Flexible Aging

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Chapter 1

General introduction

"Cognitive flexibility is your ability to adjust your thinking when presented with unexpected events or situations. It is our ability to think on our feet. When we do not utilize cognitive flexibility, it can have some really serious implications. Without it, we can become stagnant, despondent, disillusioned, discouraged, or depressed. Without cognitive flexibility, we can find ourselves sinking into a perpetual state of purposelessness. Cognitive flexibility can be the difference between us living our best lives or not living at all. When life starts coming at you fast, as I promise you it will at some point, the only person who has the power to save you is you. Life's trials don't come along so that we can give up and quit. Cognitive flexibility was built for those moments. It affords us the opportunity to take life's lemons and make some lemonade."

From TEDx talk – dr. Chantrise Holliman

1.1 COGNITIVE FLEXIBILITY

Simply put, 'cognitive' pertains to the mind and 'flexibility' to the ability to modify and adapt. While this understanding of cognitive flexibility seems intuitive, it is a broad concept that in the past has been understood in many different ways. Hence, different definitions of cognitive flexibility are used in the literature. In neuropsychology, cognitive flexibility is generally defined as a specific cognitive ability, such as the ability to shift thoughts, actions, mental sets or tasks (Ionescu, 2012; Steinke & Kopp, 2020). Following this definition, there are many terms used to denote cognitive flexibility such as switching ability, shifting ability, task switching, set-shifting, mental flexibility, attentional flexibility, or flexible thinking. Departing from the notion of cognitive flexibility as a specific cognitive ability means that cognitive flexibility, or shifting, is often considered to be one of the core so-called executive functions, together with working memory and inhibition (Diamond, 2013; Miyake et al., 2000), although less consensus exists in the literature as to the exact cognitive processes that are executive functions. Most broadly construed, executive functions (or cognitive control) are taken to encompass a set of high-level cognitive processes that are involved in the deliberate and voluntary control of behavior, thinking and emotions (Miyake & Friedman, 2012).

Rather than one specific cognitive ability, in this dissertation cognitive flexibility is considered as a higher order property of the cognitive system: cognitive flexibility is highly involved in the dynamic production of diverse ideas, and activation and modification of behavior and cognition (Diamond, 2013; Rende, 2000). Based on this understanding, cognitive flexibility is needed to adjust our thinking, attention, or course of action in response to a changing environment, thereby facilitating the appropriate and efficient adjustment of an individual's behavior (Dajani & Uddin, 2015). For the successful implementation of cognitive flexibility as a property of cognition, the interaction of multiple executive functions and other cognitive processes is needed. Accordingly, cognitive flexibility builds on other executive functions and generally develops only after other important executive functions such as working memory and inhibition are in place (Davidson et al., 2006; Garon et al., 2008).

Rather than considering cognitive flexibility as a core executive function, it could therefore also be conceived as building on and extending executive functions. In turn, cognitive flexibility and executive functions might share a common component of attentional control (Garon et al., 2008; McCabe et al., 2010; Miyake et al., 2000). Attentional control is the ability to choose what to pay attention to and what to ignore, and is related to executive functions (Diamond, 2013). Attentional control could therefore be inherent to employing cognitive flexibility (i.e., shifting attention / flexibly employing attentional control) and could be considered a key building block of cognitive flexibility (Garon et al., 2008).

Text box 1. Glossary

Attention – the ability to choose what to pay attention to and what to ignore; has also been used as a synonym for executive functions; key building block of cognitive flexibility

Cognitive flexibility – higher order property of the cognitive system; ability to adjust our thinking, attention, or course of action in response to a changing environment; builds on executive functions; most commonly measured with set-shifting of task-switching tasks

Cognitive reserve – the mind's resilience to brain changes; acts as a dynamic and flexible mechanism in the brain to facilitate cognitive performance and compensate for fluctuations and changes in available hardware

Executive functions – cognitive control; high-level cognitive processes that are involved in the deliberate and voluntary control of behavior, thinking and emotions. Working memory, inhibition and shifting are often considered as executive functions

Inhibition – ability to control attention, behavior or thoughts to deliberately override dominant or competing behaviors or thoughts

Working memory – ability to short-term store and maintain information

In addition to different cognitive processes interacting, different brain networks also come together in the successful implementation of cognitive flexibility; cognitive flexibility is not controlled by a single network of brain areas. Instead, cognitive flexibility has been suggested to be the result of the cooperation of brain networks in at least the frontal and parietal cortices and the cingulate cortex (Dajani & Uddin, 2015; Kim et al., 2012; Uddin, 2021). Specific brain areas that have been found to be important for cognitive flexibility include, for example, the dorsolateral and ventrolateral prefrontal cortex (dlPFC and vlPFC), inferior frontal junction (IFJ), anterior insula and posterior parietal cortex (Dajani & Uddin, 2015). More specifically, the ventrolateral prefrontal cortex has been suggested to be involved in context monitoring, selection of a new response set, and inhibition of the previous set (Dajani & Uddin, 2015). The inferior frontal junction, in turn, is involved in inhibition and updating task rule representation, and the insula and anterior cingulate cortices in shifting attention to a new response set (Dajani & Uddin, 2015). The posterior parietal areas are suggested to be involved in attentional processing. All of these brain networks together underlie cognitive flexibility, but they most likely all distinctly and uniquely contribute to it. Moreover, their involvement in cognitive processes spans beyond cognitive flexibility alone (Dajani & Uddin, 2015; Kim et al., 2012).

