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Changes in cortical and sub-cortical patterns of activity associated with aging during the performance of a lexical set-shifting task

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FRENCH ABSTRACT

Bien que le passage du temps altère le cerveau, la cognition ne suit pas nécessairement le même destin. En effet, il existe des mécanismes compensatoires qui permettent de préserver la cognition (réserve cognitive) malgré le vieillissement. Les personnes âgées peuvent utiliser de nouveaux circuits neuronaux (compensation neuronale) ou des circuits existants moins susceptibles aux effets du vieillissement (réserve neuronale) pour maintenir un haut niveau de performance cognitive. Toutefois, la façon dont ces mécanismes affectent l'activité corticale et striatale lors de tâches impliquant des changements de règles (*set-shifting*) et durant le traitement sémantique et phonologique n'a pas été extensivement explorée.

Le but de cette thèse est d'explorer comment le vieillissement affecte les patrons d'activité cérébrale dans les processus exécutifs d'une part et dans l'utilisation de règles lexicales d'autre part. Pour cela nous avons utilisé l'imagerie par résonance magnétique fonctionnelle (IRMf) lors de la performance d'une tâche lexicale analogue à celle du Wisconsin. Cette tâche a été fortement liée à de l'activité fronto-stritale lors des changements de règles, ainsi qu'à la mobilisation de régions associées au traitement sémantique et phonologique lors de décisions sémantiques et phonologiques, respectivement. Par conséquent, nous avons comparé l'activité cérébrale de jeunes individus (18 à 35 ans) à celle d'individus âgés (55 à 75 ans) lors de l'exécution de cette tâche.

Les deux groupes ont montré l'implication de boucles fronto-striatales associées à la planification et à l'exécution de changements de règle. Toutefois, alors que les jeunes semblaient activer une « boucle cognitive » (cortex préfrontal ventrolatéral, noyau caudé et thalamus) lorsqu'ils se voyaient indiquer qu'un changement de règle était requis, et une « boucle motrice » (cortex postérieur préfrontal et putamen) lorsqu'ils devaient effectuer le changement, les participants âgés montraient une activation des deux boucles lors de l'exécution des changements de règle seulement.

Les jeunes adultes tendaient à présenter une augmentation de l'activité du cortex préfrontal ventrolatéral, du gyrus fusiforme, du lobe ventral temporale et du noyau caudé lors des décisions sémantiques, ainsi que de l'activité au niveau de l'aire de Broca postérieur, de la junction temporopariétale et du cortex moteur lors de décisions phonologiques. Les participants âgés ont montré de l'activité au niveau du cortex préfrontal latéral et moteur durant les deux types de décisions lexicales. De plus, lorsque les décisions sémantiques et phonologiques ont été comparées entre elles, les jeunes ont montré des différences significatives au niveau de plusieurs régions cérébrales, mais pas les âgés.

En conclusion, notre première étude a montré, lors du *set-shifting*, un délai de l'activité cérébrale chez les personnes âgées. Cela nous a permis de conceptualiser l'Hypothèse Temporelle de Compensation (troisième manuscrit) qui consiste en l'existence d'un mécanisme compensatoire caractérisé par un délai d'activité cérébrale lié au vieillissement permettant de préserver la cognition au détriment de la vitesse d'exécution. En ce qui concerne les processus langagiers (deuxième étude), les circuits sémantiques et phonologiques semblent se fusionner dans un seul circuit chez les individus âgés, cela représente vraisemblablement des mécanismes de réserve et de compensation neuronales qui permettent de préserver les habilités langagières.

Mots clés: Cortex préfrontal, striatum, *set-shifting*, sémantique, phonologie, vieillissement, mécanismes de compensation, réserve cognitive, IRMf

ENGLISH ABSTRACT

As the one's brain is structurally altered by the passage of time, cognition does not have to suffer the same faith, at least not to the same extent. Indeed, age-related compensatory mechanisms allow for some cognitive preservation. The elderly can therefore use new compensatory neuronal networks (neural compensation) or flexible pathways that are less susceptible to disruption (neural reserve) in order to maintain high levels of performance (cognitive reserve) during cognitive tasks. However, how these mechanisms affect cortical and striatal activity during set-shifting as well as during semantic and phonological processing has not been extensively explored.

The purpose of this thesis was therefore to investigate how aging affects patterns of neural activity related to executive processes on the one hand and the use of lexical rules on the other. To this end we used functional Magnetic Resonance Imaging (fMRI) during the performance of a lexical analogue of the Wisconsin Card-Sorting Test. This task has been shown to strongly depend on fronto-striatal activity during set-shifting as well as on regions associated with semantic and phonological processing during semantic and phonological decisions, respectively. Two groups participated in our fMRI protocol: young individuals (18 to 35 years old) and older individuals (55 to 75 years old).

Both younger and older individuals revealed significant fronto-striatal loop activity associated with planning and execution of set-shifts. However, while the younger group showed the involvement of a "cognitive loop" (including the ventrolateral prefrontal cortex, the caudate nucleus and the thalamus) when instructed that a set-shift would be required on following trial, and the involvement of a "motor loop" (including the posterior prefrontal cortex and the putamen) when the set-shift had to be performed, the older participants showed significant activation of both loops during the execution of the set-shift (matching periods) only.

Young adults tended to present increased activity in the ventrolateral prefrontal cortex, the dorsolateral prefrontal cortex, the fusiform gyrus, the ventral temporal lobe and the caudate nucleus during semantic decisions and in the posterior Broca's area, the temporoparietal junction and the motor cortical regions during phonological decisions, older individuals showed increased activity in the lateral prefrontal cortex and motor cortical regions during both semantic and phonological decisions. Furthermore, when semantic and phonological decisions were contrasted with each other, younger individuals showed significant brain activity differences in several regions while older individuals did not.

In conclusion, our first study showed an age-related delayed cerebral activation phenomenon during set-shifting (previously observed only in few memory and language tasks). Based on those findings, we conceptualised the Temporal Hypothesis of Compensation (third manuscript) which is the existence of a compensatory mechanism characterised by age-related delayed cerebral activation allowing for cognitive performance to be preserved at the expense of speed processing. Regarding language processing (second study), semantic and phonological routes seem to merge into a single pathway in the elderly; these findings represent most probably neural reserve/compensation mechanisms on which the elderly rely to maintain an adequate level of performance.

Keywords : Prefrontal cortex, striatum, set-shifting, semantic, phonology, aging, compensatory mechanisms, cognitive reserve, fMRI

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
B_0	External magnetic fields
BG	Basal Ganglia
BOLD	Oxygen Level Dependant
CN	Caudate Nucleus
CR	Cognitive reserve
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
dHb	Deoxyhemoglobin
DLPFC	Dorsolateral prefrontal cortex
DMC	Dual mechanism of control
EEG	Electroencephalography
fMRI	functional Magnetic Resonance Imaging
FPC	Frontopolar Cortex
GML	General Linear Model
GPe	External globus pallidum
GPi	Internal globus pallidum
^1H	^{1}Hydrogen
HAROLD	Hemispheric Asymmetry Reduction in OLDer adults
Hb	Oxyhemoglobin
LRG	Larger
MAN	Man-made
MEG	Magnetoencephalography
MR	Magnetic Resonance
NMR	Nuclear Magnetic Resonance
MRI	Magnetic Resonance Imaging
NAT	Natural
NMV	Net Magnetic Vector
O_2	Oxygen molecule
OFC	Orbitofrontal cortex

PASA	Posterior-anterior shift in aging
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PMC	Primary motor cortex
PPFC	Posterior prefrontal cortex
preMC	Premotor Cortex
PSC	primary somatosensory cortex
SMC	Supplementary Motor cortex
SML	Smaller
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticula
SNR	Signal to noise ratio
STN	Subthalamic nucleus
TE	Time to Echo
THC	Temporal Hypothesis for Compensation
TR	Time to repeat
VF	Verbal fluency
VLPFC	Ventrolateral prefrontal cortex
WCST	Wisconsin Card Sorting Test
WWST	Wisconsin Word Sorting Task

For all of YOU and everyone else

In the memory of

NELSON MANDELA
(1918-2013)
(Civil Servant, Counsellor, Fighter, Scholar, Father of the Nation, Hero)

as well as

MAX and WHISKY MARTINS
(1994-2006)
(2001?-2012)
(*Canis lupus familiaris*, Best Friends, Squirrel Hunters, Epicureans and Stoics)

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INTRODUCTION

INTRODUCTION

Aging has long been perceived as an inexorable physical and cognitive decline. But is it always really the case? Of course, both muscular and brain age-related atrophy appear unquestionable. However, those don't prevent some older individuals from running marathons or climbing mountains. Indeed, Ramon Blanco was 60 years old when he reached the peak of Mount Everest, and how about Fauja Singh who, in 2011, became the first hundred years old runner to complete a marathon. Moreover, cognition may not be so different from physical abilities, most of us know without a doubt at least one elder whose mind appears to have not been affected by the passage of time.

But how do high performing older individuals manage to preserve cognition? What are the compensatory mechanisms that allow these people to counteract the effect of cerebral atrophy, and consequently, neuronal loss? These are the questions this thesis tried to answer. Indeed, we explored the effect of normal aging on cognition, and more precisely on executive function and language processing. Our two main objectives were to investigate how aging affected patterns of neural activity related to executive processes (set-shifting) on one hand and the use of lexical rules (language processes) on the other. We wanted to explore the compensatory mechanisms that came in to play in order to preserve those cognitive domains despite aging. To this end we used functional Magnetic Resonance Imaging (fMRI) on both young and old individuals during the performance of a lexical analogue of the Wisconsin Card-Sorting Test.

In the following chapters, we first review the key concepts and hypotheses on which our studies and articles rely (Chapters 1 to 4), before presenting those articles per se (Chapters 5 to 7). Indeed, in the first chapter (Cognition and the Wisconsin Word Sorting Task), we start by describing what executive functions are and entail. We then elaborate on two specific executive processes, namely working memory and set-shifting. Afterwards, we offer a brief review of language processing, focussing on semantics and phonology. Finally, we go over some cognitive tests employed to study those cognitive domains, especially the Wisconsin Word Sorting Task (WWST).

The second chapter (The Cortex, the Basal Ganglia and Cognition) looks at the main structures of the cerebral cortex and the basal ganglia (BG), with particular attention given to the frontal lobes and the striatum. It then explores the contribution of those structures in executive (working memory and set-shifting) and language (semantics and phonology) processing.

In the third chapter (Aging and related cerebral compensatory mechanisms), we review a number of compensatory mechanisms allowing for some cognition preservation despite aging. We start by elaborating on the concept of Cognitive Reserve (CR) and the two mechanisms it relies on: neural compensation and neural reserve. We then focus on the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH), before we finish by taking a look at the age-related delayed brain activity reported in some memory and language processing studies.

The fourth chapter (Functional neuroimaging) focuses on imaging techniques. It first explores the basic concepts underlying Magnetic Resonance Imaging (MRI); after which it reviews the functional Magnetic Resonance Imaging (fMRI) technique and related experimental designs.

The following two chapters (Article 1 and Article 2) consist in two experimental scientific papers, both based on fMRI studies using the WWST. Chapter 5 (Article 1: "Changes in Regional and Temporal Patterns of Activity Associated with Aging during the Performance of a Lexical Set-Shifting Task") explores the effects of aging on set-shifting, while Chapter 6 (Article 2: "Differences between patterns of brain activity associated with semantics and those linked with phonological processes diminish with age") studies how aging affects semantics and phonology from a brain activity pattern perspective. As previously stated, these are the two main objectives of this thesis.

Chapter 7 (Article 3) is a review article entitled "The implications of age-related neurofunctional compensatory mechanisms in executive function and language processing". It explores (similarly to Chapter 3) age-related compensatory mechanisms. However, it adds to the existing literature the findings of our own fMRI experiments (Articles 1 and 2).

Finally, this thesis concludes with Chapter 8 (Conclusion), which explores in details the contribution of our research to the field of aging, executive function and language abilities. It does so by reviewing, reflecting and elaborating on the main findings of our research.

CHAPTER 1

Cognition and the Wisconsin Word Sorting Task

CHAPTER 1

Cognition and the Wisconsin Word Sorting Task

What is “cognition”? The *Encyclopaedia Britannica* (2003) defines it as the “act or process of knowing”. It “includes EVERY mental process that may be described [...]”. So, what is “cognition” then? It is a concept whose complete understanding is way beyond our humble “cognitive abilities”. Let’s therefore settle for something more modest and address solely two (already very complex) “mental processes” (or cognitive domains), namely executive function and language processing.

1.1.Executive function

The different concepts making up what we consider today as being “executive function” appear to have been around for more than a thousand years. Indeed, the Bible seems to underlie the importance of “control/inhibition” in verses written approximately in 900 BC.: “A man without self-control is like a city broken into and left without walls” (Proverbs 25: 28). In the early 1900s, Bekterev (a Russian physician) pointed out in the *Fundamentals of Brain Function* that damaged frontal lobes resulted in a disintegration of “goal-directed behaviour”. Later, Luria (another Russian genius), described that “besides the disturbance of initiative and the other aforementioned behavioural disturbances, almost all patients with a lesion of the frontal lobes have a marked loss of their ‘critical faculty,’ i.e., a disturbance of their ability to correctly evaluate their own behaviour and the adequacy of their actions.” (Luria, 1966).

The first, though, to employ intentionally the word “executive” in the scientific literature appear to have been Baddelay and Hitch in their book *Recent Advances in Learning and Motivation* published in 1974. In that context, the phrase “central executive” was used to describe a “system of attentional capacity” whose role was to control two storage memory systems, the three systems making up the “working memory”. However, the paternity of the expression “executive function” per se appears to belong to Shallice (British neuroscientist) who, in 1982, referred to it while describing impaired the performance in information processing capacity of patients with brain lesions.

Since the Bible, Luria, and Shallice, the concept of “executive function” has become a lot more elaborated and inclusive, but somewhat more elusive as well. Indeed, its characterisation varies from one author to another and no clear consensual definition exists (like for “love”, we "know" what it means intuitively, but not necessarily explicitly). Among all its conceptualisations, let's mention a few. "Executive control functions, called into action in non-routine or novel situations, provide conscious direction to the functional systems for efficient processing of information. [...] These behavioural characteristics [...] include at least the following: anticipation, goal selection, preplanning (means-end establishment), monitoring, and use of feedback (if-then statements)" (Stuss and Benson, 1986, p. 244). "The executive functions consist of those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour" (Lezak, 1995, p. 42). "Executive functions cover a variety of skills that allow one to organize behaviour in a purposeful, coordinated manner, and to reflect on or analyze the success of the strategies employed" (Banich, 2004, p. 391).

This thesis does not intent to offer a unifying conceptualisation of "executive function" nor does it aim to study all the processes it can possibly include (as for "love", mystery is sometimes blessed). We will, however, explore two cognitive entities generally associated with executive function, namely "working memory" and "set-shifting".

1.1.1. Working memory

Baddeley and Hitch published a chapter in 1974 describing a three-part model of "working memory". Their model implies a system of attentional capacity, the "central executive", which controls (processes information from) two storage or "slave" systems, the phonological loop and the spatial sketchpad (Figure 1.1.). Baddelay and Hictch were not the primary users of the term "working memory", but they were certainly the first to specifically include an executive component (Baddeley, 2003), and even if the concept of working memory has evolved since then, in part because the "central executive" has been viewed has creating a homuculus within the brain (Zelazo and Muller, 2002), its role in processing information has not. Indeed, nowadays working memory is generally conceptualized as the ensemble of processes allowing to maintain and to immediately manipulate available information. It relies on brain systems that represent memories in an active, online form (Buckner, 2004).

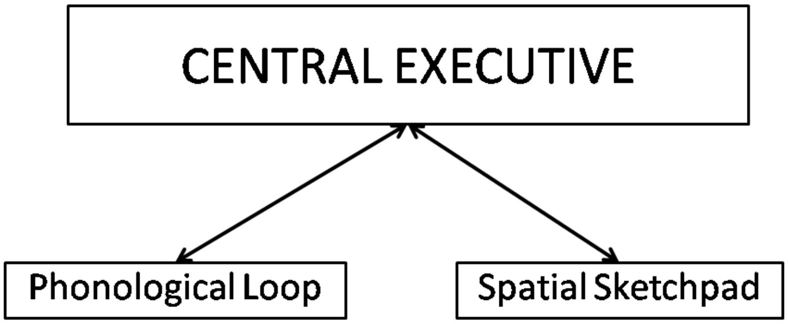

Figure 1.1. Baddeley and Hitch's (1974) model on working memory. The *central executive* controls two storage systems: the *phonological loop* and the *spatial sketchpad*.

Based on this conceptualisation, one can easily see how executive function and working memory are intimately related. Indeed, working memory is to executive function what mathematics is to physics (and pure sciences in general). One can certainly study mathematics without physics, but not physics without mathematics. In this thesis, working memory will therefore not only be considered a component of executive function, but one its core processes on which other more complex processes (such as set-shifting) rely.

1.1.2. Set-Shifting

Cognitive flexibility can be conceptualized as the mental ability to switch between two different ideas. It implies the capacity to simultaneously consider multiple aspects of an object or situation at once (Scott, 1962). Set-shifting (or task switching), on the other hand, is a specific type of cognitive flexibility characterized by the ability to shift between one attentional set, task or rule and another. Furthermore, set-shifting appears to be an executive function component that extensively relies on other executive processes, namely inhibition, planning and, of course, working memory (Miyake et al., 2000).

The importance of cognitive flexibility as a significant intellectual attribute goes without saying. On December 2nd of 1805, Napoleon and the Grande Armée carried off their finest victory at Austerlitz for "toutes les Gloires de France". That battle showed Napoleon at his best (military speaking). His great coup d'oeil for topography, his almost instinctive understanding of the enemy's behaviour, and his ability to adapt to different circumstances (or cognitive flexibility if you will) made him unbeatable. Unfortunately for "le Petit Caporal", the victory was so decisive that he started establishing copybook tactics that he would then reemploy again and again... until the English used them against him (Horne, 2006, p.64-65). Napoleon went from cognitive flexibility to cognitive rigidity, losing a continent and empire on the way.

Since studying cognitive flexibility applied to military strategy is difficult to do in a laboratory setting (and probably unethical), most neuroscientists have settled to investigate set-shifting using neuropsychological tasks, such as the Wisconsin Card Sorting Test (WCST) (e.g. Barcelo et al., 2000; 2009; Grand and Berg, 1948; Nelson, 1976; Milner, 1963; Monchi et al. 2001; Stuss et al., 2000). While performing the WCST (the version of Grand and Berg [1948] with Milner's [1963] corrections), an individual is required to match test cards (128 in total) with four reference cards according to three possible rules of classification: color (red, green, blue and yellow), shape (circle, star, scare and cross), or number of stimuli (one, two, three or four) on the cards. No rules or explanations are given to the individual beforehand (or during the test). After each match, feedback is provided enabling the participant to figure out the correct rule. Negative feedback implies that the rule was incorrect and that the individual has to try another one, while positive feedback means that the rule chosen by the participant was the right one. After ten correct matches according to a particular rule, the latter is changed without notice, and the participant must shift to a new mode of classification. The WCST is not timed and sorting continues until all cards are sorted or a maximum of six correct sorting rules have been reached.

In 2001, Monchi et al. developed as part of an fMRI study an electronic version of the WCST (Figure 1.2.) allowing for set-shifting to be separated into two groups of events, one occurring at the point of receiving negative feedback and implying that the current criteria must be changed (monitoring and planning of the shift), and the other occurring while the action is performed under the new criteria (action/execution of the shift). This electronic WCST is identical to the classical one, except for the fact that, first, the classification rule changes after six correct matches instead of ten, second, the participants are instructed of the three possible rules of classification beforehand, and third, a white or black screen (instead of a neuroscientist or clinician) instructs the participant if the matching is correct or false, respectively. Later in this chapter, we will review another task inspired from the WCST that allows investigating both "set-shifting" and "language processing".

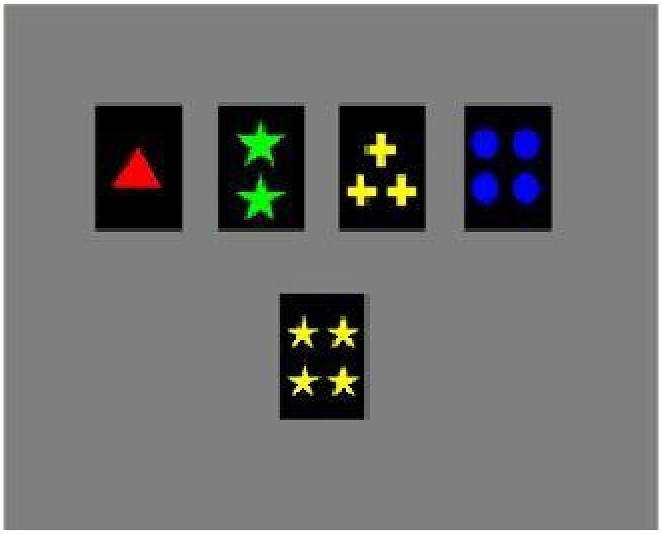

Figure 1.2. Electronic version of the Wisconsin Card Sorting Test (WCST) developed by Monchi et al. (2001)

1.2.Language processing

Language processing (or language abilities) can be broadly defined as the way human beings use words to communicate ideas and how such communications are performed and processed. Furthermore, understanding how the brain processes language is not an easy task, since language itself is a very complex concept comprising several elements. Indeed, one can study sounds (phonetics), how these sounds are organized and make up words (phonology), how words are structured (morphology), how multiple words are combined together (syntax) and how meaning is encoded (semantics). Additionally, language can be produced and understood orally (speech and speech comprehension) or in written form (writing and reading). Therefore, the diversity of these language components which interact with each other allow for many types of experiments, models and theories to co-exist within the broad umbrella that is the study of language processing.

Indeed, one could focus on syntax using a theoretical perspective for example, as did the philosopher and linguist Noam Chomsky. In his book *Syntactic Structures* (published in 1957), he developed a formal theory of syntax called “transformational generative grammar” which implies that any possible sentence is constructed using a given finite set of rules. Therefore, he postulates that this finite set of rules can “generate” a potentially infinite number of sentences in any human language. Furthermore, he has also been a proponent of the idea that much of this grammatical knowledge is innate (Universal Grammar), implying that children only need to learn some limited features of their native language in order to master it. According to Chomsky, the fact that children successfully acquire their native language in so little time is the strongest evidence for the existence of a Universal Grammar (Chomsky, 1965).

The idea of a language-specific inborn capability is far from being widely accepted however. Indeed, several linguists and neurolinguists actually argue that language emerges from usage in social contexts, using learning mechanisms that are a part of a "general-cognitive" learning process (Bates et al., 1999; Powers and Turk, 1989; Tomasello, 2008). Among the proponents of an empiric language development process imbedded in social interactions are Bloom and Lahey. In 1978 and 1988, they developed a model which identifies the normal developmental sequence of utterances that a child learning a language comprehends and expresses. In most children, they say, comprehension develops before expression: most children are likely to comprehend utterances much more complex than the utterances they are able to spontaneously express at the same time. As part of their model, they also define the elements of language through the intersection of "Form, Content, and Use". The "Form" refers to several entities including "phonetics", "phonology", and "syntax"; the "Content" refers to the meaning of the words (semantics) or word combinations; while the "Use" refers to "pragmatics" and "prosody" (Figure 1.3.). They propose that, if each skill area (or element of language) is not well developed, communication learning will not be a straightforward process because all these areas interact with each other (Bloom and Lahey, 1978; Lahey, 1988). In other words, through social interactions, children develop little by little all the language skills (elements) they need to comprehend and express utterances that, with time, become more and more complex.

The focus of this thesis does not lie in the study of syntax, language development, or even oral comprehension and expression. However, we feel that a brief opening into the theories of Chomsky as well as the models of Bloom and Lahey is useful for the reader to grasp how vast and diverse the study of language can be. Furthermore, recent definitions of language processing tend to rely on several ideas expressed in previous theories and models. For example, recently, Hauser et al. (2002) proposed a definition in which language processing can be considered as involving multiple cognitive processes allowing for the processing of a set of grammatical rules which interplays with phonology (the speech sound processing system) and semantics (the meaning processing system). Those three systems, themselves composed of several subsystems, enable us to create and understand a potentially infinite number of sentences by using various combinations of words. Clearly one can see in that definition both the idea of a generative grammar (first postulated by Chomsky) and how important is the interaction between different language elements (as argued by several, among whom Bloom and Lahey).

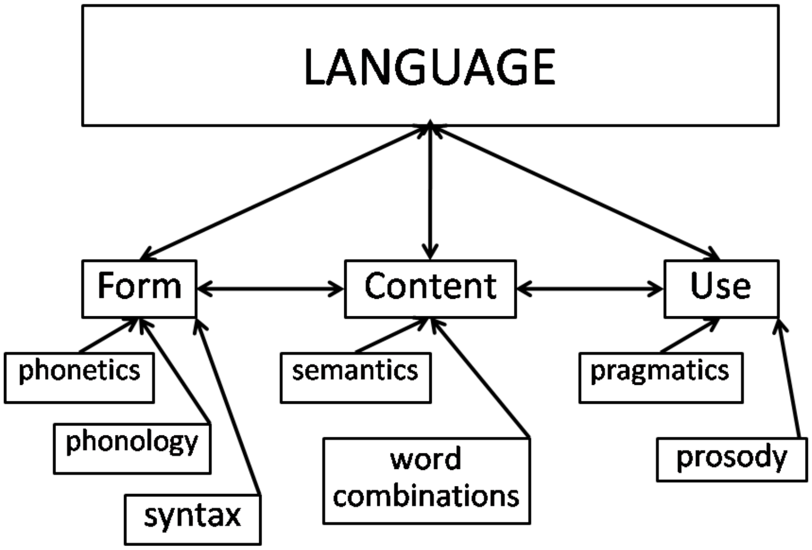

Figure 1.3. Bloom and Lahey's (1978) model on Language. *Form*, *Content*, and *Use* interact with each other to give rise to *Language*. The *Form* refers to several entities including *phonetics*, *phonology*, and *syntax*; the *Content* refers to the *semantics* or *word combinations*; while the *Use* refers to *pragmatics* and *prosody*.

