or MUSIC programs. Participants with lower CR benefitted almost equally from MUSIC and DISCOVERY but not as much from the SPANISH intervention. In contrast, those with higher or average CR benefitted most from the MUSIC intervention. Individuals with lower cognitive flexibility benefitted most from the MUSIC and SPANISH interventions, while those with higher flexibility benefitted most from DISCOVERY. These results are consistent with our hypotheses and are aligned with models suggesting that the efficacy of cognitive interventions depends on a balance between individual characteristics and intervention features (Lövdén et al., 2012; Reuter-Lorenz & Park, 2014; Stine-Morrow et al., 2014). Consequently, we propose that an adequate alignment between individual characteristics and intervention content can optimize cognitive improvement in older adults.

An important question remains: What aspects of the interventions need to be considered, or aligned, to optimize their efficacy at the individual level? In other words, which intervention features explain their efficacy in certain cases while not others? In this context, we propose that certain components of leisure activities or cognitive training might be better tailored to accommodate the cognitive needs of distinct older adults. For instance, individuals with lower baseline cognitive flexibility might exhibit more improvement from the MUSIC and SPANISH interventions. This could be attributed to the inclusion of formal executive training within these two interventions, a component notably absent in DISCOVERY. Thus, it is conceivable that individuals with lower cognitive flexibility show more memory improvement following interventions that enhance their executive capacities. The finding that differences in efficacy were found in those with executive scores in the low range, but not for those in the middle range, is consistent with this interpretation. For such older adults, personalized interventions could yield the most advantageous outcomes.

Another explanation may relate to the balance between cognitive demand and supply. Neuroplasticity models (Lövdén et al., 2012) posit that optimal interventions should incorporate cognitive demand that slightly exceeds supply, thereby stimulating neuroplastic processes. In this light, individuals with lower CR may benefit more from DISCOVERY and MUSIC interventions. This might be because these programs entail demands that slightly exceed their cognitive supply. Conversely, individuals with higher CR benefitted less from DISCOVERY. A plausible explanation is that older adults with higher CR necessitated more demanding interventions to stimulate neuroplastic processes.

Finally, individual preferences might have contributed to differences in efficacy, particularly considering the use of leisure-based interventions. While highly speculative, differences in preference might explain why women benefitted most from the MUSIC intervention, whereas men improved more from DISCOVERY than the SPANISH intervention. We employed a preference trial in this study; however, participants were not allowed to select or exclude the DISCOVERY intervention as it was a control condition. Nevertheless, it was observed that more men than women expressed a desire to be randomized into the DISCOVERY condition.

It is interesting to note that DISCOVERY, which was used as a control condition, at times yielded greater benefits than both the MUSIC and SPANISH interventions. As an active control, DISCOVERY involved discussing and watching documentaries, and provided participants with psychoeducation and video game practice. This is consistent with previous research, wherein programs centered on activity engagement, even without formal cognitive training, produced cognitive benefits in older adults (Carlson et al., 2008; Park et al., 2014; Stine-Morrow et al., 2008).

Study limitations

The study has certain limitations. First, participants were mostly female, Caucasian, and highly educated (Henrich et al., 2010). Future studies should adapt their study design and recruitment strategies to enroll participants with diverse backgrounds. Second, the study was powered to test the PRE-POST training effect rather than individual differences across intervention conditions. As these are complex interventions with different components, the precise identification of the specific factors attributing to observed individual differences remains a challenge. Third, other predictors, such as motivational (Carretti et al., 2011) and personality factors (Double & Birney, 2016; Studer-Luethi et al., 2012) as well as other outcomes (i.e., attention, transfer, or quality of life), should be examined. Finally, the ENGAGE study encompasses a longitudinal follow-up, and it will be necessary to examine if the same factors moderate long-term effects.

Conclusion

While existing literature has predominantly interpreted individual differences in efficacy through the lens of *compensation* or *magnification*, we hypothesized that their effects would depend on the intervention characteristics. Our findings are aligned with this hypothesis revealing distinct individual attributes that were associated with greater improvements in the SPANISH, MUSIC, or DISCOVERY conditions. We suggest that consideration of sex, baseline executive functioning, and CR may help optimize intervention effects on memory. Our results highlight the importance of an appropriate pairing between individual characteristics and the demands of the intervention (Lövdén et al., 2012). This alignment is particularly crucial as conditions with different cognitive demands and activities were better suited to certain subgroups. Tailoring programs to these individual characteristics may provide "optimal learning" conditions and maximize the benefits of interventions at the individual level (Metcalfe & Kornell, 2005). These results have important clinical implications, guiding professionals in recommending cognitive interventions to patients based on clinically relevant and accessible variables. This knowledge will also help in identifying the most appropriate intervention conditions for individuals at risk or with lower functional capacities, ensuring that those who require it the most can harness the benefits of cognitive interventions (Bråthen et al., 2021).