1.2 MEASURING COGNITIVE FLEXIBILITY

Just as there are many ways to understand cognitive flexibility, there are also many ways to measure it. In fact, the definition of cognitive flexibility is often closely associated with and related to the neuropsychological tests that are used to assess it. Throughout this dissertation, we assess cognitive flexibility on a behavioral level using neuropsychological tasks, and on a neural level on the basis of brain activity measures. We discuss the different methods below.

As cognitive flexibility is often considered a specific cognitive ability, cognitive flexibility is often measured using 'simple tasks', aimed at measuring only a single cognitive process. Specifically in the context of aging research, frequently used tasks to assess cognitive flexibility include the Trial Making Test (TMT) and verbal fluency tests. At this point it will come as no surprise, however, that those tests that are supposed to measure cognitive flexibility, are also typically used to measure other cognitive processes, such as inhibition or attention. No single task measures one sole cognitive process, a problem that has come to be referred to as the task impurity problem (Miyake et al., 2000). The more complex a task at hand, the more applicable task impurity becomes.

Considering cognitive flexibility as order property of the cognitive system, requiring the cooperation of different cognitive processes (e.g., inhibition, working memory, attention) and brain regions, it is difficult to measure cognitive flexibility in isolation. Cognitive flexibility is therefore perhaps best measured using more complex tasks that require the coordination of multiple cognitive processes, reflective of the complexity of cognitive flexibility itself. This is, for example, the case in set-shifting tasks (e.g., the Wisconsin Card Sorting Task; WCST) or task-switching tasks (e.g., a color-shape switching task). In set shifting tasks, multiple rules (cognitive sets) are used to complete one type of task instruction. This requires shifting attention between different cognitive sets. Task-switching tasks, on the other hand, involve switching between multiple types of task instructions. This requires holding multiple instructions in working memory and execute one while inhibiting others.

In this dissertation, the neural underpinnings of cognitive flexibility are measured using Electroencephalography (EEG) and functional near infrared spectroscopy (fNIRS). EEG and (f)NIRS are both non-invasive techniques that are widely used to measure brain activity during performance of a task, or at rest. These techniques can aid in understanding which mechanisms underlie certain cognitive processes, or (psycho)pathologies. Complementing behavioral with neural activity tasks is especially important because neural effects have been found in the absence of behavioral effects (DeLuca et al., 2020; Kousaie & Phillips, 2017).

The two types of neural data used in this dissertation are complementary in that EEG has a high temporal resolution and fNIRS a high spatial resolution.

1.3 THE IMPORTANCE OF COGNITIVE FLEXIBILITY

Cognitive flexibility is of great importance in daily life and in today's world. In this world, where changes happen constantly and in rapid succession, individuals must constantly pay attention to the environment, determine if the environment is changing or likely to change, and turn their attention to those changes. Subsequently, to alter perspectives, thoughts, or actions in response to these changes, individuals must inhibit previous perspectives, thoughts or actions, and update them in which working memory plays an important role. Several cognitive mechanisms (e.g., attention, monitoring, perception, inhibition, working memory) are thus required to achieve flexible behavior. Cognitive flexibility thus has great importance in many situations in life and dysfunctional cognitive flexibility can have serious consequences.

1.3.1 Cognitive flexibility in depression

Executive functioning and cognitive flexibility are critically involved in mental health (Gabrys et al., 2018). Cognitive inflexibility is associated with disorders such as autism spectrum disorder, attention deficit (hyperactivity) disorder, schizophrenia, obsessive-compulsive disorder, eating disorders and mood disorders (Dajani & Uddin, 2015; Uddin, 2021). These disorders are all characterized by (amongst other things) a lack of flexibility in behavior or thinking.

In the context of depressive disorders specifically, dysfunctional cognitive flexibility has been repeatedly demonstrated (Douglas & Porter, 2009; Lee et al., 2012; McDermott & Ebmeier, 2009; Murphy et al., 2012; Papmeyer et al., 2015; Roca et al., 2015; Snyder, 2013; Wagner et al., 2012). Cognitive inflexibility makes it more difficult to generate alternative ways of thinking and to switch attention to more pleasant and adaptive thoughts and behaviors (Davis & Nolen-Hoeksema, 2000; Philippot & Agrigoroaei, 2017). Deficits in cognitive flexibility may therefore result in an increased tendency to ruminate and a reduced ability to flexibly respond to emotional situations (Gotlib & Joormann, 2010). In turn, difficulties using adaptive emotion regulation strategies such as reappraisal can result in the maintenance of negative affect, mood states and depressive symptoms (Gross & John, 2003; Holtzheimer & Mayberg, 2011; Joormann & Gotlib, 2010).