The definition mentioned above appears to consider "phonology" and "semantics" as cornerstones of language abilities. Given the fact that our own studies explore precisely and exclusively those same two language attributes, we should briefly elaborate on them. Nikolai Trubetzkoy (a Russian linguist and historian) offered in 1939 one of the first definitions of phonology, that is "the study of sound pertaining to the system of language." In 1998, Lass, another linguist, referred to phonology as the discipline "concerned with the function, behavior and organization of sounds as linguistic items." Another recent definition (Clark et al., 2007) considers it as the systematic use of sound to encode meaning in any spoken language (or the field of linguistics studying this use). Therefore, phonological processing can be viewed, based on the previous explanations, as the cognitive function that processes sounds baring language significance. Those sounds can be bestowed orally or in written form. In our experiments presented in Chapters 5 and 6, we use a cognitive task relying on visual stimuli (written words). Therefore, for all instances and purposes, when we discuss about "phonological processing" in this thesis, we refer to the very narrow scope of sound processing during word reading (implying a conversion from orthography to phonology). Moreover, the same rational applies when we refer to "semantics". Indeed, in our experiments, "semantic processing" implies any word processing (such as manipulation, comparison or selection) during reading according to the semantic fields of the words in question. In linguistics, a semantic field is a set of words grouped by meaning referring to a specific subject (Jackson and Amvela, 2000).

In the next section of this chapter, we will review the cognitive task that we used in our own experiments (Chapters 5 and 6). That task allows for the study of both semantic and phonological processing as well as set-shifting. This being said, we should also point out that even if we have considered, and will continue to do so, language as a separate entity from executive function, one should be aware that in reality (and that includes during the performance of language processing tasks) those cognitive domains are often intimately linked and hard to separate since working memory is often needed during the manipulation of language elements (Martin and Saffran, 1997). Indeed, phonological working memory, is hypothesized to be a significant contributor to on-line language processing and reading comprehension (Archilbald and Gathercole, 2006, Leonard et al., 2007, Montgomery and Windsor, 2007). Furthermore, working memory has also been extensively associated with grammatical processing (Cook et al. 2006) as well as word-matching according to semantic fields as it is the case in our experiments (Simard et al. 2011).

1.3.The Wisconsin Word Sorting Task

The Wisconsin Word Sorting Task (WWST) was developed by Simard et al. (2011) as a lexical analog of the WCST used by Monchi et al. (2001) (Figure 1.4.). In the WWST, French words replace the usual pictogram cards while the two tasks maintain a strict correspondence regarding the stimuli, the rules, and the number of exemplars. Specifically, the three classification rules of the WCST are replaced by three lexical ones: one semantic and two phonological, namely syllable onset and syllable rhyme. That feature allows using the WWST not only to study “set-shifting” (as it is the case for the WCST), but to explore semantic and phonological processing as well.

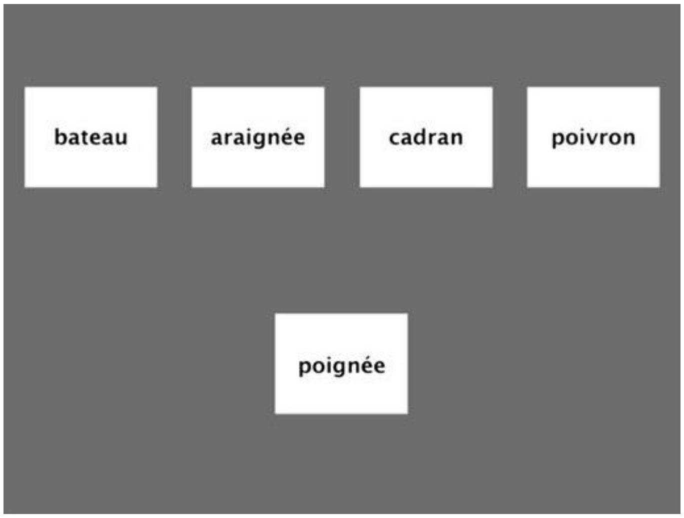

Figure 1.4. Electronic version of the Wisconsin Word Sorting Task (WWST) developed by Simard et al. (2011).

Throughout the task, four fixed reference words (bateau [ship], araignée [spider], cadran [clock], and poivron [pepper]) are presented in a row at the top of a screen, whereas a test word is shown in the middle of the screen below the reference row. Each trial, participants have to match the test word with one of the reference words based on one of the three classification rules (semantic categorization, syllable rhyme, or syllable onset). Every participant is told in advance what the three possible rules are, but he/she has to find the proper one for each trial based on the feedback he/she received following the previous selection. A change in the screen brightness indicates to the individual whether the answer is correct (bright screen) or not (dark screen). After six consecutive correct trials, the rule changes without warning and the participant has to discover the new appropriate criteria.

As for the WCST, there are four matching possibilities for each one of the categories in the WWST: four semantic categories (transportation, animals, objects, and vegetables), four phonological onset syllables (‘‘ba,’’ ‘‘a,’’ ‘‘ca,’’ and ‘‘poi’’), and four phonological rhyme syllables (‘‘au,’’ ‘‘é,’’ ‘‘an,’’ and ‘‘on’’). All the words in the task have been carefully chosen so they could have the same phonological syllabic structure according to the French lexical database ‘‘lexique 3’’ (New et al. 2004) and be considered concrete according to the concreteness scale of Bonin et al. (2003).

The same periods that were identified for the electronic WCST (Monchi et al. 2001) are present in the WWST. Therefore, each trial contains two types of periods: a matching period and a feedback period. The matching period starts with the presentation of a new test word and continues until reference word selection. The length of this period varies from trial to trial depending on the candidate’s response time. Matching is then followed by a feedback period, which lasts 2.3s and starts as soon as a selection is performed. This period ends with the presentation of the next test word on the screen initiating a new trial. A control condition in which the test word is the same as one of the four reference words has also been added (for brain activity contrast purposes in the fMRI studies). That gives rise to two other periods: control feedback (in which the brightness of the screen does not change) and control matching.

From a neuroanatomical perspective, the WWST offers the possibility (with help of functional neuroimaging) to investigate “set-shifting” by analyzing brain activity when, first, one is instructed through negative feedback to change the rule of classification (monitoring and planning of the set-shift), and, second, one is asked to select a reference word under the new criteria during the matching period following the negative feedback (action/execution of the set-shift). The WWST also permits to study “semantic” and “phonological” processing by analyzing brain activity during the matching periods following positive feedbacks. Indeed, when one matches two words according to the “semantics categorisation rule”, that individual’s brain is most probably performing semantic processing, and the same concept stands for the “phonological rules” and their corresponding matching periods.

1.4.Conclusion

As we saw, executive function and language processing are complex mental entities relying on several other processes (often interacting). This thesis will therefore address only some elements of those two cognitive domains: “working memory” and “set-shifting” for executive function, and “semantics” and “phonology” for language processing (as previously defined). All of those processes can be investigated using the WWST (a lexical analogue of the WCST). In Chapters 5 and 6, we will present two fMRI studies that used the WWST to study the effects of normal aging on “set-shifting” and “language” (semantics and phonology), respectively. In the meanwhile, the next chapter will review the underlying neurobiology of those same cognitive domains.

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CHAPTER 2

The Cortex, the Basal Ganglia and Cognition

CHAPTER 2

The Cortex, the Basal Ganglia and cognition

"He who joyfully marches to music in rank and file has already earned my contempt. He has been given a large brain by mistake, since for him the spinal cord would suffice." Those words beautifully bestowed by Albert Einstein remind us of the connection between that organ commonly known as the brain and the conscious act of "thinking" or, if you prefer, the link between the cerebrum and cognition. In the previous chapter, we have explored two cognitive domains, namely executive function and language processing. In this chapter, we will look at the main structures of the cerebral cortex and the basal ganglia (BG) as well as their contribution in executive and language processing.

2.1. Neuroanatomical concepts and structure

The human brain is a multipart organ that changes throughout one's life influenced by both endogenous (e.i. genetics) and exogenous (e.i. environment) factors. Here is an introduction to the micro and macroscopic anatomy of the brain. The cerebrum, as the rest of the nervous system, is composed of nerve cells called neurons and support cells named glial cells. Neurons are primarily responsible for signalling in the nervous system, but glial cells contribute as well. Neuronal signalling is a very complex event which will be briefly reviewed in this section.

Most neurons are composed of a cell body (which contains the nucleus – genetic material), several dendrites (short processes which receive most inputs of the cell) and axons (long processes which carry most outputs) (Figure 2.1.). Communication between neurons usually occurs at specific regions called synapses. Most synapses carry information from the axon of one neuron to the dendrite of another; however, axo-axonic and dendro-dendritic synapses also exist. At chemical synapses (the most common type), chemical neurotransmitters are released from presynaptic terminals of one neuron and bind to neurotransmitters receptors of a postsynaptic neuron. This gives rise to either excitation or inhibition of the latter cell. Communication can also take place at electrical synapses (less common) at which direct electrical coupling between neurons occurs (Purves, 2008).

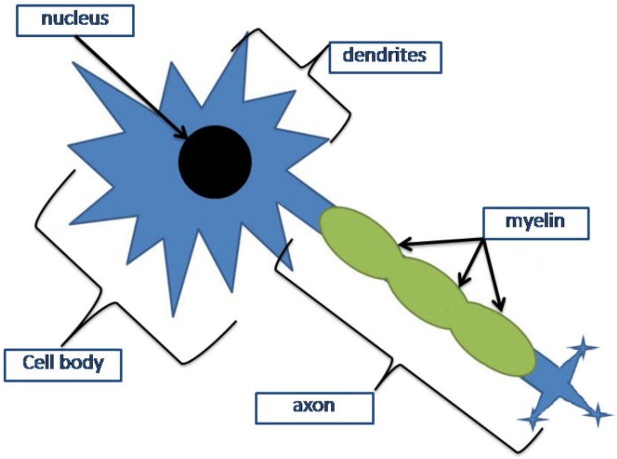

Figure 2.1. Representation of a neuron composed a cell body, nucleus, several dendrites and a myelinated axon.

When a neuron is excited by synaptic input combined with sufficient endogenous transmembrane currents, an action potential (transient voltage change) arises lasting about 1 millisecond. Action potentials usually travel at 60 meters per second from a dendritic end of a neuron along its axon up until a presynaptic terminal where it triggers the release of neurotransmitters. At this speed, one would take more or less 1 hour to go from Montreal to Quebec City (or vice versa). Axons also tend to be insulated by a myelin sheath (provided by glial cells) which speeds the rate of action potential conduction. As previously stated, once neurotransmitters are released they can either electrically excite or inhibit another neuron. Those electrical events are respectively called excitatory postsynaptic potentials and inhibitory postsynaptic potentials. Neurotransmitters have another function called neuromodulation which generally occurs over slower time scales. It consists in many cellular mechanisms involving signalling cascades that regulate synaptic transmission, neuronal growth and other functions (Blumenfeld, 2010). There are several neurotransmitters, but in the cerebrum, glutamate is the most common excitatory one and gamma-aminobutyric acid (GABA), the most common inhibitory one (Cooper, 1996).

Areas of the nervous system consisting mainly of myelinated axons make up the white matter, and areas composed mostly of cell bodies are called the grey matter. Most synaptic communications occur in the gray matter, while signals are primarily transmitted in the white matter. In the cerebrum, the gray matter makes up the outer layer of the brain known as the cerebral cortex. Gray matter is also found in large cluster of cells known as nuclei that are located within the brain, one of those being the basal ganglia (Purves, 2008). White matter pathways are called tracts or bundles. Generally, tracts carrying signals towards a structure are called afferent, while those carrying signals away from a structure are called efferent (Blumenfeld, 2010).

The cerebral cortex has numerous infoldments called sulci or fissure, as well as bumps, called gyri, that rise between the sulci. Some sulci and gyri have specific names as we will see. The cortex is 1 to 4.5 millimetres thick (Fischl and Dale, 2000) and, due to its numerous crevices, has a surface of nearly two thousand square meters (Mountcastle, 1997) which is close to that of a football field. The cortex is divided in two hemispheres (right and left) separated in the midline by the interhemispheric fissure (or longitudinal fissure). Each hemisphere can itself be separated in four major lobes known as the frontal, the temporal, the parietal and the occipital lobe (Figure 2.2.). The frontal lobes are in the front of the brain and extend back to the central sulcus of Rolando, they are also limited inferiorly and laterally by the Sylvian fissure. They include the primary motor cortex (PMC) which lies in the precentral gyrus and controls movement of the opposite side with significant contributions from the BG. They also comprise the prefrontal cortex (PFC) which plays a primordial role in cognition (especially, but not exclusively, in executive processing). Both the structure of the frontal lobes and the BG as well as their connections will be explored more extensively. The temporal lobes are separated superiorly from the frontal and parietal lobes by the Sylvian fissure, but have no sharp delimitation from the parietal and occipital lobes posteriorly. They include the transverse gyri of Heshi which makes up the primary auditory cortex. The parietal lobes are delimited anteriorly by the central sulcus of Rolando and posteriorly, from a medial aspect, by the parieto-occipital sulcus; laterally, they have no sharp demarcation from the temporal and occipital lobes. They contain, in the postcentral gyrus, the primary somatosensory cortex (PSC) involved in sensation from the opposite side of the body. Finally, the occipital lobes are located in the back of the brain and include the primary visual cortex. Furthermore, in addition to those four major lobes, another region of cerebral cortex lies within the depths of the Sylvian fissure: the insular cortex (Blumenfeld, 2010).

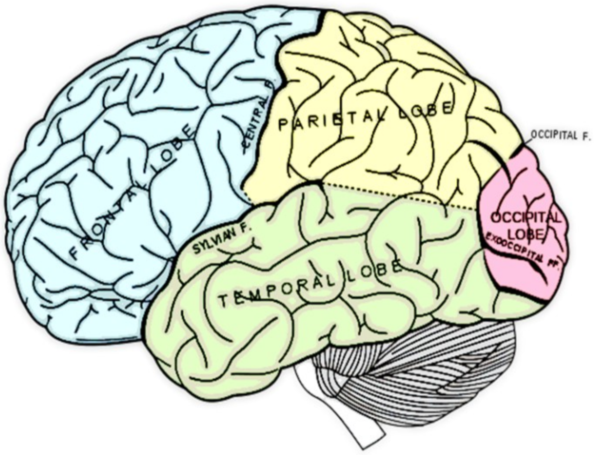

Figure 2.2. Lateral view of the cortex with its four lobes and main fissures.

There are several classification schemes for different regions of the cerebral cortex based on microscopic appearance (types of cells, different cellular densities, etc.) and function. Among those, is the one published by a German neurologist named Korbinian Brodmann in 1909. Based on microscopic studies, he divided the cortex in 52 cytoarchitectonic areas (Martin, 1996). Even if this reference is not absolute and has its limits, it turns out that a lot of the identified areas correlate reasonably well with functional areas of the cortex, that explains why Brodmann's nomenclature is still very often used today, including in this theses (Figure 2.3.).

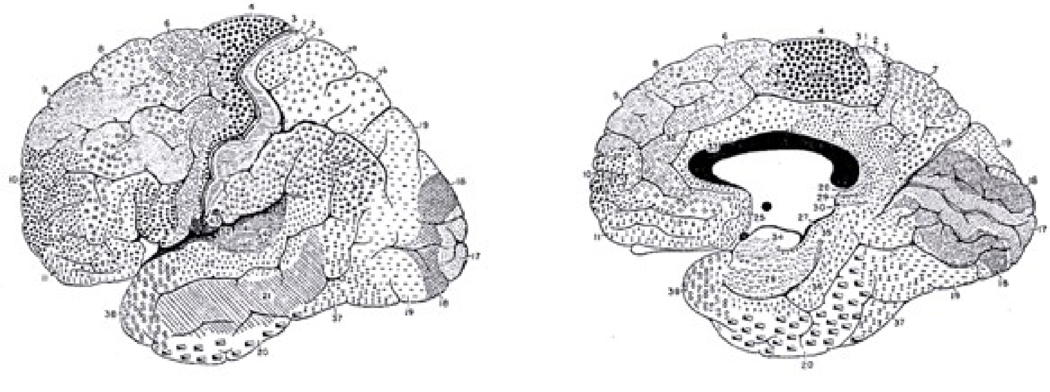

Figure 2.3. Lateral and median view of the Cortex showing several cytoarchitectonic areas (adapted from Brodmann, 1909).

2.1.1. Frontal lobes

The frontal lobes are, as we previously stated, significant players when it comes to motor control and cognition (especially executive function). In this section we will explore the different regions that constitute the anterior cortex and briefly allude to their main functions.

We shall begin by the PMC (Brodmann area 4). The PMC controls movement of the opposite side of the body and, as it is the case for the PSC, is roughly topographically organized. This means that adjacent regions of the cortex correspond to adjacent areas of the body; for example, regions representing the foot are adjacent to regions representing the leg. These somatotopic maps are called the motor (or sensory) homunculus and were first developed by the American-born Canadian neurosurgeon Wilner Peinfield (Penfield and Rasmussen, 1950). The PMC also seems to play a role in the preparation of movement as Evarts (1981) pointed out after noticing, during neuronal recording in monkeys, that some Brodmann area 4 neurons were activated before actual movements were performed. The area even appears to be recruited in cognition, namely mental rotation allowing for movement reorganisation (Berthoz, 2003).

Another region is the premotor cortex (preMC) (Brodmann area 6) that can be further divided into the lateral preMCand the supplementary motor cortex (SMC). Both the lateral preMC and the SMC appear to be particularly important for movement preparation and initiation. Indeed, studies performed on monkeys showed that the lateral preMC was involved in the selection of movements triggered by external stimuli (Jeannerod et al., 1995; Mitz et al., 1991). In humans, lesions in the lateral preMC (especially in the left hemisphere) are also known to induce ideomotor apraxia (Gross and Grossman, 2008), that is the inability to carry out common, familiar actions on command. The SMC, on the other hand, appears to play a role in the selection of internally triggered movements (Thaler and Passingham, 1989) and in the control of movement sequences (Akkal et al, 2002; Picard and Strick, 1996).

The PFC accounts for approximately one quarter to one third of the entire cortex in humans (Zelazo and Muller, 2011) and is located anterior the preMC. It is responsible (with other brain regions) for attention regulation, organizing goal-directed behaviour as well as inhibiting and engaging thoughts and actions (Arnsten and Li, 2005). Specific executive processes appear to be linked with specific subregions of the PFC. The most anterior of these regions is known as the Frontopolar Cortex (FPC) (Brodmann area 10). Its specific role is not fully understood, but it has been hypothesized to be primarily engaged in the response to and identification of internal states as well as introspective aspects of emotional processing (Ramnani and Owen, 2004). It has also been postulated that the FPC plays an important role in processing of "cognitive branching", that is enabling a previously running task to be maintained in a pending state (for subsequent retrieval and execution) upon completion of the ongoing task (Koechlin and Hyafil, 2007).

The ventrolateral prefrontal cortex (VLPFC) (Brodmann areas 45, 47 as well as 47/12) and the posterior prefrontal cortex (PPFC) (Brodmann areas 8 and posterior 44) have been associated with several executive functions (Petrides, 2005). Indeed the VLPFC has been linked to rule acquisition and rule switching, while the PPFC has been associated with attentional set shifting and the execution of set-shifts (Monchi et al., 2001; Simard et al., 2011). These regions also seem associated with inhibition of competing responses (Liddle et al., 2001; Spielberg et al., 2011) and working memory involved in the organisation of upcoming actions (Monchi et al., 2001).

The dorsolateral prefrontal cortex (DLPFC) (Brodmann areas 9 and 46) has been identified as a very important structure for executive processing. It appears to play a role in cognitive set shifting, goal-driven behaviours including planning and response selection (Miller, 2000) as well as spatial and non-spatial monitoring within working memory (Petrides, 2005). Even functional studies in infants using delayed response tasks support the relationship between the DLPFC and working memory. Indeed, a near-infrared spectroscopy study showed increased DLPFC blood flow in children who accurately searched for objects during a delayed response task compared to those who did not (Marcovitch and Zelazo, 2009).

The orbitofrontal cortex (OFC) (Brodmann areas 11 and orbital 47) has been linked with learning (Robbins and Roberts, 2007), emotional regulation (Cummings, 1993), self-awareness (Baron-Cohen et al., 1994), cognitive flexibility (Murray et al., 2007), motivation (Zelazo and Muller, 2011), cognitive and behavioural inhibition, decision making, and working memory (Elderkin-Thompson et al., 2008). It seems principally involved in reversal learning: functional studies have shown its participation during reward-associated pair learning and the concurrent ability to learn the reverse association linked to the pair (Robbins and Roberts, 2007). Damage to the OFC can also lead to euphoria and manic behaviour (Fuster, 1989). One of the most well known reported cases of presumed OFC damage and personality change is the one of Phineas Gage. In 1885, this American railroad construction foreman survived an accident in which a large iron rod was driven completely through his head destroying much of his brain's left frontal lobe and allegedly leading to a drastic and significant personality and behaviour change. Damasio and colleagues (1994) have re-examined the pictures of Gage's cranium and established that the rod had not only destroyed part the left OFC, but inflicted significant lesions in the FPC as well as the anterior cingulate cortex (ACC) (Brodmann area 32). The ACC is part of the limbic system (involved in emotional regulation) which is not going to be extensively explored in this thesis. However, it should be noted that the limbic system is closely connected with several regions of the PFC, especially the OFC (Zelazo and Muller, 2011). More particularly, the ACC appears to hold a central role in executive facets of emotion regulation and attention (Rueda et al., 2005).

As we have seen, the association between the PFC and executive processing appears unquestionable. Nonetheless, the PFC is not the only cortical region linked with cognition. More importantly, several subregions of the PFC are closely connected with each other as well as other cortical and sub-cortical areas (such as the BG) making up functional pathways or loops. Some of those pathways (especially those involved in working memory, set shifting and language) will be extensively explored in future sections.

2.1.2. Basal Ganglia

Grey matter is not exclusive to the cortex. Indeed several subcortical structures (called nuclei) have the same attribute, among which are the BG. In the following section, we will explore the anatomy and substructures of the BG as well as their intrinsic connections and cortex projections (Figure 2.4.).

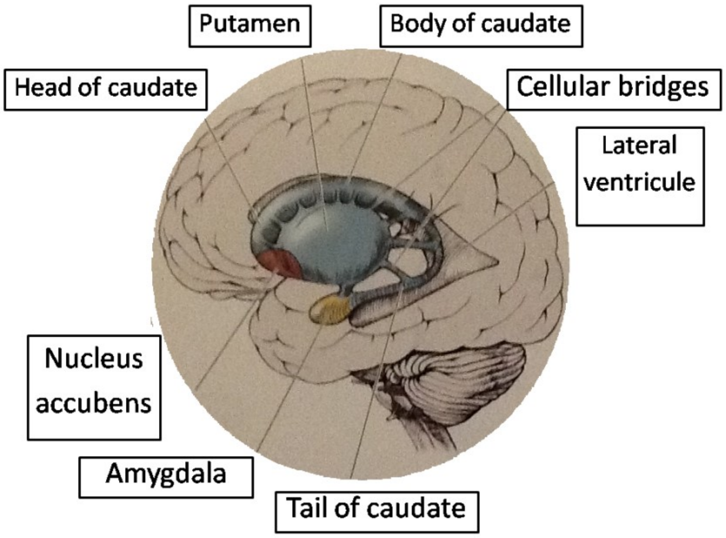

Figure 2.4. Lateral view showing basal ganglia (subthalamic nucleus, substantia nigra and globus pallidus are not shown), amygdale, and lateral ventricle of the left hemisphere (adapted from Blumenfeld, 2010, p.690).

The BG were first identified by the English physician Thomas Willis in 1664, who accessorily is also one of the founding members of the Royal Society of London for Improvement of Natural Knowledge. Willis was intrigued by two features of the ganglia. First, their place: the nuclei occupy a central position in the brain. Second, their tracks: several filaments link the BG to other brain structures, especially the cortex. Both of these characteristics hinted Willis in believing that the BG played probably an important role in the brain (whatever it was). However, that was not sufficient to compete in popularity with the “nobler” cortex, and the BG were consequently almost forgotten until the 20th century (Percheron et al., 1994).

In humans, the BG consists in a group of several substructures composed of the putamen, the caudate nucleus (CN), the internal and the external globus pallida (GPi and GPe), the substantia nigra pars compacta (SNpc) and pars reticula (SNpr) as well as the subthalamic nucleus (STN) (Figure 2.4.). These nuclei are extensively connected to each other as well as with several cortical areas (Alexander et al. 1986; Middleton and Strick, 2000, 2002). The CN and the putamen are embryologically and histologically related, and together they form the striatum (Afifi, 1994a, b).