References

Achterberg, W., Pot, A. M., Kerkstra, A., Ooms, M., Muller, M., & Ribbe, M. (2003). The effect of depression on social engagement in newly admitted Dutch nursing home residents. *Gerontologist, 43*(2), 213-218. https://doi.org/10.1093/geront/43.2.213

Aguirre, E., Hoare, Z., Streater, A., Spector, A., Woods, B., Hoe, J., & Orrell, M. (2013). Cognitive stimulation therapy (CST) for people with dementia--who benefits most? *International Journal of Geriatric Psychiatry, 28*(3), 284-290. https://doi.org/10.1002/gps.3823

Andrewes, D. G., Kinsella, G., & Murphy, M. (1996). Using a memory handbook to improve everyday memory in community-dwelling older adults with memory complaints. *Experimental Aging Research, 22*(3), 305-322. https://doi.org/10.1080/03610739608254013

Beinhoff, U., Tumani, H., Brettschneider, J., Bittner, D., & Riepe, M. W. (2008). Gender-specificities in Alzheimer's disease and mild cognitive impairment. *Journal of Neurology*, *255*(1), 117–122. https://doi.org/10.1007/s00415-008-0726-9

Belleville, S., Gilbert, B., Fontaine, F., Gagnon, L., Ménard, E., & Gauthier, S. (2006). Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: Evidence from a cognitive intervention program. *Dementia and Geriatric Cognitive Disorders, 22*(5-6), 486-499. https://doi.org/10.1159/000096316

Belleville, S., Hudon, C., Bier, N., Brodeur, C., Gilbert, B., Grenier, S., Ouellet, M.-C., Viscogliosi, C., & Gauthier, S. (2018). MEMO+: Efficacy, durability and effect of cognitive training and psychosocial intervention in individuals with mild cognitive impairment. *Journal of the American Geriatrics Society, 66*(4), 655-663. https://doi.org/10.1111/jgs.15192

Belleville, S., Moussard, A., Ansaldo, A. I., Belchior, P., Bherer, L., Bier, N., Bohbot, V. D., Bruneau, M. A., Cuddy, L. L., Gilbert, B., Jokel, R., Mahalingam., K., McGilton, K., Murphy, K. J., Naglie, G., Rochon, E., Troyer, A .K., & Anderson, N. D. (2019). Rationale and protocol of the ENGAGE study: a double-blind randomized controlled preference trial using a comprehensive cohort design to measure the effect of a cognitive and leisure-based intervention in older adults with a memory complaint. *Trials, 20*(1), Article 282. https://doi.org/10.1186/s13063-019-3250-6

Belleville, S., LeBlanc, A. C., Kergoat, M. J., Calon, F., Gaudreau, P., Hébert, S. S., Hudon, C., Leclerc, N., Mechawar, N., Duchesne, S., & Gauthier, S. (2019). The Consortium for the early identification of Alzheimer's disease-Quebec (CIMA-Q). *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring, 11*, 787-796. https://doi.org/10.1016/j.dadm.2019.07.003

Belleville, S., Moussard, A., Ansaldo, A. I., Belchior, P., Bherer, L., Bier, N., Bohbot, V., Bruneau, M.-A., Cuddy, L. L., Gilbert, B., Jokel, R., Naglie, G., Murphy, K. J., Rajah, N., Rochon, E., Steffener, J., Troyer, A. K., & Anderson, N. (2023). Effects of a program combining cognitive training and leisure activities in older adults with subjective cognitive decline: Results of the ENGAGE study [Manuscript in preparation].

Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2005). Training effects on dual-task performance: Are there age-related differences in plasticity of attentional control? *Psychology and Aging, 20*(4), 695-709. https://doi.org/10.1037/0882-7974.20.4.695

Bråthen, A. C. S., De Lange, A.-M. G., Fjell, A. M., & Walhovd, K. B. (2021). Risk- and protective factors for memory plasticity in aging. *Aging, Neuropsychology, and Cognition, 28*(2), 201-217. https://doi.org/10.1080/13825585.2020.1727834

Carlson, M. C., Saczynski, J. S., Rebok, G. W., Seeman, T., Glass, T. A., McGill, S., Tielsch, J., Frick, K. D., Hill, J., & Fried, L. P. (2008). Exploring the effects of an "everyday" activity program on executive function and memory in older adults: Experience Corps. *Gerontologist, 48*(6), 793-801. https://doi.org/10.1093/geront/48.6.793

Carlson, M. C., Erickson, K. I., Kramer, A. F., Voss, M. W., Bolea, N., Mielke, M., McGill, S., Rebok, G. W., Seeman, T., & Fried, L. P. (2009). Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 64*(12), 1275-1282. https://doi.org/10.1093/gerona/glp117

