University of Reading

BILINGUALISM AS A NEUROPROTECTIVE FACTOR IN AGEING: INSIGHTS FROM HEALTHY AND CLINICAL POPULATIONS

Submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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DEDICATION

This thesis is dedicated to my family. To my grandmother Ausma, parents Daina and Ilmārs, sister Ieva – for raising me, for your support in my career, for inspiration, and encouragement. And to my wife Kristīne, whose infinite love and care made it possible for me to complete this work. I would not be where I am today without you.

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Toms Voits

21st of September 2020, Reading, United Kingdom

DECLARATION

I confirm that this is my own work and the use of all material from other sources has been properly and fully acknowledged.

Toms Voits

ABSTRACT

In the recent decades a significant amount of research has been dedicated to study of the neurocognitive effects of bilingualism. Although most of the work in this field has been focussed on healthy young adult populations, there has recently been an increased interest in examining bilingualism in the later years of life. This trend is intensified by the discovery that bilingualism may have clinical implications; bilingualism has been shown to considerably delay Alzheimer's dementia symptom onset and age of formal clinical diagnosis. Episodic memory decline is one of the primary symptoms of dementia. This cognitive function has been linked to bilingualism-related enhancements across the lifespan. The hippocampus, a brain structure crucial for episodic memory function, is also known to be sensitive to bilingualism-induced adaptation, at least in younger populations. The aim of this thesis is to employ a more granular approach to bilingualism, as opposed to more commonly used monolingual vs. bilingual between-groups comparisons, in an investigation of the impact bilingualism might have on declining neurocognition in clinical and healthy ageing. Three studies are presented. The first two studies empirically examine the effects of bilingualism on episodic memory function and the hippocampal structure in healthy older adults and individuals with an MCI diagnosis. Results reveal bilingualism, and especially active engagement in second language use, to offer neuroprotection of the hippocampus in the older age, although behavioural differences may not always be observed. The third study is an epistemological investigation raising the question of whether bilingualism might be a more universal protective factor against cognitive and neural decline in other progressive neurodegenerative diseases, such as Parkinson's, Huntington's and multiple sclerosis. This thesis highlights the need to further evaluate the effects of bilingualism by considering it as a generalised neuroprotective factor in clinical ageing, by fusing brain data and behavioural outcomes.

CHAPTER 1: INTRODUCTION

1.1. General introduction

The global population is getting increasingly older. The average age globally tipped over 30 years old in 2019 (Ritchie & Roser, 2019). There are now twice as many individuals aged 60 and above than there were in 1980 and the number of individuals in this age bracket is forecast to reach 2 billion by 2050 (United Nations, 2015). Life expectancy at birth is steadily rising across the world and people are living increasingly longer lives. This demographic trend comes with its challenges. Cognitive and neural decline is normal in ageing; however, excessive amounts of cognitive deterioration and brain atrophy as a result of increasingly longer lives can be linked to an increased incidence of progressive neurodegenerative disorders (Pini et al., 2016). In the absence of pharmacological cures for progressive neurodegeneration, it is paramount to explore alternative strategies that promote successful ageing and longevity of healthy life (Cummings et al., 2016). Research has shown that lifestyle and environmental factors, such as education, physical activity, and engagement in a cognitively demanding lifestyle contribute to resilience against age-related neural atrophy and cognitive decline (Arenaza-Urquijo, Wirth, & Chételat, 2015). The exact mechanisms on how these factors interact with and delay neural and cognitive downturn and lead to more successful cognitive ageing are not fully understood, but they have been conceptualised as cognitive reserve and brain reserve (Mendez, 2019). A factor recently proposed to be added to this list of protective factors, and the focus of this thesis is bilingualism (Klimova, 2018).

Bilingualism has been a source of scientific interest throughout the 20th century. The field has shifted from the notion that bilingualism is undesirable and a source of cognitive impediment (Darcy, 1953), to the idea that bilingualism might provide increased ‘cognitive flexibility’ (Peal & Lambert, 1962) and that because of the management of conflict more than one language leads to bilingualism leads to increased management of cognitive conflict capabilities (Ben-Zeev, 1977), to more elaborate models of language processing and understanding of how bilinguals manage and control two or more languages in their minds (Green, 1998). With the advent and increased availability of neuroimaging methods, neurological bases of the above effects have been more extensively studied in the last two decades.

Bilingualism is a challenging experience as both languages are shown to be always active in the bilingual individual's mind (Marian & Spivey, 2003; Spivey & Marian, 1999). This experience places demands on cognitive control mechanisms, as the available languages have to be controlled for successful communication to take place; the language(s) in active use in a given context has to be activated and monitored, while the languages not appropriate for communication in the current context have to be suppressed or inhibited (Green, 1998). Brain is a plastic organ in the sense that it adapts and changes in response to different experiences (Chang, 2014). This holds true for bilingualism as well. Bilingualism has been suggested to lead to superior executive control and neural adaptations, across all stages in life, from infancy, and adolescence, through adulthood and later years in life (Bialystok, 2017; Li, Legault, & Litcofsky, 2014).

However, bilingualism and its neurocognitive effects have been subject to controversy (Mark Antoniou, 2019), particularly at the younger end of the age spectrum. The proposed effects are not universally found with some research groups consistently reporting null findings (Paap & Greenberg, 2013; Paap, Johnson, & Sawi, 2014), while others routinely report differences in cognitive abilities between matched monolingual and bilingual groups (Bialystok, Craik, Klein, & Viswanathan, 2004; Bialystok, Craik, & Luk, 2008). Note, that the lack of consistent findings in the younger populations have been explained as a result of younger individuals being at their cognitive peak, often engaging in other activities that contribute to better executive functioning. If younger individuals are at their cognitive peak, it is plausible that there is a ceiling effect with regard to their executive functioning which may obscure any additional contribution of bilingualism in these populations. Mixed findings can be explained by many factors, including insufficient control for other factors contributing to higher executive functioning, types of task used to quantify behavioural differences, or variability in ways neuroimaging data are processed and/or analysed (García-Pentón, Fernández García, Costello, Duñabeitia, & Carreiras, 2016; Valian, 2015), but a crucial one is the variability in the definitions of what can be considered a 'bilingual' (Surrain & Luk, 2019). Indeed, any results are only as good as the data from which they come from. Bilingualism has mostly been treated as a binary (bilingual/monolingual) group variable in the literature, with little regard to individual differences within the bilingual groups. In fact, bilingualism is convincingly shown to be a nuanced experience (Luk & Bialystok, 2013) and it may well be that it is not bilingualism *per se*, but the interaction and compounding

of various factors, such as patterns of language use and length of immersion in an L2 environment that drive any effects observed (Pliatsikas, DeLuca, & Voits, 2020). This variability is often not accounted for in between-groups analyses and may be the source of inconsistent findings.

The ongoing debates of whether there is a general cognitive 'advantage' linked to bilingualism is only tangentially relevant to the present thesis, as these debates are mostly linked to findings (or lack of) in younger individuals. As such, it is unfair to dismiss any contribution of bilingualism to cognition, based on findings in these populations. It is important, therefore, to shift attention to older populations, and, especially clinical populations where these effects are more likely to manifest. Examining populations where superior executive functioning as a result of bilingualism is more likely to be observed provides a window into cognition, which can be more informative about the nature of bilingual effects. Further than that, it is more important to understand these effects in older populations, given the very practical health implications bilingualism is proposed to provide in this age group.

Indeed, ageing is at the forefront of the research programme of bilingualism and neurocognition (Bialystok, 2016). The interest in studying older populations is fuelled by the finding that bilingualism is a factor that seems to delay the onset of Alzheimer's dementia symptoms by 4-5 years (Alladi et al., 2013; Bialystok, Craik, & Freedman, 2007; Chertkow et al., 2010; Craik, Bialystok, & Freedman, 2010). While this is a robust effect, confirmed by recent meta-analyses (Anderson, Hawrylewicz, & Grundy, 2020; Brini et al., 2020; Paulavicius et al., 2020) a significant amount of studies is retrospective and utilise inspection of clinical records to establish links between bilingualism and the age of clinical symptom onset and diagnosis. This is not a flawed approach *per se* but can only provide limited insight in the exact interactions between the bilingual experience and clinical outcomes. If bilingualism is to be treated with more refinement, then the granularity of data pertaining to bilingualism from clinical records is insufficient as they only tend to report the amount of languages spoken by the patient without obtaining further detail than that.

While it is important to acknowledge the findings across the age spectrum, if only, to contextualize the main focus of this thesis within the wider bilingualism, brain, and cognition literature, this thesis is primarily concerned with linking bilingualism and neurocognitive effects at the older end of the age spectrum. The questions are primarily

considering the effects of bilingualism on building up of cognitive and brain reserves (see section 1.2.4. of this thesis for more detail) in the older age and the impact on health alongside with neural adaptations. In this respect, other research questions linked to bilingualism, such as bilingualism as a source of cognitive and/or neural adaptations in children (as in Kovács & Mehler, 2009) and young adults, bilingualism and adaptations in language processing (as in Rossi & Diaz, 2016), or language deterioration as a result of the disease (as in Calabria et al., 2017) are beyond the scope of this thesis. Further than that, this thesis examines the effects of bilingualism not only in healthy, but also clinical ageing populations. As bilingualism has been suggested to be a factor that contributes to the delay of dementia symptom onset (Alladi et al., 2013; Bialystok et al., 2007), bilingualism might emerge as a potential strategy that might have impactful public health implications allowing seniors around the world to lead cognitively healthy lives for longer, and successfully age by having a shorter period of cognitive decline before death.

The present thesis contributes to this strand of research programme and broadens its approach. There is an increased interest in understanding the exact ways bilingualism and ageing interact, especially in cases of clinical ageing (Calabria, Hernández, et al., 2020; Marin-Marin et al., 2019). This thesis extends the notion of bilingualism as a multidimensional dynamic experience, which is increasingly used in research examining younger participant samples, to older and clinical populations.

The remainder of this introduction briefly reviews the literature on the neurocognitive effects of bilingualism in both younger and healthy older individuals. It provides an overview of the findings relating bilingualism to aspects of cognition, focussing on domain-general executive functioning and episodic memory. It also reviews neurological findings in these populations. Then, it discusses the available literature linking bilingualism to enhancement of cognitive and neural reserves in healthy and clinical ageing; in doing so, it discusses the multipronged nature of bilingualism that is often not properly accounted for in research studies. At the same time, it suggests that this approach might be a better way to investigate the exact effects of bilingualism on healthy and clinical ageing populations. Three studies then follow.

In Study 1 the neurocognitive effects of bilingualism in healthy older populations are examined. In particular, given the significant role of the hippocampus in the function of episodic memory, subject to decline in the older age, we focussed on this structure and episodic memory functioning as affected by bilingualism. Monolingual and bilingual

older adults immersed in an L2-speaking environment underwent behavioural testing with an experimental battery tapping into episodic and working memory functions and were subject to structural MRI scanning. Bilingualism was operationalised as a continuous variable by collecting detailed language and social background data and thus quantifying bilingualism using the Language and Social Background Questionnaire (Anderson, Mak, Keyvani Chahi, & Bialystok, 2018). The effects of bilingualism on the hippocampus and episodic memory were studied via a monolingual vs. bilingual between-groups comparison. In addition to this, the effects of degree of bilingual engagement on the abovementioned neurocognitive aspects were tested via linear regression models within the bilingual group.

Study 2 extends a similar approach to Study 1 to clinical populations. If there are effects of bilingualism, especially when bilingualism is treated as a continuous variable (i.e., engagement in bilingual language use) on neurocognition in healthy ageing, how do these effects map on the neurocognition in individuals transitioning from health to disease? This is a crucial missing step in the literature that allows to connect the bilingualism literatures in healthy ageing populations to clinical patients with Alzheimer's Disease. Studying bilingualism in MCI, which is a transitional state from healthy ageing to dementia, offers the opportunity to understand in finer detail the potential protective effects of bilingualism as individuals develop progressive neurodegenerative disease. For that reason, Study 2 examines the effects of bilingualism in the context of MCI patients. The study sample was drawn from a bilingual Spanish-Catalan environment where all participants had at least a passive knowledge of both languages. In a similar vein to Study 1, bilingualism was operationalised as a continuous variable, based on engagement in bilingual language use. As all participants were at least passive bilinguals of both languages, the main differentiator in this study was whether the participant was an active user of both languages. Engagement in bilingual language use was estimated by self-reported language use patterns and linked to changes episodic memory performance, neural adaptations, as well as MCI symptom onset and diagnosis. Data were analysed by comparing the active and passive bilingual groups as well as regressing bilingualism as a continuous variable to test the extent of bilingual language use as a predictor for adaptations in episodic memory performance of medial temporal lobe structures.

If literature shows bilingualism to have an effect on the brain and cognition across healthy ageing populations, Alzheimer's disease, and MCI, might it be that similar effects would hold for other neurodegenerative disorders as well? The third study is a review of available evidence examining the possibility of bilingualism being a more general protective factor against neurodegeneration. A comprehensive review of similarities and differences between Alzheimer's Disease and other types of progressive neurodegeneration, such as Parkinson's disease, Huntington's disease, and Multiple Sclerosis is presented, with predictions for effects of bilingualism for each disease based on what is known about its neural and protective effects from Alzheimer's disease and MCI. As such, a roadmap is presented for future research with specific hypothesis presented to be empirically tested.

Finally, the findings of all three studies are summarised in a concluding discussion, contextualised within the current literature, and interpreted in the framework of bilingualism as a contributing factor to cognitive and neural reserves in the later years of life.

1.2. Neurocognitive effects of bilingualism

1.2.1. Executive functions – a general overview

A key finding in the field has been that both languages are simultaneously activated to some degree in the bilingual individuals' mind at all times; therefore, the corresponding mental representations constantly compete for selection, requiring cognitive control (Marian & Spivey, 2003; Spivey & Marian, 1999). Specifically, for successful communication to take place, the language not in use has to be prevented from interfering, while the target language for a given communicational context has to be selected and monitored for intrusions from other non-target languages available to the bilingual speaker (Green, 1998). Bilingual language control (Abutalebi & Green, 2007; Green & Abutalebi, 2013) thus requires constant engagement of executive functions – inhibition, monitoring, and mental set-shifting (Miyake et al., 2000). Bilinguals are essentially exercising their cognitive systems related to executive control at all times. This has been suggested to lead to improvement in performance of not only linguistic tasks, but also, potentially, non-linguistic domain-general tasks, tapping into similar control mechanisms. Transfer effects from one cognitive processing domain to another,

drawing on similar supporting neural networks, have been observed before – for example, musical training has been shown to enhance the audiovisual processing of speech (Musacchia, Sams, Skoe, & Kraus, 2007). It can be, therefore, hypothesized that the constant dual activation of languages is expected to improve other, non-linguistic processing, drawing on the same executive functioning networks and fine-tuning of the neural substrate of executive control. Thus, bilingual individuals should be more efficient in tasks tapping into the domains of conflict monitoring, mental set switching and inhibition of irrelevant stimuli. The hypothesis that bilingual language control has knock-on effects on domain-general cognition is often tested by means of verbal or non-verbal tasks tapping into these cognitive domains, for example Stroop task (Stroop, 1935), Simon task (Simon & Wolf, 1963), and Flanker task (Eriksen & Eriksen, 1974), among others.

Increased engagement of bilingual language control also results in changes and adaptations in the brain. Note, that it is not only the networks responsible for language processing, but also the brain networks responsible for bilingual language control that are subject to adaptations, although, as these networks are overlapping, they cannot always be distinguished from one another (Calabria, Costa, Green, & Abutalebi, 2018). One of the first models of neural representation and control of bilingual language production (Abutalebi & Green, 2007) proposed that cognitive control is mediated by the prefrontal cortex (PFC), implicated in response inhibition, planning, conflict resolution, and working memory, anterior cingulate cortex (ACC), involved in attention and conflict monitoring, basal ganglia (putamen and the caudate nucleus), involved in task switching, inhibition, and language control, and the inferior parietal lobule (IPL) implicated in maintaining mental representations in the working memory, attention and language selection (see Fig. 1.1). The majority of these areas are not only implicated in the mental control of two languages, but also involved in language processing (Price, 2000).

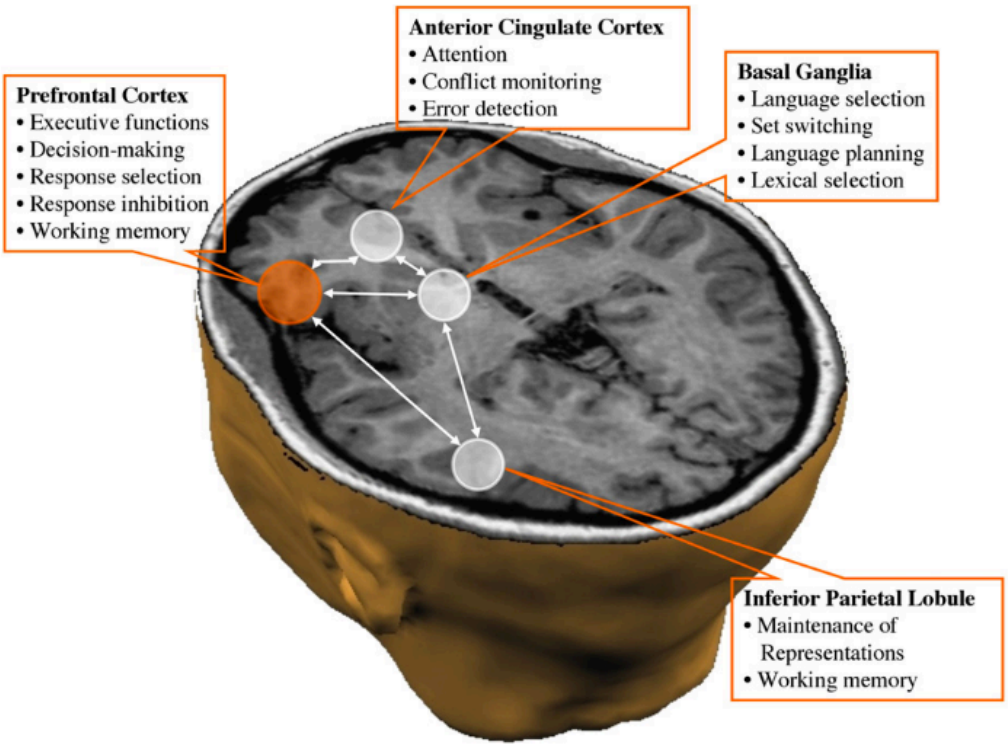

Figure 1. 1. Brain areas implicated in bilingual language control (from Abutalebi and Green, 2007)

Since then, as more empirical brain evidence has become available, further models have been devised with better understanding on the exact role each structure plays in bilingual language control. One of the most influential models up until this day remains the Adaptive Control Hypothesis (ACH) (Abutalebi & Green, 2016; Green & Abutalebi, 2013), which, in essence distinguishes eight control processes and predicts that neural adaptations would be dependent on the language control and processing demands placed on the neural system. The adaptations are dependent on interactional contexts and might be different for different types of bilinguals who may switch between their languages and engage in L2 use in a considerably different manner.

More recently a very thorough model has been proposed; the Dynamic Restructuring Model (DRM) (Pliatsikas, 2020), which treats bilingualism as a dynamic process and highlights adaptations, both increases and decreases in cortical grey matter, subcortical and cerebellar grey matter, as well as white matter depending on the duration of L2 use. Another model – Unified Bilingual Experience Trajectory (UBET) (DeLuca, Segaert, Mazaheri, & Krott, 2020) – is an attempt to summarise DRM, ACH, and other

models, not discussed herein, at an attempt to converge on findings of other models in the literature and proposing an even more complex account of how language experiences shape the brain. DeLuca and colleagues propose a set of bilingual experience categories – diversity of language use, language switching, relative proficiency, duration of L2 experiences – that all have to be considered as modulating factors for bilingualism-related neurocognitive adaptations. All in all, it is now known that a wide range of brain areas and structures have been shown to be sensitive to the bilingual experience, due to greater demands placed on language control and language processing (Pliatsikas, 2019) (see Fig. 1.2, for an anatomical overview).

Findings on the effects of bilingualism on cognition and the brain in young and older adults will be briefly discussed in further detail in the following sections.

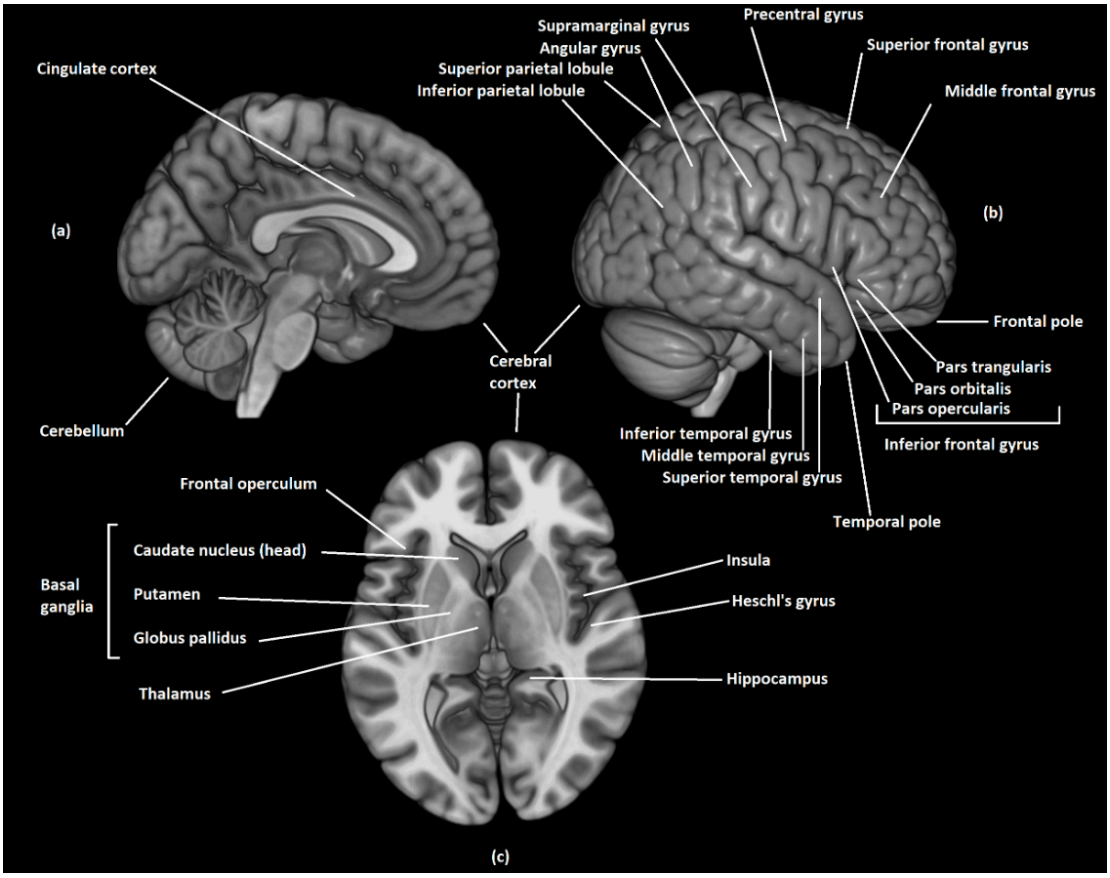

Figure 1. 2. A view of grey matter structures implicated in bilingualism research laid on a brain template image (From Pliatsikas, 2019)

1.2.2. Neurocognitive effects in young adults

Bilingualism has been associated with an array of cognitive benefits across the lifespan (Marian & Shook, 2012). As bilinguals engage executive functions to control and manage multiple languages in the brain, knock-on effects on domain-general cognition are frequently reported, however, other aspects of cognition, such as differences in working memory and episodic memory function have also been subject to research in the field. More specifically, younger bilinguals have been shown to outperform monolinguals in executive control abilities, including inhibitory control (Bialystok et al., 2008; Bialystok, Martin, & Viswanathan, 2005; Bialystok, Poarch, Luo, & Craik, 2014), conflict resolution (Costa, Hernández, & Sebastián-Gallés, 2008), attentional control (Pot, Keijzer, & De Bot, 2018),and task switching (Prior & Macwhinney, 2010). Bilingualism has also been reported to be associated with improved episodic memory performance (Ljungberg, Hansson, Andrés, Josefsson, & Nilsson, 2013), and an effect on working memory has been reported, although this is mostly limited to bilingual children (Grundy & Timmer, 2017).

However, there are studies reporting null findings regarding bilingual-monolingual differences in cognition in the literature (Hernández, Martin, Barceló, & Costa, 2013; Paap & Greenberg, 2013; Paap, Johnson, & Sawi, 2015; Ratiu & Azuma, 2015). A recent meta-analysis of 80 studies found no evidence for a bilingual advantage in interference-control tasks (Donnelly, Brooks, & Homer, 2019). Another meta-analysis of 152 studies also found no conclusive evidence for a cognitive bilingual advantage in adult populations (Lehtonen et al., 2018). Finally, a recent large-scale study, testing hundreds of participants, showed that bilingualism cannot be linked to any advantages in general cognition (Nichols, Wild, Stojanoski, Battista, & Owen, 2020). However, the measures of bilingualism were crude, (the participants were only asked what language(s) they spoke at home, and what was the total number of languages they spoke), and, therefore, did not include any detail with regards to bilingual experience or language use patterns that would provide a more comprehensive picture of the participant linguistic profile. It can also be speculated that cognitive effects of bilingualism may be masked in some young adult populations, as they are at their cognitive peak, where bilingualism cannot offer any edge in cognitive control beyond the ceiling already reached (Bialystok et al., 2005). This might be especially true in studies where participants lead a cognitively demanding lifestyle, which bolsters the executive control abilities from the baseline.

These include university or college students, which are the typically tested populations in such studies.

Research documenting cognitive adaptations associated with bilingualism is accompanied by a parallel, but related strand of this research programme, examining structural and functional neural adaptations in bilingual populations (e.g., DeLuca, Rothman, Bialystok, & Pliatsikas, 2020). At the neuroanatomical level, bilingualism has been associated with volumetric increases across grey matter structures and adaptation in white matter tracts involved in language acquisition, processing, and control. More specifically, bilinguals have been found to have increased grey matter density in the inferior parietal cortex (Mechelli et al., 2004), greater grey matter volume in the anterior cingulate cortex (Abutalebi et al., 2012), bilateral caudate nucleus, bilateral temporal lobes, hippocampus, amygdala and left insula (Li et al., 2017; Zou, Ding, Abutalebi, Shu, & Peng, 2012), putamen, left globus pallidus, thalamus (Burgaleta, Sanjuán, Ventura-Campos, Sebastian-Galles, & Ávila, 2016), bilateral DLPFC, parietal cortex (Olulade et al., 2016), and the cerebellum (Pliatsikas, Johnstone, & Marinis, 2014). In addition to changes in grey matter volume across these brain areas, there are also reports of reshaping (i.e., simultaneous local expansions and contractions) of the basal ganglia and the thalamus, which is associated with length of immersion in L2 setting (Pliatsikas, DeLuca, Moschopoulou, & Saddy, 2017). Examples of bilingualism-related factors linked to changes in the brain are age of language acquisition, where it positively correlates to cortical thickness in the left IFG and negatively to the cortical thickness in the right IFG (Klein, Mok, Chen, & Watkins, 2014), multilingual expertise, correlating positively with the volume of caudate nucleus (Hervais-Adelman, Egorova, & Golestani, 2018), and language proficiency, which is linked to increased gyrification in the posterior cingulate cortex (Del Maschio, Fedeli, Sulpizio, & Abutalebi, 2019). Additionally to changes in the grey matter, changes in white matter integrity have also been reported in white matter pathways associated with language learning and acquisition, including the corpus callosum, bilateral inferior fronto-orbital fasciculi, uncinate fasciculi, arcuate fasciculus, and superior longitudinal fasciculi (Hämäläinen, Sairanen, Leminen, & Lehtonen, 2017; Pliatsikas, Moschopoulou, & Saddy, 2015).

The above reviewed structural effects seem to be accompanied by functional effects. For example, early bilinguals engage language control areas (left caudate, left IFG and left MFG) more than monolinguals in non-linguistic switching tasks, despite

similar performance in executive functioning tasks (Rodríguez-Pujadas et al., 2013), showing greater adaptability in bilinguals via the ability to recruit additional networks for a task not related to language switching, if necessary. There is a more general difference on the recruitment of cognitive control networks – bilinguals recruit overlapping sets of regions for linguistic and non-verbal tasks, whereas monolinguals recruit individual sets of networks, depending on whether the task is verbal or non-verbal (Anderson, Chung-Fat-Yim, Bellana, Luk, & Bialystok, 2018a). Finally, bilinguals have been shown to exhibit reduced anterior activity and functionally rely more on posterior brain areas and subcortical structures, leading to a notion of the bilingual anterior to posterior and subcortical shift (BAPSS) (Grundy, Anderson, & Bialystok, 2017). These effects tell us that the bilingual experience does not only sculpt the brain anatomically, in regions and areas linked to language learning and bilingual language control, but that there are profound changes in the functional connectivity. These neural adaptations may not immediately result in cognitive and behavioural consequences in younger populations but have potential long-term impact with observable effect in the later years of life. Notably, the findings in younger populations are generally mirrored in healthy older participant samples, further discussed in the following section.

1.2.3. Neurocognitive effects in healthy older adults

The neurocognitive effects of bilingualism found in young adult populations have provided the motivation to expand the research programme and investigate bilingualism effects across the lifespan, including ageing individuals. If there are neural and cognitive adaptations in younger populations, how and do they translate in the older age? Also, if brain and cognition are subject to decline in the later years of life, it is imperative to examine bilingualism as an experience that may have beneficial neurocognitive effects in terms of increased resilience to these ageing processes.

The effects of bilingualism on cognition do seem to manifest more consistently in the older age, although these populations have been studied comparatively less (Bialystok et al., 2005). In general, it is well documented that cognitive resources tend to decline with age: processing speed, working memory, episodic memory, attention and inhibition mechanisms are all reported to suffer due to changes and deterioration of the supporting neural substrate (Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Pini et al., 2016; Schaie, 1989). However, older bilinguals rather consistently outperform

their monolingual peers across a number of cognitive domains. This includes better performance in older bilinguals in tasks tapping into executive functioning, such as Simon, Stroop, and Flanker tasks (Abutalebi, Canini, Della Rosa, Green, & Weekes, 2015; Bialystok et al., 2004, 2008). Moreover, bilingualism is associated with a smaller age-related decline in inhibitory control (Armstrong, Ein, Wong, Gallant, & Li, 2019; Blumenfeld, Schroeder, Bobb, Freeman, & Marian, 2016), bilingual individuals have been shown to have better working memory (Bialystok, Poarch, et al., 2014) and episodic memory (Schroeder & Marian, 2012). The latter was linked to earlier L2 acquisition and longer engagement in L2 use. Furthermore, in a longitudinal study examining participants tested at 11 years of age in 1947 and retested 60 years later between 2008 and 2010, bilinguals were found to perform significantly above their expected cognitive abilities in the older age. The most effects were found in general intelligence, suggesting bilingualism confers a positive effect on general cognition in the older age (Bak, Nissan, Allerhand, & Deary, 2014). Better performance in verbal abilities and processing speed is also associated not only with bilingualism, but predicted as a function of number of languages spoken (Ihle, Oris, Fagot, & Kliegel, 2016), suggesting a further effect of multilingualism beyond speaking just two languages. In this age group, there are fewer studies reporting null findings in bilingual vs. monolingual comparisons on cognitive functioning (e.g., Papageorgiou, Bright, Periche Tomas, & Filippi, 2018).

Although healthy older bilinguals do tend to outperform their monolingual peers, thus showing a more consistent pattern to that found in younger populations, findings with regard to neural adaptations generally follows the patterns observed in young adults. Similar to findings in younger populations, in healthy older individuals, bilingualism tends to be associated with better preserved brain structures, increases in grey matter volume and white matter integrity. Specifically, older bilinguals exhibit better preserved anterior temporal lobe (Abutalebi et al., 2014) and maintenance of cortical thickness (Olsen et al., 2015), increased grey matter volume in the anterior cingulate cortex (Abutalebi, Guidi, et al., 2015), prefrontal cortex, and inferior parietal lobule (Del Maschio, Sulpizio, et al., 2018), without exhibiting any behavioural between-groups differences in executive functioning. Bilinguals have also been shown to have a greater grey matter volume in the left IPL and IFG, when compared to monolinguals, but it is subject to a more rapid decline longitudinally (Heim et al., 2019). White matter tracts are also better preserved in older bilinguals, in terms of higher structural integrity, measured

via indices of water diffusivity, such as fractional anisotropy and mean diffusivity within the tract. Bilingualism leads to greater frontal lobe white matter volume in ageing individuals (Olsen et al., 2015) and white matter integrity is better preserved in tracts implicated in bilingual language control, and domain-general executive control, such as the corpus callosum, superior longitudinal fasciculi and right inferior fronto-occipital fasciculus (Anderson, Grundy, et al., 2018; Gold, Johnson, & Powell, 2013; Luk, Bialystok, Craik, & Grady, 2011). As most of the research in the field in cross-sectional, it is not always possible to disentangle direction of these effects. The differences might signify structural growth and strengthening in the neural structure for older bilinguals; yet, it is equally plausible, that the same effect can be interpreted as a bilingualism-induced resilience to normal age-related neural decline (i.e., faster decline for monolinguals).

Finally, there are differences in the functional connectivity and efficiency in network recruitment between older monolinguals and bilinguals. Older bilingual adults show better intrinsic resting state functional connectivity in the fronto-parietal cortex and the default mode network (Grady, Luk, Craik, & Bialystok, 2015), and, while behaviourally older monolinguals and bilinguals might perform on the same level in switching or inhibition tasks, it has been found that network recruitment is more efficient in bilinguals (Berroir et al., 2017; Gold, Kim, Johnson, Kryscio, & Smith, 2013). That is, recorded activation during these tasks is smaller in bilinguals than in monolinguals, meaning they are more efficient on a neural level.

Taken all of the evidence together, bilingualism seems to have an effect on both brain and cognition in the older age. It is crucial to view bilingualism in the general context of ageing, global effects on cognition and the brain. A signature element of the ageing brain is a general shift from functional reliance on posterior to frontal areas (Grady et al., 1994). These age related changes showing reduction in occipitotemporal activity, along with increased frontal activity that is termed the posterior to anterior shift in ageing (PASA), and has been replicated for a variety of cognitive functions, such as attention, working memory, and episodic memory (see Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008 for an overview). This phenomenon has been linked to a compensatory account; namely, declines in posterior functional connectivity are compensated for by increased recruitment of frontal cortex.