The CN is a C-shaped structure which head and body form a bulge in the lateral wall of the lateral ventricle, while its tail lies just posteriorly to the amygdale (almond shape nuclei part of the limbic system). It is separated from the putamen by the internal capsule. The putamen, on the other hand, forms the lateral portion of the BG. Just medially to it lie the GPi and GPe. Together, the putamen and the globus pallidus are called the lenticular nucleus. Separated from the GPi by the internal capsule (as it is the case for the putamen and the CN) is the SNpr which contains cells that are very similar to those of the GPi. The dorsal portion of the substantia nigra is known as the SNpc and it contains darkly pigmented dopaminergic neurons explaining its name. Finally, under the thalamus (walnut-shaped nucleus receiving several outputs from the BG) lies a cigar-shaped nucleus known as the STN (Blumenfeld, 2010).

Virtually all inputs to the BG appear to be excitatory in nature (glutamate) and arrive from the cortex via the striatum (CN or putamen) while all outputs leave via the GPi or the SNpr and appear to be inhibitory (GABA). Within the BG there are also a variety of complex inhibitory and excitatory connections mediated by several neurotransmitters (primarily glutamate, dopamine and GABA). Regarding those intrinsic BG connections, there appear to be two predominant pathways from input to output nuclei. One is the direct pathway that travels directly from the striatum to the GPi or the SNpr (inhibitory connection – GABA); while the other is the indirect pathway that goes first from the striatum to the GPe (inhibitory connection – GABA), then the STN (inhibitory connection – GABA), before finally reaching the Gpi or the SNpr (excitatory connection – glutamate). The net effect of the direct pathway is excitation of the thalamus (which in turns excites the cortex), while the effect of the indirect pathway is inhibition of the thalamus (which therefore inhibits the cortex) (Blumendeld, 2010) (Figure 2.5.).

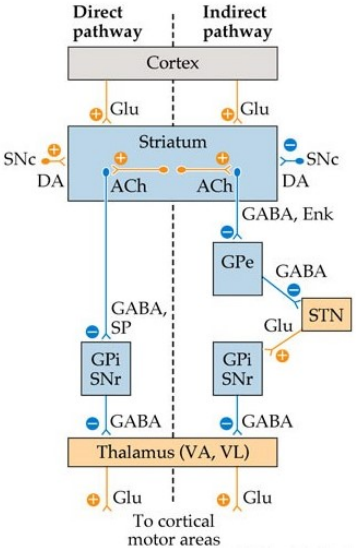

Figure 2.5. Circuit diagram showing Basal Ganglia internal connections – direct and indirect pathways (adapted from Blumenfeld, 2010, p.700). Ach: acetylcholine; DA: dopamine; Glu: glutamate; Enk: enkaphalin; SNc: substantia nigra pars compacta; SNr: substantia nigra pars reticula; GPe: globus pallidus pars externa; GPi: globus pallidus pars interna; STN: subthalamic nucleus; VL: ventral lateral nucleus; VA: ventral anterior nucleus.

Furthermore, there seems to be several parallel pathways in the BG for different functions. Those were postulated by Alexander and colleagues in 1986 and consisted in the existence of five fronto-striatal loops relying on different regions of the BG, thalamus and frontal lobes. Each of those loops or channels was believed to be independent of each other and to assume a specific role: one motor loop involving the SMC and the putamen, one oculomotor loop involving the frontal eye fields and the CN, two cognitive loops involving the PFC (DLPFC and OFC) and the CN, as well as one limbic loop involving the ACC and the ventral striatum (including the nucleus accumbens). Since then, some adjustments have been made to this "parallel pathway model" in order to include other cortical, subcortical and thalamic regions, but the overall hypothesis stands (Postuma and Dagher, 2006). Among those adjustments, one should mention the work of Middleton and Strick (2000, 2002) who found other cortico-striatal loops involving the inferior temporal cortex and the posterior parietal cortex. Nonetheless, the putamen continues to be linked primarily with motor function since most its projections come from the PMC, the SMC and the preMC, while the CN remains more extensively associated with cognition receiving inputs from the lateral PFC and the OFC (Middleton and Strick, 2000).

Now that we have established that the PFC and the BG are extensively connected to each other through fronto-striatal loops, and that those loops play important roles in cognitive function, we shall explore more in detail some specific cognitive processes and their underlying neurobiology. In other words, we will take a deep look at particular executive functions, namely working memory and set-shifting, as well as language abilities (semantics and phonology) and their related cerebral pathways.

2.2. Executive functionand cerebral structures

2.2.1. Working memory

Working memory is defined as the capacity to keep information online and use it effectively (as we saw in Chapter 1). Consequently, it is most probably at the root of any executive process, as one can difficultly make a plan, take a decision, or solve a problem without previous data. In this section we will therefore explore the underlying neurobiology (from an anatomical perspective) of working memory.

The lateral PFC has accumulated substantial amounts of evidence suggesting that it is a significant player (if not the "most valuable player") in working memory. Indeed, several lesion and electrophysiological recording experiments in animals as well as frontal excision reports in patients and functional neuroimaging studies in humans have shown its implication in actively assessing and monitoring information (e.g. Courtney et al., 1996; Monchi et al., 2001; Owen et al., 1990,1996a; Petrides and Milner, 1982; Petrides et al., 1993; Simard et al., 2011; for review see Petrides, 2005). Of course, other cortical regions such as the FPC (Koechlin and Hyafil, 2007) and the posterior parietal cortex (Zhou et al., 2012) are also often recruited in working memory tasks, but not nearly to the same extent. For this reason (and in the interest of time), the remaining of the section will therefore focus exclusively on the lateral PFC.

The lateral PFC can be divided in two subregions: the VLPFC and the DLPFC. In non-human primate brains, the VLPFC occupies the inferior frontal convexity of the sulcus principalis and is constituted of areas 47/12, 45 as well as the ventral portion of area 46 (Petrides and Pandya, 2002), while in the human brain, it mainly occupies the inferior frontal gyrus and is composed largely of areas 47, 47/12 and 45 (Petrides, 2005). In terms of connections, it has extensive projections with the inferotemporal cortex (Kuypers et al., 1965;

Barbas, 1988; Ungerleider et al.,1989) and the posterior parietal cortex (Petrides and Pandya, 1984; Schwartz and Goldman-Rakic, 1984; Cavada and Goldman-Rakic, 1989) in monkeys. The DLPFC, on the other hand, lies within and around the banks of the sulcus principalis and the adjacent cortical areas in monkeys, while it occupies mainly the middle part of the superior and middle gyri in human cerebrums (Petrides, 2005). In both cases, it is primarily constituted of areas 9 and 46, and connects extensively with the VLPFC (Barbas and Pandya, 1989; Watanabe-Sawaguchi et al., 1991) and the medial temporal cortex (Adey and Meyer, 1952; Goldman-Rakic et al., 1984). These differences in terms of connectivity and cytoarchitecture led to the emergence of essentially two competing hypotheses regarding the possibility of distinct functions for each lateral subregion.

One hypothesis, known as the “modality-specific” or “domain-specific” model proposed by Goldman-Rakic (1995), states that working memory processes are organized according to the modality of information being processed, that is the DLPFC being principally concerned with memory for spatial material, while the VLPFC deals primarily with non-spatial information (Figure 2.6.). The other hypothesis proposed by Petrides (1995) and known as the “process-specific” model argues, on the other hand, that working memory processes are organized according to the nature of the processingneeded rather than the modality of information. More specifically, the VLPFC is primarily involved with conscious, explicit data retrieval from posterior cortical regions, while the DLPFC is recruited only when active manipulation and monitoring of information within working memory is required (regardless of the modality) (Figure 2.6.).

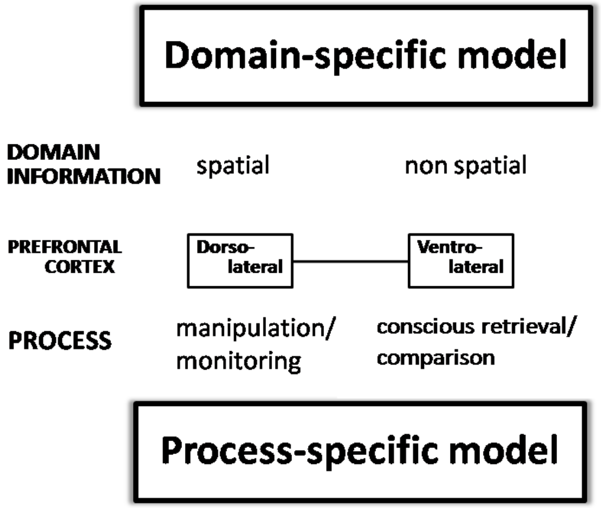

Figure 2.6. Diagram comparing the *Domain-specific model* developed byGoldman-Rakic (1995) and the *Process-specific model* developed by Petrides (1995).

The "domain-specific" model has some appeal given the fact that, for non-human primates, in posterior cortical regions visual information appears to be organized into two anatomically distinct pathways, a "dorsal stream" specialized for identifying spatial locations (the occipitoparietal pathway), and a "ventral stream" specialized for dealing with object features (the occipitotemporal pathway) (Ungerleider and Mishkin, 1982). Furthermore, in humans, clinical data from patients with lesions in the temporal and parietal areas correlate with the primate electrophysiological studies from which the model was derived (Damasio and Damasio, 1989). It is therefore reasonable to wonder if the frontal cortex has a similar organisation.

Funahashi et al. (1989, 1990) recorded from single neurons in the lateral PFC during a delayed response task that required monkeys to make deferred eye movements towards or away from a cued location. Their findings showed that neurons in this region appeared to spatially code the location of an object in a manner analogous to the visual receptive fields of visual cortical neurons. Even more interestingly, Wilson et al. (1993) recorded from some VLPFC neurons (area 47/12) in monkeys during an oculomotor delayed response task in which responses were guided by remembered locations or patterns. Their results showed that neurons in and around area 47/12 were selectively recruited when responses according the “pattern stimulus” were required, but not (or to a lesser extent) when responses were triggered by the “spatial stimulus”. It is therefore based on those studies and on the way visual information appears to be processed in the posterior lobes that Goldman-Rakic (1995) has suggested the “domain-specific” model in which the DLPFC and the VLPFC support different informational domains (rather than processes).

The “process-specific” model proposed by Petrides (1995, 1996) offers an alternative framework: the lateral PFC is divided according to two levels of working memory processing. At the first level, the ventrolateral area is recruited for explicit and conscious retrieval and organization of information from posterior association regions as well as for active comparisons between data held in short-term memory. While at the second level of processing, the dorsolateral area is recruited only when active data manipulation and monitoring is required. Based on this model, it is therefore the nature of the processing rather than the informational modality that explains the difference between the DLPFC and the VLPFC. This hypothesis is also largely based on non-human primate studies. Indeed, it has been shown that lesions in the VLPFC (areas 45 and 47/12) in monkeys can produce impaired performance is spatial and nonspatial versions of delayed alternation tasks (Mishkin et al., 1969). Furthermore, damage to the DLPFC (area 9) also seems to impair performance on certain nonspatial working memory tasks, those requiring active monitoring (Petrides, 1991, 1995). Therefore, these findings suggest that it is the mnemonic demands of the tasks rather than the modality of the information being processed that determine whether or not a specific region will be recruited.

Up until the twenty-first century, not many functional imaging studies had tried to specifically address which of the two models was the most accurate in humans. Among those that had, however, we should mention the ones from McCarthy et al. (1996) and Backer et al. (1996) that found that both spatial and nonspatial modalities activated similar DLPFC areas. Later, an fMRI study by Stern et al. (2000) used two nonspatial visual working memory tasks to investigate the issue. In the first task, participants had to view a sequence of three pattern stimuli, and then identify which one of three simultaneously presented stimuli was the one that had not been shown in the previous array. While in the second task, participants had to observe an identical sequence of three selected pattern stimuli and then, they had to select those same stimuli in the order of presentation. Bilateral DLPFC and right VLPFC activity was recorded in both memory tasks. However, the first task (believed to have higher monitoring requirements) yielded significantly greater signal intensity changes in the DLPFC (area 9/46). Interestingly, a review of functional imaging studies on working memory published in the same year (D'Esposito et al., 2000) also concluded after reviewing the evidence that the lateral PFC is anatomically organized according to types of cognitive processing (and not information domain). Finally, since then, several other fMRI studies including those using an electronic version of the WCST (Monchi et al., 2001) and the WWST (Simard et al., 2011) have shown the involvement of both the DLPFC and the VLPFC in nonspatial working memory processing (those studies will be reviewed in detail in the next section).

In summary, the functional neuroimaging evidence seems to favour the "process-specific" model over the "domain-specific" one. However, one could easily imagine (and for scientists, as Einstein pointed out, "imagination is more important than knowledge") that both realities coexist (Owen, 1997). Indeed, nothing in the "process-specific" hypothesis excludes the possibility that within the DLPFC and the VLPFC, there is some separation according to the modality of information. Therefore, at larger scales, the lateral PFC would be divided according to the type of working memory process it performs, while at a smaller scale (within each sub-region) the division could still be "domain-specific". Nonetheless, far from the debate lies a consensus: the lateral PFC plays a primordial role in working memory processing. We will now extend our discussion to another and more complex executive function, namely set-shifting, and to other PFC areas as well as the BG.

2.2.2 Set-Shifting

Set-shifting can be defined as the ability to shift between one attentional set or rule and another (as we saw in Chapter 1). This ability allows individuals to adapt to different situations and relies extensively on working memory. Indeed, in order to switch from one attentional set to another, individuals are required to retrieve the sets, keep them in an online form, compare them and finally manipulate them. In this section, we will explore the underlying neurobiology (from an anatomical perspective) of set-shifting.

Since 1948, the WCST has been widely used to study set-shifting (e.g. Grant and Berg, 1948; Milner, 1963; Nelson, 1976; Stuss et al., 2000, Monchi et al., 2001).While performing the task, an individual is required to match test cards with reference cards according to three possible rules of classification: color, shape, or number of stimuli on the cards. The correct rule is not given to the participant and he/she has to find it by trial and error. After a fixed number of correct matches according to a particular rule, the latter is changed without notice, and the participant must once again find the new criteria of classification (refer to Chapter 1 for more details).

In 2001, Monchi et al. developed an electronic version of the task (refer to Chapter 1 for more details) allowing for set-shifting to be separated into two groups of events, one occurring at the point of receiving negative feedback and implying that the current set must be changed (planning of the set-shift), and the other occurring while the action is performed under the new set (execution of the set-shift). This electronic version of the WCST was used in an fMRI study performed on eleven participants. The results showed the involvement of the DLPFC (areas 46 and 9/46) during either positive or negative feedback periods (two events believed to require information monitoring in working memory), while the VLPFC (area 47/12) was more extensively recruited during the reception of negative feedback (which presumably requires more active comparison of information than the positive counterpart). Those findings appear therefore to be in agreement the “process-specific” model postulated by Petrides (1995). Furthermore, there was also significantly increased activity in the PPFC during reception of feedback events (negative and positive) and the response after negative feedback period. However, the fact that the PPFC was the only PFC region recruited during the response period suggests an association between that area and specific actions to stimuli. Its involvement in the organisation of upcoming actions has been hypothesised in other works as well (Diamond, 2006). Monchi et al. (2001) also showed significant activity in the BG, more specifically, in the CN during the reception of negative feedback and in the putamen during the response after negative feedback.

The BG had been shown to be involved in cognition way before the year 2001, as we previously mentioned. Indeed, not only had Alexander et al. postulated the existence of two cognitive cortico-striatal loops in 1986, but as early as in 1968, Divac was already showing that anterior lesions in the CN could significantly impair performance during delayed response tasks in cats. Moreover, in 1978, it was postulated that cognitive deficits in neurodegenerative illnesses such as Huntington disease could be due to striatum deterioration (Divac et al. 1978).

Since then, several other studies, including functional imaging ones, have shown the involvement of the striatum in executive processing (e.g. Lewis et al., 2004;Monchi et al. 2001; Nagahama, et al., 2001; Owen et al., 1996b; Rogers et al., 2000). However, by 2006, its exact role in cognition was still somewhat elusive. This is why Monchi et al. (2006) tried to specifically explore striatal involvement in the context of set-shifting. They elaborated a functional imaging study that allowed distinguishing between shifts in classification when the rule is implicitly given by the task from shifts requiring planning. Their results showed that the CN and the putamen were recruited only in conditions in which cognitive planning was required. From those findings, they suggested that the CN plays a role in the planning of a self-generated novel action, while the putamen is involved in its execution.

Based on those experimental studies (Monchi et al., 2001, 2006), Monchi postulated an up-dated version of the "process-specific" modelin which the striatum plays a specific role in planning and carrying through self-generated novel actions (Figure 2.7.). Indeed, in this new model, there are three fronto-striatal loops recruited during set-shifting, one "cognitive loop" involving the VLPFC and the ventral portion of the CN (explicitly required when information is compared and selected so that a novel action can be planned), another "cognitive loop" involving the DLPFC and the dorsal portion of the CN (explicitly required during information monitoring and planning of the novel action), and finally a "motor loop" involving the PPFC and the putamen (explicitly required during the execution of the self-generated novel action). When performing the WCST, one seems to rely on the "cognitive loops" (the VLPFC, the DLPFC and the CN as well as the thalamus) to plan and select a new rule of classification and on the "motor loop" (the PPFC and the putamen) to apply the new selected rule (Monchi et al., 2001).

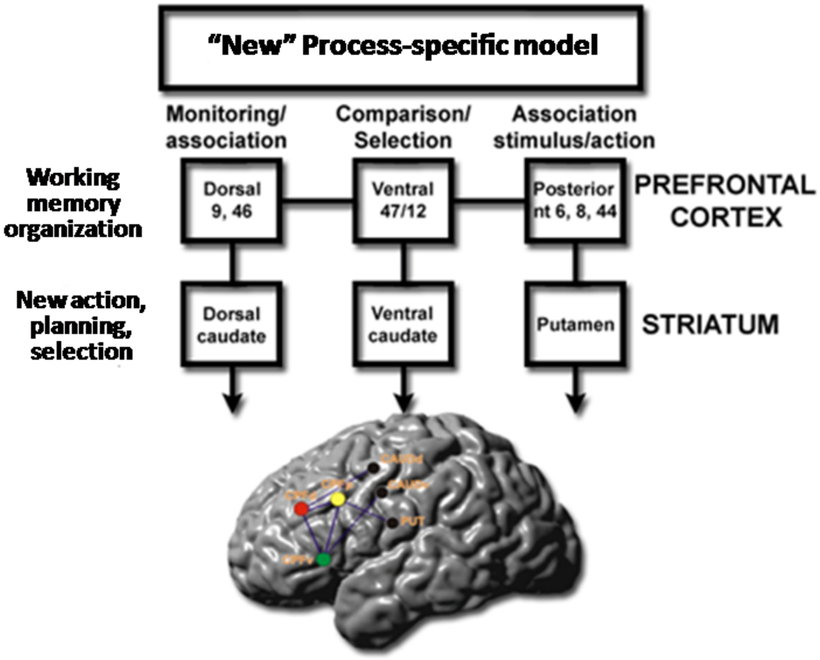

Figure 2.7. Diagram showing the *Process-specific model* of Petrides (1995) up-dated by Monchi (based on findings from Monchi et al., 2001, 2006).

In order to test the validity of the new model beyond purely visual stimuli, Simard et al. (2011) developed a lexical equivalent of the WCST, namely the WWST. In this new test, words (instead of cards) are matched according to semantics, syllable onset or syllable rhyme, the other attributes of the task remain the same as for the original (refer to Chapter 1 for more details). The results of the fMRI study showed thatfourteen young healthy adults recruited cortico-striatal "cognitive loops"(including areas 45 and 47/12 of the VLPFC, area 9/46 of the DLPFC and the CN) during negative feedbacks (planning of a set-shift), and another "motor loop" (including areas 6, 8 and 44 of the PPFC and the putamen) during the matching period following negative feedbacks(execution of a set-shift). Therefore, those findings seem to provide evidence that the functional contributions of the fronto-striatal loops involved in set-shifting are not dependent on the modality of the information to be manipulated but rather on the specific processes required.

In summary, recent functional neuroimaging studies have shown extensive recruitment of fronto-striatal loops during set-shifting. “Cognitive loops” relying on the VLPFC, the DLPFC and the CN appear essential for the planning of a set-shift, while a “motor loop” relying on the PPFC and the putamen seems required for executing the set-shift. Furthermore, these “cognitive” and “motor” loops appear to be involved in self-generated set-shifting actions regardless of the modality of the information being processed. In Chapter 5 we will explore how aging affects those same loops by comparing brain activity (using fMRI) in healthy old individuals to that of young healthy candidates during the performance of the WWST. In the meanwhile, the next section of this chapter will briefly focus on the neurobiology underlying another cognitive domain, namely language processing.

2.3. Language processing and cerebral structures

Several neuropsychological models of language have been elaborated so far, and most probably, many others are yet to come. However, to simplify our discussion (and existence, since spending several hours reading this thesis should not be the primarily goal of anyone valuing their life), let’s mention, once more, as we did in Chapter 1, that when we refer in the body of this work to language processing, we mainly allude to the ensemble of cognitive processes allowing for the interplay between phonology (the speech sound processing system) and semantics (the meaning processing system) during word reading since these are the only language attributes that can be investigated using the WWST. Indeed, all the other aspects of language (including syntax, morphology, pragmatics, etc.) are beyond our scope. Therefore, in this section, we will only focus on the underlying neurobiology (from an anatomical perspective) of phonological and semantic processing during reading.

The association between language and the brain is not new, already by the end of the nineteenth century, Wernicke, Broca and Dax had shown that the two were clearly connected. Most of their work was based on post-mortem studies of individuals with head injuries that had lost the ability to speak (aphasia). At the time, all language processing was associated with the left hemisphere of the cerebrum, and primarily with two of its regions: the Broca’s area (posterior portion of the frontal inferior gyrus, mainly areas 45 [anterior] and 44 [posterior]) responsible for speech production, and the Wernicke’s area (posterior portion of the superior temporal gyrus, mainly Brodmann area 22) responsible for speech comprehension (Kandel et al., 2000; Blumenfeld, 2010). The hegemony of the left hemisphere continued almost unquestioned until the middle of the twentieth century when Eisenson (an American speech scientist) noticed that more "subtle" language impairments could also arise after lesions in the right hemisphere (Eisenson, 1954). Since then, both hemispheres have been associated with language processing (with the left hemisphere continuing to play a more prominent role). Even sub-cortical areas, such as our beloved striatum, have been implicated in several functional imaging studies (e.g. Moro, et al., 2001; Price, et al., 1999; Tettamanti, et al., 2005).

In 2001, Bokde et al. reported in a fMRI study significant functional correlation between the posterior-dorsal inferior frontal gyrus (corresponding approximately to Brodmann area 44) and occipito-temporal regions for orthographic stimuli (i.e., words, pseudo words, and letter strings), but not for false fonts. They also found a strong correlation between the more anterior-ventral regions of the inferior frontal gyrus (roughly Brodmann areas 47 and 45) and occipito-temporal areas for meaningful stimuli (i.e., words), but not for pseudo words, letter strings, and false fonts. No distinction between the different posterior temporal areas was made. Nonetheless, the authors postulated the possibility for two distinct functional pathways: one primarily involved with "phonology" (relying on posterior and frontal dorsal regions such as area 44 which was recruited during all orthographic stimuli that could be converted into sounds) and another, with "semantics" (relying on posterior and frontal ventral regions such as areas 45 and 47 which were exclusively recruited during meaningful stimuli). This was not the first time that such a dual pathway model for semantic and phonological processing was hypothesised (Devlin, 2008); however, the fact that Bokde et al. (2001) elaborated their model based on orthographic rather than sound stimuli makes it particularly relevant for us. Mechelli et al. (2005) expended on the idea using fMRI and a reading task during which candidates had to read pseudo words and exception words (words that may be exceptions to spelling rules or words which use a particular combination of letters to represent sound patterns in a rare or unique way). Their results showed that pseudo words preferentially increased activity in the left dorsal preMC (area 6), while exception words primarily increased activity in the left VLPFC (pars triangularis - ventral portion of the inferior frontal gyrus - Brodmann area 45). Furthermore, significant activation in the dorsal preMC was associated with a selective increase in effective connectivity from the posterior fusiform gyrus (Brodmann area 19), while significant activation in the VLPFC was associated with an increase in effective connectivity from the anterior fusiform gyrus (roughly Brodmann areas 20 and 37). Therefore, the authors postulated the existence of distinct neuronal mechanisms for semantic and phonological contributions to word reading.

Based on those findings as well as other functional connectivity and topography studies (e.g. Horwitz et al. 1998; Kujala et al. 2007), Devlin (2008) proposed the existence of a "semantic" pathway and a "phonological" route in the left hemisphere during word reading. The "semantic" route appears mainly composed of the ventral temporal pole (Brodman areas 20 as well as 38), the fusiform gyrus (Brodmann area 37) and the pars orbitalis/trianfularis (VLPFC – Brodmann areas 45 and 47); while the "phonological" route is composed of several dorsal and posterior regions including the fusiform gyrus (Brodmann area 37), the posterior parietal cortex (Brodman areas 39 and 40), the preMC (Brodman area 6) and the PPFC (Brodmann areas 8 and 44).

The right hemisphere regions homologous to the ones involved in those pathways have also been shown to play a significant role in language. Indeed, Duffau et al. (2008) studied the configuration of the language routes within the right hemisphere in nine left-handed individuals undergoing a neurosurgical operation. Their results, not only mirrored the left hemisphere model, but also showed that impairment in the DLPFC (Brodmann areas 9 and 46) as well as the CN could lead to semantic paraphasia, therefore arguing for the involvement of the entire lateral PFC in semantic processing (as well as BG).