Carretti, B., Borella, E., Zavagnin, M., & De Beni, R. (2011). Impact of metacognition and motivation on the efficacy of strategic memory training in older adults: Analysis of specific, transfer and maintenance effects. *Archives of Gerontology and Geriatrics, 52*(3), e192-e197. https://doi.org/10.1016/j.archger.2010.11.004

Chapman, K. R., Bing-Canar, H., Alosco, M. L., Steinberg, E. G., Martin, B., Chaisson, C., Kowall, N., Tripodis, Y., & Stern, R. A. (2016). Mini Mental State Examination and Logical Memory scores for entry into Alzheimer's disease trials. *Alzheimer's Research & Therapy, 8,* Article 9. https://doi.org/10.1186/s13195-016-0176-z

Chertkow, H., Borrie, M., Whitehead, V., Black, S. E., Feldman, H. H., Gauthier, S., Hogan, D. B., Masellis, M., McGilton, K., Rockwood, K., Tierney, M. C., Andrew, M., Hsiung, G. R., Camicioli, R., Smith, E. E., Fogarty, J., Lindsay, J., Best, S., Evans, A., … Rylett, R. J.

(2019). The Comprehensive Assessment of Neurodegeneration and Dementia: Canadian Cohort Study. *The Canadian Journal of Neurological Sciences, 46*(5), 499-511. https://doi.org/10.1017/cjn.2019.27

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ, 337*, Article a1655. https://doi.org/10.1136/bmj.a1655

Craik, F. I., Bialystok, E., & Freedman, M. (2010). Delaying the onset of Alzheimer's disease: Bilingualism as a form of cognitive reserve. *Neurology, 75*(19), 1726-1729. https://doi.org/10.1212/WNL.0b013e3181fc2a1c

Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: an update. *Journal of the International Neuropsychological Society,* 10(2), 301–303. https://doi.org/10.1017/S1355617704102191

Elwood, R. W. (1991). The Wechsler Memory Scale-Revised: Psychometric characteristics and clinical application. *Neuropsychology Review, 2*(2), 179-201. https://doi.org/10.1007/bf01109053

Engle, R. F. (1984). Wald, likelihood ratio, and Lagrange multiplier tests in econometrics. In Z. Griliches, & M. D., Intriligator (Eds.), *Handbook of Econometrics*. *Vol. 2*. (pp. 796–801). Elsevier.

Gabryelewicz, T., Styczynska, M., Luczywek, E., Barczak, A., Pfeffer, A., Androsiuk, W., Chodakowska-Zebrowska, M., Wasiak, B., Peplonska, B., & Barcikowska, M. (2007). The rate of conversion of mild cognitive impairment to dementia: Predictive role of depression. *International Journal of Geriatric Psychiatry, 22*(6), 563-567. https://doi.org/10.1002/gps.1716

Gagnon, L. G., & Belleville, S. (2012). Training of attentional control in mild cognitive impairment with executive deficits: Results from a double-blind randomised controlled study. *Neuropsychological Rehabilitation, 22*(6), 809-835. https://doi.org/10.1080/09602011.2012.691044

Hanna-Pladdy, B., & Gajewski, B. (2012). Recent and past musical activity predicts cognitive aging variability: Direct comparison with general lifestyle activities. *Frontiers in Human Neuroscience, 6*, Article 198. https://doi.org/10.3389/fnhum.2012.00198

Henrich, J., Heine, S. J., & Norenzayan, A. (2010). The weirdest people in the world? *Behavioral and Brain Sciences, 33*(2-3), 61-135. doi:10.1017/s0140525x0999152x

Hess T. M. (2014). Selective Engagement of Cognitive Resources: Motivational Influences on Older Adults' Cognitive Functioning. *Perspectives on Psychological Science: a Journal of the Association for Psychological Science*, *9*(4), 388–407. https://doi.org/10.1177/1745691614527465

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K. A., van der Flier, W. M., Glodzik, L., van Harten, A. C., de Leon, M. J., McHugh, P., Mielke, M. M., Molinuevo, J. L., Mosconi, L., Osorio, R. S., Perrotin, A., … Wagner, M. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association, 10*(6), 844-852. https://doi.org/10.1016/j.jalz.2014.01.001

Jessen, F., Wolfsgruber, S., Wiese, B., Bickel, H., Mösch, E., Kaduszkiewicz, H., Pentzek, M., Riedel-Heller, S. G., Luck, T., Fuchs, A., Weyerer, S., Werle, J., van den Bussche, H., Scherer, M., Maier, W., & Wagner, M. (2014). AD dementia risk in late MCI, in early MCI, and subjective memory impairment. *Alzheimer's & dementia: the Journal of the Alzheimer's Association, 10*(1), 76-83. https://doi.org/10.1016/j.jalz.2012.09.017