On the other hand, bilingualism is a factor that seems to delay this process – in older bilinguals there is increased activation in the posterior and occipital regions of the brain, which also correlates with volumes of the caudate nucleus (de Frutos-Lucas et al., 2020). This pattern of effects has been suggested to signify reduced PASA in ageing bilinguals (Grant, Dennis, & Li, 2014). This might be a result of more consistent engagement of these areas due to bilingual language control demands in posterior regions such as the medial temporal lobe, and the inferior parietal cortex, as well as connectivity of these regions with the prefrontal cortex and the basal ganglia. So, it may seem that engagement of posterior and subcortical areas associated with bilingualism leads to delayed 'regular' ageing signature markings. This is directly addressed by the BAPSS model, (Grundy et al., 2017), where bilingual experience has been shown to result in functional adaptations leading to increased reliance from anterior to posterior and subcortical structures. If posterior and subcortical structures are engaged more in bilinguals, this may lead to increased functional integrity in these areas and, as a result, counteract or delay the development of the PASA ageing signature in bilinguals.

1.2.4. Cognitive and brain reserves

As mentioned above, deterioration in processing speed, episodic and working memory, and executive functions is normal in healthy ageing. However, there is a variable between-individuals trajectory of cognitive decline. While some adults age optimally, others experience starker decline (Cabeza et al., 2018). This variability depends, among other things (such as genetics, beyond the scope of this thesis), on environmental lifestyle factors, including higher educational and occupational attainment, engagement in cognitively stimulating leisure activities, and regular physical exercise (Valian, 2015). Research has shown that lifestyle and environmental factors have an impact on cognitive and brain ageing, and it is even the case that lifestyle factors protect against the onset of AD clinical manifestations (although not necessarily delay the structural deterioration of the underlying anatomical structures) (Arenaza-Urquijo et al., 2015). Based on literature reviewed above and what is known about the cognitive and neural aspects of the bilingual experience, bilingualism can also be listed among the above factors. We know that it is a cognitively demanding task, which has been shown to strengthen and protect the brain via contributing to resilience against age-related brain atrophy.

This variability of ageing trajectories, and the extent to which they are influenced by environmental factors has brought about the notion of cognitive reserve, brain reserve (Stern, 2002, 2009) and, more recently, brain resilience (Stern et al., 2018). Brain reserve refers to a phenomenon where there is a measurable and observable strengthening of neural tissue, through increases of grey matter volume/density and/or white matter integrity. It follows, logically that if there is a build-up of neural tissue, it will take longer for these areas to atrophy to a point where there are behavioural manifestations of neurodegeneration. Cognitive reserve, on the other hand, is a concept that is used to describe the apparent mismatch between brain atrophy and severity of neurodegeneration symptoms. Essentially, individuals with high cognitive reserve are able to utilise the brain resources available to them in a way that they are able to cope with neurodegeneration by maintaining better cognitive functioning that would be expected. This is thought to be the core mechanism that leads to later onset of AD symptoms (see Fig. 1.3 for a theoretical illustration of cognitive reserve effects on AD onset). This is supported by the finding that individuals with experiences suggestive of high CR may exhibit more extensive brain atrophy than low CR individuals in cases of clinical neurodegeneration, provided their behavioural performance is at par. It is impossible to anatomically measure one's cognitive reserve – it is purely a theoretical construct. It has to be noted that brain reserve and cognitive reserve are not mutually exclusive. Build-up of both are likely to interact, but cognitive reserve is unlikely to manifest unless the brain undergoes clinical neurodegeneration, resulting in subsequent potential decline of cognitive abilities.

There have been suggestions on how accumulation of said reserves can be explained, especially in relation to bilingualism. Constant engagement and corresponding increase of activity of the frontostriatal and frontoparietal networks associated with bilingualism might result in increased glucose metabolism and oxygenation of these areas. This mechanism could then lead to increased myelination, strengthening the white matter tracts, angiogenesis and synaptogenesis in these areas thus increasing their resilience to age-related degradation (Gold, 2015). Increased integrity of these areas can then be used as a compensatory supporting network, allowing bilinguals access to neural resources, thus reducing the effects of typical PASA and maintaining optimal cognitive functioning (for discussion see Gallo, Myachykov, Shtyrov, & Abutalebi, 2020). However, the exact mechanisms of how cognitive and brain reserves are built are still not understood well, apart from the fact that they appear to contribute to development of

more efficient brain, able to adapt for better coping with age- or disease-related neurodegeneration. Moving forwards, it is important, therefore, to further study these reserves in general and the relative contribution of bilingualism to them.

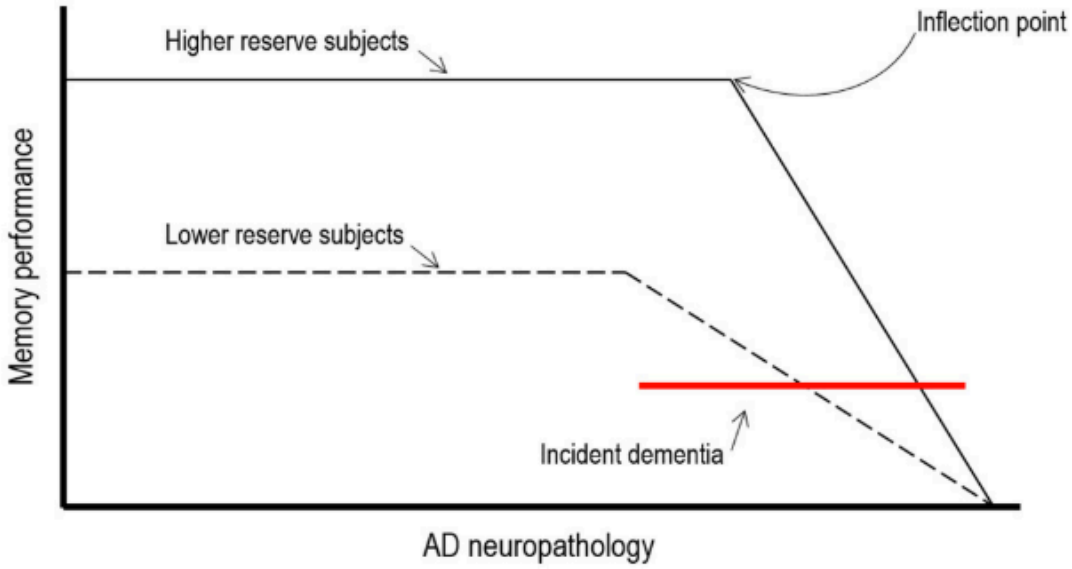

Figure 1. 3. A theoretical illustration of how cognitive reserve may mediate memory performance and onset of dementia (From Arenaza-Urquijo et al., 2015)

1.2.5. Neurocognitive effects of bilingualism in clinical ageing populations

The previous sections highlighted the involvement of bilingualism in preservation of neurocognition in older populations and role of speaking two languages in promoting successful cognitive ageing. This is a finding that has been reported rather consistently in the bilingualism and ageing literature; the proposed effects incur via accumulation of brain reserves promoting resilience to ageing-related decline, and motivated researchers in the field to investigate whether the bilingual effects extent to clinical ageing populations. Thus, research has been devoted to test if bilingualism-related accumulation of cognitive and brain reserves play a role in cases of clinical progressive neurodegeneration. Notably, the initial studies linking bilingualism to clinical populations focussed on Alzheimer's disease in particular.

Investigations linking bilingualism, brain, and cognition are few and far between. In these populations bilinguals with AD have been found to exhibit increased brain

atrophy, compared with their monolingual counterparts, when matched for cognitive status (Schweizer, Ware, Fischer, Craik, & Bialystok, 2012), indicating that bilingualism provides a cognitive reserve. Similar findings stem from MCI patients, where bilingual individuals were found to have smaller global parenchymal volume, compared to monolingual patients matched on cognitive status (Costumero et al., 2020). However, findings with regard to white matter in MCI patient populations are somewhat mixed, with a recent study finding simultaneous local increases and decreases of white matter integrity across white matter tracts (decreased white matter integrity in the fornix, while increased integrity in parahippocampal cingulum and the uncinate fasciculus) in MCI patients matched on cognitive level and education, thus painting a complex picture of the interaction between clinical ageing, bilingualism, and brain structure (Marin-Marin et al., 2019). Another landmark study examined bilingual and monolingual groups with AD and MCI and found evidence for neural reserve in the language and cognitive control areas and disease-related areas in bilinguals with MCI (e.g., greater grey matter than monolinguals in the left and right inferior frontal gyri, left medial superior frontal gyrus, bilateral anterior temporal gyri, left parietal lobule, bilateral cerebellum), however, bilinguals with AD exhibited more atrophy in over monolinguals with AD in the posterior parahippocampal gyri, and the rhinal sulci, thus suggesting the effects of increased cognitive reserve to become more pronounced as the disease progresses (Duncan et al., 2018). In PET studies, bilinguals with AD were found to exhibit severe hypometabolism in executive and default mode networks, as well as the left cerebellum, while behaviourally performing the same level, suggesting a greater compensatory effect for neurodegeneration in bilingual individuals (Kowoll et al., 2016; Perani et al., 2017).

Furthermore, bilingualism has been shown to lead to improved ageing and clinical outcomes in the older age. A key finding has associated lifelong bilingualism as a powerful cognitive reserve factor to delaying the onset of dementia symptoms by approximately 4-5 years (Bialystok et al., 2007). Alzheimer's disease is a progressive neurodegenerative disorder characterised by initial atrophy of the medial temporal lobe structures, the hippocampus and entorhinal cortex, expanding to a more widespread cortical, subcortical and white matter deterioration as the disease progresses (Price et al., 2009). The symptoms include episodic memory impediment and more complex behavioural changes, leading to consequent non-memory cognitive disturbances (Mucke, 2009). This bilingualism-related delay of symptom onset has been found in across

different populations, covering North American samples (Craik et al., 2010), European populations (Woumans et al., 2015), China, where Cantonese/Mandarin bilingualism is common (Zheng et al., 2018) and also, populations in India, where multilingualism is prevalent (Alladi et al., 2013).

It has to be mentioned that there are also studies finding that bilingualism offers no delays of symptom onset in clinical ageing. No delay in the age of dementia onset was found in community-dwelling bilingual Hispanic Americans, when compared to monolinguals from the same community (Lawton, Gasquoine, & Weimer, 2015). The nun study, looking at religious sisters age 75 and above, found no difference of dementia onset delay (Hack, Dubin, Fernandes, Costa, & Tyas, 2019). This study also found that self-reported multilinguals (speaking 4 languages and more) were less likely to develop dementia than monolinguals. Similar absence of bilingualism effects in delay of dementia symptom onset have been found in Welsh-English bilinguals residing in Wales (Clare et al., 2014), Japanese-Americans residing in Hawaii (Crane et al., 2010), Spanish-speaking immigrants in New York City (Zahodne, Schofield, Farrell, Stern, & Manly, 2014). Null findings were also reported in two meta-analyses on this subject (Mukadam, Sommerlad, & Livingston, 2017; Van den Noort et al., 2019). Null findings can potentially be explained by effects of bilingualism being obscured by presence of other cognitive reserve factors or absence of finer detail in terms of how bilingualism is operationalised (see following subsection for more discussion). For example, educational attainment is also a significant contributor to cognitive reserve; The delay of AD symptom onset has been shown to manifest in bilingual low education populations, as opposed to highly educated bilinguals (Gollan, Salmon, Montoya, & Galasko, 2011). In support of this finding, the seminal study by Alladi and colleagues (2013) found delay of AD symptom onset to be the largest in illiterate populations, reaching 6 years. This suggests that bilingualism might contribute cumulatively along other factors to cognitive and brain reserves. For example, if an individual has high cognitive reserve, as indicated by presence of other contributor factors, the relative contribution of bilingualism may appear to be relatively smaller. Indeed, more recent meta-analyses have established that null effect of the bilingual experience on ageing is mathematically impossible; however, while bilingualism is a factor that contributes to delaying the onset of dementia symptoms, it is not the case that bilinguals are less likely to get dementia (Anderson et al., 2020; Brini et al., 2020; Paulavicius et al., 2020). There are also reports that bilingualism might not be

sufficient for any effects to manifest – but there are delays in symptom onset in those, who speak more than two languages, although this delay is linked to immigrant status (Chertkow et al., 2010). When compared to bilinguals, the incidence of cognitive impairment is lower in those who speak at least three languages (Perquin et al., 2013), indicating that the number of languages spoken can also be a predictor for successful cognitive ageing. These results are supported by work of Kavé et al., (2008), who longitudinally followed a large sample of bilingual, trilingual, and multilingual Israeli older adults over a period of 12 years and found a positive main effect of the number of languages spoken on cognitive test scores across all three testing sessions, even when the participants were 90 years old.

1.3. The false dichotomy of bilingualism

The study of bilingualism and the neurocognitive effects of it across the lifespan has been riddled with controversy (Mark Antoniou, 2019). Some studies and research groups find an effect of bilingualism on executive functioning (Bialystok et al., 2008), others fail to replicate these findings and argue that the effects are null (Paap & Greenberg, 2013), or that any effects observed may be a result of publication bias (de Bruin, Treccani, & Della Sala, 2015), or that they are generally unreliable and only manifest under certain conditions (Paap et al., 2015). While this has been mostly linked to variability in behavioural findings in young adult populations, and fervent debates on whether there is a cognitive 'bilingual advantage' or not, there is some irregularity in findings in the older age too. This applies to both healthy and clinical populations, as exemplified by the diametrically opposite findings by recent meta-analyses that advocate either for (Anderson et al., 2020) or against (Mukadam et al., 2017) advantages conferred by bilingualism.

Nonetheless, the 'bilingual advantage' debate seems to have exhausted itself to the point where calls have been made to move away from it and remove the contention by reframing the issue of when and how any cognitive adaptations associated with bilingualism manifest (Poarch & Krott, 2019). Instead of asking the question of whether bilingualism results in a cognitive 'advantage', it is imperative to consider in finer detail the elements of cognition where any effects can be observed, conditions or language contexts under which these effects manifest, and a more nuanced approach to bilingualism, taking into account factors that are individually variable, such as age of L2

acquisition, L2 proficiency, patterns of language use, etc. (Leivada, Duñabeitia, Westergaard, & Rothman, 2020; Valian, 2015). Yet, the false dichotomy of bilingualism and operationalising this phenomenon as a binary variable prevails in the literature, whereas underlying variance should be seriously considered, as it might affect the pattern of results.

At this point there seems to be little common ground on how bilingualism is operationalised. Surrain and Luk (2019) examined 186 studies published between 2005-2015 and found that 23% of studies did not report any information on L2 proficiency and that 61% of all studies did not report the extent to which the L2 was used relative to the L1. The lack of proficiency and usage information is problematic especially because several studies have demonstrated not only the importance of L2 proficiency, but also immersion and usage of the L2 on brain structure and function (DeLuca, Rothman, Bialystok, & Pliatsikas, 2019; DeLuca, Rothman, & Pliatsikas, 2019; Pliatsikas et al., 2017, 2020). A good example of this is the study by Pot et al. (2018), where data analysis revealed null results in a crude between-groups monolingual vs. bilingual analysis (taking into account language knowledge factors, such as language proficiency, number of languages known, and simultaneous vs. subsequent language acquisition) for cognitive functioning in older adults. However, once the intensity of multilingual language use and language use patterns, operationalised as a continuous variable based on contextual language switching and across-domain use of languages, were taken into account, bilingualism was shown to predict enhanced attentional control.

The literature on linking bilingualism to cognitive and brain adaptations in clinical contexts is relatively small and mostly limited to data gathered from memory clinics and hospitals. Data from hospital records lacks any nuance with regard to bilingualism, which would allow to account for individual differences within the bilingual populations, as opposed to the binary approach to bilingualism (i.e., either one is bilingual or not), most commonly found in the literature. It is a rather clear finding that bilingualism contributes to the delay of AD and MCI symptom onset, although this might be dependent on the type of bilinguals examined and reliant on specific language experiences and language use patterns, as evidenced by some null findings in these populations too.

Therefore, it is paramount to collect comprehensive demographic information, data that reveal language use patterns and other linguistic variation, and, especially in

older adults, information regarding cognitive reserve contributor factors and others known to contribute to enhancement of executive functions (Naeem, Filippi, Periche-Tomas, Papageorgiou, & Bright, 2015). We need to understand that comparing bilingual populations with largely different language use patterns may not yield comparable results (Bak, 2016a; Ooi, Goh, Sorace, & Bak, 2018). Empirical evidence has revealed that factors such as L2 age of acquisition and measures of language entropy (quantification of language use patterns) are important to keep in mind when investigating bilingualism, as they have a gradient effect on neuroplasticity and neural connectivity (Gullifer, Chai, Whitford, Pivneva, & Baum, 2018; Gullifer & Titone, 2020; Luk & Bialystok, 2013; Sulpizio, Maschio, Mauro, & Fedeli, 2019). What might be even more important and is often overlooked in the bilingualism literature is the length of residence in an L2 environment (Higby & Obler, 2016). This is potentially even more important in ageing literature, as length of immersion in L2 environment might be a more influential variable than age of L2 acquisition. As bilingualism is a dynamic experience, older individuals may have experienced greater variability of L2 use patterns in their lives than their younger counterparts since their L2 age of acquisition.

If this complex and multidimensional nature of bilingualism is accepted, then it becomes possible to move away from trying to find universal effects of bilingualism characteristic across all bilingual populations, and move towards finding a more nuanced answer to what aspects of bilingualism result in neurocognitive adaptations, and under what conditions (Blanco-Elorrieta & Pylkkänen, 2018; Leivada, Duñabeitia, et al., 2020). With the recently developed understanding of bilingualism as a multidimensional spectrum, which has proved to be fruitful in better understanding the links and relationship between individual language experiences and changes in brain and cognition, it is now time to turn to a more detailed examination of the effects of bilingualism in the older age and in clinical populations. This is not only subject to purely academic interest. As more and more individuals live increasingly longer lives, and there is an increasing number of people with dementia, linked to the later years of life it is important to better understand if bilingualism could be used as a tactic to promote healthy cognitive ageing. The proposed clinical significance of bilingualism is especially interesting to consider given the absence of pharmacological treatment and cure for dementia. However, the mixed findings highlight a need for a better understanding of the exact contributions of bilingual experience factors in building up the cognitive and brain reserves as well as

establish conditions and contexts in which the protective effects of bilingualism manifest in older and clinical populations (Del Maschio, Sulpizio, et al., 2018).

1.4. Principle aims of the thesis

Bilingualism has been shown to interact with brain and cognition across the lifespan, as well as contribute to a delayed onset of Alzheimer's disease symptoms via cognitive and brain reserve mechanisms. However, there is a dearth of studies linking bilingualism, brain, and cognition in the older and, especially, clinical populations. It is somewhat paradoxical, that there are a plethora of studies reporting delayed symptom onset, but the focus has not been on the brain structures that underlie the initial symptoms of Alzheimer's disease, namely episodic memory disturbances, linked to medial temporal lobe structures and the hippocampus in particular. There are good reasons to examine bilingualism in the context of episodic memory function and the hippocampus, as they have been shown to be impacted by bilingualism, at least in younger populations (DeLuca, Rothman, Bialystok, et al., 2019; Mårtensson et al., 2012; Schroeder & Marian, 2012).

Finally, if bilingualism is linked to delayed onset of symptoms related to Alzheimer's disease and MCI, might it be that similar effects extend to other progressive neurological disorders, which have some overlapping features in terms of brain atrophy and/or symptomatic profile? This is largely unchartered territory, as there is very limited empirical research on this topic, however, overlapping effects might reveal bilingualism to be not only a specific protective factor for Alzheimer's dementia and MCI, but a more general protective factor in neurodegeneration, acting through the accumulation of cognitive and brain reserves.

The principle aims of this doctoral research project, therefore, are to 1) identify the effects of bilingual language experience on episodic memory in healthy older individuals and those on the cusp of dementia, i.e., with an MCI diagnosis, as episodic memory impairment is the primary symptom of AD and episodic memory has been shown to be affected by bilingualism; 2) understand the effects of bilingualism on medial temporal brain structures in healthy and clinical older populations, with a focus on the hippocampus, a structure that supports episodic memory function, is subject to decline in ageing and has been shown to be sensitive to the bilingual experience; 3) use the available evidence to examine whether bilingualism has the potential to be a protective factor in

other neurodegenerative diseases in the same way it has been proposed for AD. Three studies on the subject are presented. In the first study bilingualism is cross-sectionally evaluated as a continuous variable in healthy older populations, looking at bilingualism as a predictor for hippocampal volume and episodic memory performance. This is done by quantifying bilingual use across different contexts using a comprehensive language and social background questionnaire (Anderson, Mak, et al., 2018). In the second study we use a similar approach in MCI patients. All participants in this study are bilinguals, but they differ in their active use in the language. Whole-brain cortical grey matter volume, as well as volumes of the hippocampus, caudate nucleus, putamen and amygdala, and episodic memory performance are analysed as a function of language engagement as well as between-groups differences between active and passive bilinguals are determined. In the final, epistemological study, we critically evaluate current literature and draw links to bring attention to the possibility of bilingualism as a more general reserve factor beyond progressive neurodegeneration studied mostly thus far – Alzheimer's Disease and Mild Cognitive Impairment. To do so, we use an example of three progressive neurodegenerative diseases – Huntington's disease, Parkinson's disease and Multiple Sclerosis.

CHAPTER 2: THE EFFECTS OF BILINGUALISM ON THE STRUCTURE OF THE HIPPOCAMPUS AND ON MEMORY PERFORMANCE IN AGEING BILINGUALS

Abstract

Long-term management of more than one language has been suggested to lead to changes in cognition and the brain. This is particularly documented in older age, where bilingualism is associated with protective effects against decline, for example, affording compensation for symptoms of Alzheimer's disease leading to delayed diagnosis relative to non-bilinguals. Herein, we focus on potential bilingualism effects in the hippocampus, a brain structure related to memory that is particularly vulnerable to cognitive ageing. Hippocampal volume has been shown to increase as a result of second language learning and use in younger adults. However, we do not know if this is maintained over the lifespan, that is, what the long-term effects might be examined in ageing. Herein, we examine hippocampal volume and performance in episodic memory tasks in healthy ageing long-term bilinguals compared to monolinguals. Results show greater hippocampal volume for the bilinguals, which was correlated to individual-level quantified use of the two languages. Thus, our results mirror that of immersive active bilingualism in younger populations. No significant effects of bilingualism were reported on episodic memory task performance. Our findings suggest that long-term active bilingualism leads to neuroprotective effects in the hippocampus, which we discuss in the context of the proposed bilingualism-induced brain reserve in older age literature.

2.1. Introduction

The experience of being a bilingual has been shown to have an impact on domain general cognition (e.g., Marian & Shook, 2012), in particular in the domain of executive functions (Bialystok et al., 2004, 2008) and episodic memory performance (Schroeder & Marian, 2012). It has also been shown to be a source of neural plasticity. Specifically, increased cognitive control demands associated with management of more than one language result in structural and functional adaptations in brain regions comprising networks related to language acquisition and processing, as well as domain general cognitive control (e.g., Grundy et al., 2017; Pliatsikas, 2019). Notably, and although bilingualism effects can be observed across the lifespan, effects on behaviour are more robustly observed in ageing populations. Specifically, ageing bilinguals outperform monolinguals in task testing executive functioning (e.g., Bialystok, Craik, Klein, & Viswanathan, 2004; Sullivan, Prescott, Goldberg, & Bialystok, 2016), a set of cognitive control processes, such as mental set shifting, updating, and inhibition (Miyake et al., 2000). With regard to neuroanatomical changes in these age groups, bilingualism has been associated with greater grey matter volume and white matter integrity across brain structures involved in bilingual language control, language learning, and language processing (Anderson, Grundy, et al., 2018; Duncan et al., 2018; Gold, Kim, et al., 2013). The findings regarding beneficial effects of bilingualism on the ageing brain and cognition are of particular importance, as it is the same period in life where cognition and the brain are expected to decline; therefore, it is interesting to investigate how the effects of bilingualism interact with those of ageing. The following section will provide a brief overview of our current knowledge on the effects of ageing and bilingualism on the brain with a particular focus on episodic memory and a key brain region that underlies it, the hippocampus. This will be followed by evidence on how these effects might interact, including the underlying mechanisms.

Overall, general cognition, including episodic memory, and the supporting neural architecture, are subject to decline in the older age, otherwise referred to as cognitive ageing. At the brain level, cognitive ageing is perhaps most clearly identifiable in anatomical brain changes such as reductions in grey matter (GM) volume and/or white matter (WM) integrity, especially in the prefrontal cortex and hippocampus, and/or decreased efficiency (i.e. increased recruitment of implicated networks) in task performance (e.g., Bettio, Rajendran, & Gil-Mohapel, 2017; Farokhian, Yang, Beheshti,

Matsuda, & Wu, 2017; Giorgio et al., 2010; Nyberg et al., 2010; Persson et al., 2006; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005). However, there is a general variability in cognitive ageing trajectories across the population. Some individuals seem to be more resilient to cognitive decline in the older age. In addition to genetic factors as determinants of individual differences (e. g. possession of the *APOE* e4 allele or polygenic scores), this variability can be explained by the concepts of cognitive reserve, brain reserve, and brain maintenance (Stern et al., 2018). Cognitive reserve refers to preserved cognitive ability in the face of neural damage or neurodegeneration and can manifest as better-than-expected cognition in cases of progressive neurodegeneration. Brain reserve, however, refers to the build-up of neural tissue, as a structural reinforcement of the brain, via volumetric increases caused by neurogenesis or dendritic branching. This added neural tissue then acts as a reinforcing scaffolding, meaning that the neurodegenerative processes need to take longer before any cognitive and behavioural symptoms manifest. Due to its nature, brain reserve can be observed in healthy individuals. A variety of factors, including lifestyle enrichment factors, such as education, general mental stimulation, psychical exercise, leisure activities/choices and occupation attainment are thought to contribute to increased reserves and, as such, would predict more successful cognitive ageing (Cabeza et al., 2018; Darwish, Farran, Assaad, & Chaaya, 2018; Foubert-Samier et al., 2012; Hötting & Röder, 2013; Perneczky et al., 2019; Ritchie et al., 2019; Yaffe et al., 2009). Bilingualism can also be considered to be a factor that promotes healthy cognitive ageing by building cognitive and/or brain reserves. Several studies have reported that bilingualism contributes to the delay of the onset of dementia symptoms in neurodegenerative diseases, most commonly in Alzheimer's disease or Mild cognitive impairment (Alladi et al., 2013; Anderson et al., 2020; Bialystok et al., 2007). As such, interventions in the form of second language learning have also been suggested to have the potential of slowing down decline associated with older age (Mark Antoniou, Gunasekera, & Wong, 2013), albeit additional language learning as an indirect intervention has been insofar trialled with mixed results (Berggren, Nilsson, Brehmer, Schmiedek, & Lövdén, 2020; Bubbico et al., 2019).

If bilingualism has such a strong effect in brain structure, it is worth looking at its effects on brain regions implicated in some prominent dementia symptoms, such as difficulties with episodic memory (Hugo & Ganguli, 2014). One of such regions is the hippocampus, a grey matter structure located deep in the medial temporal lobe. The

hippocampus is subject to atrophy in healthy ageing by annual loss of 0.85%; this rate of atrophy surpasses that of other brain structures and becomes increasingly rapid with older age (Fjell et al., 2009; Fraser, Shaw, & Cherbuin, 2015). The hippocampus is mostly associated with supporting episodic memory function, but it also underlies other important aspects of cognition, such as recognition, spatial processing of cognitive spaces (time and space), language learning, emotional behaviour and mental imagery (Anand & Dhikav, 2012; Bellmund, Gärdenfors, Moser, & Doeller, 2018; Bird & Burgess, 2008; Ullman, 2004). Previous work has linked reductions in hippocampal size with verbal and non-verbal episodic memory performance decline in healthy ageing (Gorbach et al., 2017; O'Shea, Cohen, Porges, Nissim, & Woods, 2016) and global cognition decline in clinical patients (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015; Rosselli et al., 2019). These findings expand to a variety of neurodegenerative diseases, such as Parkinson's disease (Brück, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Das, Hwang, & Poston, 2019; Wilson, Niccolini, Pellicano, & Politis, 2019) and Relapsing-Remitting Multiple Sclerosis (Debernard et al., 2015; Koenig et al., 2014). Moreover, hippocampal atrophy is an established indicator for conversion from healthy ageing process to development of mild cognitive impairment and dementia (Fotuhi, Do, & Jack, 2012) and smaller hippocampal size is a predictor for an increased risk of and faster conversion from Mild Cognitive Impairment to Alzheimer's Disease (Apostolova et al., 2006). However, the hippocampus has been shown to be plastic and respond to changes in behaviour. For example, behavioural or physical interventions can impact hippocampal volume and improve memory performance in the older age, effectively reversing age-related hippocampal tissue loss (Erickson et al., 2011; Firth et al., 2018; Lövdén, Schaefer, et al., 2012). Early life intellectual enrichment has been linked to increased hippocampus (Sumowski et al., 2016) and increased volume of this structure has been shown to contribute to cognitive resilience in clinical ageing brain (Erten-Lyons et al., 2009). In sum, not only the hippocampus appears to be a malleable brain region, but this malleability seems to have correlates in behaviour, and to be particularly affected by external stimulations and/or experiences. In the light of this, it is interesting to look at whether a challenging experience such as bilingualism might have an effect on the structure of the hippocampus, and how these would be expressed in older age.

As already mentioned, the cognitive challenges that bilingualism poses often lead to restructuring of brain regions involved in language acquisition and control (Pliatsikas,

2020). Since the hippocampus is a key structure for processes like vocabulary acquisition (Breitenstein et al., 2005), it is a good candidate structure for structural effects of bilingualism to emerge. Indeed, bilingualism has been shown to affect the shape and size of the hippocampus, at least in healthy adult populations that are active learners and/or users of an additional language. For example Mårtensson et al. (2012) examined Swedish interpreter students and found a significant volumetric increase in the right hippocampus following an intensive 3 month language course. Similarly, Bellander et al. (2016) also reported expansion of the right hippocampus in young Swedish speakers as they acquired Italian vocabulary over the course of 4 months; interestingly, expansions were not related to the amount of vocabulary acquired, but to the amount of time spent studying the L2. In a more recent longitudinal study, DeLuca, Rothman, & Pliatsikas (2019) tested bilinguals living in an immersive L2 environment for three years and reported significant reshaping of the right hippocampus in the form of simultaneous expansions and contractions of different portions of the structure. Since these effects have been reported in younger bilinguals, it could be hypothesised that long-term bilingual experience would lead to brain reserve in the hippocampus, in the form of larger structures in bilinguals versus monolinguals, similar to what has been reported for other brain regions. However, the available evidence remains limited (see Zhang, Wu, & Thierry, (2020), for a review). For example, Li and colleagues (2017) used a region of interest approach to compare hippocampal volumes between highly proficient bimodal Mandarin Chinese - Chinese Sign Language bilinguals and Mandarin Chinese monolinguals (aged 29-67). They reported enlarged hippocampus for the former group, who also reported to engage in active use of both their languages on a regular basis. However, Olsen and colleagues (2015) failed to report volumetric differences in the hippocampus between 70-year old bilinguals and monolinguals, although they did report differences in other parts of the temporal lobe.

It becomes apparent that the limited available information on how bilingualism affects the hippocampus remains mixed, justifying the need for further studies and different approaches to the issue. One of these approaches concerns how bilingualism itself is operationalised; indeed, the vast majority of the studies looking at the effects of bilingualism in the young and old have treated it as a dichotomous variable and performed straightforward cross-sectional between bilinguals versus monolinguals, an approach that might lead to a significant variability within the bilingual group to be lost. Consequently,

there has recently been a push to rather explore the individual differences *within* bilinguals, expressed by measures such as age of L2 acquisition and language use patterns across a variety of contexts; in other words, an approach that treats bilingualism in a more nuanced way as a *continuum* by finding ways to quantify the bilingual experience (Bak, 2016b; Bialystok, 2016; Luk & Bialystok, 2013; De Cat, Gusnanto & Serratrice, 2018; Gullifer et al., 2018; Beatty-Martínez et al., 2019; DeLuca et al. 2019, 2020). To date, no study has investigated the effects of long-term immersive bilingualism on the brain structure in the older age, while treating bilingualism as a spectrum of experiences. As the hippocampus is sensitive to both bilingualism and ageing processes, we examined if the findings in bilingual younger populations can be replicated in older individuals; that is, whether bilingual experience can predict any volumetric changes in this brain structure, and also whether any structural effects would be accompanied by commensurate effects on memory performance.

With the above in mind, the overall aim of this study was to examine the effects of long-term naturalistic immersion in a second language environment on the hippocampus in older healthy populations. Highly proficient speakers of English as a second language and monolingual controls underwent a behavioural and MRI testing battery assessing their memory and hippocampal structure, accompanied by collection of their detailed language background information. The specific aims of the present study were twofold: First, to carry out a cross-sectional comparison between the two groups in order to assess the effects of bilingualism on cognition and hippocampal shape and volume. Second, to investigate whether individual differences in language use patterns can further explain variability in cognition and the brain in older age.

In light of previous results, four hypotheses regarding the hippocampal structure and memory performance were raised. First, and in line with previous findings in younger groups, as all participants were cognitively healthy, we expected to see an increased volume of the hippocampus in the bilingual group. Second, we expected bilingual experience, quantified as a bilingualism composite score, to be a significant predictor of hippocampal volumes. Altogether, these effects would indicate a potential neuroprotective effect of bilingualism in the older age, which would relate to the individual experiences of the bilinguals. The third hypothesis related bilingualism to cognitive performance and memory. Specifically, if bilingualism contributes to expansions in the hippocampal volume, better episodic memory performance can be

expected in bilinguals. Finally, our fourth hypothesis was that, if the quantified bilingual experiences significantly predict hippocampal volume, a similar effect should be predicted for performance in episodic memory tasks.

2.2. Methods

2.2.1. Participants

Forty-eight healthy older adults (30 females, *m*Age: 62.19, SD: 9.62, range: 48-84) were recruited for the study. Of these, 23 were bilingual or multilingual speakers of L2 English (16 females, *m*Age: 58.48, SD = 6.77, range: 49-73) (henceforth referred to as 'bilinguals') and 25 were functionally monolingual native English speakers (mAge = 65.60, SD = 10.68, range: 48-84) (henceforth referred to as 'monolinguals'). All participants were right-handed and reported no neurological disorders or history of speech and language impairments, and they were all residents of the UK at the time of testing. Prior to participation, subjects provided written informed consent and reported no counterindications to MRI scanning. All participants scored within the normal range of the ACE-III cognitive score (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013) suggesting no indications of cognitive impairment (see table 2.1).