In the context of depression, in the DSM-5 (the widely used manual for categorizing mental disorders; American Psychiatric Association, 2013), deficits in cognitive flexibility and cognitive functioning in general are operationalized as difficulties in concentration. Concentration difficulties are among the symptoms of Major Depressive Disorder (MDD), along with (near) constant depressed mood, loss of interest and pleasure, unintentional changes in weight, sleep disturbances, loss of energy, psychomotor deficits, feelings of worthlessness or guilt, and thoughts about death or suicide. Neuronally, deficits in cognitive flexibility in MDD have been linked to lower activity in the lateral- and medial prefrontal cortex and inferior parietal cortex (Remijnse et al., 2013), regions important for emotion regulation (Heller et al., 2013; Kalisch, 2009; Ochsner et al., 2012; Wager et al., 2008). Lower activation in the PFC has in turn been related to inadequate top-down control over limbic regions, which could give rise to problems in daily emotion regulation and rumination (Johnstone et al., 2007; Mayberg, 1997; Servaas et al., 2014; van Tol et al., 2013). Moreover, it has been shown that functional and structural abnormalities of the lateral- and medial prefrontal cortex persist into the remitted phase (Smoski et al., 2014; van Kleef et al., 2022; van Tol et al., 2010, 2013). Retrospectively, this indicates that the abnormalities in frontal regions and in cognitive control and cognitive flexibility may represent a vulnerability marker for depression.

1.3.2 Cognitive flexibility in aging

Cognitive inflexibility is also associated with normal aging. Aging is often regarded as a gradual process whereby physical and mental abilities decrease and induce late-life dependence. With increasing age, a multitude of neuro-anatomical and physiological changes occur which may directly or indirectly result in cognitive changes (Craik & Salthouse, 2008; Greenwood, 2007). Many such age-related changes are attested in all physically and mentally healthy older adults. However, not all cognitive processes decline with age, nor do they all follow the same rate of deterioration (Stern et al., 2019; Verssimo et al., 2021). Cognitive processes that are highly dependent on frontal lobe functioning may decline more rapidly and in a more pronounced way than other cognitive processes because the frontal lobes are particularly affected by aging (Reuter-Lorenz & Lustig, 2005).

Owing to neurobiological age-related changes in frontal brain areas and the dependency of cognitive flexibility on adequate frontal lobe functioning, cognitive flexibility is one cognitive process that is especially subject to decline in older adults (Gajewski et al., 2018; Giller & Beste, 2019; Head et al., 2009; Richard's et al., 2021; Roldán-Tapia et al., 2017; Wecker et al., 2005; Wilson et al., 2018). Older adults have furthermore been found to show difficulties maintaining information in working memory, as well as updating such information, and they often exhibit ineffective interference control (Braver & Barch, 2002). It is therefore typically difficult for older adults to adapt to changes in the environment (Head et al., 2009; Ridderinkhof et al., 2002). In other words, older adulthood is often characterized by reduced

Text box 2. EEG and fNIRS explained

Neurons in the brain communicate with each other through electrical impulses and neurotransmitters. The summed electrical activity of thousands of neurons can be captured using EEG, by placing electrodes on the scalp and plotting the oscillatory activity over time. EEG can detect changes in electrical activity and show presence or absence of specific brain activity with an accuracy that lies in the millisecond range. The oscillations carry information on frequency (number of waves per second) and amplitude (height) (see for example Luck, 2005 for more information).

Functional near infrared spectroscopy (fNIRS) records blood flow in the brain, which is a proxy of neuron activation rather than a direct measurement of the brain's electrical activity, as measured using Electroencephalography (EEG). As neurons fire electrical impulses, they consume oxygen. When brain areas become more active and there is increased neural activity in these areas, there is also an increased demand for oxygen. This requires a short-term increased supply of oxygen, which is provided by the flow of oxygenated blood to these areas. This increase in oxygenated cerebral blood flow relates to increased neural activity, also referred to as neurovascular coupling. fNIRS as a measure depends on this relationship; changes in oxygen level can be detected using NIRS. Oxygen is bound to hemoglobin molecules in red blood cells. Oxygenated hemoglobin (hemoglobin molecules with oxygen; oxy-hb) and deoxygenated hemoglobin (hemoglobin molecules without oxygen; deoxy-hb) have different optical properties, meaning that they differently interact with light. fNIRS uses near-infrared light to infer the concentration of oxy-hb and deoxy-hb as an indication of neural activity.

cognitive flexibility. Crucially, cognitive flexibility in older adults has been found to be an important predictor of performance in activities that are essential to everyday life, more so than other cognitive functions (Bell-McGinty et al., 2002; Richard's et al., 2021). Cognitive flexibility could therefore be considered as a key determinant of adaptive cognitive functioning with aging.

