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Effects of Individual Experience on Prevention and Compensation of Age-Related Cognitive Decline: Neural and Behavioral Evidence

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Approbation and introduction of results

The dissertation was prepared at the Centre for Cognition and Decision Making, Institute of Cognitive Neuroscience, National Research University Higher School of Economics. Results presented in this dissertation have also originated from research internships at Università Vita-Salute San Raffaele, Milan, Italy, and Karolinska Institutet, Stockholm, Sweden, supported by HSE University.

Peer-reviewed journals

Three published articles have been selected for defense:

First-tier publications[1]

1. Del Maschio, N., Sulpizio, S., **Gallo, F.,** Fedeli, D., Weekes, B. S., & Abutalebi, J. (2018). Neuroplasticity across the lifespan and aging effects in bilinguals and monolinguals. *Brain and Cognition, 125,* 118-126. doi:10.1016/j.bandc.2018.06.007
2. **Gallo, F.,** Novitskiy, N., Myachykov, A., & Shtyrov, Y. (2021). Individual differences in bilingual experience modulate executive control network and performance: Behavioral and structural neuroimaging evidence. *Bilingualism: Language and Cognition, 24,* 293-304. doi:10.1017/S1366728920000486
3. **Gallo, F.,** Kalpouzos, G., Laukka, E. J., Wang, R., Qiu, C., Bäckman, L., Marseglia, A., Fratiglioni, L., & Dekhtyar, S. (2021). Cognitive trajectories and dementia risk: A comparison of two cognitive-reserve measures. *Frontiers in Aging Neuroscience*, *13*, 540. doi:10.3389/fnagi.2021.737736

The results of the candidate's work on this topic have also been published in the following articles:

First-tier publications[1]

[1] First-tier publications include papers indexed in the Web of Science (Q1 or Q2) or Scopus (Q1 or Q2) databases, as well as peer- reviewed collections of conferences that appear in CORE rankings (ranks A and A*).

4. **Gallo, F.,** DeLuca, V., Prystauka, Y., Voits, T., Rothman, J., & Abutalebi, J. (2022). Bilingualism and Aging: Implications for (Delaying) Neurocognitive Decline. *Frontiers in Human Neuroscience, 16,* 819105. doi: 10.3389/fnhum.2022.819105

5. **Gallo, F.,** Ramanujan, K., Shtyrov, Y., & Myachykov, A. (2021). Attriters and Bilinguals: What's in a Name?. *Frontiers in Psychology*, *12*, 2747. doi:10.3389/fpsyg.2021.558228

6. **Gallo, F.,** Bermudez-Margaretto, B., Shtyrov, Y., Abutalebi, J., Kreiner, H., Chitaya, T., Petrova, A., Myachykov, A. (2021). First language attrition: what it is, what it isn't, and what it can be. *Frontiers in Human Neuroscience, 15*, 513. doi: 10.3389/fnhum.2021.686388

7. **Gallo, F.,** Kubiak, J., & Myachykov, A. (2022). Add Bilingualism to the Mix: L2 Proficiency Modulates the Effect of Cognitive Reserve Proxies on Executive Performance in Healthy Aging. *Frontiers in Psychology, 13,* 780261.

8. Bermúdez-Margaretto, B.*, **Gallo, F.*,** Novitskiy, N., Myachykov, A., Petrova, A., & Shtyrov, Y. (2022). Ultra-rapid and automatic interplay between L1 and L2 semantics in late bilinguals: EEG evidence. *Cortex, 151,* 147-161.

   *The authors share first-authorship

   Second-tier publications[2]

9. Malyshevskaya, A., **Gallo, F.,** Bermudez-Margaretto, B., Shtyrov, Y., Chitaya, T., Petrova, A., Myachykov, A. (2021). Language attrition: mechanisms of occurrence, features of study and prospects for further research [Elektronnyi resurs]. *Sovremennaia zarubezhnaia psikhologiia = Journal of Modern Foreign Psychology*, *10,* 111-124. doi:10.17759/jmfp.2021100111. (In Russ., abstr. in Engl.)

[2] Second-tier publications are papers published in journals included on HSE's list of high quality journals or indexed in the Web of Science (Q3 or Q4) or Scopus (Q3 or Q4) databases, as well as peer-reviewed collections of conferences appearing in CORE rankings (rank B).

10. Bermúdez-Margaretto, B., **Gallo, F.,** Pokhoday, M., Shtyrov, Y., Kreiner, H., & Myachykov, A. (2021). Understanding Language Attrition through Orthography. *Languages, 6,* 199.