Using the WWST (refer to Chapter 1 for more details) and fMRI, Simard et al. (2013) aimed to compare fronto-striatal activations in semantic and phonological processing. Their results showed a pattern similar to the one proposed by Devlin (2008) and corroborated by Duffau et al. (2008) in which semantic decisions required significant activity in the VLPFC, the DLPFC, the fusiform gyrus, the ventral temporal lobe and the CN, while phonological decisions produced increased activity in the PPFC (Brodmann area 44), the preMC and the temporoparietal junction.

In summary, during word reading, there seems to be a functional neuroanatomical pathway for semantic processing involving both hemispheres and relying primarily on the VLPFC (areas 45 and 47), the DLPFC (areas 9 and 46), the fusiform gyrus (area 37) and the ventral temporal lobe (areas 20 and 38) as well as the CN; and a route for phonology processing relying on more posterior and dorsal regions namely the fusiform gyrus (area 37), the posterior parietal cortex (areas 39 and 40), the preMC (area 6) and the PPFC (areas 8 and 44) (Figure 2.8.). In Chapter 6 we will explore how aging affects those language pathways by comparing brain activity (using fMRI) in healthy old individuals to that of young healthy candidates during the performance of the WWST.

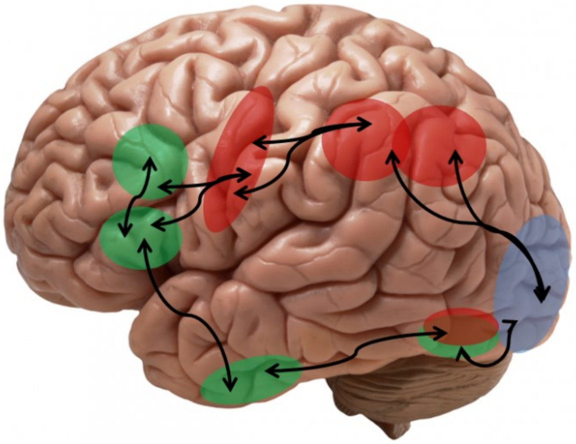

Figure 2.8. A neurocognitive framework for language during word reading. The components of the semantic pathway (areas 9, 20, 37, 38, 45, 46 and 47) are shown in green and those of a phonological pathway (areas 6, 8, 37, 39, 40 and 44) are shown in red. Visual areas (areas 17, 18 and 19) are shown in blue. This diagram is based on the works from Devlin (2008) and Duffau et al. (2008).

2.4. Conclusion

In this Chapter, we have reviewed the main structures of the cerebral cortex (especially in the frontal lobes) and the BG from a neuroanatomical perspective. We have then looked at the contribution of those same structures to executive (working memory and set-shifting) and language (semantics and phonology) processing during word reading. The cognitive and motor fronto-striatal loops presented above (part of the "new" process specific model) are extensively recruited during set-shifting in the WWST and therefore constitute the neuroanatomical framework for our first study (Chapter 5) which explores the effects of aging on executive processing. Similarly, in the WWST, semantic and phonological processes rely, respectively, on the semantic and phonological pathways described earlier. Consequently, a good understanding of those language pathways is essential to appreciate the full extent of our second study (Chapter 6) which explores the effects of aging on language processing. In the chapter to come, we will primarily focus on the age-related compensatory mechanisms allowing for cognition to be preserved despite aging.

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CHAPTER 3

Aging and related cerebral compensatory mechanisms

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During adulthood, the cerebrum loses 1 to 2% of its mass each year as well as white matter structural integrity (Caserta et al., 2009). Actually, it has been widely found that its weight declines at a rate of around 5% per decade after age 40 with the actual rate of decline increasing significantly particularly over age 70 (Scahill et al., 2003). Furthermore, a decrease in dendritic synapses or loss of synaptic plasticity has also been described (Bames, 2003). Those changes in integrity and volume appear to be particularly important in the PFC, the striatum and the hippocampus, regions of primordial significance in executive functioning and memory (Raz, 2004). However, the impact of those alterations on different cognitive domains is not straightforward. Indeed, findings tend to be somewhat inconsistent. Regarding language processing, for example, while some studies appear to indicate that there is little age-related performance decline (Burke et al., 2000; Burke and Shafto, 2008; Waters and Caplan, 2005), others have shown that older individuals may display impaired execution during language production tasks (Bona, 2014; Ivnik et al., 1996), more errors when accessing phonological word forms (Shafto et al., 2007), decreased speech comprehension (Schneider et al., 2005) and perception not related with hearing loss (Bilodeau-Mercure et al., 2014) as well as more tip-to-the-tongue states (White and Abrams, 2002). However, it appears that at least some of these findings could be explained by a decline in working memory instead of actual language processing per se (Waters and Caplan, 2005).

Therefore, enlightened by this last statement, one could then argue that there is less age-related decline in language processing contrarily to working memory and executive function. But the truth is that even studies on executive processing and aging have revealed inconsistent behavioural findings. Indeed, it has been shown in some experiments that the age-related decline in performance would disappear if non-executive components (e.g. motor-speed) were considered (Fristoe et al., 1997; Parkin and Java, 1999). Some studies have even suggested that there is no age-related executive decline at all (Boone et al.. 1990). Moreover, other cognitive domains, such as semantic knowledge (Burke and Shafto, 2008; Craik and Jennings, 1992; Laver, 2009; Park et al., 2002; Verhaeghen, 2003) and emotional regulation (Carstensen et al., 2003; 2011), are clearly maintained with age.

History certainly gave us examples of great accomplishments performed by people who would be considered elders. Sir Winston Churchill became prime minister of the United Kingdom in 1940 at the age of 65 years old, and again at the age of 76. He played a significant role in the outcome of the Second World War and made sure that the World would remember it by writing a six volumes book on the subject. History was kind to him as was the Swedish Academy who awarded him the Nobel Prize of Literature in 1953 (Manchester and Reid, 2012). Therefore, given the fact that, at least for some high performing individuals, both language (e.g. writing skills) and executive functions (e.g. military strategy) may be preserved with age (or less impaired than brain atrophy would suggest), let's explore the compensatory mechanisms that would allow for this preservation to occur.

3.1.Cognitive reserve

The cognitive reserve (CR) hypothesis is a "functional" model conceptualized by Stern (2002) that reflects the inter-individual ability to effectively use cognitive processes and brain networks; two CR mechanisms have been proposed: neural compensation and neural reserve (Stern, 2009). Neural compensation is the use of new compensatory brain networks after pathology or normal aging disrupted those typically recruited. The hypothesis was in part based on the fact that several episodic memory, semantic memory, working memory, perception and inhibitory control studies have reported that high performing older individuals tended to show bilateralization of cerebral activation (Cabeza, 2002; Reuter-Lorenz 2002; Reuter-Lorenz et al. 2000; Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Park, 2010) as well as intrahemispheric reorganization of activation, mainly from the occipitotemporal to the frontal cortex (Cabeza 2004; Cappell et al., 2010; Grady et al. 1994, 2005; Madden et al., 1997; Reuter-Lorenz et al., 2000). These findings led, respectively, to the proposition of the HAROLD (Hemispheric Asymmetry Reduction in OLDer adults) model by Cabeza (2002) and the PASA (Posterior-Anterior Shift in Aging) phenomenon by Denis and Cabeza (2008). The HAROLD model states that, under similar circumstances, prefrontal activity during cognitive performances tends to be less lateralized in older adults than in younger individuals, it is believed that this "delateralization" has a compensatory function and reflects regional or network mechanisms (Cabeza, 2002). The PASA phenomenon, additionally, has also been shown to reflect the effects of aging (and not differences in task difficulty for example), furthermore age-related increases in frontal activity have been positively correlated with cognitive performance and negatively correlated with the age-related occipital decreases (Davis et al., 2008). Therefore, as previously stated, these patterns of brain activity reorganization may represent a compensatory mechanism based on the recruitment of new brain networks in order to maintain performance (Figure 3.1.). Neural reserve, on the other hand, emphasizes pre-existing efficiency or capacity differences in neural networks. It consists in using flexible brain networks or cognitive resources that are less susceptible to age or pathology disruption.

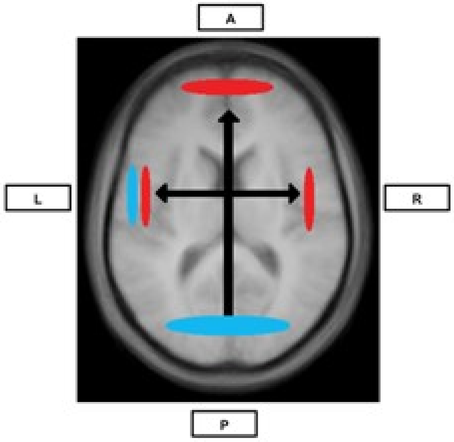

Figure 3.1. Neural Compensation. Brain image showing an age-related hemispheric asymmetry reduction in brain activity (HAROLD) and a posterior-anterior brain activity shift (PASA), two phenomena believed to represent age-related neural compensatory mechanisms. Blue represents activity in younger individuals and red represents activity in older individuals. A: Anterior; P: Posterior; L: Left hemisphere; R: Right hemisphere.

In order to conceptualize those mechanisms, let's use another historical, but more recent, analogy. In 1966, William Hartnell, English actor, was playing the leading role in the British science-fiction series *Doctor Who*. At the time, Hartnell's health was starting to significantly decline as were his cognitive abilities. Those issues led to his departure from the show on that same year, which ironically allowed *Doctor Who* to continue for more than 50 years. Indeed, the show producers came up with a very original idea: since "the Doctor" is an alien, he can regenerate into in a different body every time he dies. As of 2014, there have been twelve iterations of "the Doctor". But if we come back to our analogy, it seems that Hartnell's memory was so impaired by the end of his career that he had difficulty remembering his lines. He then had to frequently rely on two different strategies while acting. The first strategy (analogous to neural compensation) consisted in using paraphrases (alternative pathways) to replace complicated words. While the second strategy (analogous to neural reserve) implied using simpler and more usual words (networks less susceptible to disruption) to replace more complicated ones (McDonough, 2013). Of course, beyond those analogies, Hartnell's brain was most probably relying heavily on neural compensation and reserve to maintain his acting skills at an acceptable level.

3.1.1. Neural compensation

In the next section, we shall explore neural compensation and its role in executive function (especially in working memory). We shall then look at the role of the compensatory mechanism in language processing. We shall do so by reviewing some significant neuroimaging functional studies addressing aging and the two cognitive domains.

3.1.1.1. Executive function

In 2007, Zarahn et al. published an fMRI study in which young and old participants were compared while performing the letter Stemberg task (a working memory task) using Multivariate Linear Modeling (MLM). Their results showed that load-related activation during the retention phase of the task was characterized by two spatial patterns: one composed of areas often associated with working memory (including the cerebellum, the insula, the inferior and middle frontal gyrus, the hippocampus, the superior frontal gyrus, the inferior and superior parietal lobules and cingulate), and another composed only of the right hypocampal gyrus. While the first pattern was used by both the young and the elderly, the second one was only used by the older subjects. Interestingly, the activation of the second network was linked with a decrease in performance.

There are two possible explanations for this finding. One is that it cannot be a compensatory mechanism since as older individuals increasingly rely on the alternative network, worse is their performance. However, one could also argue that this alternative network is needed to maintain function as age-related neural changes diminish the efficacy of the first (primary) network. In other words, those older individuals using the primary and alternative network would perform even worse if they relied only on their (impaired) primary pathway. If the latter explanation proves to be true, the second network would then be an example of neural compensatory.

Steffener et al. (2009) tried to shed some light on this dilemma. They predicted that, if the second network was compensatory, individuals who express the second pathway should have age-related neural changes that affect the primary network. To explore their hypothesis, they used voxel based morphometry (VBM) to test if atrophy in the primary pathway was related to expression of the secondary network, and they found that a decrease in grey matter density of the left pre-central gyrus was linked with an increase in secondary pathway recruitment. They also found that there was a correlation between gray matter density in the pre-central gyrus and age, but only in the elderly. Based on those findings, they postulated that the elderly increasingly recruit alternate pathways when the primary networks are affected by age-related atrophy. Therefore, this is an example of neural compensation in which older individuals use an alternate network to partially maintain (at a lower level) task performance. In other words, it is exactly the same phenomenon as using alternative routes or streets when one wants to go from a point A to a point B and the faster route is blocked or in bad condition. The alternative options are not optimal, but they still allow for one to go where one wants to go.

As previously mentioned, several studies exploring different cognitive modalities have shown brain activity patterns compatible with neural compensation. Among the findings more frequently reported is the tendency for high performing older individuals to show interhemispheric dedifferentiation of cerebral activation (Cabeza, 2002;Reuter-Lorenz, 2002; Reuter-Lorenz et al. 2000;Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Park, 2010) and intrahemispheric reorganization of activation, mainly from the occipitotemporal to the frontal cortex (Cabeza, 2004; Cappell et al., 2010; Grady et al. 1994, 1998, 2005; Madden et al., 1997; Reuter-Lorenz et al., 2000) : the HAROLD model and the PASA phenomenon.

More recently Springer et al. (2005) have shown using a working memory task that high performing older individuals tend to rely more extensively on frontal regions and that those regions tend to be bilaterally activated. This observation is in agreement with both the HAROLD and PASA phenomena. However, their complementary analysis did not show any significant correlation within older participants either between frontal activity and performance, or between frontal activity and level of education. Based on those findings, it is difficult to argue for or against the compensatory nature of this increase in frontal recruitment. Nonetheless, it should be noted that, in some studies in which the elderly presented impaired performance, age-related decreased frontal activity has been reported both in Positron Emission Tomography (PET) (e.g. Reuter-Lorenz and Cappell, 2008) and fMRI studies (e.g. Hampshire et al., 2008) suggesting that increased frontal and bilateral activity are indeed neuronal compensation mechanisms.

3.1.1.2. Language processing

Several neuroimaging studies that looked at language abilities have also reported increased bilateral activity in high performing older people compared with younger individuals during verbal generation (Persson et al., 2004) and naming tasks (Wierenga et al., 2008). More recently, Obler et al. (2010) have even shown anatomical evidence (using diffusion tensor imaging) that older individuals with high naming skills tended to rely more extensively on right-hemisphere frontal regions (peri-Sylvian and the midfrontal areas). Those results seem to indicate that language function tends also to depend on neural compensation to maintain high performance as years pass by.

Grossman et al. (2002a) published an article in which brain activity of young, older good and older poor performers were compared while the participants were performing a language task. The task consisted in answering a probe question about who performed the action described in a sentence previously presented. The older good performers were as accurate as their younger participants, while the older poor performers showed impaired sentence comprehension compared to the young individuals. The difference between the poor performers and the other two groups of participants became more important as sentences became more syntactically complex.

Regarding brain activity patterns, older good performers showed significant increased activation in two areas compared to their younger peers. Indeed, the dorsal portion of the left inferior frontal cortex (roughly area 44), an area known to play a role in working memory (as we saw in Chapter 2) including maintaining and rehearsing stored verbal information (Chein and Fiez, 2001; Smith et al., 1998), was more activated in the older group. Moreover, the more successful older adults also showed additional activation in the right posterolateral temporal-parietal region (while the left counterpart was more activated in the younger group). Those two findings are in agreement with neural compensation, and they seem to show the co-occurrence of the PASA phenomenon and the HAROLD model.

When the activation pattern of the poor performers was compared to the one of the good performers, it was revealed that the poor performers had increased DLPFC activity. The DLPFC has been reported in several studies implying problem-solving activities, regardless of the nature of the material (e.g. Monchi et al., 2001; Paulus et al., 2001; Ramnani and Owen, 2004; Simard et al., 2011; refer to Chapter 2 for more details). That region was not activated in the younger group. Therefore, it seems that the less successful older participants were attempting to understand more grammatically complex sentences by using a problem-solving approach that was not very effective for this particular task. This finding may as well be another example of neural compensation in which poor performers recruit the DLPFC in an attempt to compensate for age-related insults; unfortunately, contrarily to the good performers, their “strategy” is not sufficient to maintain adequate sentence comprehension. Imagine a person using a table knife to cut a piece of paper because her scissors are broken, she may eventually manage to cut the paper, but not as easily as she would have with the scissors, and more importantly, the piece of paper she ends up with may not have exactly the same shape as the one she had aimed for (lower level of performance). You will have most probably noticed by now that we have been alternatively employing the pronouns “he/him”, “she/her” and “they/their” to refer to an indeterminate person given the absence of consensus regarding indeterminate gender pronouns in the English language (this has nothing to do with neural compensation, but remains a statement we felt compelled to bestow).

In 2010, Tyler et al. explored syntactic processing in older individuals and found that bilateral recruitment of frontotemporal regions was correlated with improved performance. More recently, Ansado et al. (2013) studied the comprehension of word semantics using a semantic judgment task. During the fMRI experiment, young and old participants had to indicate if a given word presented on a screen identified an animal or not. Behavioural results were similar for both groups, with slightly longer response times for the older one. The fMRI results, on the other hand, showed that older individuals had more parietal and temporal bilateral activations as well as left fusiform activations, while younger subjects had more DLPFC activations. In the same article, Ansado et al. also presented data from another preliminary study in which young and older healthy individuals had to perform a verbal fluency (VF) task which involved eight alternating 90-s blocs of four orthographic and four semantic VF conditions as well as a reference condition (repeating the months of the year). The neuroimaging results showed that older individuals had increased bilateral temporal activations during semantic conditions, while similar frontal activations were observed in both groups. However, older participants showed more frontal bilateral activations during orthographic conditions. Both studies showed that the elderly had a pattern of activation compatible with the HAROLD model. However, the apparent posteriorization of some activation in the older group (during semantic judgment and semantic fluency) is in contradiction with the PASA phenomenon.

The authors mention that the discrepancy between their results and what is usually shown in the literature may suggest that during the semantic judgment task, older individuals rely more on their semantic memory and knowledge (processes more associated with posterior regions) while younger individuals rely more on an executive strategy (which imply the involvement of the PFC). They also point out that semantic fluency tends to rely on temporal regions whereas orthographic fluency is more dependent on frontal regions (Henry and Crawford, 2004) which would explain the results of the VF experiment. These observations are actually congruent with other semantic neuroimaging studies (Hazlett et al., 1998; Wingfield and Grossman, 2006) in which older participants presented increased posterior activation. Therefore, Ansado et al. (2013) propose that the nature of a task seems to be a determinant factor for neurofunctional reorganization in aging. This being said, both age-related anteriorisation and posteriorisation of activation are examples of neural compensation. Consequently, different language domains appear to rely on similar compensatory mechanisms, namely neural compensation even if the form of the neural compensation may vary. Let's use culinary utensils to illustrate this idea, if one is in front of a bowl of rice and a piece of steak with one spoon and a knife, but no fork. One will most probably use the spoon for the rice and the knife for the stake. Therefore, one compensates for the lack of fork using a similar strategy, but using different utensils depending on the situation.

Similar neural compensatory mechanisms have also been found during speech comprehension. Indeed, age-related hearing loss is accompanied by auditory cortex atrophies (Harris et al., 2009; Peelle et al., 2011; Eckert et al., 2012), explaining why older adults likely have to recruit different neural resources in order to maintain appropriate speech comprehension. That explains why Eckert et al. (2008) observed an age-related upregulation of frontal areas during an easy word recognition task in older individuals, while younger adults recruited these areas merely during difficult listening conditions. Wong et al. (2009) also found that during single word recognition tasks older subjects, when compared to younger ones, showed reduced activation in the auditory cortex but an increase in working memory and attention-related cortical areas (prefrontal regions). Both of these findings are compatible with the PASA phenomenon. More recently, Erb and Obleser (2013) studied neural speech processing in a group of older adults with varying degrees of sensorineural hearing loss and a group of younger individuals with normal hearing. All the subjects had to hear and repeat back degraded sentences. Their results showed that the older adults adapted to degraded speech at the same rate as younger listeners; however, for correct speech comprehension, older individuals relied on the middle frontal gyrus in addition to a core speech comprehension network recruited by the young which is suggestive of a compensatory mechanism.

3.1.1.3. Are phenomenon such as PASA and HAROLD necessarily compensatory?

Most of the studies presented in this chapter rely on functional neuroimaging to "measure" brain activity. However, one has to be careful when interpreting fMRI data. While it is appropriate to consider BOLD signals as measures of neural activity of a specific brain region in healthy young adults, the validity of such interpretations is less robust when comparing signals across individuals or states during which significant variations in physiology may prevail. Indeed, increasing evidence suggests that changes in neurovascular coupling (due to medication, disease, age, etc.) have the potential to significantly modify task-related BOLD responses (Carusone et al., 2002; D'Esposito et al., 2003; Iannetti and Wise, 2007; Lindauer et al., 2010; see Liu, 2013 for review). Therefore, the PASA phenomenon, for example, may as well represent age-related changes in patterns of brain activity as changes in vascularity.

Secondly, age-related over-recruitment, particularly bilateralization of cerebral activity, has been interpreted as compensatory both when the correlation between bilateral activity and performance was positive (Obler et al., 2010; Persson et al., 2004; Springer et al., 2005; Wierenga et al., 2008), as well as negative (de Chastelaine et al., 2011; Steffener et al., 2009). Indeed, as previously mentioned, Steffener et al. (2009) postulated that increased recruitment of the right hippocampal region by the elderly (Zarahn et al., 2007) during the performance of a working-memory task was compensatory even if the overall performance was worse in the older group compared to the younger one. de Chasterlaine et al. (2011) also found, during a verbal encoding memory task, that increased right frontal activity in older adults was negatively correlated with memory performance, and they too postulated that this increased right hemisphere recruitment could nonetheless reflect the engagement of processes that compensate only partially for age-related neural degradation, therefore the impaired performance. Cabeza and Dennis (2012) expanded on this idea and hypothesized the existence of three different types of compensation: "attempted", "unsucessful", and "successful" compensation. When there is a mismatch between available cognitive resources and task demands, additional neural resources are recruited, reflected in increased brain activity. This over-recruitment is called "attempted compensation". If the increase in brain activity is associated with better task performance, it then becomes an example of "successful" neural compensation. On the other hand, if it is associated with worse task performance (as for the examples presented above), it is then defined as "unsuccessful" neural compensation.

Another possible explanation for increased brain activity in the elderly is that it does not represent any type of compensation at all, but is actually a manifestation of age-relate brain disruption. Such hypothesis has been favored in some studies in which over-recruitment was associated with impaired cognition (e.g. Duvern et al., 2009). With age, one would lose the ability to inhibit certain regions of the brain, those areas would therefore be more activated in older individuals during the performance of a cognitive task, but they would not contribute to cognition. Differentiating "unsuccessful compensation" from "disrupted over-activation" is almost impossible, especially since both mechanisms can most probably concomitantly occur.

We have mentioned earlier that certain cognitive domains don't appear to show any performance decline with aging (e.g. emotional regulation) (Carstensen et al., 2003; 2011), some may even show improvement, such as semantic knowledge (Burke and Shafto, 2008; Craik and Jennings, 1992; Laver, 2009; Park et al., 2002; Verhaeghen, 2003). Thus, is it appropriate to talk about "compensation" when performance improves? Therefore, we would like to offer yet one more possible explanation for increased brain activity in the elderly regarding those particular cases, and that is the ability for older individuals to rely on neural over-recruitment, not as means of compensation, but as a “strategy” to increase cognitive performance.

In the present thesis, the PASA phenomenon, age-related activity dedifferentiation or bilateralization and general neural over-recruitment have been considered manifestations of neural compensation. However, one should keep in mind that this is just one possible interpretation; age-related over-activation could also be a sign, as stated above, of dysfunction (the inability to inhibit certain brain areas) especially when it is correlated with impaired performance; or, on the contrary, improved function when it is associated with better performance.

3.1.2. Neural reserve

Neural reserve has also been studied in the context of working memory and, to a lesser extent, language processing. In this section we shall explore some significant neuroimaging studies that addressed those issues.

3.1.2.1. Executive function

Zarahn et al. (2007) scanned young and old individuals while performing the letter Sternberg task, a task involving the presentation of a list of letters to memorize (stimulus phase), followed by a period during which the participants must maintain the list in memory (maintenance phase), because afterwards they are asked to respond if new letters presented to them were in the list they had to memorize or not (probe phase). In that study, it was determined that both the younger and the older groups showed similar spatial patterns during the stimulus and probe phases of the task. The authors decided to address the question of whether there were age-related differences in network efficiency between the two groups as they both showed the activation of similar patterns. Interestingly, they found that as the task got more difficult, the elderly increased network recruitment to a greater extent in the stimulus phase than the younger participants; however they also benefitted less from the network recruitment in terms of performance (they made more errors in the probe phase). This result seems to show how age-related neural changes may impair network efficiency even when the network itself remains unchanged. This being said, the fact that the older group was capable of activating the networks to the same degree as the younger one demonstrates that neural reserve is a compensatory mechanism on which older individuals may rely.

In 2009, Holtzer et al. conducted a similar analysis of data resulting from young and old participants performing the shape Sternberg task. This task is similar to the letter Sternberg task, but uses shapes as stimuli rather than familiar letters. This last feature is believed to make the task more challenging than its close relative. However, once again, both the young and the elderly used similar brain networks during the performance of the stimulus and probe phases. But in this case, they found that the “probe phase” network expression was greater in the younger group compared to the older one. In other words, the younger individuals performed better and showed increased expression of the underlying brain network, which suggests a capacity difference between the two age groups (that is a difference in the ability to recruit the network in question). It is quite probable that the use of the shape Stemberg task, which is more demanding than its letter counterpart, explains why the two age groups show differences in capacity in this study (Holtzer et al. 2009), but not in the previous one (Zarham et al. 2007). Indeed, the first study was not challenging enough for either group to reach their capacity potential, while the second one was: the elderly reached their capacity limits before the young. Imagine two long distance runners; one is an elite athlete that trains every day while the other one is an amateur that trains once or twice per week. If we ask both athletes to run 1000 meters, chances are that the elite athlete will be faster, but none of the runners will have exhausted all their resources by the end of the ordeal. On the other hand, if the task becomes to run a marathon, then not only will the elite athlete be faster, but he will be “hitting the wall” (which corresponds to the depletion of glycogen stores in the liver an muscles) later than the less trained individual. The amateur runner will reach its capacity limits earlier than the elite one. If we get back to the age-related decline in capacity, it does not equate with elderly inability to rely on neural reserve as a compensatory mechanism, however, it emphasises the need for the co-occurrence of other compensatory mechanisms if function is to be preserved.