Why there is such great variability in the degree of decline in cognitive functioning and cognitive flexibility in older adults remains unclear. One possibility is that differences in brain plasticity and life experiences allow some individuals to compensate for existing brain pathology and maintain good cognitive functioning levels. This has been referred to as "cognitive reserve", a concept that is related to cognitive resilience in the face of reductions in brain function (Stern et al., 2019, 2020). It becomes evident when two individuals with the same brain pathology perform differently on the same cognitive tasks. Indeed, some individuals seem to be able to compensate for age-associated brain changes better than others; they have the capacity to maintain normal cognitive functioning in the presence of brain pathology. The brain attempts to cope with neural changes by using pre-existing neural pathways more efficiently, or by invoking compensatory approaches (i.e., recruitment of additional neural pathways; Stern, 2002). Cognitive reserve thus acts as a dynamic and flexible mechanism in the brain to cope with aging by facilitating cognitive performance and compensating for fluctuations and changes in the brain.

Cognitive reserve has been proposed to account for individual differences in the trajectories of normal cognitive aging and in pathological brain changes such as those that occur in age-related neurodegenerative diseases and dementia. According to the DSM-5, a major neurocognitive disorder (i.e., dementia) is defined as substantial cognitive decline in one or more cognitive processes which interferes with independence in everyday activities. In case of a minor neurocognitive disorder (i.e., Mild Cognitive Impairment; MCI), losses in cognitive functioning may be more substantial than what may reasonably be expected for cognitive aging in healthy older adults, but the cognitive deficits are not sufficient to interfere with independent living. MCI is generally considered as a transitional phase between normal ageing and Alzheimer's Disease because MCI often, though not always, is prodromal to dementia (Petersen et al., 2014). MCI, in turn, may progress from a stage of subjective cognitive decline (SCD). SCD is a self-perceived decline in any cognitive process over time, but the deficits remain undetected in clinical settings: individuals still perform within the normal range on standard cognitive tests (Jessen et al., 2014). SCD is believed to be the earliest indication of preclinical dementia as individuals with SCD are at an increased risk for future cognitive decline and dementia (Mitchell et al., 2014). Accordingly, SCD may be a critical stage for early diagnosis and intervention of dementia because cognitive deficits could still be reversible at this stage (Si et al., 2020; Studart Neto & Nitrini, 2016), by means of cognitive interventions that stimulate cognitive reserve (Si et al., 2020).

Cognitive reserve likely builds up during life. It is important to understand and identify factors that can influence cognitive reserve. However, it has proven difficult to precisely determine what factors contribute to cognitive reserve and how. There is evidence of enriching lifetime experiences, such as (former) occupation, socio-economic status, educational background but also lifestyle and stimulating leisure activities, like reading or fitness activities, affecting cognition throughout the lifespan and contributing to cognitive reserve (Cabeza et al., 2018; Craik & Salthouse, 2008; Kramer et al., 2004). Importantly, it has been suggested that cognitive reserve can be enhanced at any life stage, as there remains a degree of neuroplasticity even in older adults (Stern, 2021). In addition to lifetime experiences and building on the finding that cognitive reserve can still be enhanced in older adulthood, engagement in late-life (cognitively stimulating) leisure activities or interventions have the potential of contributing to cognitive reserve (Stern, 2021). Essentially, it is likely that the wider the spectrum of lifetime experiences and new engagement in later life, the greater acquired cognitive capacity, the more cognitive flexibility, and thus the more cognitive reserve is likely to be enhanced, potentially mitigating the effects of aging on cognitive decline (Burke et al., 2019; Krivanek et al., 2021; Stern, 2012, 2021). Optimizing cognitive reserve can thus be an important target of preventive interventions and in reducing the burden of disease of cognitive aging. More needs to be uncovered about what and how (late-life) experiences can contribute to maintaining cognitive functioning or even improving it. This could inform the development of promising strategies to build reserve and preserve cognitive functioning in aging individuals.

1.4 STIMULATING COGNITIVE FLEXIBILITY

From the sections above it follows that, especially because cognitive flexibility is highly dependent on prefrontal cortex functioning, cognitive flexibility is prone to be impaired in aging individuals and individuals suffering from depression. It is therefore reasonable to assume that stimulating cognitive flexibility can be beneficial in daily life and benefit older adults' mood states and their general cognitive health. Stimulating cognitive flexibility in old age could promote cognitive and neural enhancement and strengthen the general ability to adapt one's responses to the demands of the current situation (Nguyen et al., 2019).