Conference presentations

The results were presented at the following conferences:

1. 25th Architectures and Mechanisms of Language Processing (AMLaP) Conference, 6-8 September 2019, (National Research University Higher School of Economics, Moscow, Russia). Report: *Proficiency matters: Bilingual experience affects executive control and its cortical network.*
2. Bilingualism Matters Research Symposium 2019, 21 September 2019, (University of Edinburgh, Edinburgh, United Kingdom). Report: *Fluctuations in bilingual experience linked to executive control task performance and brain anatomy.*
3. Night Whites 2019. The Fifth St. Petersburg Winter Workshop on Experimental Studies of Speech and Language, 16-17 December 2019, (St. Petersburg State University, St. Petersburg, Russia). Report: *Individual differences in bilingual experience modulate executive control and its brain network: Behavioral and neuroanatomical data*.
4. International CCCP Symposium 'Cross-Language Interplay in a Bilingual Mind' and I-Brain Erasmus+, 10-12 December 2020, (National Research University Higher School of Economics, Moscow, Russia and Ecole Normale Supérieure de Paris, Paris, France). Report: *Individual differences in bilingual experience modulate executive control network and performance: Behavioral and structural neuroimaging evidence.*
5. 20th World Congress of Psychophysiology, 7-11 September 2021 (International Organization of Psychophysiology and University of Electronic Science and Technology of China). Report: *Ultra-Rapid and Automatic Interplay between L1 and L2 Semantics in Late bilinguals: Eeg Evidence*.

1 Introduction

1.1 Research problem

Average life expectancy has been steadily increasing worldwide over the last decades (Kontis et al., 2017). Alongside the advantages of an extended life span, this phenomenon brings about some undesirable consequences, including an ever-growing incidence of age-related deficits and disorders – most notably, dementia – and consequent increases in the expenditures for public governments' welfare systems (Wimo et al., 2017). At the neural level, aging has been linked to structural as well as functional changes (Walhovd et al., 2011), resulting in cognitive impairments (Lindenberger, 2014). Nonetheless, considerable interindividual variability has emerged in the degree of cognitive decline resulting from age-related brain damage (Cosentino & Stern, 2019). Based on existing evidence, several mechanisms of preservation and compensation of age-related cognitive impairment have been proposed. The main theoretical framework centers around the concept of *cognitive reserve*, defined as the level of resilience of an individual's cognitive processes to age-related brain deterioration (Stern et al., 2020). Whereas much is yet to be understood regarding the nature of cognitive reserve, what is known is that it develops gradually during the lifespan and is supported by a number of experiential factors (Stern, 2009), including maximal educational attainment, occupational complexity, and the extent of the individual's social network (Dekhtyar et al., 2019). One factor that has been linked to the build-up of cognitive reserve is bilingualism (Gallo et al., 2020; Gallo, DeLuca, et al., 2022): by means of a constant additional cognitive effort required to control dual-language use (Kroll et al., 2015), bilinguals strengthen their neural substrate – both at the structural and the functional levels (Abutalebi & Green, 2016; Bialystok, 2017). This is believed to result in a protective effect that counteracts age-related cognitive decline and is mediated by the cognitive reserve mechanism (Del Maschio et al., 2018; Gallo, Kubiak, et al., 2022).

The **main aim** of this dissertation was to examine the role of individual life experiences, bilingualism in particular, in promoting the development of cognitive reserve during the whole lifespan. Moreover, with the aim of tackling the long-standing issue of cognitive reserve measurability, I devised a novel method (by refining recent approaches) for measuring cognitive reserve directly and tested its validity by comparing it with traditional approaches to cognitive reserve measurement, for the first time in the literature.

1.2 Goals of the dissertation

1. To examine the role of bilingualism as a factor supporting the development of cognitive reserve during senescence;
2. To shed light on the mechanisms underlying bilingualism's effects on cognitive reserve, both at the neurostructural and behavioral levels;
3. To illuminate the relationship between bilingualism-induced consequences for the brain and bilingualism-induced consequences for cognition, and clarify how individual differences in bilingual experience may modulate such a relationship;
4. To investigate whether bilingualism-induced effects on cognitive reserve commence in youth or are exclusive to late life stages;
5. To devise a novel methodological approach to the operationalization and measurement of cognitive reserve;
6. To test the validity of this novel approach and compare its predictive power with that of traditional approaches.

1.3 Research methodology

Overall, 540 participants, including 66 young adults (18-35 years old) and 474 seniors (60+ years old) were included in the three investigations. For each of the three studies, participants signed informed consent before taking part in the experiments. All experiments were approved by ethical committees: Study 1 was approved by The Human Research Ethics Committee at the University of Hong Kong and The Human Research Ethics Committee at Università Vita-Salute San Raffaele, Study 2 was approved by the

Institutional Review Board of the Higher School of Economics, and Study 3 was approved by The Regional Ethical Review Board in Stockholm.

