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MULTIMODAL DIFFUSE OPTICAL IMAGING EVIDENCE OF AGE-RELATED CHANGES IN NEURAL SUBSTRATES OF SEMANTIC WORDS PROCESSING

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MULTIMODAL DIFFUSE OPTICAL IMAGING EVIDENCE OF AGE-RELATED CHANGES IN NEURAL SUBSTRATES OF SEMANTIC WORDS PROCESSING

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DEDICATION

To my family

Able to stay so close while so far,

making me believe I could achieve such ambitious works under such circumstances.

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RÉSUMÉ

Le vieillissement rapide de la population au Canada changera les aspects démographiques à l'avenir par le fait que les personnes âgées de 65 ans et plus vont dépasser en volume les jeunes de moins de 20 ans. En sachant les coûts associés au traitement et au soutien des personnes âgées atteintes par une ou plusieurs démences cognitives, on admet l'importance des études gériatriques pour mieux comprendre les mécanismes neurophysiologiques du vieillissement. L'intérêt principal est de trouver un lien entre les effets neurologiques du vieillissement et ceux du déclin cognitif afin d'établir des stratégies qui encourageront un vieillissement en santé. Notre compréhension du cerveau a beaucoup évolué au cours des dernières décennies grâce à de nouvelles techniques en imagerie cérébrale. Pourtant, l'interprétation de ces données reste un défi. Dans le cas de l'imagerie fonctionnelle par résonance magnétique (IRM) ou par optique diffuse (IOD), la réponse neuronale est indirectement dérivée de l'hémodynamique. Cette dernière est sujette à de complexes interactions entre l'oxygénation du cerveau, le volume et le débit sanguin, ainsi que la structure hétérogène du cortex. Ces interactions rendent difficile une interprétation quantitative des données. Dans le cas des études en vieillissement cognitif, ces paramètres sont de plus modifiés par l'âge, ce qui mène à une importante variabilité interindividuelle dans l'interprétation des données. La caractérisation des effets neurophysiologiques du vieillissement sur les signaux d'imagerie cérébrale est donc essentielle pour permettre des études rigoureuses du déclin cognitif avec l'âge. Vu les limites en rapport avec les signaux intrinsèques de chacune des modalités d'imagerie non-invasive, l'intérêt pour les études multimodales s'accroît car elles permettent de calibrer avec plus de précision les données fonctionnelles. L'intégration des données complémentaires acquises via différentes modalités de neuroimagerie, dans cette étude, nous a permis de quantifier les activations neuronales et de surveiller leurs modifications reliées au vieillissement. Un montage de spectroscopie en temps résolu, fait au laboratoire, nous a fourni des données au repos sur la concentration en oxy- et déoxyhémoglobine, ainsi que sur le volume sanguin. En imagerie par résonance magnétique, une séquence anatomique nous a servi à 1) évaluer une potentielle corrélation entre l'épaisseur corticale (matières grise et blanche) et le niveau de la réponse hémodynamique et 2) Recaller la carte d'activité cérébrale de chaque participant sur son image anatomique. On rajoute ces dernières mesures comme régresseur à un modèle linéaire généralisé de la réponse hémodynamique. En faisant l'hypothèse que ces changements de bases sont liés à la physiologie,

leur régression permet de prendre en compte le changement de la physiologie de base. Celui-ci renforce les inférences statistiques basées sur les changements de la concentration d'hémoglobine qui sont dus à l'activité neuronale et pas aux effets du vieillissement.

Cette recherche ouvre des perspectives cliniques intéressantes en termes de diagnostic et d'amélioration de la qualité de vie, en proposant notamment des axes de réflexions pour traiter les déficits cognitifs. De plus, ce projet, en haussant la rigueur dans les analyses statistiques de groupes, a le potentiel d'améliorer la puissance d'interprétation de futures études d'imagerie.

ABSTRACT

The demographic features of the population of Canada will experience an unprecedented historical change in the near future by the number of individuals above 65 years surpassing the number of youngsters under 20 years. Considering the costly consequences of age-related cognitive decline, both for individuals and the society, studying the neurophysiological mechanisms of these unfavorable changes has become an utmost priority in health research. The main goal of this field is to link the effects of cerebral aging to those of cognitive aging in order to stablish strategies promoting healthy aging. Normal cerebral aging is accompanied by some neurophysiological and neuroanatomical alterations depending on epigenetics of individuals. Amongst neurophysiological deteriorations causing cognitive decline, one should account for the neural loss, cortical density reduction, neurovascular, metabolic, and neurotransmission dysfunctions. Taken together these alterations with age, we were interested to determine whether older adults are affected in their cognitive abilities by more than one simple factor. In another word, we aimed at exploring the potential relationship between the abovementioned age-related alterations with cognitive performance. However, the main challenge of such study appears when interpreting functional data regarding baseline measures of each individual. Thus, the increased inter and intra-individual variability in cognitive studies is mainly due to their large variations in structural and neurophysiological characteristics in the course of their lifespan.

In this project, we defined a multi-modal neuroimaging protocol with the aim of calibrating the functional measures of task-related activity by measured individual baseline neurophysiological characteristics. To assess individuals` cerebral blood flow at rest, one of the constituent of hemodynamic response, we used an arterial-spin labeling sequence of magnetic resonance imaging. This technique based on tagging water in blood, gives the blood quantity emerging to brain. Carotids, the main arterial vessels that supply blood to brain, neck and face, are well known to be affected by age inter-individually and play as a non-functional moderator in hemodynamic response formation. As an estimate of total blood volume and baseline concentration of oxy- and deoxyhaemoglobin, we used a home-made 4-chanel time resolution optical device to acquire data from each participant’s prefrontal lobe. To refine the spatial resolution of non-invasive optical imaging, we also acquired anatomical MR images of each participant to 1) calculate cortical thickness with the objective of evaluating the correlation

between grey matter and white matter volumes and the task-evoked hemodynamic response and 2) co-register functional map of each participant on her/his anatomical image. The hemodynamic response was measured by an optical imaging system using near-infrared light. This emerging technique is based on the absorption properties of the biological tissue illuminated with near-infrared range of light.

This research opens up interesting perspectives in terms of clinical diagnosis and quality of life improvements. It includes new reflection axes to deal with cognitive deficits. In addition, this project has the potential to improve the power of interpretation of future imaging studies showing more rigors in groups' statistical analysis.

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LIST OF SYMBOLS AND ABBREVIATIONS

aMRI	Anatomical Magnetic Resonance Imaging
ASL	Arterial-Spin Labeling
BOLD	Blood Oxygen Level Dependent
CBF	Cerebral blood flow
CBV	Cerebral blood volume
$CMRO_2$	Cerebral metabolic rate of oxygen consumption
CSF	Cerebrospinal fluid
CW	Continuous wave
DPF	Differential pathlength factor
DOI	Diffuse optical imaging
GLM	General linear model
fMRI	functional magnetic resonance imaging
HbO_2	Oxygenated haemoglobin
HbR	Deoxygenated haemoglobin
HbT	Total haemoglobin
HRF	Hemodynamic response function
MTLs	Middle temporal lobes
MTG	Middle temporal gyri
NIRS	Near-infrared spectroscopy
OAs	Old adults
PFC	Prefrontal cortex
$SatO_2$	Blood oxygen saturation
SNR	Signal-to-noise ratio

TD-NIRS	Time domain-NIRS
TRS	Time-resolved spectroscopy

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CHAPTER 1 INTRODUCTION

By 2025, the demographic features of the population in Canada will experience an unprecedented historical change: the number of individuals above 65 years will surpass the number of youngsters under 20 years. The undeniable decline in age-related sensory processing, motor performance, and cognitive processes affects the quality of older adults' life in their intellectual, physical and social activities. In an ideal framework, in which our aging population is merely undergoing a natural process of decline, understanding the mechanisms underlying healthy aging is very important to both individuals and society, to encourage a healthy life style. Normal aging is characterized by changes in brain's anatomy and physiology, a phenomenon that varies depending on brain's region and component (Raz et al., 2005). For instance, the global volume of the cerebral cortex decreases by 0.35% per year in adult individuals of over 52 years. Yet it is important to note that this reduction differs across brain regions and individuals. Raz and colleagues, in their meta-analysis of 14 studies, have found that the frontal lobe has the steepest rate of atrophy among others. However, neural loss and myelin breakdown causing white matter integrity reduction are not the only indicators of aging (Bucur et al., 2008). For instance, neurovascular architecture, brain metabolism as well as neurotransmitter dysfunctions should also be taken into account as indicators of aging. Hence, exploring the correlation between theses physical substrates of cognitive aging and performance requires a comprehensive research protocol in the aging studies. With this objective in mind, we believed that contemplating a multifaceted investigation would clarify the increased inter and intra-individual variability in cognitive performances. In other words, the reduced performance caused by aging is dependent on the type of cognitive domains (Grady, 2008; Grady, Springer, Hongwanishkul, Mcintosh, & Winocur, 2006) and on the individual characteristics (Cabeza, 2002), developed in the course of lifespan.

To explore the above-mentioned structural and neurophysiological features underlying age-related cognitive decline in different task environments, neuroscientists have been using neuroimaging techniques of different modalities. Soon after the advent of X-Ray (Wilhelm Röentgen 1895), imaging has found its way in the field of medical studies (Spiegel, 1995). Now after more than a century, with the emergence of new techniques, both structural and functional brain characteristics can be studied using several methods such as: X-ray computed tomography

(CT) scan (Allan Cormack & Godfrey Hounsfield, early 1970s), nuclear positron emission tomography (PET), electroencephalography (EEG), event-related potentials (ERP), magnetic resonance imaging (MRI), ultrasound and optical imaging.

One of the most extensively used functional neuroimaging technique, functional magnetic resonance imaging (fMRI), is based on quantifying neural activities evoked by hemodynamic changes in cerebral tissues. Neuronal firing in the brain demands energy that gives rise to blood tissue perfusion (Raichle, 1998) and concomitantly venous blood oxygenation (Ogawa et al., 1992). In other words, the hemodynamic consequences of neural firing are the summation result of vasodilation/constriction signaling, glucose uptake, and tissue oxygenation changes. So far, two hypotheses explain the local regulation of the cerebral blood flow (CBF) increase and cerebral metabolism; the metabolic hypothesis and the neurogenic hypothesis. The metabolic hypothesis states that CBF increases by neuronal activity-induced metabolic energy consumption. This later sends signal to the feeding vasculature causing a local increase in CBF. In the neurogenic hypothesis, neural activities provoke parallel mechanisms of blood flow and energy consumption, and provide feed-forward signaling to release neural activity related neurotransmitter. Numerous functional neuroimaging studies have proven that the augmentation of CBF measured via hemodynamic response is correlated with post-synaptic activity (Arthurs & Boniface, 2002; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Ritter & Villringer, 2006). Yet, a thorough comprehension of the metabolic state change and CBF increase, which is known as *neurovascular coupling*, is not well achieved (Logothetis, 2008).

Functional MRI (fMRI) signal is based on the susceptibility effects of deoxygenated haemoglobin in venous blood in a strong magnetic field (more than 1.5T) reflecting blood oxygen level dependent (BOLD) (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Ogawa, Lee, Nayak, & Glynn, 1990). Since the advent of fMRI, a growing number of studies were published on the use of endogenous BOLD contrast as a marker of neural activity. With time, as critiques became important on the ambiguous representation of neural activity by BOLD signal, significant progress has been made in exploring BOLD signals by models which examined the degree of relation between the BOLD contrast in one hand and cerebral blood volume (CBV) and CBF on the other hand (Buxton and Frank, 1996, Ogawa et al, 1998).

Another technique in brain imaging has been developed in the end of last century, using optical properties of trans-illuminated cortical tissues. The principle of diffuse optical imaging (DOI) is based on the light intensity changes as a result of its interaction with cortical tissue. The optical properties of biological tissues change depending on the light intensity and frequency with the occurrence of a neuronal activity (Jobsis, 1977). Since this discovery, an increasing number of researchers in various fields of neuroscience have used DOI to assess changes in the brain. The use of non-invasive DOI technique in research studies was first established for mapping cortical activity (Grinvald, Lieke, Frostig, Gilbert, & Wiesel, 1986). The principle of optical measures lies on optical property changes that are intrinsic to the tissue itself (Aitken, Fayuk, Somjen, & Turner, 1999). This technique uses haemoglobin, the main absorbing chromophore in the range of visible to near-infrared light spectrum, as an endogenous contrast mechanism in the brain. The changes in the haemoglobin concentration following neural activities affect optical density (effective photon absorption) and lead to a contrast in optical signal, proportional to the extent of activation. Since both oxy- and deoxyhaemoglobin (HbO_2 and HbR respectively) are the components of hemodynamic response, acquiring measurements at two wavelengths is then necessary to resolve each species. The advantage of near-infrared spectroscopy (NIRS) sensitivity to both HbO_2 and HbR (instead of HbR in BOLD signal) has put forward the utility of NIRS in non-invasive brain mapping in human studies. Measuring the alterations in HbO_2 and HbR concentration ($[HbO_2]$ and [HbR] respectively) gives an estimate of blood volume (Total hemoglobin concentration $[HbT] = [HbO_2] + [HbR]$) as well as blood oxygenation ($[HbO_2] / [HbT]$) which is more advantageous in studies seeking to map the cortical surface, due to the limited depth of penetration with DOI. Moreover, the low cost along with the natural setting of the signal acquisition have allowed researchers in neuropsychology to assess behavioral tests in a much more convenient environment.

Presently, the compromise in choosing NIRS over the well-established fMRI is the lack of spatial resolution and sensitivity in the former. There are different DOI instrumentation techniques offering different types of measurement, which will be discussed in another chapter in details. Continuous-wave (CW) NIRS measures HbO_2 and HbR concentration changes with sampling frequency as high as 100Hz, while other methods (frequency-domain and time-resolution spectroscopy) provide an absolute change of tissue haemoglobin concentrations with slower acquisition rates (Wolf, Ferrari, & Quaresima, 2007). The CW NIRS device measurements are

dependent on the baseline physiological and vasculature state, so the measured hemodynamic response could change uncorrelated from the extent of neural activities. To overcome this flaw, we proposed a multimodal imaging protocol to assess baseline cerebral blood flow, haemoglobin concentrations, and oxygenation, which will be described further later in this manuscript.

The growing corpus of brain imaging technologies has advanced research in fields of neuropsychology and cognitive aging. Indeed in the last few decades, new mechanistic insights have emerged on the psychological constructs of aging in each domain. Behavioral assessments of aging, both in longitudinal and cross-sectional studies, have found a consistent pattern of cognitive declines; including working memory, inhibition, and processing speed (Hedden & Gabrieli, 2004). Regarding the converging findings of the importance of age-related prefrontal cortex atrophy (Naftali Raz, 2000) it is believed that those cognitive tasks that demand mental efforts and involve executive functions are more severely affected by age. On the other hand, some studies have shown no significant decline in autobiographical memory, semantic knowledge and short-term memory. It is suggested that a compensatory mechanism expresses some degree of neural recruitment to maintain performance while anatomo-physiological changes appear as a natural consequence of aging.

Evidences from various studies suggest that older adults confront cognitive aging by either adapting compensatory processing procedure or changing cognitive strategies (Backman et al., 2002). In that sense, numerous neuroimaging studies clearly indicate the presence of an inter- and intra-hemispheric functional reorganization associated with aging (Cabeza, 2002; Grady et al., 2006). Decreased or increased brain activities accompanied by reduced or preserved performance have all been observed in different experimental conditions. Decreased neuronal activity has often been interpreted as a deficit; however, an increase could be seen as either a reflection of inefficient neural underpinning, compensatory mechanism or a reduction in the selectivity of the supporting neural circuitry (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2011; Reuter-Lorenz & Park, 2010; Salthouse, 2011). From all these observations, we can infer that aging has distinctive effects on cognitive faculties and thus needs to be investigated more comprehensively by overpassing intrinsic challenges the age-related studies present. To do so, one should bear in mind the unique adult lifespan which gives rise to variable vulnerability and compensatory functional reorganization, both at structural and physiological levels, in face of aging. This issue involves cross-sectional studies in which we compare older adults (OAs) to

their younger counterparts, and also, those neglecting salient neurophysiological declines that compromise cognition.

The concept of "Active Aging[1]" does not only consist of longevity of the population but also the maximum span of effective functioning. Amongst cognitive abilities, language and communication are undoubtedly of profound importance in social aspect of a successful aging and life quality. Investigating the neuronal substrates of this complex cognitive function would delineate a framework in which we could explore the brain mechanism supporting a preservation of cognitive function and/or adapting the clinical management of elderly stroke survivors. For instance, studying semantic word processing could lead neuroscientists in research on aging, to explore semantic markers in the diagnosis of degenerative dementia. Also, despite age-equivalent performance accuracy to semantic processing tasks, imaging studies have revealed activation differences in brain regions. In reaction time (RT) measures of lexical decision task, the observed age-related slowing is justified by white matter integrity decline (Bucur et al., 2008). This later could be one of the potential moderators of between individual differences. My goal during my PhD was to assess the morphological and physiological changes underpinning preserved semantic memory, specifically in the lexical-semantic brain networks, during normal healthy aging. The research protocol consisted of a well-established lexical-semantic decision task and two imaging modalities; MRI and DOI. Anatomical and blood perfusion (Arterial Spin Labeling; ASL) MRI as well as time-resolution spectroscopy (TRS) optical imaging were used to measure age-related baseline changes in the brain for each individual. A functional CW NIRS device was utilized in the protocol to acquire indirectly stimulus-evoked neuronal activities by means of hemodynamic response. We intended to explore the importance of complementary measures of hemodynamic responses components, i.e. brain circulation, tissue and venous-blood oxygenation, and cerebral metabolism, for the understanding of healthy aging brain. We believed that hemodynamic changes provoked by brain activity are biased by baseline state of neurovascular and neurophysiological factors. Thus, to quantify and localize the neural activation, studying the ill effects of aging seemed primordial to us while designing the research protocol. There is a corpus of inconsistency in specific aspects of aging process affecting neuroimaging data. Here we

[1] http://who.int/ageing/publications/active_ageing/

covered the most important ones in consequential physiological events resulting to the formation of hemodynamic response. In addition a priori morphological information of each individual, which would contribute to functional data measures, was provided by means of anatomical MRI (aMRI). Cortical thickness as well as white matter integrity acquired by aMRI would give insights on the background support to neural activation in response to cognitive stimuli. In order to understand if whether cognitive-specific declines have neural basis or brain mechanistic correlations, in comparison of the degree and the extent of neural activity in elder population with their younger counterparts, it was then essential to consider an analytical methodology. We set the main objective of this study in normalizing acquired data to cancel out the effects of baseline age-group differences since in case of hemodynamic-based NIRS technique, provoked neural activity is observed via oxy- and deoxyhaemoglobin concentration changes, resulting from a complex physiological and neurovascular interaction. Moreover, this approach would certainly augment the power of statistical analysis inference in group studies by taking into account the inter-subject differences.

1.1 Summary of problems in studies on Aging

Age-related changes in brain vascular architecture and physiological systems affect the hemodynamic response profile, thus hamper the field of cognitive neuropsychology of aging aiming to understand the physical substrates of cognitive declines. In addition to the vague relationship between hemodynamic response components, there are large numbers of evidences depicting age-related changes of these factors. Aging processes influence baseline values of (CBF), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen consumption ($CMRO_2$) as well as their functional changes. Yet no firm consensus does exist on either global decrease or increase of one or another factor with age. As a result, the associated geriatric studies that aim to study the causal relation of small cognitive changes and neural activity become even more complicated (Mark D'Esposito, Deouell, & Gazzaley, 2003; Farkas & Luiten, 2001; Nagasawa et al., 1979). In this regard, to account for individual's neurophysiological characteristics, a multimodal brain imaging approach seems essential. In the case of hemodynamic-based imaging techniques, the incongruent pattern of physiological aging has led scientists in fMRI studies to calibrate the functional measures of neural activity (Richard D. Hoge, 2012). The term *calibrated* fMRI was first introduced by Davis and colleagues (Davis,

Kwong, Weisskoff, & Rosen, 1998) as a method to quantify BOLD signals. He proposed a hypercapnia approach (carbon dioxide breathing) to measure oxidative metabolism changes independent of CBF.

The promising applicability of NIRS in clinical studies has put forward this technique of brain mapping over fMRI. Still one would need to normalise fNIRS data to surpass the above-mentioned confounds in results interpretation. Since we have felt the necessity of understanding the neural substrates of semantic processing with a perspective on clinical rehabilitation (i. e., aphasic patients), the necessity of a comprehensive research protocol was undeniable. For a more quantitative analysis of optical measurements, the idea in this work was to perform a multimodal experimental protocol combining optical imaging and MRI to acquire complementary data which would allow us identifying factors of aging that impact hemodynamic based neuroimaging data (i. e., brain tissue shrinking, decreased blood volume and flow as well as diminished cerebral metabolism).

1.2 Goals and hypothesis

As mentioned in section 1.1, we intended to compare the hemodynamic response of young adults versus elderly while undergoing a lexical-semantic decision task to study the neuronal response and cognitive performance related to age. We believed that validating the applicability of a low cost, convenient, and thoroughly non-invasive imaging technique could play a trivial role tracing the early onsets of physiological decline and the presence of compensatory functional reorganization. By improving insights into a high-functioning aging brain, clinical researchers and neuropsychologists could ameliorate the precision of diagnosis and the effectiveness in treatment once more personalized therapies would be applied.

Objective 1:

I. To evaluate the neural response to a semantic task by including the measures of baseline blood flow with ASL and haemoglobin concentration with NIRS, and also evaluate the impact of the structural changes between subjects as a function of age.

II. To compare the hemodynamic response of young adult versus elderly ones while undergoing a lexical decision task to study the neuronal response and cognitive performance correlation with age.

Hypothesis 1: We evaluate the impact of age-related neurophysiological changes on the cognitive performance, measured by fNIRS, with the perspective of cancelling out the baseline level difference. This approach would reinforce the existence of compensatory mechanisms by exploring any changes in the activated neural substrates. This hypothesis is motivated by the importance of precision in interpreting functional data, due to the complex nature of neurovascular coupling and inter-subject variability in brain aging pattern.

Objective 2:

I. To develop and to validate a method to estimate the structural parameters underlying neural activation by the use of combining anatomical MRI and NIRS, in order to characterize different population as a function of their ages.

II. To measure the cortical thickness and brain volume in order to study any potential correlation between neural architecture and hemodynamic response.

Hypothesis 2: By correlating the gray and white matters thickness with performance, we could evaluate the individual differences by their anatomical differences along with the cognitive reserve hypothesis that posits the mode in which tasks are processed (more or less efficient manner). On the other hand, exploring any correlation between the cortical brain volume along with the GM thickness and hemodynamic response would shed lights on the interpretation of age-group functional differences with the same behavioural performances.

CHAPTER 2 GENERAL CONTEXT

Increased life expectancy in developing countries, due to the improvement in health conditions, has brought the attention of health organizations to the issue of population aging. Policy makers in health organizations face the challenge of how to bring supports to the fragile older population with age-related cognitive problems. The concerns of health care and insurance systems as well as family members about the life quality of older people have put forward the interest in health promotion and prevention policies. The answer to this strategic plan is in the hands of multidisciplinary researchers in any kind of aging-related studies. In the following sections, I will discuss the context of this problematic, works done in related studies, drawbacks and advantages of multidisciplinary research, and finally introduce my research proposal for the designed protocol realized in this PhD project.

2.1 Cognitive neuroscience of aging

We all desire to age well, but why would some people maintain their cognitive abilities into old age (i.e. memory, attention, reaction speed, multitasking, etc.) while others do not? Similar to other organs in the body, we do need to have strategies to maintain brain's health as we age. Studies show that by doing exercise, eating well and avoiding stressful environment we may improve our health conditions (Bherer, Erickson, & Liu-Ambrose, 2013; Marioni, Valenzuela, van den Hout, Brayne, & Matthews, 2012; Rohwedder & Willis, 2010), however neuroscientists actively search for efficient strategies (e.g., adopting healthy lifestyle) to encourage a healthy brain aging and to prevent degenerative diseases.

Before describing the problem, it is important to distinguish between neurogenic and psychogenic effects of aging (Cabeza, Nyberg, & Park, 2004) Neurogenic effects consist of any structural or functional changes in the brain causing a modification in the process of cognitive abilities. Post-mortem analyses were the origin of neurogenic investigation on behavioral and perceptual declines. Recently the progressing technologies in neuroimaging allow researchers to assess neural measures in-vivo. Psychogenic effects are changes in the neural substrates of a particular task influenced by changes in the cognitive patterns. For instance, a recent trend of studies on the effect of age of retirement in different countries acclaims that after the retirement, the brain suffers in an accelerated pace (Rohwedder & Willis, 2010). This axe of aging studies

suggests that an intellectually active life leads to buffering the aging population, against brain declines.

To establish a background for this work, first I review existing models of cognitive aging on one hand and the neural mechanisms of aging on the other hand. At last, I depict the necessity of studying the relationship between these two domains.

2.1.1 Neural correlates of age-related cognitive decline

Since the advent of neuroimaging techniques, cognitive abilities were portrayed by their neural bases at the specific brain regions. Aging decline in fluid cognitive functions could be mostly explained by structural and physiological changes in the aging brain. We can acquire information on brain's structures, baseline physiology, and neuronal activities by means of different imaging modalities. In this regard, cognitive neuroscientists, in the field of aging, trust to find a solid pattern between neural structure, neural function, and behavioural age-related changes. In accordance with earlier post-mortem studies, evidences from neuroimaging studies depict gray matter (GM) atrophy and white matter (WM) integrity degradation with age, but in a heterogeneous fashion (for review Kemper, 1994). In addition, aging causes changes in neurovascular architecture, in cerebral metabolism, as well as in oxygen uptake. A complex combination of these causes leads older adults to undergo cognitive challenges in everyday life. Here I go through an ensemble of evidences for each of these alterations with the aim of analyzing the major problem in the field of cognitive aging.