A wide range of ideas and interventions have been suggested over the years to promote successful cognitive aging, without one optimal intervention emerging as superior (Krivanek et al., 2021). Well-known to the general public are, for example, computerized and commercial 'brain games'. Although there is no harm in engaging in these games, they have not robustly proven to be effective in improving general cognitive ability (Kable et al., 2017). By contrast, lifestyle interventions that have been found to be effective are, for example, engaging in physical activities, music therapy, and complex cognitive training interventions (Fusar-Poli et al., 2017; Klimova et al., 2017; Krivanek et al., 2021). A combination of several intervention types that are repeated several times a week is likely to yield the best results (Klimova et al., 2017; Krivanek et al., 2021).

Cognitive training interventions, focused on training one or more cognitive functions, are in particular a popular topic in cognitive aging research given their potential to improve cognitive reserve and slow down cognitive decline (Burke et al., 2019; Kelly et al., 2014), often without having to rely on pharmaceutical alternatives. For interventions aimed at cognitive change to be effective, they should consistently tax core cognitive processes (Park

& Bischof, 2013), and interventions that stimulate cognitive flexibility seem particularly promising (Buitenweg et al., 2012). It is important that cognitive training interventions foster far transfer effects, meaning that not just the directly underlying cognitive process (near transfer or indeed merely the trained task) is trained, but that spill-over effects can be observed to processes that are more distant from the specific skill being trained (Buitenweg et al., 2012; Park & Bischof, 2013). As cognitive flexibility as a process integrates multiple cognitive functions, such a multitude of processes are affected by interventions aimed at strengthening cognitive flexibility, stimulating neuroplasticity to a great degree. Training cognitive flexibility therefore has the potential to foster far transfer effects and improvements of untrained processes. Other aspects important for cognitive interventions is that they should involve sustained cognitive effort and promote cognitive and social engagement (Krivanek et al., 2021; Park & Bischof, 2013). In essence, promoting healthy cognitive aging requires complex multidisciplinary interventions that stimulate multiple cognitive processes in order to achieve a generalized effect.

At this point, it is, however, largely unknown how best to stimulate and promote cognitive flexibility. As stated before, it has been suggested that a wide spectrum of experiences is better to build cognitive reserve, but this has only been sparsely investigated. The chapters in this thesis form a multidisciplinary and interdisciplinary contribution to explore the question how cognitive flexibility is affected throughout life, whether there is a cumulative effect of multiple different experiences, and whether it can be modified and enhanced later in life through cognitive interventions. In this thesis, we focus on one particular experience that has been crucially associated with cognitive flexibility, involves sustained cognitive effort, promotes social engagement, and is usually sustained with considerable pleasure: speaking multiple languages.

1.5 EFFECTS OF SPEAKING MULTIPLE LANGUAGES ON COGNITIVE FLEXIBILITY

Speaking multiple languages has been related to enhanced cognitive control and flexibility, particularly in older adults, as it is at this life stage that such processes are generally subject to change (Bialystok et al., 2004; Gold et al., 2013; Hilchey & Klein, 2011; Teubner-Rhodes et al., 2016). Multilingualism has therefore been put forward as a lifelong cognitive engagement that could protect against neurodegenerative disorders, enhance cognitive flexibility and related processes, ultimately contributing to cognitive reserve (Bialystok, 2017; Bialystok et al., 2007; van den Noort, Vermeire, et al., 2019; Voits et al., 2022).

Individuals who speak more than one language essentially have to juggle their languages, all of which have been claimed to be constantly active in one mind at any time (Kroll & Gollan, 2013). Compared to monolinguals, multilinguals need to exert multiple control processes to monitor the context for environmental cues, switch from speaking one language to another when needed, and avoid interference from other languages, requiring cognitive flexibility. Although the precise mechanisms are unclear, it is theorized that the increased use of these language control processes works as implicit training of cognitive control and flexibility (there are spill-over effects between from language control to increased cognitive control; in other words: a transfer effect occurs).

In recent years, many studies have explored cognitive advantages in multilingual speakers and a plethora of studies, but not all, provided empirical evidence for this claim (for recent reviews, see e.g., Bialystok, 2017; Lehtonen et al., 2018; van den Noort, Struys, et al., 2019). Conflicting evidence about the effect of multilingualism on cognition has led to a fierce debate on the topic. At this point, evidence for cognitive advantages to ensue from speaking multiple languages is inconclusive and controversial (Lehtonen et al., 2018). However, the picture is less controversial for older adults, as there is more robust evidence in favor of enhanced cognitive control in older multilingual adults (van den Noort, Struys, Bosch, et al., 2019). Recent meta-analyses and review studies show that multilingualism might contribute to cognitive reserve and as a result have a protective effect against age-related cognitive decline in older adults, but here too, results are mixed (van den Noort, Vermeire, et al., 2019; Zhang et al., 2020). Nevertheless, numerous studies and reviews of studies show that symptoms of dementia manifest approximately 4 to 5 years later in multilingual compared to monolingual older adults (Bialystok, 2016; Freedman et al., 2014; Gold, 2015; Perani & Abutalebi, 2015; van den Noort, Vermeire, et al., 2019). Additionally, recent studies show that active and sustained engagement with additional languages may have a neuroprotective effect in older adults (Sala et al., 2022; Voits et al., 2022).