Studies 1 and 2 adopted a cross-sectional design, while Study 3 was based on data from a longitudinal investigation. All experiments deployed structural magnetic resonance imaging (MRI). Studies 1 and 2 used a region-of-interest (ROI), atlas-based morphometry approach, while Study 3 adopted a whole-brain voxel-based morphometry (VBM) approach. Neuroimaging data analyses software packages utilized in the three studies included SPM 12[3], FreeSurfer 5.1[4] and CAT12 (Gaser & Dahnke, 2016).

Cognitive assessments deployed in the three studies included the Flanker Task (Fan et al., 2005), the digit cancellation task (Zazzo, 1974), the pattern comparison task (Salthouse & Babcock, 1991), word recall and word recognition tasks for episodic memory (Laukka et al., 2013), semantic memory tasks (Dureman, 1960; Nilsson et al., 1997), letter fluency and category fluency tasks, and the Mini-Mental State Examination (MMSE; Cockrell & Folstein, 2002). Stimulus presentation and response collection software used for cognitive assessment included NBS Presentation 18.1 (Neurobehavioral Systems, Inc., 2020) and Opensesame 3.0 (Mathôt et al., 2012).

Statistical methods utilized in the three studies included Structural Equation Modeling, linear and logistic mixed-effects regressions and Cox proportional hazard models. The statistical analysis software utilized in the three studies included R (R Core Team, 2013) and Stata16 (StataCorp., 2017).

1.4 Scientific novelty

1.4.1 Main aspects of theoretical novelty

The adoption of a continuous operationalization of the bilingual experience constitutes a major novelty introduced by the research summarized in this dissertation. Relatively to the traditionally adopted group comparisons, this novel approach is more ecological and allows for a better description of bilingualism-induced neuroplastic

[3] https://www.fil.ion.ucl.ac.uk/spm/
[4] http://surfer.nmr.mgh.harvard.edu/

trajectories, as demonstrated by the present research. We therefore strongly recommend adopting this approach to other scientists in the field.

A second aspect of theoretical novelty is undoubtedly the development of a residual-based approach to the operationalization of cognitive reserve. This new method stems from a change of perspective on the definition of cognitive reserve, and it provides researchers with a direct, individualized and time-sensitive measure, strongly linked to individual levels of neural integrity. Furthermore, the direct comparison of the validity and predictive power of this novel measure with those of traditional, proxy-based measures of cognitive reserve is, to our knowledge, unprecedented in the literature.

1.4.2 Main aspects of methodological novelty

Unless environmental conditions prevent it (e.g., the pandemic forcing suspension of offline data collection), we always aim to include both neuroimaging and behavioral data when investigating the concept of cognitive reserve. Indeed, only by combining these two data sources it is possible to obtain conclusive evidence of cognitive reserve as a mitigator of the relationship between age-related neural deterioration and cognitive decline. Notwithstanding its importance, this practice is still used rather sparsely, particularly in bilingualism research. Thus, its consistent adoption throughout the studies presented in this dissertation marks a change of pace in the field.

A second aspect of methodological novelty is the combined deployment of structural equation modeling and regression approaches used to derive composite residual- and proxy-based cognitive reserve measures. Indeed, such an approach has rarely been used prior to the investigation presented in this dissertation.

1.5 Theoretical and practical significance

1.5.1 Theoretical significance

The research presented in this dissertation contributes to illuminating the role played by bilingualism in promoting successful aging, as well as providing us with a tool

that may prove to be key for expanding our general knowledge of mechanisms underlying cognitive reserve effects.

Results from Study 1 suggest that bilingualism confers protection against cognitive aging in late life stages, and shed light on the mechanisms underlying this phenomenon. The acting route for these effects appears to be two-fold: first, bilingualism induces neuroplastic changes that *directly* mitigate the effects of age-related neural deterioration. Second, bilingualism supports the emergence of compensating mechanisms that allow individuals to maintain optimal cognitive performance even when such a deterioration does occur.

Study 2 demonstrates the importance of a continuous approach to bilingual experience's operationalization. Indeed, such an approach allowed us to unveil the trajectory underlying bilingualism-induced neuroplastic changes, as well as to observe that bilingualism's protective effect against cognitive aging may actually be rooted already in early life stages. Both these results significantly expand our knowledge of the cognitive consequences of speaking multiple languages.