Karbach, J., & Verhaeghen, P. (2014). Making working memory work: a meta-analysis of executive-control and working memory training in older adults. *Psychological Science, 25*(11), 2027-2037. https://doi.org/10.1177/0956797614548725

Katz, B., Jones, M. R., Shah, P., Buschkuehl, M., & Jaeggi, S. M. (2021). Individual differences in cognitive training research. In T. Strobach & J. Karbach (Eds.), *Cognitive training: An overview of features and applications* (pp. 107–123). Springer Nature Switzerland AG. https://doi.org/10.1007/978-3-030-39292-5_8

Köhler, S., van Boxtel, M. P. J., van Os, J., Thomas, A. J., O'Brien, J. T., Jolles, J., Verhey, F. R. J., & Allardyce, J. (2010). Depressive symptoms and cognitive decline in community-dwelling older adults. *Journal of the American Geriatrics Society, 58*(5), 873-879. https://doi.org/10.1111/j.1532-5415.2010.02807.x

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Medicine*, *11*(11), Article e1001756. https://doi.org/10.1371/journal.pmed.1001756

Langbaum, J. B., Rebok, G. W., Bandeen-Roche, K., & Carlson, M. C. (2009). Predicting memory training response patterns: Results from ACTIVE. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 64*(1), 14-23. https://doi.org/10.1093/geronb/gbn026

Leahy, F., Ridout, N., & Holland, C. (2018). Memory flexibility training for autobiographical memory as an intervention for maintaining social and mental well-being in older adults. *Memory, 26*(9), 1310-1322. https://doi.org/10.1080/09658211.2018.1464582

Legault, C., Jennings, J. M., Katula, J. A., Dagenbach, D., Gaussoin, S. A., Sink, K. M., Rapp, S. R., Rejeski, W. J., Shumaker, S. A., & Espeland, M. A. (2011). Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: the Seniors Health and Activity Research Program Pilot (SHARP-P) study, a randomized controlled trial. *BMC Geriatrics, 11*, Article 27. https://doi.org/10.1186/1471-2318-11-27

López-Higes, R., Martín-Aragoneses, M. T., Rubio-Valdehita, S., Delgado-Losada, M. L., Montejo, P., Montenegro, M., Prados, J. M., de Frutos-Lucas, J., & López-Sanz, D. (2018). Efficacy of cognitive training in older adults with and without subjective cognitive decline is associated with inhibition efficiency and working memory span, not with cognitive reserve. *Frontiers in Aging Neuroscience, 10*, Article 23. https://doi.org/10.3389/fnagi.2018.00023

Lövdén, M., Brehmer, Y., Li, S.-C., & Lindenberger, U. (2012). Training-induced compensation versus magnification of individual differences in memory performance. *Frontiers in Human Neuroscience, 6*, Article 141. https://doi.org/10.3389/fnhum.2012.00141

Marr, C., Vaportzis, E., Dewar, M., & Gow, A. J. (2020). Investigating associations between personality and the efficacy of interventions for cognitive ageing: a systematic review. *Archives of Gerontology and Geriatrics, 87*, Article 103992. https://doi.org/10.1016/j.archger.2019.103992

Metcalfe, J., & Kornell, N. (2005). A region of proximal learning model of study time allocation. *Journal of Memory and Language, 52*(4), 463-477. https://doi.org/10.1016/j.jml.2004.12.001

Mewborn, C. M., Lindbergh, C. A., & Stephen Miller, L. (2017). Cognitive interventions for cognitively healthy, mildly impaired, and mixed samples of older adults: a systematic review and meta-analysis of randomized-controlled trials. *Neuropsychology Review, 27*(4), 403-439. https://doi.org/10.1007/s11065-017-9350-8

Mondini, S., Madella, I., Zangrossi, A., Bigolin, A., Tomasi, C., Michieletto, M., Villani, D., Di Giovanni, G., & Mapelli, D. (2016). Cognitive reserve in dementia: Implications for cognitive training. *Frontiers in Aging Neuroscience, 8*, Article 84. https://doi.org/10.3389/fnagi.2016.00084

Morris, J. C. (1997). Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International Psychogeriatrics, 9*(S1), 173-178. https://doi.org/10.1017/s1041610297004870

Moussard, A., Bermudez, P., Alain, C., Tays, W., & Moreno, S. (2016). Life-long music practice and executive control in older adults: an event-related potential study. *Brain Research, 1642*, 146-153. https://doi.org/10.1016/j.brainres.2016.03.028