Table 2. 1. Cognitive measures and outcomes (Study 1)

	Monolinguals (N=25)	Bilinguals (N=23)	Overall (N=48)
ACE-III total score			
Mean (SD)	94.0 (4.67)	94.5 (3.72)	94.2 (4.20)
ACE-III memory domain score			
Mean (SD)	23.8 (2.57)	25.0 (1.36)	24.3 (2.15)
Episodic memory score (NIH toolbox)			
Mean (SD)	96.2 (12.4)	103 (11.7)	99.3 (12.4)
Working memory score (NIH toolbox)			
Mean (SD)	97.5 (10.5)	99.7 (6.99)	98.5 (8.98)

The bilingual participants spoke a variety of first languages but converged on English being an additional language. Most of these participants (N=22) reported speaking an additional language or languages to English and their respective L1. In terms of language proficiency, two individuals reported English to be their most proficient language, 16 reported English as their second most proficient language, 3 individuals

reported English as their third most proficient language, and one reported English as their fourth most proficient language. These participants usually acquired English at school age (*m*AoA: 10.65; SD: 6.12; range: 0-30). The majority of this group were born outside the UK and had moved to the UK at various ages. Two participants in this group were born in the UK but did not speak English at home and started learning English upon commencement of formal education. One participant was born in the Netherlands and reported growing up in a bilingual Dutch/English household. Three participants reported English as their most proficient language at the time of testing. Participants in this group had been immersed in their second language environment for an extended period of time (mean length of residence in the UK = 29.52 years; SD = 17.20; range 1-60) and were using English for everyday communication and were competent and highly proficient users of this language (see Table 2.2).

Table 2. 2. Language scores and proficiency measures (Study 1)

	Monolinguals (N=25)	Bilinguals (N=23)	Overall (N=48)
LSBQ L2 Home score			
Mean (SD)	-12.3 (2.50)	5.23 (4.52)	-3.92 (9.56)
LSBQ L2 Social score			
Mean (SD)	-6.06 (2.86)	51.8 (8.40)	21.6 (29.8)
LSBQ Bilingualism composite score			
Mean (SD)	-5.94 (1.58)	17.0 (3.43)	5.07 (11.9)
English proficiency measures (bilinguals only)			
Speaking			
Mean (SD)		8.48 (1.28)	
Reading			
Mean (SD)		8.95 (0.996)	
Writing			
Mean (SD)		8.47 (1.37)	
Understanding			
Mean (SD)		8.82 (1.16)	

Of the monolingual group, 13 participants reported some exposure to an additional language, usually at school age. However, none of the monolinguals reported continuous engagement with their additional languages at the present day, mostly advising 'occasional use while on holiday'. Active engagement with their L2 was

normally in a classroom setting during adolescence that was decades prior to testing. Language and Social Background Questionnaire (see below) suggests bilingualism composite scores under -3.12 as firmly bilingual and scores over 1.22 as firmly monolingual. Individuals scoring between these values lie in a 'grey area', with ambiguous language background. Only two participants in this group did not score firmly in the 'monolingual' category, as defined by the LSBQ; one of these participants had no working knowledge of any other languages but reported growing up in an environment where he was surrounded by other languages. The other participant had extensive experience with French, although they were not actively engaging in use of French in their everyday life. Therefore, these two participants were not excluded from the 'monolingual' group. No participants were excluded from analysis based on their linguistic background. For full language and demographic information, see Table 2.3.

2.2.2. Data collection

Behavioural testing and MRI scanning sessions were mostly conducted on the same day, although in some cases, where it was not feasible to conduct all aspects of testing in one day, participants returned for a second round of testing at a later date. The maximum time period between the testing sessions was 3 months.

Table 2. 3. Demographic information (Study 1)

	Monolinguals (N=25)	Bilinguals (N=23)	Overall (N=48)
Age (years)			
Mean (SD)	65.6 (10.7)	58.5 (6.77)	62.2 (9.62)
Sex			
F	14 (56.0%)	16 (69.6%)	30 (62.5%)
M	11 (44.0%)	7 (30.4%)	18 (37.5%)
Education (NIH toolbox scoring)			
Mean (SD)	19.1 (3.59)	20.5 (3.16)	19.8 (3.43)
First language			
English	25 (100%)	0 (0%)	25 (52.1%)
Catalan	0 (0%)	1 (4.3%)	1 (2.1%)
Croatian	0 (0%)	1 (4.3%)	1 (2.1%)
Danish	0 (0%)	1 (4.3%)	1 (2.1%)
Dutch	0 (0%)	9 (39.1%)	9 (18.8%)
French	0 (0%)	1 (4.3%)	1 (2.1%)
German	0 (0%)	2 (8.7%)	2 (4.2%)
Italian	0 (0%)	1 (4.3%)	1 (2.1%)
Latvian	0 (0%)	2 (8.7%)	2 (4.2%)
Polish	0 (0%)	1 (4.3%)	1 (2.1%)
Punjabi	0 (0%)	1 (4.3%)	1 (2.1%)
Swedish	0 (0%)	1 (4.3%)	1 (2.1%)
Ukrainian	0 (0%)	2 (8.7%)	2 (4.2%)
English age of acquisition (years) (bilinguals)			
Mean (SD)		10.7 (6.12)	
Length of immersion/residence in the UK (years) (bilinguals)			
Mean (SD)		29.5 (17.2)	

2.2.2.1. Behavioural data collection

2.2.2.1.1. Language and Social Background Questionnaire (LSBQ)

The participants completed the language and social background questionnaire (LSBQ) (Anderson, Mak, et al., 2018)**,** adapted for the UK context (see Appendix A). The LSBQ is a questionnaire that allows to collect detailed information about one's social (professional attainment, country of birth, etc.) and linguistic background (spoken languages, self-rated proficiency, age and context of acquisition), and the extent of language use across different contexts. Bilingual experience is quantified via a bilingualism composite score (BCS) as a sum of various quantitative experience-based factors such as extent of L2 use in home and social settings (DeLuca, Rothman, Bialystok, et al., 2019; DeLuca, Rothman, et al., 2020). The BCS allows for measurement and treatment of bilingualism as a continuous variable, as opposed to more commonly used stratification of participants in monolingual and bilingual language groups (de Bruin, 2019; Pliatsikas et al., 2020; Surrain & Luk, 2019).

The participants were asked to complete a paper copy of the LSBQ on their own, but an examiner was present to answer any questions participants may have and provide clarification, if needed. As LSBQ presumes English to be the native or first language by default, the calculations using the factor score calculator were canonical for the native English speakers, whereas the calculations for those with other first languages were altered for their native language to be treated as the baseline, and English regarded as L2. This required inversion of some scores from the questionnaire upon input in the calculator (as in DeLuca, Rothman, Bialystok, et al., 2019).

2.2.2.1.2. NIH Toolbox

A modified cognition battery of the NIH Toolbox (Weintraub et al., 2013) was used to assess the cognitive functioning of the study participants. The NIH toolbox is an iPad-based testing battery. For the present study in particular, two tests were of interest: the NIH-TB Picture Sequence Memory Test (testing episodic memory performance) and NIH-TB List Sorting Test (testing working memory performance). Hippocampus is typically associated with episodic memory performance, while working memory relies on frontal and parietal networks (Nee & D'Esposito, 2015). Nonetheless, hippocampal volume has been shown to correlate with performance in the specific NIH toolbox working memory task in ageing populations (O'Shea et al., 2016). Inclusion of two tasks

tapping into different types of memory allows to test the specificity of the results to cognitive function with the hippocampus and for involvement of this structure in working memory processes. In the List Sorting Working Memory Test participants were presented with cartoon pictures of different foods and animals, with accompanying audio presentation and written text naming the item. The participants were then asked to say the items back to the examiner listing them in size order from the smallest to the biggest. In the first condition, participants are asked to recall stimuli from one category. In the second condition, participants are presented with stimuli from two categories (foods and animals) in mixed order and have to recall the items in size order for each category separately. The number of items in each trial increases until two trials of the same length are failed. All items were of high frequency, easily recognisable and unambiguous. Test is scored as the total items correct across all trials.

In the Picture Sequence Memory Test sequences of pictured objects and activities were presented in a particular order. The participants were then asked to reproduce the same order on the screen. The pictures are presented in two trials: one with a 15-step sequence and the other with an 18-step sequence. The second sequence is a repetition of the same 15 items, with 3 novel items added in the middle of the sequence. The score is derived by the cumulative number of adjacent pairs remembered correctly over the learning trials.

Both NIH toolbox tests were automatically scored with three types of scores: uncorrected standard scores (normative mean = 100, SD = 15), age-corrected standard scores, and fully corrected T-Scores, which account for age and other demographic characteristics – the demographic information is submitted prior to behavioural testing. For this study uncorrected standard scores were used to measure behavioural performance; moreover, age and education measures, also collected as part of the behavioural data via the NIH toolbox, were included in the analysis as covariates.

2.2.2.1.3. Addenbrooke's Cognitive Examination (ACE-III)

Participants were asked to complete the Addenbrooke's Cognitive Examination (ACE-III) testing battery (Hsieh et al., 2013). ACE-III is a widely used screening tool for cognitive deficits in Alzheimer's Disease and Frontotemporal Dementia. It is scored out of 100 and covers five cognitive domains – attention, memory, fluency, language, and visuospatial processing, where an overall score of less than 82 suggests dementia. The

domain of primary interest in this study was memory. The tasks tapping into memory are scattered throughout the exam and tap into working and semantic memory. More specifically, the participants are asked to recall previously repeated words, memorise and recall a fictional name and address, and recall well-known historically significant people (Bruno & Vignaga, 2019). The memory domain is scored out of 26. The score provides a baseline information of one's composite memory performance and were used in addition to NIH toolbox cognitive battery episodic and working memory tasks.

2.2.2.2. MRI data acquisition

For the purpose of structural brain analysis, high resolution T1 anatomical scans were acquired using a MPRAGE sequence on a 3T Siemens MAGNETOM Prisma_fit MRI scanner, with a 32-channel Head Matrix coil and Syngo software (256 sagittal slices, 0.7mm slice thickness, in-plane resolution 250 x 250, acquisition matrix of 246 x 256mm, 224mm FoV, TR=2400ms, TE=2.41ms, inversion time = 1140ms, flip angle = 8°). The scan lasted approximately 10 minutes.

2.2.3. MRI data processing

2.2.3.1. Preprocessing

Structural neuroimaging data were pre-processed and analysed with software pipelines in FSL. The raw neuroimaging data were converted from dicom to nifti file format and stored in a BIDS structure format using pyBIDSconv1.1.7. (Lindner, 2018). All T1-weighted scans were then anatomically pre-processed using the fsl_anat pipeline in FSL 5.0.9 (Smith et al., 2004). This involves a standard use of various MRI processing tools including the brain extraction tool (BET) used for skull stripping the raw T1 images and bias field correction as part of the pipeline. Bias field corrected T1 images were used for segmentation of the hippocampus. The brain extractions were manually checked for quality control. This revealed that five participants had unsatisfactory extraction, and this was addressed by applying custom extraction parameters and rerunning BET until we yielded satisfactory skull-stripped brain extractions.

2.2.3.2. Volume

Segmentation of the bilateral hippocampus was performed using FIRST, a toolbox of FSL. FIRST performs registration, segmentation based on Bayesian

appearance and boundary corrections to produce segmented subcortical structures (Patenaude, Smith, Kennedy, & Jenkinson, 2011). Hippocampal extractions were verified visually and were not deemed satisfactory for one participant. While all other segmentations were performed on bias-corrected full T1 images, for the unsatisfactory segmentation, the pipeline was run again on the brain-extracted image, which produced a satisfactory subcortical segmentation of the structure. Hippocampal raw volumes were calculated using fslstats. Hippocampal volume was normalised by dividing it by total brain volume as estimated from the skull stripped image.

As FIRST provides two volumetric values – one for the left hippocampus, and one for the right – we initially ran a linear fixed effects model including a main effect of Language group (i.e., monolingual vs. bilingual), Hemisphere (i.e., left vs right) and the interaction between the two as predictors of hippocampal volume.

Subsequently, we used a hierarchical regression to investigate whether degree of bilingualism predicts hippocampal volume beyond other demographic factors and memory performance. To do so, we used demographic measures, individual test scores from the NIH toolbox and ACE-III and the LSBQ scores to build and compare several linear fixed effects models in an increasing order of complexity. The models were built and executed in R version 4.0.0. All continuous predictors of hippocampus volume (age, education, length of immersion, L2 Home, L2 social, BCS, List Sorting Working Memory Test scores, Picture Sequence Memory Test scores, ACE-III memory domain scores) were mean-centred[1]. The normalised hippocampal volumes were normally distributed in this participant sample ($W = 0.989$, $p = 0.586$).

The initial model (Model 1) explains hippocampus volume as a function of age, education, and hemisphere. The second model (Model 2) adds memory performance measures as the independent variables to the model. The decision to include memory performance measures as predictors in this model (whereas, more typically one would see brain measures as predictors for behaviour) was done to account for the individual variance in the hippocampal volume which has been shown to account for behavioural performance in other studies. In other words, like the demographical variables, memory

[1] Given the age of our participants, we did not use age of acquisition as a reliable predictor because many bilingual individuals reported learning English at school, which does not accurately portray the actual engagement in English use across the lifespan and at the time of testing.

performance is effectively acting as a predictor of no interest. The third model (Model 3) introduces our main predictor of interest, the LSBQ BCS[2].

2.2.3.3. Shape

As part of the FIRST pipeline, vertex analysis was also performed on the bilateral hippocampus to establish if BCS is a predictor for changes in the hippocampal shape. The standard procedure was implemented in FIRST, by which each structure was linearly registered (using 6 degrees of freedom) to the sample-specific average surface and mapped in MNI space. Analysis was carried out using the Randomise pipeline in FSL, in which permutation-based non-parametric analysis, with 10000 permutations for each factor of interest testing were run and corrected for multiple comparisons using threshold-free cluster enhancement (Smith & Nichols, 2009). The correlational design matrix contained the factor of interest, BCS, and covariates of age and education. This resulted in spatial maps showing local contractions and expansions of the structure (i.e., perpendicular displacement from the study-specific template average surface) of interest as a function of bilingualism, thresholded at $p=<0.05$.

The participant with unsatisfactory hippocampal segmentations from the complete T1 scan had to be excluded from shape analysis as it could not be included in the generation of the study-specific template of the hippocampus. Therefore, the study-specific template of the hippocampal vertices for the shape analysis was created without this participant. Note that the manual extraction of the hippocampal volume from the brain-extracted image was successful for this participant, meaning there is a discrepancy in the number of data points between the volumetric and shape analyses.

2.2.4. Behavioural analysis

Pertaining to the third and fourth hypotheses, we aimed to explore if bilingualism as a continuous variable and also as a group variable predicts memory performance when other variables, including hippocampal volume, are accounted for. The models were built

[2] A version of Model 3 was also envisaged with L2 home and L2 social use scores as measures of bilingualism, and the interaction of two, instead of the LSBQ composite score. However, as these scores heavily contribute to the LSBQ composite score (L2 Home and L2 Social scores have 33% and 30% weighting in the BCS calculation), and they were highly correlated between them (cor = 0.95; $p<0.001$), it was deemed inappropriate to include these scores as separate predictors in the same model as they introduce significant multicollinearity issues

in a similar manner to the volumetric analysis models of the hippocampus. For this analysis, hippocampal volumes were summed across hemispheres and the total hippocampal volume was used as a predictor for memory performance.

First, we ran models to examine whether the two groups performed differently on behavioural tasks, with age included as a nuisance covariate. Then, BCS was examined as a predictor for performance in individual memory tasks, controlled for age, education, and total hippocampal volume. This included running separate models for all three memory performance measures – NIH toolbox episodic memory score, NIH toolbox working memory score and ACE-III memory score. In Model 4 each memory measure as a dependent variable was predicted by age and education as independent variables. In the following step, Model 5, total hippocampal volume was added to the list of independent variables. Finally, LSBQ BCS was added as an independent predictor in Model 6. All continuous variables were mean-centred.

2.3. Results

2.3.1. Neuroimaging results

2.3.1.1. Volume

Our between-groups comparison revealed a significant main effect of bilingualism on the hippocampus volume ($p<0.05$), where non-native speakers of English exhibiter larger hippocampal volume. There was no significant main effect of hemisphere ($p=0.82$), nor a significant hemisphere by language group interaction ($p=0.66$) (see Fig. 1). This result suggests that overall bilingual individuals have increased hippocampal volume bilaterally.

The next set of analyses (see Table 2.4) used hierarchical regression models to investigate whether the observed increased hippocampal volumes can be predicted by the amount of bilingual experience. Results from Model 1 revealed a significant negative effect of age, such that with increasing age the observed hippocampus volumes became smaller, and a significant positive effect of education where higher educational attainment predicts higher hippocampal volume. No significant effects of hemisphere were observed.

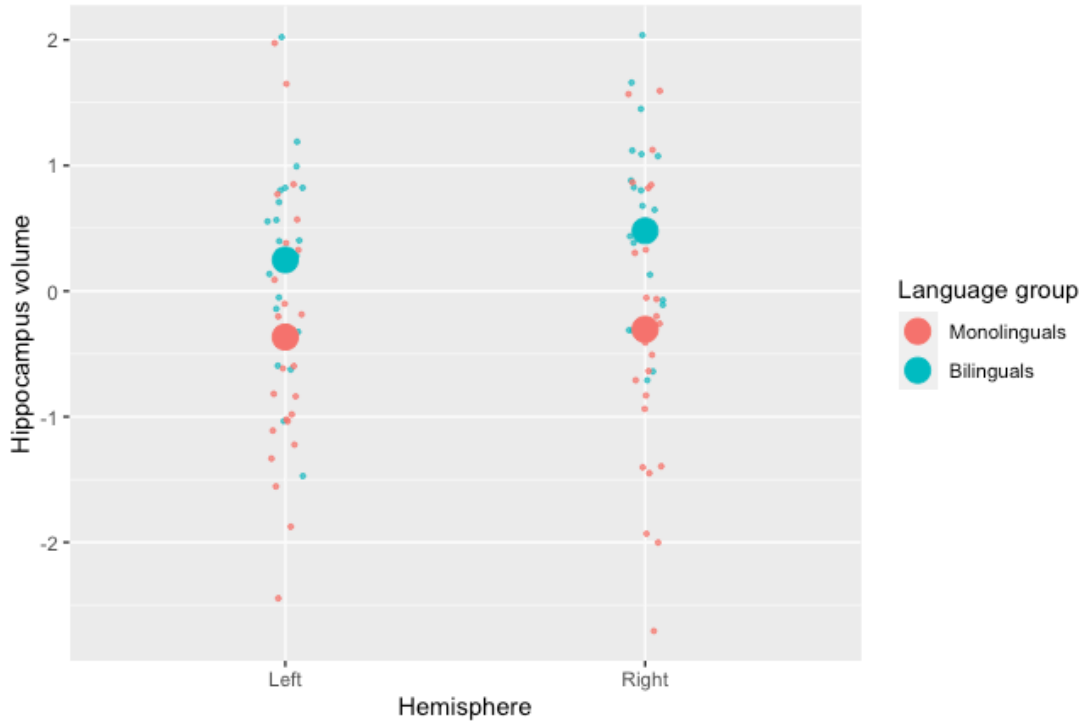

Figure 2. 1. Effect of language group by hemisphere on the hippocampus volume (Study 1)

Results from Model 2 revealed that age and education remained significant contributors to the hippocampal volume, whereas hemisphere was not. Moreover, overall composite memory performance, measured by the memory subdomain of ACE-III, correlated positively with hippocampal volume, whereas performance in the episodic memory task of the NIH toolbox correlated negatively, and performance in the working memory task of the NIH toolbox was not significantly associated with hippocampal volume

Finally, Model 3 revealed that, while the effects of age, education, and episodic memory performance remained significant, BCS also emerged as a highly significant unique contributor to the hippocampal volume, with higher BCS being positively associated with hippocampal volume (see Fig. 2.2).

Akaike Information Criterion (AIC) was established for all models to determine the goodness of fit and choose the most appropriate model for the data. The lowest AIC, indicating the best model fit for the data was for the most complex model (Model 3).

Table 2. 4. Hippocampal volume model comparison (Study 1)

	Model 1					Model 2					Model 3				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	-2.599 ***	0.008	-0.065	-0.476	**<0.001**	-2.599 ***	0.008	-0.065	-0.502	**<0.001**	-2.599 ***	0.007	-0.065	-0.522	**<0.001**
Age	-0.013 *	0.006	-0.230	-2.297	**0.024**	-0.019 **	0.006	-0.323	-3.200	**0.002**	-0.014 *	0.006	-0.234	-2.293	**0.024**
Education	0.014 *	0.006	0.232	2.319	**0.023**	0.018 **	0.006	0.303	3.095	**0.003**	0.016 **	0.006	0.278	2.943	**0.004**
Hemisphere	0.008	0.011	0.130	0.673	0.503	0.008	0.011	0.130	0.710	0.479	0.008	0.010	0.130	0.738	0.462
ACE-III memory performance						0.013 *	0.006	0.229	2.424	**0.017**	0.009	0.006	0.150	1.579	0.118
NIH toolbox episodic memory performance						-0.017 **	0.006	-0.284	-2.662	**0.009**	-0.018 **	0.006	-0.300	-2.919	**0.004**
NIH toolbox working memory performance						-0.008	0.006	-0.132	-1.388	0.169	-0.008	0.005	-0.141	-1.541	0.127
LSBQ Bilingualism Composite Score											0.017 **	0.006	0.289	2.867	**0.005**
Observations	96					96					96				
R^2 / R^2 adjusted	0.138 / 0.110					0.251 / 0.201					0.315 / 0.261				
AIC	-278.580					-286.134					-292.704				

** p<0.05 ** p<0.01 *** p<0.001*

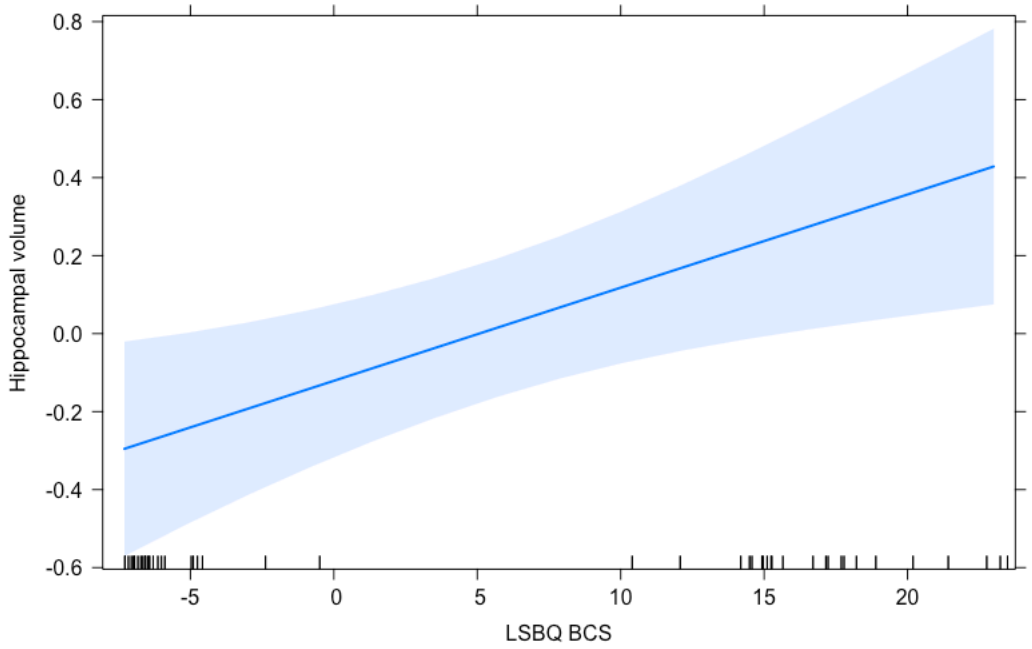

Figure 2. 2. Main effect of the LSBQ Bilingualism Composite Score on the hippocampal volume (Model 3) (Study 1)

2.3.1.2. Shape

Vertex analysis revealed no significant local expansions or contractions of the bilateral hippocampus as a function of BCS.

2.3.2. Behavioural results

Group performance in the three memory tasks is illustrated in Figures 3-5. No significant between-groups differences emerged for any of the memory scores, although there was a trend for bilinguals to perform better in the ACE-III memory domain ($p=0.054$). However, it is difficult to interpret these results due to the near ceiling effect in ACE-III (see Fig. 2.3) – this was to be expected due to the nature of the test, which is to act as a dementia screening tool.

In the hierarchical regressions relating BCS as a continuous measure of bilingualism the results were as follows. For the NIH toolbox working memory task hierarchical regressions showed that none of the predictors (age, education, total hippocampal volume, BCS) significantly explained working memory performance (see Table 2.5).

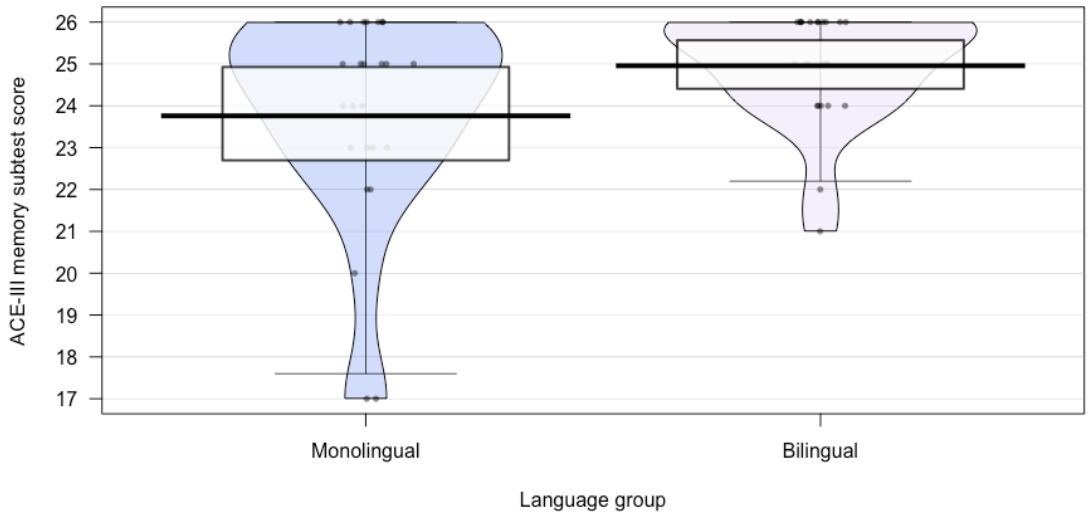

Figure 2. 3. ACE-III memory performance measure by language group (Study 1)

For the NIH toolbox episodic memory task, age was a significant predictor in the Model 4 and remained a significant predictor in Models 5 and 6, so that with increased age episodic memory performance is subject to decline. Education was a significant positive predictor in Models 5 and 6. Hippocampal volume also predicted episodic memory performance in Model 6, however, the relationship was negative. In Model 6, BCS did not significantly contribute to episodic memory performance. From all three models Model 6 was also the best fit for data with an adjusted R^2 of 0.239 and the lowest Akaike Information Criterion indicating the best fit (see table 2.6).

For the ACE-III cognition battery memory domain, across all three models no independent variables significantly predicted composite memory performance, apart from a trend for BCS in Model 6 (p=0.064), suggesting that higher BCS might predict better performance in the ACE-III memory domain (see table 2.7).

Unlike the models explaining the volumetric variation of the hippocampus as a result of demographic variables, memory performance, and bilingualism, these linear regression models explaining the variance in memory performance were not a good fit for the data. In all cases, model comparison revealed the increasingly complex models not to improve their explanatory power over the data. The only exception to this were models explaining NIH episodic memory scores as a function of the above described IVs, where most complex model offered a marginal improvement over the simpler models (p=0.059). Therefore, only the episodic memory performance can be measured as a

function of age, education, hippocampal volume, and bilingualism. See hierarchical regression model comparison for all three memory scores in tables 2.5-2.7.

2.4. Discussion

In the present study we examined the effects bilingualism might have on the ageing brain with a particular focus on the hippocampus and related cognitive abilities. The hippocampus is a structure subject to volumetric decline with ageing (Fjell et al., 2009). Bilingualism on the other hand has been shown to reinforce the structure of a variety of brain regions, including the hippocampus (Pliatsikas, 2020), an effect that could bolster neural and cognitive reserves in the older age (Perani & Abutalebi, 2015), processes that have direct implications in variability of ageing trajectories (Anderson et al., 2020). This is of particular importance with respect to the hippocampus, because any reinforcement of this structure might have important implications for memory abilities in older age, but also in the timing for conversion from healthy ageing to dementia (Fotuhi et al., 2012). Indeed, the hippocampus has been shown to change in shape and increase in volume following intensive, immersive language experiences, particularly in young adult populations (DeLuca, Rothman, & Pliatsikas, 2019; Li et al., 2017; Mårtensson et al., 2012).

Our results corroborate those of previous studies and extend them to older populations that are immersed in bilingual environments (but see Olsen et al., 2015). Specifically, long-term immersive engagement in our sample was revealed to have a significant positive effect on the bilateral hippocampal volume when compared to a monolingual control group. Moreover, through quantification of bilingualism and treatment of this factor as a continuum, we showed that greater engagement in second language use predicts increased hippocampal volumes. However, these volumetric differences did not translate into significant effects on the hippocampal shape; this effect is harder to interpret, but it also challenges the relationship between volume and shape as they are assessed by out tools- besides, the few available studies have, similarly to ours, typically reported effects on one metric only, not both (DeLuca, Rothman, & Pliatsikas, 2019; Li et al., 2017; Mårtensson et al., 2012). Moreover, episodic and working memory performance of our samples was also tested with three different tasks, but bilingualism was not shown to be a significant predictor on behavioural performance. The remainder of this section will discuss our structural findings against theoretical

Table 2. 5. Behavioural hierarchical regression. Performance in the NIH toolbox working memory task (Study 1)

	Model 4					Model 5					Model 6				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	-0.000	0.147	-0.000	-0.000	1.000	-0.000	0.147	-0.000	-0.000	1.000	-0.000	0.147	-0.000	-0.000	1.000
Age	-0.055	0.153	-0.055	-0.362	0.719	-0.098	0.158	-0.098	-0.624	0.536	-0.055	0.164	-0.055	-0.335	0.739
Education	0.106	0.153	0.106	0.694	0.491	0.149	0.158	0.149	0.943	0.351	0.143	0.158	0.143	0.905	0.371
Hippocampus volume						-0.173	0.161	-0.172	-1.069	0.291	-0.224	0.170	-0.222	-1.317	0.195
LSBQ Bilingualism Composite Score											0.165	0.168	0.165	0.980	0.333
Observations	48					48					48				
R^2 / R^2 adjusted	0.017 / -0.026					0.042 / -0.023					0.063 / -0.024				
AIC	142.881					143.649					144.589				

** p<0.05 ** p<0.01 *** p<0.001*

Table 2. 6. Behavioural hierarchical regression. Performance in the NIH toolbox episodic memory task (Study 1)

	Model 4					Model 5					Model 6				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	0.000	0.132	0.000	0.000	1.000	0.000	0.128	0.000	0.000	1.000	0.000	0.127	0.000	0.000	1.000
Age	-0.338 *	0.137	-0.338	-2.463	**0.018**	-0.406 **	0.138	-0.406	-2.939	**0.005**	-0.348 *	0.141	-0.348	-2.460	**0.018**
Education	0.229	0.137	0.229	1.669	0.102	0.296 *	0.138	0.296	2.143	**0.038**	0.288 *	0.136	0.288	2.116	**0.040**
Hippocampus volume						-0.270	0.141	-0.268	-1.908	0.063	-0.337 *	0.146	-0.336	-2.307	**0.026**
LSBQ Bilingualism Composite Score											0.220	0.145	0.220	1.517	0.137
Observations	48					48					48				
R^2 / R^2 adjusted	0.206 / 0.171					0.267 / 0.217					0.304 / 0.239				
AIC	132.647					130.833					130.331				

** p<0.05 ** p<0.01 *** p<0.001*

Table 2. 7. Behavioural hierarchical regression. Performance in the ACE-III memory domain (Study 1)

	Model 4					Model 5					Model 6				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	0.000	0.148	-0.000	-0.000	1.000	0.000	0.148	-0.000	-0.000	1.000	0.000	0.143	-0.000	-0.000	1.000
Age	-0.043	0.154	-0.043	-0.282	0.779	0.002	0.159	0.002	0.015	0.988	0.085	0.160	0.085	0.529	0.599
Education	0.036	0.154	0.036	0.236	0.814	-0.009	0.158	-0.009	-0.056	0.956	-0.020	0.154	-0.020	-0.129	0.898
Hippocampus volume						0.183	0.162	0.182	1.127	0.266	0.087	0.166	0.086	0.523	0.604
LSBQ Bilingualism Composite Score											0.312	0.164	0.312	1.900	0.064
Observations	48					48					48				
R^2 / R^2 adjusted	0.004 / -0.040					0.032 / -0.034					0.107 / 0.024				
AIC	143.524					144.158					142.291				

** p<0.05 ** p<0.01 *** p<0.001*

suggestions for the effects of the bilingualism on the brain, followed by a discussion on the apparent mismatch between structural and behavioural findings, and the relevant implications for cognitive ageing and bilingualism.

Our findings on hippocampal structure are in line with the hypothesis that continuous engagement with an additional language would present structural reinforcement of the brain (Borsa et al., 2018; Pliatsikas et al., 2017). Similar effects are not uncommon among studies looking at brain structure in bilingualism; indeed, there is a lot of evidence that the cognitively challenging experience of acquiring and controlling two languages leads to structural adaptations of implicated areas with the aim of achieving maximum efficiency (Hayakawa & Marian, 2019); notably these adaptations have been suggested to be dynamic in nature, with temporal tissue increases being followed by return to baseline volume but with more resilient local connections, which in turn that could be more resistant to age-related decline (Pliatsikas, 2020). Based on this, our findings can have one of two possible but interrelated explanations: first, that the observed difference reflects a volumetric increase for bilinguals, similar to what has been claimed for such findings in younger bilinguals; second, this perceived increase could actually signify *slower age-related decline* of the hippocampus for bilinguals when compared to monolinguals, therefore providing evidence that bilingualism boosts resilience against age-related deterioration of the hippocampus, what has also been characterised as a *brain reserve* (Stern et al., 2018). The particular age range of our participants, who are young enough to be cognitively healthy, but potentially on the cusp of the symptoms of cognitive and brain decline to emerge, does not allow us to differentiate between the two mechanisms, which remain equally plausible, and might even feed each other; nevertheless, evidence form this exact pivotal point in cognitive ageing might prove useful in explaining effects in later life in bilinguals, including the mechanism behind the emergence of MCI and its conversion to dementia (Berkes, Bialystok, Craik, Troyer, & Freedman, 2020; Costumero et al., 2020; Duncan et al., 2018). Notably, the finding that the bilingual experience can affect the hippocampus structurally follows from similar findings in younger bilinguals (DeLuca, Rothman, & Pliatsikas, 2019), but most importantly it constitutes the first piece of evidence that brain reserves in older bilinguals are modulated by the bilingual experience.