3.1.2.2. Language processing

Grossman et al. (2002b) have shown that when both older good and poor performers were compared while performing a sentence-comprehension task (which consisted in reading a sentence and answering a question about who performed the action described in the given sentence), poor performers engaged significantly less activation of some important sentence-processing areas in the left inferior frontal cortex and the left posterior-superior temporal cortex relative to good performers. This finding seems to show that old good performers are able to rely more extensively than old poor performers on some well-preserved language networks, therefore using neural reserve as a compensatory mechanism.

In the study of Erb and Obleser (2013) (mentioned above) exploring neural speech processing in a group of older adults with varying degrees of sensorineural hearing loss and a group of younger individuals with normal hearing, the authors found that both groups relied on the left anterior insula when presented with degraded more than clear speech. However, anterior insula recruitment in the older group was dependent on hearing acuity. Therefore, older individuals with less impaired hearing were able to rely more extensively on the left anterior insula similarly to the young which represents an example of neural reserve.

Regarding semantic and phonological processing which are the two language functions investigated in our own experiments (Chapter 6), there appears to be some evidence that the first relies more extensively on neural reserve than the latter. Indeed, Diaz et al. (2014), have found that when younger and older adults were asked to make semantic and phonological decisions about pictures, the older group was as accurate and efficient as the younger one in the semantic task, but not during the phonological task. Interestingly, both groups also showed increased activity of similar left-hemisphere language regions during semantic decisions, while they presented more bilateral and widespread activations during the phonological task (especially in the older group). Therefore, the older adults were able to recruit more efficiently left-hemisphere language regions (neural reserve) during semantic processing than during phonological processing which correlated with better behavioral results.

3.2. Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH)

Some of the studies reported have shown that compensatory mechanisms (brain over-activation) are not limited to older individuals, but they also occur in younger people when task demands increase (e.g. Braver et al., 2001; Grady et al., 1998; Holtzer et al., 2009; Logan et al., 2002; Paxton et al., 2008; Rypma and D'Esposito, 2000; Schneider-Garces et al., 2010; Zarahn et al., 2007). Other studies in verbal working memory have also shown that the elderly don't always reveal increased brain activity compared with the young, but under-activation instead, mainly at the level of the DLPFC (Ansado et al., 2013; Rypma and D'Esposito 2000, Rypma et al., 2001). These observations led Reuter-Lorenz and Cappell (2008) and Reuter-Lorenz and Lustig (2005) to propose a model implying that people will generally activate more cortical regions as task load increases (Compensation-Related Utilization of Neural Circuits Hypothesis; CRUNCH). However, given age-related processing decline, older individuals might need to engage more neural resources/areas at lower levels than younger adults. It should be noted that this hypothesis does not enter in conflict with the CR one proposed by Stern (2002), on the contrary, it complements it. Indeed, as age advances and cognitive reserve diminishes, older individuals will need to rely more heavily on task specific pathways (neural reserve) and/or other brain areas (neural compensation) at low task loads. Therefore, it is expected for older individuals compared to younger ones, to reach their resource limitations at lower levels of cognitive demand, leading to a decline in performance as demand increases. At this "crunch" point, brain activity may plateau or even decrease with increasing task loads, explaining why some studies report that the elderly show reduced brain activity compared to the young or higher performing individuals (e.g. Reuter-Lorenz and Cappell, 2008; Hampshire et al., 2008) (Figure 3.2.). Remember the long-distance runners metaphor, the "crunch" point is like "hitting the wall", once one does, one's performance usually decreases drastically, an untrained athlete may even be unable to continue running and may have to walk for the remaining of the distance (which could be analogous to showing decreased brain activity).

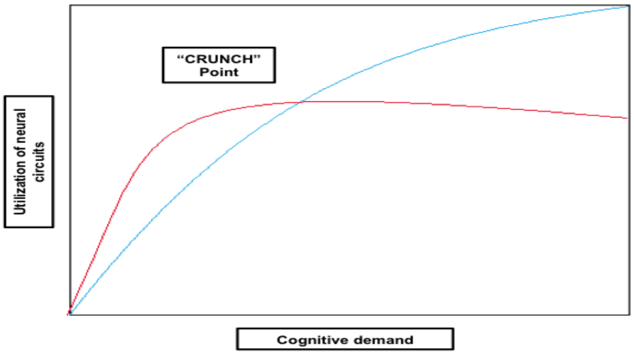

Figure 3.2. Theoretical illustration of how neural circuit utilization varies with an increase in cognitive demand in old (red) and young (blue) individuals according to the Compensation-Related Utilization of Neural Circuit Hypothesis. This model implies that people will generally activate more cortical regions as task load increases; however old individuals need to engage more neural resources at lower levels of cognitive demand than young adults. Old individuals also reach their resource limitations (shown in the figure as the "CRUNCH point") at lower levels of demand, after which their brain activity may plateau or even decrease as does performance.

Some studies have been designed to explore the CRUNCH model, especially in the context of working memory. For example, Cappell et al. (2010) scanned (using fMRI) young and old adults while performing a verbal memory task with a load varying between four, five and seven letters. Older adults performed as well as the younger ones when verbal memory loads were of four or five items, but less accurately for memory loads of seven letters. Interestingly, and with agreement of the predictions of the CRUNCH model, the elderly showed brain over-activation when their performance was similar to the young and under-activation with increased memory load and reduced performance (mainly in the right DLPFC and VLPFC). Another study performed by Schneider-Garces et al. (2010) showed similar results. Indeed, in that experiment, young and old subjects were scanned while performing the letter Stemberg's task with memory set sizes varying from two to six letters. The behavioural data indicated that the older group had significantly more difficulty with the task than the younger one, especially when set sizes were larger than four items. On the other hand, the fMRI data showed that several brain regions (including the PFC) had significant bilateral increases of activity as set sizes got larger and thus for both groups. However, while older adults presented a large increase in brain activation between set sizes of two and four letters as well as a negligible further increase at larger set sizes, younger adults showed most of their increase at larger set sizes (five and six letters). Once again, the elderly tended to rely on compensatory mechanisms at lower levels of cognitive demand and reached their resource limitations faster than the young.

It should also be noted that, even if the study of Grosman et al. (2002b) was not designed to explore the CRUNCH model in sentence comprehension, it nonetheless shows quite elegantly how the model may apply to language processing. Indeed, in that study, older poor performers show significantly less activation of some important sentence-processing areas when compared to old good performers, and thus especially when task load increases. Meinzer et al. (2012a,b) have also shown, using fMRI and a VF task during which participants had to generate in a limited amount of time as many words as possible under specific category conditions (e.g. animals), that increased bilateral compensatory activity (especially in the frontal inferior gyrus) was mediated by task difficulty more than by age. In other words, as task demands increased, both the young and the elderly showed more bilateral activations which is congruent with the CRUNCH model. Finally, Eckert et al. (2008), in a study presented earlier, observed an increase in activity in frontal regions during an easy word recognition task in older individuals, while younger adults only recruited these areas during difficult listening conditions. Therefore, over-recruitment was not solely due to aging, but to task difficulty as well in accordance with the CRUNCH model.

3.3. Delayed brain activity

All of the previous compensatory mechanism described so far presented spatial functional reorganization of brain activation. However, there is still the possibility of another compensatory mechanism involving not so much WHICH regions of the brain show increased activation, but WHEN are these same regions activated.

In 2007, Velanova et al. have suggested the existence of an age-related compensatory mechanism that consists of a shift from early to late selection processing during memory retrieval (the load-shift model). In fact, using the concepts of Rugg and Wilding (2000), who divided retrieval into three entities: retrieval orientation (anticipation of retrieval demands), retrieval effort (access of information), and postretrieval monitoring (evaluation of the appropriateness of the recollected information), Velanova et al., (2007) postulated that older participants would most probably rely more on retrieval effort and post-retrieval monitoring and less on retrieval orientation than younger individuals. To explore their hypothesis, they did two fMRI experiments. Thrity-six young and thirty-height old subjects participated in the first one, while twenty-nine young and thirty-seven old subjects were part of the second one. In both studies, participants had to distinguish new words from words that have been previously presented to them (old words), the difference being that in the second experiment there were low (with old words repeatedly studied) and high control conditions (with old words only presented in the incidental deep encoding task; that was the only condition for experiment 1). Data from both experiments showed that older adults had increased and delayed recruitment of frontal regions compared with the younger ones during demanding retrieval. Based on these results, the authors stated that this strategy shift could explain the retention of high-level cognitive function in some older individuals but at the expense of less flexible and slower performance on demanding cognitive tasks.

Paxton et al. (2008) contrasted the activity dynamics of younger and older adults during the performance of a cognitive control task (the Continuous Performance Test – AX version) relying on some executive processing (mainly discrimination ability and sustained attention). During the test, individuals are instructed to respond with a mouse press whenever the stimulus is an X that was preceded by an A. Their results showed a significant age-related temporal shift in lateral PFC regions: older adults presented both reduced cue-related (letter A) activation and increased probe-related (letter X) activation relative to younger adults. These findings are consistent with previous behavioral studies, in which older adults showed smaller cue-based expectancy effects but larger probe-related interference effects compared to younger individuals (Braver et al., 2001; 2005; Paxton et al., 2006). Based on those results, Braver and colleagues (Braver et al., 2007) developed a theory, named dual mechanisms of control (DMC), which postulates a distinction between proactive and reactive modes of cognitive control. During the proactive control mode, individuals actively maintain in a sustained/anticipatory manner goal-relevant information before the occurrence of cognitively demanding events. On the other hand, in the reactive mode, attentional control is mobilized only when and if needed. Therefore, proactive control relies on the anticipation of interference before it occurs, while reactive control relies on the resolution of interference after its onset.

Jimura and Braver (2010) compared brain activity dynamics in healthy old and young adults during the switch and performance of two semantic classification tasks. During the first task, participants were required to make a decision as to whether a word described an object that is either larger or smaller than a computer monitor. During the second task, subjects had to make a decision as to whether the object was man-made or natural. Before every comparison (for both tasks), a cue appeared and signaled to the participants the semantic classification judgment to be made (LRG-SML or MAN-NAT). There were two block conditions in the study: the mixed-block condition during which the classification task to be performed varied randomly from trial to trial, and the single-task condition during which a single task was performed. Relative to young adults, older individuals presented decreased sustained activity in the anterior PFC during task-switching blocks, but increased transient activity on task-switch trials. Also, younger individuals showed a cue-related response during task-switch trials in the lateral PFC and posterior parietal cortex, whereas older adults presented switch-related activation during the cue period in posterior parietal cortex only. These results are in agreement with the DMC hypothesis and therefore suggest that older individuals shift from a proactive to reactive cognitive control strategy as a means of retaining relatively preserved behavioral performance despite age-related neurocognitive changes. It should be noted that this study is as much an executive function experiment (set-shifting) as it is a language processing experiment (semantic categorization).

Cook et al. (2006) have also performed an fMRI study on young adults in which they explored the neuroanatomic substrate and time course (using early and late time windows) associated with processing different grammatical features in a sentence. They used a grammatical test in which the participants had to judge the coherence of sentences that did or did not contain a grammatical violation. There were three possible violations: an inflectional form of the past participle (*ed* was omitted), a noun-verb substitution (rehearsed would be replaced by rehearsal for example), and a transitivity violation (a sentence containing a verb that cannot be expressed in a passive form because the verb is intransitive). These three violations are presented in an ascending order regarding cognitive (especially working memory) demand. In early time windows, the participants showed significant left inferior frontal cortex recruitment in low-demanding judgments, and bilateral inferior frontal cortex recruitment in more-demanding judgments. In late time windows (BOLD activity levels measured 2 seconds later than the usual point at which the BOLD signal is monitored), the young participants did not show any activation during low-demanding conditions, but presented left inferior frontal cortex recruitment in the noun-verb substitutions and transitivity violations. Wingfield and Grossman (2006) presented, in their review article, that data with additional results from older individuals who performed that exact same task. The older participants showed a completely different pattern. Indeed, they increasingly activated the ventral portion of left inferior frontal cortex (VLPFC) during the late time windows for even the simpler conditions; furthermore they also showed bilateral inferior frontal cortex activation during the more-demanding violations in the late time window (contrarily to unilateral activation for the young). Therefore, not only are those results compatible with the HAROLD model of neural compensation, they also show that the compensatory hypothesis may extend to the temporal domain for language processes.

In conclusion, age-related delayed brain region activation has been reported in memory, attention, semantic categorisation and grammatical processing experiments. Furthermore, it seems to play a role in the preservation of cognitive performance. It may even allow for cognitive resources to be used “more wisely”, that is when they are absolutely necessary. Therefore, it appears to be a compensatory mechanism that may interact with other compensatory mechanisms such as neural compensation and neural reserve. If you will, “delayed activation” is analogous to waiting until the last moment to study for an exam. Imagine two students X and Y, X studies diligently after each class while Y waits until the last day. Chances are that a couple of hours before the exam, X will have finished her review while Y will still be memorizing data. However, if the amount of information to retain is not too substantial, both strategies may give rise to a good grade. Furthermore, waiting may even have some advantages. Indeed, if the exam is cancelled one week before its scheduled date, X would have studied for “nothing”, but not Y. Of course, this example is simply a way to illustrate “delayed activation” and its potential utility, not a suggestion for students on how they should manage their time.

3.4. Conclusion

As the passage of time structurally alters one’s brain, cognition does not have to suffer the same faith, at least not to the same extent. Indeed, the concept of CR coined by Stern et al. (2002) implies that with age, decline in cognitive performance can be totally or partially compensated. Compensatory mechanisms, can take the form of neural compensation and neural reserve. Neural compensation is the use of new, compensatory brain networks different from those pathways typically recruited for particular tasks (e.g. the HAROLD model, the PASA phenomenon). Neural reserve, on the other hand, consists in using primary flexible brain networks or cognitive resources that are less susceptible to disruption.

It has been shown that these compensatory mechanisms can also be used by young individuals when cognitive demands become significant. This observation led to the proposal of a model implying that people will generally activate more cortical regions as task load increases (the CRUNCH model). However, since older individuals might need to engage more neural resources at lower levels than younger adults (due to age-related brain atrophy), it is expected for them to reach their resource limitations at lower levels of cognitive demand as well, leading to a decline in performance as demand increases. At this point, brain activity may plateau or even decrease with increasing task loads. Overall, the CRUNCH model does not enter in contradiction with the concept of CR, it just points out the limitations of CR.

The previous compensatory mechanisms presented spatial functional reorganization of brain activation. However, some studies have also shown delayed brain activation in older individuals compared to the young. Furthermore, those findings are associated with cognitive preservation. Therefore, it could be postulated that they represent another form of compensatory mechanism.

In the following chapter we will review one of the functional neuroimaging techniques, that is fMRI. In Chapters 5 and 6 (Articles 1 and 2), we will focus on the main objectives of this thesis as stated in the Introduction. Indeed, we will look at two fMRI studies that investigate how aging affects the patterns of neural activity related to executive functions (Article 1) and those related to the use of lexical rules 1 (Article 2). Several of the compensatory mechanisms presented in this chapter will be explored in Chapters 5 and 6 given the high performing nature of the older individuals who participated in our studies. Finally, in Chapter 7 (Article 3), we will revisit the same compensatory mechanisms (including most of the same studies discussed in this chapter), but while adding new information obtained from the experiments presented in Chapters 5 and 6.

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CHAPTER 4

Functional neuroimaging

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Functional Neuroimaging

First, there were public entertainers known as mentalists. Second, there was the Marvel Universe with telepath superheroes and supervillains such as Professor Xavier and Emma Frost. Third, there was Star Trek and the Vulcan mind meld. Then, there was Doctor Who and the terrible Master. Finally, came functional neuroimaging, and mind reading became a reality, at least partially. Functional neuroimaging doesn't really allow for mind reading, but with it, one can "measure" brain activity... and therefore be a little closer to understanding how the mind works.

There are several functional neuroimaging techniques (e.g. Positron Emission Tomography [PET], Electroencephalography [EEG], Magnetoencephalography [MEG], etc.), but this thesis will exclusively focus on functional Magnetic Resonance Imaging (fMRI), since the latter has become increasingly popular in the last twenty years due to its precision and presumed harmlessness (Huettel et al., 2009), and because it is the technique used in our own studies (Chapters 5 and 6). This chapter will first explore the basic concepts underlying Magnetic Resonance imaging (MRI); after which it will review the fMRI technique and its related experimental designs.

4.1. Magnetic Resonance Imaging (MRI)

The principals underlying Nuclear Magnetic Resonance (NMR - eventually simply called Magnetic Resonance [MR]) were exposed by two independent teams, one from Harvard (Edward M. Purcell) and one from Stanford (Felix Bloch), in 1946. However, it is not until 1952 that a first one-dimensional NMR image is produced as part of Herman Carr's (American physicist) PhD thesis (Carr, 2004); the same year that Bloch and Purcell receive the Nobel Prize in physics for the development of NMR. MRI (or what would eventually become MRI) is then born, not so much "with a bang but a" whisper from a then unknown PhD graduate.

The Bang comes in the early 1970s! Primary, Ramond Damadian (an American physician and Professor at State University of New York) creates the first MRI machine and patents it in 1972 (Damadian, 1974). Secondly, and more importantly, Paul Lauterbur (another American scientist) improves and expends the technique. Already in 1974, Lauterbur generates the first MRI cross-sectional image of a living mouse (Lauterbur, 1974). Some years later, Sir Peter (or Professor Mansfield if you will, British physicist) develops a mathematical technique allowing scans to take seconds rather than hours. Both Lauterbur and Mansfield are recognized for their contribution and awarded the Nobel Price of Medicine in 2003, with an angry Damadian and a forgotten Carr left behind (Carr, 2004). Regardless of the controversy, MRI has since then become a medical imaging technique that one cannot ignore, so let's review some of its principals.

4.1.1. Physics and basics of MRI

Let's start with some definitions, shall we. The atom is the smallest unit of matter to constitute a chemical element. It is composed of a nucleus (formed by protons and neutrons) and electrons that move around it. The protons are positively charged, while electrons are negatively charged. The neutrons, as you most probably guessed, have no charge at all.

All the subatomic particles (neutrons, protons and electrons) possess a spin (an intrinsic form of rotational momentum). In the nucleus, the spins of the neutrons and the protons cancel each other out. Therefore, only nuclei with an uneven number of neutrons and protons possess a "net spin", which generates a small magnetic field. The magnitude and the direction of the magnetic field are called the magnetic moment (and are usually represented by a vector).

Now the beauty of magnetic moments is that they can be influenced by an external magnetic field (B_0) (as the one emitted from an MRI machine magnet). Moreover, the larger the magnetic moment, the more susceptible it is to B_0 ("the taller they are, from higher they fall"). Therefore, when a magnetic resonance (MR) active nucleus (that is a nucleus possessing a magnetic moment such as ^{1}Hydrogen (^{1}H)) is faced with a B_0, it "aligns" its axis (direction of the vector) to the external field. Given the fact that ^{1}H is very abundant in biological tissue (fat and water) and that almost all hydrogen atoms have one proton and no neutrons (a sea of ^{1}H with some drops of ^{2}H), it is not surprising that ^{1}H is the most commonly used MR active nucleus in MRI (Orrison, 1995).

When the nuclei align with B_0, they can either align parallel (low-energy state) or anti-parallel (high-energy state – opposing B_0). The stronger the external magnetic field (magnetic fields provided by MRI machine magnets usually vary between 0.5 and 7 Tesla), the harder it is for the nuclei to align anti-parallel. Therefore, there are always more parallel alignments than anti-parallel ones and the ratio increases with the strength of B_0. This is an important phenomenon since parallel and anti-parallel alignments cancel each other. Consequently, it is the sum of the non-opposed parallel aligned nuclei that result in a combined magnetic field conceptualized as the Net Magnetic Vector (NMV) which ultimately is the source of the MR signal (Hennel et al., 1993) (Figure 4.1.).

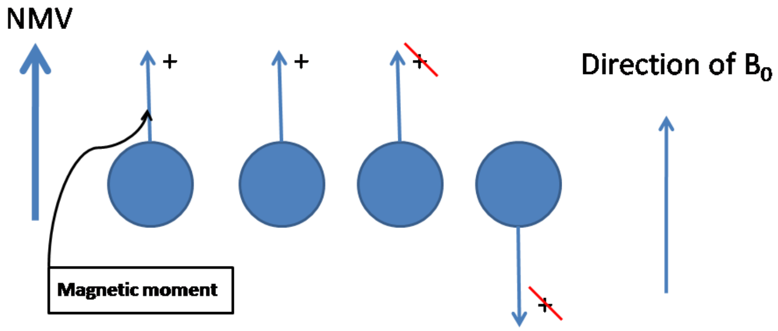

Figure 4.1. The Net Magnetic Vector (NMV) is the sum of all the Magnetic moments aligned parallel with the direction of the Magnetic Field (B_0), minus those aligned anti-parallel.

While aligned with B_0, the magnetic moments of the nuclei don't remain still, but instead "spin around" the B_0 axe at a certain frequency (called the precessional or Larmor frequency) which is specific for each type of MR active nucleus (e.g.^{1}H). Now, what happens if a "transmitter coil" (one of the MRI machine components) administers to the MR active nuclei a radio frequency (RF) pulse similar to their Larmor frequency? Well, the nuclei gain energy (a phenomenon called excitation) which causes them to start "vibrating" (resonate) and eventually, they "flip" so that the alignment of the NMV becomes perpendicular to the alignment of B_0 (transverse plane). Not all RF pulses flip the NMV into the transverse plan, but the ones that do can be referred to as 90 RF pulses. Moreover, the 90 RF pulse also pushes the magnetic moments of the nuclei to rotate (precess) in phase with each other. Each MRI machine is also equipped with at a "receiver coil" placed in the transverse plan. Therefore, every time the "in phase" nuclei precess, "they sweep" the receiver coil which induces an electric current with each passage. That current is what constitutes the MR signal (Brown et al., 2010).

When the “transmitter coil” stops emitting the 90 RF pulse, the protons gradually lose energy and realign with the B_0. This process is referred as Recovery of Longitudinal Magnetization or T1 Relaxation. T1 Recovery, on the other hand, refers to a time constant when 63% of the longitudinal magnetization has recovered (Figure 4.2.a). Furthermore, when the RF pulse is turned off, the magnetic moments of the nuclei dephase, giving rise to T2 Relaxation (which results in a decrease in signal intensity). Similarly to the T1 Recovery concept, T2 Decay is a time constant that represents the time it takes for 63% of the NMV to diphase (Figure 4.2.b). Finally, we should also mention that it is partially possible to rephase the nuclei by administrating a “rephasing pulse” (e.g. 180^{o} RF pulse), the ensuing signal (after the “rephrasing pulse”) is referred to as an “echo” (Brown et al., 2010).

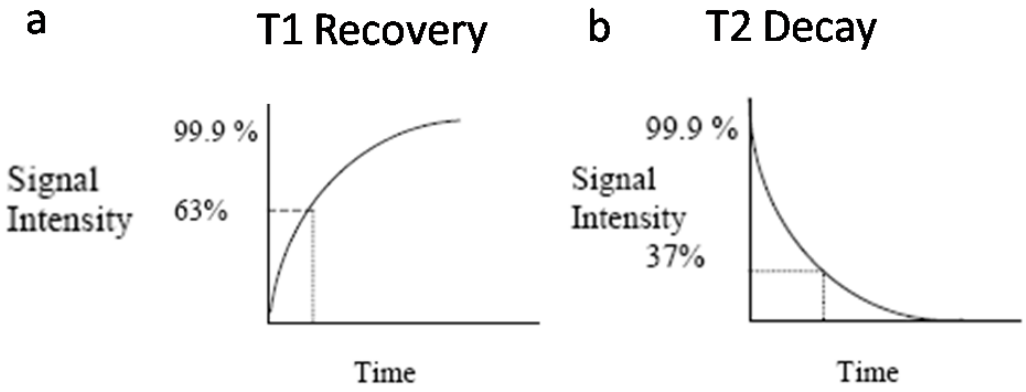

Figure 4.2. (a) T1 Recovery: time when 63% of the longitudinal magnetization has recovered. (b) T2 Decay: time it takes for 63% of the Net Magnetic Vector to diphase.

Different tissue types, such as water, fat, white matter and gray matter, have specific and different T1 Recovery and T2 Decay rates (Horowitz, 1995). Therefore, differences between tissues based on their T1 Recovery rates are called T1 Contrasts. In the same way, differences between tissues based on their T2 Decay rates are called T2 Contrasts. The type of contrast used to produce an image is referred to as “Image Weighting” which is largely determined by “pulse timing parameters” (Time to repeat [TR] and Time to Echo [TE]). TR is the time between main excitation RF pulses, while TE is the time between when the initial excitation RF pulse is emitted and when the peak of the “echo” is measured (Figure 4.3.).