Finally, the residual cognitive reserve approach presented in Study 3 may contribute to advancing the theoretical framework of cognitive reserve – currently a subject of considerable debate (see Stern et al., 2020, for a review). Indeed, such a measure – individual, continuous, direct and brain-related – allows new levels of comparability and manipulability that will aid future studies. This, in turn, enables new lines of research, such as longitudinal investigations of the validity of factors putatively considered to support cognitive reserve.

1.5.2 Practical implications

The results of the research presented in this dissertation also hold the potential to make concrete beneficial contributions to society.

For instance, by identifying specific factors – bilingualism, in this case – that naturally postpone and mitigate the cognitive consequences of brain aging and their underlying mechanisms, this type of research may equip governments with a tool to

improve older adults' quality of life. At the same time, our findings provide a roadmap to ease the pressure on healthcare systems and public funds, which are well known to be disproportionally burdened by expenses devoted to older strata of the population (see e.g., Wimo et al., 2017).

In addition, methodological advancements such as those described in Study 3 may also hold significant practical implications. Indeed, the novel residual cognitive reserve measure may inform the clinical practice by allowing clinicians to draw an individual profile of each patient's cognitive decline trajectory. This, in turn, would enable the design of truly personalized care plans and thus the achievement of better results in the prevention and rehabilitation of age-related cognitive diseases.

1.6 Key ideas to be defended

1. Bilingualism fosters the development of both brain reserve and cognitive reserve during senescence;

2. A continuous operationalization of bilingual experience reveals a neuroplastic trajectory that impacts the neural substrate at the structural level in the initial stages of L2 acquisition, eventually shifting to functional changes;

3. Bilingualism-induced development of cognitive reserve takes place already during young adulthood;

4. A residual-based approach to the operationalization of cognitive reserve is a more reliable predictor of cognitive decline trajectories and dementia incidence, as compared to a proxy-based approach.

1.7 Author contribution

Study 1: study conception and design, data analyses and interpretation, manuscript draft and revision.

Study 2: study conception and design, data collection, data analyses and interpretation, manuscript draft and revision.

Study 3: study conception and design, data analyses and interpretation, manuscript draft and revision.

2 Summary of the dissertation

2.1 Introduction

While it is known that, overall, some cognitive abilities are impaired more severely than others by the aging process (Craik & Salthouse, 2011), a high degree of interindividual variability has been consistently observed in the trajectories of age-related cognitive decline (Cosentino & Stern, 2019). To account for such variability, Yaakov Stern proposed the concept of *cognitive reserve* (Stern, 2002). Since its first appearance in the scientific literature, the working definition of cognitive reserve has been continuously developed in line with the increasing amount of available research data (see e.g., Stern et al., 2020). Currently, cognitive reserve is commonly defined as the level of resilience of an individual's cognitive processes to age-related brain deterioration (Stern et al., 2020). Such resilience is thought to result from enhanced efficiency, capacity, flexibility of brain networks at the functional level, which in turn originate from different life-experience factors, such as high levels of education, occupational complexity, or intellectually stimulating activities (Barulli & Stern, 2013).

Among life-experience factors, increasing evidence suggests a role of bilingualism in supporting the development of cognitive reserve (Gallo et al., 2020; Gallo, DeLuca, et al., 2022; Gallo, Kubiak, et al., 2022; Gold, 2015; Perani & Abutalebi, 2015; Zhang et al., 2020). The mechanisms behind the beneficial effect of bilingualism has been related to an elevated cognitive effort entailed by communicating in two languages on a daily basis. Indeed, it has been repeatedly observed that both co-represented languages are simultaneously activated in a bilingual brain, notwithstanding which of the two is being used at a specific moment (e.g., Kroll et al., 2014). This overlapping activation results in a cognitive conflict for the bilingual speaker, who must continuously control interference arising from the non-target language. Bilinguals manage this conflict through *language control*, a cognitive device whose neural underpinnings overlap with the executive control network (Abutalebi & Green, 2007;

Green & Abutalebi, 2013). This sustained control effort is thought to eventually lead to benefits for bilinguals' executive functions, both at the neural and at the cognitive levels (Abutalebi & Green, 2016; Bialystok, 2017). Indeed, bilinguals have been repeatedly shown to outperform monolinguals on a number of executive function tasks (for a review see Bialystok, 2017) and to display higher brain tissue density and functional efficiency than monolinguals in the executive network (for a review see Li et al., 2014). While evidence supporting these claims is steadily increasing, it has to be noted that some studies have failed to replicate such results, stimulating the debate on the actual veracity of bilingualism-induced beneficial effects (Antón et al., 2014; Gathercole et al., 2014; Paap et al., 2015). The reasons for such inconsistencies have recently been related to the practice, common in bilingualism research, of reducing the spectrum of bilingualism (an intrinsically complex and multifaceted experience) to a binary variable (i.e., presence versus absence) and thus favoring group comparisons between bilinguals and monolinguals over a detailed and individualized assessment of the bilingual experience (Luk & Bialystok, 2013; Mishra, 2015; Surrain & Luk, 2019). As a result, bilingualism research is currently experiencing a shift towards an approach that treats the bilingual experience as a continuum (Del Maschio et al., 2020; DeLuca et al., 2019; Gallo, Kubiak, et al., 2022; Gallo, Novitskiy, et al., 2021; Hervais-Adelman et al., 2018). This shift has opened new research avenues and enabled a better understanding of the mechanisms underlying the cognitive consequences of bilingualism, including its beneficial contributions to the development of cognitive reserve (Gallo, Kubiak, et al., 2022; Gallo, Novitskiy, et al., 2021).