Finally, we also looked what effects bilingualism might have on the performance in cognitive domains typically associated with the hippocampus – most notably, episodic

memory. With the potential effects of demographic factors, such as age and educational attainment, and hippocampal volume all accounted for, bilingualism did not emerge as a significant predictor for memory performance across any of the three tests we administered.

This pattern of results calls for an explanation for the apparent discrepancy between the effects of bilingualism on brain structure and cognitive performance. Recall that the average age of our participants is 62 years, which, as already mentioned, puts them on the 'younger' end of the ageing spectrum. While some ageing processes may have already begun, these participants are still cognitively healthy individuals with no signs of memory impairment, which is also attested by the near-ceiling score of both groups in the ACE-III memory domain. Nevertheless, our structural findings indicate that the processes that underlie the building of a brain reserve in bilinguals are already in action, but without measurable equivalents in behaviour. This pattern is reminiscent of recent evidence suggesting that the mapping of behaviour to brain *function* is also not straightforward, at least in healthy populations (DeLuca et al., 2020), and further suggests that studying task performance alone might not be sufficient to assess the effects of bilingualism on the brain.

Our findings call for further and more focused investigations on the effects of bilingualism on the ageing brain, and in particular on age ranges similar to ours, where the first signs of cognitive decline might emerge. Moreover, longitudinal designs would allow to further examine the underlying mechanisms in more detail, including their onset and trajectory, as well as the factors they may interact with. Importantly, such designs should not just account for bilingualism as a categorical variable, but also look at the extent of it, based on linguistic experiences and patterns of language use. Examining bilingualism as a continuous variable allows to account for within groups variability which may be lost in a more classically defined monolingual vs bilingual groups comparison (Leivada, Westergaard, Duñabeitia, & Rothman, 2020; Luk & Bialystok, 2013; Surrain & Luk, 2019). Moreover, focused studies similar to this one, are required with clinical populations too, to add to a small but growing literature that will help us better understand the potential clinical implications both in healthy and pathological ageing (Voits, Pliatsikas, Robson, & Rothman, 2020).

To conclude, the results of this study contribute to the literature examining the effects of bilingualism on ageing; specifically, we have shown greater volume of the

hippocampus on bilinguals vs monolinguals, which is also predicted by the amount of bilingual experiences; these findings were not accompanied by comparable effects of bilingualism in episodic memory performance. These findings shed further light on how speaking more than one language may contribute to building up of a brain reserve in the older age. Moreover, the results of this study further our understanding on the effects immersive, long-term bilingualism confer to the brain structure and memory performance in the later years of life.

CHAPTER 3: BILINGUALISM-RELATED NEURAL ADAPTATIONS IN MILD COGNITIVE IMPAIRMENT PATIENTS ARE MODULATED BY LANGUAGE EXPERIENCES

Abstract

Bilingualism has been shown to contribute to neurocognitive adaptations in the older age. Most notably, bilingualism has been widely reported to delay the onset of symptoms and diagnosis of Alzheimer's Disease. Most studies linking bilingualism and clinical neurodegeneration do so via behavioural measures; structural and/or functional brain data are seldom available. Moreover, bilingualism is often operationalised as a dichotomous group factor, despite it being a nuanced experience, which may result in distinct neurocognitive adaptations. Herein, we present a study of bilingual MCI patients who differ in their language engagement, namely, active bilingual speakers of Spanish and Catalan and bilinguals who have a good receptive comprehension of both languages. We relate bilingual engagement, cortical and subcortical grey matter structure volume, episodic memory performance, and age of symptom onset and MCI diagnosis. The results reveal active bilingualism statistically significantly delays the onset of MCI symptoms. Active bilingualism is also shown to result in increased cortical grey matter in the right supramarginal gyrus, increased bilateral hippocampal volume and reshaping of the right amygdala and right caudate nucleus. Nevertheless, neither bilingualism nor hippocampal volume predict episodic memory performance in these clinical populations.

3.1. Introduction

The management of more than one language in the brain is a cognitively demanding task. It requires constant conflict resolution, as competing mental representations of all languages available to the bilingual individual are always active (Kroll & Bialystok, 2013; Marian & Spivey, 2003). Although this management might seem effortless, it places increased demands on cognitive control resources for selecting the appropriate language in a given communicative context, monitoring use and controlling intrusions from other languages available to the bilingual individual (Green, 1998). This leads to neurocognitive adaptations (Green & Abutalebi, 2013) that can be observed at all stages of life, from bilingual children to older adults (Bialystok, 2017). In particular, the neurocognitive differences between monolingual and bilingual individuals seem to be more pronounced in the later years of life (Bialystok et al., 2004), and interact with typical cognitive and neural decline (Zhang et al., 2020). The remainder of this introduction will focus on evidence from ageing bilinguals, including healthy populations and patients diagnosed with mild cognitive impairment (MCI) and Alzheimer's dementia.

3.1.1. Bilingualism and healthy ageing

In terms of cognition, healthy older bilinguals have been shown to outperform monolingual individuals in executive functioning (Bialystok et al., 2004; Del Maschio, Sulpizio, et al., 2018; Gold, Kim, et al., 2013), episodic memory (Ljungberg et al., 2013; Schroeder & Marian, 2012), and working memory (Bialystok, Poarch, et al., 2014).

Alongside cognitive adaptations, bilingualism has been shown to lead to structural and functional changes in the healthy ageing brain, particularly in brain areas and networks supporting bilingual language control, domain-general executive control, and language processing, as these networks are at least partially overlapping (Calabria et al., 2018). The lifelong demands for language control and processing that bilingual experience is argued to induce puts additional burden on implicated brain areas. In turn, this leads to adaptions in their structure and integrity, a process that is likely to underlie the observed behavioural effects (Gold, 2015). Such adaptations can be observed in both cortical and subcortical grey matter as well as in white matter, and are shown to be sensitive to individual differences within bilingualism, at least in younger bilinguals (Li, Legault, & Litcofsky, 2014; Deluca et al. 2019, 2020). Specifically, larger grey matter volume has been observed in an array of structures and areas which are implicated in

cognitive control, such as bilateral inferior parietal lobules (Abutalebi, Canini, et al., 2015), anterior cingulate cortex, prefrontal cortex (Abutalebi, Guidi, et al., 2015; Del Maschio, Sulpizio, et al., 2018), anterior temporal lobe (Abutalebi et al., 2014), bilateral hippocampus (Voits, Robson, Rothman, & Pliatsikas, 2020) and the amygdala (Li et al., 2017). Increasing age has been linked to decreasing temporal pole cortical thickness in monolinguals, but no such relationship has been observed for bilinguals (Olsen et al., 2015). In terms of white matter, older bilinguals have increased white matter volume in frontal and temporal lobes (Olsen et al., 2015). Bilingualism is also associated with greater white matter integrity in the older age across the corpus callosum, and other white matter tracts (Anderson, Grundy, et al., 2018; Luk et al., 2011). However, even though these increases in white and grey matter volumes systematically suggest a build-up of additional neural tissue, these differences even out with age, as the slope of neural decline in healthy bilinguals tends to be steeper (Heim et al., 2019). Bilingualism also contributes to changes in functional connectivity in the older age, which seem to relate to adaptations in structural connectivity, as measured by WM integrity (Luk et al, 2011). For example, bilinguals exhibit enhanced posterior functional networks, countering the opposite effect normally associated with ageing (de Frutos-Lucas et al., 2020), frontoparietal control network and default mode network (Grady et al., 2015) than monolinguals. This is interpreted as increased neural efficiency of these networks. The evidence so far suggests that bilingualism results in an increased brain reserve (Satz, 1993) in healthy ageing. Brain reserve can be thought of as a build-up of structural reinforcement, a "scaffolding" of sorts leading to increased number of synapses and increased myelin, which allows for a longer time before age- or disease-related changes in the behaviour manifest (Stern et al., 2018). There are two possible explanations for the discrepancies between monolinguals and bilinguals. Either bilinguals experience growth and volumetric increases of their brain structures, when compared to monolinguals, or monolinguals experience sharper decline with age. Nonetheless, both of these can be explained as increased brain reserve in bilinguals. Direction of effects is not easy to determine in cross-sectional studies in the absence of longitudinal investigations.

3.1.2. Bilingualism and dementia

This reinforcement seems to play a role in cases when healthy ageing individuals convert to clinical neurodegeneration. Perhaps the most staggering finding linking

bilingualism and dementia reveals that speaking more than one language delays the onset of dementia symptoms by as much as 4-5 years (Alladi et al., 2013; Bialystok et al., 2007; Craik et al., 2010; Woumans et al., 2015; Zheng et al., 2018). Although some studies show null results (i.e., no difference in onset of dementia symptoms between monolingual and bilingual populations) (Ljungberg, Hansson, Adolfsson, & Nilsson, 2016), or have suggested that the effects of bilingualism may be difficult to disentangle from other co-occurring factors (Calvo, García, Manoiloff, & Ibáñez, 2016; Lawton et al., 2015; Mukadam et al., 2017; Van den Noort et al., 2019; Zahodne et al., 2014), recent meta-analyses of the available literature establish a clear effect of bilingualism as an independent factor leading to a later diagnosis of Alzheimer's disease (Anderson et al., 2020; Paulavicius et al., 2020), although the incidence of AD is not reduced (Brini et al., 2020).

Unlike the findings linking bilingualism to increased neural reserve in healthy ageing, the findings in clinical populations point to a different direction. Although there is a relative dearth of studies on the topic in clinical populations, available results suggest that bilinguals with dementia, matched for cognitive status with monolinguals, exhibit *more* brain atrophy in brain areas associated with Alzheimer's dementia (see Mendez, 2019 for review), such as the medial temporal lobe (Schweizer et al., 2012). These findings have been corroborated by Duncan and colleagues (2018), who found bilingual individuals with AD to have sustained more degeneration in the parahippocampal gyri and rhinal sulci (related to memory function), while performing at the same level in the memory domain as their monolingual counterparts (note that similar effects on the white matter have also been reported in a single study with healthy bilingual populations (Gold, Johnson, et al., 2013)). Bilingualism in clinical populations is also associated with significant reduction of glucose metabolism across frontotemporal and parietal regions, as well as the left cerebellum in matched participant groups (Kowoll et al., 2016) (see also Perani et al., 2017).

In sum, for bilingual populations who suffer from clinical neurodegeneration, and Alzheimer's disease more specifically, the ability to maintain a level of cognition seems to be better than expected for the extent of sustained brain atrophy. That is, the brain is likely able to compensate for neurodegeneration by recruiting alternative networks for maintaining aspects of cognition when facing brain atrophy. These effects of bilingualism

can be operationalised as cognitive reserve (Abutalebi & Green, 2016; Perani & Abutalebi, 2015).

Brain reserve and cognitive reserve are, therefore, two mechanisms that help alleviate any symptoms of healthy and clinical ageing. Commonly brain reserve can be observed in healthy ageing, where there is an extra "neurobiological capital" that can be observed via brain imaging techniques. On the contrary, higher cognitive reserve is commonly observed in cases of clinical neurodegeneration, where high cognitive reserve individuals with more pronounced atrophy can cognitively perform above what would be expected (Stern, 2002; Stern et al., 2018). The concepts of brain reserve and cognitive reserve are not unique to bilingualism – various other factors such as education, engagement in mentally stimulating leisure activities, occupational attainment have been shown to contribute to building up of these reserves and delay the onset of dementia (Valenzuela & Sachdev, 2006). To sum up, bilingualism, among other factors, has been increasingly recognised as a significant contributor factor to cognitive and brain reserves in the older age (for a recent overview, see Gallo, Myachykov, Shtyrov, & Abutalebi, 2020).

Taking all the evidence into account, it becomes apparent that, rather than preventing the brain from the deterioration effects of AD itself, bilingualism contributes to accruing of cognitive reserve, which compensates for the effects of neurodegeneration at the behavioural level. In other words, bilinguals mask the symptoms of disease progression via increased resilience in cognitive functioning despite significant underlying brain decay. While most research has been focussed on the clinical effects of bilingualism as a reserve factor in AD there are good reasons to consider related effects in other types of clinical neurodegeneration too (Voits, Pliatsikas, et al., 2020). Nevertheless, it remains important to investigate the interaction between different reserve mechanisms and cognitive aging. Bilingualism is established as a contributor factor to cognitive and brain reserves and studying it further might shed light on the exact nature of manifestation of said reserves. In other words, it is crucial to learn whether and how the bilingual brain resorts to resources accumulated from long-term experience in dual language use, when faced with disease. Perhaps the best avenue is the study of Mild Cognitive Impairment (MCI), an important pivotal point in transitioning from healthy ageing to disease.

3.1.3. On the cusp between healthy ageing and dementia: evidence from MCI

In comparison with literature on bilingualism effects in healthy ageing or Alzheimer's Disease, bilingualism effects in MCI has been subject to less research. MCI is defined as a memory impairment that is more severe than would be expected in healthy ageing, but not severe enough to warrant a dementia diagnosis (Kelley & Petersen, 2007). While MCI is a risk factor for onset of Alzheimer's disease, MCI patients may not progress to Alzheimer's disease or other types of dementia (Pandya, Clem, Silva, & Woon, 2016).

Similarly to findings linking Alzheimer's disease symptom onset and bilingualism, MCI onset is delayed in bilinguals when compared to matched monolinguals (Berkes et al., 2020; Bialystok, Craik, Binns, Ossher, & Freedman, 2014; Ossher, Bialystok, Craik, Murphy, & Troyer, 2013). Delay in onset of MCI symptoms is even more impressive than Alzheimer's disease, with some studies finding a delay of onset up to 7.7 years when compared to monolingual individuals (Ramakrishnan et al., 2017). Higher levels of foreign language and music instruction during childhood and adolescence are found to be associated with lower risk of developing MCI in the old age (Wilson, Boyle, Yang, James, & Bennett, 2015). However, the delay of symptom onset and diagnosis may be conditional on whether both languages are actively used, as opposed to passive understanding without active engagement (Calabria, Hernández, et al., 2020).

Evidence so far suggests that, at the brain level, bilingualism in MCI is mostly associated with increased structural reinforcement, i.e., building up of brain reserves; notably, the findings in MCI patients seem to affect the same regions that are shown to be affected by Alzheimer's disease (Voits et al., 2020), including medial temporal lobe structures, such as the hippocampus, implicated in AD neuropathology and decline of episodic memory. However, the evidence remains inconclusive. Duncan et al. (2018) examined monolingual and bilingual patient groups with MCI, that were matched for demographic and cognitive variables. The results showed that MCI bilingual patients exhibited thicker cortex across areas implicated in language and cognitive control, as well as areas that are known to be sensitive to neurodegeneration. Namely, there was an effect of bilingualism on the bilateral inferior frontal gyri, left medial frontal gyrus, right ventromedial prefrontal cortex, bilateral anterior temporal gyri, left parietal lobule and bilateral cerebellum, where bilingualism was linked to greater grey matter density.

Bilingualism was also associated with greater grey matter volume in the entorhinal cortex and the bilateral hippocampus. Bilingual MCI patients also exhibited a trend for higher tissue density in the bilateral parahippocampal gyri and bilateral rhinal sulci than monolinguals, suggestive of a brain reserve in these areas. Correlations were also found between episodic memory recall scores and cortical thickness in language and cognitive control areas including the left inferior frontal gyrus, left anterior temporal gyrus, left supramarginal gyrus and the right cerebellum, indicating that this network is responsible for maintenance of memory function, typically affected by clinical neurodegeneration. This observation was further supported by a recent study, where evidence suggestive of a bilingualism-related brain reserve was found in the ventral diencephalon, the thalamus and the brainstem in patients with probable AD (i.e., exhibiting AD symptoms, but diagnosis not confirmed with biomarker evidence) (Raji, Meysami, Merrill, Porter, & Mendez, 2020). However, in a prospective longitudinal study of monolingual and bilingual MCI patients, bilinguals exhibited *less* whole-brain parenchymal volume, with this effect being most pronounced in the right supramarginal gyrus and the left lingual gyrus, while cognitively performing on the same level (Costumero et al., 2020). In the follow-up scan 7 months later, monolinguals had lost more parenchymal volume and also experienced comparatively more cognitive decline than bilinguals. This indicates cognitive reserve in bilingual MCI patients and also bilingualism being a factor that delays the worsening of cognitive symptoms of MCI to potential next stages of AD. In addition, a recent study focussing on verbal and non-verbal memory in MCI, found that bilinguals and monolinguals did not differ on hippocampal volumes, yet bilinguals performed better on some memory measures (Rosselli et al., 2019). Finally, changes in white matter integrity in bilingual and monolingual individuals with MCI are mixed with bilinguals simultaneously exhibiting decreased and increased regional white matter integrity across the brain (higher mean diffusivity in the fornix, but lower mean diffusivity in the parahippocampal cingulum, and lower radial diffusivity in the right uncinate fasciculus) (Marin-Marin et al., 2019).

In sum, bilingualism has been shown to interact with the brain and cognition in healthy and clinical ageing. Data supporting interpretation of brain reserve is usually seen in healthy individuals, which seems to contribute to later onset of MCI at the earlier stages of disease progression. At the same time, conversion of MCI to AD is more rapid in bilingual populations, other demographic factors being accounted for (Berkes et al.,

2020). This might be explained by structural brain reserves being exhausted at the MCI stage of neurodegeneration. The exact ways brain reserve and cognitive reserve interact and complement each other is not clear. There may be an inflection point where cognitive reserve manifests after brain reserve gets exhausted, or there may be a more complementary nature of the interaction of these reserves. As MCI lies in a transitionary stage between healthy ageing and Alzheimer's disease, it is important to examine whether bilingualism is associated with brain reserve (like in healthy ageing) or cognitive reserve (like in Alzheimer's disease) in this patient group, or the interaction of the two.

3.1.4. This study

In the present study we sought to investigate the effects of bilingualism on brain structure and memory performance in an MCI patient population using structural MRI and behavioural testing. In line with previous results in the literature, we expected bilingual experience to predict delayed onset of MCI symptoms, and manifest as more preserved brain structures, i.e., data which can be interpreted as brain reserve. As bilingualism is shown to affect different cortical regions of the brain and subcortical structures, such as the striatum (consisting of the caudate nucleus and putamen) and the hippocampus, we expected active bilinguals to present with volumetric increases in these regions. Furthermore, we explored cognitive outcomes associated with medial temporal lobe structures. These structures are involved in episodic memory performance – a cognitive function sensitive to clinical neurodegeneration and ageing. If active bilingualism leads to more preserved cognition, we expected to see a positive association between the bilingual experience, medial temporal lobe structure volumes, and episodic memory performance.

In doing so, we chose to move away from traditional cross-sectional comparisons and, instead, view bilingualism as a continuum of experiences. If one looks at bilingualism as a spectrum, rather than a monolingual-bilingual dichotomy, there is no need for a monolingual control group; instead it is possible to further examine neurocognitive differences driven by individual-level factors within bilingualism. This follows from recent studies highlighting the need to consider the granularity and the dynamic nature of the bilingual experience with many contributing factors to it and, as such, cannot be painted black and white (Leivada, Duñabeitia, et al., 2020).

There is a scarcity of studies, especially in the older clinical populations, where bilingual language use patterns are accounted for. This dictates a need for closer inspection of said factors, such as age of acquisition, L2 proficiency, language use patterns, etc., (DeLuca, Rothman, Bialystok, & Pliatsikas, 2019; Luk & Bialystok, 2013) that differentially modulate neural adaptations (DeLuca, Segaert, et al., 2020; Pliatsikas, 2020; Pliatsikas et al., 2020). This more nuanced approach on bilingualism is especially important in ageing populations as better understanding the effects of bilingualism in this age group may carry clinical implications. If bilingualism can allow for an extension lasting multiple years of healthy cognitive ageing, it is important to understand what are the conditions under which these effects can manifest (Del Maschio, Fedeli, & Abutalebi, 2018). Adaptations and protective effects in ageing may be driven by regular exposure and use of second language (e.g., Borsa et al., 2018). For the above reasons, in this study we looked at a participant sample that were all bilingual in Spanish and Catalan and they differentiate in their extent of active engagement in Catalan. We operationalised bilingualism as a continuum, based on participant self-reported ability to converse in both Spanish and Catalan, as well as their engagement in the use of both languages. Alongside with the bilingualism-as-a-spectrum approach, the participants were placed in either 'active' or 'passive' bilingual groups, with those who reported being able to speak Catalan alongside Spanish considered active bilinguals. All participants spoke Spanish. Use of Catalan, alongside Spanish, in their everyday life was the main between-groups differentiator. Particularly, we sought to examine the effects of regular active bilingual engagement on brain structure and cognition. The data were analysed in two ways, using bilingualism both as a categorical and a continuous variable.

3.2. Materials and methods

3.2.1. Subjects

Forty patients with a diagnosis of MCI were recruited for the study (12 women) with a mean age of 73.75 (SD = 4.27). Detailed language and demographic information data were collected. Participants were subject to structural MRI scanning; T1 scans were obtained. The majority of the patients reported Spanish as their L1 (N=30), 9 participants spoke L1 Catalan, and one participant spoke L1 Galician. Second languages, other than Spanish or Catalan, were not reported. All participants self-reported early exposure (most

at birth, a few at ages 4-6) and high fluency in Spanish, with variable exposure, engagement and fluency in Catalan. Due to issues in MRI processing (see MRI data processing below), two participants were excluded from the analysis. The final analysis was conducted on a sample of 38 bilingual individuals. Subjects reported a variable age of MCI symptom onset (range 58-80) (based on a report of the relatives or according to the clinical history) and formal MCI diagnosis (59-81) (see table 3.1.). The data were collected from 4 hospitals in Catalonia, Spain. All subjects were residents in Spain, were self-reported highly proficient users of Spanish, and had at least a passive understanding of Catalan (see table 3.2).

Table 3. 1. Group and overall demographics; in age, education, MMSE status, cognitive reserve index, age of MCI diagnosis, and symptom onset (Study 2)

	ACT (N=23)	PAS (N=15)	Overall (N=38)
Mean age (SD)	74.7 (4.16)	73.3 (3.53)	74.1 (3.94)
Sex			
F	10 (43.5%)	2 (13.3%)	12 (31.6%)
M	13 (56.5%)	13 (86.7%)	26 (68.4%)
First language (number of speakers)			
Catalan	8 (34.8%)	0 (0%)	8 (21.1%)
Galician	1 (4.3%)	0 (0%)	1 (2.6%)
Spanish	14 (60.9%)	15 (100%)	29 (76.3%)
MMSE score			
Mean (SD)	27.2 (1.44)	27.0 (1.07)	27.1 (1.29)
Total Cognitive Reserve Index			
Mean (SD)	100 (18.3)	83.5 (11.7)	93.6 (17.8)
Age of symptom onset			
Mean (SD)	70.7 (5.07)	69.1 (4.21)	70.1 (4.75)
Age of diagnosis			
Mean (SD)	73.7 (4.31)	72.2 (4.25)	73.1 (4.29)

Depending on whether participants reported switching between languages in their everyday life, assessed by the Bilingual Switching Questionnaire (BSWQ) (Rodriguez-Fornells, Krämer, Lorenzo-Seva, Festman, & Münte, 2012), they were placed in active and passive bilingual groups. Subjects also completed the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), and Cognitive Reserve

Index questionnaire (CRIq), a tool which allows for estimation and quantification of cognitive reserve, by taking into account education, work, and leisure activities (Nucci, Mapelli, & Mondini, 2012). The CRIq, however, does not take into account the bilingual experience.

Table 3. 2. Spanish and Catalan proficiency of the subject sample (Study 2)

	ACT (N=23)	PAS (N=15)	P value
Catalan comprehension (of 4)			
Mean (SD)	3.87 (0.344)	3.07 (0.704)	**<0.001***
Catalan reading (of 4)			
Mean (SD)	3.70 (0.559)	2.13 (1.13)	**<0.001***
Catalan fluency (of 4)			
Mean (SD)	3.70 (0.703)	1.13 (0.516)	**<0.001***
Catalan pronunciation (of 4)			
Mean (SD)	3.65 (0.714)	1.13 (0.516)	**<0.001***
Catalan writing (of 4)			
Mean (SD)	2.09 (1.12)	1.00 (0)	**<0.001***
Spanish comprehension (of 4)			
Mean (SD)	4.00 (0)	4.00 (0)	n/a
Spanish reading (of 4)			
Mean (SD)	4.00 (0)	3.87 (0.352)	0.164
Spanish fluency (of 4)			
Mean (SD)	4.00 (0)	4.00 (0)	n/a
Spanish pronunciation (of 4)			
Mean (SD)	4.00 (0)	4.00 (0)	n/a
Spanish writing (of 4)			
Mean (SD)	3.57 (0.728)	3.33 (0.724)	0.343

Subjects also self-reported measures of bilingual exposure in terms of percentage of time spent in either a Spanish- or Catalan-dominant environment, where a score of 0 means Spanish-only environment, 100 means Catalan-only, whereas 50 denotes a

perfectly balanced exposure. We transformed this measure to create a 'delta bilingual use' score measure, where, regardless of whether the participant was Spanish- or Catalan-dominant the score showed the distance from monolingual end of the scale (i.e., scores of 20 and 80 are both 20 points away from the monolingual end of the scale). As a result, the 'delta bilingual use' score, used as a continuous predictor in the analyses ranged from 0 (no engagement in bilingual language use) to 50 (perfectly balanced bilingualism).

Active and passive bilingual groups were matched on age and MMSE scores, however passive bilinguals had a significantly lower cognitive reserve index ($p<0.01$). Educational attainment was not used in analyses as this was accounted for by the cognitive reserve index scores.

3.2.2. Neuropsychological Test Battery

Neuropsychological test battery included an episodic memory task, based on the recognition memory paradigm (old/new, unknown faces) (for details, see Calabria et al., 2020). In short, participants were shown 30 greyscale photos of unfamiliar faces and asked to rate whether they found them attractive or not. Participants were also asked to try and remember the faces. This was followed by a delayed recognition task where previously seen faces were presented alongside 30 novel faces and participants had to indicate whether the stimulus was presented in the encoding phase, or not. Performance is measured as D' scores. In addition, participants completed the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Memory task, also measuring verbal episodic memory (Morris et al., 1989). This is a free recall test sensitive to dementia. The participants are presented a word list of 10 words over 3 trials with scrambled presentation order in each trial. The participants then had to recall as many words as they can.

3.2.3. MRI acquisition protocol

For the purposes of structural brain analysis, high resolution T1 anatomical scans were acquired using a 3T MRI scanner MRI data acquisition was performed on a 3T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany) using a 12-channel head coil. Participants (196 sagittal slices, 1mm slice thickness, TR=9.532ms, TE=3.716ms, flip angle = 12°, matrix 256x256, voxel size 1mm isotropic).

3.2.4. MRI data processing

3.2.4.1. Preprocessing

Structural neuroimaging data were pre-processed and analysed with software pipelines in FSL 5.0.9 (Smith et al., 2004). All T1-weighted scans were anatomically pre-processed using the fsl_anat pipeline. Brain extraction tool (BET), a part of the fsl_anat pipeline was used for skull stripping the native T1 images and bias field correction as part of the pipeline. The brain extractions were visually checked for quality control, which revealed unsatisfactory brain extractions for six participants. For these participants, the bias field-corrected T1 images were skull stripped manually by applying custom brain extraction parameters in BET, which resulted in successful brain-extraction.

3.2.4.2. Volumetric and shape analysis of the subcortical structures

We used FIRST, a toolbox of FSL, to create segmentations of subcortical structures, using the run_first_all processing pipeline in FSL 5.0.9. FIRST performs registration, segmentation based on Bayesian appearance (Patenaude et al., 2011) and boundary corrections (De Jong et al., 2008) to produce segmented subcortical structures. Bias field corrected T1 anatomical images were used for the segmentation of the subcortical structures in FIRST. The segmentations were then visually inspected by two researchers by overlapping them on the native T1 structural images using fsleyes. Segmentations failed for two subjects which were subsequently excluded from further subcortical analyses. The remainder of subcortical extractions were deemed to be of satisfactory quality. Subcortical raw volumes were calculated using the fslstats tool and corrected for total intracranial volume prior to further statistical analyses.

For the volumetric analyses, we implemented fixed effects models in R 4.0.0. We ran two sets of models. The first set operationalised bilingualism as a group variable (i.e., active vs. passive bilinguals), whereas the second treated bilingualism as a continuous variable based on the extent of bilingual language engagement (i.e., the ‘delta bilingual use’ score). The linear models were implemented to establish the relationship between the bilingual experience, and volumes of subcortical regions of interest, shown to be sensitive to bilingualism in ageing individuals (the hippocampus, caudate nucleus, amygdala, and the putamen). Models 1a and 1b looked at the effects of bilingualism on the hippocampus. Models 2a and 2b looked at the effects of bilingualism on the caudate

nucleus; Models 3a and 3b on effects of bilingualism on the amygdala; and finally, models 4a and 4b on the effects of bilingualism on the putamen. Models 'a' treated bilingualism as a dichotomous variable, while models 'b' employed 'delta bilingualism score' as a continuous measure of bilingualism. For all models we used normalised bilateral subcortical structure volumes as dependent variables. Along with the measure of bilingualism, the models included covariates of age, total cognitive reserve index scores, and hemisphere.

For the shape analysis, as part of the FIRST pipeline, two separate vertex analyses were performed on all extracted subcortical structures of interest. In the first analysis, the design matrix, implemented in FSL, compared the shape differences between active and passive bilingual groups; in the second analysis we used the 'delta bilingual use' score as a predictor for changes in the shape in these structures. In all cases age and cognitive reserve index were included in the design matrix as nuisance covariates. The standard procedure was implemented in FIRST, each structure was linearly registered (using 6 degrees of freedom) to the sample-specific average surface, mapped in MNI space. We used the Randomise pipeline in FSL, with 10000 permutations for each factor of interest testing, and corrected for multiple comparisons using threshold-free cluster enhancement. For each participant, two spatial maps were generated showing local contractions and expansions of the structure of interest (i.e., the perpendicular vertex-wise displacement from the study-specific template average surface) as predicted by bilingual experience (both bilingualism as a group variable, and bilingualism as a continuous variable), thresholded at $p=<0.05$.

3.2.4.3. Voxel-based morphometry

Between group (i.e., active vs. passive bilinguals) and correlational analysis with 'delta bilingual use' score as a continuous predictor for voxel-wise changes in the surface grey matter volume were analysed with FSL-VBM (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimised voxel-based morphometry (VBM) protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). VBM is a method that, in its core, involves voxel-based comparison of the local grey matter between two groups of subjects, thus allowing to establish anatomical differences in the grey matter. Following this pipeline, structural images were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear

registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3mm. Finally, voxel-wise GLM was applied using permutation-based non-parametric testing with 10000 permutations, correcting for multiple comparisons across space. As with the FIRST pipeline, GLM included age and cognitive reserve index as nuisance covariates.

3.2.5. Bilingualism as a predictor for MCI onset

As above, for subcortical volumetric analyses, we built and implemented linear fixed effects models in R 4.0.0. to estimate the effects of bilingualism on the age at MCI symptom onset and age of MCI diagnosis. Two sets of analyses were carried out. First, in models 5a and 5b, bilingualism (as a group factor and as a continuous predictor respectively) and CRI total scores were used as a predictor for the age of MCI symptom onset. Then, in models 6a and 6b, the same variables were used as predictors of age of MCI diagnosis.

3.2.6. Behavioural analysis

We also carried out analysis to estimate episodic memory performance as a function of brain and behavioural data. As participants had completed two tasks tapping in the same cognitive domain (episodic memory), we performed an unrotated PCA on the face recall task D' scores and CERAD word recall scores to reduce the number of variables in the regression and create a summary score variable capturing episodic memory performance. This component captured an approximately equal amount of variance from both individual episodic memory measures (53.9% CERAD; 46.1% Face recall). Then, we ran a stepwise regression. In step 1 (Model 7), episodic memory performance was examined as a function of age, cognitive reserve index, and total hippocampal volume. This model was then expanded into two different follow-up models to account for two ways of how bilingual experience can be operationalised. In step 2a (Model 7a) bilingualism as a group variable was added as an independent predictor to the

model. In step 2b (Model 7b) bilingual engagement as ‘delta bilingualism score’ was added to the model.

3.3. Results

3.3.1. Subcortical volumetric and shape results

3.3.1.1. Between groups analyses

Bilingual engagement (‘delta bilingual use’ score) led to increased volume of the hippocampus (main effect of language group ($p<0.05$) (see tables 3.3-3.6). There was no significant main effect of bilingualism on the volume of amygdala, caudate nucleus, putamen. No significant reshaping of any subcortical structure of interest was found between active and passive bilinguals.

3.3.1.2. Correlational analyses

No significant associations were found between the volume of any of the subcortical structures of interest and ‘delta bilingual use’ score, when age, cognitive reserve index and hemisphere effects were accounted for (see tables 3.3-3.6).

Shape analysis revealed local expansions in the frontolateral right caudate (cluster of 51 voxels, peak location 70; 146; 82) and the anterior and posterior aspects of the right amygdala (a cluster of 168 voxels, peak coordinates 26, 0, -18; and a cluster of 126 voxels, peak coordinates 23; 0; -18) to positively correlate with increased bilingual engagement (see figure 3.1).