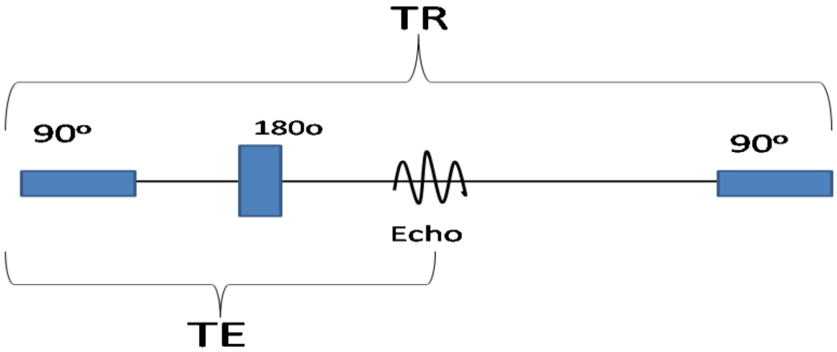

Figure 4.3. Time to Repeat: Time between initial excitation radio frequency pulses. Time to Echo: Time between initial excitation radio frequency pulse and the peak of the echo. 90º: excitation radio frequency pulse; 180º: rephasing radio frequency pulse; TR: Time to repeat; TE: Time to Echo.

By selecting different TRs and TEs, one can maximize one type of contrast over another. Consequently a relatively short TR and a short TE tend to maximize T1 Contrasts and create T1-weighted images. On the other hand, a long TR and a long TE maximize T2 Contrasts and give rise to T2-weighted images. All we need now, in order to actually be able to create an image is some spatial information. Luckily, signals can be localized by linearly altering the magnetic field in a predicable manner. In order to do so, usually "gradients" coils (corresponding to three orthogonal axes) are required. Those are special types of coils with conductive loops that are closer at one end and spread out at the other. The more tightly spaced are the loops, the greater is the strength of the induced magnetic field. The gradients impose changes in the magnetic field that cause the precessional frequency of the nuclei and their phase to vary in a systematic fashion allowing for spatial localization. Indeed, a matrix can then be created using perpendicular frequency and phase axes. Therefore, by overlapping information from both the frequency and the phase dimensions, one can localize the signal to one cell of the data matrix, leading ultimately (after mathematical transformations) to spatial localization at the pixel (2D), then voxel (3D) level. After that, all one needs is to take the information from all the voxels... *et voilà!* Behold the brain (or any other organ as a matter of fact) (Charkeres et al. 1992).

The principals and concepts exposed above give a rapid review on how an MRI machine uses both MR signals and the fact that different tissues have different magnetic characteristic properties to create three dimensional representations of organic matter. But how does one measure brain activity? The next section will explore that very same question.

4.2. Functional Magnetic Resonance Imaging

What is fMRI? It is a technique using MRI equipment that “measures” brain activity by detecting associated changes in blood flow (Huettel et al., 2009). Indeed, the association between brain function and blood flow has been known for more than a century (Toga and Mazziotta, 2002), however we had to wait until 1990 (Ogawa et al.) to discover that deoxyhemoglobin and oxyhemoglobin in the blood have different magnetic properties that can cause measurable changes in the MRI signal when blood flow varies accordingly with brain activation. Indeed, fMRI offers the possibility to visualize which regions of the brain are recruited while one is performing a cognitive, motor or sensorial task, or even no task at all (resting state). For the last twenty years, fMRI has come to dominate functional neuroimaging research (Huettel et al., 2009), therefore the following section will review some of its basic principals as well as different types of fMRI experimental designs, how fMRI data is analyzed and the main advantages and limitations of the technique.

4.2.1. Blood Oxygen Level Dependant (BOLD) response

Hemoglobin is the iron-containing oxygen-transport protein in the erythrocytes (red blood cells) of all vertebrates (Davey et al., 2001). When oxygen (O_2) binds to it, it is referred to as oxyhemoglobin (Hb), whereas deoxyhemoglobin (dHb) refers to the protein once O_2 has been removed. Blood is delivered to brain tissue via arteries, and arterioles which have high concentration of Hb. The O_2 and glucose are then taken up by brain cells (at the capillary level), and the deoxygenated blood eventually leaves the brain via the venuoles and veins. However, blood flow is not the same everywhere; indeed, regions with increased cellular activation have more oxygenated blood delivered to them, up to the point that there seems to be an oversupply of Hb (compared to the actual amount of O_2 needed) in those areas. Therefore, the BOLD response is based on those fluctuations in the ratio of Hb and dHb within and near the brain activated regions (Jessard et al., 2001).

A substance that is temporarily susceptible to the effects of an external magnetic field is called paramagnetic. When the hemoglobin molecule is not bound to O_2, it contains four "free electrons" which create a negatively charged "zone" around the dHB and give rise to its paramagnetic properties. Indeed, that negative "zone" increases the inhomogeneities in the external magnetic field which cause the surrounding ^{1}H nuclei to dephase faster from each other, consequently decreasing the MR signal. On the other hand, Hb lacks the paramagnetic properties of dHB and, on this account, does not decrease the MR signal (Ogawa et al., 1990). Therefore, based on what was said earlier, "active regions" (displaced dHb) should have a higher signal than "inactive regions" (fairly constant rate of dHb). Then, the BOLD response represents the change in MR signal in those same "activated regions". The response is first composed of a brief decrease in signal (dip due to initial O_2 consumption), followed by an important increase known as the positive response (due to oversupply of Hb and displacement of dHb), and ends with a return to baseline (preceded by another small dip). Usually, the positive response lasts for more than twelve seconds while its peak occurs 4 to 6 seconds after neuronal activity (which only lasts for some milliseconds) (Huettel et al., 2009) (Figure 4.4.).

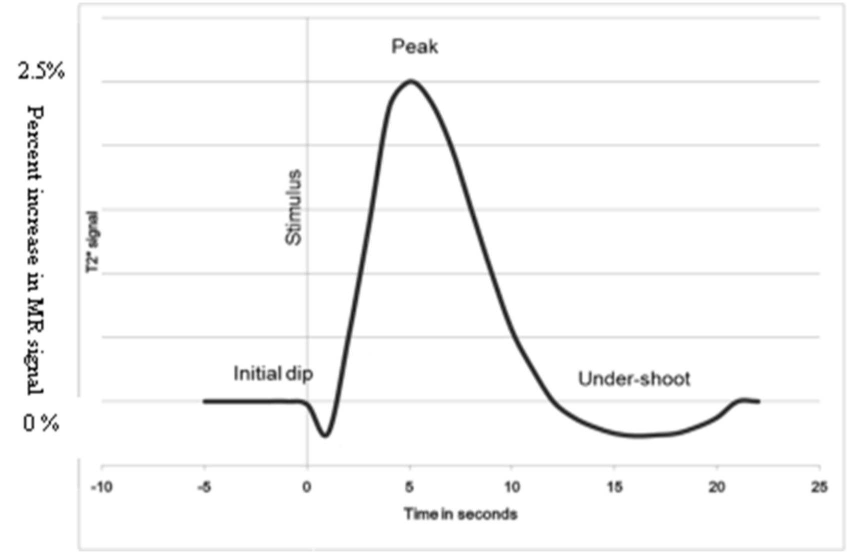

Figure 4.4. Recording of a BOLD response after a stimulus.

The BOLD response varies with the strength of the magnetic field provided by the MRI magnet (around 2.5 % of signal change at 1.5 Tesla versus 10-15% at 4 Tesla). Furthermore, some physiological phenomena or functions including respiration and head motion can also cause MR signal changes that are on the same order of magnitude (leading to "noise" or "artefacts"). Therefore, one has to try to optimise the signal to noise ratio (SNR) while keeping in mind that it generally involves a trade-off. Indeed, one way to increase the signal is to increase the scanning period time (scan time); however, shorter scan times diminish the risk of some artefacts as well (such as those caused by significant head movements). Another strategy is to increase the pixel or voxel sizes: larger the voxel, larger the signal detectable in that area. Unfortunately, that comes with a cost too, namely a decrease in spatial resolution. Furthermore, vascular artefacts also tend to be more prominent as pixel or voxel size is increased. Finally, one can also decrease the temporal resolution, but with the risk of missing brief cognitive processes (Huettel et al., 2009).

In summary, fMRI "measures" brain activity by detecting MR signal changes (BOLD response) associated with variations in the ratio of Hb and dHb (measured via dHb only). BOLD responses tend to be relatively small in magnitude and therefore susceptible to physiological artifacts. Nonetheless, they offer a good indirect measure of brain activity. In the following section, we will see how one can use those properties in an experimental setting.

4.2.2. Experimental protocols

Task based fMRI studies involve the comparison of the BOLD signals measured during the experimental conditions of a task and those acquired during the control conditions (or other experimental conditions or resting states). The choice of a specific task (as well as its control) depends largely on the cognitive, sensory or motor function one wants to investigate (e.g. the WCST can be chosen to explore set-shifting). The same can be said about the type of protocol design one decides to follow. All protocols have their advantages and flaws, as we shall see in this section (Jezzard et al, 2001).

4.2.2.1. Block design

In a block design paradigm, there is a series of "identical" trials (trials that involve the same type of cognitive, emotional, sensorial or motor processing) presented for a specific period of time (referred to as "on block" conditions). Each "on block" period is then followed by a similar period of time when no trials are presented ("off block" condition), after what the pattern (alternation between "on" and "off block" periods) is repeated a certain number of times. All of the BOLD signals of the "on block" periods are then grouped or averaged together, as are all the signals from the "off block" periods. Finally, the grouped or averaged signal from the "off block" periods is subtracted from the one of the "on block" periods, and a functional image is obtained.

It is also possible to create a multi-task block design in which blocks of different types of experimental conditions are compared to each other or to a control condition instead of resting states (Condition B/Control instead of "off block" periods). The overall procedure remains, however, the same as the one presented above (Figure 4.5.).

Figure 4.5. Illustration representing the block design paradigm. Condition A consists in a series of identical trials (experimental or control) presented for several seconds. Condition B consists in another series of identical trials.

The main advantage of a block design is that it is the simplest paradigm to implement. It is also a powerful tool to detect brain activity in a region. On the other hand, it is more susceptible than the other paradigms to habituation and the emergence of "undesired" cognitive strategies.

4.2.2.2. Slow event-related design

In the slow event-related design paradigm, first an event is presented, then the subsequent BOLD response is measured, then another event is presented, BOLD signal is measured again, etc. Events can randomly follow one another and the interval between each event also varies (as long as events are presented at least 8 to 12 seconds apart). Afterwards, all the BOLD signals acquired after "identical" trial types (that is, as for the block design, all the trials involved in the same type of processing) are grouped or averaged together, and those averaged responses are compared to the ones elicited by other experimental or control conditions (Figure 4.6.).

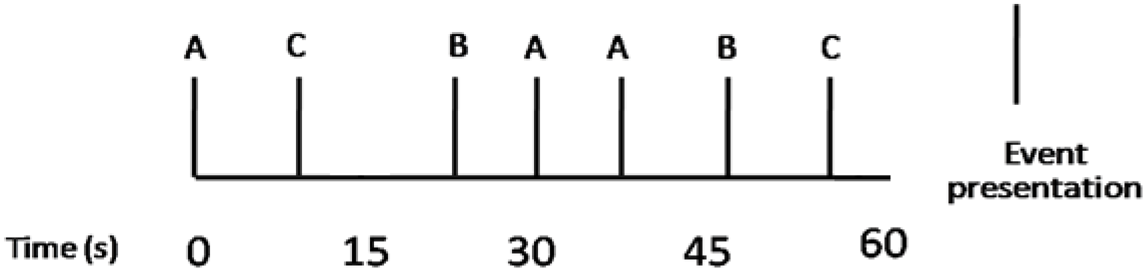

Figure 4.6.Illustration representing the slow event-related design paradigm. Each event or stimulus is presented at least 8 to 12 seconds apart.

The main advantage of such a design (over the block paradigm) is that it allows for increased randomization of trial presentation, therefore decreasing the anticipation phenomenon (that is the ability of a candidate to predict the next stimulus). It also has the advantage of precislely estimating the BOLD response linked to different events as very little overlap occurs. However, since a BOLD response takes several seconds to return to baseline, this design is very time consuming and doesn't allow for many events to be presented during one session. Consequently, it is almost never used.

4.2.2.3. Fast event-related design

The fast event-related design involves the presentation of short events (or trials) every 3 seconds (more or less) with, consequently, BOLD signals overlapping (Figure 4.7.). However, given the fact that BOLD responses approximately summate linearly for events presented at least 3 seconds apart and that each single event triggers a BOLD response, it is therefore possible to detect significant changes in BOLD signal associated with each trial. The interval between each event can vary from one another randomly or not as long as it remains close to or above 3 seconds. Once isolated, the BOLD responses elicited from the trials for each condition are averaged together and compared as it was the case for the other designs.

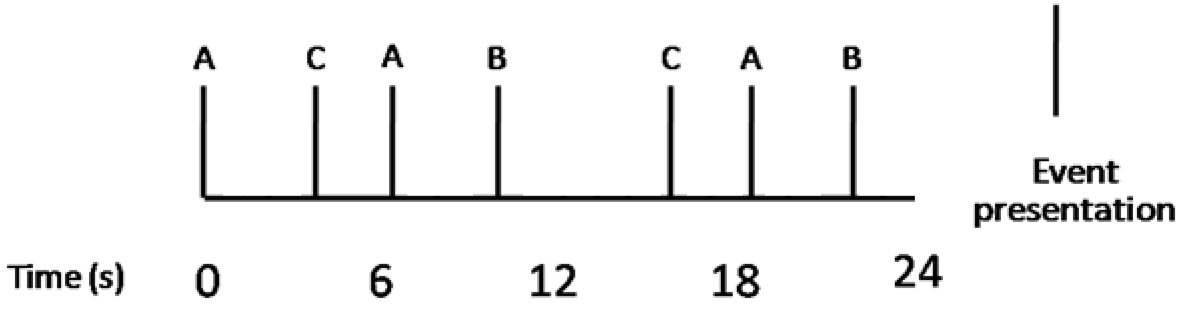

Figure 4.7. Illustration representing the fast event-related design paradigm. A, B and C are different events/stimuli presented randomly a couple of seconds apart.

The main (very small) setback of this design is that it involves more complex analyses than those required for the previous designs. This being said, with today's computers and automatic analyses tools, the concern is more theoretical than practical. On the other hand, the fast event-related design offers several benefits. It allows for increased speed of stimuli presentation compared to the slow event-related design. It is less susceptible to habituation and fatigue than the block design. The randomisation of events also reduces the anticipation phenomenon. Furthermore, the fact that any type of event can follow any other type of event allows for more freedom in the experimental design. Indeed, the presentation of events doesn't have to be totally random, but can instead follow a pattern conceived to study a specific "real-life" situations or cognitive process (e.g. If candidate responds X to condition A, follow with condition B, while if candidate responds Y to condition A, follow with condition C). Finally, every trial can be analyzed accordingly with the participant's performance (e.g. one can chose to analyse only correct answers and discard BOLD responses during mistakes) which cannot be done with a block design.

4.2.2.4. Mixed design

In this design, the trials are organized in blocks, but stimuli are presented approximately every 3 seconds or so and there is some variation in the interval duration between events as for the fast event-related design. Therefore, several trials from one condition are presented in a block and then there is another block containing trials of another condition, etc. However, the blocks themselves are usually presented in a randomized fashion or following a pattern conceived to study a particular situation or cognitive process. Furthermore, within each block, trials can still be separated and analyzed accordingly with the participants' performance or any other criteria deemed pertinent (e.g. one can chose to analyse only correct answers in a block and discard BOLD responses during mistakes)

This paradigm has most of the advantages and flaws of a fast-event related design. Moreover, it is very appropriate for fMRI studies using functional tasks similar to the WCST or the WWST given the fact that those tasks are conceived as a succession of conditions, each of which is itself composed of several trials during which participants' performance varies – correct answers versus errors (refer to Chapter 1 for more details).

4.2.3. Statistical Analyses of fMRI Data

Before the data can be properly analyzed, a series of corrections ("pre-processing") should be applied. Those include slice-timing corrections, motion corrections, filtering, spatial smoothing, etc. Afterwards, statistical analyses can be performed with the goal of obtaining accurate activation maps (images displaying the regions of activation related to a particular type of motor, sensory, emotional or cognitive processing). In order to create those maps, activation patterns have to be determined on a voxel by voxel level based on a statistically determined threshold of signal change intensity. To do so, we tend to use a General Linear Model (GLM), which is a statistical linear model. The GLM allows for great flexibility within analyses: different contrast combinations can be easily explored and combining data from within and between participants (or groups of participants) is relatively simple. The GLM also allows taking in consideration in the model confounding factors that contribute to data variance (i.e. head movements). A linear model relies on the following assumptions: 1) experimental designs determine almost entirely the responses, 2) BOLD responses have the same shape and duration throughout all the regions of the brain, 3) Consecutive and overlapping BOLD signals can be summated linearly (as previously stated), and 4) all the trials within one given condition should give rise to a same response. Those assumptions don't entirely reflect reality, but they're close enough for a linear model to be used in fMRI analyses without major issues.

The GLM can be written as follows: $\gamma_i = \chi_j\beta + \varepsilon_i$, where γ is a matrix with series of multivariate measurements (data from brain scanners), χ is a design matrix (our model –

design and confound variables), β is a matrix containing parameters that usually have to be estimated (the weight of the model), and ε is a matrix containing errors or noise (what the model has not taken into consideration). The goal is therefore to find parameters that minimize the errors ($\sum\varepsilon_i^2$), which based on the previous equation means finding the β that minimises $\sum(\gamma_i - \chi_i\beta)^2$, and that for each voxel. Consequently, if, within a voxel Z, for condition A, the weight of the model (β_A) is superior to the one for condition B (β_B), voxel Z should show increased activity in condition A compared to condition B. The statistical significance of the increased activity, however, is based on a t value: ($c\beta$)/std($c\beta$), where c is the contrast of condition A versus condition B.

But how does one choose which conditions to contrast? Usually, one tries to contrast (or subtract) two conditions that are identical in every way except on the process of interest. This principal of subtraction has been used in cognitive sciences for more than a century, especially in reaction time studies. For example, let's imagine an experiment during which a participant has to press on a button when a picture of an animal is presented to her or him and the three following conditions: 1) Press the button every time you see a picture of an animal; 2) Press the button every time you see the picture of a cat, but not the picture of a dog; and 3) Press the left button when you see the picture of a dog and the right button when you see the picture of a cat. One could argue, based on the principal of subtraction, that the necessary time to distinguish between two animals (cats and dogs) is equal to the reaction time in 2) minus the reaction time in 1), one could also postulate that the necessary time to take a decision would be equal to the reaction time in 3) minus the reaction time in 2). The same logic applies to functional neuroimaging studies, but instead of measuring reaction times, one "measures" brain activity and tries to determine which regions are more "activated" during a specific cognitive process of interest by subtracting "brain activations" between conditions that differ only in respect to that precise process of interest.

The specific steps involved in pre-processing and statistical analysis of fMRI data as well as the software used to perform those analyses are described in some more detail in the scientific papers constituting Chapters 5 and 6. Therefore, refer to those for more information.

4.2.4. Functional and effective connectivity

Let’s briefly allude to functional connectivity MRI even if no connectivity analyses were performed in our experiments. Functional connectivity is the connectivity between brain areas that share functional properties. More specifically, one can define it as the temporal correlation (statistical dependencies) between spatially remote neurophysiological events (Biswal et al., 1997). In order to perform functional connectivity, one usually choses one region of interest and looks at the other regions that correlate with it. It can both be applied to resting state studies and task state studies. However, correlations can arise in a variety of ways. Indeed, regions A, B and C could each be “functionally connected” to each other, or A, for example, could be connected to C only through B. Functional connectivity does not allow to distinguish between those two scenarios.

Therefore, integration within a distributed system is usually better understood in terms of effective connectivity: that is the influence that one neural system exerts over another. Aertsen and Preißl (1991) proposed that ‘‘effective connectivity should be understood as the experiment and time-dependent, simplest possible circuit diagram that would replicate the observed timing relationships between the recorded neurons.’’ This implies two important aspects: effective connectivity is dynamic, and depends on a model of interactions or coupling. Thus, when one wants to perform effective connectivity, one usually choses several regions of interest as well as one possible correlated region, and determines if the correlations are direct or not. Consequently, effective connectivity allows to distinguish between the two scenarios involving regions A, B and C presented above.

Let’s close this little opening on functional and effective connectivity by stating that these type of analyses are more and more popular in fMRI studies since they allow to investigate functional networks more accurately than simply looking at which regions show increased activity for a given contrast.

4.2.5. Advantages and limits of fMRI

The main advantage of fMRI compared to other functional neuroimaging techniques resides in the fact that it does not require people to undergo surgery, or to ingest substances, or be exposed to radiation. It is therefore a fairly safe imaging method. This being said, it doesn’t mean that every single individual can have an fMRI scan. First, all participants in an fMRI study have to be alive; there is strong discrimination against dead people (just to be clear, this is a comic relief). Second, no loose metallic objects allowed (from jewellery to braces). Third, implanted medical devices such as pacemakers could malfunction because of the rapid current switching produced by the gradients. Fourth, the current switching in the static magnetic field also induces Lorentz forces which manifest themselves by very loud noises (therefore, participants have to put on ear-plugs or a helmet). Fifth, participants have to remain as imobile as possible during the sessions in order to reduce movement induced artifacts. Finally, because the space within the machine is very small, people suffering from claustrophobia are usually unable to go through the scanning process (Huettel et al., 2009).

The fact that fMRI uses BOLD responses to indirectly measure brain activity brings its own limitations. Indeed, the BOLD response is slow to peak. Therefore, the time resolution of fMRI is quite low (seconds) especially compared to the time scale of activation of neural networks (milliseconds). BOLD signals are also sensitive to physiological factors and changes such as respiration and heart rate which can lead to artifacts as we mentioned. Finally, vascular artifacts are also a major concern in certain regions of the brain where they can completely mask the BOLD signal.

Finally, the principal of subtraction discussed above comes with its own caveats. Indeed, it assumes that one can add a cognitive process to a task without affecting the other processes already involved (assumption of pure insertion). However, such assumption is rarely completely true. For example, let’s say one wants to study how the brain processes movement and therefore compares two conditions, one (1) during which static squares are presented on a screen and another (2) during which moving squares are presented. One could postulate that by subtracting the activity measured in (1) from the activity measured in (2), one would be able to localise which regions are involved in visual movement processing; however, it is also possible that by adding movement in (2), that very same condition became more salient for the participant therefore drawing more attention to it. Consequently, the contrast (2) minus (1) may show increased activity in brain regions involved in attentional processing on top of visual movement processing.

4.3. Conclusion

Among all the functional neurimaging techniques, fMRI has taken the leading role in the last twenty years. It uses MR signals and the fact that different tissues have different magnetic characteristic properties to create three dimensional representations of the brain, to which images displaying “activated areas” are added. The indirect measure of brain activity is based on BOLD responses that reflect MR signal changes associated with variations in the ratio of Hb and dHb.

While performing a task based fMRI study, one can use different types of protocol designs: block-related, event-related or mixed design. Every protocol has its advantages and flaws, and the choice depends largely on the process being investigated and the task being employed. In the following two chapters, we will present two fMRI studies using a mixed design. The first one investigates the effect of aging on “set-shifting” (Article 1), while the second explores how aging affects two language processes: semantics and phonology (Article 2). Both studies use the WWST and compare the brain activity of old individuals to that of younger participants.

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CHAPTER 5

Article 1

CHAPTER 5

Article 1

Authors' contributions

Ruben Martins was the primary author of the experimental protocol that led to Article 1. This protocol (detailed in the Materials and Methods section of the paper) was inspired by the one elaborated by France Simard (refer to Simard et al. 2010 in the References section). It was also conceived under the guidance of Oury Monchi (main supervisor). Ruben Martins trained 14 individuals aging from 55 to 75 years old (old group) on the WWST and supervised all the fMRI sessions for each of these participants (the data from 10 of the 14 participants was used). France Simard had previously trained and scanned 14 young (from 18 to 35 years old – young group) individuals whose results were used in this study. Ruben Martins performed the data analysis (for the older group as well as the intergroup analysis), after receiving training from Jean-Sebastien Provost. The results were interpreted by Ruben Martins under the supervision of Oury Monchi. The article was entirely written by Ruben Martins. France Simard, Jean-Sebastien Provost and Oury Monchi provided useful feedback and suggestions on the different drafts of the article before the final version was completed and submitted.

5.1. Introduction

The first article was published on June 2012 (electronically on August 2011) in *Cerebral Cortex* (Oxford University Press). It was also the subject of a press release (August 2011) and received extensive international media coverage. Furthermore, it allowed its primary author (Ruben Martins) to receive a CIHR - Brain Star Award and a CIHR - Age+ Prize in 2012. It should be noted that the article and its references are presented in this Chapter respecting the submission formatting requirements of *Cerebral Cortex*.

The article is based on an fMRI study that used the WWST to explore differences between younger (18 to 30 years old) and older (55 to 75 years old) individuals regarding the recruitment of the fronto-striatal loops (introduced in Chapter 2) involved in set-shifting, namely cognitive loops including the VLPFC (area 47/12), the DLPFC (areas 9 and 46), the CN and the thalamus responsible for the monitoring and the planning of set-shifts, and a motor loop important in the execution of set-shifts that includes the PPFC and the putamen. Before we continue, let's just mention that the only reason why the older group included individuals below 65 years old was purely practical, so that the recruitment of high functioning participants would be easier.

This article addresses the first major objective of this thesis: to investigate how healthy aging affects patterns of neural activity related to executive processing (set-shifting). More precisely, given the high performing nature of the older participants, it informs on some compensatory mechanisms that allow for preservation of executive functioning despite aging. Indeed, the older participants in the study show delayed recruitment of the cognitive loops compared to the younger individuals. As mentioned in Chapter 3, this phenomenon is most probably of compensatory nature allowing for performance to be preserved at the expense of speed processing.