The relation between speaking multiple languages and enhanced cognition and cognitive reserve thus appears to be complex and may not be a robust and universal phenomenon. Previous inconsistencies in results between studies in search for a relation between cognitive performance and multilingualism have to a large part been attributed to methodological differences. Many studies, for one, have compared groups of multilinguals to groups of monolinguals based on the premise that these groups are homogeneous, but this is most likely not the case. Individual multilingual experiences are characterized by extensive individual variation. Factors such as number of spoken languages, age of acquisition, language proficiency, dominance, exposure, and frequency of use and language switching are all likely to modulate the multilingual experience and differently impact cognitive performance (cf. Pot et al., 2018). This individual variation is of great importance and recognized as such in recent years (Backer & Bortfeld, 2021; Salig et al., 2021). At the same time, only few studies to date have directly modeled individual multilingual experiences as predictors of cognitive performance in older adulthood.

Despite doubts about the beneficial effects of speaking multiple language, it is worth investigating further the conditions under which speaking multiple languages does and does not benefit cognition, given the enormous potential in multilingualism as mitigating aging effects. If speaking multiple languages can result in increased cognitive flexibility and cognitive reserve in older adults, then encouraging individuals – from childhood to older adulthood – to speak multiple languages may be a lifestyle intervention to improve flexibility. In fact, in old age, speaking multiple languages could be employed as a cognitive training intervention to stimulate and promote cognitive flexibility, build reserve and preserve cognitive function.

1.5.1 Foreign language learning

Learning to speak a new language at a later age has been put forward as a cognitive training regime to promote healthy cognitive aging (Antoniou et al., 2013; Liu & Wu, 2021). Learning a foreign language is hypothesized to engage neural networks that decline with aging and are associated with depression (Antoniou & Wright, 2017). It therefore has the potential to benefit all older adults, but especially those vulnerable for depression and cognitive decline. Effectively, learning to speak a new language could be considered as an enriching exercise that has the potential to contribute to neuroplasticity, without the side effects of pharmacological interventions (Liu & Wu, 2021; Uddin, 2021). Especially people with a lower cognition level could benefit from a language intervention (Kliesch et al., 2021).

However, again, evidence for a positive effect of language learning interventions on healthy cognitive aging is highly mixed (Klimova & Pikhart, 2020; Pot et al., 2019; Ware et al., 2021). Some third-age language learning intervention studies have found small effects on attentional switching (Bak et al., 2016; Long et al., 2020), executive functioning (Meltzer et al., 2021), inhibition (Pfenninger & Polz, 2018), global cognition (Bubbico et al., 2019; Wong et al., 2019), and working memory (Wong et al., 2019). Others have found no improvements in any of these domains (Berggren et al., 2020; Kliesch et al., 2021; Ramos et al., 2017; Ware et al., 2017). Some studies have focused not on cognitive, but on socio-affective outcomes and showed improvements in well-being and self-confidence (Pfenninger & Polz, 2018; Ware et al., 2017). At a rudimentary level, several studies have shown that participants experienced language learning as enjoyable and were successful at it, supporting the idea that language learning can be feasible as a cognitive intervention tool (Kliesch et al., 2018; Pfenninger & Polz, 2018; Ware et al., 2017).

As with the observational studies focusing on enhanced cognition and cognitive reserve in multilingual older adults, intervention studies show great variability in methodology, which could explain the differences in results (reviewed in Pot et al., 2018 and Ware et al., 2021). For example, large differences are attested in how studies approach a language learning intervention: there are major differences in the duration and intensity of the intervention, the language that is taught, and how that language is taught. In large part, these differences can be explained by the fact that the field of third-age language learning has only recently emerged and best practices for language learning are lacking. There are also vast differences in study designs, relating for instance to sample size, which has ranged from around 10 to 160, and the use of control groups. Studies either used no control group at all (Kliesch et al., 2018; Ware et al., 2017), only one passive control group (Bubbico et al., 2019; Pfenninger & Polz, 2018; Ramos et al., 2017), or only one active control group (Berggren et al., 2020). Only few studies used multiple control groups (Bak et al., 2016; Kliesch et al., 2021; Wong et al., 2019). Carefully constructed control groups are important to ascribe any attested effects to language learning per se, or simply to novel cognitively stimulating activities, or even social activities, both of which are inherently present in language learning. Even most recent or ongoing work lacks passive and active control groups (Grossmann et al., 2021). In addition, previous work often employed just a single cognitive functioning task to measure the effect of language learning on sustained cognitive functioning. That task itself also differed across studies, which has been signaled as a more general problem in the field of multilingualism research at large (van den Noort, Struys, Bosch, et al., 2019). Furthermore, studies to date have not looked integratively at the cognitive (behavioral and neural), socio-affective, and language learning outcomes of a language intervention. The integration of different domains is important because aging itself is an integrative process and any effect of language learning most likely span all these domains. Moreover, an effect may be observed in one domain, but not in another. From earlier work on younger adults, we know that especially brain measures seem to be sensitive to measure effects of language learning interventions (Bellander et al., 2016; Mårtensson et al., 2012; Schlegel et al., 2012), but brain measures have only been employed once in research targeting older adults (Bubbico et al., 2019).