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Olazarán, J., Muñiz, R., Reisberg, B., Peña-Casanova, J., del Ser, T., Cruz-Jentoft, A. J., Serrano, P., Navarro, E., García de la Rocha, M. L., Frank, A., Galiano, M., Fernández-Bullido, Y., Serra, J. A., González-Salvador, M. T., & Sevilla, C. (2004). Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. *Neurology, 63*(12), 2348-2353. https://doi.org/10.1212/01.wnl.0000147478.03911.28

Ophey, A., Roheger, M., Folkerts, A.-K., Skoetz, N., & Kalbe, E. (2020). A Systematic Review on Predictors of working memory training responsiveness in healthy older adults: methodological challenges and future directions. *Frontiers in Aging Neuroscience, 12,* Article 575804. https://doi.org/10.3389/fnagi.2020.575804

Park, D. C., Lodi-Smith, J., Drew, L., Haber, S., Hebrank, A., Bischof, G. N., & Aamodt, W. (2014). The impact of sustained engagement on cognitive function in older adults: the Synapse project. *Psychological Science, 25*(1), 103-112. https://doi.org/10.1177/0956797613499592

Park, S., Ryu, S.-H., Yoo, Y., Yang, J.-J., Kwon, H., Youn, J.-H., Lee, J.-M., Cho, S.-J., & Lee, J.-Y. (2018). Neural predictors of cognitive improvement by multi-strategic memory training based on metamemory in older adults with subjective memory complaints. *Scientific Reports, 8*(1), 1095. https://doi.org/10.1038/s41598-018-19390-2

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., Ritchie, K., Rossor, M., Thal, L., & Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology, 58*(12), 1985-1992. https://doi.org/10.1001/archneur.58.12.1985

Rahe, J., Liesk, J., Rosen, J. B., Petrelli, A., Kaesberg, S., Onur, O. A., Kessler, J., Fink, G. R., & Kalbe, E. (2015). Sex differences in cognitive training effects of patients with amnestic mild cognitive impairment. *Neuropsychology, Development, and Cognition. Section B, Aging, neuropsychology and cognition, 22*(5), 620-638. https://doi.org/10.1080/13825585.2015.1028883

Rami, L., Valls-Pedret, C., Bartrés-Faz, D., Caprile, C., Solé-Padullés, C., Castellvi, M., Olives, J., Bosch, B., & Molinuevo, J. L. (2011). Cognitive reserve questionnaire: Scores obtained in a healthy elderly population and in one with Alzheimer's disease. *Revista de Neurologia, 52*(4), 195-201. https://neurologia.com/articulo/2010478

Rebok, G. W., Langbaum, J. B., Jones, R. N., Gross, A. L., Parisi, J. M., Spira, A. P., Kueider, A. M., Petras, H., & Brandt, J. (2013). Memory training in the ACTIVE study: How much is needed and who benefits? *Journal of Aging and Health, 25*(8 Suppl), 21S-42S. https://doi.org/10.1177/0898264312461937

Rebok, G. W., Ball, K., Guey, L. T., Jones, R. N., Kim, H. Y., King, J. W., Marsiske, M., Morris, J. N., Tennstedt, S. L., Unverzagt, F. W., & Willis, S. L. (2014). Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *Journal of the American Geriatrics Society, 62*(1), 16-24. https://doi.org/10.1111/jgs.12607

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology Review, 24*(3), 355-370. https://doi.org/10.1007/s11065-014-9270-9

Roheger, M., Kessler, J., & Kalbe, E. (2019). Structured cognitive training yields best results in healthy older adults, and their APOE4 state and baseline cognitive level predict training benefits. *Cognitive and Behavioral Neurology, 32*(2), 76-86. https://doi.org/10.1097/wnn.0000000000000195

Roheger, M., Kalbe, E., Corbett, A., Brooker, H., & Ballard, C. (2020a). Lower cognitive baseline scores predict cognitive training success after 6 months in healthy older adults: Results of an online RCT. *International Journal of Geriatric Psychiatry, 35*(9), 1000-1008. https://doi.org/10.1002/gps.5322

Roheger, M., Kalbe, E., Corbett, A., Brooker, H., & Ballard, C. (2020b). Predictors of changes after reasoning training in healthy adults. *Brain and Behavior, 10*(12), Article e01861. https://doi.org/10.1002/brb3.1861

Roheger, M., Liebermann-Jordanidis, H., Krohm, F., Adams, A., & Kalbe, E. (2021). Prognostic factors and models for changes in cognitive performance after multi-domain cognitive training in healthy older adults: a systematic review. *Frontiers in Human Neuroscience, 15*(199). https://doi.org/10.3389/fnhum.2021.636355

Rosi, A., Del Signore, F., Canelli, E., Allegri, N., Bottiroli, S., Vecchi, T., & Cavallini, E. (2018). The effect of strategic memory training in older adults: Who benefits most? *International Psychogeriatrics, 30*(8), 1235-1242. https://doi.org/10.1017/S1041610217002691