5.2. Changes in Regional and Temporal Patterns of Activity Associated with Aging during the Performance of a Lexical Set-Shifting Task

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Abbreviated title

Age-related changes in brain activity patterns during lexical set-shifting

Keywords: Prefrontal cortex, striatum, set-shifting, aging, compensatory mechanism, lexical processing, fMRI

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Abstract

Some older individuals seem to use compensatory mechanisms to maintain high level performance when submitted to cognitive tasks. However, whether and how these mechanisms affect fronto-striatal activity has never been explored. The purpose of this study was to investigate how aging affects brain patterns during the performance of a lexical analogue of the Wisconsin Card-Sorting Task which has been shown to strongly depend on fronto-striatal activity. In the present study, both younger and older individuals revealed significant fronto-striatal loop activity associated with planning and execution of set-shifts, though age-related striatal activity reduction was observed. Most importantly, while the younger group showed the involvement of a “cognitive loop” during the receiving negative feedback period (which indicates that a set-shift will be required to perform the following trial), and the involvement of a “motor loop” during the matching after negative feedback period (when the set-shift must be performed), the older participants showed significant activation of both loops during the matching after negative feedback event only. These findings are in agreement with the “load-shift” model postulated by Velanova and al. (2007) and indicate that the model is not limited to memory retrieval, but also applies to executive processes relying on fronto-striatal regions.

Introduction

Aging is not always correlated with significant cognitive decline, functional neuroimaging studies have indeed reported that some elderly people could perform almost as well as younger ones on cognitive tasks (see Ansado, 2009 for review). These individuals often showed bilateralization of activation (Cabeza, 2002; Reuter-Lorenz, 2002) as well as intrahemispheric reorganization of activation, mainly from the occipitotemporal to the frontal cortex (Grady et al., 1994; Grady et al., 2005; Madden et al., 1997; Reuter-Lorenz et al., 2000; Cabeza, 2004), an observation referred by Dennis and Cabeza (2008) as the Posterior-Anterior Shift in Aging (PASA) phenomenon. Furthermore, since over-recruitment in the elderly has been shown in high performing individuals (people with substantial cognitive reserve (CR)), it has been suggested that this additional cerebral network recruitment represents a form of plasticity which may serve as neural compensation for age-related loss in brain structure. This could explain why language performance, for example, does not decline proportionally to age-related brain atrophy (Park et al. 2002). Indeed, several functional neuroimaging studies have shown increased bilateral activity in high performing older individuals when compared with younger participants during naming (Wierenga et al., 2008) and verb-generation tasks (Person et al. 2004). Obler et al. (2010) have even shown anatomical evidence (using structural Magnetic-Resonance Imaging and Diffusion Tensor Imaging) for increased reliance on right-hemisphere regions mainly in the peri-Sylvian and the mid-frontal areas in older individuals with high naming skills.

Beside neural compensation, CR may also rely on another mechanism, known as neural reserve (see Stern, 2009 for a review), which is the utilization by the elderly of pre-existing brain networks that are more efficient and less susceptible to age induced disruption. Both mechanisms are not mutually exclusive and may actually coexist. Indeed, in a study by Ansado et al. (submitted), older individuals performing a two level load-condition visual letter-matching task showed greater prefrontal cortex (PFC) activity in both low and high-load conditions as well as similar parietal activity to the younger ones in the high load-condition, indicating the use of both neural compensation (frontal activity) and neural reserve (parietal activity) to cope with increasing task demands.

Recently, Velanova et al. (2007) have also suggested the existence of another age-related compensatory mechanism which consists of a shift from early to late selection processing during memory retrieval (the load-shift model). In other words, using the concepts of Rugg and Wilding (2000) who divided memory retrieval into three entities: retrieval orientation (anticipation of retrieval demands), retrieval effort (access of information) and post-retrieval monitoring (evaluation of the appropriateness of the recollected information), Velanova et al. (2007) hypothesized that older participants would rely more on retrieval effort and post-retrieval monitoring and less on retrieval orientation than younger ones. Indeed, their results showed that older adults presented increased and delayed recruitment of frontal regions compared with the younger ones during demanding retrieval. They theorized that this strategy shift could underlie the retention of high-level cognitive function in some older individuals, but at the expense of less flexible and slower performance on demanding cognitive tasks.

While older adults have been shown to perform more poorly than younger ones on many neuropsychological tasks (traditionally used to access executive functions) such as the Wisconsin Card-Sorting Task (WCST) (Parkin and Walter, 1992; Kramer et al., 2004) and the color-word Stroop task (Brink and McDowd, 1999), most age-related functional neuroimaging experiments have focused primarily on memory, perception and language processes, not on executive functions per se. These latter functions may be loosely defined as the collection of processes involved in planning, cognitive flexibility, rule acquisition, initiation of appropriate actions and inhibition of inappropriate ones, as well as execution of novel actions, (Stuss and Knight, 2002). A possible explanation for such a lack of functional neuroimaging studies on executive processes and aging could be the fact that behavioral findings are actually quite inconsistent. Indeed, several studies have either shown that the age-related decline in performance would disappear if non-executive components (eg. Motor-speed) were considered (Frisoe et al, 1997; Parkin and Java, 1999), or found no age-related performance decline at all (Boone et al, 1990). Furthermore, the separation between different executive processes can also be quite challenging. Nonetheless, some, as Hampshire et al. (2008), successfully managed to use fMRI to investigate how aging affected executive function. They arrived at the conclusion that there was indeed some age-related loss in efficient problem solving associated with decreased activity in the ventrolateral PFC and posterior parietal cortex, as well as in the dorsolateral PFC at a very old age.

The majority of functional neuroimaging experiments on age-related changes associated with executive processing, such as the one of Hampshire et al. (2008), have largely focused on cognitive decline and alterations in cortical patterns of activity. Yet the idea of executive functions related compensatory mechanisms was not explored nor was the effects of aging on subcortical areas like the basal ganglia. However, it has been shown in neuropsychological studies with Parkinson's (PD) and Huntington's (HD) disease patients that the basal ganglia contributes to executive functions, such as planning and set-shifting (Owen et al., 1996; Dubois and Pillon, 1997). Amongst the different striatal nuclei, the caudate nucleus is traditionally thought to play a greater role in executive processes, while the putamen seems more associated with motor activities. Results from our laboratory have suggested that the caudate nucleus and the putamen are respectively important in the planning and execution of self-generated novel actions (Monchi et al., 2006). Furthermore, structural degradation has been reported to occur in the striatum with aging (Wang et al., 2009**).** Indeed, the caudate nucleus and the putamen are known to have dense dopaminergic innervations which, combined with a strong evidence for an age-related loss in pre- and postsynaptic dopamine markers (D1 and D2 receptor densities) and fronto-striatal atrophy, explains this reduction in striatal activity (Bäckman and al. 2006).

Monchi et al. (2001) previously used an electronic version of the WCST to study fronto-striatal involvement in executive processes in young healthy adults. During task performance, participants were asked to match test cards with reference ones according to the color, shape, or number of stimuli on the cards. If they received the instruction that their matching was correct (positive feedback), participants had to continue matching according to the same rule as in the previous trial. On the other hand, if they were instructed that their matching was incorrect (negative feedback), they needed to choose a different rule (plan a set-shift) and then execute their matching according to the new rule they had chosen. With this experiment, Monchi et al (2001) showed the participation of two different cortico-striatal loops associated with the task: the planning of a set-shift (recorded during negative feedback periods) involved a cognitive loop that includes area 47/12 of the mid-ventrolateral PFC, the caudate nucleus, and the thalamus, while the execution of a set-shift (recorded during matching following negative feedback periods) involved the posterior PFC and the putamen. These results were replicated in a more recent study by Nagano-Saito et al. (2008) .

In a later experiment, Simard and al. (2010) developed a lexical version of the WCST, the Wisconsin Word-Sorting Task (WWST), and scanned young healthy participants during task performance using fMRI. The principles governing the WWST were exactly the same as the pictogram WCST version, but instead of matching cards, participants were asked to match test words with reference words according to semantic categorization, syllable rhyme, or syllable onset. In the study, Simard and al. (2010) showed the involvement of the cognitive loop during negative feedback periods and the involvement of the motor loop during the following matching periods. These results (similar to the ones of Monchi et al., 2001) seem to indicate that fronto-striatal loops contribute to the same executive processes regardless of whether they are applied to visual or language domains.

The aim of the present study was to explore how the patterns of activity observed in the cognitive and motor fronto-striatal loops during the performance of the WWST developed by Simard and al. (2010) changed with aging. We hypothesized that, as for young participants, the elderly would show fronto-striatal loop activity associated with planning and execution of a set-shift, but with reduced striatal recruitment due to an age-related striatal degradation (Wang et al., 2009). We also expected to see some neural compensation such as the PASA phenomenon to occur. This hypothesis was based on the fact that our older participants were expected to be high performing individuals, since they were all active professionals. Indeed, it has been shown that the PFC tends to be under-activated in older individuals whose performance becomes impaired both in PET (Reuter-Lorenz and Cappell, 2008) and fMRI studies (Hampshire et al., 2008).

We predicted that unlike the younger group, the older one would recruit similar frontal regions for both positive and negative trials as both types of trials should require compensatory mechanisms involving the frontal cortex, while only the negative trials would require frontal involvement for the younger participants. Finally and most importantly, we also wished to investigate whether the processes suggested by the load-shift model and proposed in the context of memory retrieval (Velanova et al. 2007) also occurred in tasks involving executive processes. In the present study, this would be reflected by a shift of activity from the planning period (feedback) to the execution period (matching) of a trial.

Materials and Methods

Subjects

Twenty-four French-speaking right-handed subjects (fourteen [group 1] whose mean age was 26 years old [range from 18 to 35, standard deviation: 5; 6 males, 8 females], and ten [group 2] whose mean age was 62 years old [range from 55 to 75, standard deviation: 8; 6 males, 4 females]) with no personal nor familial history of neurological or psychiatric disorder participated in this study. The age difference between the two groups proved to be very significant ($t = 13.44, p < 0.001$). The two groups were matched for level of education. Data from the young participants have been previously reported by Simard and al. (2010). Handedness was assessed by the Edinburgh Handedness Inventory. All candidates gave written informed consent to the protocol which had been reviewed and approved by the research ethics committee of the Regroupement Neuroimagerie Québec (CMER-RNQ). This committee follows the guidelines of the Tri-Council Policy Statement of Canada, the civil code of Quebec, the Declaration of Helsinki, and the code of Nuremberg.

Cognitive task

The Wisconsin Word Sorting Task (WWST) developed Simard et al. (2010) was administered, using a stimulus presentation software (Media Control Function; Digivox, Montréal, Canada). The WWST is a lexical analog of the computerized Wisconsin Card Sorting Task (WCST) used by Monchi et al. (2001) in which French words are used instead of the usual pictogram cards. A strict correspondence regarding the stimuli, the rules, and the number of exemplars was established between the WWST and the original WCST. Specifically, the three classification rules of the original task (i.e. classification according to color, shape, and number of visual stimuli) were replaced by three lexical ones: one semantic and two phonological rules that consisted of the syllable onset (attack) and syllable rhyme.

Throughout the task, four fixed reference words (bateau (ship), araignée (spider), cadran (clock) and poivron (pepper)) were presented in a row at the top of the screen: while a test word was shown in the middle of the screen below the reference row (Fig.1). During scanning, we projected the computer display onto a mirror in the MRI scanner. Each trial, participants had to match the test word with one of the reference words based on one the following rules: (1) semantic categorization, (2) syllable rhyme or (3) syllable onset. Word selection was performed by pressing the appropriate button of a magnetic resonance imaging compatible response box held with the right hand by the participant: the left button moved a cursor under the reference card from left to right, and the selection was made by pressing the right button. Every participant had to find the proper classification rule and apply it based on the feedback he/she received following each selection. A change in the screen brightness indicated to the subject whether the answer was correct (bright screen) or not (dark screen). After six consecutive correct trials, the rule changed without warning and the participant had to discover the new appropriate rule.

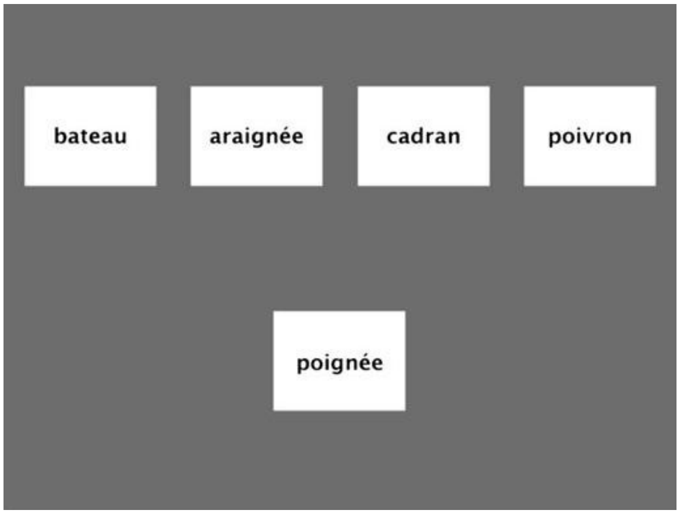

Fig.1 **An example of a typical trial of the WWST**
In this example, the participant is presented with the word *poignée* (handle) as a test stimulus. Matching according to semantics would require selection of the word *cadran (frame)*, according to rhyme syllable would require selection of the word *arraignée (spider)*, and according to onset syllable the word *poivron (pepper)*. (From Simard et al., 2010).

As in the original WCST, there were four matching possibilities for each one of the categories in the WWST: 4 semantic categories: transportation, animals, objects, and vegetables; 4 phonological onset syllables: ‘ba’, ‘a’, ‘ca’, ‘poi’; and 4 phonological rhyme syllables: ‘au’, ‘é’, ‘an’, ‘on’. The words have been all carefully chosen so they could have the same phonological syllabic structure according to the French lexical database *lexique 3*

(Pallier, 2005) http://www.lexique.org/, and be considered concrete according to the concreteness scale of Bonin et al. (2003). Word length ranged from four to nine letters and the number of syllables from two to three. Also, they were all selected out of over the 135,000 words contained in the French lexical database *lexique 3* (Pallier, 2005). First, the onset and rhyme syllables in which there were the most words were selected. Then, from this selection, the words that shared the same onset and rhyme syllables we picked and matched. And finally, from this later selection, the words that shared the same semantic category were chosen.

The same periods that were identified for the WCST version of Monchi et al. (2001) were defined for the present lexical equivalent. The WWST trials contained two types of periods: a matching period and a feedback period. The matching period started with the presentation of a new test word and continued until reference word selection. The length of this period varied from trial to trial depending on subject's response time. Matching was followed by a feedback period, which lasted 2.3 sec. and started as soon as a selection was made. This period ended with the presentation of the next test word on the screen initiating a new trial. Thus, inside those two periods, four different experimental events were defined: event 1, receiving negative feedback indicated by a dark screen and informing the subject that the selection was incorrect and therefore that a shift was required (the need to plan a set-shift); event 2, matching following negative feedback, which was the execution of the first match following negative feedback (the execution of a set-shift); event 3, receiving positive feedback indicated by a bright screen informing the subject that the current classification rule was the correct one (the need to maintain the same rule as in the previous trial); and event 4, matching following positive feedback, which was the execution of matching according to the current rule. A control condition was added in which the test word was the same as one of the four reference words and the participant was asked to match the test word to its reference twin. In this condition, two other event periods were defined: event 5, control feedback where the brightness of the screen did not change; and event 6, control matching.

All subjects participated in one fMRI session. Each scanning session contained four functional runs; each of one was made up of four task blocks. Each block consisted of three experimental (corresponding to each one of the three rules) and one control condition presented in a pseudo-random fashion. Just before the scanning session began, subjects were fully trained on the task using a personal computer. They practiced until their performance reached a plateau and with less than 6% of perseverative and non-perseverative errors. Finally, prior to training, participants were also familiarized with the test word list in order to verify that they knew all the words being used and could classify each one within one of the four semantic categories.

fMRI scanning

Participants were scanned at the Unité de Neuroimagerie Fonctionnelle of the Institut de gériatrie de Montréal using a 3T Siemens TIM MRI scanner (Siemens AG, Erlangen, Germany). Each scanning session began with a high-resolution T1-weighted three-dimensional volume acquisition for anatomical localization (voxel size, 1 x 1 x 1 mm^3), followed by acquisitions of echoplanar T2*-weighted images with BOLD contrast (TE, 30 msec; FA, 90°). Functional images were acquired in four runs containing 210 volumes each acquired every 2.5 sec. Volumes contained 36 slices with a matrix size 64 x 64 pixels (voxel size, 3.5 x 3.5 x 3.5 mm^3). The stimulus presentation and the scanning were synchronized at the beginning of each run.

Data analysis

The fMRI data was analyzed following the same method as in our previous studies (Monchi and al., 2001, 2004a, 2006, 2007; and Simard and al. 2010) and made use of the fMRIstat software developed by Worsley et al. (2002). The first three frames in each run were discarded. Images from each run were first realigned to the fourth frame for motion correction and smoothed using a 6 mm full width half-maximum (FWHM) isotropic Gaussian kernel. The statistical analysis of the fMRI data was based on a linear model with correlated errors. The design matrix of the linear model was first convolved with a difference of two gamma hemodynamic response functions timed to coincide with the acquisition of each slice. The correlation structure was modelled as an autoregressive process. At each voxel, the autocorrelation parameter was estimated from the least squares residuals, after a bias correction for correlation induced by the linear model. The autocorrelation parameter was first regularized by spatial smoothing and was then used to 'whiten' the data and the design matrix. The linear model was re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors. The resulting effects and standard effect files were then spatially normalized by non-linear transformation into the MNI 305 standard proportional stereotaxic space, which is based on that of Talairach and Tournoux (1988), using the algorithm of Collins et al. (1994). Anatomical images were also normalized to the same space using the same transformation. In a second step, runs and subjects were combined using a mixed effects linear model for the data taken from the previous analysis. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a Gaussian filter. Inter-group analyses were performed by direct comparisons using the effects and standard deviations files of all individuals from both groups. The amount of smoothing was chosen to achieve 100 effective degrees of freedom (Worsley et al., 2002, 2005). Statistical maps were thresholded at $p < 0.05$ correcting for multiple comparisons using the minimum between a Bonferroni correction and random field theory in the single and inter-group analysis. This yields a threshold of $t > 4.70$ for a single voxel or a cluster size >534 mm^3 for a significance assessed on the special extent of contiguous voxel (Friston et al., 1995). Peaks within the basal ganglia, thalamus, and PFC that were observed in our previous studies using the WCST in young healthy adults (Monchi et al., 2001) were considered predicted and are reported at a significance of $p < 0.001$ uncorrected [indicated by an asterisk (*) in the tables].

Six contrasts were generated for statistical analysis by subtracting the appropriate control period trials from that of the experimental event periods: (1) receiving negative feedback minus control feedback; (2) matching following negative feedback minus control matching; (3) receiving positive feedback minus control feedback; (4) matching following positive feedback minus control matching; (5) receiving negative feedback minus receiving positive feedback; (6) matching following negative feedback minus matching following positive feedback.

Behavioral data (errors and reaction times) were also collected and inter-group analyses were performed using SPSS 15.0 for Windows. A comparison between the two groups for each matching condition: (1) control matching, (2) matching following positive feedback and (3) matching following negative feedback was performed using T-Tests (one for each condition).

The same procedure was used to analyze errors: (1) set-loss errors (the participant changes of classification rule after having correctly applied it at least three times), (2) perseverative errors (incorrect and repetitive, more than twice, use of the same classification rule following negative feedback) and (3) control errors (incorrect classification during control trials); as well as incorrect classifications after a change in rule (related to the search for a correct rule). Note that these incorrect classifications are not considered errors, because subjects could not know the new classification rule on the first attempt after a set-shift.

Results

Behavioral performance

On average, in the younger group, control matching lasted 1286 msec (± 154 msec), matching following positive feedback lasted 1628 msec (± 183 msec) and matching following negative feedback lasted 1990 msec (± 187 msec). In the older group, control matching lasted 1794 msec (± 293 msec), matching following positive feedback lasted 2295 msec (± 525 msec) and matching following negative feedback lasted 2775 msec (± 465 msec).Matching following positive feedback proved to be significantly longer in the older group than in the younger one ($t = 3.845$, $p = 0.003$), so was matching following negative feedback ($t = 5.107$, $p < 0.001$) as well as control matching ($t = 5.001$, $p < 0.001$).

The younger candidates made on average 0.06 % perseverative errors and 2.38 % set-loss errors per experimental classification, as well as 0.05 % errors per control classification. They also made an average of 13.42 % incorrect classifications per experimental classification.The elderly made on average 0.11 % perseverative errors and 4.15 % set-loss errors per experimental classification, and 0.04 % errors per control classification. They also made an average of 14.29 % incorrect classifications per experimental classification. The number of set-loss errors proved to be significantly larger in the older group than in the younger one ($t = 2.383$, $p = 0.042$). However, this number remained very low in both groups, indicating that both our younger and older individuals were high performing participants. No other comparison between the two groups was significantly different (perseverative errors :$t = 2.001$, $p = 0.072$; control errors : $t = 0.520$, $p = 0.608$; and incorrect classifications after a change in the rule : $t = 1.619$, $p = 0.120$).

fMRI results

For each group, we compared the average BOLD signal obtained during the receiving and matching periods according to semantics, onset, and rhyme (combined) with the BOLD signal obtained during the corresponding periods in the control trials. We also performed inter-group analysis.

As predicted these analyses revealed, in both groups, the involvement of two different cortico-striatal loops during the performance of the WWST: one composed of the mid-ventrolateral PFC (area 47/12), the caudate nucleus and the thalamus, and another composed of the posterior frontal cortex and the putamen. However, the two loops were not activated during the same periods for the young and the elderly. Indeed, in younger adults, the analyses showed the involvement of the first fronto-striatal loop in the receiving negative feedback vs. control feedback contrast and the second one in the matching following negative feedback vs. matching following positive feedback contrast, while, in the elderly, both loops were significantly activated only during the matching following negative feedback vs. control matching contrast (Table VI).

Due to these differences in fronto-striatal loop activation timing, we computed two other contrasts in order to compare fronto-striatal activity between the two groups overall. In these contrasts the feedback and matching period were combined together, in order to look at the trials as a whole, i.e.: (7) [receiving negative feedback plus matching following negative feedback] minus [control feedback plus control matching] or put more simply [whole negative trial vs. whole control trial] and (8) [receiving positive feedback plus matching following positive feedback] minus [control feedback plus control matching] or put more simply [whole positive trial vs. whole control trial]. Only inter-group analyses are reported for these two last contrasts since intra-group analyses showed exactly the same activated regions as the corresponding receiving and matching periods put together.

As predicted, this further analysis revealed significantly reduced caudate nucleus activity in the older compared with the younger group in the negative events (Table IV). They also showed increased frontopolar area activity in older adults compared with younger ones in both the negative and positive event periods (Tables IV and V).

Only significant activations in the frontal, striatal and thalamic regions for the younger adults, older adults and intergroup comparisons are reported in the text below and the tables. The complete results for the younger group can be found in Simard and al. (2010).

(1) Receiving negative feedback

Younger adults

When receiving negative feedback was compared with the control feedback (Table I, and Fig.2), significant activations were observed bilaterally in the frontopolar cortex (area 10), the mid dorsolateral PFC (areas 9/46, 46), the mid-ventrolateral PFC (area 47/12) and the supplementary motor cortex (area 6). There was also increased activity in the left hemisphere in the anterior cingulate cortex (area 32), the posterior PFC (junction or areas 6,8 and 44) and the lateral premotor cortex (area 6). Furthermore, the thalamus and the caudate nucleus were also significantly activated.

When receiving negative feedback was compared with receiving positive feedback, the same pattern of activation was shown except for the posterior PFC (junction or areas 6,8 and 44) which proved to be significantly activated both in the left and the right hemisphere.

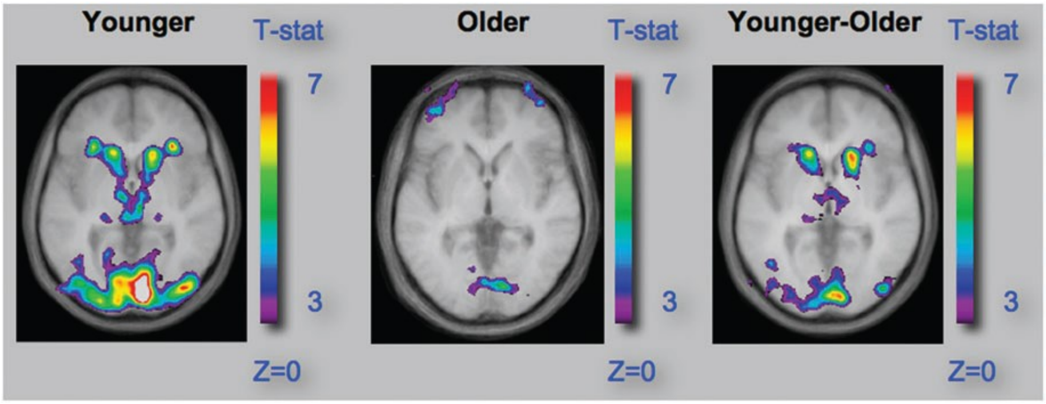

Fig.2 **Location of frontal and striatal peaks during receiving negative vs. control feedback.**
The younger group (cf. left) shows the activation a corticostriatal loop composed of the mid-ventrolateral PFC (area 47/12), the caudate nucleus and the thalamus, while the older group (cf. center) shows increased activity in the frontopolar cortex (area 10). When compared to the older group (cf. right), the younger one continues to show increased activity in the corticostriatal loop. The anatomical MRI images are the average of the T1 acquisitions of the 14 younger subjects (cf. left), the 10 older subjects (cf. center) and all 24 subjects (cf. right) transformed into stereotaxic space. The color scale represents the T statistic.