Neurophysiology of aging

Aging is influenced by a combination of both neurovascular and nonvascular dysfunctions which are difficult to classify as normal or pathological age-related indices. Nonvascular changes consist of physiological characteristics' alterations such as synaptic loss, neural death, and metabolic slowing (Bertsch et al., 2009; Kennedy & Raz, 2009). Those of neurovascular changes include blood oxygen saturation and blood flow decreases (Ances et al., 2009); Meyer et al., 1994). However there is great variability among aging individuals. The main challenge in aging studies is then to dissect these mechanisms of aging and evaluate their influences on cognitive performance. Even though any changes in cognitive faculties imply changes in structural components, and vice versa, it is important to explore the direction of neural characteristics'

changes underpinning the cognitive decline. Roberto Cabeza and colleagues (Cabeza et al., 2004) have introduced a simple model to account for the principal elements of the problem; "Aging is a gradual process during which molecular and cellular processes deteriorate progressively, often leading to such pathological conditions as vascular and metabolic disorders and cognitive decline." Yet, it is not obvious that the direction of this deterioration is as described by Cabeza. Moreover, it has been shown that vascular dysfunctions were implicated as a potential mechanism for age-related global neural tissue deterioration (Chen, Rosas, & Salat, 2013).

Blood supply. Aging is accompanied by a decrease of resting cerebral blood flow (CBF) in studies with healthy older adults (Kawamura et al., 1993; Lu et al., 2010). This observation is explained by age-related changes in the vascular architecture (Gauthier et al., 2015; Gazzaley & D'Esposito, 2004) and alterations in glial and neuronal control of brain blood flow (Attwell et al., 2010; Takano et al., 2006). Since an increase in cerebral blood flow following neuronal activation is one of the initiators of hemodynamic response formation, the age-related changes in any component of CBF would affect the amplitude of the hemodynamic response.

Metabolism. Blood oxygen saturation, cerebral metabolic rate of oxygen ($CMRO_2$), and oxygen extraction fraction are variables that are subject to aging (Lu et al., 2011; Peng et al., 2014). Supposed that CBF decreases with age, in order to provide the metabolic demand, oxygen extraction should augment. Peng and colleagues have shown that the resting brain metabolic rate increases with aging, while earlier studies showed a decrease in older adults (Aanerud et al., 2012). Either these changes are due to brain atrophy, cerebrovascular reactivity (CVR) or physiological modulators; this phenomenon causes an age-related difference in functional measures of hemodynamic response.

Neuroanatomy of aging

There is a consensus in aging studies that brain volume decreases as we age, manifested by cortical thinning and ventricular expansion due to the reduction in neuronal density (Reuter-Lorenz & Park, 2010). Imaging techniques such as high resolution anatomical MRI is the most reliable non-invasive method for such structural assessment. However in MRI studies of cortical thickness, there are discrepancies in results which hinder the understanding of neuroanatomical changes of aging. We could enumerate two possible reasons for this observation; on the one hand, cumulative evidence suggests that brain regions are affected heterogeneously by age (Raz

et al., 1997; Raz et al., 2005; Salat et al., 2004). On the other hand, different brain imaging sequences and image processing procedures could give rise to the inconsistency of results (Salthouse, 2011) in order to assess whether these discrepancies are group samples' or technique's dependent. Fjell and colleagues (Fjell et al., 2009) conducted a meta-analysis over 6 studies with different groups of participants for a total of 883 individuals. Overall, they observed widespread age-related cortical thickness and volume differences. The frontal cortices (superior, middle, and inferior frontal cortices) though were mostly affected by age across all 6 samples, and lateral inferior temporal lobes were the best preserved with age. In another study over 465 individuals, Good and colleagues found that gray matter decreases linearly with age (Good et al., 2002), but white matter volume doesn't change significantly. Evidences from longitudinal studies have shown a relation between gray matter thickness in frontal areas and executive function (Marquis et al, 2001).

Synaptic density. Aging can affect the neural networks by synaptic dysfunction and contact loss. Any alteration in white matter microstructure can reflects breakdown of myelin, certain constituents of cytoskeleton, and axon density.

Vascular structure. Aging affects the morphology of arteries by reducing the diameter of arterioles and capillary loss due to the dysfunctional blood pressure regulation and blood vessel stiffness. Known as arteriosclerosis, the manifestation of aging on the neuro-vasculature is the result of either hypertension or the mere aging process. Anyhow, these alterations cause a reduction in both flow and volume of the blood supply to a focal cluster of firing neurones.

White matter integrity. With aging, the myelinated axon's cytoskeleton is disrupted as the manifestation of white matter hyperintensity in MR images (Gunning-Dixon & Raz, 2000) or hypodensity in computed tomography scans (Freedman et al., 1984). This later is the result of disruption in the integrity of myelin sheath and/or the linear orientation of neurofilaments (Alan Peters, 2002), causing connection loss. Normal aging has been linked to the reduction in the number and length of myelinated fibers (Marner, Nyengaard, Tang, & Pakkenberg, 2003). White matter integrity evaluated with diffuse-tensor imaging (DTI) is positively related to cognitive functions (Brickman et al., 2006; Naftali Raz, 2000).

2.1.2 Aging brain and language

A consensus amount of recent functional brain imaging studies have shown that the human conceptual knowledge is represented in distinct brain regions with specific roles working in parallel to associate knowledge (Jeffrey R. Binder, Desai, Graves, & Conant, 2009; Bookheimer, 2002; Démonet, Thierry, & Cardebat, 2005; Price, 2012). Language processing is comprised of various independent tasks from acoustic analysis to categorical concept identification. Depending on the nature of the task, one should first identify phonemes and access lexical skills to yield the recognition of words, and later perform a semantic analysis in the context of sentence. At the most basic level in linguistics, semantics refers to the meaning of words. Thus, to understand language, the brain must carry out connections between the perceptual representations of words and the associated conceptual knowledge. Considering this complex procedure of language processing, it is interesting to remind that older adults do relatively preserve their language abilities comparing to other cognitive faculties, such as working memory and speed of processing. For instance, reading skills remain relatively stable in aging populations, but neurophysiological measures such as the reduction in left-lateralization could suggest lower efficiency of lexical information processing (Kemmotsu et al., 2012). In response to this observation, another study shows that the performance in the older adults is preserved despite gray matter atrophy by increased activity in right hemisphere frontotemporal regions. Another study also has showed that right hemispheric homologous of Broca's and Wernicke's areas are engaged in healthy older adults (Van Ettinger-Veenstra, Ragnehed, McAllister, Lundberg, & Engström, 2012) with good performance at reading, language ability, fluency, and non-word discrimination tasks. Madden and collaborators investigated semantic decision processing among older adults and found that both age groups activated left inferior prefrontal cortex (IPFC) and occipitotemporal regions responsible for word form recognition (Laurent Cohen et al., 2000).

The quest for the understanding of a healthy aging brain by means of studying a preserved cognitive skill is getting more attention since last decade. Relying on functional brain imaging evidence, researchers believe in the existence of compensatory neural networks, which take part in language processing.

Shedding light on words processing

Isolated visual word recognition has been central to researches aiming at comprehending different levels of language processing in human. Lexical units are ideal to analyze functional roles of letters, graphemes, phonemes, and morphemes apart from their semantics (Petersen, Fox, Snyder, & Raichle, 1990); a journey from features to meanings. There are distributed brain's region representations in object categories' recognition (i. e., object form, object motion, use-associated motor movement, and unique object), which are in parts distinct from lexical entities. Several studies have shown that there is a fine-grained selective brain specification in the semantic system about identification of nonanimate objects versus living things and food, and even a within category specific organization (Hart, Berndt, & Caramazza, 1985; Warrington & Shallice, 1984). Studies aiming at semantic memory identification, define semantic processing by non-living and non-action semantic entities versus pseudo-word stimuli (Petersen et al., 1990) (M. E. Raichle et al., 1994). Such a task could be presented using visual stimuli or audio single word assessments. Several studies (M. Beeman et al., 1994; M. J. Beeman & Chiarello, 1998; Bouaffre & Faita-Ainseba, 2007; Hagoort, Brown, & Swaab, 1996; Nocentini, Goulet, Roberts, & Joanette, 2001) have provided support to the idea of different role of two brain hemispheres for lexical-semantic processing. More specifically, the left hemisphere is understood to be responsible for close semantic relationships (fine coding) whereas the right hemisphere is hypothesized to deal with more distantly related items (coarse coding). Specifically, the left inferior prefrontal cortex (LIPFC) is involved in semantic memory manipulation to access semantic information restored elsewhere.

Modern neuroimaging techniques have allowed neuroscientists to investigate the neural networks underlying semantic word processing. Starting from the very basic element in pattern recognition, Peterson et al., (1990) have shown some blood flow changes in the striate cortex of the occipital lobe for feature-like detection. This activation occurred when analyzing visual word stimuli in contrast to letter-like forms of pseudo-words. A decade later, Cohen et al., endorsed this finding by providing evidence from a hemispheric split-field word presentation to the middle portion of left fusiform gyrus and left inferior temporal region engagements (Laurent Cohen et al., 2000; McCandliss, Cohen, & Dehaene, 2003). This later known as visual word form (VWF) system devoted to the processing of letter strings. Notably, and to the best of our knowledge, most of the studies on the word imageability and concreteness issues of semantic properties (Bedny &

Thompson-Schill, 2006; Jessen et al., 2000; Pexman, Hargreaves, Edwards, Henry, & Goodyear, 2007; Sabsevitz, Medler, Seidenberg, & Binder, 2005) have been done by means of fMRI. Here, for the first time, we aim to investigate the age-related changes in brain semantic networks and the impact of possible cognitive enrichment effects by an event-related experimental paradigm with fNIRS.

2.2 Functional neuroimaging

When the great experimental physiologist Ivan Pavlov said "if we could look through the skull into the brain of a consciously thinking person… , then we should see playing over the cerebral surface, a bright spot with fantastic, waving borders constantly fluctuating in size and form…", his vision was seen for many years a mere fantasy. It has taken almost forty years since then for the emerging technology of brain imaging permitting scientists to fill the gap between physiology and psychology. Meanwhile, the only opportunity to study brain-behavior relationship was through animal studies and experiments on patients with brain deficits. In this perspective, the very first scientist who showed interest in brain blood flow and mental activity was the Italian physiologist Angelo Mosso. In 1881 he recorded the pulsation of the human cortex during a mental activity and acclaimed a regional increase of the brain circulation depending on the neuronal activity (particularly mental arithmetic). Since then, a new chapter in studies of the brain circulation and metabolism has been opened. The very first recordings of quantitative changes in regional blood flow (Landau, Freygang, Roland, Sokoloff, & Kety, 1955; Lewis, Sokoloff, Wechsler, Wentz, & Kety, 1960; Sokoloff & Kety, 1960; Sokoloff, Mangold, Wechsler, Kenney, & Kety, 1955) in the brain following neuronal function gave the insight to the developing brain imaging techniques in the 1970s. These emerging techniques were mainly positron emission tomography (PET) and magnetic resonance imaging (MRI). With the later introduction of glucose metabolism measurements (Sokoloff et al., 1977), more recognition was received by the pioneers of these quantitative methods to enhance our understanding of brain function through bridging human behavior and neural events (Marcus E. Raichle, 2011). In the last few decades, functional NIRS (fNIRS) also has found its way among functional neuroimaging techniques. I will go through more details of fNIRS in next chapter because of its importance in this thesis study.

Vascular-based functional imaging approaches, as opposed to the cellular electrophysiological assessments techniques (EEG, ERP), measure neurovascular changes, which are induced by local arteriolar vasodilation. These methods measure the magnitude and the localisation of the brain activation by following the vascular response (Buxton, Uludag, Dubowitz, & Liu, 2004; Logothetis et al., 2001). This change in local blood supply, known as neurovascular coupling, consists of the consequent increase in cerebral blood flow (CBF) and blood volume (CBV). Since brain activities lead to glucose and oxygen consumption, an increase in the oxygenated blood, provided through neurovascular coupling, changes local blood oxygenation (Villringer & Dirnagl, 1994). This coupling is the basis of most of the functional neuroimaging techniques. The increase in oxygen delivery exceeds the demand associated with a metabolic rise for oxygen consumption (Fox & Raichle, 1986; Richard D. Hoge et al., 1999), therefore cerebral oxygenated-haemoglobin increases locally and deoxygenated-haemoglobin decreases (washout). There are two hypotheses explaining neurovascular coupling, which is discussed in the next section.

2.2.1 From firing neurons to the hemodynamic response

Neurons are able to transmit information by generating electrical pulse signals known as *action potentials.* A neuronal response to a stimulus, such as light or sound, is represented by depolarization of the membrane potential to fire a postsynaptic neuron. This action potential can be measured by measuring relative changes of spiking activity from an active to resting state (Arthurs & Boniface, 2002). This direct measurement of neuronal activity was used invasively in animal studies for more than a century and in patients when clinical intervention obliged. The method of implanting electrodes to measure single-unit cell electrical activity had given its place gradually to non-invasive techniques that were indexing neural activity by measuring electrical or electromagnetic fields on the surface of the scalp. Yet the limitation of these non-invasive techniques was their spatial resolution. Another way to assess neuronal activity was the indirect measurements of its metabolic correlates. In 1930s, two American chemists found the magnetic properties of haemoglobin. They showed that deoxyhaemoglobin is paramagnetic, which means that it is able to distort magnetic fields (Pauling & Coryell, 1936). It took several decades for this discovery to be used in a neuronal activity assessment device; functional MRI (Kwong et al., 1992; Ogawa et al., 1992). As oxygen supply augments following oxygen consumption induced

by neuronal activity, local deoxygenated haemoglobin diminishes. Knowing deoxygenated haemoglobin as a compound of brain activity, Thulborn and colleagues showed that T_2* contrast of MRI changed when its concentration locally changes (Thulborn, Waterton, Matthews, & Radda, 1982). Although, it is fair to mention that PET imaging was used prior to MRI for functional brain imaging, it was considered invasive because of the use of radioactive contrast agents. I don't discuss the principles of PET here for the matter of consistency

Changes in brain metabolism following neuronal activity provoke an increase in CBF by an important percent change, but less in CBV (Fox, Raichle, Mintun, & Dence, 1988). This uncoupling in the vascular system supply causes an initial increase in deoxygenated haemoglobin for a few seconds and an important decrease thereafter. This result is explained by the fact that excessive CBF flushes deoxyhaemoglobin from capillaries and downstream venules (Malonek & Grinvald, 1996; Mandeville et al., 1999). Measuring these post-stimulus changes in oxy- and deoxyhaemoglobin accompanying neuronal activity is the indirect way used in functional hemodynamic-based brain imaging methods. While the coarse correspondence between neuronal activity and hemodynamic response is well established through thousands of MRI studies, the detail of its mechanism giving rise to it is not clearly understood.

2.3 The necessity of calibrated functional imaging in aging studies

Up to here, I offered an assessment of hemodynamic response itself and in the next chapter will entail NIRS methodology, leaving aside intrinsic problematic of neurobiology of aging. Recalling the origin of hemodynamic response, which is constituted of concomitant local changes in CBF, CBV, and oxidative metabolism, we assume that any changes with age in these compounds could significantly affect the signal. For instance, increased rigidity in brain vessels could potentially lead to a diminished blood supply in response to a given fixed metabolic demand. If we assume that hemodynamic-based modalities are limited to the mass action measurements (Logothetis, 2008), we note that any potential alteration in factors underlying the hemodynamic response would create an ambiguity in interpreting signals. Moreover, across populations, there are various sources of confounds in the hemodynamic response measured via neuroimaging methods such as fMRI and fNIRS. For example, one important issue is that the functional data acquired through neuroimaging techniques may be dependent on both global brain structures and those underpinning the activity region of interest. As a result, baseline age-related difference in

$CMRO_2$ and/or oxygen saturation, which are the oxygen-metabolic constituents of functional hemodynamic response, would be cancelled-out once the data are corrected for brain structure reduction (Aanerud et al., 2012; Lu et al., 2011). Another example is that the $\Delta CBF/\Delta CMRO_2$ ratio plays a role in age-differences in BOLD signal and thus cognitive performance (Joanna L Hutchison, Lu, & Rypma, 2013).

One logical approach to this concern is a direct investigation of the components of functional data in a multimodal paradigm. For instance, the relation between brain volume and the strength of neural activation could be of interest to overcome the ambiguity of any hemodynamic response pattern variation (Brodtmann, Puce, Darby, & Donnan, 2009; Tyler et al., 2010). One classic approach recently administered is hypercapnia-calibrated BOLD. This methodology is a reliable physiological probe of neuronal activation, providing measures of the changes in cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen ($CMRO_2$). But it is not totally non-invasive and repeatable. Here in this study, I proposed a multimodal brain imaging to acquire data from baseline physiology and brain structures which were used to calibrate my functional NIRS signals. This multivariate analysis would augment the reliability of any inference from observations on aging.

CHAPTER 3 DIFFUSE OPTICAL IMAGING

Diffuse optical imaging (DOI) is a functional imaging technique using near-infrared light propagation in biological tissues in the diffusive regime. Since its advent by Jöbsis in 1977, noninvasive optical imaging is emerging in the medical imaging applications as a low-cost alternative or a complementary imaging modality. Functional optical signals reflect the physiological changes evoked by brain activity. To understand how this technique can be used to generate functional brain maps, we need to assume that the brain activity changes the optical properties of inter- and intracellular (we note that at the range of near-infrared light, photons are mainly affected by intravascular optical changes; haemoglobin). Then, we describe 1) how optical photons interact with brain tissues, 2) elaborate in which ways photons are responding to these interactions, and 3) finally discuss how to quantify or/and qualify the detected optical signals based on the underlying neurophysiological changes.

3.1 Biomedical optics

In 1949, Hill and Keynes (Hill and Keynes, 1949) reported that optical properties of the brain cells are associated with neural activity. Since then, a variety of invasive optical imaging was developed with different spatial and temporal resolution (for a comprehensive review see Obrig & Villringer, 2003). Brain tissue could affect light via different types of interactions, which change the parameters of emitted light accordingly. Optical imaging methods based on this principle include measuring the relevance of reflected, absorbed or Doppler shifted optical signals with functional state of neuronal tissue. Early studies of intrinsic optical signals (IOS) for the assessment of brain activity were mostly invasive because of using visible light wavelengths where the brain lacks tissue transparency (this subject will be discussed later in this subsection). Thus, the optical parameters under investigation were mainly scattering and phase retardation, and in some cases absorption when cytochrome oxidase ($CytOx_{diff}$) state changes were expected. Among optical topography application we could enumerate monitoring of single-unit activity of the exposed cortex in neurosurgical operations (Hill and Keynes, 1949), in vitro brain structure examination (Aitken et al., 1999), action potential extension (Svoboda, Denk, Kleinfeld, & Tank, 1997), mitochondrial metabolism (Hackenbrock, 1966) and synaptic activity in response to external simulations (MacVicar & Hochman, 1991). Mostly, early studies of IOS were done

under bloodless preparation to eliminate the confounding effect of hemodynamic response, except in cases of the functional cellular monitoring in exposed cortex.

High temporal and spatial resolution of IOS with ease of assessment brought this technique on top of that time dominant PET and MRI application. But later, a critical question on the specific origins of optical signals arose which would become even more complex when the vascular response factors were added to the signal. One solution to this hurdle was opting for a different methodology based on the wavelength specificity of IOSs.

The emergence of near-infrared (NIR; a wavelength band where light penetrate deeper into tissues) imaging showed that IOS could be used to assess neural activity through an intact skull. Invisible near-infrared light can penetrate few centimetres from the surface; well enough to probe the gray matter tissues, assessing neural activity. An array of light sources illuminates the tissue, which is diffusive, and a combination of detectors collects photons coming back to the surface.

3.2 Diffuse optical tomography

The principle of diffuse optical tomography (DOT) is studying neuronal activation by the optical imaging of biological tissues through measurements of the optical property changes in the transilluminated tissue. Huppert and collaborators did an extensive comparison of fMRI BOLD and DOT to confirm the legitimacy of the technique (Huppert, Hoge, Diamond, Franceschini, & Boas, 2006). They revealed that there was correlation between fMRI BOLD and HbR signal in DOT.

According to the type of light source, DOT is divided into two imaging categories; frequency and time domains (TD). In the frequency domain, the signal is either continuous wave (CW) or amplitude modulated by an AC signal at a RF frequency. In CW mode, the source signal is time-invariant and, when more than one light wavelength is used, can be time-multiplexed or modulated at low frequency to encode different source-detector measurements. Time domain uses a brief short pulsed-source and a photon-counting detector to time the arriving photons at high temporal resolution. Due to the restriction of counting a single photon with low probability, time domain systems have an inherently low SNR for an equivalent integration time. Since NIR light from 650 to 900 nm can penetrate up to 3 centimetres beneath the surface (Boas, Chen, Grebert, & Franceschini, 2004), DOT can be used to image human brain and breast (I will not

discuss breast optical imaging issue in this manuscript). The penetration depth is also dependent on the source-detector geometry; the higher the distance separating sources and detectors is, the pair collects photons from deeper tissues. The probability of the photon migration is illustrated in Figure 3-1. and depicts the role of source-detector configuration as discussed. The most common geometry being used in brain imaging is *reflective* in which the distribution of sources-detectors is placed on the same tissue boundary (Boas et al., 2001).

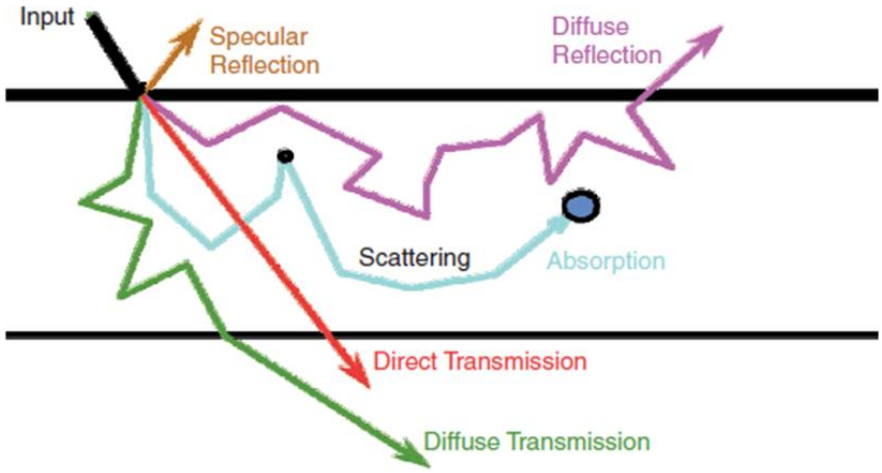

Figure 3-1 The probability of the photon migration in the biological tissue.
Image taken from Boas et al, 2001

3.3 Near-infrared spectroscopy

Almost 25 years after the advent of optical imaging, Jöbsis succeeded in measuring non-invasively the intracellular oxygen metabolism using endogenous contrast mechanisms (Jöbsis, 1977). Jöbsis found that *cytochrome c oxidase* has a weak absorption range from 780 to 870 nm with a broad maximum between 820 and 840 nm. In *redox reaction*, this enzyme plays a singular importance in oxygen consumption chain in cellular metabolism. Exploiting the relative transparency of highly scattering biological tissues to light in the spectral window of 650nm to 950nm, monitoring blood oxygenation changes is possible. As mentioned above, the low attenuation of the near-infrared light in biological tissues permits photons to penetrate few centimeters under the surface. The number of photons reflected from the cortical surface and detected is closely related to the absorption coefficient in the tissue. In the visible and near-infrared spectrum, haemoglobin is the dominant chromophore having intrinsic absorption

contrast. Thus, measuring changes in absorption can be used to monitor changes in hemodynamics arising from neural activity. In 1986, the applicability of intrinsic optical signals to image brain function was demonstrated via haemoglobin absorption changes (Grinvald et al., 1986). There, by estimating the haemoglobin changes within the illuminated area of the intact brain, functional recordings of neurovascular events could be acquired.

According to the physics of the medium, light interacts differently with biological matter by reflection, refraction, absorption, and scattering. The amount of detected transilluminated light through a translucent medium depends on the combination of these interactions (Jobsis, 1977; Max Born & Emil Wolf, 1999; Vo-Dinh, 2014). Biological tissues are known to be highly scattering (*turbid media*), while optical absorption is weak in the therapeutic optical window. For a comprehensive illustration, optical properties of biological tissue in the range of 400 to 2000 nm are demonstrated in Figure 3-2. Overall, it shows a significantly extended mean path length of the order of 10-100 mm for absorption comparing to scattering that is 0.1 mm. So we could assume that the only property of the biological tissue which changes attenuate the emitted light is the *absorption coefficient* (μ_a). The probability of a photon being absorbed in a medium is defined as the absorption coefficient. When a photon is absorbed by a molecule, its orbital electron reaches a higher quantum state. Once in a different spin state, electrons drop to the ground state by either emitting heat (irradiation) or another photon (photoluminescence). In case of re-emitting photons, excited electrons could relax into the ground state instantly as in fluorescent material or with

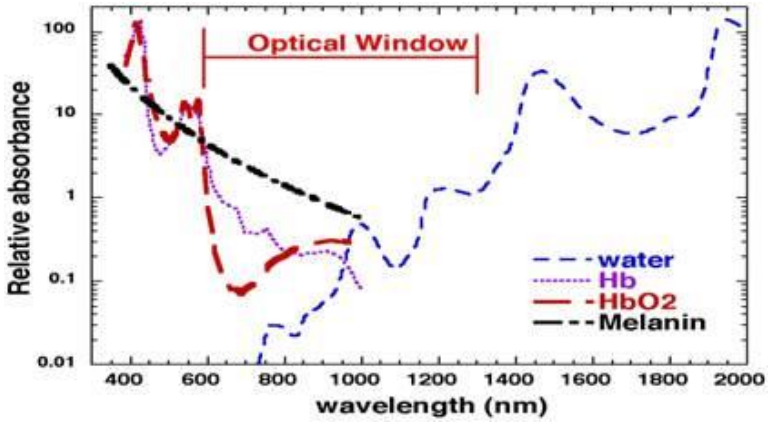

Figure 3-2 Optical windows in biological tissue. The graph is taken from SPIE Newsroom. DOI: 10.1117/2.1200906.1669

delay as in phosphorescence. This delay is due to the fact that the re-emission comprises energy state transitions ("forbidden") to achieve the ground state. In NIRS the former process is considered dominant.