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2012). Depressive symptoms predict longitudinal change in executive control but not memory. *International Journal of Geriatric Psychiatry, 27*(1), 89-96. https://doi.org/10.1002/gps.2697

Sánchez-Cubillo, I., Periáñez, J. A., Adrover-Roig, D., Rodríguez-Sánchez, J. M., Ríos-Lago, M., Tirapu, J., & Barceló, F. (2009). Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society*, *15*(3), 438–450. https://doi.org/10.1017/S1355617709090626

Schaie, K. W., & Willis, S. L. (1986). Can decline in adult intellectual functioning be reversed? *Developmental Psychology, 22*(2), 223-232. https://doi.org/10.1037/0012-1649.22.2.223

Schmidt, M. (1996). *Rey auditory verbal learning test: A handbook*: Western Psychological Services Los Angeles, CA.

Scogin, F., Rohen, N., & Bailey, E. (2000). Geriatric Depression Scale. In *Handbook of psychological assessment in primary care settings.* (pp. 491-508). Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers.

Sharifian, N., Gu, Y., Manly, J. J., Schupf, N., Mayeux, R., Brickman, A. M., & Zahodne, L. B. (2020). Linking depressive symptoms and cognitive functioning: the mediating role of leisure activity. *Neuropsychology, 34*(1), 107-115. https://doi.org/10.1037/neu0000595

Smart, C. M., Karr, J. E., Areshenkoff, C. N., Rabin, L. A., Hudon, C., Gates, N., Ali, J. I., Arenaza-Urquijo, E. M., Buckley, R. F., Chetelat, G., Hampel, H., Jessen, F., Marchant, N. L., Sikkes, S. A. M., Tales, A., van der Flier, W. M., & Wesselman, L. (2017). Non-pharmacologic interventions for older adults with subjective cognitive decline: Systematic review, meta-analysis, and preliminary recommendations. *Neuropsychology Review, 27*(3), 245-257. https://doi.org/10.1007/s11065-017-9342-8

Stine-Morrow, E. A. L., Parisi, J. M., Morrow, D. G., & Park, D. C. (2008). The effects of an engaged lifestyle on cognitive vitality: a field experiment. *Psychology and Aging, 23*(4), 778-786. https://doi.org/10.1037/a0014341

Stine-Morrow, E. A. L., Payne, B. R., Roberts, B. W., Kramer, A. F., Morrow, D. G., Payne, L., Hill, P. L., Jackson, J. J., Gao, X., Noh, S. R., Janke, M. C., & Parisi, J. M. (2014). Training versus engagement as paths to cognitive enrichment with aging. *Psychology and Aging, 29*(4), 891-906. https://doi.org/10.1037/a0038244

Studer-Luethi, B., Jaeggi, S. M., Buschkuehl, M., & Perrig, W. J. (2012). Influence of neuroticism and conscientiousness on working memory training outcome. *Personality and Individual Differences, 53*(1), 44-49. https://doi.org/10.1016/j.paid.2012.02.012

Traut, H. J., Guild, R. M., & Munakata, Y. (2021). Why does cognitive training yield inconsistent benefits? A meta-analysis of individual differences in baseline cognitive abilities and training outcomes. *Frontiers in Psychology, 12*, Article 662139. https://doi.org/10.3389/fpsyg.2021.662139

Troyer, A. K. (2001). Improving memory knowledge, satisfaction, and functioning via an education and intervention program for older adults. *Aging, Neuropsychology, and Cognition, 8*(4), 256-268. https://doi.org/10.1076/anec.8.4.256.5642

Tse, Z. C. K., Cao, Y., Ogilvie, J. M., Chau, B. K. H., Ng, D. H. C., & Shum, D. H. K. (2023). Prospective memory training in older adults: a systematic review and meta-analysis. *Neuropsychology Review, 33*(2), 347-372. https://doi.org/10.1007/s11065-022-09536-5

Vaportzis, E., Niechcial, M. A., & Gow, A. J. (2019). A systematic literature review and meta-analysis of real-world interventions for cognitive ageing in healthy older adults. *Ageing Research Reviews, 50*, 110-130. https://doi.org/10.1016/j.arr.2019.01.006

Wechsler D. (1997). WMS-III: Wechsler Memory Scale administration and scoring manual (3rd ed.). Psychological Corp.