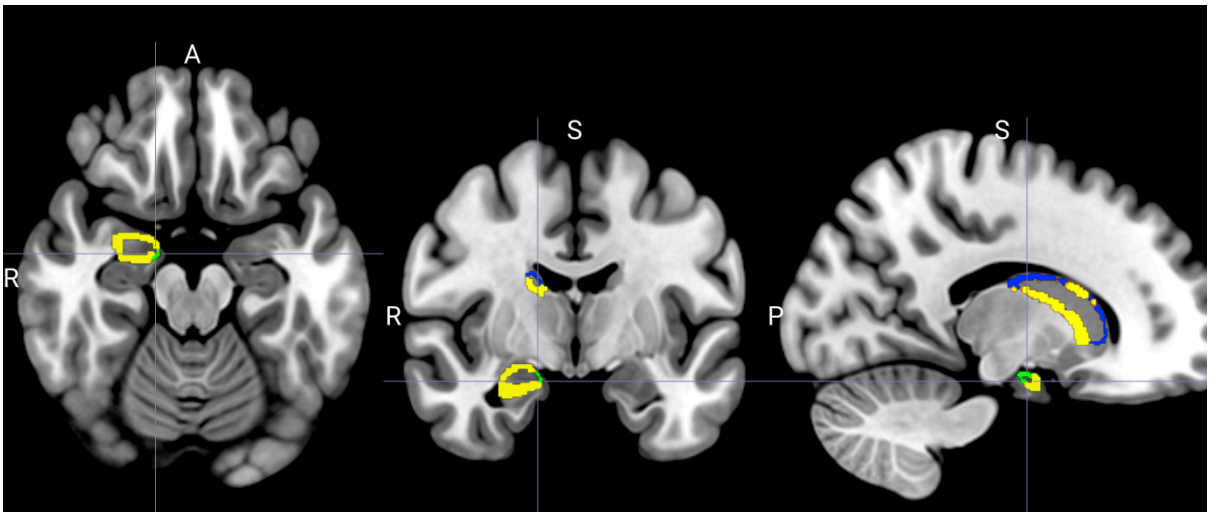

Figure 3. 1. Vertex analysis. Right caudate nucleus in blue; right amygdala in green. Yellow shows local expansions in both structures, corrected for multiple comparisons by TFCE ($p<0.05$) (Study 2)

3.3.2. Voxel-based morphometry

3.3.2.1. Between groups analyses

A whole brain VBM analysis revealed increased grey matter volume in the right supramarginal gyrus (a cluster of 53 voxels, peak voxel location 46; -30; 42) in the active bilingual vs passive bilingual group. (See figure 3.2.)

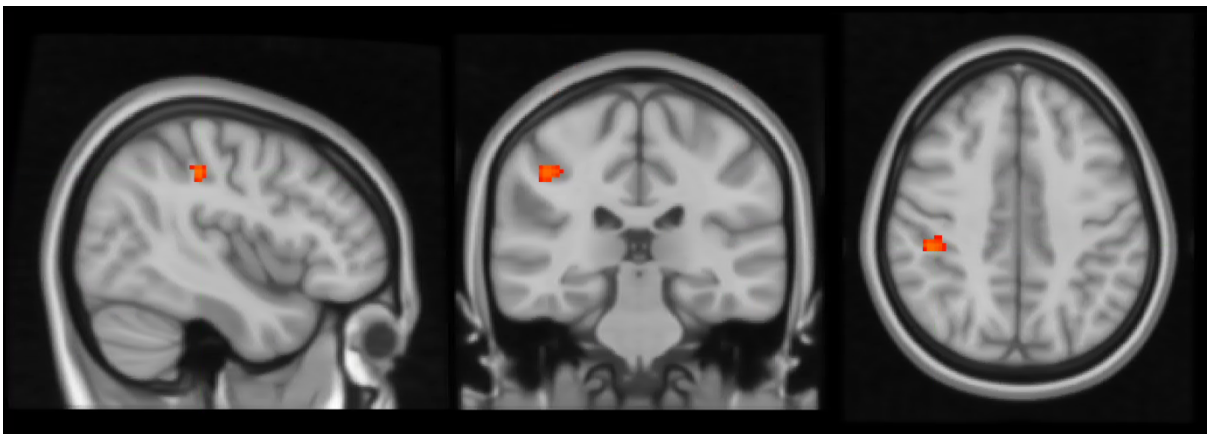

Figure 3. 2. VBM analysis. Active>passive bilinguals at $p<0.05$ (Study 2)

3.3.2.2. Correlational analyses

No significant relationship between the grey matter volume and 'delta bilingual use' score, was found in a continuous correlational design.

3.3.3. Age of MCI symptom onset/diagnosis

Active bilingualism as a group factor was associated with a later age of MCI symptom onset (Table 3.7; Fig. 3.3)

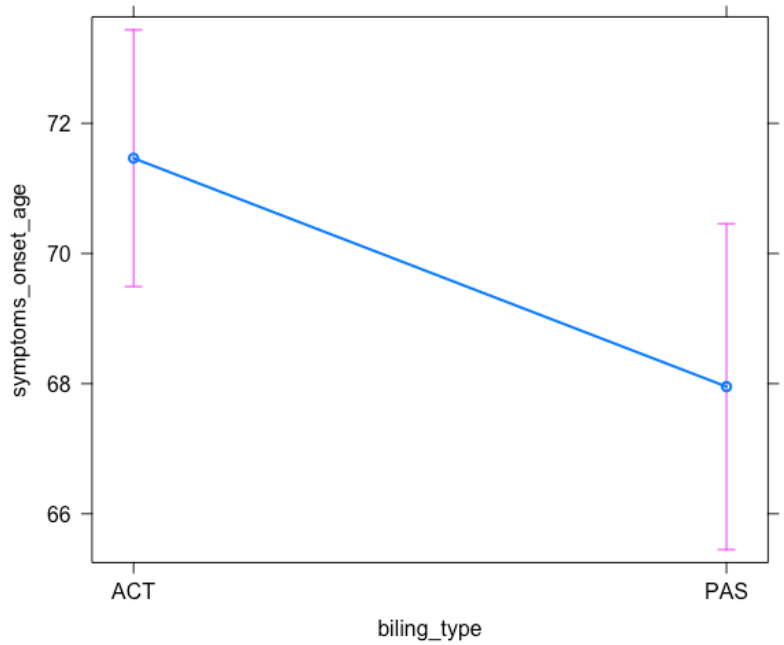

Figure 3. 3. Main effect of bilingualism (as a group factor) on age of symptom onset (ACT – active; PAS – passive bilinguals) (Study 2)

When bilingualism was treated as a continuous variable, bilingual engagement ('delta language use' score) showed a trend towards significance as predictor for both age of MCI symptom onset and also age of MCI diagnosis, when CRI total scores are included in the model as a nuisance variable (see Fig. 3.4 and Table 3.8).

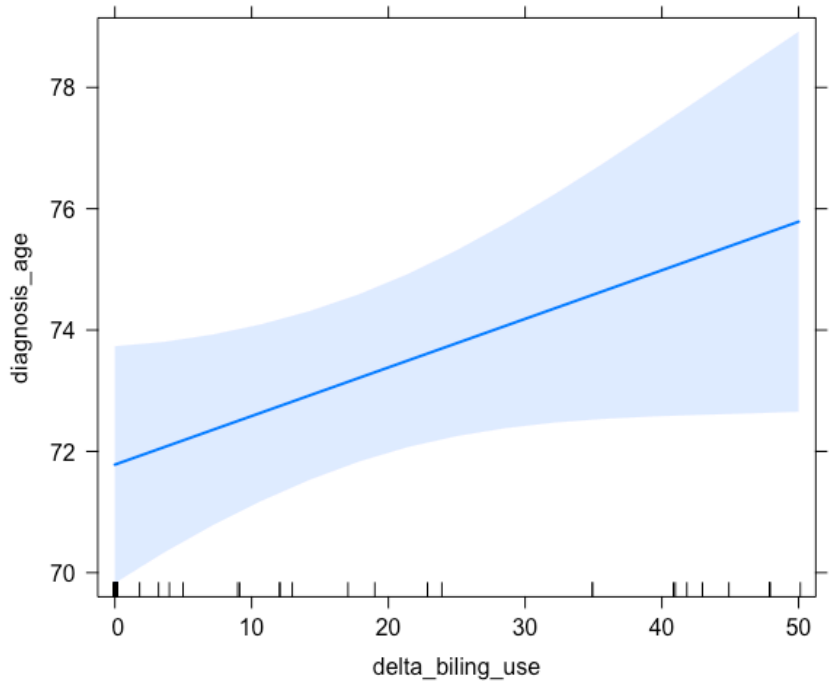

Figure 3. 4. Main effect of bilingualism ('delta bilingual use' score) on the age of diagnosis (Study 2)

3.3.4. Behavioural results: Episodic memory

A total of three models (Models 7, 7a, and 7b) were run to establish the effect of bilingualism, age, cognitive reserve index and normalised total hippocampal volume on episodic memory performance. In all three models there was only a significant positive main effect of the cognitive reserve index on episodic memory performance ($p<0.01$ in all models). Hippocampal volume and age were not significant predictors of episodic memory performance. Models where bilingualism were included also explained less variance and had higher AIC values, indicating that bilingualism does not contribute to episodic memory performance beyond other cognitive reserve factors and hippocampal volume (see Table 3.9.)

Table 3. 3. Effect of bilingualism on hippocampus volumes (Study 2)

Hippocampus volume

	Bilingualism as between-groups variable					**Bilingual engagement as continuous variable**				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	0.004 ***	0.001	0.067	0.355	**<0.001**	2.457	2.545	-0.168	-1.050	0.338
Age	-0.000	0.000	-0.163	-1.400	0.166	-0.039	0.031	-0.151	-1.241	0.219
Cognitive reserve index	-0.000	0.000	-0.033	-0.253	0.801	0.001	0.008	0.013	0.093	0.926
Bilingualism as between-groups variable	-0.000 *	0.000	-0.595	-2.241	**0.028**					
Hemisphere	0.000	0.000	0.336	1.515	0.134	0.336	0.226	0.336	1.484	0.142
Bilingual engagement as continuous variable						0.010	0.007	0.194	1.418	0.161
Observations	76					76				
R^2 / R^2 adjusted	0.115 / 0.065					0.078 / 0.026				
AIC	-990.488					220.474				

** p<0.05 ** p<0.01 *** p<0.001*

Table 3. 4. Effect of bilingualism on caudate nucleus volumes (Study 2)

Caudate volume										
	Bilingualism as between-groups variable					Bilingual engagement as continuous variable				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	5.033	2.547	-0.126	-0.659	0.052	6.263 *	2.525	-0.078	-0.490	**0.016**
Age	-0.060	0.030	-0.234	-1.978	0.052	-0.071 *	0.031	-0.279	-2.308	**0.024**
Cognitive reserve index	-0.008	0.007	-0.136	-1.037	0.303	-0.012	0.008	-0.217	-1.632	0.107
Bilingualism as between-groups variable	0.123	0.270	0.123	0.455	0.650					
Hemisphere	0.155	0.225	0.155	0.691	0.492	0.155	0.225	0.155	0.692	0.491
Bilingual engagement as continuous variable						0.005	0.007	0.101	0.743	0.460
Observations	76					76				
R^2 / R^2 adjusted	0.088 / 0.037					0.093 / 0.042				
AIC	219.650					219.283				

** p<0.05 ** p<0.01 *** p<0.001*

Table 3. 5. Effect of bilingualism on amygdala volumes (Study 2)

Amygdala volume										
	Bilingualism as between-groups variable					**Bilingual engagement as continuous variable**				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	0.001 *	0.000	0.180	0.913	**0.039**	0.001	0.000	0.118	0.731	0.199
Age	0.000	0.000	0.055	0.452	0.653	0.000	0.000	0.137	1.112	0.270
Cognitive reserve index	0.000	0.000	0.055	0.405	0.687	0.000	0.000	0.201	1.480	0.143
Bilingualism as between-groups variable	-0.000	0.000	-0.157	-0.565	0.574					
Hemisphere	-0.000	0.000	-0.237	-1.019	0.312	-0.000	0.000	-0.237	-1.034	0.305
Bilingual engagement as continuous variable						-0.000	0.000	-0.213	-1.533	0.130
Observations	76					76				
R^2 / R^2 adjusted	0.031 / -0.024					0.058 / 0.005				
AIC	-1106.722					-1108.856				

** p<0.05 ** p<0.01 *** p<0.001*

Table 3. 6. Effect of bilingualism on putamen volumes (Study 2)

Putamen volume

	Bilingualism as between-groups variable					**Bilingual engagement as continuous variable**				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	1.163	2.628	0.070	0.356	0.659	2.465	2.573	0.048	0.295	0.341
Age	-0.023	0.031	-0.090	-0.737	0.464	-0.037	0.031	-0.144	-1.173	0.245
Cognitive reserve index	0.007	0.008	0.116	0.857	0.394	0.001	0.008	0.026	0.190	0.850
Bilingualism as between-groups variable	-0.058	0.278	-0.058	-0.207	0.837					
Hemisphere	-0.095	0.232	-0.095	-0.410	0.683	-0.095	0.229	-0.095	-0.417	0.678
Bilingual engagement as continuous variable						0.011	0.007	0.206	1.482	0.143
Observations	76					76				
R^2 / R^2 adjusted	0.029 / -0.025					0.058 / 0.005				
AIC	224.403					222.132				

** p<0.05 ** p<0.01 *** p<0.001*

Table 3. 7. Effect of bilingualism on the age of symptom onset (Study 2)

Age of symptom onset										
	Bilingualism as between-groups variable					**Bilingual engagement as continuous variable**				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	82.404 ***	4.698	0.292	1.427	**<0.001**	79.194 ***	4.165	-0.000	-0.000	**<0.001**
Cognitive reserve index	-0.117 *	0.046	-0.439	-2.542	**0.016**	-0.112 *	0.047	-0.420	-2.375	**0.023**
Bilingualism as between-groups variable	-3.511 *	1.657	-0.739	-2.118	**0.041**					
Bilingual engagement as continuous variable						0.081	0.045	0.317	1.796	0.081
Observations	38					38				
R^2 / R^2 adjusted	0.178 / 0.131					0.151 / 0.103				
AIC	225.783					227.018				

** p<0.05 ** p<0.01 *** p<0.001*

Table 3. 8. Effect of bilingualism on the age of MCI diagnosis (Study 2)

Age of diagnosis										
	Bilingualism as between-groups variable					**Bilingual engagement as continuous variable**				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	80.349 ***	4.467	0.239	1.112	**<0.001**	78.572 ***	3.846	-0.000	-0.000	**<0.001**
Cognitive reserve index	-0.066	0.044	-0.276	-1.519	0.138	-0.073	0.043	-0.302	-1.672	0.103
Bilingualism as between-groups variable	-2.603	1.576	-0.606	-1.652	0.108					
Bilingual engagement as continuous variable						0.080	0.041	0.349	1.931	0.062
Observations	38					38				
R^2 / R^2 adjusted	0.090 / 0.038					0.113 / 0.063				
AIC	221.963					220.966				

** p<0.05 ** p<0.01 *** p<0.001*

Table 3. 9. Effect of bilingualism on episodic memory index (Study 2)

Episodic memory index

	Base model					**Bilingualism as between-groups variable**					**Bilingual engagement as continuous variable**				
Predictors	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*	*Estimates*	*std. Error*	*std. Beta*	*Statistic*	*p*
Intercept	-3.378	3.431	0.000	0.000	0.332	-5.151	3.924	-0.139	-0.657	0.198	-4.976	3.811	0.000	0.000	0.201
Age	0.008	0.040	0.029	0.189	0.851	0.019	0.042	0.075	0.464	0.645	0.022	0.043	0.086	0.519	0.607
Cognitive reserve index	0.026 **	0.009	0.453	2.926	**0.006**	0.030 **	0.010	0.533	3.009	**0.005**	0.031 **	0.010	0.541	3.009	**0.005**
Hippocampus volume	78.600	244.133	0.050	0.322	0.749	145.674	254.852	0.092	0.572	0.571	122.193	248.493	0.077	0.492	0.626
Bilingualism as between-groups variable						0.358	0.382	0.352	0.936	0.356					
Bilingual engagement as continuous variable											-0.010	0.010	-0.180	-0.967	0.341
Observations	38					38					38				
R^2 / R^2 adjusted	0.211 / 0.141					0.231 / 0.138					0.232 / 0.139				
AIC	109.055					110.059					109.994				

** p<0.05 ** p<0.01 *** p<0.001*

3.4. Discussion

The present study investigated the effects of active bilingualism on brain structure and episodic memory performance in individuals with a diagnosis of MCI. In the older age, bilingualism has been shown to result in more preserved grey matter and white matter across brain areas linked to bilingual language control and language processing, indicating increased brain reserve (Abutalebi, Guidi, et al., 2015; Zhang et al., 2020). However, in clinical populations with a diagnosis of Alzheimer's disease, bilingual individuals exhibit greater brain atrophy, when compared to monolingual AD patients matched for cognitive status, suggesting a compensatory mechanism at play, such as increased cognitive reserve (Perani & Abutalebi, 2015). These contradictory findings in healthy and clinical older populations suggest that there might be an interplay between the two reserve mechanisms, which is difficult to disentangle due to the often-used cross-sectional designs that capture cognitive and brain status as a snapshot in time. To better understand the precise effects of bilingualism in healthy and clinical populations, in the present study we looked at populations transitioning from healthy ageing to dementia, namely, individuals diagnosed with MCI, an underresearched demographic in the field, which has produced mixed findings (Duncan et al., 2018; Marin-Marin et al., 2019; Raji et al., 2020). We carried out a between groups analysis comparing active and passive bilinguals on the integrity in the brain structures sensitive to ageing and clinical neurodegeneration and implicated in episodic memory function. Additionally, in line with recent suggestions in the literature (DeLuca, Rothman, Bialystok, et al., 2019; Luk & Bialystok, 2013), we quantified bilingualism as a continuous variable based on engagement in bilingual language use. We also tested the claims that bilingualism can delay the onset of cognitive symptoms and MCI diagnosis, routinely reported in the literature (Berkes et al., 2020; Bialystok, Craik, et al., 2014). In doing so, we accounted for other factors that could induce similar effects (operationalised as Cognitive Reserve Index).

Our first set of analyses for all metrics applied comparisons between a group of active and a group of passive bilinguals as defined by self-reported engagement in bilingual language use. Our results revealed active bilinguals to have a greater grey matter volume in the bilateral hippocampal volume, and in a cluster in the right supramarginal gyrus. Active bilinguals also reported significantly later age of MCI symptom onset. Our

second set of analyses revealed that increased engagement in bilingual language use predicted local expansions in the right amygdala and right caudate nucleus. However, unlike the between-group comparisons, increased bilingual engagement did not linearly predict volumetric changes in the hippocampus, nor any significant effects were observed in cortical grey matter in a whole brain VBM analysis. There was a trend for bilingual engagement to predict later age of symptom onset and later age at diagnosis, however it did not reach significance when Cognitive Reserve Index was included in the model. In both sets of analyses bilingualism did not emerge as a significant predictor for episodic memory performance.

Similar to previous literature comparing monolinguals and bilinguals, this study showed a significant main effect of active bilingualism on delayed onset of MCI symptoms. Here, the self-reported onset of MCI symptoms was delayed by 1.5 years in active compared to passive bilinguals, though no significant delay of formal MCI diagnosis was found in this sample. This partly echoes findings from the literature on dementia, where bilingualism is often reported to delay the onset of Alzheimer's disease symptom onset by 4-5 years (Alladi et al., 2013; Bialystok et al., 2007) in bilinguals compared to monolinguals. Similar effects have been observed in another study with MCI patients (Ossher et al., 2013); interestingly, the delay of about 1.5 years is less than reported in that study. This discrepancy might be explained by the participant profile in this study – all individuals were bilingual, and only differed in their language use patterns, suggesting that active engagement in bilingual language use may offer this additional amount of time before symptom onset. This is further corroborated by our finding that amount of balanced bilingualism positively predicts the age of symptom onset (see also Calabria et al., 2020).

The findings above were accompanied by structural findings in the bilateral hippocampus, right supramarginal gyrus, right amygdala and right caudate nucleus. Bilingualism has been linked to structural increases in the hippocampus in immersed younger populations (DeLuca, Rothman, & Pliatsikas, 2019; Mårtensson et al., 2012), as well as healthy older adults (Voits, Robson, et al., 2020). Thus, the finding of hippocampal volumetric increases in this participant sample that are associated with active bilingualism is not surprising. It seems that a build-up of grey matter in the hippocampus remains present in early stages of clinical ageing (i.e., MCI). It can even vary between bilingual groups of different experiences, thus potentially providing a

neural reserve for this structure. Furthermore, as hippocampus is shown to be sensitive to ageing (Fjell et al., 2009), and also, as atrophy of the hippocampus and medial temporal lobe structures in general is linked to development of AD (Fox & Schott, 2004), evidence for brain reserve in this region suggests increased neuroprotective effect of bilingualism, which may be the underlying mechanism of the reported delayed progression to Alzheimer's dementia. Our findings suggest that the precursors of these process, as least as far as the hippocampus is concerned, can be detected at the MCI stage of disease progression. Moreover, these effects can be observed even *within* bilingual populations, based on the extent of bilingual language engagement.

Increases in grey matter volume were also found in the supramarginal gyrus for the active group. This region and its left hemisphere homologue are related to verbal fluency, and its volume has been shown to negatively correlate with age of L2 acquisition, and positively correlate with vocabulary size and L2 fluency in younger individuals (e.g., Hosoda et al., 2013; Mechelli et al., 2004). The present finding, therefore, is not surprising, as older bilinguals actively engaging in production of two languages, are more likely to "exercise" this area, leading to potential accumulation of neural tissue. Alternatively, this additional volume might signify greater vocabulary size for the active group, but it is difficult to adjudicate between the two possibilities. Finally, the finding of the reshaping of the right caudate nucleus and the right amygdala as a function of active bilingualism is also not unexpected. The caudate nucleus is involved in language switching and control processes and shown to be increased in volume, at least in younger populations, as a result of the increased needs for language control in bilinguals (Zou et al., 2012). Although most research finds structural effects in the left caudate nucleus, as a function of bilingualism, bilateral effects have also been observed (Pliatsikas et al., 2017). Amygdala is a subcortical structure primarily associated with regulation of emotion and behaviour (Angrilli et al., 1996). However, it has been shown to reshape in response to immersive bilingualism (DeLuca, Rothman, & Pliatsikas, 2019) and to be structurally protected by bilingualism in healthy ageing (Li et al., 2017). Our findings suggest these effects also apply to clinical populations. To summarise, our results reveal greater grey matter volume for active vs passive bilinguals in regions related to bilingual language processing and control. These results are in line with some previous literature suggesting that bilingualism might present a brain reserve in MCI and suggest that active

engagement in bilingual language use is a factor that adds to the building up and solidifying of said reserves.

Of particular interest in this study is that the effects in the neural substrates were not reflected in behavioural effects in episodic memory performance. This result can be explained by the fact that the MCI patients here are still relying on their accumulated brain reserves, if such reserves are accrued; however, this cannot be established with certainty for the passive group in the absence of a monolingual control group. In addition, while hippocampus is linked to episodic memory function (Nyberg, 2017), no direct brain-to-behaviour mapping can be inferred (i.e., greater hippocampal volume does not straight-forwardly imply superior episodic memory performance). Although our active bilinguals do not present any behavioural advantages, these reserves may allow for longer period of healthy life prior to onset of MCI symptoms. Having said that, episodic memory performance, although not predicted by bilingual experience *per se* was subject to improvement as a result of higher total cognitive reserve index. This makes sense within the wider brain reserve framework and maps well on previous findings in healthy ageing individuals (Voits, Robson, et al., 2020).

Finally, it is worth pointing out CRI, added as a covariate in the analysis, was also revealed to be a significant predictor for the age of symptom onset. Similar to another study with MCI patients (Calabria, Hernández, et al., 2020), it was inversely related to age of diagnosis, meaning that higher cognitive reserve index predicted earlier age of onset in this participant sample. Thus, it seems that bilingualism is working *against* other cognitive reserve factors, a finding that is not straight-forward to explain.

The present results fit well within the context of wider bilingualism and ageing literature linking bilingualism with development of cognitive and brain reserves (Perani & Abutalebi, 2015). Individual variability in cognitive ageing trajectories has long been observed in the literature. Variable cognitive ageing patterns have been linked to environmental and lifestyle factors, such as educational attainment, occupational attainment and engagement in cognitively demanding leisure activities. With age, cognitive decline occurs in a variety of domains, including episodic memory, working memory, and attention (Cabeza et al., 2018), and the abovementioned factors have been suggested to delay cognitive decline, and the deterioration of the involved brain regions. The present pattern of results qualifies bilingualism as one of these factors. More than

that, not only it extends these findings to MCI, but also reveals variability *within* bilingualism linked to active language use.

Recall that evidence from bilingualism and MCI is limited and has produced mixed findings (Duncan et al., 2018; Marin-Marin et al., 2019; Raji et al., 2020), thus, not providing a clear idea of the processes and decline in the brain in this transitionary period. Our results highlight that regular and active use of two languages materialises as neural adaptations suggestive of increased neural reserve and bilingualism predicts a later MCI symptom onset and MCI diagnosis when other cognitive reserve factors are accounted for. With this study we have extended the previous literature on neurocognitive effects of bilingualism and the brain in clinical contexts by introducing a much-needed granularity in the concept of bilingualism.

This study presents some potential limitations. Although a monolingual control group is not required for correlational designs, it would allow to directly compare the differences between a monolingual group, and different types of bilinguals. Having such a group would allow to study the extent of brain reserve in the bilingual groups with monolinguals as a reference point. We also need to be mindful of the data and what it can tell. Linking behaviour to brain structure and function can only provide a piece of the puzzle. Total functional integrity of a network in addition to structurally sound cortical and subcortical brain structures are both important to ensure successful cognitive ageing, therefore a multimodal approach studying these elements and their relationship longitudinally are needed.

To conclude, this study contributes to the literature examining neurocognitive effects of bilingualism in clinical ageing. It is the first to show that the effects of bilingualism on cognition and the brain in MCI patients might be modulated by the bilingual experience. Active bilingualism contributes to brain reserve in MCI patients and active use of more than one language in everyday life delays the onset of MCI symptoms and subsequent MCI diagnosis. With an increasingly ageing population and no pharmacological cure for progressive neurodegeneration, such as MCI or Alzheimer's disease, it is imperative to explore alternatives that may provide for healthier and longer lives. It has been argued that bilingualism a 'solution hiding in plain sight' for this impeding public health crisis (Bialystok, Abutalebi, Bak, Burke, & Kroll, 2016); still, it is crucial to understand the exact effects of bilingualism on brain and cognition and the mechanisms that afford the delays in symptom onset and diagnosis moving forward. This

is an important aspect as promotion of bilingualism as a public health strategy could potentially delay the onset of neurodegeneration symptoms, promote healthier lives for longer in the older age, and also reduced the burden on clinical and social care services. With the present study we have established an effect of language engagement within a clinical bilingual population.

CHAPTER 4: BEYOND ALZHEIMER'S DISEASE: CAN BILINGUALISM BE A MORE GENERALIZED PROTECTIVE FACTOR IN NEURODEGENERATION?

Abstract

Bilingualism has been argued to have an impact on cognition and brain structure. Effects have been reported across the lifespan: from healthy children to ageing adults, including clinical (ageing) populations. It has been argued that active bilingualism may significantly contribute to the delaying of the expression of Alzheimer's disease symptoms. If bilingualism plays an ameliorative role against the expression of neurodegeneration in dementia, it is possible that it could have similar effects for other neurodegenerative disorders, including Multiple Sclerosis, Parkinson's and Huntington's Diseases. To date, however, direct relevant evidence remains limited, not least because the necessary scientific motivations for investigating this with greater depth have not yet been fully articulated. Herein, we provide a roadmap that reviews the relevant literatures, highlighting potential links across neurodegenerative disorders and bilingualism more generally.

4.1. Introduction

The brain adapts, structurally and functionally, in response to new experiences and acquired skills, such as learning a musical instrument or participating in sports (see Chang, 2014, for a review). Such findings have led researchers to investigate whether the acquisition/learning and/or management of more than one language would also affect the structure and function of the bilingual brain (Bialystok et al., 2004; Bialystok, Craik, & Luk, 2012; Gold, Kim, et al., 2013; Luk & Pliatsikas, 2016; Pliatsikas, 2020). Active bilingualism stands out as a good candidate due to its ubiquity in daily life coupled with the fact that both languages are always simultaneously active in the bilingual brain, and this constitutes a sustained, highly engaging mental exercise (e.g., Green, 1998; Kroll and Stewart, 1994; Spivey and Marian, 1999; but see Finkbeiner, Gollan, & Caramazza, 2006). That is, the constant requirement for continuous suppression/inhibition might, in turn, anatomically and functionally affect the underlying neural substrates supporting this operation.

Controlling two or more languages, keeping them separated, and selecting the appropriate one for use in a given context is termed 'bilingual language control' (Abutalebi & Green, 2007). While the precise mechanisms are yet to be fully understood, the general idea is that with high engagement language control in bilingualism can have knock-on effects to domain-general cognition, specifically to some domains of executive functions (as defined by Miyake et al., 2000). Irrespective of how they are acquired (i.e. simultaneously or via sequential language acquisition), the presence of more than one language creates mental competition. For successful communication to take place, the language(s) not needed/used at any given time must be suppressed/inhibited while the language in active use has to be monitored for any incursions of the other language(s) (e.g., Abutalebi and Green, 2007). Yet the inhibited language must remain idle in the background since the need to switch language at a millisecond´s proverbial notice is something often needed, yet unreliably predictable. Given the task at hand, the executive functions of conflict monitoring, updating, interference suppression and working memory are all straightforwardly implicated in the successful juggling of more than one language.

Executive control is the regulation of the set of cognitive processes related to individual executive functions. Ubiquitous involvement of the abovementioned executive functions in bilingualism, similar to other activities of high engagement (Maguire et al.,

2000), is argued to fine-tune executive functioning more globally. This should relate to improved efficiency in cognitive processing (see Grundy et al., 2017, for review). While subject to ongoing research, there is evidence suggesting at least a partial overlap in the brain areas and neural networks serving bilingual language control and executive functions. This is evidenced by recruitment of these same networks for linguistic and non-linguistic tasks (see Calabria et al., 2018, for review), suggesting that bilingual language control and executive control are not only linked by means of behaviour but also by aspects of supporting neural substrates.

The constructs of *cognitive reserve* (CR) and *brain reserve* (BR) are crucial to the discussion herein[3]. Both pertain to potential disconnects between apparent cognitive (behavioural) functioning and diagnosable neurodegeneration. When there is a positive imbalance between what one would expect in light of measurable neurodegeneration and behavioural ability, some cognitive resilience providing compensation is at play. CR and BR are abstract constructs argued to underlie this compensatory resilience.

In brief, CR refers to the building up of compensatory cognitive ability. It is a bank account of cognitive functioning of sorts, where gains from demanding and engaging tasks/experiences over the lifetime make proverbial deposits for later withdrawal. CR is influenced by various factors such as general cognitive ability (or intelligence), education, occupation, physical exercise, etc. (Stern et al., 2018). BR refers to progressive structural "reinforcement" of the brain, both in grey matter (GM) and white matter (WM). Consequently, this additional structural reinforcement allows the brain to cope for longer until the extent of neurodegeneration becomes severe enough for cognitive symptoms to become apparent (Perani & Abutalebi, 2015; Stern et al., 2018). Like most reserves, overt evidence of its size and depth is more likely to be observed when a compensatory withdrawal is needed. CR, therefore, is best appreciated in the presence of neural degeneration, associated either with brain ageing and/or pathology. For example, it can be seen when behavioural expression of clinical symptoms at the

[3] We acknowledge the distinction between *brain maintenance* and *brain reserve* (see Stern et al., 2018). Brain maintenance and brain reserve both relate to the anatomical structure of the brain and are effectively indistinguishable from one another in cross-sectional designs. Brain maintenance—resilience to development of pathology over time (Nyberg et al., 2012)—requires the tracking of brain deterioration in ageing over time.

individual level is masked and cognition remains stable in the presence of brain pathology (Stern, 2002, 2009). Differently from CR, which is seen as an expression of behaviour, BR can be measured directly via neuroimaging.

However, the exact mechanisms underlying the building up of CR and/or BR are still not fully understood and subject to ongoing research. One hypothesis is that increased activity in the relevant brain areas introduces a greater extent of oxygenation and glucose delivery with cascading beneficial effects, such as increased myelination and potential angiogenesis (Gold, 2015; Mandolesi et al., 2017; Perani et al., 2017). This idea has been supported recently by the work from Arenaza-Urquijo et al. (2019). They examined cognitively resilient older adults who maintained normal cognition even when facing Alzheimer's Disease neuropathology and identified a 'metabolic signature for resilience'. When compared with matched individuals, the cognitively stable older individuals exhibited increased glucose metabolism in bilateral anterior cingulate cortex (ACC) and anterior temporal pole (ATP). In the cohorts tested, it was exactly this metabolic signature and total amyloid burden that were strong predictors of global cognition.

It should be noted that CR and BR are theoretical constructs. They are terminological umbrellas or theoretical links for observable outcome asymmetries. As such, there are no precise ways to formally quantify them at present. Rather, they are typically operationalized via the quantification of various proxies (i.e., contributor factors). There are many factors that are thought to contribute to CR and BR, including occupation, engagement in specific leisure and cognitive activities, brain volume, synaptic density, etc., which may provide independent and interactive contributions to neuroprotection in the older age (for review see Arenaza-Urquijo, Wirth, & Chételat, 2015). Recently, Arenaza-Urquijo & Vemuri (2018) identified numerous and, likely, interrelated pathways that may lead to increased cognitive resilience in older age. According to this framework, several predictors, such as vascular risk, sex, genetics, and lifestyle enrichment activities may lead to a combination of (1) reduced β-Amyloid (Aβ) and Tau protein accumulation via maintenance of efficient clearance mechanisms; (2) maintenance of brain structure, glucose metabolism and functional networks; (3) neural compensation, or more efficient rewiring of functional networks as well as compensatory increase of glucose metabolism. Although most other potential contributor factors are beyond the scope of the present discussion, we will argue that various practices associated

with (active) bilingualism should be considered as an independent lifestyle enrichment factor, which under certain conditions can contribute to increased cognitive resilience in the older age.

Bilingualism has been shown to be an additive contributor to CR and BR (Craik et al., 2010; Guzmán-Vélez & Tranel, 2015; Perani & Abutalebi, 2015). Healthy ageing bilingual brains have greater overall volume and show higher resistance to deterioration in the posterior regions as compared to monolingual ones (Heim et al., 2019). The effects of bilingualism are potentially more evident in lower education, or even illiterate, populations where there is the potential for more ground to be covered (Alladi et al., 2013; Gollan et al., 2011). Since different factors contributing to increased reserve (e.g. educational level; occupational status; bilingualism) are likely to co-exist and have similar behavioural manifestations, statistical control is required in order to tease the impact of various proxies for engagement with bilingual experiences of language usage from other contributory factors, in order to identify (degree of) bilingualism's potential independent contribution.