While the cognitive reserve concept serves as an important framework to evaluate the consequences of different lifestyle factors for cognitive aging, the understanding of the concept itself tightly depends on these same factors. Indeed, the use of such factors as proxies of cognitive reserve constituted for many years the main (if not only) way to investigate its underlying neural mechanisms. This interdependency leads inevitably to the risk of developing circular arguments and explanations of what cognitive reserve is

and how it works. The proxy approach also presents other disadvantages. First, proxies are indirect measures of cognitive reserve: for instance, education - the most widely used proxy - has a wide range of effects on an individual's life, which may impact its ability to compensate for age-related neural deterioration in multiple ways, not all of them necessarily related to cognitive reserve. Moreover, proxies, by being usually self-assessed by senior individuals, are subject to the risk of recollection bias. Finally, the issue of reverse causation cannot be ruled out with the proxy approach: taking again education as an example, we cannot exclude that people with higher cognitive functional capacity are more likely to attain higher educational levels, and that such higher cognitive functioning may end up protecting them from the consequences of cognitive aging, irrespective of cognitive reserve. To tackle these issues, a new approach to operationalize cognitive reserve has been proposed. This approach stems directly from the operational definition of cognitive reserve as *the discrepancy between the observed and the expected level of cognitive impairment, given the observed level of age-related neural deterioration* (Stern, 2009). Building on this definition, this approach proposes to operationalize reserve as a *residual*. Indeed, in the statistical regression framework, a residual represents exactly the discrepancy between observed and expected values of a dependent variable, relative to the fluctuations of a certain independent variable. Thus, the *residual-reserve* approach, first proposed by Reed and colleagues (Reed et al., 2010), quantifies cognitive reserve as the residual variance in cognitive performance, not explained by the observed levels of age-related neurodegeneration. This approach presents multiple advantages: (i) it allows to avoid the abovementioned issues of circularity, recollection bias and reverse causality; (ii) reserve, which ultimately acts through neural mechanisms, is measured directly, based on neural indicators, and not on proxies that have an indirect effect on the functional and structural levels of the neural substrate; (iii) reserve is measured via a quantitative, continuous, and individual indicator, which allows to perform any kind of statistical analysis; (iv) reserve can be reassessed over time in a dynamic fashion, based on time-related fluctuations in the

relationship between neural deterioration and resulting levels of cognitive performance. This, in turn, allows tracking the developing trajectory of an individual's cognitive reserve and ultimately may provide us with measures used to adjust interventions, ensuring a more personalized approach to senior-care and higher quality of life in late life stages.

The residual reserve approach is only starting to gain popularity: initially developed in a clinical sample of individuals suffering from Alzheimer's Disease (Reed et al., 2010), it has scarcely been replicated, particularly in samples of healthy, non-institutionalized seniors. Crucially, its effectiveness is yet to be compared to that of traditional proxy-based approaches to cognitive reserve.

2.2 Overview of the scientific content

Below, I provide a brief overview of the studies that comprise my research project.

In Study 1 (Del Maschio et al., 2018), we investigated the relationship between bilingualism and successful cognitive aging by comparing brain and cognitive reserve levels between young and older bilingual and monolingual adults. Brain reserve was operationalized as gray matter volumes (GMVs) in regions of the executive/language control network (Abutalebi & Green, 2007; Green & Abutalebi, 2013), while cognitive reserve was measured from performance on the Flanker Task (Fan et al., 2005), a task that taps into executive control. Bilingualism appeared to be associated with enhanced brain reserve both in the young and the senior age groups, with bilinguals showing higher GMVs than monolinguals in regions of the executive brain network. Moreover, senior bilinguals displayed increased cognitive reserve, outperforming monolinguals at the behavioral level, independently of GMV variations in the executive network.