The quantity of photons, at a specific wavelength, being absorbed in the biological medium depends on its optical properties. According to this definition, light intensity attenuates in an absorbing medium proportional to the distance it propagates. The following equation resumes this statement in the form of a Beer-Lamber attenuation law:

$$I(d) = I_0 . exp(-\mu_a . d) \qquad \text{(Equation 3-1)}$$

where I_0 is the light intensity emitted at the source, and I is the detected light at detector at a distance of d.

Thus, by estimating the proportion of detected light to the light at the source, nonionizing optical tomography provides quantitative information about changes in asborption (chromophore) in the medium along the trajectory between light source and detector. The equation below shows the relation between the measured raw data of differential optical density ΔOD dependent on wavelength and emitted and received photon fluence Φ differences:

$$\Delta OD(t,\lambda) = -ln\left(\frac{\Phi(t,\lambda)}{\Phi_0(\lambda)}\right) = -ln\left(\frac{\mathrm{I}(t,\lambda)}{\mathrm{I}_0(\lambda)}\right)$$

$$= \Delta\mu_a(t,\lambda).d \qquad \text{(Equation 3-2)}$$

with $\mu_a$described in relation with extinction coefficient ε as following:

$$\mu_a(\lambda) = \varepsilon^{\lambda}_{Hbo2}(C_{HbO2}) + \varepsilon^{\lambda}_{HbR}(C_{HbR}) \qquad \text{(Equation 3-3)}$$

where the extinction coefficients ε of haemoglobin were calculated in-vitro as a function of λ (Prahl, 1999).

Optical signals can be transformed to haemoglobin concentrations C_{HbO2} and C_{HbR}, applying the Beer-Lambert law. With two unknowns in the equation (see equation 3.4), we need to measure optical intensities at two different optical wavelengths. By normalizing:

$$\begin{bmatrix} C_{HbO2}(t) \\ C_{HbR}(t) \end{bmatrix} = \begin{bmatrix} \varepsilon_{HbO2}^{\lambda_1} & \varepsilon_{HbO2}^{\lambda_2} \\ \varepsilon_{HbR}^{\lambda_1} & \varepsilon_{HbR}^{\lambda_2} \end{bmatrix}^{-1} \begin{bmatrix} \Delta OD(t,\lambda_1) \\ \Delta OD(t,\lambda_2) \end{bmatrix} \quad \text{(Equation 3-4)}$$

This law holds only if photons go straight from the source to the detector, which is not the case in reality. The trajectory of each photon is perturbed because of significant scattering and high substance concentration (Villringer & Chance, 1997). Therefore, the formula need to be modified that taking into account the longer path length. The modified Beer-Lambert law (Delpy et al., 1988a) is written with an additional wavelength- dependent term which accounts for the longer path length:

$$\begin{bmatrix} C_{HbO2}(t) \\ C_{HbR}(t) \end{bmatrix} = \begin{bmatrix} \varepsilon_{HbO2}^{\lambda_1} & \varepsilon_{HbO2}^{\lambda_2} \\ \varepsilon_{HbR}^{\lambda_1} & \varepsilon_{HbR}^{\lambda_2} \end{bmatrix}^{-1} \begin{bmatrix} \Delta OD(t,\lambda_1)/(d \cdot \ell_{DPF}(\lambda_1)) \\ \Delta OD(t,\lambda_2)/(d \cdot \ell_{DPF}(\lambda_2)) \end{bmatrix} \quad \text{(Equation 3-5)}$$

where ℓ_{DPF} is the differential path length factor standing for the chaotic photon trajectory between each source and detector. The haemoglobin concentrations measured this way are just reflecting changes of the formers from time of acquisition, and are not the absolute measures of concentration at time t. If the path length $d \cdot \ell_{DPF}(\lambda)$ can be calculated, we could estimate the absolute concentrations of $HbO2$ and HbR. One approach to measure this is the direct measure of the time of flight in a TD system.

3.4 Issues with NIRS

Our understanding of brain activity has been expanded over last decades thanks to the developing techniques of cerebral imaging. Since the end of last century, an increasing number of researchers in various fields of studies have used NIRS and DOT in cognitive neuroscience. Here in this work, rather than recounting the success of NIRS, we chose to focus on its limitations. The major drawback of NIRS, in aging studies, is its lack of quantification. Two issues stand out preventing proper quantification: first, the hemodynamic based neuronal response, obtained from this modality, is sensitive to random measurement error and systemic errors arising from the assumed model parameters. For example, the limited depth resolution of DOT causes considerable partial volume error leading to amplitude inaccuracies of the haemoglobin concentrations, calculated during brain activation (Boas et al., 2004). Yet improvements of these issues are limited due to the large amount of diffusion and the unknown activation location.

Second, in hemodynamic-based functional neuroimaging of cognitive aging, the hemodynamic based neuronal responses are subject to interpretation difficulties due to the interaction of blood flow, volume and oxygenation (R D Hoge et al., 2005; Richard D. Hoge & Pike, 2001; Hyder et al., 2001), as well as tissue optical properties that change with age (Duncan et al., 1996). Since the background image properties are unknown, these changes with age increase the ambiguity of the model. Considering these interactions is essential in studies that aim to better understand modifications of cognitive performance with age and to distinguish the physiological changes from the underlying neuronal activation in response to a cognitive stimulus. Furthermore, in the brain, light propagation is complex and the absorption and scattering properties change from one layer of the tissue to another (white matter, gray matter, CSF, scalp and skin). Our main aim in this work will be to use prior information from MRI and time-domain NIRS to quantify and constrain model parameters with a focus on aging studies.

Data analysis of NIRS signals also faces two major challenges: first, separating the systemic physiology and device noise from the stimulus-evoked functional data, second, tomographic reconstruction from 2D signal acquisitions with the use of anatomical MRI images as a prior. For the first issue, the classical approach uses filtering of raw data to eliminate noises such as cardiac pulse and respiration. The issue with this approach is the resemblance of the functional data to some periodic noises with physiological source. Using rigid filtering, one risks removing information from the stimulus-evoked signal. Nevertheless, other methods such as denoising of the raw data by using Bayesian's GLM has been explored (Cohen-Adad et al., 2007).

CHAPTER 4 GENERAL METHODOLOGY

In this project, we used one unique behavioral and imaging protocol to test our hypotheses which are discussed in the following articles. An event-related fNIRS paradigm was designed to assess a lexico-semantic decision language task in a more natural fashion. The study is cross-sectional in which we compared elderly groups to their young counterparts. Both groups were matched meticulously by their cognitive scores to a well-established selection of neuropsychological batteries. We chose a population of participants having greater than 13 school years, non-smoker with no history of neurological or neurovascular disease. In a post-mortem aging study, it has been shown that synaptic density was constant throughout adult life until the seventh decade of age, and then a slight decline in observed after the age 74 years (Huttenlocher, 1979). Old adults were thus intentionally chosen within the bracket of 65 and 75 years old due to the documented early appearance of cognitive aging in that range, before the onset of any pathological decline (Small, Dixon, & McArdle, 2011). Participants participated in the study either in the morning or at the beginning of afternoon. I tried to counter-balanced the effect of time of the day as we know that some physiological aspects of cognitive functions varies accordingly. For instance, $CMRO_2$ varies across different times of the day (Peng et al., 2014).

4.1 Language task

To provide a framework for investigating the underlying substrates of semantic word processing in neuroimaging studies, it is necessary to build a robust tractable word list. To do so, we needed to break down words into smaller bits with controlled lexical variables which influence perceptual word processing. Thus, we narrowed down word's characteristics by controlling for their age of acquisition, objective frequency, familiarity, number of letters, orthographical structure, and neighborhood. For more details on the effects of lexical and sublexical (number of letters) on age-difference lexical decision making processes, I encourage readers to see the study published by Whiting and colleagues (Whiting et al., 2003) on this matter. Moreover, we aimed at exploring the effect of imageability on neural circuitry involving semantic memory. For this purpose, we acquired two lists of non-living and non-action words largely enough separated by their concreteness scores, defined in the range of 1 to 7.

Daselaar, Browndyke, and Cabeza in the chapter of Functional Neuroimaging of Cognitive Aging (in the ("Handbook of Functional Neuroimaging of Cognition, 2nd Edition | MIT CogNet," n.d.) have summarized number of studies in aging and language. In particular they state that if the secondary processing demand of the language task is kept under control, older adults show no differences in activation language areas. Based on this assumption, I tried to firmly control for all lexical aspects of chosen words to sort out only the semantic processing activity.

4.2 Image acquisition protocol

The study has been conducted in two phases with two age groups of healthy individuals with comparable cognitive performance. For this, each participant was evaluated for basic cognitive functions related to the study; consisting of a language vocabulary assessment, response time and strategy making set of behavioral cognitive tests. Neuroimaging acquisitions included anatomical and Arterial Spin-Labeled (ASL) MRI as well as near-infrared diffused optical imaging (NIRS and TRS). Fusion of these two modalities was hypothesized to provide complementary measures of brain metabolism correlates of neural activity, to obtain oxy- and deoxyhaemoglobin levels of the involved regions in response to word semantic tasks. The first phase of the study consisted of MRI scanning of the recruited participants to measure their anatomical parameters (aMRI) as well as their cerebral blood flow at rest (CBF_0) (Buxton, Wong, & Frank, 1998). In the second phase, participants underwent the optical acquisition sessions for both TRS and functional NIRS. The first part was to assess the baseline oxygenation of each individual at the time of fNIRS data collection. The importance of auxiliary measures was to account for the differences in vascular physiology of those participants of different group age that might exhibit a change rather than functional one in our data.

4.2.1 Magnetic resonance imaging (MRI)

4.2.1.1 Anatomical MRI

Anatomical information initially permitted us to evaluate the optical source-detector configuration of the functional NIRS imaging. An ensuing spatial co-registration was done later to achieve more accurate signal superposition on the regions of interest. In addition, a surface-based segmentation procedure (FreeSurfer) was done on anatomical images to assess cortical

morphological differences across participants. Anatomical atrophy and brain size reduction have been observed by several researchers motivated by studying neuroanatomy of aging (Fjell et al., 2009; Kaup, Mirzakhanian, Jeste, & Eyler, 2011; Lemaître et al., 2005; Naftali Raz et al., 2005). Degeneration of cortical gray matter is common in the old population and is believed to be correlated with cognitive decline. Although the sample size in this project is quite small, they still could lead to an age effect on the language related cortical regional thickness. To reduce the effect of size, a study specific normalization template has been created by calculating a mean image within each segmented image to create a prior probability maps.

4.2.1.2 Arterial Spin Labeling

Various brain imaging techniques were explored to measure directly or indirectly neural activity and default networks. Arterial spin labeling (ASL) measures blood perfusion by using the water in the blood as a tracer. This non-invasive technique acquires absolute quantities of cerebral blood flow at rest (CBF_0) or in response to an increase in cerebral metabolism (ΔCBF). Prior to the advent of ASL technique, researchers have been using other imaging modalities (i. e., Positron Emission Tomography (PET)) in which exogenous contrast agents (inhaled or intravascular tracers) was administered to tag water in the blood. For instance, in PET scanning, radiotracers would circulate through the body's vasculature emitting positrons detectable by the equipment. This way, areas with greater signal showed higher level of labeled water or in another word blood flow. ASL borrows the same principle but with magnetically labeled water which is completely non-invasive. In ASL, a radiofrequency (RF) inversion pulse is applied at the level of arterial inflow to tag water and then image a slice of the cortical tissue above the inversion field. In order to obtain the tissue perfusion in that particular slice, we need two images; labeled image of the paramagnetic water molecules flowing into the imaged slice, after a certain transit time, and a control image where no RF is applied. This transit timing is important to be long enough allowing labeled blood to enter the target tissue (> tissue T1). By subtracting the labeled image from the control one, the quantity of tagged water is obtained which is closely related to the amount of blood perfusion in the imaged tissue.

In this project, the absolute CBF_0 was measured in arbitrary units by the constant component of a long relaxation time ASL scan (ASL_0) using the quantitative approach described by Wong and colleagues (Wong, Buxton, & Frank, 1997). This value was then converted to physiologically

relevant units (mL blood /100 g tissue per minute) using a general kinetic model fit for the ASL signal (Buxton et al., 1998; Wong et al., 1997). The model defines a relationship between the measured signal and CBF_0 assuming blood longitudinal relaxation time T1 and fully relaxed magnetization M_0 are known:

$$CBF_0 = \frac{ASL_0}{6 \times 10^6 \cdot 2 \cdot TI1 \cdot \exp(^{-TI2}/_{T1b}) \cdot M_{0b}}$$

(Equation 4-1)

Where TI1 = 1400 ms, TI2 = 2000 ms, T1b = 1932 ms at 3T and the factor 6x106 converts the units for CBF_0 to mL/min/100g. The value for M_{0b}, the fully relaxed magnetization of blood, was calibrated using that of white matter measured in the M_0, scan (Wong et al., 1997):

$$M_{0b} = M_{0WM} \cdot \frac{1}{\lambda} \cdot \exp\left(TE \cdot \left(\frac{1}{T_{2WM}} - \frac{1}{T_{2b}}\right)\right)$$

(Equation 4-2)

With M_{0WM} the average value of the M_0 scan in a ROI selected from the segmented white matter, the brain-blood partition coefficient for water λ = 0.9 mL/g (Herscovitch & Raichle, 1985), TE = 12 ms, T2WM = 70 ms and T2b = 275 ms at 3T. The blood flow measurement was then regressed against the functional NIRS data to evaluate its impact.

Caffeine abstinence. Caffeine, a neural stimulant widely consumed in the world, was recently the subject of attention among scientists trying to assess brain physiology. This stimulant substance can easily cross the blood-brain barrier and bond to adenosine receptors. This mechanism causes vasoconstriction and as a results baseline CBF diminishes (Behzadi & Liu, 2006; Liu & Wong, 2005), It has been also shown that vasoconstrictive agents could affect the amplitude and temporal signature of BOLD signal (Behzadi & Liu, 2005). Although its effect on blood oxygenations and glucose metabolism was not conclusive, an uncoupling of CBF and cerebral metabolism is suggested (Perthen, Lansing, Liau, Liu, & Buxton, 2008). For these

reasons, we decided to eliminate this confounding element and ask the participants to not consume caffeine on the day of experimentation.

4.2.2 Diffuse optical imaging

Two different optical devices have been used in this study. As described thoroughly in previous chapter, functional data acquired via NIRS technique is the subject of exploration in this study to map neural substrates of semantic memory. For the matter of age-group comparison, another modality of DOI could offer us the absolute blood oxygenation quantities serving as complementary data. The ΔOD signal, acquired by NIRS, does not give the absolute hemodynamic response to the stimuli, but the mere changes of Hb concentration from its baseline level. Thus, it is primordial to account for the initial concentration of Hb as the potential physiological brain capacity to respond to the stimulus-evoked metabolism augmentation. The optical modality which allows an absolute quantification of Hb concentration is time-resolved spectroscopy (TRS). With TRS, we are able to calculate temporal response to a single pulse light source which gives a measure of the amount of Hb under the illuminated brain region.

4.2.2.1 Time-resolved spectroscopy

To recover haemoglobin concentrations from optical parameters we assumed that oxy- and deoxyhaemoglobin, as well as water, were the dominant absorbers between 690 and 850 nm wavelengths. A brief pulse of light at the order of few hundred *ps* was sent to the scalp at four different wavelengths of 690, 750, 800, and 850 nm. According to the time of flight for each cluster of photons, transilluminated light was detected at four different distances from the source (10, 15, 25, and 30 mm) by four single-photon counting avalanche detectors (SPADs). The raw data acquired by detectors consisted of photon distributions of time-of-flight (DTOF) in the head (it is also called temporal point spread function TPSF). Photons were collected for a time-course of approximately 5 minutes to generate sufficient statistics. In order to calculate the hemodynamic parameters in the brain, we needed first to estimate the absorption coefficient at each wavelength by fitting the measured time series of DTOF with an exponential law (Chance et al., 1988). The fitting procedure was done via a non-linear optimization routine (MATLAB function *lsqcurvefit*) with μ_a, μ_s from the literature and an amplitude factor to fit with the theoretical model (Gagnon et al., 2008). To estimate optical parameters μ_a and μ'_s, theoretical

DTOFs of the medium, which is the head, were convolved with the instrument impulse response function (IRF). At the end, haemoglobin concentrations were recovered by inversion of the Equation 4-3.

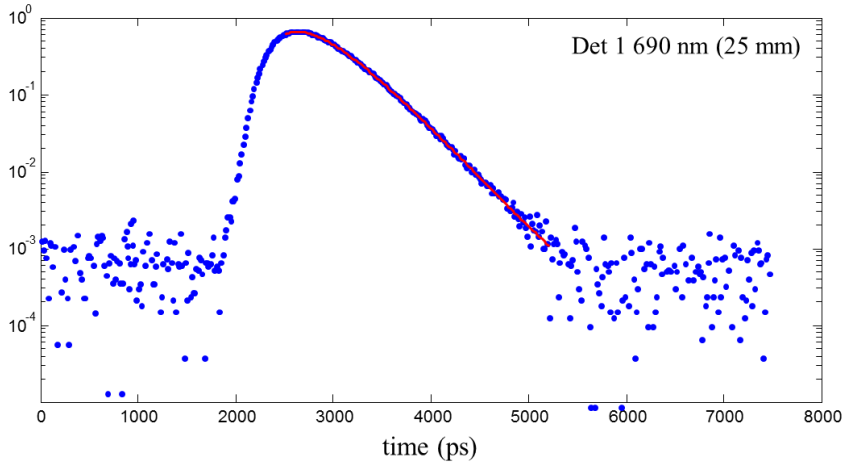

Figure 4-1 : TRS measurements (x-axis: number of photons) for detector 1 at the distance of 25 mm from the light source at 690 nm. The red curve shows here a perfect fit to the raw data (blue dots).

The equation below depicts the linear system describing the relationship between the extinction coefficient ε(λ) (taken from the literature) and the absorption coefficient $\mu_a(\lambda)$ (calculated from TRS measurements):

$$\mu_a(\lambda) = 2.303.\varepsilon(\lambda).C$$

$$\begin{bmatrix} \mu_a(\lambda_1) \\ \mu_a(\lambda_2) \\ \mu_a(\lambda_3) \\ \mu_a(\lambda_4) \end{bmatrix} = \begin{bmatrix} \varepsilon_{HbO_2}(\lambda_1) & \varepsilon_{HbR}(\lambda_1) & \varepsilon_{H_2O}(\lambda_1) \\ \varepsilon_{HbO_2}(\lambda_2) & \varepsilon_{HbR}(\lambda_2) & \varepsilon_{H_2O}(\lambda_2) \\ \varepsilon_{HbO_2}(\lambda_3) & \varepsilon_{HbR}(\lambda_3) & \varepsilon_{H_2O}(\lambda_3) \\ \varepsilon_{HbO_2}(\lambda_4) & \varepsilon_{HbR}(\lambda_4) & \varepsilon_{H_2O}(\lambda_4) \end{bmatrix} \begin{bmatrix} C_{HbO_2} \\ C_{HbR} \\ C_{H_2O} \end{bmatrix}$$

(Equation 4-3)

We further assumed that biological tissues contained 70% water, reducing the above system (eq. 4.1) to four equations with two unknowns. A pseudo-inversion of the equation with a least-square fit provided *C*, the haemoglobin concentrations (Patterson, Chance, & Wilson, 1989).

4.2.2.2 Near-infrared spectroscopy

The details of this modality were exhaustively described in the previous chapter. Here we outline parameters of the NIRS equipment used in this project. A 32-channel continuous wave NIRS instrument (TechEn CW6) with a sampling rate of 25 Hz was at our disposition for the duration of data acquisition. TechEn uses two light sources of continuous frequency modulated wavelengths at 830 and 690 nm within the therapeutic optical window. In order to cover the language-related brain regions (frontal and temporal lobes), we designed and made a helmet holding tightly 58 optical channels (a combination of 5 sources and 14 detectors per hemisphere while guarantying proper probe positioning. The real-time monitoring of the signal allowed us verifying signal quality as a result of a good skin contact. To maintain a consistency in optical fibers' positioning, we adjusted the front edge of our helmet on EEG standard electrode position Fp_0 according to the 10-20 EEG system.

Short source-detector distance measures. The NIRS signal is known to be contaminated by the systemic physiology within the superficial layers of the head. Recently, it has been shown that including short separation (SS) source-detector recordings could improve the contrast to noise ratio (CNR) (Gagnon et al., 2011; Yamada, Umeyama, & Matsuda, 2009; Zhang, Strangman, & Ganis, 2009). Since SS signal only contains the superficial hemodynamics, by using it as regressor in the GLM, we can reduce the interference of surface signals in the detection of the hemodynamic response induced by a cognitive task. Here in this study, I chose to include a SS channel with 1.35 cm separation on the frontal right lobe and assumed that the superficial physiology is homogeneous across the head. It should be noted that this assumption is flawed: there is not a clear consistency in this measurement across the head (Gagnon et al., 2012).

4.3 Efficient experimental paradigm

It is important to bear in mind that none of the hemodynamic based imaging techniques offer absolute measurements of the cerebral activity. In fact, there is no simple method allowing us to evaluate quantitatively blood oxygenation and blood volume. Thus, the solution is to design an experimental paradigm to contrast an activation state against a given reference according to the "cognitive subtraction" principle (Friston et al., 1998). When the reference is considered as the regional brain activity at rest one calls it simple-condition paradigm, while in the case of having

another activity evoked condition it is called differential paradigm. The advantage of a differential paradigm is to diminish the artifact caused by large veins in the proximity of the region of interest by differentiating two conditions.

The cycle and frequency of the provoked neuronal activity can be modulated in an experimental paradigm. Blocked design gathers trials of the same condition in block lengths of 20s to 60s, in average, to obtain a large hemodynamic response by means of time-integrated averaging. The activity within each bloc could be a repetitive action like rapid finger tapping or a continuous act like reading a text. In contrast, an event-related design is based on the brief presentation of different trial-types in a randomized or staggered fashion. There is an optimum choice in the distribution of stimulus onset asynchrony (SOA or interstimulus interval) to improve experimental design in order to maximize the efficiency of response estimation (Friston, Zarahn, Josephs, Henson, & Dale, 1999). However, one design could be efficient for one condition but not for another. For instance, one issue to consider is the staggering and the length of trials presentation according to the sampling rate of the imaging device. The distinction between *deterministic* and *stochastic* design is based on the probability that an event occurs at a specific timing or not. The most efficient design for a differential response (our case) is a rapid presentation of nonstationary trials with the maximum possible duration and repetition (Boynton, Engel, Glover, & Heeger, 1996; Dale & Buckner, 1997; Friston et al., 1999). This method offers

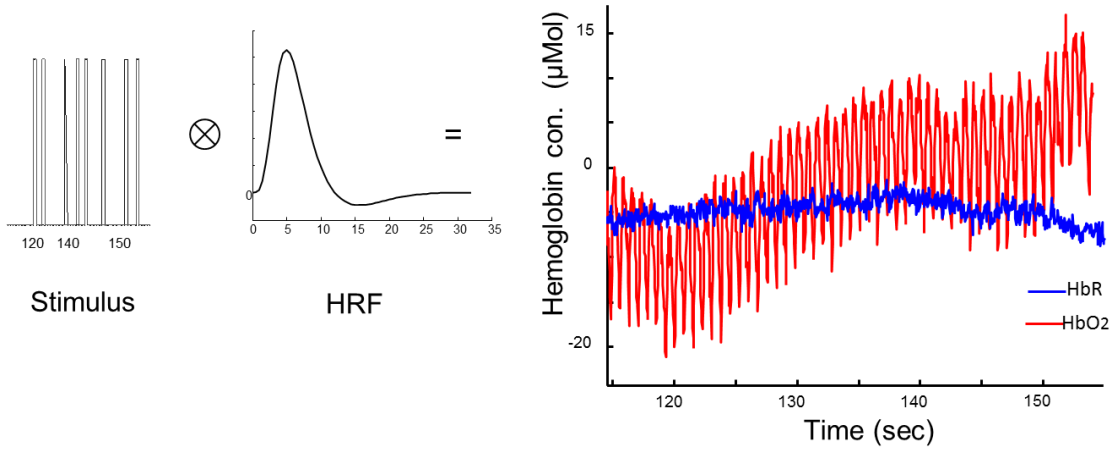

Figure 4-2 Predicted data to the convolution of HRF by a random SOA stimuli is shown by measured HbR and HbO2 as hemodynamic response to stimuli.

several advantages, among them randomized counterbalancing presentation of trials eliminates the bias caused by preceding trial-types. Also, such paradigm allows a *post hoc* analysis. At the same time, it is important to note that post-stimulus undershoot of the hemodynamic response may last up to 30 s for a single brief trial (Chen & Pike, 2009).

4.3.1 Design matrix

When we conduct an experiment in which we compare the significant effect of one variable over other variables, classical hypothesis testing is to be used. In this study, we measure the response variables to a single "event" at each channel with a definite number of observations. Also, for each observation we have a set of covariates. Time between events (SOA) in our design was chosen from 3s to 11s, so the successive responses would overlap. If we consider the signal to a session of NIRS acquisition as time series (K. J. Friston et al., 1994), we could model it with a general linear model (GLM) via a convolution with a hemodynamic response function (HRF). The following equation describes GLM as a function of time:

$$y(t) = \mu + X(t)\beta + \varepsilon(t)$$

(Equation 4-3)

where $y(t)$ is the measured response variable, μ is a constant term of the model, $X(t)$the matrix of covariates (explanatory variables), and β is the vector of time-invariant unknown parameters corresponding to each covariates. The error $\varepsilon(t)$ of the model is an independent variable with normal distribution around zero and the variance σ^2. The advent of event-related methods (Dale & Buckner, 1997) was based on linear convolution models of a canonic HRF, $h(\tau)$, which is represented by a kernel function:

$$h(\tau) = \sum_{k=1}^{K} \beta_k \, f_k \, (\tau)$$

(Equation 4-3)

where $f_k \, (\tau)$ is the basis function. It has been assumed that the kernel can be expanded over k (Pouliot et al., 2012).