Zinke, K., Zeintl, M., Rose, N. S., Putzmann, J., Pydde, A., & Kliegel, M. (2014). Working memory training and transfer in older adults: Effects of age, baseline performance, and training gains. *Developmental Psychology, 50*(1), 304-315. https://doi.org/10.1037/a0032982

Appendix A

Results of Variable Addition Test Based on Delayed Memory Composite Score at POST

Predictor variables	Partial r^2	R or F test	p
Age (years)	.016	-.127	.228
Sex	.173	18.77	<.001
Years of formal education	.041	.201	.056
CRQ	.053	.230	.036
GDS	.005	.069	.514
TMT	.092	.303	.005
D-KEFS Inhibition	.073	-.269	.010
Logical memory	.174	.418	<.001

Note. Sex = Sex assigned at birth; CRQ = Cognitive Reserve Questionnaire; GDS = Geriatric Depression Scale; TMT = Trail Making Test completion time condition B – A; D-KEFS Inhibition = Delis-Kaplan Executive Function System Color-word interference test, Inhibition condition completion time. Lower scores for the TMT and D-KEFS Inhibition condition indicate better performance. Higher scores indicate better performance on all other tests.

Appendix B

Estimates of Fixed Effects on Delayed Memory Composite Score

Model	Predictor	Fixed effect	Coefficient	SE	95% CI LL	95% CI UL	T score	p	Effect size - Eta (Fixed effect)
1	Sex	InterventionMUSIC	-.085	.08	-.241	.070	-1.09	.279	.045 (Intervention)
		InterventionSPANISH	.059	.07	-.088	.206	.79	.432	.290 (Time)
		Time	.242	.04	.156	.327	5.57	<.001	.012 (Sex)
		Sexmale	.341	.35	-.358	1.040	.96	.337	.071 (Intervention x Time)
		InterventionMUSIC x Time	.113	.06	-.004	.231	1.90	.059	.131 (Time x Sex)
		InterventionSPANISH x Time	-.019	.06	-.136	.098	-.32	.750	.968 (Sex x PRE)
		InterventionMUSIC x Time x Sexmale	-.097	.05	-.200	.005	-1.87	.063	.217 (Intervention x Time x Sex)
		InterventionSPANISH x Time x Sexmale	-.184	.04	-.264	-.104	-4.55	<.001	.217 (Intervention x Time x Sex)
		Intercept	-.287	.18	-.648	.074	-1.57	.119	.031 (Intercept)
2	CRQ	InterventionMUSIC	-.099	.11	-.313	.116	-.91	.365	.022 (Intervention)
		InterventionSPANISH	.022	.10	-.175	.219	.22	.822	.217 (Time)
		Time	.902	.20	.503	1.301	4.47	<.001	.147 (CRQ)
		CRQ	.062	.02	.027	.096	3.52	<.001	.221 (Intervention x Time)
		InterventionMUSIC x Time	-.200	.17	-.540	.139	-1.16	.246	.137 (Time x CRQ)
		InterventionSPANISH x Time	-.613	.15	-.901	-.326	-4.21	<.001	.963 (CRQ x PRE)
		InterventionMUSIC x Time x CRQ	.018	.01	.002	.034	2.19	.030	.240 (Intervention x Time x CRQ)
		InterventionSPANISH x Time x CRQ	.032	.01	.019	.045	4.76	<.001	.240 (Intervention x Time x CRQ)
		Intercept	-.931	.24	-1.405	-.456	-3.88	<.001	.173 (Intercept)
3	TMT	InterventionMUSIC	-.079	.17	-.414	.256	-.47	.641	.004 (Intervention)
		InterventionSPANISH	.015	.16	-.295	.325	.10	.922	.394 (Time)
		Time	.821	.11	.612	1.030	7.75	<.001	.006 (TMT)
		TMT	.006	.01	-.009	.021	.75	.455	.198 (Intervention x Time)
		InterventionMUSIC x Time	-.333	.13	-.587	-.078	-2.58	.011	.266 (Time x TMT)
		InterventionSPANISH x Time	-.553	.12	-.781	-.325	-4.78	<.001	.803 (TMT x PRE)
		InterventionMUSIC x Time x TMT	-.009	.00	-.013	-.005	-4.68	<.001	.375 (Intervention x Time x TMT)
		InterventionSPANISH x Time x TMT	-.010	.00	-.013	-.007	-7.41	<.001	.375 (Intervention x Time x TMT)
		Intercept	-.623	.16	-.932	-.314	-3.98	<.001	.146 (Intercept)
4	Inhibition	InterventionMUSIC	-.048	.11	-.265	.170	-.43	.666	.016 (Intervention)
		InterventionSPANISH	.074	.11	-.140	.288	.68	.497	.027 (Time)
		Time	.234	.16	-.072	.541	1.51	.133	.000 (Inhibition)
		Inhibition	.000	.01	-.010	.011	.05	.960	.061 (Intervention x Time)
		InterventionMUSIC x Time	.312	.18	-.037	.660	1.77	.079	.005 (Time x Inhibition)
		InterventionSPANISH x Time	-.108	.13	-.368	.152	-.82	.414	.935 (Inhibition x PRE)
		InterventionMUSIC x Time x Inhibition	.004	.00	-.001	.010	1.53	.127	.029 (Intervention x Time x Inhibition)
		InterventionSPANISH x Time x Inhibition	.000	.00	-.003	.003	-.08	.940	.029 (Intervention x Time x Inhibition)
		Intercept	-.229	.23	-.682	.224	-1.00	.319	.012 (Intercept)
5	Logical memory	InterventionMUSIC	-.150	.11	-.361	.061	-1.40	.162	.034 (Intervention)
		InterventionSPANISH	.021	.10	-.181	.223	.20	.839	.063 (Time)
		Time	.337	.14	.060	.613	2.41	.017	.111 (Logical memory)
		Logical memory	.059	.02	.023	.095	3.27	.001	.085 (Intervention x Time)
		InterventionMUSIC x Time	.217	.12	-.015	.449	1.85	.066	.002 (Time x Logical memory)
		InterventionSPANISH x Time	-.104	.11	-.311	.104	-.99	.324	.946 (Logical.memory x PRE)
		InterventionMUSIC x Time x Logical memory	-.006	.01	-.019	.008	-.82	.412	.020 (Intervention x Time x Logical memory)
		InterventionSPANISH x Time x Logical memory	.004	.01	-.009	.016	.54	.588	.020 (Intervention x Time x Logical memory)
		Intercept	-.698	.20	-1.091	-.305	-3.50	<.001	.125 (Intercept)