In Study 2 (Gallo, Novitskiy, et al., 2021), to overcome issues related to the binary categorization of bilingualism (Luk & Bialystok, 2013; Mishra, 2015; Surrain & Luk, 2019), we operationalized the bilingual experience as a continuum, computed over three indicators: L2 age of acquisition (AoA), L2 proficiency and daily exposure to L2.

Moreover, in line with theories of cognitive reserve (see e.g., Tucker & Stern, 2011), we investigated whether the resilience mechanism mitigating age-related cognitive impairment begins at early life stages also in the case of bilingualism. We investigated the effect of individual differences in such variables on participants' executive control, both at the behavioral and at the neural levels. We again deployed ROI-based structural MRI and the Flanker task (Fan et al., 2005) to test such effects. Finally, we carried out a conjunct brain-behavior analysis to test whether variations in the bilingual experience modulate the relationship between neural substrate and cognition, *i.e.*, the ultimate proof of cognitive reserve, as follows from its definition (Zahodne et al., 2013). The continuous operationalization of bilingualism revealed that bilingualism-induced neuroplasticity may follow a reverse u-shape trajectory, in accordance with recent models (Pliatsikas, 2020). Moreover, the conjunct analysis replicated results from Study 1, revealing that beneficial effects of bilingualism on cognitive reserve development are rooted in early life stages (see next section for more detailed discussion).

Finally, Study 3 (Gallo, Kalpouzos, et al., 2021) spanned beyond the role of bilingualism in fostering successful aging, approaching the cognitive reserve topic from a more general standpoint. We aimed at advancing the field with regards to the problem of reserve's operationalization. To achieve this goal, by drawing from data collected over a 15 year span at the Karolinska Institutet in the context of the SNAC-K longitudinal study (Lagergren et al., 2004) we derived a *residual-based* measure of cognitive reserve from multiple structural MRI and cognitive ability indicators. Additionally, for the first time to our knowledge, we tested this new measure's potential to predict cognitive trajectories and dementia incidence over a 12-year follow-up period by comparing it with a proxy-based composite index which combined contributions from education, work complexity, social network, and leisure activities. For each participant, we calculated an individual index of cognitive reserve, computed as the portion of variance in episodic memory performance not accounted by a composite brain integrity index, further controlled for age and sex. Furthermore, we used structural equation modeling to derive

a second measure of cognitive reserve which combined information from early-life education, mid-life work complexity and late-life social network and leisure activities. We then compared the two measures in terms of their ability to predict trajectories of cognitive decline and dementia incidence over a 12-year period, using linear mixed-effects longitudinal models. Both measures predicted cognitive decline over time, but only the novel, residual-based measure appeared to mitigate the impact of neural damage on cognitive performance and to effectively predict dementia incidence over the 12-year follow-up.

After this brief overview, the design, findings and implications of each study are discussed below in greater detail.

2.2.1 Study 1. Bilingualism boosts cognitive reserve during late life stages

In this study, our sample comprised four groups of 22 individuals each (total N= 88): i) young adult monolingual Italian speakers from Milan (14 females; mean age= 20.86; SD ± 1.64); ii) older adult, non-demented monolingual Italian speakers from Milan, (10 females; mean age= 62.05, SD ± 5.88); iii) young adult early, balanced bilinguals from Hong Kong, speaking Cantonese as first language (L1) and English as second language (L2; 11 females; mean age= 20.5; SD ± 1.74); iv) older adult, non-demented, early, balanced bilinguals from Hong Kong. Half spoke Cantonese as L1 and English as L2, the other half spoke Cantonese as L1 and Mandarin as L2 (11 females; mean age= 62.32; SD ± 5.73). The bilingual and monolingual groups were matched for age, gender distribution, general intelligence, maximal educational attainment and socio-economic status, all factors that are known to influence trajectories of cognitive aging (Meng & D'Arcy, 2012; Sattler et al., 2012). Participants with a history of neurologic or psychiatric impairment, as well as senior participants with a MMSE (Cockrell & Folstein, 2002) score ≤ 27, indicative of the possible presence of Mild Cognitive Impairment (MCI), were excluded from the study. We compared age-matched groups both at the neural and at the behavioral level, to test whether bilingual experience affects the