Given the fact that the HRF has not a constant shape over brain regions and between participants, a time and dispersion derivative of its function needed to be considered in our study; three basis functions.

4.3.2 Statistical inference

Our general linear model (GLM) analysis proceeded in 3 levels: 1- for each session of each subject; 2- averaging the sessions of each subject and 3- inter-subject. 1) Raw fNIRS signal intensities were normalized to the unit median before being converted to haemoglobin concentrations using the Beer-Lambert law, then low-pass filtered (0.67 Hz cutoff). We then fitted a GLM to the concentration signals for each optical channel using the canonical HRF of SPM with a cosine basis to model drifts (cutoff at 0.01 Hz) and a constant. We considered in a separate stream of analysis the time and dispersion derivatives of the HRF to cover for the latency and amplitude differences. To localise brain activity, we produced an activation map of cortical oxygenation changes, by interpolating the GLM responses and projecting onto 2-dimensional left and right views of the cortex. 2) We averaged the maps over the 3 sessions, for each subject. 3) We averaged the resulting maps over the subjects, or performed ANOVAs, to evaluate the power of GLM estimation for between and within subject differences. Finally, to determine a statistically significant effect of each pixel for a given contrast, we applied a threshold which was calculated using the theory of inhomogeneous random fields by Ye et al. in order to correct for multiple comparisons, by correcting the threshold in order to avoid Type I error.

Contrast specification. In our experiment we manipulated more than one factor concurrently: words versus pseudo-words, and each factor is associated with two levels (condition) of abstract and concreteness. Such design allows tests of differences between levels of each factor (main effect) as well as the effect of one factor over the level of another factor (interaction). The case of four event types in this study is treated as a subtraction design. The null hypothesis is whether the differential response of two conditions is equal to zero.

CHAPTER 5 ARTICLE 1: FNIRS EXPLORATION OF THE HEMODYNAMIC CHANGES ALLOWING FOR THE SEMANTIC PROCESSING OF WORDS IN NORMAL AGING

In this manuscript, in addition of functional data, we show differences between age groups in baseline hemoglobin concentrations, oxygen saturation and cerebral blood flow for both left and right frontal lobes. Thus, we suggest our findings would appeal to the researchers in aging studies the importance of complimentary measurements regarding the physiological aspects of aging and quantifying functional neuro-imaging data accordingly. This article is published in Frontiers in Neurology (2014), 5, p. 249.

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5.1 Abstract

Like other neuroimaging techniques assessing cerebral blood oxygenation, near-infrared spectroscopy (NIRS) has been applied in many neurocognitive studies. With NIRS, neural

activation can be explored indirectly via hemodynamic changes in the imaged region. In studies of aging, changes in baseline physiology and brain anatomy confound NIRS measures seeking to investigate age-related changes in neuronal activity. The field is thus hampered by the complexity of the aging process itself, and statistical inferences from functional data acquired by optical imaging techniques must be interpreted with care. Multimodal integration of NIRS with both structural and baseline physiological assessments is crucial to avoid misinterpreting neuroimaging signals. In this study, a combination of two different optical techniques, anatomical MRI and Arterial Spin Labeling (ASL) was used to investigate age-related changes in activation during a lexical-semantic processing task. Quantitative analysis revealed decreased baseline oxyhaemoglobin and cerebral blood flow in the older adults. Using baseline physiology measures as regressors in the investigation of functional concentration changes when doing analyses of variance, we found significant changes in task-induced areas of activity. In the right hemisphere, more significant age-related activity was observed around the junction of the inferior frontal gyrus and inferior precentral sulcus, along with engagement of Wernicke's area. In the left hemisphere, the degree and extent of frontal activation, including the dorsolateral prefrontal cortex and inferior frontal gyrus, differed between age groups. Measuring background physiological differences and using their values as regressors in statistical analyses allowed a more appropriate, age-corrected understanding of the functional differentiations between age groups. Age-corrected baselines are thus essential to investigate which components of the NIRS signal are altered by aging.

5.2 Introduction

Given the growing proportion of elderly adults in the population due to increased longevity, studies investigating and promoting healthy cognitive aging are of the utmost importance. By 2050, the number of elderly individuals will be 16% higher than the number of children and adolescents under 15 (J. E. Cohen, 2003). In this context, the number of dementia cases in the aging population is expected to grow exponentially. Prevalence studies in all world regions estimate that 24.3 million people currently have dementia and predict that the number of persons with Alzheimer's disease will double every 20 years, rising to 81.1 million by 2040 (Ferri et al., 2005). This trend supports the importance of characterizing the mechanisms underlying healthy

cognitive aging in order to optimize healthy aging and possibly contribute to delaying the manifestations of dementia.

Normal aging is characterized by significant modifications of the brain's anatomy and physiology, which vary depending on the brain region and component (F. I. M. Craik & Salthouse, 2000). The overall volume and weight of the brain decreases with each decade of age but displays regional variability. For example, in a five-year longitudinal study, Raz and colleagues have examined age-related differences in regional brain volume (Naftali Raz et al., 2005). A significant negative correlation between age and volume of the lateral prefrontal cortex, orbitofrontal cortex and prefrontal white matter was observed. In the temporal association cortices, a more moderate shrinkage with age was also found. These anatomical changes are associated with widening sulci and synaptic loss, but negligible neural loss has been observed.

Age also affects sensory and cognitive abilities but in a heterogeneous fashion, varying with cognitive domain. A first hypothesis to explain this observation is that there is a correlation between structural changes and functions. Depending on the cognitive domain (Grady et al., 2006) and individual characteristics (Cabeza, 2002), cognitive abilities are affected differently. Amongst brain functions that are better preserved with aging, older adults have shown a good preservation of semantic word processing and conceptual knowledge organized to depict the relationship between words and stored knowledge of the world. Given that the language-related brain regions (e.g., prefrontal and superior temporal cortices; (Bookheimer, 2002; Démonet et al., 2005; Mummery, Patterson, Hodges, & Price, 1998; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) are affected by age (Hedden & Gabrieli, 2004; Naftali Raz & Rodrigue, 2006), investigating the mechanisms underlying the relative preservation of language abilities is essential to better understand how the aging brain handles structural and physiological decline.

A major obstacle to these studies is that interindividual variability in cognitive domains increases with aging and this makes it difficult to apply inferences from individual observations over the entire elderly population. To interpret this variability, one can posit that interindividual differences are mainly due to large variations in the anatomical and/or neurophysiological structures underpinning cognitive performance with age (Lu et al., 2011). An alternative hypothesis is that some older adults compensate for cognitive aging by either adapting compensatory processing procedures by means of an inter- and/or intrahemispheric functional

reorganization or changing cognitive strategies (Bäckman and Dixon, 1992; Cabeza, 2002; Grady et al., 2006; Hertzog, 1985), relying on what has been conceptualized as their cognitive reserve (Stern, 2003). With the aim of revealing cognitive changes associated with age, numerous neuroimaging studies have investigated age-related neurophysiological changes associated with functional brain activities (Mark D'Esposito et al., 2003; Joanna L. Hutchison, Lu, & Rypma, 2012; Joanna Lynn Hutchison, Shokri-Kojori, Lu, & Rypma, 2013; Wong et al., 1997). Despite overall similarities in basic neuronal activity in young and older adults, older individuals show less activity in some brain regions and/or over-recruitment of other brain regions (Grady, 2008) in response to complex tasks. Over-recruitment can be interpreted as a compensatory mechanism or as an indication of neuronal inefficiency. Thus, the challenge in cognitive aging research is to distinguish between these two mechanisms.

To investigate the complex phenomenon of aging, functional near-infrared spectroscopy (fNIRS) has been used in cognitive neuroscience because of its moderate running costs, portability and potential for examinations in a natural setting (Ansaldo, Kahlaoui, & Joanette, 2012). This non-invasive imaging technique allows researchers to probe the hemodynamic response evoked by neural activity in the first centimeters of cortical tissues. By emitting near-infrared light (650–950 nm) through the scalp and measuring the photons attenuated by absorbing compounds primarily composed of oxy- and deoxygenated haemoglobins (HbO_2 and HbR respectively), estimates of neural activation can be recovered (Delpy et al., 1988a; Villringer, Planck, Hock, Schleinkofer, & Dirnagl, 1993). One advantage of fNIRS measures over the blood-oxygen level dependent (BOLD) signal obtained from functional magnetic resonance imaging (fMRI) is its ability to measure oxygenation level. However, in hemodynamic-based functional neuroimaging techniques, such as fMRI and fNIRS, neural activity is measured indirectly through neurovascular coupling as a function of changes in cerebral blood flow, blood volume and oxygenation (Buxton et al., 2004). Signals are therefore subject to interpretation difficulties due to the ambiguous interaction of the neurophysiology and vasculature underpinning the hemodynamic response (Fox & Raichle, 1986; R D Hoge et al., 2005; Richard D. Hoge & Pike, 2001; Hyder et al., 2001). Thus, changes in measured activation response are related not only to neuronal activity but also to modifications of the underlying physiology with age. There is evidence from the literature that global cerebral blood flow (CBF) decreases with age, while the cerebral metabolic rate of oxygenation ($CMRO_2$) increases (Ances et al., 2009; Joanna Lynn

Hutchison et al., 2013; Lu et al., 2011), and that microvascular capacity in response to strong demand for oxygenation also declines (D'Esposito et al., 2003). It is therefore essential for studies to consider these confounding factors if they aim to distinguish the observed physiological changes with age from the underlying neuronal activation in response to a cognitive stimulus.

Other methodological difficulties specific to the NIRS signal are partial volume effects (Villringer et al., 1993) and tissue optical properties that change with age (Bonnéry et al., 2012; Duncan et al., 1996). The age-related changes in tissue properties and capillary circulation in the skin (de Rigal et al., 1989) and how these changes interact with light propagation in the head may bias NIRS measurements when young and elderly individuals are compared. Time-resolved spectroscopy (TRS) systems provide measure of optical properties of cerebral tissues with the ability to distinguish between superficial layers [skin, skull and cerebrospinal fluid (CSF)] and brain tissue. Thus, intra- and extracerebral haemoglobin concentrations can be determined for each individual separately (Gagnon et al., 2008).

The aim of the present study was to assess the physiological and functional changes that occur in parts of the language processing network during normal aging by means of a lexical-semantic decision task and two imaging techniques: anatomical and blood perfusion (arterial spin labeling; ASL) MRI and fNIRS, as well as time-domain optical imaging TRS. By integrating each individual's baseline CBF, oxy- and deoxyhaemoglobin concentrations and structural characteristics, obtained with ASL-MRI, TRS and anatomical MRI, respectively, with the functional hemodynamic responses from NIRS, the goal of this study was to investigate the effect of intrinsic interindividual variability on the hemodynamic responses measured. Specifically, we hypothesized that each individual's baseline physiology, reflecting his or her neurovascular health, was related to the preservation of semantic memory and cognitive performance. We also hypothesized that higher levels of CBF and oxygen saturation ($SatO_2$) from TRS measurements should account for the percentage changes of [HbO_2] and [HbR] in response to our lexical-semantic decision task. Controlling for these age-related factors is crucial if one wishes to distinguish the presumed age-related neurofunctional reorganization of the brain for cognitive ability, such as the semantic processing of words, from the basic neurophysiological changes linked to the aging brain's hemodynamics.

5.3 Materials and methods

5.3.1 Participants and protocol

In this study, 46 healthy French-speaking individuals divided into two groups of elderly people (n = 23), aged 65 to 75 (mean age = 69.6 ± 4.1), and young people (n = 23), aged 20 to 35 (mean age = 23.4 ± 2.7), were recruited. Because language knowledge is embedded in the social and cultural context, we restricted our participants to French speakers from Quebec. The elderly cohort was chosen from this specific age bracket because of the delicate transition to old age (> 65) and the increased prevalence of cognitive decline (from 4.97% to 24.19%) after the age of 80 (Plassman et al. 2007). The study was approved by the ethics committee of the Institut universitaire de gériatrie de Montréal (IUGM) and all participants gave their written consent. Exclusion criteria were claustrophobia, hypertension or any cardiovascular disease, smoking, thyroid dysfunction, diabetes, taking any medication known to be vasoactive, as well as psychiatric or neurological illness. Participants were all right-handed according to the Edinburgh Handedness Inventory (Knecht et al. 2000; Oldfield 1971). For the measurement of baseline cerebral blood perfusion, they were also asked to abstain from drinking coffee the day of acquisition (Chen and Parrish 2009; Perthen et al. 2008).

Participants were screened for their level of cognitive performance by standardized cognitive assessments including the Trail Making Test A/B (Reitan 1985), the Montreal Cognitive Assessment (MoCA; (Nasreddine et al. 2005), and five subtests of the short-form Wechsler Adult Intelligence Scale (WAIS-III; (Axelrod 2002; Schrimsher et al. 2007; Wechsler 1991), namely Vocabulary, Block Design, Similarities, Matrix Reasoning, and Direct and Inverse Digit Spans. In this way, it was possible to exclude those with mild cognitive decline according to age-corrected norms. These tasks assess phonological short-term memory storage as well as processing capacities and evaluate general intellectual ability, planning, visual exploration, attention, mental flexibility and verbal inhibition.

The activation task represents a robust, well-studied lexical-semantic task: lexical decision (Balota et al. 2004). Stimuli were chosen from the specific categories of nonaction words (nouns) denoting nonliving objects in order to isolate the peripheral effects in networks associated with semantic processing. Words generated from a French lexical database (OMNILEX database from

the Cognitive Psychology of Language Laboratory, University of Ottawa, Canada) were matched according to their lexical frequency, grammatical category (nouns), age of acquisition, orthographic structure and length in letters. It is important to note that, in visual lexical decision tasks, word length affects reaction time (RT), with stable RTs for words four to six letters long (New et al. 2006). Concreteness of the words (abstract vs. concrete) was manipulated by the imageability index on a scale of 1 to 7 to investigate the effect of word imageability within a lexical decision test (n = 60 for each category). Pseudo-words were then created from the real words (n = 120) by changing two consonants. All items (words and pseudo-words) were then matched by bigram frequency and length in letters (Lexique database, Paris Descartes University, France). A pilot study of 15 young adults was done prior to the main study to eliminate outliers within each category. Participants were presented with words and pseudo-words on the screen and were instructed to answer whether or not the letter string constituted a real word. Each trial started with a fixation point (+) that appeared at the center of the screen and was followed by the stimulus. A blank screen provided time to answer with a yes/no button on the computer keyboard. The task was executed using E-prime software (version 2.1), which also recorded the RTs and correct responses.

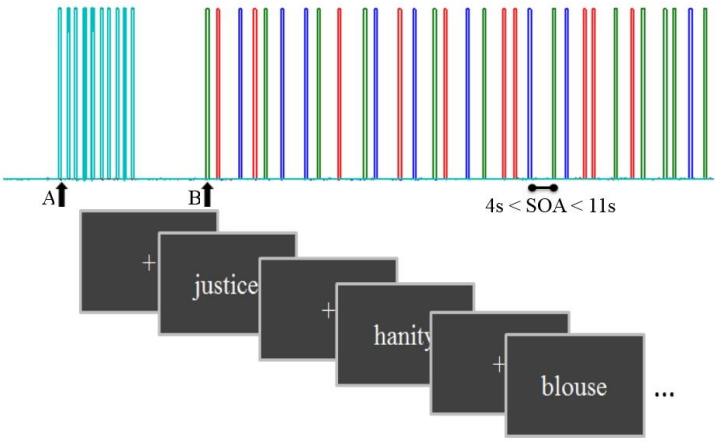

Figure 5-1 A schema of the task diagram with inter stimulus interval = 1.36 s and stimulus onset asynchrony from 4 s to 11 s. Triggers from the computer presenting the task were sent to the NIRS computer after synchronization: A = start control task, and B = start main task. Each color bar represents a different condition: concrete, abstract and pseudo words.

The paradigm was designed in an event-related (ER) fashion. The ER design presented each stimulus at a specific time, allowing the investigation of the evoked hemodynamic response delayed by 2 to 3 seconds from stimulus-induced neuronal activity (K. J. Friston et al. 1994a). Stimuli from different categories (e.g., experimental conditions; word vs. pseudo-word.) were presented in a random intermixed order for 4 s to 11 s (Figure 6-1).

5.3.2 Diffuse optical measurements

5.3.2.1 NIRS

Task-induced changes in optical intensity were measured with a 32-channel continuous wave NIRS instrument (TechEn CW6) with a sampling rate of 25 Hz. TechEn uses two continuous frequency modulated wavelengths at 830 and 690 nm, within a wavelength range where HbO_2 and HbR are the dominant light absorbers. Using two different wavelengths, we were able to assess the changes in haemoglobin concentration from absorption coefficients (μ_a) by measuring light attenuation (modified Beer-Lambert law; (Delpy et al., 1988a). In this study, we used two patches of 29 channels (a combination of 5 sources and 14 detectors) for each hemisphere, covering the entire frontal and temporal regions of the cortex (Figure 2). To reliably position the posterior edge of the optical helmet, we used the electrode positions Fp_0 and inion as references according to the 10-20 EEG system.

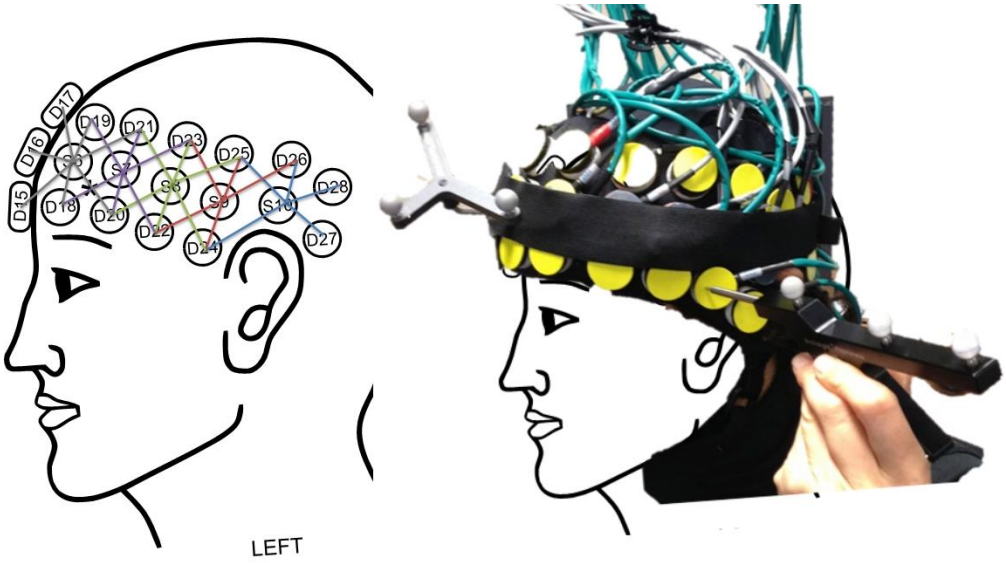

Figure 5-2 Left: the schema of the multi-distance optical source-detector design based on the 10-20 standard to cover brain-language regions. Right: the home-made optical helmet used in this study with the reference and pointer of the stereotaxic system used to register optode positioning for later coregistration on each participant's anatomical image.

5.3.2.2 TRS

A TRS system using four pulsed lasers with wavelengths of 690, 750, 800 and 850 nm, temporally multiplexed, illuminated the participant's forehead. Four detectors at distances of 10, 15, 25 and 30 mm from the point of illumination collected the backscattered light and were then focused on the detection surface of photon-counting avalanche photodiodes with a 20X microscope objective. The experiment took place in a dark room to reduce the noise on the single-photon counter detectors.

The measurements obtained were fit to a double-layer analytical model (Gagnon et al., 2008). Thus, the head was modeled as a heterogeneous medium, with the first layer consisting of skin, skull and CSF and the second layer including both gray and white matter. The model yielded absolute estimates of the optical properties [absorption (μa) and scattering (μs) coefficients] in each layer.

5.3.3 MRI acquisition

Anatomical MR images were obtained on a 3T Siemens Trio MRI (Siemens Medical Solutions, Erlangen, Germany) using a 32-channel receive-only head coil at the Unité de Neuroimagerie Fonctionnelle of the IUGM. A volumetric Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was used to acquire a high-resolution T1-weighted 3D anatomical image, using the following parameters: TR = 2.3 s, TE = 2.91 ms, TI = 900 ms, flip angle = 9°, FOV = 240 x 256, voxel size = 1 x 1 x 1 mm3. This sequence was followed by an ASL sequence at rest, without sensory deprivation. The imaging sequence was a PICORE labeling geometry (Wong et al., 1997) and Q2TIPS tag duration control (Luh, Wong, Bandettini, & Hyde, 1999) to quantify the baseline cerebral blood flow (CBF_0; (Buxton et al., 1998). A post-label delay of 900 ms and label duration of 1500 ms were used, with repetition time (TR) and echo time (TE) of 3 s and 20 ms, respectively. The ASL signal is evoked by the local magnetization differences following the diffusion of the magnetically labeled blood to quantitatively measure blood perfusion. A single M_0 scan was also acquired to compute the blood perfusion parameters. This acquisition was done with the same parameters as the ASL sequence except for the TR, which was set to be very long (10 s) to yield a measurement of the fully relaxed magnetization. The whole acquisition including the MPRAGE took approximately 20 minutes.

5.3.4 Coregistration

A stereotaxic system (Brainsight, Rogue Research Inc.) was used to align anatomical images from each individual's MRI and the patch holding the optical fibers. The registered positions of each optode were then mapped into normalized brain coordinates from Montreal Neurological Institute (MNI) template for group analysis.

5.4 Data analysis

5.4.1 Behavioral and task performance

Z-scores for each cognitive test were calculated from the normative reference data available for different age groups. Only participants whose results were above the normal guideline were kept for further analysis. The RTs and the accuracy of responses to the lexical-semantic task were analyzed using SPSS (IBM, New York). A two-way repeated measures analysis of variance

(ANOVA) was applied to RTs for correct answers as a dependent variable with the factors of age (young, elderly) and condition (word, pseudo-word).

5.4.2 NIRS data signal processing and statistical analysis

Both signal processing (heart rate regression, intensity to concentration conversion, normalization and smoothing) and statistical analysis (general linear model) were performed using an SPM8-compatible toolbox made in-house (Karl J. Friston, Ashburner, Kiebel, Nichols, & Penny, 2006) based on NIRS-SPM v3.2; NIRS10.

Changes in optical density, ΔOD were computed from emitted and received photon fluence Φ:

$$\Delta OD(t,\lambda) = -ln\left(\frac{\Phi(t,\lambda)}{\Phi_0(t,\lambda)}\right)$$

A heart rate analysis was done to eliminate channels without physiological signals. A coregistration of the source-detector positions on the MNI's MRI template was done to ensure coherent optode positioning for group analysis. Optical signals were then transformed into haemoglobin concentrations C_{HbO2} and C_{HbR}, applying the modified Beer-Lambert law with

$$\begin{bmatrix} C_{HbO2}(t) \\ C_{HbR}(t) \end{bmatrix} = \begin{bmatrix} \varepsilon_{HbO2}^{\lambda_1} & \varepsilon_{HbO2}^{\lambda_2} \\ \varepsilon_{HbR}^{\lambda_1} & \varepsilon_{HbR}^{\lambda_2} \end{bmatrix}^{-1} \begin{bmatrix} \Delta OD(t,\lambda_1)/(d \cdot \ell_{DPF}(\lambda_1)) \\ \Delta OD(t,\lambda_2)/(d \cdot \ell_{DPF}(\lambda_2)) \end{bmatrix}$$

where ℓ_{DPF} is the differential path-length factor accounting for the random photon trajectory between each source and detector (Duncan et al., 1996).

Haemoglobin concentration changes were filtered with a Gaussian kernel (1.5 s FWHM) and high pass filtered by a second-order Butterworth filter with a cutoff frequency of 0.01 Hz. The significance of each effect of interest (abstract, concrete and pseudo-word) was determined using the theory of Gaussian fields (K. J. Friston et al., 1994). A general linear model (GLM) was fit using a canonical hemodynamic response function (HRF). Contrasts over sessions (intrasubject) were analyzed using a fixed effects model, while testing for contrasts in the intersubject analysis was done by estimating the ratio of the random effects variance to the fixed effects variance. An expected Euler correction based on Lipschitz-Killing curvatures was applied to the threshold on the HbR/HbO_2 t-statistic images to account for the spatial correlation. The GLM method was

based on the precoloring method of NIRS-SPM toolbox (Ye, Tak, Jang, Jung, & Jang, 2009a) for noise treatment.

5.4.3 TRS data

To determine the value of the background absorption and scattering coefficients of the brain, a reflectance curve was fit for each source-detector pair of the time-domain system (Gagnon et al., 2008). The curve-fitting procedure was done by a nonlinear optimization MATLAB function (*Isqcurvefit*) with fit parameters of absorption and reduced scattering coefficient (μ_a and μ_s' respectively) and amplitude to the theoretical temporal point spread function (TPSF). We applied the appropriate analytical model to fit the reflectance curve. This model was validated by applying a Monte Carlo simulation and with *a priori* information about the thickness of the first layer, including skin, skull and CSF, obtained from the segmented anatomical MR images (using SPM8). With a high-resolution T1-weighted anatomical image, the maximum errors on the haemoglobin concentrations were expected to be no more than 15% (Gagnon et al., 2008).