Bilingualism fits nicely within the framework discussed above, precisely because it is a cognitively demanding, pervasive, yet separable factor related to lifestyle. Roughly half the world is bi- or multilingual (Marian & Shook, 2012; Romaine, 1995) and the process of juggling more than one language in the mind confers high demands on neurocognitive systems. As such, bilingualism or certain aspects of it (e.g., a threshold for active bilingualism, the distribution of how the languages are used) may contribute to the maintenance of cognitive stability more generally, which might include many types of neurodegeneration, such as Parkinson's Disease (PD), Huntington's Disease (HD) and Multiple Sclerosis (MS).

Indeed, examining mind/brain consequences induced by relevant experience with bilingualism has not only been increasingly studied in recent years, but has also met with debate (see e.g. Antoniou, 2019; Bialystok, 2017; Paap et al., 2015; Valian, 2015, for reviews). To date, the majority of the bilingual cognition literature has examined healthy adult populations, producing mixed results (see Grundy, submitted; Hilchey and Klein, 2011; Lehtonen et al., 2018; Paap et al., 2015; Van den Noort et al., 2019, for reviews and meta-analyses). Failure to replicate the same behavioural cognitive effects across populations tested under distinct conditions of bilingualism are not, nor should be, surprising *per se* (see Bak & Robertson, 2017; Bialystok, 2017; Leivada, Westergaard,

et al., 2020; Valian, 2015). It does, however, underscore the importance of investigating potential bilingual effects in a more nuanced way to understand what the conditions are, if any, under which bilingualism results in neurocognitive adaptations (Dash, Berroir, Joanette, & Ansaldo, 2019; De Cat, Gusnanto, & Serratrice, 2018; DeLuca, Rothman, Bialystok, et al., 2019; DeLuca, Rothman, et al., 2020; Gullifer & Titone, 2020; Luk & Bialystok, 2013; Sulpizio et al., 2019).

Acknowledging the above epistemological debate is important for any study in this general remit, however, implications of it are of greater or lesser consequence depending on several factors. Since the present discussion concerns the links bilingualism might have with cognitive/brain reserves and thus protective effects to neurodegenerative disorders, the present debates are of minimal consequence to our goals herein for at least two reasons. Notwithstanding the genuine issues of replication in measuring cognitive functions across all bilinguals, one cannot ignore the rather robust body of literature that does show bilingual effects to cognition across the lifespan. While future research must qualify the conditions under which bilingualism impacts domain-general cognition, we are unlikely to be able to confidently exclude any effect at all (but see Paap et al., 2015). Further to the point, while replication is a *bona fide* issue, it is largely limited to specific measurements on behavioural tasks, for example, with Stroop, Flanker and other similar types of tasks. Given concerns regarding the granularity of such tasks and general replication issues within them regardless of what they are used for (Hedge, Powell, & Sumner, 2018), it is not clear that replication failures reliably indicate the absence of cognitive adaptations (any more than one could argue these tasks index adaptations if an effect is found).

The effects of bilingualism on cognition are only part of the story related to potential effects on neurodegeneration anyway. To the extent that bilingualism confers neuroanatomical and functional changes to the brain that can be meaningfully attributed to protection against atypical, pathological decline, conclusions reached in the above debate, independently of the resolution, have limited effects for the present discussion. Therefore, of equal, if not greater, importance is the parallel literature on neuroanatomical changes to the bilingual brain. Bilingual experience changes the physical characteristics of the brain and in areas specifically associated with bilingual language control (see Pliatsikas, 2020, for review). Such changes, for example to GM volume and WM integrity, are of significant relevance to the discussion at hand not the least because

neurodegeneration negatively affects them directly (e.g., Auning et al., 2014; Gold et al., 2012; Zarei et al., 2009). Taken together, there is an empirical basis upon which it is reasonable to continue forward with studies examining the effects of bilingualism on neurodegeneration, regardless of how the debates on cognitive effects turn out. In fact, given that this involves the health sciences in practical terms, there is a moral imperative to do so.

Indeed, a growing sub-literature on clinical implications of bilingualism for Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) shows promising results. Recent meta-analyses are clear: having competence in and using more than one language over the lifespan correlates with later onset of symptoms and, thus, diagnosis of clinical dementia as much as 5 years later relative to comparable monolinguals, even though brains are accruing underlying neuropathology similarly (Anderson et al., 2020; Brini et al., 2020; Paulavicius et al., 2020). Our question herein is: How generalizable is this so-called protective factor? Would bilingualism-related reserve extend to neurodegenerative disorders in general, such as HD, PD, MS, and potentially others? It is reasonable to believe, if on the right track at all, that bilingual experiences should have a similar pattern of compensation for clinical symptoms across neurodegenerative disorders which include executive dysfunction. Herein, we explain: (1) *why this should be*, (2) *what evidence there currently is to support (or not) this view from neurodegenerative disorders* as well as (3) *what directions are recommended to test this hypothesis more directly in the near future.*

4.2. Motivating the program: Why should this be?

The first step in contextualizing whether bilingualism can provide a protective effect in neurodegeneration disorders beyond dementia of Alzheimer type is to understand what mechanisms might underlie the link between bilingualism and neurocognitive effects, especially regarding what the hypothesized path would be through which bilingualism could have an impact on neurodegenerative diseases. As discussed above, bilingual language control inevitably aligns with domain-general executive control. If some executive functions are more engaged, potentially on a continuum related to bilingual practices such as density of code-switching (Green and Wei, 2016; Hofweber et al., 2016) or patterns of social language use (e.g., DeLuca et al., 2020, 2019; Gullifer and Titone, 2020), then engagement in this task over a sustained

period of time could lead to the accruing of CR and changes to neuroanatomical structure (opportunities for gains in BR) (Pliatsikas et al., 2020). Effects at any point along the life-span continuum, different as their surface manifestations might seem, should, in principle, relate back to the same mechanisms and processes as above described. We now turn to what the literatures at various ages indicate.

4.2.1. Healthy bilingual brain in young(er) populations

Studies carried out over the last two decades have shown that (some groups of) bilingual individuals perform better than their monolingual peers in executive control tasks, including working memory tasks (Grundy & Timmer, 2017; Luo, Craik, Moreno, & Bialystok, 2013), switching (Hernández et al., 2013; Poldrack, 2006), updating (Bialystok et al., 2004), and inhibition (Costa et al., 2008; but see e.g. Valian, 2015, for critical review). Recall from the introduction that monolingual versus bilingual differences are not always attested (de Bruin, Bak, & Della Sala, 2015; Lehtonen et al., 2018; Paap & Greenberg, 2013; Paap et al., 2015). In light of variable data from behavioural measures of executive control, a more reliable outlet to look for traces of potential cognitive and brain reserves is in neuroimaging.

Neuroimaging studies are more consistent in showing changes associated with bilingualism in young(er) populations (from childhood to young adulthood), which include increased cortical and subcortical GM volume, and WM integrity in areas and tracts associated with bilingual language control. Some examples of regions affected include areas related to conflict monitoring and control of language production (ACC and left inferior frontal gyrus (IFG)), areas contributing to switching abilities between languages, (inferior parietal lobule (IPL)), and areas implicated in motor movements and inhibitory control among other roles (basal ganglia) (see Abutalebi, 2008; Abutalebi and Green, 2007). Within the basal ganglia, for example, bilingualism is linked to the increased GM volume in the left caudate nucleus. This structure is implicated in both language control and broader executive control (Zou et al., 2012). Even the cerebellum, a structure traditionally associated with the motor system, but also implicated in aspects of executive control (for a review see Bellebaum and Daum, 2007) and language processing, shows increased GM volume in bilinguals (Filippi, Tomas, Papageorgiou, & Bright, 2020; Pliatsikas et al., 2014). WM tracts are also potentially affected by management of two languages. This includes increased integrity of tracts implicated in

typical language processing and second language acquisition (e.g., inferior fronto-occipital fasciculus (IFOF) bilaterally), and also the strengthening of corpus callosum (CC), which has been implicated in domain-general executive control and interhemispheric communication (Hämäläinen et al., 2017; Pliatsikas et al., 2015).

Beyond adaptations to neuroanatomy, recent work provides evidence suggesting adaptations in brain function as well. In other words, bilingualism can seemingly have an effect also on the brain's functional organisation (Pliatsikas & Luk, 2016) and sometimes in ways that might not be readily detected behaviourally (DeLuca et al. 2020). For example, Anderson and colleagues (2018a) found that monolingual and bilingual individuals differ in cognitive network recruitment for executive functioning tasks. More specifically, they found that, when faced with two different types of a switching task (verbal and non-verbal), bilinguals utilised one common network for both tasks, while monolinguals recruited distinct brain networks, depending on the type of the task. This finding corroborates previous ones that have shown similar overlaps in brain regions utilised for both language control and domain general cognitive control (Coderre, Smith, Van Heuven, Walter, & Horwitz, 2016; Weissberger, Gollan, Bondi, Clark, & Wierenga, 2015). Further to that, effects of bilingualism have even been reported in task-free (resting state) designs, where bilinguals have demonstrated increased functional connectivity within brain networks underlying executive control (see Pliatsikas and Luk, 2016 for review on the effects of bilingualism on task-based and resting state brain function).

4.2.2. Healthy brains in older populations

Bilingualism effects seemingly manifest more profoundly in older age, with older (usually tested at ages 60 and above) neurotypical bilinguals performing better than comparable monolinguals in tasks associated with executive control (Abutalebi, Guidi, et al., 2015; Baum & Titone, 2014; Bialystok et al., 2004; Bialystok, Poarch, et al., 2014). Number of languages spoken also predicts higher cognitive screening test scores, with those individuals speaking a higher number of languages exhibiting better preserved cognitive abilities longitudinally over 12 years of testing (Kavé et al., 2008).

Turning to the neuroanatomy of the brain, evidence from older populations echoes the results found in young adult populations. Bilingualism in older adults is associated with higher GM volume in cortical areas and subcortical structures of the brain linked to

language learning and bilingual language control (Abutalebi, Guidi, et al., 2015; Borsa et al., 2018; Del Maschio, Sulpizio, et al., 2018). More specifically, examples of the areas affected by bilingualism include dorsolateral prefrontal cortex (PFC), an area implicated in language control and conflict resolution (Abutalebi, Guidi, et al., 2015; Del Maschio, Sulpizio, et al., 2018) , and the hippocampus, a region involved in episodic memory, including aspects of language learning (Li et al., 2017; Voits, Robson, et al., 2020), which are both better preserved in ageing bilinguals. The ACC is also found to have increased GM volume in ageing bilinguals (Abutalebi et al., 2012) as is the ATP (Abutalebi et al., 2014). Although the latter is not implicated in executive control *per se*, it does relate to language in serving as a conceptual hub where semantic information is stored (Abutalebi et al., 2014). This shows that not only areas directly involved in bilingual language control and executive control, but also brain areas associated with aspects of language processing are affected by bilingualism. Effects extend to WM structures; just like their younger counterparts, older bilinguals exhibit greater integrity in their interconnecting WM tracts. For example, this has been found in the CC, superior longitudinal fasciculi bilaterally and right IFOF (Luk et al., 2011). Mirroring these results, Gold et al. (2013) found better WM integrity in the ILF/IFOF, fornix and parts of CC. Anderson and colleagues (2018) also found similar group differences, namely, bilinguals exhibiting higher integrity in parts of the CC, left superior temporal longitudinal fasciculus and anterior IFOF, but also in the right external capsule and bilateral superior posterior corona radiata. These differences have been interpreted as potential neuroprotective effects in healthy older populations because they largely represent better preservation and/or reserve in combating the processes of natural cognitive decline. To summarise, the areas that have been shown to differ between healthy ageing bilingual and monolingual populations underlie executive control and bilingual language control (see Grant et al., 2014, for review).

4.2.3. Bilingual brain in ageing clinical populations: Alzheimer's Disease and Mild Cognitive Impairment

The reporting of suggested neuroprotective effects of bilingualism in older age prompted some researchers to investigate whether and how this neuroprotection interacts with pathological neurodegeneration caused by progressive disease (Gold, Johnson, et al., 2013; Schweizer et al., 2012). This has been particularly true for Alzheimer's Disease

(AD), which is the most prevalent form of dementia globally (Ferri et al., 2005). Before reviewing the evidence on bilingualism and AD, it is useful to review the mechanism underlying the condition.

According to the Amyloid Cascade Hypothesis (Karran, Mercken, & Strooper, 2011), the dominant theory in AD research, in this type of dementia the brain is subject to aggregation of Aβ protein, and formation of cortical amyloid plaques. The varying distribution of this pathology results in presentation of different AD subtypes. The above leads to eventual progressive synaptic degeneration, hippocampal neuron loss and overall cerebral atrophy via formation of paired helical filaments of tau protein. However, the exact mechanism of how aggregation of Aβ protein and tauopathy leads to neurodegeneration is not yet well understood (Scheltens et al., 2016; Swerdlow, 2007). Visible atrophy in typical AD is usually localised at early stages in the disease, primarily affecting the medial temporal lobe including the hippocampal formation and entorhinal cortex. This pattern parallels initial episodic memory symptoms, however, atrophy to these regions has also been detected in pre-symptomatic individuals (J. L. Price et al., 2009). Atrophy spreads as the disease progresses following a trajectory of temporal-parietal-frontal regions, corresponding to increasing non-memory symptoms in the disease (Mucke, 2009). Subcortical regions are similarly vulnerable with atrophy affecting the caudate nucleus, striatum and putamen within the basal ganglia, basal forebrain, the amygdala and thalamus bilaterally. Extensive disruption of white matter tracts also occurs, including, but not limited to, the CC, fronto-occipital fasciculus, ILF, and fornix (for a review see Pini et al., 2016).

The concept of MCI has only been introduced in the last few decades. The most common type, amnestic MCI, can be characterised as a state of memory impairment worse than what would be expected for a given age and educational level, but not meeting criteria for a mild AD diagnosis. It can be considered as a transitional state between healthy ageing and AD, although MCI does not always advance to AD (however, people with MCI are at greater risk of developing the disease) (Petersen et al., 1999). People with MCI do not have adversely affected daily functioning, although it might take longer than before the onset of symptoms to perform certain tasks. The main symptoms include changes in cognitive performance, for example, increased forgetfulness (Petersen, 2016).

The cognitive effects of bilingualism observed in healthy populations, as discussed above, seemingly translate into health-related implications in clinical contexts.

Most notably, there is an increasing body of evidence suggesting that bilingualism is a lifestyle enrichment factor that contributes to delaying the onset of AD symptoms by 4-5 years in bilingual individuals when compared to education- and age-matched monolinguals (Alladi et al., 2013; Bialystok et al., 2007; Woumans et al., 2015; but see e.g., Zahodne et al., 2014; for reviews see Guzmán-Vélez and Tranel, 2015, Anderson et al., 2020; Brini et al., 2020; Calvo et al., 2016; Paulavicius et al., 2020). Mirroring the evidence for delayed onset of AD symptoms in bilingual individuals, there is also some support for later diagnosis of MCI in bilinguals (Bialystok, Craik, et al., 2014; Ossher et al., 2013; Ramakrishnan et al., 2017). Degree of engagement in bilingual communication, or active use of more than one language in the older age is thought to be key in this process of delayed MCI symptom onset (Calabria, Hernández, et al., 2020).

While this research suggests bilingualism to be a factor that delays the onset of clinical dementia symptoms (i.e., cognition and behaviour), little is known about the neurological mechanisms by which this effect occurs. Research undertaken in the neurotypical population operates under the hypothesis that compensation comes at the cross-roads of bilingualism-induced (i) brain reserve (BR) and (ii) cognitive reserve (CR) accrued over the course of the lifespan. The BR hypothesis suggests that some areas of atrophy in AD overlap with those structurally reinforced through active bilingualism. Increased BR could result in a protective effect against the disease pathology, slowing the progression of the disease, at the initial stages, but this remains an open hypothesis (for relevant discussions see Bialystok et al., 2018; Perani and Abutalebi, 2015). This hypothesis is consistent with the finding that AD and MCI bi- or multilingual patients exhibited higher cortical thickness than their monolingual counterparts in areas related to language control and executive control (including the IFG, supramarginal gyri, and anterior temporal gyri bilaterally, left medial superior frontal gyrus, right ventromedial PFC, left IPL, and the cerebellum) (Duncan et al., 2018). Given the nature of relationship of behavioural symptoms for MCI and AD diagnosis itself, to the extent that CR is implicated and such symptoms are compensated for, it is likely that BR will have already been diminished at the time of diagnosis and that bilinguals will be in the CR compensation phase. However, we would expect to find evidence of increased BR to be documented in the medial temporal lobe regions associated with atrophy in MCI and early AD in healthy aging bilinguals. If that is established, it would then follow that comparable bilingual AD patients too would have had similar neuroplastic adaptations at

the onset of disease, slowing progression in the brain. While structural differences in the hippocampi have not been prominent within the bilingualism literature, there is emerging evidence of increased hippocampal grey matter volume bilaterally in the younger and, crucially, older adult bilingual population in comparison to the monolingual populations (DeLuca, Rothman, & Pliatsikas, 2019; Mårtensson et al., 2012; Voits, Robson, et al., 2020). The CR part of the hypothesis suggests that increased functional efficiency within the executive control network enables bilingual individuals with AD to maintain functioning for longer in the face of atrophy to the network (Perani & Abutalebi, 2015). Compensation through CR then suggests that enhanced executive networks could provide additional resources to compensate for decline in networks supporting other cognitive functions (Stern et al., 2018). This hypothesis allows for the impact of bilingualism when areas of atrophy do not overlap with areas of documented BR e.g. atrophy to the lateral temporal lobes. If on the right track, we should expect to see bilinguals, relative to monolinguals and when cognitive functioning level are held constant across the groupings, to be significantly older on average and/or for their brains to show increased pathological deterioration; indeed, recent meta-analyses show that this is a reliable finding (Brini et al. 2020; Paulavicius, et al. 2020; Anderson, Hawrylewicz & Grundy, 2020). Further support for the hypotheses related to CR in that when cognitive functioning is not held constant, AD bilinguals tend to exhibit better cognitive functioning relative to higher levels of dementia-related brain atrophy, although this was not found in an MCI bilingual patient group (Duncan et al., 2018). However, in a more recent study, bilingual MCI patients had a greater reduction in global parenchymal volume than monolingual MCI controls while performing at the same cognitive level (Costumero et al., 2020). Bilingual individuals with AD who are matched to monolinguals on cognitive performance have been found to have greater hypometabolism in a range of cortical regions (Kowoll et al., 2016; Perani et al., 2017), also suggesting a degree of compensation. The compensation through CR hypothesis is consistent with functional changes observed in the ageing bilingual population. A posterior-to-anterior shift has been well documented in typical aging in monolingual populations (Davis et al., 2008), whereas for bilinguals ageing is characterised with an increased functional reliance on posterior and subcortical areas and structures (Grundy et al., 2017). This pattern suggests functional adaptations in the ageing brain and development of a specialised network linked to additional language processing which may be recruited and

utilised for non-linguistic tasks if primary networks for executive control and memory are affected by AD neuropathology (Anderson et al., 2020).

The above is consistent with the finding that conversion from MCI to AD happens at a faster rate in bilinguals (Berkes et al., 2020), potentially providing further evidence indicating an initial increase in BR that maintains a pre-clinical phase/delay symptom onset. Once the reserve is used up, however, symptoms progress rapidly. Similarly, bilinguals may initially rely on higher CR but once the reserves become diminished or network disruption becomes too great to compensate for, cognitive decline rapidly accelerates as the neural substrate has already undergone significant atrophy.

4.2.4. Interim Summary: The motivational links

The above subsections (4.2.1.-4.2.3.) provide links between behavioural and biological clinical effects of bilingualism overall, and how they manifest in AD and MCI. If bilingualism has such effects, then we should ask if it has comparable effects in other progressive diseases, particularly those which affect components of the executive control network as these may be prime targets for both BR support and CR, but also those which affect wider cognitive networks which may be able to draw on increased CR as a compensation mechanism. In fact, we might turn that question around and ponder how it could not, if the explanations/links offered to date are on the right track. Extending the question of potential bilingual effects to neurodegeneration more generally, thus, has theoretical importance beyond the obvious practical health benefits. Indeed, if previously observed effects are valid and replicable and the proposed theoretical bases are accurate, then we should expect to see similar effects in other neurodegenerative disorders. If not, this would provide motivation to rethink claims at the most basic conceptual and theoretical levels. If bilingualism offers provisions for cognitive and brain reserves with knock-on ameliorative effects in AD and MCI but not for other neurodegenerative diseases, it would raise questions and provide insight into the neuronal and cognitive mechanisms underpinning the documented impact in AD. Similarly, if the effects of bilingualism are observed in additional neurodegenerative conditions, comparison of the time-course, nature and extent of the impact and how these factors interact with the neural and cognitive profile of the disorders can provide complementary neuropsychological evidence into how bilingualism interacts with the brain.

Although there is a wide range of progressive and non-progressive neurological conditions that result in cognitive impairment and loss of neural tissue, the available literature on these disorders is mostly focused on the effects that age- or disease-related neurodegeneration has on one's language ability and associated executive control, and not the effects bilingualism *per se* may have on the progression of and/or onset of symptoms related to neurodegeneration. The last relevant comprehensive review relating to bilingualism (Paradis, 2008) was published more than a decade ago, but even so the focus there was on understanding how neurological disorders impair language processing in bilinguals, not on the effects bilingualism might have on cognition and brain structure. Given the now proposed neuroprotective effects of bilingualism in ageing (virtually non-existent 12 years ago), it is important and timely to re-examine the literature through this new lens.

4.3. Beyond dementia of Alzheimer type: Bilingualism as a protective factor in neurodegenerative disorders?

Even in the absence of research specifically designed to ask and answer questions related to bilingualism links in neurodegeneration in a broader sense, it follows from the evidence discussed above that bilingualism could have an impact on the surface manifestations of neurological disorders in general (i.e. more than in AD). Despite the dearth of research focused on this question, there are indeed some very promising results to which we now turn.

Although available studies are limited to a small subset of progressive neurodegenerative disorders, we assemble herein the available literature and evidence on the effects of bilingualism on a range of neurodegenerative diseases. We discuss a disease per subsection and review the literature looking at established and potential effects of bilingualism on clinical outcomes for each condition, focusing on areas where BR might occur and existing evidence for the impact of CR on the conditions. We cover three progressive neurodegenerative disorders, other than AD and MCI, namely Huntington's disease (HD), Parkinson's disease (PD), and Multiple Sclerosis (MS). Although these are unique disorders with their own cognitive profiles, there is a degree of overlap at the symptom level between the conditions and AD (at least at the level of sensitivity provided by current neuropsychological testing). All three disorders and AD present with a range of executive control impairments, raising the possibility that increased CR in bilingualism

may impact the manifestation of symptoms in each of the disorders. Similarly, there is divergence and overlap in terms of what structures and brain areas are targeted by each disease with many regions demonstrating evidence for BR in neurotypical bilingual ageing. However, it is important to note that the diseases differ in their pathological basis and, given the lack of evidence regarding the neuronal mechanisms of increased BR in bilingualism, there remains a possibility that the relationship between AD and bilingualism could be pathology-specific or that the mechanisms of increased BR could interact with different pathologies in different ways. For example, Estanga et al., (2017) found lower cerebrospinal fluid (CSF) total-tau (t-tau) concentration in *healthy* bilingual middle-aged individuals than monolingual individuals. CSF t-tau levels serve as a biomarker for AD (Blennow, Vanmechelen, & Hampel, 2001); this study is the first to show a more favourable CSF AD-biomarker profile associated with bilingualism and might show that bilingualism works in a way to reduce the probability of tau pathology development. We propose that comparison of different neurodegenerative conditions will provide a powerful tool for unpacking the multiple and interacting theoretical positions regarding the impact of bilingualism on ageing and neurodegeneration and we aim to start the discussion by reviewing the current evidence for CR and the potential for bilingualism driven BR in HD, PD and MS. The goal herein, then, is to reveal the underlying logic and links we believe make this a line of research particularly worth pursuing. In the end, what we highlight are empirical questions that further research will adjudicate.

4.3.1. Huntington's Disease

Huntington's Disease (HD) is an inherited, genetic neurodegenerative disorder caused by a mutation in the huntingtin gene resulting in an abnormal number of repetitions of cytosine-adenosine-guanine bases (CAG). In contrast to AD, HD is *typically* diagnosed in middle age; individuals with more than 35 CAG repetitions will experience an onset of HD at roughly 45 years of age. The number of CAG sequence repetitions correlate with earlier onset and severity of HD symptoms as well as associated changes in the brain, primarily in the striatal areas (Kassubek et al., 2004). In general, the progression of HD can be divided into three stages – preclinical, prodromal and symptomatic. In the preclinical stages, carriers of the mutant huntingtin gene do not behaviourally differ from healthy individuals. Prodromal stage implies some

deterioration in domains associated with HD; however, this does not impede everyday functioning and in itself is not sufficient for establishing a HD diagnosis. The symptomatic stage is characterised by a HD diagnosis based on presence of motor impairment (Ross & Tabrizi, 2011).

Behaviourally HD usually manifests as a progressive motor disorder accompanied by cognitive and neuropsychiatric deficits. Chorea (involuntary jerky movements) is the primary motor symptom the early stage of HD. This hyperkinetic phase is caused by damage to the indirect motor pathway, whereby inhibition of cortical motor areas is released resulting in unwanted movements (Gilbert & Frucht, 2010). As the disease progresses, additional hypokinetic motor symptoms are observed including bradykinesia (slowness of movement) and rigidity (McColgan & Tabrizi, 2018; Ross et al., 2014). Cognitive deficits manifest as executive function deficiency in planning, organisation, adapting and learning new skills (see Papoutsi et al., 2014; Walker, 2007 for reviews). Episodic memory impairments are also consistently demonstrated (Montoya, Price, Menear, & Lepage, 2006), however, the comparison of AD and HD indicates that the nature of the episodic memory is qualitatively different; individuals with AD experience a loss of memory, whereas impairments in HD are related to deficits in retrieval of information from memory (Hodges, Salmon, & Butters, 1990). Neuropsychiatric symptoms include emotional disorders, such as depression, irritability, and personality changes. In rare cases HD patients experience delusions, hallucinations, and compulsive behaviour (Craufurd, Thompson, & Snowden, 2001). Cognitive and neuropsychiatric symptoms are detectable in the pre-clinical phase of HD, observable, in some cases, years before diagnosis (Tabrizi et al., 2009). To this day, there is no pharmacological cure or treatment available for HD (Ross et al., 2014).

4.3.1.1. The neural basis of cognitive impairments in HD: Links to Bilingualism Effects. Subcortical grey matter

Although there is a certain amount of heterogeneity in the clinical phenotype between individuals with HD, at the population-level there is consistency between clinical symptoms and patterns of cortical and subcortical atrophy and functioning (Coppen, Jacobs, van den Berg-Huysmans, van der Grond, & Roos, 2018; Rosas et al., 2008; Scahill et al., 2013). Importantly, there is considerable overlap between regions displaying BR in bilingualism and atrophy in HD and the associated cognitive functions/symptoms of these areas.

Primarily and universally, HD is associated with structural and functional decline in the striatum (caudate nucleus, putamen and globus pallidus). Additionally to striatal decline, and with greater individual variation, other subcortical GM structures, such as the thalamus, hypothalamus, and substantia nigra are also affected by the disease (see Walker, 2007, for an overview). Degeneration and dysfunction in these regions have been identified using a range of measures. Volumetric GM reductions and changes in structural integrity have been observed in the striatum and thalamus (Aylward et al., 2011; Douaud et al., 2009; Jan Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005). Diminished striatal functioning has been inferred through reduced glucose metabolism (Ciarmiello et al., 2006). Structural changes can be observed in presymptomatic as well as symptomatic HD patients (Liu, Yang, Burgunder, Cheng, & Shang, 2016) and increasing decline can be longitudinally observed as the disease progresses (Aylward et al., 2011).

The integrity of these subcortical structures has been found to correlate with the severity of behavioural symptoms in HD including, and of particular interest to this discussion, executive functioning. Atrophy of the thalamus bilaterally was found to co-vary with cognitive performance as measured by lower scores in letter fluency, digit symbol and Stroop tasks, signalling reduced inhibition and cognitive control (Kassubek et al., 2005). Alterations in putamen and caudate nucleus volume and local dopaminergic metabolism correlates with visuospatial abilities (Ray Complex Figure, copy and WAIS-R, Block Design test), perceptual speed (WAIS-R, Digit Symbol test), reasoning (WAIS-R, Picture Arrangement test) and verbal fluency (Controlled Oral Word Association Test) (Backman et al,1997). While there is limited functional imaging data available from HD samples, the bilateral putamen has been shown to be hypoactive during tasks with high working memory load in pre-HD individuals (Wolf et al., 2008). The same study showed that pre-HD individuals also exhibit reduced functional connectivity in networks within the left DLPFC and the left superior parietal cortex, including bilateral putamen. From here, lesser activation within the left putamen accounts for variation on behavioural measures in the Unified Huntington's Disease Rating Scale (UHDRS).

4.3.1.2. White matter

Individuals with HD are also vulnerable to WM degeneration. Global WM volume reductions can be observed early in presymptomatic HD gene carriers when compared to healthy individuals (Aylward et al., 2011), and WM atrophy can precede

GM atrophy (Ciarmiello et al., 2006). The CC is particularly vulnerable. Reduced CC integrity has been observed through increased mean diffusivity (Bohanna et al., 2011) and reduced fractional anisotropy, suggesting demyelination or degeneration of WM axons (Della Nave et al., 2010; Rosas et al., 2010). These findings align with observations of reduced myelin content in the CC using macromolecular proton fraction (MMPF) measures (Bourbon-Teles et al., 2019). Beyond the CC, there is evidence of reduced integrity in numerous WM structures such as frontostriatal tracts, internal capsule and subcortical tracts, including IFOF and ILF (Di Paola et al., 2012; Rosas et al., 2006).

WM integrity has been related to motor and wider cognitive functions. Of particular interest, callosal degeneration has been linked to performance on cognitive and functional components of Unified Huntington's Disease Rating Scale (UHDRS) (measuring overall severity of the disease), including Symbol Digit Modalities Test (attention, perceptual speed), Verbal fluency (updating, lexical access speed), Stroop tasks (Rosas et al., 2010) and general cognitive/executive impairment (excluding working memory) (Bohanna et al., 2011; Bourbon-Teles et al., 2019). Performance on the Stroop task has also been related to the structure of bilateral IFOF and sub-regions of the internal capsule (Della Nave et al., 2010; Rosas et al., 2006).

4.3.1.3. Cortical grey matter

Unlike subcortical GM and WM, no selective significant atrophy can be observed longitudinally in cortical GM in prodromal HD patients (Aylward et al., 2011). There have even been reports of increased cerebral GM in preclinical HD patients when compared to matched controls suggesting a compensatory mechanism is at play (Paulsen et al., 2006). Although cortical thinning in HD is heterogeneous, it has been related to various neuropsychiatric and executive behaviours. For example, the cingulate cortex is reported to be approximately 10% smaller in early symptomatic HD patients compared to healthy controls, and this has been related to impairments in visual memory (Hobbs et al., 2011). Cingulate cortex has also been shown to exhibit hypometabolism in HD (Eidelberg & Surmeier, 2011). Reductions in frontal cortex volume has been related to impairments in switching (Trail Making Test-B; Wisconsin Card Sorting Task) and episodic memory (Rey-Osterrieth's Complex Figure-memory; Word Recall task) (Backman et al., 1997). Reduced glucose metabolism has also been observed in frontal areas as well as temporal areas (Ciarmiello et al., 2006) and reduced activity from the

medial frontal gyrus, bilateral ACC, superior frontal gyrus and middle frontal gyrus was observed in HD participants while performing a Go/Nogo task (measuring inhibition) (Beste et al., 2008).

4.3.1.4. Evidence for general cognitive/brain reserve in HD

Bilingualism can only impact the progression of HD if the (progression of the) disease can be ameliorated by environmental factors that have neural consequences. Recall that, at present, there is no treatment or cure for HD (Ross et al., 2014), however, there are reasons to believe that CR/BR mechanisms might reduce the severity or even delay onset of HD symptoms. There is now evidence for the role of environmental factors that slow down the expression of motor and cognitive HD symptoms in animal models, implicating BR and/or CR as potential modulators of the clinical progression of HD (see Nithianantharajah and Hannan, 2011, for a review). In humans, it has been shown that HD individuals with 'cognitively active' histories (e.g. engagement with higher education, cognitively challenging professional activities) have less severe clinical profiles (Lopez-Sendon et al., 2011), experience onset of HD symptoms 4.6 years later than those leading passive lifestyles (Trembath et al., 2010) and perform better on working memory, inhibition and switching executive function measures (Garcia-Gorro et al., 2019). This is the case even when the genetic predisposition to HD severity, namely, number of CAG repeats, is controlled for (Chao et al., 2017). At a neural level this cognitive engagements results in differences in functional connectivity between the bilateral ACC and angular gyrus (Garcia-Gorro et al., 2019). Factors such as premorbid intelligence, occupational status, and level of education, have been longitudinally shown to delay deterioration in aspects of cognition and volume loss in the bilateral caudate nucleus and putamen (Bonner-Jackson et al., 2013). These findings can be interpreted as evidence for a compensatory mechanism in HD associated with environmental and lifestyle factors.

Behavioural motor and cognitive rehabilitation techniques in HD have been shown to increase the volume of right caudate nucleus and the DLPFC bilaterally. Increased GM volume has been observed in superior thalami, left inferior temporal pole, right subcallosal cortex, and parasagittal primary motor areas. These volumetric increases in GM have been correlated to significant improvements in verbal learning and memory (Hopkins Verbal Learning Test-R) (Cruickshank et al., 2015), indicating that

neuroplasticity/reserve mechanisms can be behaviourally modulated in HD. As a result, there have been calls to consider these possible reserve mechanisms and implement large scale studies on how cognitive and/or motor interventions might ameliorate the symptoms via the reserve mechanism (Andrews, Domínguez, Mercieca, Georgiou-Karistianis, & Stout, 2015).

4.3.1.5. HD and bilingualism

Overall, there is close alignment between the atrophy patterns related to executive function impairments in HD and the regions where BR is observed in bilingualism, including several subcortical structures, such as the caudate nucleus, putamen, thalamus, and WM tracts, such as the IFOF, ILF and CC. Additionally, the cognitive impairments in HD associated with these regions are linked to the cognitive functions that are hypothesised to be enhanced through active bilingual experience, indicating that a bilingualism-mediated increase in CR may support functioning.