Given that language training results in improved language skills, that it can be a pleasant experience, and that it potentially protects against cognitive aging, at the very minimum is never hurts to learn a new language. However, at this point it is unclear whether foreign language learning in old age can positively benefit cognition, and cognitive flexibility specifically. The question whether language learning can serve as a cognitive training intervention to mitigate aging effects therefore remains unanswered. Furthermore, it is unknown whether language learning is unique in bringing about such effects and how broad, global and generalizable to other domains the potential effect of language learning is. Up until now, multilingualism and healthy (cognitive) aging have been studied in relative isolation and a multidisciplinary and interdisciplinary approach is largely lacking.

And yet, investigating how cognitive flexibility is affected by lifelong multilingual experiences and language training is a process that calls for a multidisciplinary and interdisciplinary approach. Cognitive flexibility is linked to depression and other mood disorders which calls for a clinical (neuro-)psychological approach. The link between cognitive flexibility and aging involves geriatrics. To tease apart the effects of language training from learning other complex skills or social interaction, a randomized controlled trial (RCT), often used in the medical field, is a suitable design in this respect. So far, a well-designed and well-controlled RCT has not been a common procedure to investigate the effects of language training. However, without a solid applied linguistics foundations on how new languages are best learned and taught, the language training is unlikely to be of a sufficient quality to induce any cognitive effects. And, indeed, to measure the effects of such a language training intervention on cognitive flexibility, measurement methods from neurosciences and cognitive psychology should be applied.

1.6 THIS DISSERTATION

In this dissertation, it is aimed to better understand whether speaking multiple languages can influence cognitive flexibility in older adulthood and whether it can serve as a unique training intervention to mitigate cognitive aging effects. Up until now, cognitive flexibility has been viewed and studied from different angles by different research fields that, until now, have hardly interacted. The work in this thesis aims to bring together these perspectives using a multidisciplinary and interdisciplinary approach in combining perspectives and methods conventionally employed in different fields. In different chapters, it is investigated how cognitive flexibility is influenced by speaking multiple languages and how this relates to mental and cognitive health in older adults.