To determine haemoglobin concentrations from optical parameters, we assumed that oxy- and deoxyhaemoglobin and water were the dominant absorbers between the 690 and 850 nm wavelengths. The linear system describing the relationship between the extinction coefficient $\varepsilon(\lambda)$ (taken from the literature) and the absorption coefficient $\mu_a(\lambda)$ (calculated from TRS measures) is given by:

$$\mu_a(\lambda) = 2.303.\varepsilon(\lambda).C$$

$$\begin{bmatrix}\mu_a(\lambda_1)\\ \mu_a(\lambda_2)\\ \mu_a(\lambda_3)\\ \mu_a(\lambda_4)\end{bmatrix} = \begin{bmatrix}\varepsilon_{HbO_2}(\lambda_1) & \varepsilon_{HbR}(\lambda_1) & \varepsilon_{H_2O}(\lambda_1)\\ \varepsilon_{HbO_2}(\lambda_2) & \varepsilon_{HbR}(\lambda_2) & \varepsilon_{H_2O}(\lambda_2)\\ \varepsilon_{HbO_2}(\lambda_3) & \varepsilon_{HbR}(\lambda_3) & \varepsilon_{H_2O}(\lambda_3)\\ \varepsilon_{HbO_2}(\lambda_4) & \varepsilon_{HbR}(\lambda_4) & \varepsilon_{H_2O}(\lambda_4)\end{bmatrix}\begin{bmatrix}C_{HbO_2}\\ C_{HbR}\\ C_{H_2O}\end{bmatrix}$$

We also assumed that biological tissues contained 70% water, reducing the above system to four equations with two unknowns. A pseudo-inversion of the equation with a least-square fit provided *C*, the haemoglobin concentration.

5.4.4 Anatomical MRI

Coregistration. The anatomical images served two purposes in this study. First, at the individual level, we normalized the anatomical images to the MNI space including the subject's fiducial coordinates. Then, to achieve better spatial resolution for fNIRS analysis, we projected the optodes' positioning coordinates, collected from the Brainsight 3D camera, on the cortex (Figure 3). For group analysis, we needed to transform all images to the MNI template.

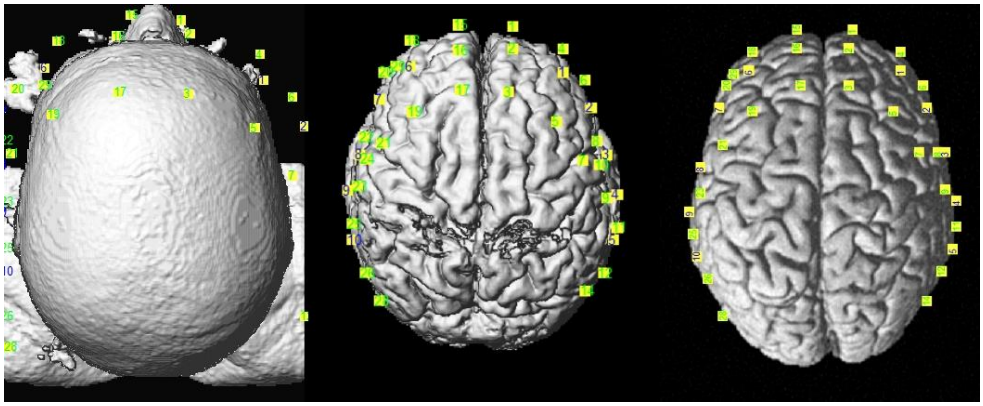

Figure 5-4 Coregistration of the optodes' positions from Brainsight© over the reconstructed anatomical images. **(A)** real, **(B)** MNI subject, and **(C)** MNI template spaces.

5.4.5 ASL data

The absolute CBF was measured in arbitrary units by the constant component of an ASL scan (ASL_0) using the standard quantitative approach described by Wong et al. (1998). This value was then converted to physiologically relevant units (mL blood /100 g tissue per minute) using a general kinetic model fit to the ASL signal (Buxton et al., 1998; Wong et al., 1997). This model defines a relationship between the measured signal and CBF_0 assuming blood longitudinal relaxation time TI and fully relaxed magnetization M_0 are known

$$CBF_0 = \frac{ASL_0}{6 \times 10^6 \cdot 2 \cdot TI1 \cdot \exp(^{-TI2}/_{T1b}) \cdot M_{0b}}$$

where $TI1$ = 1400 ms, $TI2$ = 2000 ms, $T1b$ = 1932 ms at 3T and the factor 6 x 10^6 converts the units for CBF_0 to mL/min/100 g. The value for M_{0b}, the fully relaxed blood magnetization, was calibrated using that of the white matter measured in the M_0 scan (Wong et al., 1998):

$$M_{0b} = M_{0WM} \cdot \frac{1}{\lambda} \cdot \exp\left(\mathrm{TE} \cdot \left(\frac{1}{\mathrm{T_{2WM}}} - \frac{1}{\mathrm{T_{2b}}}\right)\right)$$

with M_{0WM} the average value of the M_0 scan in a region of interest (ROI) selected from the segmented white matter, the brain-blood partition coefficient for water λ = 0.9 mL/g (Herscovitch & Raichle, 1985), TE = 12 ms, T_{2WM} = 70 ms and T_{2b} = 275 ms at 3T. The blood flow measurement was then regressed against the functional NIRS data to evaluate its impact.

5.5 Results

5.5.1 Neuropsychological performance

There was no difference ($p > .05$) between the two age groups' mean years of education (older = 16 ± 2.33 and younger = 16.95 ± 1.78). Both age groups were also matched for sex and consisted of 15 women and 8 men. They were compared on the neuropsychological measures of memory, vocabulary, and executive functions described earlier. The older adults performed worse on a number of subtests evaluating executive functions, but consistently with our hypothesis, the results of the vocabulary test showed no significant difference between the two groups (Table 1). Since responding correctly to the lexical-semantic decision task does not require planning or strategic changing skills, we expected these differences to have no impact on results.

Table 5-1 Demographic variables and cognitive characteristics. Results from neuropsychological batteries by age group. MoCA: Montreal Cognitive Assesment; WAIS: Wechsler Adult Intelligent Scale; Hayling: test for inhibitory control. * $p < .05$, ** $p < .0001$

	Variable	Young (n=23) mean (SD)	Older (n=23) mean (SD)	F-test	t (p-value)
	MoCA	29.23 (1.30)	27.27 (2.47)	0.0054	0.0037*
WAIS	Vocabulary	43.65 (7.68)	37.64 (14.75)	0.027	0.15
	Similarity	21.23 (5.08)	17.73 (3.92)	0.32	0.008*
	Block design	61.82 (3.15)	35.27 (7.93)	0.0002	0.000**
	Matrix	23.12 (2.87)	15.91 (5.70)	0.007	0.000**
	Digit spans	19.06 (4.34)	18.64 (3.99)	0.72	0.15

Hayling	Automatic	6.94 (0.24)	6.91 (0.29)	0.3	0.65
	Inhibition	5.47 (1.18)	4.82 (1.65)	0.1	0.15
	Final score	19.29 (1.61)	17.5 (2.70)	0.47	0.12

5.5.2 Task performance

Both groups performed equally accurately across conditions except on pseudo-words derived from concrete words [F (1, 55) = 6.1, p = .017]. Young participants were faster in all conditions except for concrete words. We applied a two-standard-deviation cut-off on the RTs of correct responses. RTs for correct trials are presented in Figure 4. Results from two 2-way ANOVAs showed no age x lexicality [F (1, 176) = .621, p > .05] or age x condition [F (1, 176) = .275, p > .05] interactions. There was a simple effect of lexicality [F (1, 179) = 11.4, p = .001], irrespective of age.

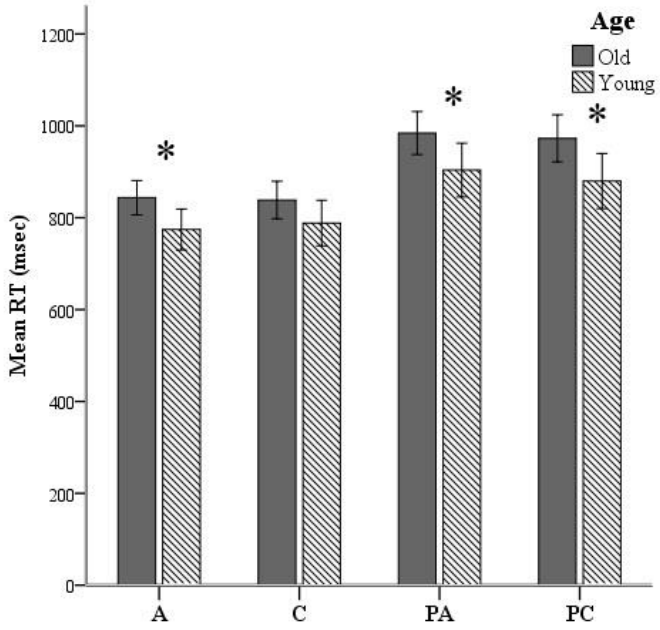

Figure 5-5. Mean reaction times (RTs) shown here over all lexical-semantic conditions of the task: A = abstract, C = concrete, PA = pseudo-abstract (pseudo-words derived from abstract stimuli) and PC = pseudo-concrete (pseudo-words derived from concrete stimuli).

5.5.3 TRS

We calculated the absolute oxy- and deoxyhaemoglobin concentrations ([HbO_2] and [HbR], respectively) as well as oxygen saturation ($SatO_2$) in both right and left prefrontal lobes covered by our four-channel TRS patch. Considerable intersubject variability was observed in the measures of haemoglobin concentrations, as previously reported in the literature (Gagnon et al., 2008). Group mean comparisons were inspected for the homogeneity of variance assumption. When the variance test of homogeneity was significant, the *p*-value of the equal variances for one-tailed t-tests was reported. TRS measures of right and left frontal areas were analyzed separately. Older adults showed a resting [HbO_2] and [HbT] (HbT = HbO_2 + HbR) decrease in the left hemisphere compared to the right and an overall reduced [HbO_2] compared to young adults (Table 2). A one-tailed comparison revealed a decrease in $SatO_2$ in both left and right prefrontal lobes for the elderly group ($p = .045$ and $p = .029$, respectively). Because we observed a different trend in hemispheric changes in the measured haemoglobin concentrations across age, we applied a two-way ANOVA to investigate the effect of the baseline physiology of aging and laterality. The results showed no significant interaction between age and laterality.

Table 5-2. Results from TRS measurements. Oxy- and deoxyhaemoglobin concentrations and oxygen saturation calculated in both hemispheres from TRS measures in micromoles, * $p < .05$, ** $p < .001$.

	LH		**RH**	
	Old	Young	Old	Young
[HbO2]	40.9 (±1.7)	49.1 (±2.1)	42.6 (±1.8)	46.5 (±1.3)
t-test	0.002**		0.039*	
[HbR]	25,8 (±1.1)	28.2 (1.0)	25.9 (±1.1)	25.6 (±1.0)
t-test	0.056		0.428	
SatO2	61.2 (±0.7)	63.3 (±0.9)	62.2 (±0.7)	64.6 (±1.0)
t-test	0.045*		0.029*	

5.5.4 **Resting-state CBF**

Analysis of tagged ASL images revealed different group averages over the segmented white and gray matter anatomical images applied as explicit masks. Mean baseline CBF calibrated with the use of individual voxel values of the M_0 sequence was computed for both age groups and a significant difference was observed for global (p = .001) and gray matter (p = .02) blood perfusion (Figure 5). To investigate regional effects, we calculated mean CBF within regions of interest (ROIs) defined by the optical helmet. Temporal and frontal ROIs were created by applying a 35 mm diameter disk around optical channels covering the temporal and frontal regions. At rest, older adults had significantly lower blood flow (p = .01) in both temporal and frontal lobes than their younger counterparts.

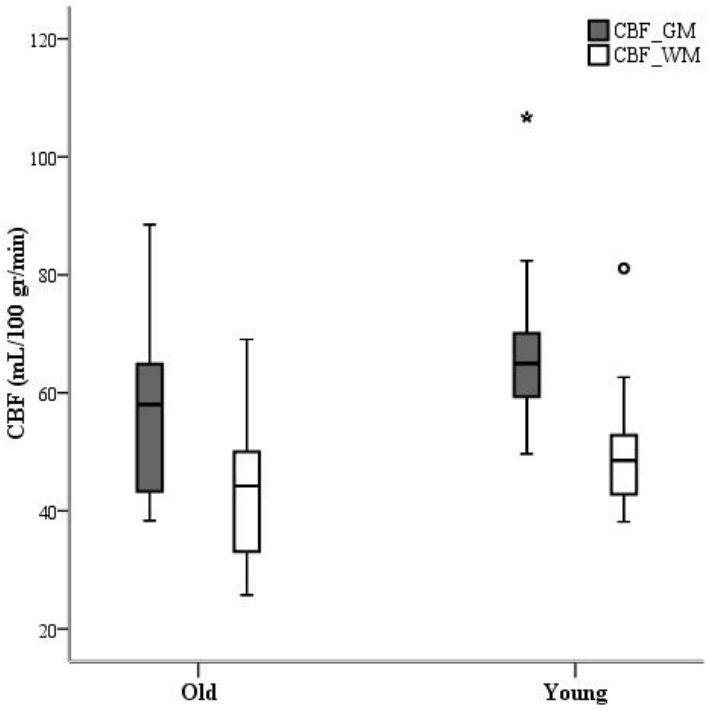

Figure 5-6 White and gray matter segmented images as ROI masks were used to calculate mean CBF. Only gray matter blood perfusion yielded a difference between age group averages.

5.5.5 **Functional optical recordings**

Stimulus-dependent activation of all 58 channels was measured within the areas covered by the optodes. Significant changes were defined at p-values of less than 0.05. The activation map was

then obtained via interpolation of the beta values calculated from the GLM model over the localized optodes coregistered on the MNI template, although a lack of spatial resolution made it difficult to identify activation areas with any precision.

The regions of activation for group average, obtained from the intersection of individuals' activation maps, were impacted by variability induced in the positioning of optodes. Thus, a smaller group-level significant activation map was obtained, although the pattern of activation followed the same language network areas at the individual level. Brain regions activated by the lexical-semantic task were partially different for word and pseudo-word stimuli. In response to semantic word processing, a decrease in [HbR] concentration was observed in the elderly adults group in the left frontal region, at the intersection of the right inferior frontal gyrus (IFG) and the superior temporal gyrus (STG). In young adults, pseudo-word stimuli generated diminished [HbR] and increased [HbO_2] in the left IFG but an inverse response (decreased [HbO_2] and increased [HbR]) in the left inferior temporal (IT) and frontal lobes. In contrast to elderly participants, activated areas remained in the temporal sulci for other types of stimuli (concrete and abstract) but again in an inverse fashion.

An ANOVA for the main effect of age depicted significant [HbO_2] and [HbR] changes in both right and left hemispheres when older and younger adults were compared. Activation differences were mainly found in the bilateral dorsolateral prefrontal cortex (DLPFC) and IFG, and right posterior middle temporal and occipitotemporal gyri. Younger participants showed increased [HbR] and decreased [HbO_2] in the DLPFC and IFG in response to the semantic processing task (so-called inverse response). Conversely, pseudo-words led to a significant right ventral anterior premotor cortex decrease [HbR], which could be interpreted as an effort to analyze the stimulus by covert reading.

5.5.5.1 TRS regressors

Taking into account the measures of baseline physiology from the TRS system by including individual measures as regressors, we investigated their contribution to the observed age difference in [HbO_2] and [HbR] stimulus-dependent changes. In the right hemisphere, the main effect of age faded significantly in the frontal lobe for both [HbO_2] and [HbR], and [HbR] seemed to become more significant at the intersection of the IFG, STG and caudal border of the

anterior central gyrus (BA43) (Figure 6). In the same fashion, a post hoc ANOVA on the effect of age on lexicality (pseudo-words), revealed significant [HbR] differences in right BA43. However

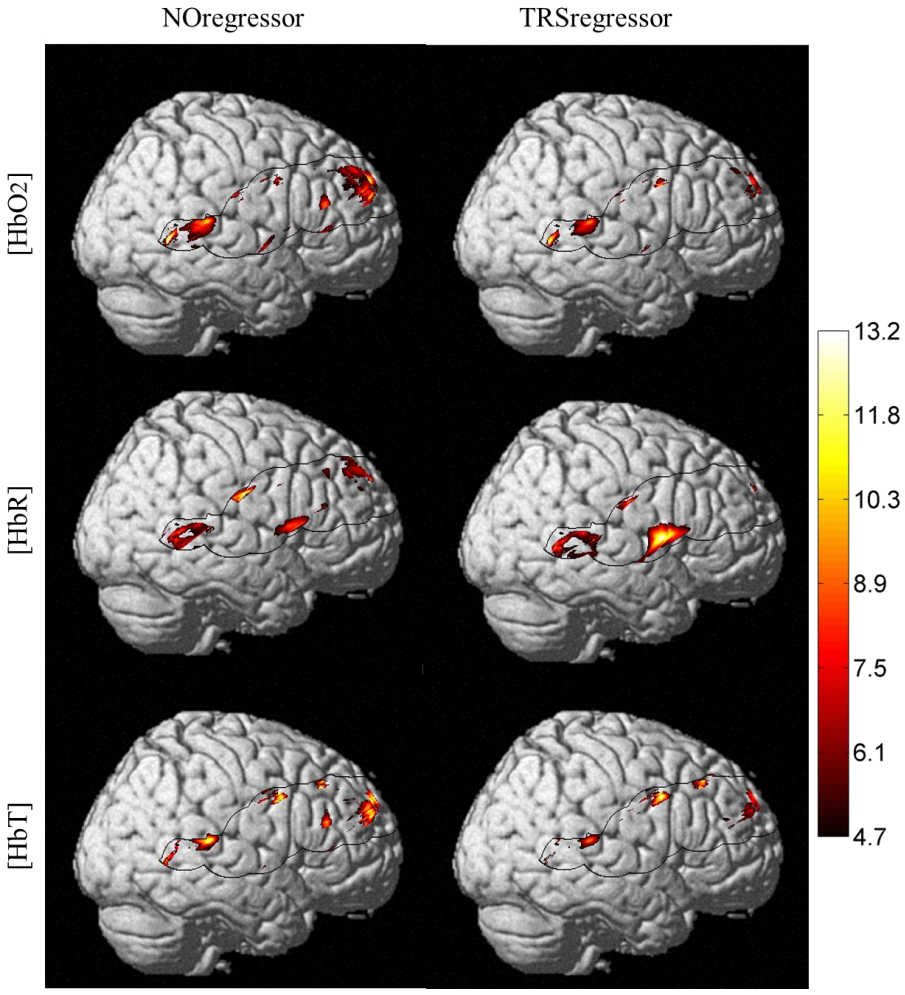

Figure 5-7 NIRS activation maps of the haemoglobin concentrations for the main effect of age. With TRS measures of baseline haemoglobin concentrations regressed against stimulus-dependent activation, we observed a different pattern of posterior-inferior alteration as an effect of age. But this pattern is more pronounced at the [HbO_2] and [HbR] level and not for [HbT], which is an estimate of the cerebral blood volume. Left panel shows Δ[Hb] age differences without taking into account baseline physiology measures and right panel depicts activation differences once applying TRS regressors into ANOVA.

there was no such effect on total haemoglobin concentration [HbT] differences with regressors, which could suggest that the blood supply alters with age, if we use [HbT] as an estimate of

cerebral blood volume. In the left hemisphere, there was an age difference in the frontal lobe (Figure 7), with no effect of TRS regressors. An interaction between age and condition was present only at the [HbR] level, with changes found in the IFG. A post hoc analysis revealed an effect of age on pseudo-word processing in the DLPFC and IFG. In the left hemisphere, we did not find any significant differences in the temporal regions.

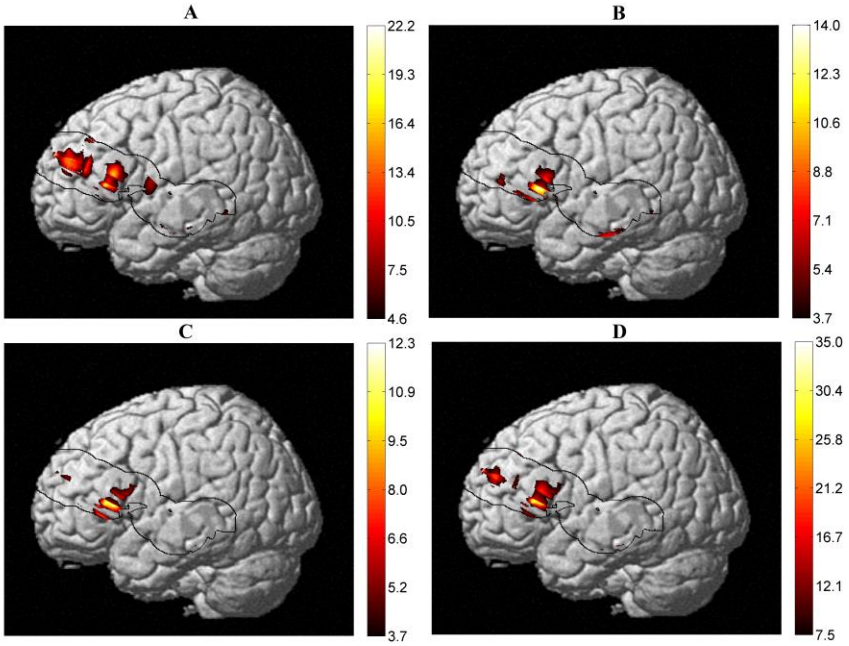

Figure 5-8 Results of a two-way ANOVA on [HbR] examining the factors of age and condition (of lexical-semantic task) on the activation maps. **(A)** Main effect of age, **(B)** main effect of condition, **(C)** interaction between age and condition, and **(D)** effect of age on pseudo-word processing are shown. An IFG age difference was present in all four types of analysis but with different extents of activation. A post hoc analysis revealed an effect of age on pseudo-word processing in the DLPFC and IFG. No significant [HbO_2] or [HbT] differences were observed.

5.5.6 Correlation analyses

A correlation coefficient was calculated to examine the associations between age, performance and baseline physiology (ASL and TRS measures). Here we sought relationships between RT and physiological measures while controlling for the effects of age and performance. The partial correlation coefficient between RT and [HbO_2], [HbR], $SatO_2$ and CBF was calculated by

adjusting for age and performance scores. We presumed that both variables of correlation were linearly related to age and performance on the neuropsychological tests.

Inspection of the correlations between RT and CBF measures revealed no significant relationship. Pearson's coefficient of correlation between RT and [HbO_2], [HbR] and $SatO_2$ dropped significantly once we removed the effect of age (from r (42) = .35 to r (40) = .06). It is interesting to note that, even though there were no significant correlations between the variables under investigation, the variations tended to move in opposite directions when younger and older adults were compared (see Figure 8). The tendency graphs revealed that slower responding elderly participants had slightly elevated baseline [HbO_2], [HbR] and $SatO_2$, whereas younger individuals showed the opposite pattern (i.e., slower respondents had lower baseline levels).

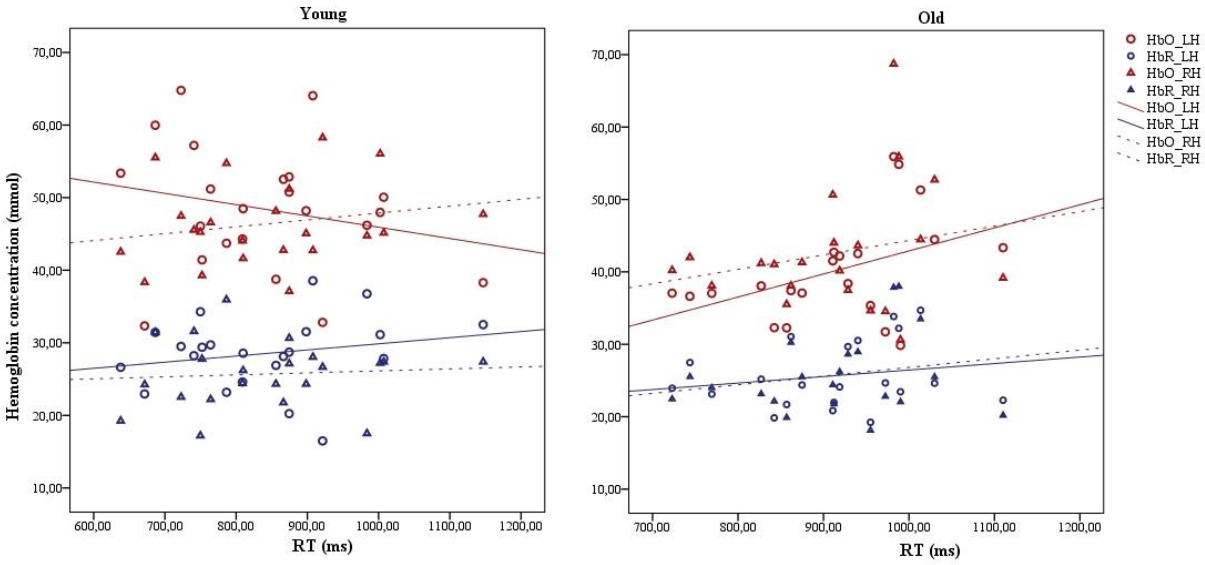

Figure 5-9 Scatterplots of mean RT (x-axis, in milliseconds) vs. TRS baseline physiology measures (absolute [HbR] and [HbO]; y-axis, in micromoles) for the younger and elderly groups are shown for both right and left hemispheres (RH and LH). Pearson's r coefficien

5.6 Discussion

The goal of this study was to evaluate the validity of the assumption that, when different age groups are compared, the hemodynamic response is a direct indicator of neuronal activity in response to a cognitive stimulus. The main result showed that, when each participant's baseline physiology is taken into account, the degree and extent of neural activity varied significantly in

the right hemisphere – an observation that could change the interpretation of less asymmetrical language-related neural engagement. The present study supports the reliability of single-word processing studies using fNIRS while urging caution in the interpretation of functional signals. RTs and accuracy on the lexical-semantic task showed the presence of a lexicality effect for both age groups. However, a different pattern of brain activation was found for young and older participants. We observed that searching for semantic knowledge while processing words vs. pseudo-words in the lexical-semantic task engaged largely overlapping brain regions in the left hemisphere, including the posterior temporal gyri, which is consistent with the notion that activity in the left temporal regions is linked to the verbal abilities of word retrieval rather than the lexical class to which the stimulus belongs (Grabowski et al., 2001).

A right frontal [HbT] difference between the young and older samples could be in line with findings from TRS measures for lower oxygen saturation in the elderly group. In response to neural activity and to compensate for reduced baseline HbO_2 concentrations and CBF, older adults may need greater blood volume in their compensatory networks. Thus, controlling for baseline physiology is expected to make the interpretation of results more reliable.