development of brain reserve and cognitive reserve (Stern, 2009), respectively. At the brain level, we deployed structural MRI, performing atlas-based morphometry with a ROI approach in order to compare brain volumes within the language control network (Abutalebi & Green, 2007; Green & Abutalebi, 2013) between monolingual and bilingual groups. At the behavioral level, we utilized the Flanker task, a benchmark test for assessing cognitive control (Fan et al., 2005), to compare conflict monitoring and inhibition abilities between language groups. We hypothesized that, due to the continuous training in the simultaneous management of two languages, bilinguals would develop higher levels of brain and cognitive reserve in the executive control network/cognitive ability. While the young groups showed significant GMV differences only in the neural substrate (i.e., brain reserve), the older bilinguals showed both higher GMVs and better executive performance than monolingual peers. The absence of a difference in the executive performance of young groups was attributed to the variety of cognitively demanding experiences taxing the executive control system that non-bilingual young adults undergo on a daily basis (e.g., work, study, videogaming, social interactions, driving etc.), which might have masked the beneficial effects of bilingualism. This did not happen among the older participants, who tend to abandon most of the cognitively challenging activities in late life stages, with the exception of multiple language use, which remains a crucial part of their daily lives. To ultimately test the role of bilingualism as a booster of cognitive reserve, we conducted a conjunct analysis combining neural and behavioral data among senior participants. With this analysis, we aimed to investigate whether bilingualism modulates the structural brain-behavior relationship between the executive neural network and executive performance. Such modulation would constitute the ultimate proof of cognitive reserve, following from its definition (Zahodne et al., 2013). Indeed, while senior monolinguals showed a relationship between lower levels of executive GMV (i.e., brain atrophy) and executive performance (i.e., cognitive impairment), bilinguals were able to optimize their performance *independently* of GMV variations, suggesting that bilingualism may

support the development of cognitive reserve and mitigate age-related cognitive impairment in the presence of brain atrophy.

2.2.2 Study 2. Individual differences in bilingual experience modulate the executive control network and performance

As discussed above and as also emerging from the young data in Study 1, evidence suggesting a beneficial effect of bilingualism on the executive network and performance appears to be inconsistent across the literature. This is particularly true when samples of young adults are investigated. Thus, some questions regarding the benefits of bilingualism remain open: when does the beneficial effect start to emerge? Is it already present at earlier life stages or does it only appear during senescence? Recent theoretical views identify a possible reason behind the failure to obtain consistent results in young age groups (Luk & Bialystok, 2013; Mishra, 2015; Surrain & Luk, 2019). Indeed, a common tendency of bilingualism research has historically been to operationalize bilingualism, for convenience reasons, as a binary variable. In other words, despite bilingual abilities being a spectrum, with different levels of L2 exposure and proficiency, different age of acquisition, as well as a variety of possible language combinations and the very number of languages, researchers have shown a tendency to dichotomize such variable as something that is either present or absent, favoring group comparisons (bilinguals vs. monolinguals) over a continuous and individualized operationalization of the bi-/multilingual experience. This tendency confounds the validity of used experimental samples to the real-life context, exposing the researcher to the obvious risk of losing information as well as limiting the sample's variability. To overcome these issues, in Gallo et al., 2021, we adopted a continuous operationalization of the bilingual experience across the three dimensions of L2 AoA, daily exposure and proficiency (henceforth, *bilingual experience factors*, BEFs), with the purpose of investigating the trajectories of bilingualism-induced cognitive reserve development in younger adult age groups. To this end, we collected a sample of 22 young adults (13 females; mean age = 22.95, SD ± 4.38), speaking Russian as L1 and

English as L2, with varying degrees of proficiency and daily exposure, and diverse L2 AoA. Besides this choice, we kept the experimental design coherent with that of Study 1. The continuous operationalization revealed interesting results both in neuroimaging and in behavioral data analyses. In the neuroimaging analysis, the data indicated the presence of a reverse u-shaped trajectory in bilingualism-induced neuroplasticity. Indeed, while GMVs showed an increase at initial stages of the bilingual experience (i.e., when BEFs were initially increasing but still low), with further increases in BEFs the neuroplastic changes reached a plateau stage, to eventually revert to pre-bilingualism levels when bilingual experience reached high levels. This result can only be interpreted together with those of the conjunct neuroimaging-behavioral data analysis. Here, similarly to Study 1, we investigated whether variations in the bilingual experience modulated the executive structural brain-behavior relationship. Once again, bilingualism appeared to play a role in mitigating such relationship: i) individuals with high levels of bilingual experience showed the best performance in the executive task; ii) while individuals with low bilingual experience showed a relationship between GMV variations and performance level (i.e., lower GMVs predicted worse performance), highly expert bilinguals were able to optimize executive performance *independently* of GMV variation.

Our results are in line with a recently developed model, the dynamic restructuring model (DRM; Pliatsikas, 2020), which suggests that the grey matter structures associated with bilingual language control should show volumetric increases at the beginning of the L2 acquisition process, due to the increased effort required for simultaneous control of two languages. However, with increasing bilingual experience, individuals would affine their executive neural network from the functional standpoint, thus making the extra neural structure redundant or even unnecessary. Hence, through the process of pruning, the expert bilingual brain would trim such unnecessary substrate, going back structurally (but not functionally) to pre-bilingualism levels. The pattern of results emerging from our analyses seems to confirm the DRM's assumptions. In

conclusion, the adoption of a continuous operationalization of the bilingual experience has allowed us to show that bilingualism-induced development of cognitive reserve begins well before senescence, in early life stages. This result is in line with cognitive reserve theoretical models and recent studies (Tucker & Stern, 2011).