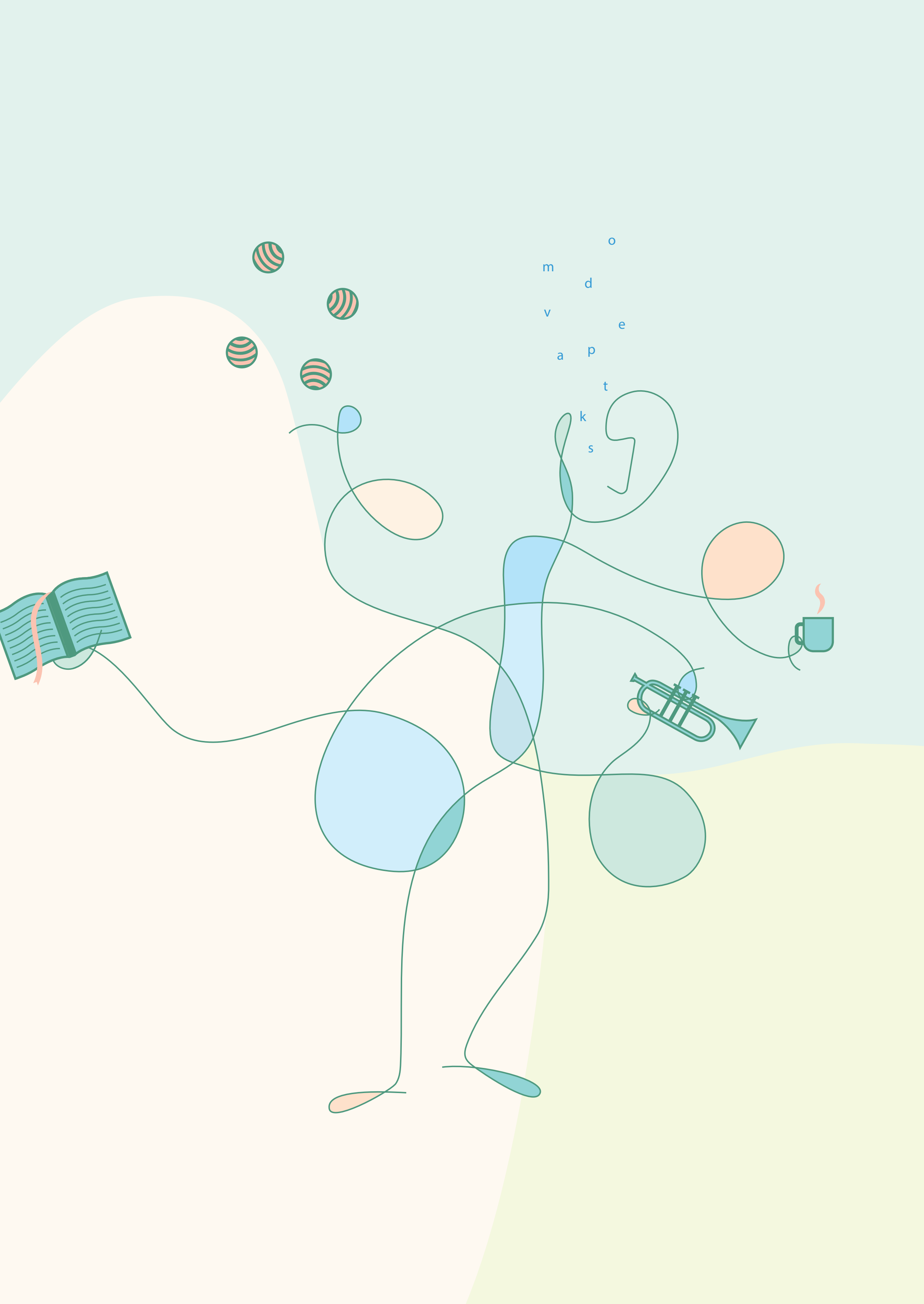
This dissertation is divided into two sections. In the first section (comprising Chapters 2 and 3), an observational approach is taken to study how individual variations in multiple language use and exposure to different cognitive challenging experiences, including speaking multiple languages, relate to cognitive performance. In the second section (Chapters 4 and 5), an experimental approach is taken using a randomized controlled trial (RCT) design to study the effect of a language training intervention vis a vis other intervention.

Chapter 2 investigates the relation between individual differences in multilingual language use and cognition using behavioral and fNIRS data in young adults. It is specifically aimed to investigate how variability in individual multilingual language experience and use relates to attentional control in young adults. As stated above, it is considered increasingly important to characterize individual variability. It is therefore investigated whether a single metric covering multiple aspects of multilingualism related to attentional control in which is considered an essential component of cognitive flexibility. In addition, fNIRS data is analyzed to investigate how individual variations in multilingual experiences impact brain functioning involved in attentional control.

Building on the suggestion (see above) that a combination of experiences may yield a greater benefit on cognitive flexibility, **Chapter 3** examines how complex life experiences, such as speaking multiple languages, contribute to healthy aging in a large population-based cohort study of older adults. The question whether the accumulation of multiple different complex experiences is related to enhanced cognition, and thus to building cognitive reserve was investigated. Data from the large population-based Lifelines Cohort Study is analyzed. For this study, data of more than 5000 older adults is analyzed to study whether lifetime musical and multilingual experiences differently and/or cumulatively relate to cognition and well-being in older adults.

Chapter 4 details the study protocol of our RCT to study effects of a language learning intervention. The primary aim of this intervention study is to examine the unique effects of a foreign language training on cognitive flexibility in older adults. The population in this study are older adults with subjective cognitive decline, a population at risk for cognitive decline and depression. The secondary aim of this study is to assess whether any changes in cognitive flexibility will ultimately lead to improvements in (subjective) cognitive decline, depressive symptoms, and general mental health. Chapter 4 presents these aims in more detail and presents the tools used to test these aims.

Chapter 5 reports the effects of the language learning intervention on cognitive flexibility and mental health. This chapter focusses on the unique effect of language training on a behavioral level compared to other complex skill learning (musical training) and social activity. After determining whether the language intervention was successful (improvements in language proficiency), effects on the primary outcome of cognitive flexibility and the secondary outcome of mental health are assessed. In a supplement (supplement 5.E) to Chapter 5, it is explored how the language learning intervention versus the control interventions impacted neuroplasticity. Specifically, it is explored whether foreign language learning in older adults can incur unique changes (compared to control groups) to the brain's resting state networks measured using EEG reflecting enhanced cognitive flexibility as a function of the language training. Finally, the main findings of the combined chapters are summarized in **Chapter 6,** where clinical implications, methodological considerations, and directions for future research are discussed.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