The presence of right DLPFC, frontotemporal cortex, occipitotemporal and angular gyri (homologue to areas known as the visual word form area; (McCandliss et al., 2003) activation in the elderly cohort is compatible with the idea that bilateral neural activity increases with age (Donnelly, Allendorfer, & Szaflarski, 2011; Van Ettinger-Veenstra et al., 2012), although it is important to note that this age-related pattern of activity was observed by means of Δ[HbR] differences in the frontotemporal cortex and [HbO_2] variation in the DLPFC. Without [HbT] variation and Δ[HbR] differences, it could be assumed that this latter observation is due to mere neural activity and not to baseline physiological differences.

In the contrast between pseudo-words and real words, we found an age-different cluster of activation in the right IFG-STG intersection, bilateral DLPFC and left IFG, which is consistent with previous findings claiming for the compensatory mechanism of the brain activity with effort in accordance with the behavioral finding that RTs are longer for pseudo-words (J R Binder et al., 2003; Donnelly et al., 2011). It can be noted that the hemispheric laterality for language is relative and that it relies on a stronger engagement of the left hemisphere for syntactic and semantic processing, which nevertheless coexists with right-hemisphere activation. Thus, when

the different age groups are compared, the difference in hemispheric patterns of activation could express over-recruitment of reserve networks, meaning that activation becomes less lateralized. Moreover, controlling for the baseline physiology strengthened the analyses, as it revealed differences in mere neural activity triggered by the task and not in the absolute haemoglobin concentration differences (data shown in TRS results). However, a question remains about whether bilateral frontal activity in older adults is driven by task difficulty per se or whether baseline physiological differences compared to their younger counterparts led to this differentiation.

The inverted hemodynamic response in the young group could be due to local coarse regulation of oxidative metabolism, provoked by the increase in neuronal activity, which is overwhelmed by an increase in CBF. In this regard, Woolsey and colleagues (Woolsey et al., 1996) postulated that there is a hemodynamic "steal" effect. The "steal phenomenon" may explain this observation by accounting for subsequent CBF changes: some arterioles were metabolically dilated while others in neighboring areas were constricted (Ances, 2004; Harel, Lee, Nagaoka, Kim, & Kim, 2002).

More generally speaking, this study confirms the usefulness and sensitivity of hemodynamic-based corrected fNIRS imaging in investigating the neurofunctional reorganization of word processing and cognition with age. The same technique could be used after brain lesion and in recovery. This study also confirms the existence of a form of neurofunctional reorganization that corresponds to compensatory mechanisms, allowing for the preservation of linguistic abilities despite the neurophysiological changes present in aging.

In summary, while the combination of absolute and relative changes in haemoglobin concentration eliminates some of the assumptions previously required in NIRS data analysis, further improvements are needed. Future studies will be augmented by parallel ASL measurements of blood flow variation during brain activation, to provide a detailed measurement of quantitative events accompanying neuronal activation. Individual brain volume analyses would also provide a better estimation of the optimal source-detector distances for different age groups. In the case of atrophy in the elderly population, it is important to correct for the source-detector distances to allow for optimum light penetration and differences in light scattering and absorption.

5.7 Acknowledgement

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CHAPTER 6 ISSUES & CHALLENGES

As discussed in the course of this text, in geriatric studies, discrepancies in the literature are arising from differences in observations and interpretations of data. These inconsistencies are mainly due to two distinguished origins of the problem; first of all, not all studies use the same protocol and data acquisition techniques. Second, differences between individuals increase with age because of different patterns of aging in the course of their lifespan. These alterations consist of both structural and neurophysiological features. Therefore, when comparing two groups of age with different baseline characteristics, inter-subject variations become more critical. In other words, when aiming at differentiating age-related brain activity, precision in measured functional signal is of primordial importance. Moreover, the representation of these functional data is not separated from the structural framework. FNIRS data were acquired from the scalp without structural information of the cortex. To form a continuous activity map, a correspondence between NIRS channel positions and the underlying cortical surface is thus necessary. Scalp landmarks were based on 10-20 system that defines 21 electrode locations. This system describes scalp landmarks relative to some primary references being the nasion, inion, and right and left pre-auricular points (Figure Annexe-1). Then, a stereotaxic system has been used for later transformation of these points to the standard brain space.

NIRS poses an intrinsic problem which is the lack of structural information. Thus, in order to spatially assess fNIRS data, the position of each source-detector probe has been registered on the scalp by means of a stereotaxic system (Brainsight). To position the optical helmet on the head, we first took the measures of head size and nasion – inion points then the helmet was placed accordingly. These two spaces were integrated across participants to generate a unified reference. To map spatially continuous functional activity images, fNIRS contrasts (multi-channel data) have been then transformed via spatial interpolation on the cortical structures of the anatomical template. But unfortunately, due to the different head size, there were inconsistencies in the source-detector positioning after spatial transformation across individuals (Figure 6-1).

In this dissertation, we also aimed at the exploration of fNIRS data to understand semantic words processing with age focused on the neural substrates of concreteness effect. In the primary statistical analysis, the importance of this main effect was compromised by both lack of spatial resolution and inter-subject variability. To overcome these inevitable drawbacks and to extract

abstract versus concrete words processing effect, we needed to develop a more fastidious analysis. To explore the effects of imageability of words in the context of a lexical-semantic decision task on language brain areas, and to examine if these effects change with age, a 3-way ANOVA on the voxel-wise results of activations was done. Having done the statistical analysis,

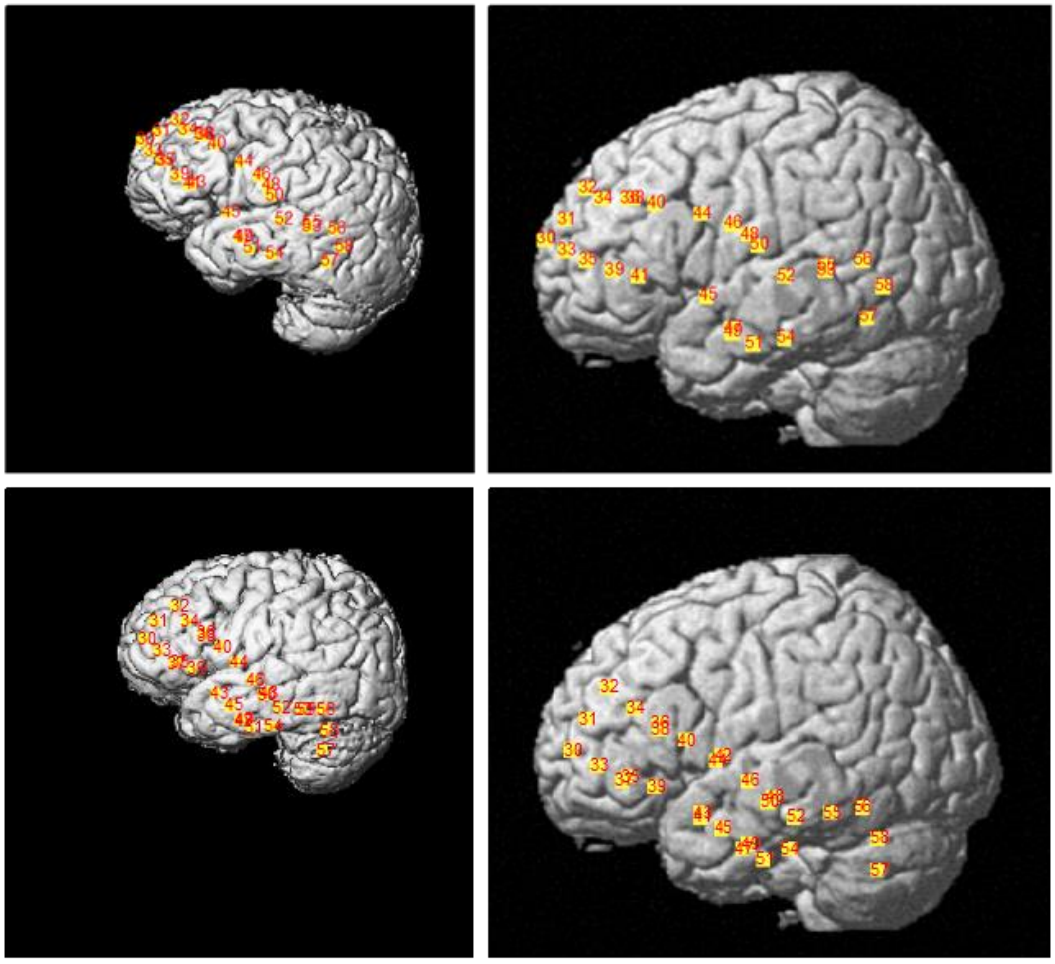

Figure 6-1 Here there are 2 examples of the incongruent co-registration of the optodes on the cortex, resulting from different positioning of the head in the MRI scanner and head size. Left) native cortical space. Right) template MNI space.

surprisingly we did obtain small areas of significance on activation maps for any effect of concreteness with aging or lexicality, whereas the effect of concreteness was observed at the individual-level. To investigate the origin of this minor interaction result, we examined subject to subject channel positioning before the transformation to the template's space. A broad

inconsistency in the placement of optical channel was noticed despite having used the standard 10-20 system as markers when placing optical helmet. Thus, inconsistency in optical helmet positioning, different size and form of the scalp and potentially different position of the head in MRI tunnel cause inhomogeneous results from co-registration.

A Rogue Research device, a 3-D digitizer (Brainsight ©), was used when the optical helmet and all fNIRS optodes were installed on the head of the participant. The position of the helmet was secured by using the scalp landmarks based on the 10-20 systems. These reference points were then used to co-register fNIRS optodes' position acquired by Brainsight to the participant's own anatomical MRI. In a group study, we needed to standardize all brain shapes and sizes to a common platform. We chose to use MNI (Montreal Neurological Institute) as a template. This reference was created by averaging 152 human brains via co-registration. The result is a smooth surface since the averaging eliminates individual differences and provides a common space (Collins, Neelin, Peters, & Evans, 1994). Since fMRI data are presented mostly in MNI space, it is best appreciated for fNIRS data to be mapped based on this template as well.

Once source-detector channels were located on the MNI template, fNIRS data are expressed as discrete channel-wise data. To validate the null hypothesis, we adopted a channel-wise statistical analysis approach for group analyses (Schroeter, Zysset, Kupka, Kruggel, & Yves von Cramon, 2002). To overcome the abovementioned problem, we proposed a region of interest (ROI) approach by weighted averaging of optical channels over language-related regions for the specific task of concreteness. Also individual's physiological parameters were included to explore the effect of baseline oxygenation and CBF on functional data for each ROI. Regarding the number of channels per hemisphere (29ch per hemisphere for a total of 58ch), ROIs were defined accordingly and we obtained a total of 16 ROIs by bundling those channels meeting the same criteria for the within channel variability. In line with the literature commonly used the same analysing procedure, we then proceeded to compare oxygenation changes in ROIs, defined as described, over the entire bilateral frontotemporal areas. To assess the oxygenation changes in language-related brain regions defined by optical channels, the general linear model was applied on stimulus-dependant signals acquired from all 58 channels. The neuronal response was then estimated by calculating the GLM fit of signal over a canonical hemodynamic response function (HRF). Beta coefficients for significant changes were defined in a subset of source-detector pairs at p-value $< .05$. In Figure 6-2, betas for HbO_2 and HbR are presented for concrete words

processing for both groups of young and older adults. Some ROIs showed the age effect on concrete words processing, but the direction of these differences varies. According to ROIs described in Annex Figure 2, we could observe a bilateral frontal and left parietal pattern of activation differences.

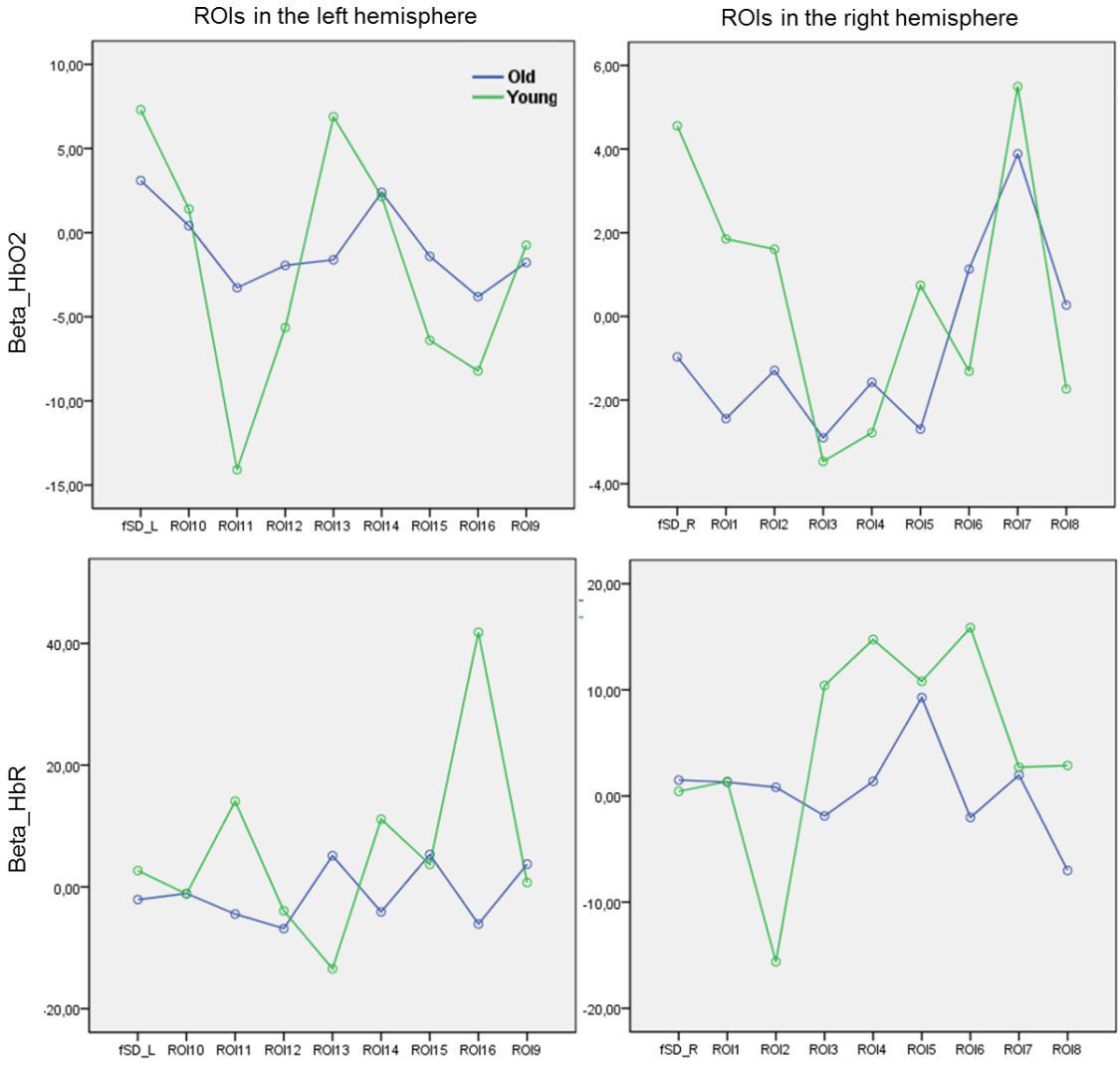

Figure 6-2 Age-related difference of beta values for concrete words processing, calculated by GLM for both chromophores HbO_2 and HbR. Green line: Young adults and blue line: Older adults. Note that the fSD channels stand for the short source-detector separation.

The regions of activation at the subject's level showed a diverse pattern of activity within the language-related brain areas amongst younger adults. Group level significant effects were impacted by this inter-subject variability in addition to the inconsistency in optode positioning. Nevertheless, restricted areas activated by the lexico-semantic task at group level were different

for words and pseudo-words stimuli. Different trend of HbO_2 and HbR concentration changes in frontal and temporal regions could imply an association with baseline where this area's CBF and haemoglobin concentration differed. But before going through this investigation, we needed to make sure the assumption about the homogeneity of the optical channel positioning is held.

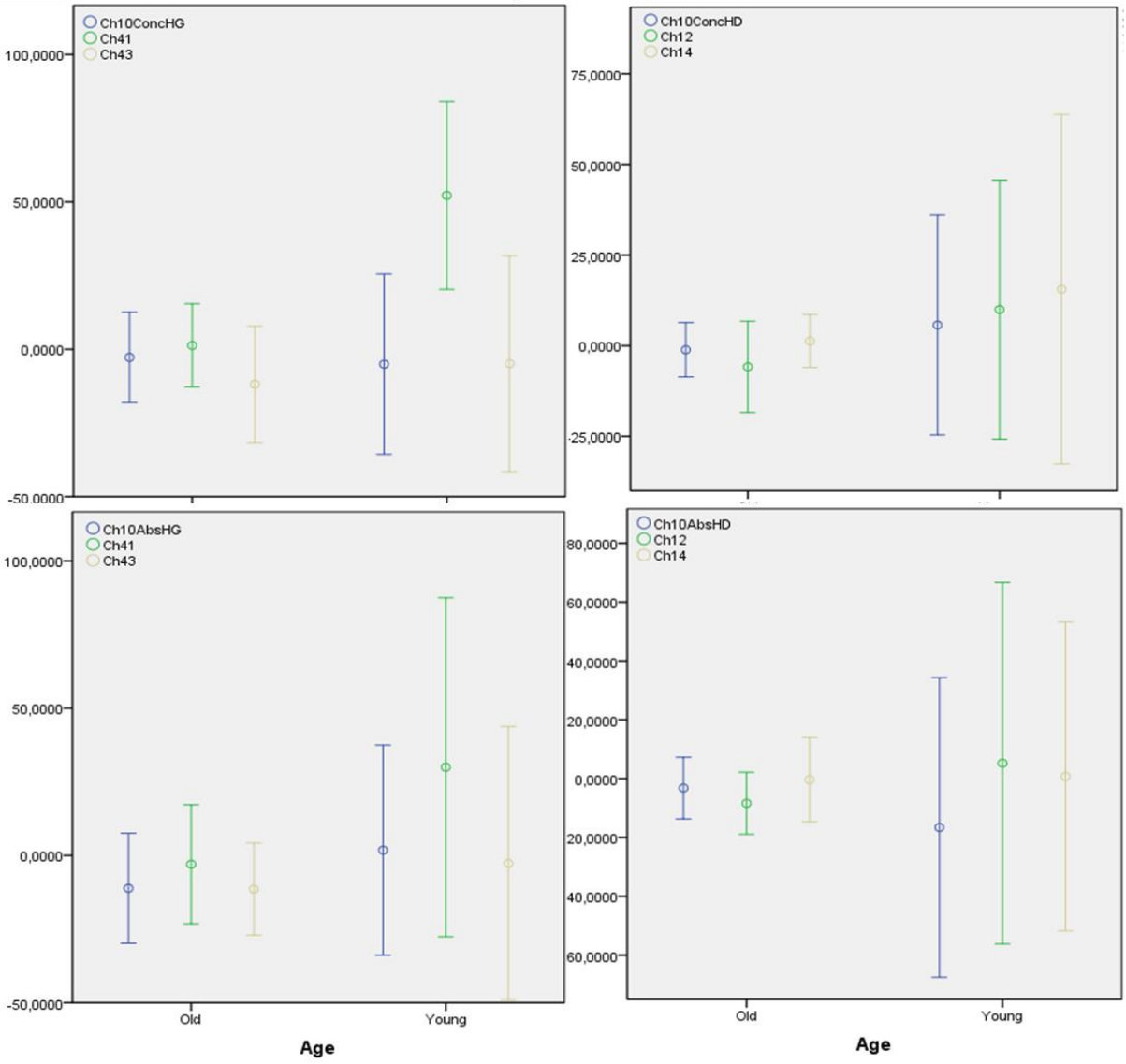

Figure 6-3 Means and standard deviations of beta-values for some random channels are presented for young and older adults.

Going through the beta values of GLMs for individual channels and subjects, we found another source of variability at the level of significant activations. The standard deviations of beta-values per channel for young adults were significantly greater than those values for old adults (Figure 6-

3). Thus, the comparison of means values was not valid because of the inhomogeneity of variance.

With ROI-wise comparison, we hoped to compensate for the lack of precision of optode placement, as well as low SNR. But the second problem from another nature shows the sensitivity of GLMs to the noised data of [Hb] calculation. In order to overcome low SNR we would have needed to consider more physiological assessments to pre-process more accurately fNIRS data. For instance, integrating more short distance source-detector pairs would improve removing of the superficial physiology contamination (Gagnon et al., 2012; Gagnon, Yücel, Boas, & Cooper, 2014). The last but not the least, the installation of the optical helmet needs to be improved. Khan and colleagues (Khan et al., 2012) have proposed a new method for optodes design with brush to ameliorate the contact with the skin. This way we would also increase the SNR.

CHAPTER 7 ARTICLE 2: THE EFFECT OF CORTICAL MORPHOLOGY OF NORMAL AGING ON THE HEMODYNAMIC RESPONSE MEASURED BY FNIRS; A LANGUAGE STUDY

This article explores the potential effects of brain structures on the baseline and functional neurophysiology of aging. We hypothesized that cortical volume plays a role on the extent of the functional data, and when taking into account, we could cancel-out the size effect and examine merely the importance of functional response. In this study, with cortical thickness measures of each participant, we found an age-related right prefrontal cortex activity in response to a lexical-semantic decision task. Results showed a preservation of cortical thickness with age at right lateral frontal cortex that supports findings from functional data obtained from near-infrared spectroscopy technique. This manuscript if submitted on 23rd of March 2016, at Cerebral Cortex.

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7.1 Abstract

Anatomical magnetic resonance imaging (aMRI) studies have shown age-related cortical thickness and volume changes across the brain. However, the relationship between the impact

and the location of these changes are still a matter of debate. To investigate the effects of morphological parameters on the functional brain measurements and cognitive performance, we acquired data from two modalities; magnetic resonance imaging (MRI) and diffuse optical imaging (DOI). We measured the baseline cerebral blood flow (CBF), the absolute hemoglobin oxygenation concentrations and functional changes in concentrations, cortical thickness and cortical surface area. Twenty six young and 23 older adults underwent a scanning session at rest and another session performing a language task. A MPRAGE anatomical and a dual-echo pseudo-continuous arterial spin labeling (pCASL) MRI sequences were performed at rest. Time-domain (TD) optical measures of the baseline cerebral blood oxygenation and fNIRS data during the assessment of a language task were acquired. Whole brain and regional gray matter measurements of CBF and morphometric analyses (FreeSurfer) of cortical thickness and cortical surface area were conducted. Grey matter CBF was 66.5 and 57 ml/100 g/min in young and older subjects respectively ($p < 0.05$). There was no significant difference between age groups with respect to white matter CBF (49.6 vs 44.1 ml/100 g/min for young and older participants respectively, $p = .08$). FreeSurfer measurements displayed significant differences in cortical volume between age groups ($p < 0.001$), white matter volume ($p < 0.05$), gray matter volume ($p < 0.001$), cortical surface area ($p < 0.001$), and cortical surface holes ($p < 0.05$) with older adults having greater values for the last measurement. Cortical atrophy in old adults was bilateral and independent of hemisphere, but there was an interaction between age and hemisphere ($p < 0.001$). In addition, anterior and mid corpus callosum (CC) were affected by age, except for posterior CC. This later observation could account for greater reaction times of the old adults in the language task.

7.2 Introduction

Human brain experiences/goes through morphological changes as we age and investigating these changes has become an important aspect in geriatric studies (Good et al., 2002; Kennedy & Raz, 2009; Perez-Gonzalez et al., 2014; Piguet et al., 2009; Rajah & D'Esposito, 2005). Several post-mortem and brain imaging studies have reported correlation between brain volume and aging, and that decrease seems to happen in a heterogeneous fashion. In addition to region-based volume reduction, differences in age-related gray matter (GM) and white matter (WM)volume reduction have been observed (Courchesne et al., 2000; Fjell et al., 2009; Jernigan et al., 2001;

Kennedy & Raz, 2009; Naftali Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010). For instance, in a study performed on 465 healthy adults, Good and colleagues reported a global GM volume reduction that was linear with age, while it was not the case for WM volume, even though faster local volume decrease was observed (Good et al., 2002). Nonetheless, from in-vitro histological to magnetic resonance imaging (MRI) studies, all have reported an age-related global reduction in GM volume with a particular regional emphasis onto the frontal areas (Allen, Bruss, Brown, & Damasio, 2005; I. Craik & Grady, 2002; Fjell et al., 2009, 2009; Gazzaley & D'Esposito, n.d.; Kemper, 1994b; Naftali Raz, 2000; D. H. Salat, Stangl, Kaye, & Janowsky, 1999; David H. Salat et al., 2004). Other brain imaging studies observed that age-related GM volume reduction is greater than WM decrease (de Leeuw et al., 2000; Gunning-Dixon & Raz, 2003). Even though healthy aging is correlated with white matter integrity and not with cortical thickness *per se* (Ziegler et al., 2010).

While earlier studies suggested that brain atrophy reflects cortical neuronal loss as the source of these overall volumetric reductions (Flood & Coleman, 1988; Henderson, Tomlinson, & Gibson, 1980), others reported a drastic loss of dendrites, unmyelinated axons and glial cells (Pakkenberg et al., 2003; A. Peters, Morrison, Rosene, & Hyman, 1998) that may exceed neuronal loss. It is important to note that it was previously well-accepted that, neuronal density was considered to be correlated with total number of neurons, but with the development of more advanced techniques for counting neurons, this view has been challenged (Morrison & Hof, 1997). From a morphological point of view, decreasing cortical thickness is not directly related to neuronal loss or decreasing neuronal density. It has been shown that over time some brain regions (e.g., lateral and mesial prefrontal areas, and inferior parietal area) maintain a relatively constant cortical thickness and neuronal density, whereas in other regions, neuronal density linearly decreased with increased thickness (la Fougère et al., 2011). Thus, lower cortical thickness does not necessarily mean neuronal loss, but rather loss of neuronal and dendritic architecture, e.g., reduced size of neuronal cell body, reduced dendritic arborization or the loss of presynaptic terminals (Freeman et al., 2008). Additionally, local surface area might reflect the state of the underlying white matter fibres, as more tension or shrinkage of these fibres could lead to deeper sulci and extended cortical surface area. Thus cortical surface area can also indirectly reflect white matter tract damage (Essen, 1997). Similar to GM index of aging, all WM deteriorations tend to be more pronounced anteriorly in the brain.