Note. CI = Confidence interval; LL = Lower limit; UL = Upper limit; Sex = Sex assigned at birth; CRQ = Cognitive Reserve Questionnaire; TMT = Trail Making Test completion time condition B – A (reversed); Inhibition = Delis-Kaplan Executive Function System Color-word interference test, Inhibition condition completion time (reversed).
Covariables for Model 1 = Baseline delayed memory composite score, Age (years), Years of formal education; Covariables for Models 2,3,4 and 5 = Baseline delayed memory composite score, Age (years), Sex and Years of formal education. Degrees of freedom (df) for fixed effects = 17 for Model 1 and df = 15 for Models 2, 3, 4 and 5.

Appendix C

Group Comparisons for Fixed Interaction Effects on Delayed Memory Change from PRE to POST

Model	Fixed effect	Subgroup	Comparison				Statistical test		
			Group 1	β	Group 2	β	|Δβ|	χ2	p
1	Time x Group x Sex	Sex : Female	SPANISH	.223	MUSIC	.355	.132	5.735	.017
			SPANISH	.223	DISCOVERY	.242	.019	.117	.732
			MUSIC	.355	DISCOVERY	.242	.113	.212	.040
		Sex : Male	SPANISH	.234	MUSIC	.453	.219	15.702	<.001
			SPANISH	.234	DISCOVERY	.437	.203	13.502	<.001
			MUSIC	.453	DISCOVERY	.437	.016	0.083	.773
2	Time x Group x CRQ	CRQ : -1 SD	SPANISH	.261	MUSIC	.482	.221	45.926	<.001
			SPANISH	.261	DISCOVERY	.432	.171	27.421	<.001
			MUSIC	.482	DISCOVERY	.432	.050	2.373	.123
		CRQ : Average	SPANISH	.254	MUSIC	.424	.170	27.290	<.001
			SPANISH	.254	DISCOVERY	.308	.054	2.731	.098
			MUSIC	.424	DISCOVERY	.308	.117	12.754	<.001
		CRQ : +1 SD	SPANISH	.247	MUSIC	.367	.120	13.477	<.001
			SPANISH	.247	DISCOVERY	.184	.063	3.729	.053
			MUSIC	.367	DISCOVERY	.184	.183	31.385	<.001
3	Time x Group x TMT	TMT : -1 SD	SPANISH	.231	MUSIC	.391	.161	9.461	.002
			SPANISH	.231	DISCOVERY	-.007	.237	20.626	<.001
			MUSIC	.391	DISCOVERY	-.007	.398	58.025	<.001
		TMT : Average	SPANISH	.246	MUSIC	.432	.186	12.668	<.001
			SPANISH	.246	DISCOVERY	.344	.098	3.482	.062
			MUSIC	.432	DISCOVERY	.344	.089	2.867	.090
		TMT : +1 SD	SPANISH	.262	MUSIC	.473	.211	16.343	.001
			SPANISH	.262	DISCOVERY	.695	.432	68.451	.001
			MUSIC	.473	DISCOVERY	.695	.221	17.900	.001

Note. Sex = Sex assigned at birth; CRQ = Cognitive Reserve Questionnaire; TMT = Trail Making Test completion time condition B – A (reversed).