Although the literature directly examining this hypothesis is scarce, recent studies have shown that inhibition (as measured by a cross-lingual Stroop task) was better preserved than language skills in bilingual individuals with HD (Calabria, Pérez Pérez, et al., 2020), and also that higher degrees of bilingual use predict better inhibitory abilities in HD patients (Martínez-Horta et al., 2018). Moving from behaviour to effects of bilingualism on brain structure and function in HD specifically, Martínez-Horta and colleagues (2018) recently reported active bilingualism to be associated with increased GM volume in the right IFG. While they did not explore for any effects on WM or subcortical GM, they also used Positron Emission Tomography relative standardised uptake value (SUVr) and reported significant positive correlations between degree of bilingual use and brain glucose metabolism in various clusters across the brain, including the dorsal ACC, the ventromedial orbital PFC, the insula, the superior orbital PFC, the left IFG and the right inferior temporal gyrus. These findings indicate better preserved brain function and structural integrity in early and mild HD: increased metabolism in mostly fronto-temporal areas of the brain, all known to be affected by HD, and increased volume of the IFG serves as evidence for build-up of BR in the presence of lifelong bilingualism.

It is important to note that neural changes in HD gene carriers can be observed well before any clinical symptoms manifest in the prodromal stage. Changes in the brain

can be detected 20 years before onset of clinical symptoms, while mild changes in behaviour can be observed as early as 10 years before diagnosis (Papoutsi et al., 2014). This creates a different scenario than the typical case of AD where diagnosis before clinical symptom onset is extremely rare. There is, then, an opportunity to measure potential hypothesized BR effects prior to them being exhausted in favour of CR compensation only. Although the impact of bilingualism is more variably detected in younger adults than older adults (Valian, 2015), it might be expected that the presence of behavioural deterioration in the pre-symptomatic phase is reduced in active bilinguals, potentially delaying the onset of the symptomatic phase, as seen in individuals with HD with cognitively active lifestyles. If this were a direct result of bilingualism, it might be hypothesised that symptom reduction is specific to cognitive components of the disorder, rather than motor or neuropsychiatric. The limited behavioural data from bilingual individuals with HD indicates that this reduction in symptoms could be maintained into the symptomatic phase.

4.3.2. Parkinson's Disease

Parkinson's Disease (PD) is another neurodegenerative disease primarily associated with motor impairment. Age of onset for PD is somewhat older than in HD, predominantly above 65 years, although diagnosis at a younger age is not uncommon (Pagano, Ferrara, Brooks, & Pavese, 2016; Wickremaratchi, Ben-Shlomo, & Morris, 2009). Motor symptoms in PD are wide ranging. Diagnosis requires the presence of bradykinesia plus rigidity or tremor at rest or both (Postuma et al., 2015). Additional motor symptoms can include akinesia (inhibition of initiation of movement), dystonia and postural instability. Other supportive factors for PD diagnosis include positive response to dopamine treatment (Postuma et al., 2015) following the pathology of PD which is characterised by degeneration of dopaminergic neurons in substantia nigra and subsequent depletion of dopamine in the basal ganglia (Lotharius & Brundin, 2002). PD is accompanied by non-motor symptoms including sensory, pain and cognitive impairments. Although cognitive impairment is the most common non-motor symptom, there is a wide range in severity of presentation (Aarsland et al., 2017). The variability in the expression of cognitive impairment in PD, ranges from healthy cognitive ageing to mild cognitive impairment (PD-MCI) to dementia (PDD). Development of MCI and dementia in PD is associated with cortical deposits of Aβ plaques and other factors typical

of development of AD (Petrou et al., 2015). Although impairments are detectable in early PD, direct comparison indicates that cognition is less severely affected than in HD (Cope, Georgiou, Bradshaw, Iansek, & Phillips, 1996; Hanes, Andrewes, & Pantelis, 1995). Cognitive impairment in PD can manifest as impairment in executive functioning (Kudlicka, Clare, & Hindle, 2011), memory and visuospatial abilities (Watson & Leverenz, 2010) and deterioration in social cognition (Kawamura & Koyama, 2007). A recent meta-analysis has shown that even in PD patients without dementia there are comprehensive deficits in attention, working memory, visuospatial and verbal memory abilities, when compared to healthy controls (Curtis, Masellis, Camicioli, Davidson, & Tierney, 2019). Like dementia of the Alzheimer's type, the exact cause of PD is unknown, but it is thought to develop as a result of a combination of genetic and environmental factors. This makes PD a heterogeneous disorder with commonalities to both AD and HD *at the symptom level*. Similarly, there are no curative pharmacological treatments for the underlying neurodegenerative process in PD. Available treatments only reduce symptoms (Kalia & Lang, 2015). There are numerous reviews summarising the structural and functional neurobiological changes in PD and the associated symptoms (e.g., Chaudhuri et al., 2006; Kalia and Lang, 2015). Below, we briefly identify key structural and functional characteristics of the disease, particularly with respect to structures relevant to the neurobiology of bilingualism.

4.3.2.1. The neural basis of cognitive impairments in PD. Subcortical grey matter

Subcortical GM structures have mostly been linked to motor symptoms in PD. To further tease apart individual involvement of specific components within the subcortical structures on motor function, a recent study (Li, Xing, Martin-Bastida, Piccini, & Auer, 2018) looked at a large sample size (n=392) of PD patients drawn from a PD MRI scan repository and correlated them to Universal Parkinson's Disease Rating Scale (UPDRS) scores, measuring severity of PD-related impairment and disability (Goetz et al., 2008). The total MDS-UPDRS III (motor) score was significantly negatively correlated bilaterally with GM density in the putamen and caudate nucleus. Lower anterior striatal GM density was significantly associated with higher rigidity subscores, whereas left-sided anterior striatal and precentral cortical GM reduction were correlated with severity of axial symptoms, such as postural instability and trunk posture alterations. No significant morphometric associations were demonstrated for tremor subscores. Smaller

bilateral caudate nucleus volumes were associated with severity freezing of gait symptoms in PD (Herman, Rosenberg-Katz, Jacob, Giladi, & Hausdorff, 2014).

While PD motor symptoms are associated with basal ganglia impairment, relatively less is known about the neurological changes and mechanisms underlying wider cognitive decline in PD (Aarsland et al., 2017). To some extent the basal ganglia also seem to mediate cognitive outcomes in PD. Subcortical and basal ganglia lesions are occur alongside executive function deficits in PD patients (Ardila, Fatima, & Rosselli, 2019). In a longitudinal study, PD patients showed significant volumetric reductions across 18 months between visits in thalamus, caudate nucleus, putamen, hippocampus, amygdala, nucleus accumbens (Vasconcellos et al., 2018). These reductions were accompanied by worse outcomes in attention, executive functioning, visuospatial processing measures and overall cognitive decline, although it is unclear whether neuropathology directly predicts cognitive symptoms (Aarsland et al., 2017).

There is evidence from functional brain MRI scans implicating specific subcortical structures and certain cortical areas to executive function decline in PD (Gawrys et al., 2014). This study found the neural substrate of executive dysfunctions in PD to be found within the fronto-parietal-striatal areas of the brain. Lower activation in right central opercular cortex, left putamen, and left intracalcarine cortex was linked with decreased inhibition, and lower activation in right IFG, right caudate nucleus and right putamen was linked with lower task switching ability.

4.3.2.2. White matter

Structural and functional impairment of WM precedes deterioration of GM in PD. Reduced structural integrity (decreased FA) in CC is associated with reduced visuoconstruction abilities (Auning et al., 2014). Global cognition in PD patients (measured by MMSE scores) significantly correlates with FA measures in the parietal WM regions bilaterally (Hattori et al., 2012).

As with HD, CC shows reductions in both structural integrity and volume in individuals with PD. Reductions in WM integrity of CC have been associated with decreased performance in a variety of executive functioning domains, such as attention, working memory, language performance and visuospatial processing (Bledsoe, Stebbins, Merkitch, & Goldman, 2018). Overall decline of WM volume has been shown to predict cognitive decline and conversion to MCI in cognitively asymptomatic PD patients (Wen

et al., 2015). These results are mirrored in a volumetric study of the CC, where reduced CC volume was found in the mid-anterior and central regions in PD in comparison to healthy controls. Significant differences were observed within the PD cohort with total CC volume significantly shrinking as cognitive symptoms progressively worsened from PD with no cognitive impairment to PD-MCI to, eventually, PDD. Regional callosal atrophy predicted cognitive domain performance such that central volume was associated with the attention and working memory domains; mid-posterior volume with executive function, language, and memory domains; and posterior volume with memory and visuospatial domains (Goldman et al., 2017).

Other WM structures implicated in PD include frontal and parietal tracts, including the superior and inferior longitudinal fasciculi (SLF and ILF) and the IFOF (Duncan et al., 2016). WM deficiencies have also been explicitly linked to development of PD-MCI. A longitudinal study found that among a cohort of comparable PD patients at baseline, those who develop MCI have greater WM reductions over time when compared to patients who remained cognitively healthy. However, longitudinal changes in GM volume does not predict development of MCI in PD patients in the same way WM atrophy does (Wen et al., 2015).

4.3.2.3. Cortical grey matter

Similar to HD, there is considerable heterogeneity in cortical GM atrophy in PD, which may account for varied clinical cognitive profiles among patients. In general, cognitive deficits and development of dementia are associated with widespread cortical thinning. Volumetric reductions are found rather globally, in frontal, parietal, temporal lobes, and the parahippocampal and cingulate cortices (for detailed reviews see Hall and Lewis, 2019; Yousaf et al., 2017). Generally, progressive cortical GM atrophy can be observed as the disease develops and is associated with both motor symptom severity and global cognitive impairment (Wilson et al., 2019). Some bilateral prefrontal atrophy can be observed in cognitively healthy PD patients. While cognitive impairment in this case is not sufficiently severe for a MCI diagnosis, it has been expressed as poorer attention (Brück et al., 2004). Moreover, frontal, temporal, and parietal GM thinning have been associated with reduced semantic fluency and executive function performance in PD patients (Duncan et al., 2016).

When compared with healthy controls, non-demented PD patients showed significant reduction of cortical GM primarily in the frontal and parieto-occipital regions and reduced performance in fine motor speed and set-shifting (Lee et al., 2013). Patients that have converted to the next stage of the disease and diagnosed with PD-MCI exhibit greater cortical volume loss across occipital, temporal, parietal, and frontal cortices (for review see Aarsland et al., 2017). Longitudinally, there is a faster rate of cortical thinning in PD-MCI, when compared to PD with healthy cognition, in the temporal lobe, supplementary motor area and medial occipital lobe (Hanganu et al., 2014), as well as in frontal and temporo-parietal cortices (Mak et al., 2015). This indicates these areas to be most involved in supporting cognitive functioning in PD. Note, not all of these areas are overlapping with the set of areas associated with changes caused by the bilingual experience and have been included for completeness. Another measure, GM density, is lower even in cognitively healthy PD patients, when compared to healthy control groups scattered across numerous frontal, parietal, temporal and occipital areas, including left anterior cingulate gyrus, middle and inferior frontal gyrus, inferior parietal gyrus, and bilateral insula. These reductions are even more severe in PD-MCI patients (Chen et al., 2016). With regards to specific cognitive deficits, PD-MCI patients exhibit poorer performance in executive functions (phonemic fluency, processing speed), immediate verbal memory and visual recognition memory in comparison with PD patients with healthy cognition (Lee et al., 2013).

Severity of dementia in PDD positively correlated with GM reductions in the medial temporal lobe (Pan et al., 2013). Another study found no difference between cortical thickness in PD patients and healthy controls, however, the surface area of the cortex was larger in PD patients (Jubault et al., 2011). This indicates increased folding at the cortical level and the authors hypothesised that this may be due to shrinkage of underlying WM giving rise to deeper sulci and thus leading to increased cortical surface area.

To summarise, cognitive dysfunction and dementia in PD is linked to a widespread atrophy across the cortical GM. The more severe the dysfunction, the greater and more scattered the loss of cortical GM, especially in frontal and temporoparietal cortices.

4.3.2.4. Evidence for general cognitive/brain reserve in PD

There is evidence that the behavioural manifestation of PD is modulated by the degree of cognitive and brain reserve in individuals (e.g., Armstrong et al., 2012). From potential contributor factors to CR , education is the only proxy that has been systematically studied in PD. Better cognitive performance in highly educated individuals with PD (for a review see Hindle et al., 2014) and higher educational attainment predicts better maintenance of global cognitive performance once levels of cortical Aβ pathology have been controlled for (Lucero et al., 2015). Higher estimated premorbid IQ and years of education (both widely used proxies for CR) are associated with reduced likelihood of progressing from PD with no cognitive impairment to PD-MCI (M. J. Armstrong et al., 2012; Koerts, Tucha, Lange, & Tucha, 2013). The impact of education or 'cognitive lifestyle' on executive functioning specifically is somewhat mixed with one study identifying a positive effect on executive neuropsychological tests (e.g. WAIS similarities subtest and Digit Span Forward (Guzzetti, Mancini, Caporali, Manfredi, & Daini, 2019) while another found no relationship (Hindle et al. 2017). Perhaps unexpectedly, a link has also been identified between CR and motor outcomes. Low educational attainment and low scores in the Cognitive Reserve Index questionnaire (CRIq) (Nucci et al., 2012) —a questionnaire that permits a quantification of a Cognitive Reserve Index, by taking into account education, working activities and leisure activities—are associated with more severe motor impairment in PD after controlling for age and disease duration (Guzzetti et al., 2019; Kotagal et al., 2015).

A recent review of cognitive training studies in PD suggests a general trend for cognitive training attenuating cognitive decline in individuals with PD (Leung et al., 2015). While the literature is admittedly small (review of seven studies), improvements following cognitive training were noted across multiple domains, including overall cognition, working memory, processing speed and executive functioning. The authors argue that the current small body of literature promising and call for future studies exploring and establishing standards for cognitive training in PD populations. If behavioural cognitive training can affect clinical outcomes in PD, there are reasons to believe that active bilingualism would as well. Recent evidence has shown bilingual language switching training affects both linguistic and non-linguistic switching task performance in healthy bilinguals (Timmer, Calabria, & Costa, 2019). These findings suggest an overlap between processes underlying shifting in the linguistic and more

general non-linguistic domains. If bilingual language control has an effect on cognition in a more general sense and cognitive training affects PD outcomes, it is reasonable to assume then that the associated cognitive load of managing more than one language can be considered a form of cognitive training in itself, thus offering similar clinical effects in the long run.

4.3.2.5. PD and bilingualism

Similar to HD, there is an overlap between the neural structures displaying brain reserve in bilingualism and the structures associated with cognitive and motor decline in PD, particularly in subcortical structures such as the basal ganglia and in WM tracts such as the CC, IFL and IFOF. Taken together with the evidence for the impact of CR on the expression of PD, it indicates that bilingualism may have a neuroprotective role in PD. To date only a single study has addressed this hypothesis, where a group of English-Welsh bilinguals with PD displayed no difference on neuropsychological assessments of mental generativity, working memory, inhibition and switching when compared to a group of monolingual English speakers with PD (Hindle et al., 2015). No structural brain imaging data were available for these participants and, therefore, it cannot be ruled out that the bilingual speakers were performing similarly to the monolingual speakers while having greater neural atrophy/dysfunction (i.e. displaying increased CR). Hindle and colleagues also did not explicitly state whether cognitive impairment was present in this participant cohort and the mean MMSE scores were near ceiling with small standard deviations, indicating that most participants were cognitively healthy. As such, there may have been insufficient variation in this study to observe the impact of bilingualism.

In sum, as with AD and HD, the patterns of neurodegeneration associated with cognitive decline and the evidence for the impact of CR on the progression of the disease presents a promising basis for the potential impact of bilingualism on at least the cognitive components of the condition. However, along with pathological, genetic and clinical differences, there are onset and time-course differences which may result in the influence of bilingualism manifesting in qualitatively different ways in PD. For example, the age of onset in PD is on average later than in HD. Given that the impact of bilingualism is more detectable in the older adult population—e.g. the timeframe of accrual might be longer before the reserves are used—this could indicate a relatively greater, or at least more easily detectable/measurable, influence of bilingualism in PD. In

contrast, however, cognitive impairments usually occur later in the progression of PD than in HD or AD (Aarsland et al., 2017; Braak, Ru, & Tredici, 2006), raising some questions about the extent to which BR or CR can be maintained into later stages – particularly given evidence of rapid deterioration observed in bilingual individuals with AD. Lewy body pathology is associated with PDD and when individuals experience severe cognitive deterioration in advance or alongside the development of motor symptoms they receive a diagnosis of dementia with Lewy bodies (Tsuboi & Dickson, 2005). Comparison of the impact of bilingualism on dementia with Lewy bodies and AD indicates a significantly weaker impact on the former, in that onset of symptoms relative to monolinguals are not significantly delayed (Alladi et al., 2013). This may be a consequence of the relatively greater deficits in visual attention and visuoperception in dementia with Lewy bodies in comparison to AD (Metzler-Baddeley, 2007) – domains and neural substrates not typically influenced by bilingualism. Taken together, the greater variation in the onset and time-course of cognitive impairments in PD and the differences in pathology, we might expect greater qualitative differences of the degree and nature of the impact of bilingualism within PD than within HD or typical AD.

4.3.3. Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease that has traditionally been associated with progressive inflammatory neurodegeneration of WM within the brain and spinal cord. The characteristic neuropathology includes axonal and neuronal loss, demyelination, and astrocytic gliosis (non-specific changes in astroglia, indicative of central nervous system pathology). This occurs secondary to inflammation following an autoimmune response specific to the central nervous system (Lassmann, Van Horssen, & Mahad, 2012; Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018). MS targets the insulating myelin on axons in the central nervous system, destroying them to varying degrees. As the sum total of these smaller lesions compounds, this demyelination and neurodegeneration leads to 0.5%-1.35% total brain volumetric loss annually (De Stefano et al., 2014) and widespread lesions within the spinal cord. These lesions are diffuse and can be found in both neural GM and WM. The disorder is understood to be caused by a combination of genetic, environmental, and lifestyle factors (Olsson, Barcellos, & Alfredsson, 2016). Onset of MS symptoms happens much earlier in life than it typically does in HD or PD, commonly in early adulthood. Clinically, early MS is usually

expressed via acute episodes of neurological deficits, known as relapses. The symptoms experienced during relapses are specific to the area of the central nervous system affected and the extent of neurodegeneration (Thompson et al., 2018). Deficits span motor, cognitive, and neuropsychiatric domains which may manifest independently of each other or in any other co-occurring combination (Feinstein, Deluca, Baune, Filippi, & Lassman, 2013). As a result, the symptom profile in MS is heterogeneous.

There are four clinical courses of the disease, based on the rate of disease progression. Relapsing-remitting MS (RRMS) is characterised by sudden intensification of symptoms followed by periods of remission. Primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive-relapsing MS (PRMS) are defined by their continuous nature. In PPMS and SPMS the patients do not experience remission as the neural deterioration and symptoms become gradually worse. Most RRMS patients will develop SPMS as the disease progresses, whereas PPMS patients experience the progressive nature of MS from the onset. In PRMS there are no periods of remission or improvements between acute relapses as the symptoms get gradually worse over time (Chiaravalloti & DeLuca, 2008). Although statistics suggest a very high likelihood of RRMS patients developing SPMS (~80%), there are indications that, if the disease is actively managed, only 11.3% of patients transition from RR to SP MS stages within a ten-year follow-up (Cree et al., 2016). In other words, evidence suggests that progression can be ameliorated with taking appropriate measures. At the moment, pharmaceutical treatments have been developed for relapsing-remitting stages of the disease and those target neuroinflammation, not neurodegeneration *per se*. This is to reduce the severity of new demyelination episodes and relapses (Lassmann et al., 2012). Non-pharmacological treatments, such as exercise, physiotherapy, cognitive behavioural therapy, occupational therapy are also used (Thompson et al., 2018). There are no current pharmacological treatments for later, progressive stages of MS.

Among other symptoms, cognitive impairment has been recognised as a core component of MS, occurring in approximately 40-65% of patients (Amato, Zipoli, & Portaccio, 2006; Julian, 2011). Where present, cognitive symptoms develop early in the disease. There is individual variability in the expression of the symptoms, depending on the MS subtype (Sumowski et al., 2018). Progressive variants of MS result in more severe cognitive deficits when compared to RRMS (Julian, 2011). Cognitive deficits manifest as decreased information processing speed and efficiency, reduced complex attention,

poorer executive functioning, verbal fluency, and long term memory (Chiaravalloti & DeLuca, 2008).

4.3.3.1. The neural basis of cognitive impairments in MS. White matter

Traditionally MS has been associated with WM damage. MRI is routinely used as a diagnostic tool (Sumowski et al., 2018) and cognitive impairments are usually linked to accumulation of WM lesions seen as T2-weighted MRI hyperintensities on MRI scans (Calabrese et al., 2009; Yildiz, Tettenborn, Radue, Bendfeldt, & Borgwardt, 2014). Widespread WM deterioration is present across the whole brain. More specifically, structural WM atrophy can be found diffusely spanning frontal lobe regions, such as superior part of corona radiata, forceps minor, bilateral superior longitudinal fasciculus, through to temporo-occipital lobes – cingulum, bilateral fornix, bilateral ILF, bilateral IFOF, cortico-spinal tract, forceps major, bilateral cerebellar hemispheres, dorsal part of the pons, rostral part of the medulla oblongata, bilaterally. CC, corona radiata and thalamic radiations are also disrupted by the disease (Riccitelli et al., 2012; see Roman and Arnett, 2016, for review). This list of regions helps to illustrate the widespread nature of WM atrophy – and total WM lesion volume and area, as well as measures of global WM structural connectivity are linked to impaired executive functioning performance and global cognitive impairment (Nourbakhsh et al., 2016; Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989). This relationship between WM integrity and cognitive impairment can be observed in very early stages of MS diagnosis and, over time, cumulative increases in WM lesion volume parallel the progression of cognitive decline (Ouellette et al., 2018).

However, there is some further granularity in terms of WM damage and direct links to cognitive and executive deficits. It seems that mostly CC and frontal WM are implicated in executive deficits in MS. Similarly to HD and PD, disruption to the CC has been associated with impaired cognitive processing in MS, particularly reduced processing speed (Roosendaal et al., 2009). These patterns have also been observed in the benign phenotype of MS, where symptom expression is minimal, although not absent, for considerable periods post onset. Benign MS patients also display decreased FA values in the CC genu, associated with impaired verbal learning and memory, and decreased FA in the CC body, associated with poorer executive functioning more generally (Bester et al., 2013).

WM damage has been observed in frontal executive control and working memory networks, particularly in WM tracts connecting bilateral ACC, bilateral thalami, middle and IFG (Audoin et al., 2007). Decreased FA and increased Apparent Diffusion Coefficient (indicating neurodegeneration) in the frontolateral WM regions have been associated with reduced information processing speed and executive functioning (Roca et al., 2008). Decreased integrity in frontoparietal networks has been linked to lower attention (Llufriu et al., 2017). Reduced frontal WM volume has been linked to impaired inhibition (Ternes, Clough, Foletta, White, & Fielding, 2019). Although not a WM structure *per se*, thalamic WM atrophy has been linked to poorer executive control, as measured by a battery of cognitive tests (Benedict et al., 2013). This is not surprising as thalamus is robustly implicated in MS in general.

Although WM connectivity is reduced at the whole brain level in MS, regional increases in WM connectivity correlating with impaired attention have also been observed (Llufriu et al., 2017). This pattern is mirrored in measures of functional connectivity where regional increases in functional connectivity can be observed despite global reductions in activity (Rocca et al., 2018). Overall reduction in resting state functional connectivity correlates with T2 lesion load and severity of cognitive impairment, and as such these patterns may indicate compensatory mechanisms, potentially similar to the compensation through CR mechanism by which bilingualism may have an impact. Alternatively, the need for such compensatory alterations may be reduced in bilingual individuals with MS if there is greater CR within an affected network, maintaining function in the presence of damage and reducing the need for additional support.

4.3.3.2. Subcortical grey matter

Despite the clinical focus on WM impairment in MS, deterioration in both cortical and subcortical GM can be observed, although the exact pathogenesis and cause of demyelination and neuroaxonal degeneration of GM is not fully understood in this disease (Geurts & Barkhof, 2008). Even in the earliest stages of MS diagnosis, RRMS patients exhibit reduced volumes of the bilateral thalamus, hippocampus, caudate nuclei and putamen. Volumetric reductions in these structures have been linked to reduced processing speed, attention, working memory, executive functioning and wider cognitive impairments although neural impairment does not manifest behaviourally in the early

stages of MS (Audoin et al., 2010). The thalamus and putamen are further associated with impairment on verbal fluency and category switching measures of executive control and reduction in thalamic and hippocampal volume is linked to visuospatial and visuoperceptual impairment (Debernard et al., 2015). Hippocampal volume has also been related to episodic memory and information processing speed (Koenig et al., 2014).

The structure most robustly showing links to cognitive impairment in MS, however, is the thalamus. This GM structure has been consistently implicated in MS and remains the most sensitive biomarker of the severity of neuropsychological decline (Papathanasiou et al., 2015; Schoonheim et al., 2015) with volume decreasing linearly as the disease progresses (Ouellette et al., 2018). Thalamic deterioration has also been showed to impact performance across a variety of cognitive domains. Benedict et al. (2013) showed that thalamic volume predicted performance in tasks measuring verbal learning and memory, cognitive processing speed in visual and auditory modalities, and higher executive function. These findings have been supported by results from a large multicentre study showing decreased thalamic volume and also increased functional activation to predict poorer information processing speed and executive functioning (Koini et al., 2016). These results indicate structural damage, which may be temporally ameliorated by increased BR, and altered function, which may be supported by increased CR within the network. Indeed, bilingualism has been shown to have an effect on thalamic shape and contribute to volumetric expansion of the structure in healthy adults (Burgaleta et al., 2016; Pliatsikas et al., 2017), as a structure which has been implicated in a network underlying executive control and language control in bilingual individuals (Abutalebi & Green, 2016).

4.3.3.3. Cortical grey matter

MS can result in widespread deterioration in cortical GM across the frontal, parietal, temporal, and occipital lobes of the cortex, the bilateral insula and posterior cingulate cortex and bilateral cerebellum (Riccitelli et al., 2012). The scattered nature of cortical GM deficit is evident and a general association between global cortical GM volume and cognitive performance has been established (Calabrese et al., 2009; Fenu et al., 2018). There are also reports showing correlations between cortical GM thinning and both WM lesion volume and severity of cognitive impairment. This is most evident in the cingulate gyrus, insula and, and frontal regions of the brain (Charil et al., 2007). In a

large multicentre study, it was found that while there was a global cortical GM atrophy in MS, there were only marginal differences in cortical GM thinning between cognitively impaired and cognitively preserved MS patients. Links between GM thinning in the parietal regions and visual memory performance, as well as thinning in the insula and verbal memory were also established (Tillema et al., 2016).

While cortical GM decline is rather widespread and general, one structure that seems to contribute to cognitive performance in MS is the cerebellum. Studies have found atrophy in the right cerebellum to correlate with scores of the Extended Disability Status Scale (EDSS) (although there is a rather significant motor component to EDSS) (Audoin et al., 2010) and there is evidence, supplementing previous knowledge of cerebellar involvement in motor dysfunction in MS, showing correlation between the cerebellar volume and cognitive performance in MS (Weier et al., 2014). Looking at the cerebellum in finer detail, deterioration of some parts of it would underlie motor disability, while others would predict to cognitive deficits (Grothe, Lotze, Langner, & Dressel, 2017).

In sum, global GM damage predicts the severity of cognitive impairment. However, on a regional level, cortical GM atrophy does not seem to play a role in MS-related cognitive and executive deficits comparable to the effects arising from precise and localised WM and subcortical GM deterioration.

4.3.3.4. Evidence for general cognitive/brain reserve in MS

There is extensive evidence that cognitively active lifestyles have an impact on cognitive and neural outcomes in MS. Factors such as premorbid intelligence measures (Sumowski, Chiaravalloti, Wylie, & Deluca, 2009), engagement in reading and writing (Sumowski et al., 2016), education level, premorbid leisure activities and IQ (Amato et al., 2013; Fenu et al., 2018) are associated with higher functioning, Longitudinally, MS patients with more years of education and higher North American Adult Reading Test (NAART) scores (measure of verbal intelligence) showed less cognitive decline over time a five year period (Benedict, Morrow, Weinstock Guttman, Cookfair, & Schretlen, 2010). These data suggest that cognitively demanding activities improves brain health and ensures longer protection from cognitive impairment in MS (Giovannoni et al., 2016) and, indeed, cognitive intervention in MS patients leads to improved neuropsychological outcomes (Flavia, Stampatori, Zanotti, Parrinello, & Capra, 2010).

4.3.3.5. MS and bilingualism

Despite MS being a neurologically heterogeneous disease, there is still a considerable overlap between the neural substrates frequently implicated in MS and the substrates displaying evidence of BR in bilingualism. In particular, the CC and thalamus are candidates for increased BR with the potential to delay the onset of associated executive function symptoms. There is some evidence that neural compensation, through increased regional connectivity, is a mechanism already drawn on in MS and an increasing body of literature indicating that cognitive active lifestyles may build CR reducing the severity of symptoms. However, so far, only very limited research has directly examined the cognitive and neural effects of bilingualism on MS patients. Two recent, small-scale studies have found positive indicators for the impact of bilingualism on executive control tasks in MS. First, using a modified flanker task (following Costa et al., 2009), as a measure of inhibition and monitoring, Aveledo et al., (2020) showed that while there were no effects of bilingualism on inhibition in MS, bilingual MS patients showed similar monitoring performance to healthy bilingual controls. This was in contrast to monolingual participants where MS patients showed significantly larger monitoring cost than healthy monolingual controls. What these results suggest is evidence for bilingualism as a cognitive reserve factor in multiple sclerosis, manifesting as preserved monitoring functions. Although inhibition was not seemingly affected by bilingualism, the authors of the study rightfully point to an important limitation of this study, that is the fact that the bilinguals tested, although fluent and proficient L2 users, were not active and immersed users of their L2. Recall, that active engagement in bilingual language use is thought to drive the effects in brain function and structure (DeLuca, Rothman, Bialystok, et al., 2019; DeLuca, Rothman, et al., 2020), therefore more work is warranted in active bilingual MS patient populations to better understand any effects of bilingualism in MS. Thus, the preliminary results by Aveledo et al. are, indeed, promising and suggestive of bilingualism as a reserve factor adding to maintenance of executive functioning, at least monitoring abilities in MS. Second, bilingual participants with RRMS were found to display better non-verbal executive functioning in comparison to monolingual participants matched for age, sex, and socio-economic status (Soltani et al., 2018). While these studies indicate some degree of neuroprotection from the bilingual experience it should be noted that no differences between the bilingual and monolingual cohorts were found on Flanker reaction times or

verbal executive function measures in the same studies. Nevertheless, given the low participants numbers and consequently low statistical power, the results from these initial studies are promising and warrant further exploration of the impact of bilingualism on the cognitive profile in MS. To the best of our knowledge, only one study to date has investigated the impact of bilingualism on the MS brain: Ehling and colleagues (2019) administered L2 training to MS patients with bilateral lesion in the insula and temporal pole and healthy controls, who they also scanned pre- and post-L2 training. In line with literature showing that L2 training can lead to structural changes in the healthy brain (Hervais-Adelman & Babcock, 2019; Mårtensson et al., 2012; Stein, Winkler, Kaiser, & Dierks, 2014), the authors reported increased volume in right hippocampus, parahippocampal gyrus and putamen, whereas the healthy group showed volumetric increases in the left insula. The two groups did not differ in terms of their L2 proficiency at the end of the training. Ehling and colleagues treated their findings as indicators of unusually increased involvement of right hemispheric structures in L2 learning, and interpreted this as evidence for compensation in order to maintain normal cognitive function in the face of disease-related decline of other brain regions, therefore providing some evidence for CR in bilinguals with MS.

Despite all this promising evidence, it is worth pointing out that the impact of bilingualism may prove more challenging to measure in MS than in other conditions. The age of MS onset is younger – where the evidence for the impact of bilingualism is more variable; there are different subtypes and progressions of MS and significant heterogeneity in symptoms – resulting from diffuse damage in the condition. This variability would make the impact of bilingualism highly variable within the condition, particularly if the impact was mediated by BR or CR within executive function networks. In contrast, if bilingualism was found to have a relatively stable impact across MS despite different symptom profiles, this might indicate a compensation through increase CR mechanisms.

4.4. Discussion and Conclusions: Recommended directions to test bilingualism and general neurodegeneration more directly in the near future

Having discussed the cognitive and neuroanatomical literatures for both healthy (younger and older) bilinguals, as well as those pertaining to neurodegenerative clinical populations, a few points stand out related to the goals of this discussion. In light of gains in cognitive and neural reserves that active bilingualism is likely to provide, the evidence

across the lifespan that supports such a claim and especially the promising indications from work on AD and MCI, there is a strong case to be made that more linking research is warranted. Nevertheless, investigating bilingualism as an ameliorative factor has not yet been fully capitalized on. Indeed, the notion of cognitive and brain reserve is pervasive throughout the studies of neuropathology of degenerative disorders in general, yet few are the studies that investigate bilingualism within this general remit, despite very compelling reasons to the contrary. To the extent that bilingualism is one ubiquitous, lifestyle enrichment activity that could promote the accumulation of cognitive and brain reserves over time, it makes sense that research on bilingualism and neurodegenerative disorders should be more prolific than it presently is and, more importantly, that there would be a centralized goal of such research. At present, as discussed above, there is too little research juxtaposed against the importance of the potential gains on multiple fronts. Not least, the study of potential effects of bilingual engagement within an array of neurodegenerative diseases pertaining to maintenance of better cognitive functioning and/or increased brain integrity for longer can shed unique light on the nature of underlying mechanisms that remain elusive, from those related to the constructs of reserves themselves to those specific to the pathologies of distinct disorders. For the existent, yet scant research—good as much of it is—there is a lack of a central theme or goal: studies on distinct disorders do not cluster, as we submit, they should, with common questions, aims and comparability of methods/procedures. The present roadmap, beyond bringing what exists together in one place, is also meant to be a call-to-action from quantitative as well as qualitative shifts in this regard. Not only are more studies needed, but the links between them need to be better understood. Instead of studying bilingualism and AD or bilingualism and HD, for example, we would be wise to see each as part of a general program to study the potential effects of bilingualism on neurocognitive disorders in general. This does not mean, of course, that specific questions and goals should not be asked/had for individual disorders. Conversely, we submit that larger questions transcending differences from disease-specific pathology interactions should be articulated where individual disorders provide evidence at a higher level. There is little doubt that important underlying differences between distinct disorders will translate to distinctions in how bilingualism effects will play out. However, pursuing a set of common questions as a first pass, sustained by sound linking to be empirically relevant, as we have attempted to frame herein, should add significantly to our ability to tease out

the role, if any, bilingualism can have as a lifestyle enrichment for aging and neurodegeneration more broadly.