Two approaches are generally used for morphometric comparison tests; volumetric studies (voxel-based morphometry (VBM)) versus surface based analysis (FreeSurfer: Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu). Since these two do not necessarily follow one another, it is of great importance to choose the method of investigation carefully with regards to the goal of the study. There are many criticisms about volume based VBM toolbox (e. g., on the spatial normalisation, the accuracy of inter-subject registration and warping specific brain structures to the group template without trade-off). This suggests that the voxel-to-voxel comparison might be inaccurate because of the lack of precision in the homologous cortical regions (whether the voxel of a given sulcus for one subject matches the voxel in another sulcus of the other subject) (Bookstein, 2001). Due to disparate results from VBM and FreeSurfer, few researchers have evaluated the reliability of each. One study showed that FreeSurfer provides more reliable results in detecting GM atrophy, than SPM (Rajagopalan & Pioro, 2015). Another study detected less random error in FreeSurfer compared to VBM (Sargolzaei et al., 2015). In a meta-analysis, Fjell and colleagues have found the advantage of using surface based approach in intersubject registration, which gave better results in matching homologous cortical regions (Fjell et al., 2009). For this reason and to avoid methodological flaws, we decided to use FreeSurfer as parellation analysis toolbox.

One of the issues in studies of the aging brain is the difference one observes in within-group functional brain-specific activation. By examining different trajectories of aging, in anatomical features for instance, we could be able to diminish this variability. Individual differences in successful aging studies, where healthy normal older adults are compared with their younger counterparts, could be, in part, explained by morphological features such as the size of each functional structure. Although a great body of evidence suggests that smaller brain structures are associated with poorer cognitive performance (Roth & Dicke, 2005), it is still to be investigated whether similar correlation between the size of brain structures and cognitive functions exists among successful aging adults (for a review Kaup et al. 2011). In our study we assessed the effects of structural changes on cognition by using a lexical decision task to evaluate semantic words processing with age. A large number of studies showed that semantic knowledge is preserved with age; however, processing speed is affected negatively (Lima, Hale, & Myerson, 1991; Madden, 1992). This effect has been observed in EEG studies by notably N400 reduction (Kemmotsu et al., 2012; Kutas & Iragui, 1998; Miyamoto, Katayama, & Koyama, 1998), and in

fMRI studies by smaller amplitude and increased latency in BOLD signal (Cabeza et al., 2002; Logan et al., 2002). To explain this observation, we suggested that in a cognitive task to which both age groups show similar performance, different brain regions would engage in order to support semantic words processing. In another term, we studies differential processing effects.

Our research question was influenced by both structural alterations over time, and the correlation between neuro-anatomical changes and cognitive functions. In any case, this axe of research gives insight to better understanding of brain aging processes. For instance, age-related changes in GM structures are usually thought to impact cognition and behaviour. Or, loss of nerve fibers contributes to cognitive decline due to the connection deficiency between neurons (Alan Peters, 2002). Yet, the role neuro-anatomical features play in cognitive performance remains to be clearly determined. The aim of the present study was to address this issue by investigating the presence of any correlation between cortical measures, hemodynamic response and its basal components (i.e., cerebral blood flow, oxygenation). Though the causal relationships among these variables have not been fully understood (Steffener, Brickman, Habeck, Salthouse, & Stern, 2012). We hypothesized that the size of different brain structures has an influence on the cognitive performance with age. For example, the size of global white matter would predict the reaction time (Kaup et al., 2011). We also aimed to evaluate whether greater temporal lobe volume is associated with better performance in a language task (Mummery et al. 1998, 2000). As orbital and ventrolateral PFC areas are engaged in object meaning (Petrides and Pandya 2002), we assumed that behavioural performance was correlated with these structural measures. By exploiting the aforementioned relationships, we hypothesized that functional changes in the regional language-related neuronal activities are secondary to cortical volume and/or microstructural fiber tracts reduction.

7.3 Methods

Participants and the experimental protocol were the same as in the previously published work (Amiri et al., 2014). Forty nine healthy right-handed young (male = 8, female = 18, age = 23.4 ± 2.7, range = 21-35) and older adults (male = 7, female = 16, age = 69.6 ± 4.1, range = 65-75) were recruited for this study. They both had a similar total years of education (mean years of education = 16.1 and 16.9 for young and old respectively). They were all matched by their level of cognitive performance on a set of neuropsychological batteries that included the Trail Making

Test A/B (Reitan 1985), the Montreal Cognitive Assessment (MoCA; (Nasreddine et al. 2005), and five subtests of the short-form Wechsler Adult Intelligence Scale (WAIS-III; (Axelrod 2002; Schrimsher et al. 2007; Wechsler 1991), namely Vocabulary, Block Design, Similarities, Matrix Reasoning, and Direct and Inverse Digit Spans. In this way, it was possible to exclude those with mild cognitive decline according to age-corrected norms. These tasks assess phonological short-term memory storage as well as processing capacities and evaluate general intellectual ability, planning, visual exploration, attention, mental flexibility and verbal inhibition. The cognitive task of semantic words processing was a lexical-semantic decision task (Balota, Cortese, Sergent-Marshall, Spieler, & Yap, 2004). Stimuli were chosen meticulously from the categories of nonliving and nonaction words, generated from a French Lexical database (OMNILEX) (for details on criteria applied on word generation toolbox, see Amiri et al. 2014).

7.3.1 MR image acquisition and analysis

Participants were scanned using the Siemens Tim Trio 3.0 T scanner (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle of the Centre de recherche de l'Institut Universitaire de Gériatrie de Montréal. A high-resolution MPRAGE 3-dimensional T1-weighted sequence was acquired for each participant (TR/TE/TI = 2300/2.91/900 ms, flip angle = 9°, 160 slices, field of view = 256 x 240 mm, matrix = 256 x 240, voxel size = 1 x 1 x 1 mm, 12-channel coil). For the baseline blood flow, a pseudo-continuous ASL (PICORE labeling geometry) sequence (Wong et al., 1997) was used to create a flow-dependent MRI signal with Q2TIPS tag duration control (Luh et al., 1999). The specific parameters were as following: RF labeling pulse duration = 1500 ms, post-labeling delay = 900 ms, TR/TE = 3000/20 ms, flip angle = 90°, matrix = 4 x 4 x 7. A single M_0 scan was done with the same parameters as the ASL sequence except the TR = 10 s. This acquisition was acquired to compute the blood perfusion parameters with the measurements of the fully relaxed tissue equilibrium magnetization.

Anatomical image processing

Cortical reconstruction and volumetric segmentation was performed with FreeSurfer 5.3 image analysis suite. This includes motion correction and averaging of multiple volumetric T1 weighted images, removal of non-brain tissue using a hybrid surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2004), intensity normalization (Sled et al.,

1998), tessellation of the gray/white matter boundary, automated topology correction (Ségonne et al., 2007) and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Fischl and Dale, 2000). To extract reliable volume and thickness estimates, images were automatically processed with the longitudinal stream (Reuter et al., 2012). Specifically an unbiased within-subject template space and image was created using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, significantly increasing reliability and statistical power (Reuter et al., 2012). Misclassification of tissue types was corrected by minimal manual adjustment. Cortical thickness was calculated as the closest distance from the grey/white matter boundary to the gray matter/cerebrospinal fluid boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufactures and across field strengths (Han et al., 2006; Reuter et al., 2012).

Cortical thickness was smoothed with a 10-mm full width half height Gaussian kernel to reduce local variations in the measurements (Du et al., 2007). Statistical difference maps were considered after a FDR (false discovery rate) Monte-Carlo null-Z correction using a threshold of $p = 0.05$ and 10.000 iterations as well as an uncorrected p-value of ≤ 0.001 (Lyoo et al., 2010; Hanganu et al., 2014).

We also analysed the volumes of subcortical structures, which were extracted based on the Desikan atlas (Desikan et al., 2006). Each volume was corrected using a regression to the estimated total intracranial volume (TIV). Previous studies showed that estimated TIV provides a robust method for head size correction which is equivalent to manual TIV correction (Buckner et al., 2004) and the regression-based correctional method may provide advantages over the proportion method (Sanfilipo et al., 2004).

Cerebral blood flow calculation

ASL data was processed using a home-made toolbox from our laboratory (SPM-nirs10, hmri12; Desjardins et al., 2013). In ASL data, subtraction of the control (is identical to the labeled scan only lacking the flow-dependent component) from the labeled signal isolates the purely flow-dependent ASL difference signal. To do the preprocessing analysis, the following steps were performed: 1) realignment, 2) co-registration of all images into the same anatomical image space, 3) spatial smoothing using a Gaussian kernel of 10 mm^3 at its FWHM, 4) anatomical image segmentation to be used as masks later in order to calculate CBF mean inside of each, 5) CBF measures for each control/label pair were calculated using Wang model with simple subtraction (Wang et al., 2003).

With the perspective of exploring any correlation between cortical parameters and CBF, we calculated CBF within each cortical volume by applying GM and WM segmented images as inclusive masks in the last module of the analysis stream.

7.3.2 Diffuse optical measurements and analysis

A 32-channel continuous wave fNIRS instrument (TechEn CW6) with the sampling frequency rate of 25Hz was used to measure brain activity during the language task. Using two different wavelengths at 690 and 830 nm, we were capable to assess task-induced haemoglobin concentration changes from differences in absorption coefficient by measuring light's attenuation (Delpy et al., 1988b). TD home-made system was used on the frontal lobes to acquire absolute estimates of the optical properties of the cortex. These measures yielded absolute estimates of haemoglobin concentrations at rest.

Both signal processing and statistical analysis were performed using a SPM8 compatible toolbox made in-house, based on NIRS-SPM v3.2 (Karl J. Friston et al., 2006; Ye, Tak, Jang, Jung, & Jang, 2009b)(for more details on calculations of changes in haemoglobin concentrations and analyses see Amiri et al., 2014).

7.4 Results

Tests for the basic assumption of multivariate ANOVA included normality (Kurtosis and skewness), linearity of the dependent variables (Pearson r), homogeneity of variance between groups (Leven's test), and multivariate homogeneity of covariance between groups (Box M). There was a significant difference between young and older adults (YAs and OAs respectively)

when data was considered jointly on all cortical variables. Taking Wilk's λ= .741, F(2, 27) = 4.73, *p* = .017, partial η2 = .26, a separate 2-way ANOVA was conducted on each dependant variable. Cortex volume in left hemisphere was significantly smaller in OAs (p < .001). The measure of surface holes showed a relatively different age-group structure pattern (p = .044). The same analysis has shown no differences in the right hemisphere. There was an interaction between age and hemisphere for cortical volume, but no significant interaction in white matter volume. Yet white matter hypointensities measures showed differences between the two groups (OA > YA). The evidence for differences between groups and their cortical hemispheric's measures is observable in Figure 2. CSF was not different between age groups (*p* = .39). An age-associated cortical atrophy was revealed by thinning of the cortex across the entire cortical mantle. Global thickness was examined by ANOVA with age and hemisphere as independent variables (Figure 7-1).

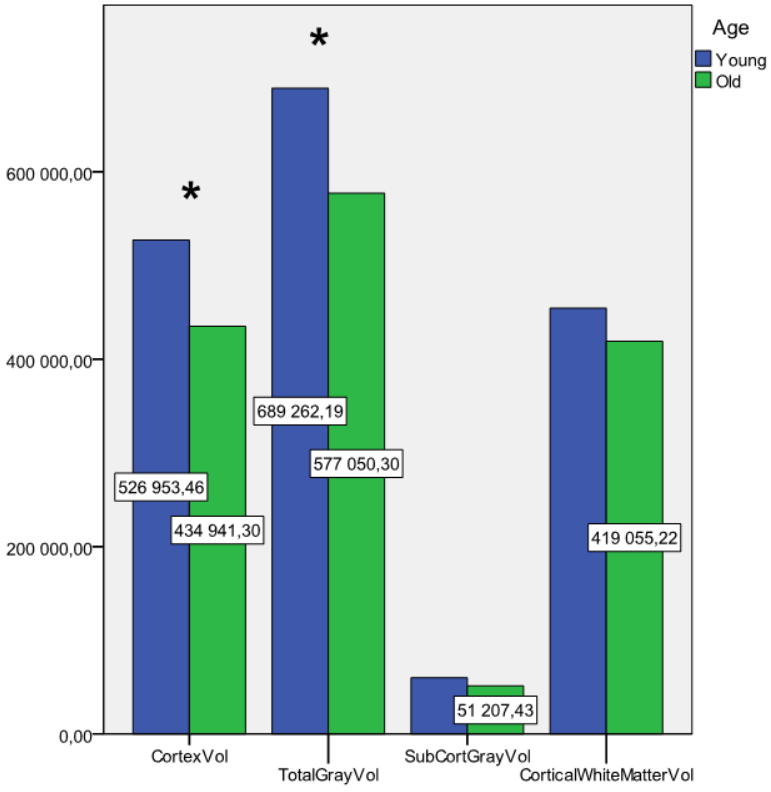

Figure 7-1. Description of cortical measurements: Mean values in voxels for cortical, subcortical and total gray volumes, as well as total white matter. There are significant differences in cortical and gray matter volumes.

Previous results from TD optical imaging data (Amiri et al., 2014) showed a lateral difference in absolute measures of [HbO_2] among OAs in the opposite direction of those measures among YAs. They showed a slight increase of [HbO_2] in the RH comparing to the LH (42.6 (±1.8) versus 40.9 (±1.7)), while these values have a different trend in YAs, which are 46.5 (±1.3) and 49.1 (±2.1) for RH and LH respectively.

Maps of the cortical thinning

Cross-sectional analysis showed an age-related cortical thinning across almost the entire cortex (Figure 7-2). The group comparison between young and older adults revealed a bilateral cortical thickness reduction, with less prominent differences in right frontal lobes, occipitoparietal junction and motor cortices. As it was shown previously in bar graphs, there is no difference in subcortical structures between age groups. Generally age had less effect on the middle temporal cortices. Lateral inferior parts of the occipital lobes and superior postcentral parts of the parietal lobes were best preserved with age.

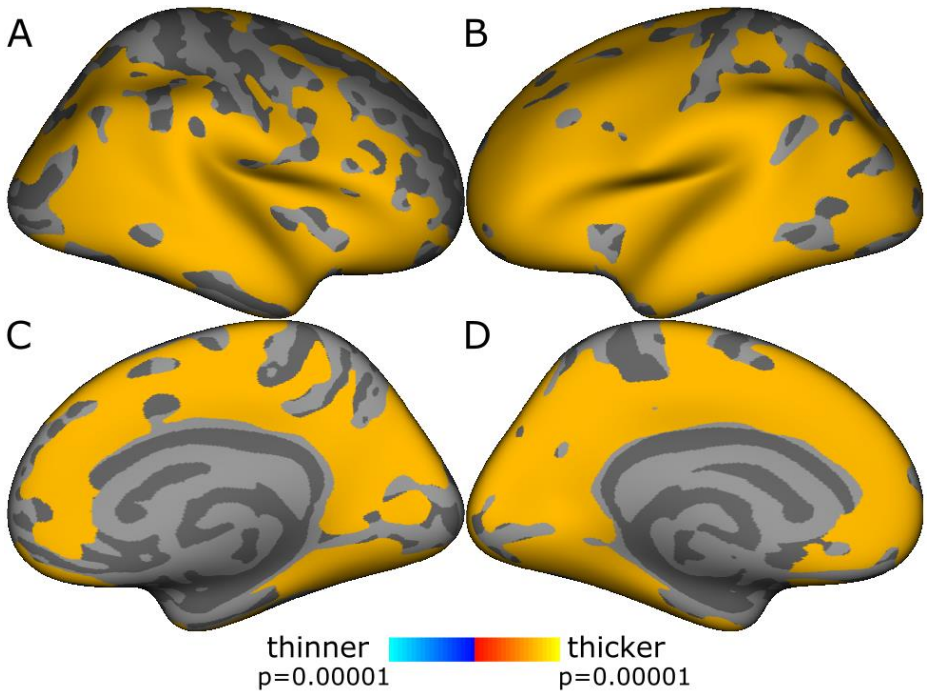

Figure 7-2 Difference of the cortical thickness between young and old adults. Clusters are FDR corrected at p=0.05. A=right hemisphere lateral view; B=left hemisphere lateral view; C=right hemisphere medial view; D=left hemisphere medial view. Hemispheres are inflated.

Once individual's age was included in the comparison as a covariate, results showed a reverse pattern of change (Figure 7-3)**.** In other words, when we corrected for the factor of age, both groups have shown similar cortical thickness, except for right superior frontal, inferior temporal and left middle temporal gyri. In agreement with compensation theory, we observe a right frontal lobe and left middle temporal gyrus increase among older adults (OAs). We could suggest that our group of performant OAs have quite thicker cortical structures, which would be in support as compensatory circuitry for the classical language areas. Along with functional data from fNIRS and baseline measures of TD optical imaging, which has shown an increase of the total hemoglobin concentration ([HbT]) in right PFC regions, we could conclude that more cerebral vascular bed does exist due to an increased brain volume in the right PFC. For temporal regions, NIRS quantified data do not support this idea**,** which could be due to the low SNR, which was recognised in this study (Amiri et al., 2014).

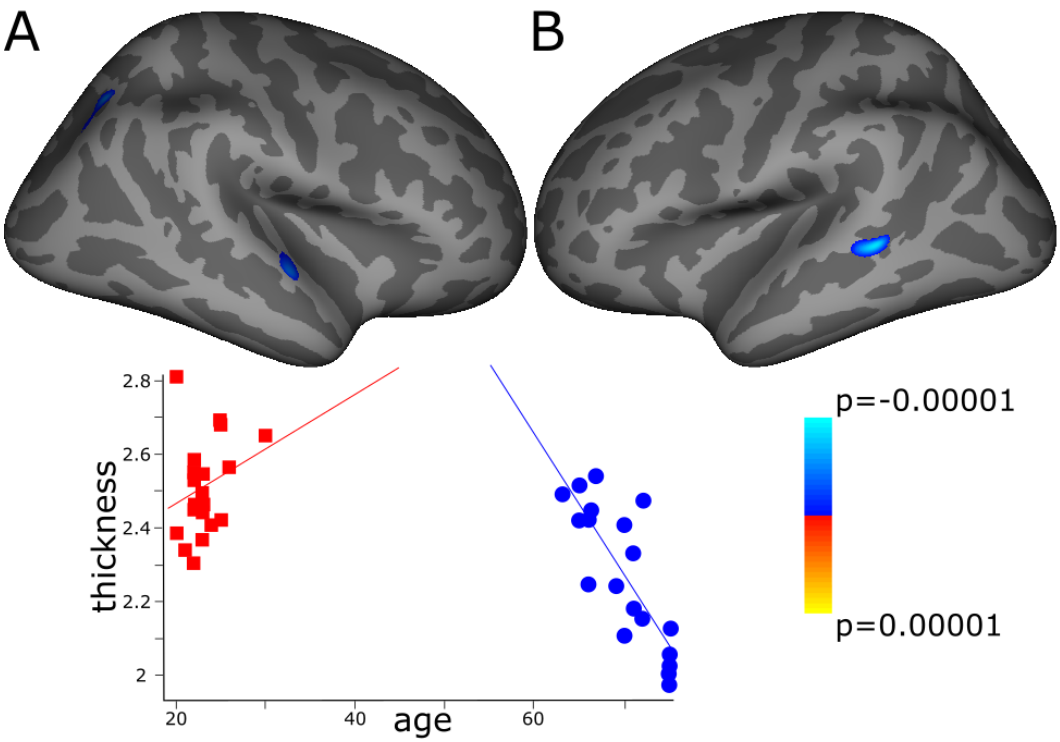

Figure 7-3 Difference of cortical thickness between young and old with age as co-variate. Clusters are uncorrected at p=0.001; A=right hemisphere lateral view; B=left hemisphere lateral view; Plot presented for the left middle temporal cluster. Red squares=young; blue circles=old. Hemispheres are inflated.

Maps of the cortical thinning in function of CBF

When taking CBF measures of the gray matter as the covariate of the cortical thickness, with FDR corrected inferior to 0.05, a right frontal difference of the average thickness between young and old adults was observed (Figure 7-4). This observation could be interpreted as the mere diminution of the cortical thickness independent of the cerebral blood flow in regions other than middle PFC. In other words, greater values of CBF in OAs do mean greater measures for the cortical thickness, but it is not the case among YAs. Thus, this suggests that our group of performant healthy OAs does maintain a compensatory vascular networks to supply the blood to neurons. Cortical thinning occurred in the left medial PFC as well.

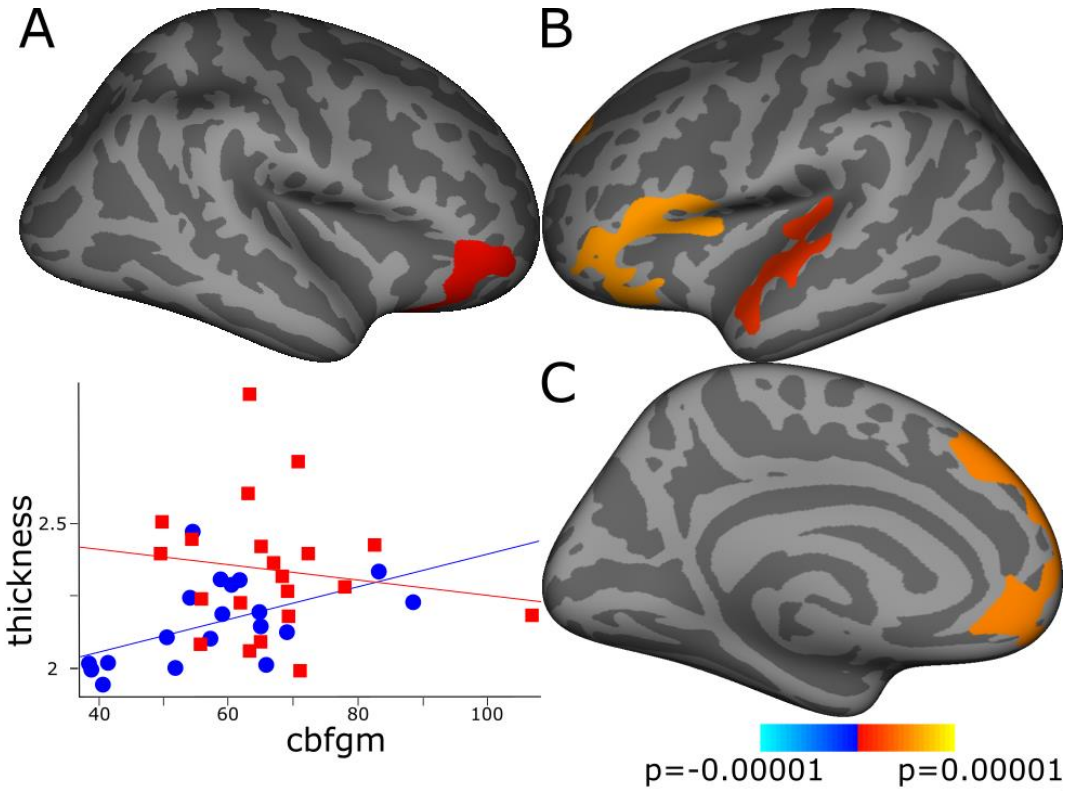

Figure 7-4 Difference of cortical thickness between young and old with cerebral blood flow measures in gray matter (cbfgm) as co-variates. Clusters are FDR corrected at p=0.05. A=right hemisphere lateral view; B=left hemisphere lateral view; C=left hemisphere medial view. Hemispheres are inflated. Plot presented for the right orbitofrontal cluster. Red squares=young; blue circles=old.

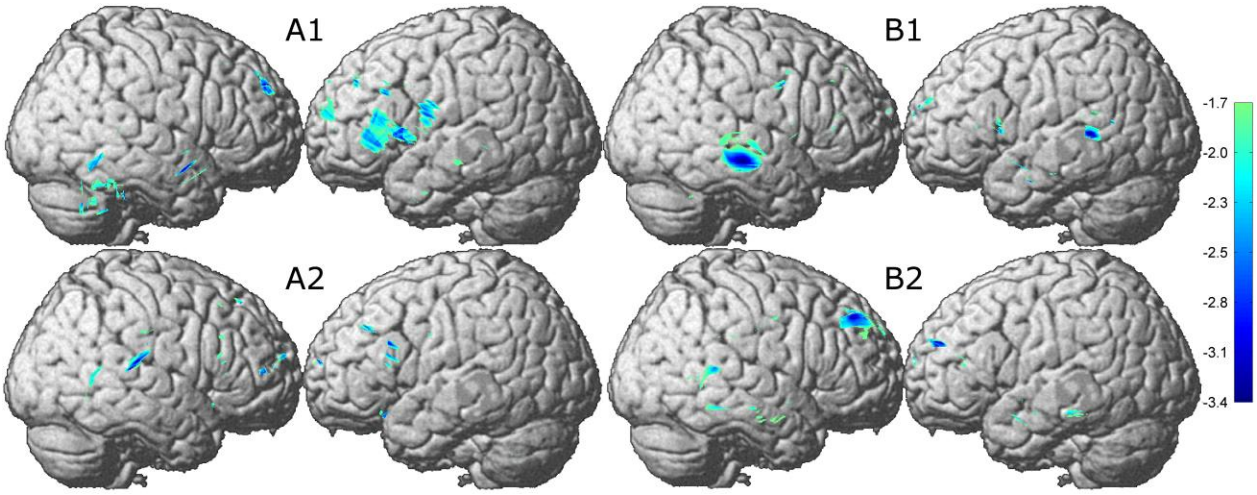

Figure 7-5 cortical maps of the activation for HbR in response to semantic words processing A) Shows neural activity measures of HbR for concrete (A1) and abstract (A2) words processing. In this panel measures of cortical thickness are used as a regressor to the group analysis.