2.2.3 Study 3. How to measure cognitive reserve efficiently? A comparison of two approaches to cognitive reserve operationalization

In this longitudinal study we investigated, for the first time, the efficiency of two different operationalizations of cognitive reserve in predicting cognitive decline trajectories and conversion rates to dementia. 430 community-dwelling older adults aged 60-99+, cognitively healthy at baseline (March 2001 to August 2004), were followed up for 12 years. The younger age cohorts (60-72 years) were re-examined every 6 years, the older ones (78-99+ years) every 3 years (Lagergren et al., 2004). Participants underwent structural MRI scanning (Ferencz et al., 2013) and a cognitive test battery (Laukka et al., 2020), as well as a set of questionnaires and nurse interviews investigating previous life experiences and health status (Lagergren et al., 2004). First, we used structural equation modeling to derive a proxy-based measure of cognitive reserve, combining information from early-life educational attainment, mid-life work complexity and late-life social network size and leisure activities frequency. Then, using structural equation modeling, we computed an index of neural integrity taking into account six different structural neuroimaging measures: whole-brain GMVs, hippocampal volume, white matter hyperintensities, lateral ventricular volume, number of perivascular spaces and number of lacunes. Subsequently, we used this index as the independent variable in a linear regression, with episodic memory performance at baseline as the dependent variable, also controlling for age and sex. We extracted the residuals from this regression, i.e., the portion of episodic memory performance variance not explained by brain integrity, age, and sex, which constituted our residual measure of cognitive reserve. This operationalization follows from the definition of cognitive reserve as the discrepancy between observed and expected cognitive performance, given the observed level of brain

integrity. Once we computed the two indices, we compared their potential to predict trajectories of cognitive decline and dementia incidence over 12 years. While both measures were associated with cognitive decline over time, only the residual-based measure mitigated the impact of neural deterioration on cognitive performance (i.e., the structural brain-behavior relationship, see studies 1 and 2 above) and efficiently predicted dementia incidence over the 12-year span. Our results suggest that a novel residual-based measure could constitute a more direct, individualized and time-sensitive indicator of cognitive reserve, compared to a proxy-based approach.

3 Conclusions

My PhD research offers important advances in the pursuit of successful healthy aging, illuminating some of its underlying mechanisms and validating tools to monitor and intervene on its trajectory. In particular, Studies 1 and 2 investigate the role of bilingualism as a factor that may protect individuals from age-related cognitive impairment. Thanks to the constant cognitive training arising from the simultaneous management of two competing linguistic systems, bilinguals seem to develop cognitive reserve starting at least in late adolescence/young adulthood (i.e., 18+ years), and maintain such reserve throughout the lifespan. These findings constitute a precious resource in our increasingly aging society: not only may they allow to significantly increase the quality of life of senior individuals, but they also point to a viable way of relieving state coffers from the growing burden of ageing-related health expenses, which constitute a disproportionate amount of most countries' public health expenditure. Hence, we invite policymakers to regard our findings and consider promoting lifelong bilingualism-related interventions, which may yield positive consequences both from the public health and the socioeconomic standpoints for societies worldwide.

Moreover, Study 3 devised and validated a new tool for future research to advance our knowledge of the construct of cognitive reserve and at the same time a useful instrument for clinicians to increase the precision of diagnoses, monitoring and treatment of age-related cognitive diseases. Indeed, the residual-based operationalization of cognitive reserve presents some advantages compared to previous approaches. First of all, it is an individual measure, strictly dependent on the individual's level of neural and cognitive integrity. Moreover, it is a direct indicator, which excludes from consideration the indirect contribution of factors that may influence cognitive reserve, but also have secondary effects that do not impact cognitive trajectories and impair our ability to precisely assess cognitive health (e.g., education). Finally, it is a time-sensitive measure: while such proxies as education or work complexity normally are, at the older age, crystalized and do not allow a longitudinal evaluation of cognitive reserve levels, a

residual-based approach changes constantly as a function of fluctuating neural integrity, e.g., due to brain damage or neurological rehabilitation. Thus, this approach may allow clinicians to constantly update their assessment and consequently adjust interventions, significantly increasing the efficiency of senior healthcare, and thus, the quality of life of individuals in late life stages.

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