The common aim is to ask and create methods to answer the following main question: *through the lens of bilingualism as a source of accruing cognitive and brain reserves, what is the linked role of bilingualism in the potential attenuation of symptom onset/progression for neurodegenerative disease*? Since previous research seems to point in the direction that bilingualism as a lifelong activity is a good candidate contributor to cognitive and brain reserves, exhaustively investigating the common question posed above is imperative and beneficial in multifarious ways. To the extent that there is some ameliorative (neutral or subtractive) effect of bilingualism across diseases (with comparable populations of bilinguals of course) then such could highlight underlying commonalities and/or dissimilarities across pathologies—where each relates to common brain structures that are better preserved or where each is otherwise subject to compensation from reserves. Differences in the same regard would provide a distinct mirror into the limits cognitive and/or brain reserve have for subparts of particular diseases. As well as similarities between the conditions, there is variation in pathological, neurological and symptom profiles between different progressive neurological disorders. Comparison of the impact of bilingualism across disorders, therefore, provides an opportunity to evaluate the neural and cognitive mechanisms underpinning the bilingualism effect. For example, MS presents with diffuse pathology, predominantly impacting WM, whereas HD and PD display a more balanced contribution of regions of focal GM and WM atrophy. Direct comparison may reveal insights into the relative contribution of GM and WM and may enable the evaluation of different mechanisms i.e. the impact of BR and CR when executive function networks are affected vs. the impact of compensation through CR when wider networks are disrupted.

As it pertains to intervention, we can appreciate perhaps the most important reasons to forge a new program. If bilingualism plays some role, then knowing precisely what this would be is all the more imperative since bilingualism is an organic process that can be supported better, promoted, avoided and/or even created where it does not currently exist. As scientists, it is not within our remit to associate evaluative labels to phenomena we observe. As such, we have tried to avoid throughout words like advantage, which is often used in bilingualism and cognition circles. While we cannot label something as being an advantage per se, it is possible to claim that something is more

advantageous to a certain desired result than something else. Such is the very remit of intervention, making the most beneficial recommendations towards a desired goal. If bilingualism creates opportunities for increases in reserves and to the extent such reserves ameliorate the devastating impact of neurocognitive diseases, if only in masking symptoms, then at present we might refer to bilingualism as an advantageous intervention. This is mainly because there are currently very few treatments for neurodegenerative disorders beyond those designed to prolong the onset of severe symptoms and palliative care. But science is advancing quickly. In the foreseeable future, many of these diseases are predicted to be much better understood or even have been cured (e.g., Lindvall and Kokaia, 2006; Wray and Fox, 2016). But early diagnosis is crucial precisely because the undoing of physiological damage to the brain is irreversible once set in. And so, while bilingualism can be viewed as an advantageous intervention today, it could be quite the opposite in decades to come. Having an onset of overt symptoms 4-5 years later while the brain's deterioration is compensated for via cognitive and brain reserve would become severely disadvantageous when better treatments become available. Nevertheless, and perhaps even more important in such a scenario, is knowing definitively if there is the loop with bilingualism we have suggested herein.

In sum, the initial findings about bilingualism as a factor delaying the onset of clinical symptoms of AD came from studies looking at medical records (e.g., Alladi et al., 2013). Since then, the field has moved on to experimental studies testing these claims and directly examining the differences between monolingual and bi- or multilingual AD and MCI patients (e.g., Duncan et al., 2018). As we have suggested, though, the field is ready to expand this more broadly to beyond these two disorders. As a first step, it would be extremely valuable to see similar studies to Alladi et al. (2013), at least looking at medical records done for the effects of bilingualism on HD, PD, MS and more. This should be attainable with relative ease, if the right demographic data are collected. At the same time, as a field, we need to begin (or continue, as is the case for MCI and AD) experimental research, examining clinical effects of bilingualism directly in patient populations – as evident from the review above, there are a mere few studies per disorder that cannot provide satisfactory amount of evidence for global conclusions. There is also a subset of literature looking at acute, non-progressive neurodegeneration and the effects of bilingualism on it, not discussed here due to the fundamentally different clinical profile of such disorders. However, akin to the studies reviewed herein, they predict better

clinical outcomes, due to hypothesized bolstered brain and/or cognitive reserves. Most prominently, it is reported that bilingualism is a predictive factor for improved post-stroke cognitive outcomes (Alladi et al., 2016), as well as less severe expression of post-stroke aphasia symptoms (Paplikar et al., 2018). These preliminary results suggest neurocognitive effects of bilingualism even in scenarios of non-progressive neurodegeneration and opens up research avenues encompassing an increasingly wider scope on interactions between bilingualism and neurological conditions.

The program that emerges will have to consider the individually complex and variable nature of the bilingual experience itself. Historically, research on bilingualism has addressed bilingualism as a binary variable – that is, either one is bilingual or monolingual. However, there are many different types of bilinguals, ranging from native bilinguals who grow up speaking two L1s, to adult second language learners who attain fluency in a second language in and outside L2 immersion settings. Although all examples could be placed in a 'bilingual' group, the variability in their bilingual language experiences could translate to important distinctions in cognitive and neural effects. Significant amounts of variability within these bilingual individuals is bound to be lost if individual differences are collapsed across to form unnuanced bilingual vs. monolingual groups. Indeed, a wealth of recent research is calling for a more nuanced exploration of bilingualism and treatment of it as a spectrum of experiences that it is (Bialystok, 2017; DeLuca, Rothman, Bialystok, et al., 2019; DeLuca, Rothman, et al., 2020; Gullifer & Titone, 2020; Leivada, Westergaard, et al., 2020; Luk & Bialystok, 2013; Pliatsikas et al., 2020). Needless to say, a monolingual vs. bilingual classification is no longer tenable to study the detailed effects of engagement with more than one language on CR/BR in the older age. Future studies should be careful about the level of detail in bilingualism profile data. To this end, it is recommended that studies adopt a single common or maximally comparable background questionnaires such as the Language and Social Background Questionnaire (LSBQ) (Anderson, Mak, et al., 2018) or Language Experience and Proficiency Questionnaire (LEAP-Q) (Marian, Blumenfeld, & Kaushanskaya, 2007). These are available in an impressive number of languages and do an excellent job in gathering relevant information and provide normed rubrics for composite scoring of key factors of engagement over the lifespan at various levels. Biological and clinical outcomes may vary depending on a range of factors, such as, but not limited to age of acquisition, frequency and context of language use, immersion in

language environments and more. It is important to capture this level of detail, which would allow one to test people within the bilingual community without the need of a monolingual control group (more ecologically valid bilinguals-to-bilinguals comparisons). Testing individuals within the same community based on their differences in bilingual language experiences and engagement may also allow us to eliminate some of the social confounding effects that are inevitable when comparing two groups drawn from distinct environmental populations.

Finally, it is important to stress that bilingualism as a CR/BR factor does not exist in isolation from other CR/BR contributors, any more than other lifestyle enrichment factors would do (e.g. high degree of psychical exercise is not mutually exclusive to higher levels of education). In fact, since more than half the world is bilingual, a much higher percentage of the general population than high education and individuals with a balanced diet and high engagement with psychical activity, bilingualism is more diverse and diffused and, thus, likely to co-occur with other relevant life-style enrichment factors. Unfortunately, many studies that investigate the effects of bilingualism on building up CR/BR, functionally ignore the potential effect of co-occurring factors (Valian, 2015), such as physical exercise, education, occupational attainment, premorbid intelligence, or engagement in intellectually demanding leisure activities. Future research has to bring together these parallel strands of research and consider bilingualism as part of wider set of CR/BR factors, alongside as well as above and beyond the effects of co-morbid lifestyle factors. Only then will it become possible to control for other potential confounds and establish with greater clarity the unique contribution of bilingualism in improving CR/BR or any of the other factors. Moreover, in our effort to make sure that this emerging program contributes to the better understanding of the underlying biological mechanisms of bilingualism and its contribution to improved clinical outcomes, future research will have to be a truly interdisciplinary enterprise.

CHAPTER 5: GENERAL DISCUSSION AND FUTURE DIRECTIONS

5.1. General discussion of the results

The literature on the neurocognitive effects of bilingualism in ageing, and especially studies linking both brain and behaviour in this context, remains relatively scarce. In general, the findings seem to converge on the fact that bilingualism provides neuroprotection in the older age, with more preserved brain structures, which can be interpreted as increase of brain reserve (Gallo et al., 2020; Luk et al., 2011; Olsen et al., 2015). Bilingualism has also been associated with better preserved executive functions, episodic memory, and even general cognition in the later years of life (Bak et al., 2014; Bialystok, Poarch, et al., 2014; Ljungberg et al., 2013; Schroeder & Marian, 2012). Moreover, bilingualism has also been linked to delayed onset of dementia symptoms such as episodic memory impairment, by about 4-5 years (Alladi et al., 2013; Bialystok et al., 2007; Craik et al., 2010). Where studies have investigated brain structure in dementia, the finding is that bilinguals, matched for monolinguals for cognitive status, would exhibit *more* atrophy in their brains (Duncan et al., 2018; Schweizer et al., 2012). Essentially, this finding illustrates a mismatch between the extent of brain atrophy and severity of the symptoms, suggesting a compensatory mechanism at play in bilingual individuals. This mismatch can be operationalised via the theoretical construct of cognitive reserve, i.e., individuals with higher cognitive reserve are able to maintain cognitive functioning when facing neurodegeneration (Perani & Abutalebi, 2015). The exact mechanisms behind accumulation of these reserves are not well known, nor is the nature of how these reserves might interact, as cross-sectional studies can only provide data from a set moment in time. However, a way to address this question could be to examine individuals transitioning from healthy ageing to disease – those with a diagnosis of MCI. Furthermore, the practice of treating bilingualism as a dichotomous variable is still very prevalent in the clinical and ageing bilingualism literature. While bilingualism has been shown to contribute to cognitive and brain reserves, very little, beyond the dementia diagnosis delay, is known about the finer detail within bilingualism and how that might affect ageing trajectories. With all above in mind, it makes theoretical sense to examine the effects of bilingualism in episodic memory and supporting neural substrate, in ageing populations. Moreover, if bilingualism offers beneficial effects with

regard to Alzheimer's disease, are there motivation for such effects to be limited only to this disease, or would said effects extend to other types of progressive neurodegeneration too? This question, while theoretically motivated, does not have a conclusive answer in absence of empirical data.

The primary goals of the thesis were to examine the links of bilingualism and the bilingual experience to episodic memory and the supporting neural structures, with a focus on the hippocampus (implicated in decline associated with healthy and clinical ageing) and use the available evidence to evaluate the possibility of bilingualism being a more generalised protective factor in other types of dementia, beyond more commonly studies Alzheimer's disease. Three studies investigating the role of bilingualism in healthy and clinical ageing were presented. The first two studies were empirical investigations on the topic by specifically focusing the effects of bilingualism on episodic memory, the hippocampus, and neural substrate known to be sensitive to bilingualism and ageing. The final study was an epistemological study – a thorough focussed review on research spanning neurodegenerative diseases and neurocognition of bilingualism, with an aim to link these parallel literatures. The results of the first study showed an effect of bilingualism on the volume of the bilateral hippocampus in healthy older individuals, although there were no significant effects of bilingualism on the episodic memory performance. The second study was run to see if similar effects extend to individuals transitioning from health to disease. Specifically, a group of bilingual individuals with an MCI diagnosis was examined with bilingualism operationalised as a continuous variable based on self-reported active engagement in bilingual language use. The group with the MCI diagnosis was chosen as it lies in a transitionary grey area and is underrepresented in the current body of research. It can also reveal the relationship and interaction between brain and cognitive reserves – the former has been predominantly shown in healthy populations, while studies examining dementia patients reveal results suggesting presence of the latter. Here, it was shown that active engagement in the use of two languages leads to volumetric increases in the hippocampus and the right supramarginal gyrus, as well as reshaping in the right caudate nucleus and right amygdala, regions related to language processing and cognitive control (Pliatsikas, 2020) and shown to be enhanced in healthy bilinguals (DeLuca, Rothman, & Pliatsikas, 2019; Mårtensson et al., 2012; Mechelli et al., 2004; Pliatsikas et al., 2017). Mirroring the results of the first study, there was no effect of active bilingualism on episodic memory function. Further than that,

active bilinguals showed a later onset of MCI symptoms and a later MCI diagnosis by about 1.5 years. This delay was significantly predicted by the extent of bilingual language engagement. The studies also built on the current direction for treating bilingualism as a spectrum, as opposed to a monolingual-bilingual dichotomy. The results of these studies are complementary to one another, showing similar outcomes of bilingualism in healthy older adults and those with MCI, suggesting of a neural reserve of this structure in the studied populations. Therefore, it is relevant to discuss the hippocampus and its significance in further detail.

The hippocampus is crucial in episodic memory function (Gorbach et al., 2017). It has is also shown to exhibit more rapid deterioration in healthy ageing, compared to other brain structures (Fjell et al., 2009). Hippocampal atrophy has been linked to development of Alzheimer's disease and more rapid transition from MCI to dementia (Anand & Dhikav, 2012; Apostolova et al., 2006). As such, this structure is firmly implicated in the symptoms exhibited by Alzheimer's disease sufferers and shown to be a key locus of neuropathology in Alzheimer's disease (Scheltens et al., 2016). If bilingualism provides brain reserve for the hippocampus in ageing, including MCI, and the symptoms associated with dementia are linked to this structure, it is entirely plausible that the neuroprotection of the hippocampus plays a key role in the behavioural delay of symptom onset in progressive neurodegenerative diseases. With this finding, the present PhD project is the first to link neuroprotection of a particular structure to wider behavioural consequences acknowledged in the literature, specifically, the body of research linking the presence of bilingualism to delayed behavioural manifestations of neural degeneration. Note that there is a disengagement between structure and function in the studied populations. While the findings show volumetric differences in the hippocampus, they do not manifest in significant behavioural differences, at least in early stages of neurodegeneration.

The question then arises, if bilingualism could present a more generalised factor, not only for AD and MCI, but also for other types of progressive neurodegeneration, such as Huntington's disease, Parkinson's disease, and Multiple Sclerosis. The results from the epistemological investigation in the final paper of this thesis suggest that there are good reasons to expect so. Alzheimer's disease has commonalities with other types of progressive neurodegeneration, such as Huntington's disease, Parkinson's disease and Multiple Sclerosis. While it is imperative to acknowledge the differences between the

diseases, there is an overlap on the brain areas known to be affected in these diseases and areas implicated in bilingualism. For example, Huntington's disease is primarily associated with decline in the striatum (Finkbeiner, 2011), Parkinson's disease patients present reductions across the basal ganglia (Vasconcellos et al., 2018), and Multiple sclerosis sufferers primarily exhibit widespread white matter deterioration, including tracts reported to be reinforced by bilingualism (Roman & Arnett, 2016). In research examining contribution of other cognitive and brain reserve factors (excluding bilingualism) to disease development, it has been found that active cognitive lifestyle provides neuroprotection in Huntington's disease (Garcia-Gorro et al., 2019), improved cognitive outcomes in Parkinson's disease (Hindle et al., 2014), and slower cognitive decline in Multiple sclerosis (Benedict et al., 2010). Based on these findings, and from research showing bilingual enhancement of the implicated structures, in this paper bilingualism is proposed to be a promising avenue for bilingualism to be viewed as a more general neuroprotective factor across different types of progressive clinical neurodegeneration.

With particular reference to the findings of the present studies is the role of hippocampal atrophy in the development in these disorders as well. Hippocampal impairments are an early feature of Huntington's disease (Begeti, Schwab, Mason, & Barker, 2016), linked to cognitive dysfunctions, including memory impairment, sometimes present in Parkinson's disease (Calabresi, Castrioto, Di Filippo, & Picconi, 2013; Das et al., 2019), and Multiple Sclerosis where hippocampal atrophy is present even before onset of linked memory impairment (Roosendaal et al., 2010; Sicotte et al., 2008). These commonalities strengthen the argument for accumulation of bilingualism-related brain reserve of the hippocampus as a potential key contributor to improved cognitive ageing trajectory and delayed development of cognitive symptoms in other progressive neurodegenerative diseases.

To summarise, the three studies of this PhD research project show promising results in terms of active bilingualism as a brain reserve contributor factor in clinical and healthy ageing populations. Crucially, the results suggest the hippocampus to be a key region, neuroprotection of which can be linked to more successful cognitive ageing and protection from dementia symptom onset, whereas some promising results are also presented for the striatum.

Note that the hippocampus, or, indeed, any effects of bilingualism on the ageing brain, have not been central to the theoretical models concerning the neurocognitive effects of bilingualism, such as the Adaptive Control Hypothesis (Green & Abutalebi, 2013), Dynamic Restructuring Model (Pliatsikas, 2020), Bilingual Anterior to Posterior and Subcortical Shift (BAPSS) (Grundy et al., 2017) or the Unifying the Bilingual Experience Trajectories (UBET) model (DeLuca, Segaert, et al., 2020). Specifically, the ACH concerns the adaptations of language and cognitive control networks in response to variable bilingual experiences and contexts; DRM explains the variability in findings in the literature as an outcome of the dynamic nature of the bilingualism; UBET considers a variety of factors, namely the diversity and intensity of language use, language switching, relative proficiency, and duration of use; BAPSS shows a functional shift to increased reliance from anterior to posterior and subcortical networks. The hippocampus has been shown to be implicated only in immersive and intensive bilingual language contexts (DeLuca, Rothman, & Pliatsikas, 2019; Mårtensson et al., 2012). Therefore, greater involvement of the hippocampus in the context of bilingualism might be specific to experienced bilingual populations. Since the hippocampus is a central structure in learning and consolidation of new explicit information, including vocabulary (Ullman, 2004), the observed effects suggest that the constant and dynamic learning provided by immersive bilingualism might lead to more generalised neuroprotective effects in the older age. This could be expressed by development of brain and cognitive reserves, so far not accounted for by any of the above models. Such findings and suggestions should be evaluated against prevalent models of cognitive ageing, such as posterior to anterior shift in ageing (PASA) (Davis et al., 2008). Future research will have to extend or adapt such models by including bilingualism effects across all age groups.

5.2. Future directions

Investigating the neurocognitive effects of bilingualism in ageing and clinical contexts is still at its infancy and thus the overall body of research is relatively small. This is especially true for clinical populations, where evidence examining the relationship between bilingualism and accumulation of brain and cognitive reserves, thus potentially altering the clinical expression of disease remains extremely limited. Bilingualism, ageing, and reserve mechanisms interact in complex ways and there is a need to understand the measures better. Further research is warranted and will have to address related questions. Moving forward, it is important to keep in mind the nuance needed

when studying bilingualism and brain reserves, as well as covariates associated with development of said reserves. In all, the following sections will highlight the factors and issues that need to be considered in future research.

5.2.1. Operationalisation of bilingualism

Traditionally, bilingualism has been considered to be a binary variable, which allowed for straight-forward between groups comparisons. This approach has recently been overhauled, with an increasing understanding that bilingualism is a dynamic, multidimensional experience, each of which can underly specific neurocognitive adaptations (DeLuca, Rothman, Bialystok, et al., 2019; Luk & Bialystok, 2013). It is, after all, intuitive that bilingual native English speakers who speak a second language but reside in the UK would exhibit different adaptations to immersed bilinguals switching between their languages on a daily basis in a multilingual context such as, for example, Luxembourg, rendering these groups almost incomparable.

So far research in ageing has seldom treated bilingualism as a spectrum, which might have contributed to the contradictory findings in the field. We have expanded on this notion in the present thesis, by using the level of active bilingual engagement as a proxy for bilingualism in some analyses. Our pattern of results decisively demonstrates a crucial role of active engagement in bilingual language use in the neurocognitive adaptations in ageing. However, further individual differences in the bilingual experience need to be accounted for in any future research. In order to bring this area of research forward, studies will need to take into account more detailed information on the individual profile of the bilinguals, especially of their language usage. This will require collection of detailed language background information, including length of second language use, language use patterns and language switching behaviours, age of L2 acquisition, etc., which would allow to build a comprehensive linguistic profile of each individual research participant. This is rather easy to do in a lab-based research context, where the participant can be asked to complete a language background questionnaire, for example the LSBQ (Anderson, Mak, et al., 2018) or LEAP-Q (Marian et al., 2007), or measuring diversity of language use contexts such as the measure of language entropy (Gullifer & Titone, 2020). It becomes more complex in studying individuals with a clinical diagnosis, where detailed language profile is not collected as part of the clinical background information. This change would not be too burdensome to implement, if only

at certain participating hospitals, which would provide a better insight in effects of bilingual language use on clinical trajectories of neurodegeneration patients.). To sum, the future lies in avoiding dichotomies; group differences may be more straightforward to observe and interpret, but this belongs to research of the past these days, as the field moves towards a more nuanced account of individual differences in bilingualism.

5.2.2. Covariates or other sources of cognitive reserve

In addition to detailed language profiles, there is a great need to collect social background information of bilingual and monolingual individuals. Bilingualism does not stand alone as a cognitive reserve contributor factor. There are other factors, that have been linked to the same effects in the older age as the bilingualism, such as educational and occupational attainment, physical activity, healthy diet, engagement in cognitively stimulating leisure activities and leading a healthy cognitive lifestyle more general (Stern, 2012). A major issue in bilingualism research has been the complex ways bilingualism interacts with such confounding variables (Bak, 2016b). Bilingualism is not the only contributor to building-up of cognitive and neural reserves, therefore more attention needs to be paid towards gathering appropriate data (Calvo et al., 2016). Further than that, the role of immigration status also has to be carefully considered when establishing the relationship between cognitive reserve and bilingualism (Guzman-Velez and Tranel, 2015).

The issue of many sources is exemplified across the parallel literatures. An important observation linked to the need to account for various covariates is the lack of overlap in methods between bilingualism and ageing literature and literature investigating ageing altogether. Investigations on bilingualism tend to focus on the unique contribution of this factor, while more general research on cognitive and neural reserves, and ageing tend to omit bilingualism as a reserve factor altogether, while using an array of other factors though to contribute to the accumulation of brain and cognitive reserves (e.g., Yaffe et al., 2009). Bilingualism should be more integrated within wider literature, as there is now a critical mass of research showing bilingualism to be a contributor to more successful cognitive ageing. Leaving this information out seems like a serious oversight, especially in light of the prevalence of bilingualism worldwide. Integrating the two parallel fields would improve the overall approach to the topic. However, when it is done,

it should be done properly, by keeping in mind the nuance associated with bilingualism as well as the interaction between bilingualism and other reserve factors.

5.2.3. Studying the effects of bilingualism in the long term

A major issue that needs to addressed is the lack of longitudinal investigations linking bilingualism and neurocognitive adaptations. As discussed elsewhere in the thesis, the differences in brain structure associated with bilingualism, can be interpreted as either build-up of brain matter, or a structural reinforcement of the brain in bilinguals. However, it is also possible that in bilinguals the implicated brain structures are just more resilient to decline, than in monolingual individuals. Therefore, in cross-sectional studies, which constitute the majority of the relevant literature, it is not possible to tell brain reserve apart from brain maintenance (i.e, reduced development of brain atrophy over time) (Stern et al., 2018), as they manifest exactly the same if measurement is taken only once. Thus, longitudinal studies across the life span are required to fully expose the emergence of brain reserve and/or brain maintenance, and manifestation of cognitive reserve, and follow the evolution of the relationship between cognitive decline and language usage (Poarch and Krott, 2019).

Directly following the discussion of the final paper of this thesis, future studies should test the protective effects of bilingualism in other neurodegenerative diseases. The current evidence is small and mixed, yet, there are very good theoretical reasons to extend the research programme to the diseases discussed in this paper. Further than that, some initial evidence links bilingualism to improved outcomes in neurological disorders that are not characterised by progressive neurodegeneration, such as epilepsy, or stroke, yet this body of literature is so small that any conclusive statements would be premature.

As a final note with regard to study design about studies examining cognitive control in bilingualism and also brain is a classical criticism of most MRI studies in general. Typical sample sizes in neuroimaging investigations by individual research groups tends to be quite small, lacking in statistical power. This is an issue related to practicalities as neuroimaging is taxing in manpower and financial costs. Therefore, multi-lab international consortia should be formed to link bilingualism, brain, and behaviour, while controlling for the covariates laid out in the previous paragraphs.

5.2.4. Public health implications and bilingualism as a potential (clinical) intervention

The proposed effects of bilingualism on clinical ageing might have an impact on public health policies across the globe. Development of disease-modifying treatments for Alzheimer's Disease is unlikely in the near future (Del Maschio et al., 2018). At the same time, invention of an effective AD therapy has been acknowledged as "the greatest unmet need facing modern medicine" (Winblad et al., 2016), and the potential of reducing the burden on health infrastructure, under increasing pressures across the world, would be of significant impact. Other than a relatively straight-forward way to promote successful cognitive ageing bilingualism may also prove to be a cost-effective way to delay the onset of dementia (Bialystok, 2016). This is especially important to do in the absence of pharmacological cures of dementia.

This possibility has already raised the discussion suggesting bilingualism as an intervention in clinical settings. Namely, there have been suggestions that training studies and second language teaching might be a solution to build cognitive reserve in older populations and thus promote postponement of ageing processes (Antoniou & Wright, 2017; Antoniou et al., 2013; Lövdén, Brehmer, Li, & Lindenberger, 2012). However, empirical studies to date find minimal or no effects on foreign language learning intervention in the older age (Bak, Long, Vega-Mendoza, & Sorace, 2016; Berggren et al., 2020; Valis et al., 2019), however, this remains an underresearched field (Klimova, 2018). Language learning intervention did not also result in enhanced switching ability (Ramos et al., 2017). Note that the training studies followed older individuals who started learning an additional language at the older age and typically tested them following a few months of language training. Therefore, the results of the present thesis suggest it is not quick training that may help build brain and cognitive reserves, especially in light of the positive correlations of bilingual language engagement and active language use with brain adaptations. However, active promotion of bilingualism may result in very tangible population health benefits.

5.3. Conclusions

It is becoming clearer that bilingualism has neurocognitive consequences in the older age. Previous research has revealed that speaking two languages can be beneficial in clinical contexts, as symptoms of neurodegeneration manifest later in life for bilingual

individuals. This PhD research project has advanced our understanding of the mechanisms behind the accumulation of cognitive and brain reserves, by integrating nuanced bilingualism data with neurocognitive measures. It is proposed that neural reserve in the hippocampus, brought about by bilingualism could be a key aspect of delaying the onset of disease symptoms. Furthermore, it is suggested that bilingualism effects may not be unique for Alzheimer's disease, but also extend to other types of neurodegeneration.

This PhD project does not provide a comprehensive answer to all questions on the relationship between bilingualism and other cognitive and brain reserve contributors, and how they can alter the course of cognitive ageing in bilingual populations. The exact interactions between various bilingual experience factors and their relative contributions to maintenance of the ageing brain are still yet to be determined, by carefully considering the aspects of bilingualism and social variables as predictors for brain status in the later years of life. However, this thesis has provided a novel insight in bilingualism-brain-behaviour links in the later years of life and suggested a roadmap for future research to be carried out in this domain.

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APPENDIX A

Language and social background questionnaire (LSBQ; Anderson et al., 2018), adapted for the UK context

YAV Reference ID _____

Appendix A

Language and Social Background Questionnaire

YORK UNIVERSITÉ UNIVERSITY

Lifespan Cognition and Development Laboratory
Ellen Bialystok, Ph.D., Principal Investigator
Department of Psychology, York University

Language and Social Background Questionnaire

Today's Date: _____ (Day Month Year) 1. Sex: Male ☐ Female ☐

2. Occupation/Student Status (i.e. FT/PT, current year of study): _____

3. Handedness: Left ☐ Right ☐ 4. Date of Birth: _____ (Day Month Year)

5. Do you play first-person shooting (FPS)/action video games? **Yes** ☐ **No** ☐
   If **yes**, on average how many hours do you play per week? _____
6. Do you have hearing problems? **Yes** ☐ **No** ☐
   If **yes**, do you wear a hearing aid? **Yes** ☐ **No** ☐
7. Do you have vision problems? **Yes** ☐ **No** ☐
   If **yes**, do you wear glasses or contacts? **Yes** ☐ **No** ☐
   Is your vision corrected to normal with glasses or contacts? **Yes** ☐ **No** ☐
8. Are you colour blind? **Yes** ☐ **No** ☐
   If **yes**, what type? _____
9. Have you ever had a head injury **Yes** ☐ **No** ☐
   If **yes**, please explain: _____
10. Do you have any known neurological impairments? (e.g., epilepsy etc) **Yes** ☐ **No** ☐
    If **yes**, please indicate: _____
11. Are you currently taking any psychoactive medications? **Yes** ☐ **No** ☐
    If **yes**, please indicate: _____

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YA Version (2016)

12. Please indicate the highest level of education and occupation for each parent:

Mother		Father	
1. _____	No secondary education	1. _____	No secondary education
2. _____	O levels/GCSE/A levels or equiv.	2. _____	O levels/GCSE/A levels or equiv.
3. _____	Some undergraduate education	3. _____	Some undergraduate education
4. _____	Undergraduate degree or diploma	4. _____	Undergraduate degree or diploma
5. _____	Graduate degree or equiv.	5. _____	Graduate degree or equiv.
Occupation:	_____	Occupation:	_____
First Language:	_____	First Language:	_____
Second Language:	_____	Second Language:	_____
Other Language:	_____	Other Language:	_____

13. Were you born in the UK? **Yes** ☐ **No** ☐

If **no**, where were you born? _____

When did you move to the UK? _____

Year

14. Have you ever lived in a place where English is not the dominant communicating language? **Yes** ☐ **No** ☐

		From	**To**
If **yes**, where and for how long?	1. _____	_____	_____
	2. _____	_____	_____
	3. _____	_____	_____
		Year	**Year**

Language Background

15. List all the language and dialects you can speak and understand including English, ***in order of fluency***:

Language	Where did you learn it?	At what age did you learn it? (If learned from birth, write age "0")	Were there any periods in your life when you did not use this language? Indicate duration in months/years.
1._____	☐ **Home** ☐ **School** ☐ **Community** ☐ **Other:** _____		
2._____	☐ **Home** ☐ **School** ☐ **Community** ☐ **Other:** _____		
3._____	☐ **Home** ☐ **School** ☐ **Community** ☐ **Other:** _____		
4._____	☐ **Home** ☐ **School** ☐ **Community** ☐ **Other:** _____		
5._____	☐ **Home** ☐ **School** ☐ **Community** ☐ **Other:** _____		

Relative to a highly proficient speaker's performance, rate your proficiency level on a scale of 0-10 for the following activities conducted in English and your other language(s).

16.1 **English**

16.2 Of the time you spend engaged in each of the following activities, how much of that time is carried out in English?

	None	Little	Some	Most	All
Speaking	☐	☐	☐	☐	☐
Listening	☐	☐	☐	☐	☐
Reading	☐	☐	☐	☐	☐
Writing	☐	☐	☐	☐	☐

17.1 **Other Language:** _____

17.2 Of the time you spend engaged in each of the following activities, how much of that time is carried out in this language?

	None	Little	Some	Most	All
Speaking	☐	☐	☐	☐	☐
Listening	☐	☐	☐	☐	☐
Reading	☐	☐	☐	☐	☐
Writing	☐	☐	☐	☐	☐

Community Language Use Behavior

18. Please indicate which language(s) you most frequently heard or used in the following life stages, both inside and outside home.

		All English	Mostly English	Half English half other language	Mostly the other language	Only the other language
18.1	Infancy	☐	☐	☐	☐	☐
18.2	Preschool age	☐	☐	☐	☐	☐
18.3	Primary School age	☐	☐	☐	☐	☐
18.4	Secondary School age	☐	☐	☐	☐	☐

19. Please indicate which language(s) you generally use when speaking to the following people.

		All English	Mostly English	Half English half other language	Mostly the other language	Only the other language
19.1	Parents	☐	☐	☐	☐	☐
19.2	Siblings	☐	☐	☐	☐	☐
19.3	Grandparents	☐	☐	☐	☐	☐
19.4	Other Relatives	☐	☐	☐	☐	☐
19.5	Partner	☐	☐	☐	☐	☐
19.6	Roommates	☐	☐	☐	☐	☐
19.7	Neighbours	☐	☐	☐	☐	☐
19.8	Friends	☐	☐	☐	☐	☐

20. Please indicate which language(s) you generally use in the following situations.

		All English	Mostly English	Half English half other language	Mostly the other language	Only the other language
20.1	Home	☐	☐	☐	☐	☐
20.2	School	☐	☐	☐	☐	☐
20.3	Work	☐	☐	☐	☐	☐
20.4	Social activities (e.g. hanging out with friends, films)	☐	☐	☐	☐	☐
20.5	Religious activities	☐	☐	☐	☐	☐
20.6	Extracurricular activities (e.g. hobbies, sports, volunteering, gaming)	☐	☐	☐	☐	☐
20.7	Shopping/ Restaurants/ Other commercial services	☐	☐	☐	☐	☐
20.8	Health care services/ Government/ Public offices/ Banks	☐	☐	☐	☐	☐

21. Please indicate which language(s) you generally use for the following activities.

		All English	Mostly English	Half English half other language	Mostly the other language	Only the other language
21.1	Reading	☐	☐	☐	☐	☐
21.2	Emailing	☐	☐	☐	☐	☐
21.3	Texting	☐	☐	☐	☐	☐
21.4	Social media (e.g. Facebook, Twitter etc.)	☐	☐	☐	☐	☐
21.5	Writing shopping lists, notes, etc.	☐	☐	☐	☐	☐
21.6	Watching TV/ listening to radio	☐	☐	☐	☐	☐
21.7	Watching films	☐	☐	☐	☐	☐
21.8	Browsing on the Internet	☐	☐	☐	☐	☐
21.9	Praying	☐	☐	☐	☐	☐

22. Some people switch between the languages they know within a single conversation (i.e. while speaking in one language they may use sentences or words from the other language). This is known as "language-switching". Please indicate how often you engage in language-switching. If you do not know any language(s) other than English, fill in all the questions with 0, as appropriate.

		Never	Rarely	Sometimes	Frequently	Always
22.1	With parents and family	☐	☐	☐	☐	☐
22.2	With friends	☐	☐	☐	☐	☐
22.3	On social media (e.g. Facebook, Twitter)	☐	☐	☐	☐	☐

Thank you for participating!