Results from the between group comparison of lexical-semantic decision task are presented in Figure 7-7 and 7-8. All between group activation maps meet uncorrected significances level of $p < 0.05$. Panel A and B show results with cortical thickness measurements are taken into account for group comparison and without cortical thickness regressors. While numbers represent concrete and abstract words processing differences. OAs showed increased frontal activation compared with younger group, but the difference is in the hemispheric preference; A1 depicts a left PFC and frontoparietal activity differences between OAs and YAs, while B2 shows a right superior frontal cortex activity difference. These results could be interpreted as following: when cortical thickness differences are considered, only for concrete words processing (A1), right prefrontal cortex showed more important increase because of the presence of atrophy among OAs. This effect is present in the homologue hemisphere for abstract words processing without cortical thickness regressor analysis, which would suggest the importance of taking structural measures underlying neural activation as *a priori*.

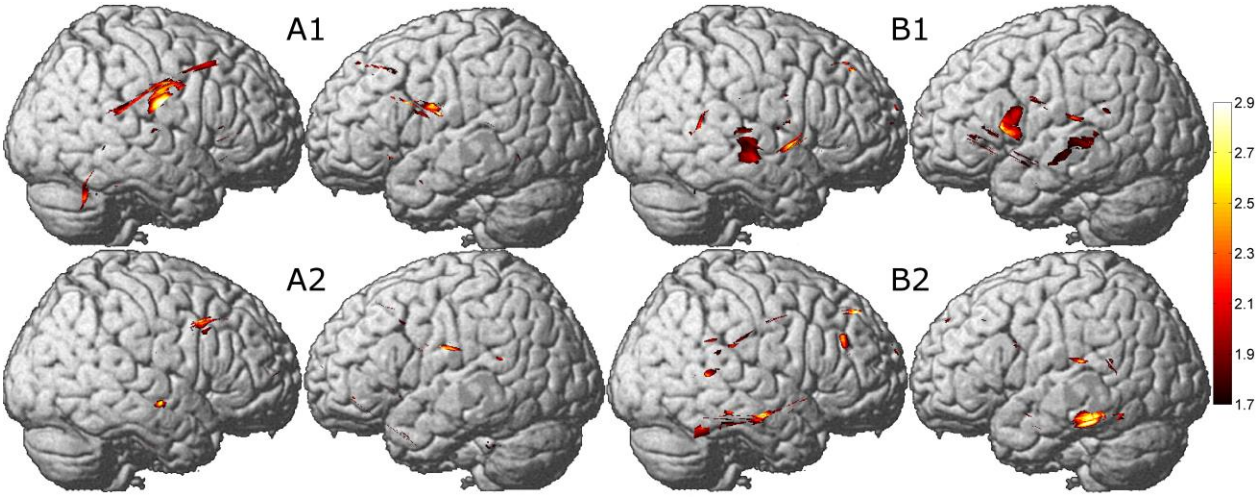

Figure 7-6 cortical maps of the activation for HbO_2 in response to semantic words processing A) Shows neural activity measures for concrete (A1) and abstract (A2) words processing. In this panel measures of cortical thickness are used as a regressor to the group analysis. Similarly B1 and B2 show activations for concrete and abstract words respectively, but without cortical measures of thickness as a regressor.

When observing results from HbO_2 activation maps, we noticed that right temporal activity for concrete words processing disappears and instead, right inferior parietal and frontoparietal activities become prominent. This observation could be seen as an engagement of sensorial cortices in the analysis of concrete words.

7.5 Discussion

The main finding of this study can be summarized in two major subsections; first, we analyzed the age difference in cortical thickness measures between YAs and OAs. Second, we discussed our results of different patterns of task-related activity and their relation to morphometric results. We also evaluated the potential correlate of age-related structural changes with baseline neurophysiology of aging. There is a consensus of evidence in the literature that aging is accompanied by a reduction in hemispheric lateralization in cognitive functions, and this is more prominent in frontal lobes (Cabeza, 2002). This phenomenon is believed to be due to the differentiation in normal aging, and consequently followed by a compensation and/or reorganisation. Regarding our results that show the existence of an important age differences in cortical thickness and volume, we can suggest that any functional changes in the pattern of

activation is caused by dedifferentiation. With normal healthy OAs maintaining high performance, as our group of participants represent, we have found in the results a reorganization pattern, or in another word; bi-lateralization. When a statistical threshold (p = 0.05) was applied, cortical thinning was observed almost across the cortical surface, except in PFC, superior parietal and posterior occipital lobes. When corrected for the CBF, the magnitude of age differences in thickness showed greater effects in the right prefrontal cortex, especially in the lateral and medial regions (orbitofrontal regions). Although it was previously shown that smaller prefrontal cortices predict poorer performance (Raz et al., 1998; Gunning-Dixon and Raz, 2003), here our observation seeks a thorough interpretation. In the frontal lobe model of aging, it is assumed that the vulnerability of the prefrontal cortices in aging is related to reduced performance in working memory, episodic memory, inhibition and strategic planning (Greenwood, 2000). In response to this degradation, contralateral homologous areas maintain their structural and/or functional capacities by potentially recruiting more neural circuitry.

In addition, it has been observed that there was a change in the neuronal activation of language-related regions particularly in PFC, after correcting for cortical volume changes. Some studies suggest that baseline oxygen metabolism actually increases with age after accounting for reductions in brain parenchyma volume (Lu et al. 2011; Peng et al., 2014). Thus, if age-related baseline oxygen metabolism changes were driving the age-related differences in oxygen metabolism during activation, greater hemodynamic response for younger than for older adults would suggest greater neuronal activity (Joanna L. Hutchison et al., 2012).

Our results support the hypothesis that subcortical brain volumes could be responsible for reaction time. With the same percentage of accuracy (88% and 90% for OAs and YAs respectively), OAs showed longer RTs comparing to YAs (910 *ms* and 835 *ms* respectively). Older adults with longer RTs for abstract and pseudo-words would recruit more frontal areas to execute the task. These results with frontal lobes atrophy among OAs are in line with previous studies that show a negative correlation between PFC volume and RT in semantic task (Gold et al., 2009). Moreover, the slight atrophy in CC could be responsible for greater RTs in old adults.

The tendency of OAs to over-recruit right occipitotemporal cortex suggests that they may rely more on visual word form recognition processes during lexical-semantic decision task than YAs. This possibility is not consistent with previous results suggesting that orthographical processes

are more affected by age (Gold et al., Allen et al., 1995). In contrast, lateral inferior parietal cortices showed greater activation in OAs has been found to contribute to high-level linguistic processes (Thompson-Schill et al., 1997). Age-related cognitive decline is associated with differences in the structure and would suggest that region-based increased activation is a compensatory response to such deficiency (Persson et al., 2005).

The present study also investigated the existence of any correlation between TD optical imaging data of absolute oxy-haemoglobin concentration ($[HbO_2]$) and frontal GM cortical thinning. Cluster map of data has shown no tendency for such a relationship ($r = 0.1$). This may suggest that neurovascular features of aging do not suffer from aging to the same faith as neuroanatomical aspects.

It has been revealed that the right middle temporal gyrus is involved in semantic processing. But when considering morphometric changes with age, this effect became less important. Similarly for the left middle temporal regions, results showed that there is a cortical thickness difference when corrected for age. Thus when regressing this age-related difference against functional activation maps, we obtained no effect of age.

We did not consider sex as a co-variate because of the small number of participants. Although, it was revealed that there were minimal sex effects after correction for intracranial volume (Salat et al., 2009).

7.6 Conclusion

Several arguments can be drawn from the findings of this study. First, the importance of anatomical images in functional neuroimaging of aging population becomes evident. Although the necessity of structural images for co-registering with functional native space images is debatable (see recent works on the proposition of template atlas for co-registration (Cooper et al., 2012; Tsuzuki et al., 2014)), their role for the normalization of functional data is primordial. In this study, we tried to explore whether neurophysiological measures of TD optical imaging or CBF are the predictor of the age-related anatomical changes. Unfortunately such correlations did not exist between our data, maybe because of the small size of our population. Thus, the acquisition of each individual's anatomical images remains necessary.

Having observed different physiological and anatomical aspects of aging, our results are supporting the conclusion that a unique causal relation between age and cognitive decline is not realistic. This perspective encourages neuroscientists to opt for multimodal imaging protocol design, which are cost-worthy even though they offer precious advantages of complementary data. In order to avoid similar expenses of the neurocognitive researches, more longitudinal multimodal imaging studies are needed for the present to come up with models of aging, with more controls on individual's characteristics.

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CHAPTER 8 GENERAL DISCUSSION

The work reported in this dissertation consists of a combination of two complementary approaches, one focused on an innovative imaging data analysis, and the other on a cognitive neuropsychology description of language changes with age. Accordingly, there were two scientific articles published and submitted, each representing a facet of this ensemble. In this chapter, I recall the main objectives of this project and evaluate each of them regarding achievements and results. Then I will discuss details according to recent literatures and finally compare them with an analytical approach. Results are discussed in three parts, in each the link between aging and cognition is drawn from a different perspective.

8.1 Language and aging

The first question raised in this study was how an aging brain could undergo age-related changes underlying its cognitive functions to support the remarkably stable language abilities in aging. Considering language as a cognitive function, we know that older adults maintain quite well their semantic memory, while other elements of memory (e.g., episodic memory, working memory) show a decline (Craik & Salthouse, 2000, 2008; Hedden & Gabrieli, 2004; Salthouse, 2011). Since one goal of this study was to evaluate how brain ages gracefully, we chose a lexical-semantic decision task to investigate the possible changes of the neural basis of semantic word processing with the presence of neurophysiological and/or neuroanatomical degradation with age. Through a lexical-semantic decision task, the complex task of semantic judgement was assessed in a subliminal fashion, so the repetition suppression[2] could not be observed explicitly. As noted previously, performing semantic tasks activate widely the left lateral PFC and mid temporal cortex (Jeffrey R. Binder et al., 2009; Martin & Chao, 2001; Price, 2012). It has been revealed that the anterior and posterior prefrontal regions are involved in semantic working memory systems responsible for manipulating semantic knowledge stored elsewhere (Gabrieli, Poldrack, & Desmond, 1998; Jung-Beeman, 2005; Poldrack et al., 1999). In contrast, Thompson-Schill and colleagues have found another role for left IPFC: selection among competing alternative or/and

[2] Repeated judgment on a specific quite complex task results in decreased neural activity in the associated brain region. This phenomenon is called *repetition suppression* (ch8 Handbook of the Neuroscience of Language).

retrieval demands. This activation was seen in our study in right homologous of IPFC when processing pseudo-words. While evidence from patient's studies has shown that damages to the left or bilateral IPFC can cause deficits to semantic processing. These results are of interests for several reasons.

The main effect of age with physiological regression analysis was seen in the left inferior central sulcus and anterior and posterior temporal lobe bordering occipitotemporal gyrus. This is in line with Damasio's proposition that the anterior temporal lobes are critical for retrieving information about unique entities (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004). Supporting this assertion is the work of McCandliss and colleagues on the visual word form areas. They have provided converging evidence that the perception of visual words and pseudo-words activate the left fusiform gyrus and occipitotemporal sulcus. As revealed by fMRI studies, these areas are sensitive to the conformity of letters in pseudo-words: well-structured letter strings with phonetic frequencies similar to real words, produce greater neuronal response than poorly structured pseudo-words (L. Cohen et al., 2003; McCandliss et al., 2003).

The interpretation that similar right PFC activation is related to compensatory networks is based on the assumption that left prefrontal engagements are well-established to be associated with semantic relative to non-semantic analysis of words (Gabrieli et al., 1998; Petersen et al., 1990). The activation in the right posterior middle frontal gyrus relative to pseudo-words may be that it is especially involved in lexical rather than semantic processing. However, the right frontal association does not cancel the importance of left middle frontal lobe activity. A [HbR] difference has been found as an effect of age between groups which is in consistency with previous fMRI studies. The fundamental contribution to language abilities of the left PFC processes is also revealed among epileptic patients. Regarding the nature of our lexical-semantic decision task, we assumed that effects of semantic and phonological processes are well distinguished. When reading visually presented single words, series of processes are happening, including orthographical processing, word form analysis, phonemic and conceptual analysis of words. With the presence of pronounceable non-words (pseudo-words), one could assume that the phonological aspect of processing is cancelled out. Regarding orthographical processing, there is little evidence that this process activates left PFC (Gabrieli et al., 1998). And lastly, visual word form analysis is well-established to be associated with activation of the left occipitotemporal areas (McCandliss et al., 2003). Therefore, we can suggest that the activation in

left PFC and middle frontal gyrus is relevant to semantic processing in a range of semantic tasks. At the end, it is important to note that regions of PFC are activated for several cognitive functions and are not exclusive to semantic processing.

Hypothesis looking at the relationship of language symptoms in individuals attained the acquired language disorder (known as aphasia) with the effect of brain damage could be done using similar protocol. NIRS functional measures could be useful to assess aphasic patients with different types of problems to understand why they have these specific symptoms, and determine which treatment would be the most useful in their recovery. By acquiring the baseline physiology, any effect of group differences would be covered and the main effect of neuropsychological test would be evaluated.

8.2 Neurophysiology of Aging

To investigate the above-mentioned questions, we needed to be aware of the potential changes of the coupling of neural activity to the hemodynamic response measured by fNIRS. We knew that differences in fNIRS signal response between young and elderly participants could not be interpreted directly as differences in neural response. In this study, we have made the assumption that baseline physiology differences between age groups are in part responsible for modulating the hemodynamic response associated with lexical-semantic decision task. We believed that this is a good assumption for the reason that neural coupling is affected by the baseline physiological changes, thus the hemodynamic response would reflect this effect.

Findings from TRS measures of lower oxygen saturation in both hemispheres between age groups revealed the potential relation between baseline [HbO_2] and changes of [HbT] in frontal lobe. Hemodynamic response was estimated taking physiological regressors into account to correct for the reduced baseline HbO_2 concentration and CBF. Being proportionally an indicator blood volume, older adults may need greater [HbT] in their compensatory networks to provide oxygenation to the metabolic demand. Thus, considering baseline physiologies in functional data interpretation could be of interest in the future functional neuroimaging studies. The nature of an inference when comparing two age groups via neuroimaging is still ambiguous. However, having taken into account physiological factors underlying the formation of hemodynamic response, we anticipate closer link between the corrected response and neural activity.

In the GLM estimation of the hemodynamic response, HRF was considered with both time and dispersion derivatives to cover for changes in time to peak and time to descend. Time to the half maximum of the hemodynamic response increases after 50 years old, which can be attributed to a decrease in vascular reactivity and/or changes in vasculature morphology (D'Esposito, Zarah, Aguirre, & Rypma, 1999). On the contrary, time to reach the initial level for the hemodynamic response does not change with age. This observation could be explained by the passive decrease of cerebral blood flow (back to the normal state) that is not affected by age (Taoka et al., 1998).

Total CBF and its cardiovascular determinants are strongly related to brain volume (Vernooij et al., 2007). This underlines the importance of considering brain morphology (atrophy) when analyzing global blood flow. The correlation analysis between CBF and cortical thickness has revealed a correlation between CBF and brain volume in older adults. This effect was statistically significant in PFC regions and internal orbitofrontal areas. Results have shown that in older adults, with increasing cortical thickness total CBF also augment. While in young group, such relation does not exist.

8.3 Neuroanatomy of aging

This study also allowed investigating the effect of age-related cortical thickness changes on fNIRS data across age groups. Several conclusions can be drawn from the findings. First, cortical thinning was observed across most of the left hemisphere cortex. In the right hemisphere, frontal regions had lower age difference, which could be interpreted as maintaining the cerebral cortex or cortical thickening to compensate the rapid thinning of the left PFC. It is here important to remind reasons behind the early thinning of left frontal cortices: according to the theory of "last in, first out" in which late development regions are those with early deterioration (Raz, 2000), among left hemisphere dominant participants. Supporting this hypothesis are strong age effects observed on the PFC especially in superior, lateral and medial regions, but further investigation through longitudinal studies are necessary. Second, the lack of age differences in right frontal regions, in line with functional activity in right PFC as a main effect of age in semantic words processing, could support the preservation of the right frontal cortex in face of structural decline in the left frontal lobe. But there is a possibility for two hypotheses; the enhanced contribution of the right PFC could either express a compensation of the way the brain is processing semantically

the words, or it is the expression of the fact that older adults execute the same task in a different way. This could be seen not only as compensation but also neurofunctional reorganization which has an impact on the anatomy.

It is worth noting that in this study, some of the previous findings of the literature were not replicated. We observed an age relative stability of the right superior, anterior and orbito-frontal regions which is not in line with most of the cross-sectional and longitudinal studies (Fjell et al., 2009; Raz et al., 2005). Although in this investigation the older adults were chosen from healthy population with high cognitive scores to the neuropsychological tests, no history of vascular disease and also high level of education, it is not clear whether that could explain for lack of consistency. We observed reliable correlation between these findings and the physiological measures at baseline. TRS measures have showed a slight trend of [HbO_2] increase in right frontal lobes relative to the left homologue.

Our study was cross-sectional limiting conclusions regarding aging and cortical thinning. For example, the relation we found between baseline blood oxygenation and brain volume could signify that there is a brain reserve or a different pattern of brain engagement in processing semantic words. But why this only happened in the right frontal lobe, it is not clear. However, it may also be that there was a reorganization, which led to the better preservation of the right frontal lobe. We cannot conclude that these simple correlations are sufficient to warrant causal conclusions. This remains to be further elucidated by a larger sample size of elderly participants. At the current time the evidence that these aspects of brain physiology and anatomy are the neurophysiological and neuroanatomical substrates of age-related cognitive decline is not strong enough. This hypothesis that was analyzed by application of multimodal imaging methods, is not possible to be approved without complementary data acquisition.

Thus, consistent with the compensation hypothesis, a hemispheric asymmetry reduction was found in older adults performing similar to young participants. The results suggest that with age, older adults recruited the same PFC networks but used it inefficiently, and in order to counteract this neural decline, they recruit compensatory networks through a functional reorganization. However, according to the frontal lobe theory (Raz, 2000) in MRI studies, the greatest cortical thickness decrease is centered in frontal lobes. Thus, there is no simple correspondence between morphometric age-related changes in PFC and reduced executive functions in aging.

Although testing the brain reserve hypothesis was not a goal of this study, the results provided are pertinent to an active reserve hypothesis. This statement claims that education would act as a proxy for neuroprotection to aging. Preserved right frontal cortex supports this hypothesis.

One of the limitations of this study is the size of our samples. This was mainly because of the strict inclusion criteria for recruiting healthy older adults, including no history of neurological and cardiovascular diseases, no intake of any drugs or excessive alcohol drinking. Also, cross-sectional studies may underestimate real morphological age changes by probably the fact that there are large inter-individual's differences. This heterogeneity intensifies over time.

Regarding the challenge of the co-registration between participant's anatomical images and the reference template represent, there are few suggestions. In addition to what has been explained in chapter 5 for data transformation to a standard space, there is another approach which is gaining popularity. There is a freeware program (FreeSurfer) that provides extensive and automated analysis of key features of human brain anatomy (Fischl & Dale, 2000; Fischl, 2012). This includes volumetric segmentation of the brain into gray and white matters (to the most macroscopically visible structures) and inter-subject alignment based on cortical folding patterns among other functionalities. Because of these two best appreciated structural information that FreeSurfer has high affinity to the fNIRS technique. Some pioneers in NIRS studies have already applied FreeSurfer-derived data for standardization spatial data (Cooper et al., 2012).

CONCLUSION

In this dissertation, several brain imaging techniques were used to investigate how an aging brain is functioning in the face of its age-related changes underpinning cognitive functions. The main findings of the current work relates to observations on baseline physiological characteristics of the brain, to the anatomical morphometric measures changing with age, and finally to the relation between these basic elements of hemodynamic response and functional data acquired with fNIRS. Baseline blood flow diminished with age, and this fact has major impact on the interpretation of the fNIRS data that varies accordingly. Thus, the use of ASL to assess differential baseline blood perfusion across age-groups and individuals brought a valuable impact in evaluating neurovascular responsiveness, despite the fact that, vascular and neuronal (resting-state) effects to ASL signal cannot be separated. This intrinsic problem could be overcome if the functional data are acquired via BOLD along with ASL imaging. Since we have had the ambition to propose fNIRS as a clinical imaging technique, we would need a similar combination of measures for optical imaging. On the other hand, to assess the hemodynamic response for each individual, the resting blood flow could not be the only indicator of the neurovascular health. In some studies reporting lowered blood perfusion caused by cerebrovascular diseases, it has been found that some patients had no abnormalities in their CBF_0 but in the demanded flow augmentation. Different ability to supply oxygen as a result of the increased oxygen metabolism could bias the interpretation of functional data.

In order to explore the extent of compensation or functional dedifferentiation in high-performance older adults, one would use a language task manipulated at its difficulty level. By comparing OAs' activity for successful versus unsuccessful stimuli, we could measure the importance of neural activity. In such study, fNIRS measures would provide both amplitude and temporal signature of the HRF. These measurements along with baseline CBF and HbT could lead to a through interpretation of age-related over-recruitment in the presence of any WM volume or/and integrity decline.

The last but not the least, our design was cross sectional so no inference about the causality of the greater intellectual engagement could be made.

In sum, this series of studies suggests that functional NIRS, like all hemodynamic-based modalities, is an appropriate tool to investigate data-based hypothesis, but it cannot be reliably

used as a unique imaging modality for mapping the exact neural networks and mechanisms underlying specific cognitive capacities. This shortcoming is the result of the measured surrogate signal whose nature is constrained by systemic and physiological limits. To be precise, complementary data acquisition would be needed to assess physiological and anatomical aspects underlying hemodynamic response formation. Moreover, in emerging discipline of cognitive neuroscience of aging, an area of research that has only now accumulated enough evidence, prospective studies are required to unravel whether these functional reorganization are secondary to structural decline or a form of cognitive reserve. These evidences would contribute to better understanding of the aging brain, which would lead to cautious generalizations about the neurofunctional pattern of healthy successful aging.

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APPENDIX 1 – Supplementary figure

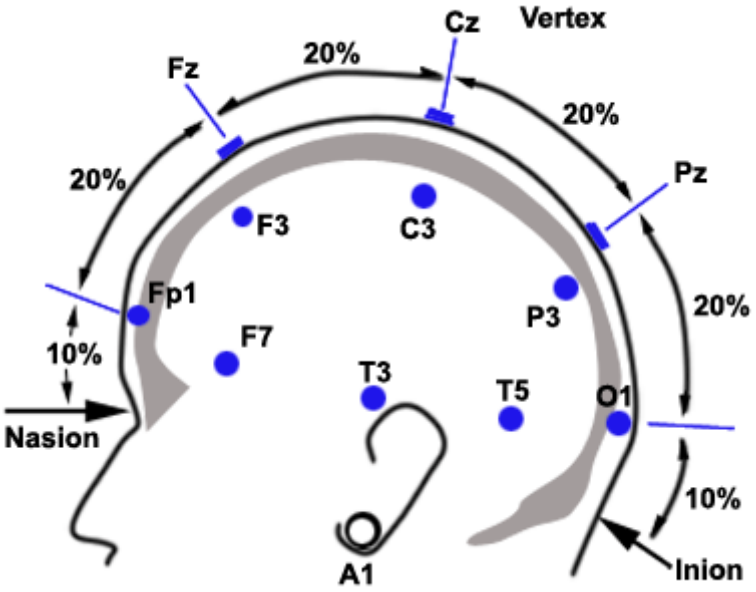

Figure Annexe-1 10-20 system of EEG electrode placement used in optical helmet placement. A1 represent below auricular left. Fp1 and Fp2 were the limits of the beginning of the optical helmet.

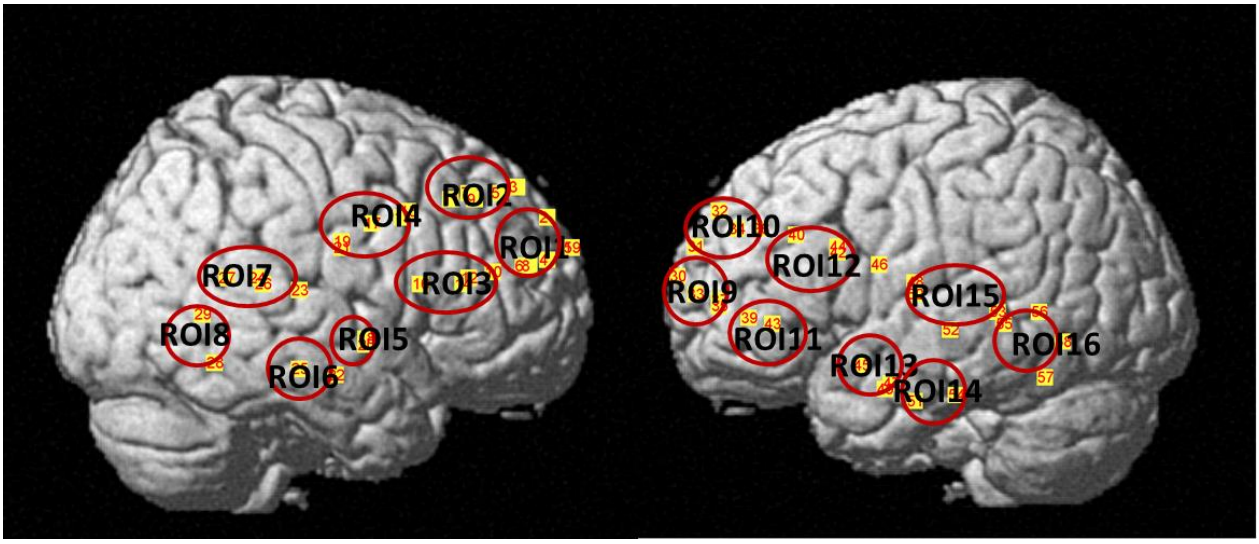

Figure Annexe-2 ROI formation according to the language-related anatomical areas.