Table I: Receiving negative feedback (event 1) minus control feedback (event 5)

YOUNG

Anatomical Area	Stereotaxic coordinates	tstat	cluster size
Frontopolar cortex (area 10)			
Left	-38 54 14	4.13	1344
Right	34 60 12	3.85	648
Anterior cingulate cortex (area 32)			
Left	-8 34 26	3.88	5000
Mid-ventrolateral prefrontal cortex (area 47/12)			
Left	-30 26 -2	6.04	> 10000
Right	32 26 0	6.49	4503
Mid-dorsolateral prefrontal cortex (areas 9, 46, 9/46)			
Left	-52 26 30	4.44	4105
Right	52 24 36	3.58*	312
Posterior prefrontal cortex(junction of 6,8,44)			
Left	-48 6 38	6.46	4204
	-36 18 26	4.86	SC
Supplementary motor cortex (area 6)			
Left	-4 14 54	4.86	5000
Right	8 16 50	4.39	5000
Lateral premotor cortex (area 6)			
Left	-50 0 54	4.39	4145
	-40 0 40	4.16	SC
Caudate Nucleus (head)			
Left	-14 22 -2	6.3	> 10000
Right	16 20 0	6.11	4400
Thalamus			
Left	-8 -14 8	4.79	> 10000
Right	8 -11 3	3.99	> 10000
Midbrain			
Left	-4 -28 -4	5.79	> 10000
	-6 -14 0	4.75	SC
Right	6 -24 -4	5.72	> 10000
	6 -16 -12	5.52	SC

OLD

Anatomical Area	Stereotaxic coordinates	t stat	cluster size
Frontopolar cortex (area 10)			
Left	-42 54 2	4.56	3520
	-30 64 12	4.08	SC
Right	38 58 8	4.13	1984
Mid-dorsolateral prefrontal cortex (area 9)			
Left	-44 12 34	4.97	3004
Right	40 24 30	4.39	1103
Posterior prefrontal cortex(junction of 6,8,44)			
Left	-40 28 52	5.04	2600
Right	42 26 50	4.99	1300
	42 6 34	4.01	SC
Supplementary motor cortex (area 6)			
Left	-4 20 48	5.90	1000
Right	6 28 46	3.84	568
Lateral premotor cortex (area 6)			
Left	-36 2 66	5.58	2501
Right	34 22 66	4.138	1005

YOUNG VS OLD

Mid-ventrolateral prefrontal cortex (area 47/12)			
Right	32 26 0	4.71	6600
Caudate Nucleus (head)			
Left	-14 20 -4	6.23	3006
Right	18 20 -2	6.08	3300
Putamen			
Left	-18 16 -6	6.23	3650
Right	20 12 -2	6.06	3300
Thalamus			
Left	-8 -14 4	3.71	600
Right	8 -16 6	4.08	648

OLD VS YOUNG

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Legend: SC: same cluster as preceding peak VS: Inter-group comparison. Average BOLD signal in the first group is significantly greater than in the second one.

Older adults

In the older group (Table I; Fig.2), when receiving negative feedback was compared with the control feedback, there were bilateral significant activations in the frontopolar cortex (area 10), the mid dorsolateral PFC (area 9), the posterior PFC (junction of areas 6, 8, and 44), the supplementary motor cortex (area 6) and the lateral premotor cortex (area 6).

Interestingly, no significant increased activity was found in the mid-ventrolateral PFC or basal ganglia in either of the contrasts.

When receiving negative feedback was compared with the receiving positive feedback, there was only significant left activation in the frontopolar cortex (area 10), and the mid-dorsolateral PFC (area 9/46).

Intergroup comparison

When receiving negative feedback was compared with control feedback, significant activation was found in the younger participants versus the older ones in the right mid-ventrolateral PFC (area 47/12). There was also bilateral significantly increased activity in the thalamus, the putamen and the caudate nucleus (Table I, Fig.2).

When receiving negative feedback was compared with receiving positive feedback, greater left activation was found in the younger adults versus the older ones in the mid-dorsolateral PFC (area 9), the posterior PFC (areas 44) and the lateral premotor cortex (area 6), as well as right activation in the supplementary motor cortex (area 6). Also bilateral activation was recorded in the caudate nucleus and left activation in the putamen.

On the other hand, the older group showed only increased left activity in the frontopolar cortex (area 10) compared with the younger one when receiving negative feedback was compared with receiving positive feedback; and no increased activity at all when receiving negative feedback was compared with control feedback (Table I).

Table II: Matching following negative feedback (event 2) minus control matching (event 6)

YOUNG			
Anatomical Area	**Stereotaxic coordinates**	**tstat**	**cluster size**
Frontopolar cortex (area 10)			
Left	-36 56 16	5.16	> 10000
Right	30 56 18	5.19	> 10000
Anterior cingulate cortex (area 32)			
Right	10 30 28	5.69	> 10000
Mid-ventrolateral prefrontal cortex (area s 45, 47/12)			
Left	-30 28 6	7.12	> 10000
	-44 28 16	4.58	SC
Right	34 28 0	5.27	4448
	56 16 10	3.63	SC
Mid-dorsolateral prefrontal cortex (areas 9, 46, 9/46)			
Left	-48 28 32	4.74	> 10000
Right	42 36 26	5.26	> 10000
Posterior prefrontal cortex(junction of 6,8,44)			
Left	-50 6 44	5.00	> 10000
	-50 14 16	3.85	SC
Right	46 20 42	4.17	> 10000
Supplementary motor cortex (area 6)			
Left	-6 -4 68	4.52	> 10000
Right	2 -4 68	4.52	SC
Lateral premotor cortex (area 6)			
Left	-44 2 40	5.34	> 10000
	-28 0 5	5.26	SC
Right	28 0 52	6.92	> 10000

OLD			
Anatomical Area	**Stereotaxic coordinates**	**t stat**	**cluster size**
Frontopolar cortex(area 10)			
Left	-30 56 12	5.55	> 10000
Right	38 58 14	5.06	4088
Mid-ventrolateral prefrontal cortex(area s 45, 47/12)			
Left	-30 28 2	6..99	> 10000
Right	32 26 0	6.11	6606
Mid-dorsolateral prefrontal cortex (areas 9, 46, 9/46)			
Left	-46 24 32	6.84	> 10000
Right	42 20 32	3..97	740
Posterior prefrontal cortex(junction of 6,8,44)			
Left	-46 1048	4.48	> 10000
	-48 14 12	4.38	SC
Right	22 14 52	4.83	1890
	34 14 28	3.67	742
Supplementary motor cortex(area 6)			
Left	-4 20 48	5.97	9004
Right	8 24 46	5.08	8080
Lateral premotor cortex (area 6)			
Left	-28 2 60	3.45	> 10000
Right	26 6 56	5.4	1862
Caudate Nucleus (head)			
Left	-14 16 6	4.55	1376
Right	16 16 2	3.5*	488
Putamen			
Left	-20 2 2	3.46*	124
Right	22 -2 10	4.03	3000
Thalamus			
Left	-8 -10 4	4.89	1002
Right	12 -10 10	5.25	2002
Midbrain			
Left	-6 -12 -6	4.68	1000
Right	6 -14 -8	4.96	998

YOUNG VS OLD			
Supplementary motor cortex (area 6)			
Left	-2 8 56	4.46	1712
Lateral premotor cortex (area 6)			
Right	320 56	4..24	856

OLD VS YOUNG			
Frontopolar cortex(area 10)			
Left	-2 58 -4	3.61	656
Right	2 60 -4	3.70	656
Mid-ventrolateral prefrontal cortex (area 47/12)			
Left	-32 36 -10	3.98*	200
Caudate Nucleus (head)			
Left	-14 16 -4	4.51	656
Putamen			
Left	-16 14 -10	4.34	600
Right	16 12 -6	4.48	1168

Legend: Same as Table I

(2) Matching following negative feedback

Younger adults

When matching following negative feedback was compared with control matching in the younger individuals (Table II, Fig.3), BOLD signal was significantly greater bilaterally in the frontopolar cortex (area 10), the mid-dorsolateral PFC (areas 9 and 9/46), the mid-ventrolateral PFC (areas 45 and 47/12), the posterior PFC (junction of areas 6, 8, and 44), the supplementary motor cortex (area 6) and the lateral premotor cortex (area 6). Significant activation was also found in the right hemisphere in the anterior cingulate cortex (area 32).

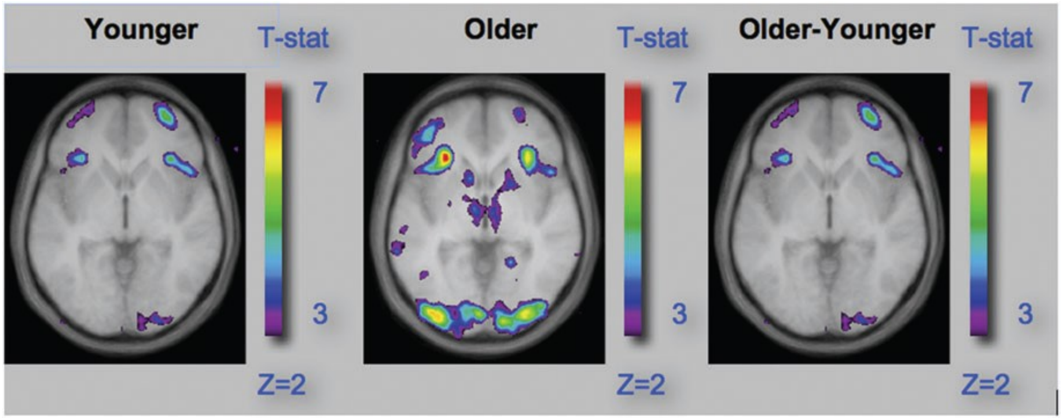

Fig.3 **Location of frontal and striatal peaks during matching following receiving negative feedback vs control matching.**
The younger group (cf. left) shows increased activity in mid-ventrolateral PFC (area 47/12) and the frontopolar cortex (area 10), while the older group (cf. center) shows increased activity in the frontopolar cortex (area 10), in a corticostriatal loop composed of the mid-ventrolateral PFC (area 47/12), the caudate nucleus, the thalamus, and the putamen (which, with the posterior prefrontal cortex, makes up another corticostriatal loop). When compared to the younger group (cf. right), the older one continues to show increased activity in the frontopolar cortex (area 10) and the ventrolateral PFC (area 47/12), as well as the caudate nucleus and the putamen (not shown in the figure). The anatomical MRI images are the average of the T1 acquisitions of the 14 younger subjects (cf. left), the 10 older subjects (cf. center) and all 24 subjects (cf. right) transformed into stereotaxic space. The color scale represents the T statistic.

When matching following negative feedback was compared with matching following positive feedback (Table III), the same cortical pattern of activation was observed except for the fact that the anterior cingulate cortex (area 32) proved to be bilaterally activated and the posterior PFC (junction or areas 6,8 and 44) showed only increased activation in the right hemisphere. However, this later contrast also showed significantly increased activation in subcortical regions, namely in the right thalamus and in the putamen bilaterally.

Table III: Matching following negative feedback (event 2) minus matching following positive feedback (event 4)

YOUNG			
Anatomical Area	**Stereotaxic coordinates**	**tstat**	**cluster size**
Frontopolar cortex (area 10)			
Left	-34 58 14	6.88	> 10000
Right	30 60 0	6.38	> 10000
Anterior cingulate cortex (area 32)			
Left	-4 42 20	5.42	> 10000
Right	2 34 18	4.64	> 10000
Mid-ventrolateral prefrontal cortex (area s 45, 47/12)			
Left	-44 18 -6	4.9	5360
Right	46 18 -8	5.44	> 10000
	54 20 16	4.12	5000
Mid-dorsolateral prefrontal cortex (areas 9, 46, 9/46)			
Left	-36 44 24	4.35	> 10000
	-42 28 36	6.01	SC
Right	40 48 24	5.09	> 10000
	44 34 40	5.64	SC
Posterior prefrontal cortex(junction of 6,8,44)			
Right	42 12 38	6.50	> 10000
Supplementary motor cortex (area 6)			
Left	-2 28 42	8.17	> 10000
Right	2 30 44	8.66	> 10000
Lateral premotor cortex (area 6)			
Left	-18 10 74	4.18	> 10000
Right	30 8 62	4.97	> 10000
Putamen			
Left	-30 6 6	3.44*	152
Right	34 2 2	4.26	5000

OLD			
Anatomical Area	**Stereotaxic coordinates**	**t stat**	**cluster size**
Frontopolar cortex (area 10)			
Left	-3460 16	5.62	9650
	-38 52 4	5.53	SC
Right	34 568	4.86	7936
Mid-dorsolateral prefrontal cortex(areas 9, 46, 9/46)			
Left	-40 36 26	5.02	8560
	-44 46 4	5.12	SC
Right	4038 36	4.58	9752
Mid-ventrolateral prefrontal cortex (area 47/12)			
Left	-30 28 0	4.80	1968
	-48 26 -8	4.10	SC
Right	4438-8	4.17	752
Posterior prefrontal cortex(junction of 6,8,44)			
Left	-482038	6.8	> 10000
	-48 16 10	3.66	888
Right	40 30 46	5.78	> 10000
Supplementary motor cortex(area 6)			
Left	-63638	5.1	9654
Right	6 2650	5.86	> 10000
Lateral premotor cortex (area 6)			
Left	-46 12 50	5.34	8620
Right	36 1860	6.17	> 10000

YOUNG VS OLD			
Putamen			
Left	-30 0 6	3.37*	200

OLD VS YOUNG
-

Legend: Same as Table I

Older adults

In the older group, when matching following negative feedback was compared with control matching or matching following positive feedback, significantly increased activity was found bilaterally in the frontopolar cortex (area 10), the mid-dorsolateral PFC (areas 9 and 46), the mid-ventrolateral PFC (areas 45 and 47/12), the posterior PFC (junction of areas 6, 8, 44), the supplementary motor cortex (area 6) and the lateral premotor cortex (area 6) (Tables II and III; Fig.3).

However, significant subcortical activation in the caudate nucleus, putamen and thalamus was only found when matching following negative feedback was compared with control matching (Table II, Fig.3).

Intergroup comparison

Greater activation was found in the younger adults compared with the elder ones in the left supplementary motor cortex (area 6) and the right lateral premotor cortex (area 6) when matching following negative feedback was compared with control matching (Table II), as well as in the left putamen when matching following negative feedback was compared with matching following positive feedback (Table III).

On the other hand, the older group showed significantly increased activity compared with the younger group bilaterally in the frontopolar cortex (area 10) and the putamen, as well as in the left mid-ventrolateral PFC (area 47/12), and the left caudate nucleus when matching following negative feedback was compared with control matching (Table II, Fig.3), but no increased activity at all when matching following negative feedback was compared with matching following positive feedback (Table III).

(3) Receiving positive feedback

Younger adults

When receiving positive feedback was compared with control feedback, there was no significant activation in the PFC or in the basal ganglia.

Older adults

In the older group, there were bilateral significant BOLD signal increases in the posterior PFC (area 8), and in no other region of the PFC or the basal ganglia.

Intergroup comparison

There was significant bilateral increased activation in the caudate nucleus in young adults compared with the older ones when receiving positive feedback was compared with control feedback. On the other hand, no significant activation was found in the PFC or the basal ganglia when comparing the older group with the younger one.

(4) Matching following positive feedback

Younger adults

Comparing BOLD signal during matching following positive feedback to control matching yielded significant activation for the younger participants in various regions, namely the right frontopolar cortex (area 10), the left and right mid-dorsolateral PFC (areas 9/46 and 46), the left mid-ventrolateral PFC (area 45 and 47/12), the left posterior PFC (area 44 and 6,8,and 44 junction), the left and right supplementary motor cortex (area 6) and the left and right lateral premotor cortex (area 6). No significant activation was found in the basal ganglia.

Older adults

The older group showed significantly increased activity in the left mid-dorsolateral PFC (areas 9 and 46), the left and right mid-ventrolateral PFC (areas 45 and 47/12), the left posterior PFC (6, 8 and 44 junction), the left and right supplementary motor cortex (junction of areas 6, 8) and the left and right lateral premotor cortex (area 6). Significantly increased bilateral activity was also found in the thalamus.

Intergroup comparison

For this comparison, no significantly greater activity was observed in young adults compared to the older ones. However, significant activation was observed in the older group compared with the younger group in the left caudate nucleus, and the right putamen.

(5) Whole negative trial vs. whole control trial

Intergroup comparison

When receiving negative feedback and matching following negative feedback were considered as a single event, we observed significantly increased activity in the frontopolar cortex (area 10) bilaterally for the older group compared with the younger one. We also found bilateral significant activation in the caudate nucleus for the younger group compared to the older one (Table IV; Fig.4).

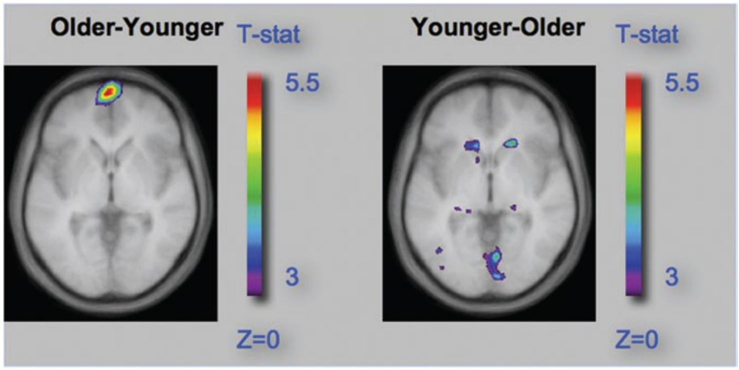

Fig.4 **Location of frontal and striatal peaks during receiving negative feedback plus matching following negative feedback vs. control feedback plus control matching.**
When compared to the younger group (cf. left), the older one shows increased activity in the frontopolar cortex (area 10), similar to the PASA phenomenon. When compared with the older group (cf. right), the younger one shows increased caudate nucleus activity. The anatomical MRI images are the average of the T1 acquisitions of all 24 subjects (cf. left and right) transformed into stereotaxic space. The color scale represents the T statistic.

Table IV: Whole Negative trial (events 1+2) minus whole control trial (events 5+6)

YOUNG VS OLD				**OLD VS YOUNG**			
Anatomical Area	**Stereotaxic coordinates**	**tstat**	**cluster size**	**Anatomical Area**	**Stereotaxic coordinates**	**t stat**	**cluster size**
Caudate Nucleus				Frontopolar cortex (area 10)			
Left	-12 220	3..84*	496	Left	-2 66 -2	5.42	3000
Right	18 24 -2	4.35	624	Right	12 60 -8	4.39	2440

Legend: VS: Inter-group comparison. Average BOLD signal in the first group is significantly greater than in the second one.

(6) Whole positive trial vs. whole control trial

Intergroup comparison

For this contrast, we observed significantly increased activity in the frontopolar cortex (area 10) bilaterally for the older compared with the younger individuals. No significant activation in the PFC or the basal ganglia was found in the younger group compared with the older one (Table V)

Table V: Whole positive trial (events 3+4) minus whole control trial (event 5+6)

YOUNG VS OLD				OLD VS YOUNG			
Anatomical Area	**Stereotaxic coordinates**	**tstat**	**cluster size**	**Anatomical Area**	**Stereotaxic coordinates**	**t stat**	**cluster size**
-				Frontopolar cortex (area 10)			
				Left	-4 66 0	4.38	980
				Right	12 58 -10	3.98	808

Legend: Same as Table IV

Discussion

The primary purpose of this study was to investigate how aging affects two different fronto-striatal loops involved in the performance of the WWST, namely a cognitive cortico-striatal loop including the mid-ventrolateral PFC (area 47/12), the caudate nucleus and the thalamus involved in the planning of a set-shift, and a motor loop important in the execution of a set-shift that includes the posterior PFC and the putamen. These regions were previously identified in studies using the WCST (Monchi et al., 2001; Nagano et al., 2008).

Simard et al. (2010) showed that significant activation is required in both of these cortico-striatal loops for set-shifting in young adults, and the present study showed the same for a group of older participants. However, the period events in which the two cortico-striatal loops were significantly activated proved to be very different between the two groups. Thus, aging influenced the timing of fronto-striatal recruitment, certainly the most important finding of this study. In fact, in younger adults, the analyses showed the involvement of the mid-ventrolateral PFC-caudate loop during the receiving negative feedback period (Tables I and VI, Fig.2) and the involvement of the posterior PFC-putamen loop during the matching following negative feedback event when compared to the matching following positive feedback event (Tables III and VI). While, in the older participants, they showed that both loops were activated during the matching following negative feedback event, and only during this event since no significant activity was observed in the ventrolateral PFC, nor the caudate nucleus in the receiving negative feedback period (Tables I, II and VI; Fig.2 and 3).

Table VI: Summary of the major results

	VLPFC	PPFC	CN	Pu	Th
RNFB-CFB	Y	Y and O	Y		Y
MNFB-CM	Y< O	Y and O	O	O	O
RPFB-CFB		O			
MPFB-CM	Y and O	Y and O			O
RNFB-RPFB	Y	Y	Y		Y
MNFB-MPFB	Y and O	Y and O		Y	

Legend :VLPFC: Ventrolateral prefrontal cortex; PPFC: Posterior prefrontal cortex; CN: caudate nucleus; Pu: Putamen; Th: Thalamus; RNFB-CFB: Receiving negative feedback minus control feedback; MNFB-CM: Matching following negative feedback minus matching following control feedback; RPFB-CFB: Receiving positive feedback minus control feedback; MPFB-CM: Matching following positive feedback minus matching following control feedback; RNFB-RPFB: Receiving negative feedback minus receiving positive feedback; MNFB-MPFB: Matching following negative feedback minus matching following positive feedback; O: significant activation in the older group; Y: significant activation in the younger group,< : implies that both groups showed significant activation, but that one showed significantly less activity than the other in the specified region.

It appears that during the performance of the WWST, younger individuals, when confronted to a set-shift, plan during the receiving negative feedback period event, and execute the set-shift during the matching event; while older individuals tend to plan and execute the set-shift during the matching following negative feedback period only. This observation corroborates the results of Velanova et al. (2007) who found that older individuals, during the performance of memory retrieval tasks, showed delayed (and increased) activation recruitment of cortical frontal regions, suggesting a shift strategy. They postulated that, during memory retrieval, younger individuals may extensively use early-selection processes and thus anticipate retrieval demands (which allows for information filtering before it is extensively processed at high levels), while older people tend to rely on late-selection processes to operate on information sequentially (access each past information serially and evaluate its appropriateness). This strategy shift, which they conceptualized in a model called the ‘‘load-shift’’, may represent an age-related compensatory mechanism which allows older individuals to maintain high-level cognitive function, but at the expense of slower performances. In our experiment and in agreement with this interpretation, older participants proved to be slower than younger ones (they took more time to match the test word with the reference word of their choice) and thus, especially during the matching following negative feedback period event. It should be noted though that slower time responses in the older group could also be attributed to increased neuronal recruitment in the elderly during matching events (Table VI). Indeed, it has been shown, in young individuals, that reaction times tend to increase as the amount of neural activity augments (Just et al., 1996). However, this explanation and the load-shift model are not mutually exclusive and both phenomena likely contribute to the current results.

Therefore, the present study seems to indicate that the "load-shift model" as postulated by Velanova et al. (2007), is not limited to memory retrieval, but may also apply to executive processes relying on cortical frontal regions (such as set-shifting). More interestingly, it shows that age-related delayed neuronal recruitment can be recorded in subcortical regions such as the striatum and not just in cortical areas. Also, since our older participants seem to wait until the moment they have to execute the task to actually plan their execution, another explanation regarding delayed recruitment may be postulated: with aging, individuals tend not to engage in costly executive processes until these become absolutely necessary. Of course, this latter hypothesis and the "load-shift model" are not necessarily contradictory and may actually co-occur. In the future, fMRI and EEG experiments using similar cognitive tasks as the WWSTor the WCST, but using feedback periods with variable lengths should be performed in order to further investigate the phenomenon.

One of our major hypothesis was that striatal activity would be significantly reduced in older individuals compared with the young (Wang et al., 2009). Indeed, the caudate nucleus and the putamen are known to have dense dopaminergic innervations which, combined with a strong evidence for an age-related loss in pre- and postsynaptic dopamine markers (D1 and D2 receptor densities) and fronto-striatal atrophy, explains the reduction of striatal activity associated with aging (Bäckman et al. 2006). In order to adequately compare young vs. elderly fronto-striatal activity, two contrasts were computed by combining brain activity during feedback and matching periods of positive and negative trials separately, and subtracting the corresponding control brain activity from it. These contrasts were necessary since the two groups showed, as previously mentioned, timing differences in striatal activity. As predicted, these analyses confirmed reduced caudate activity in the older group compared to the younger one during negative events (Table IV and Fig.4).

The present study also revealed significant age-related increased activity in the fronto-polar cortex (area 10) during both positive and negative trials (Tables IV and V; and Fig.4). This observation is consistent with the neural compensation view of the PASA phenomenon (Dennis and Cabeza, 2008) since participants in both our groups were high performing individuals. Indeed, this compensatory model implies that age-related increased prefrontal activity reflects the dynamic reallocation of resources to maintain task performance in response to altered aging brain function (Cabeza, 2004; Mattay et al., 2005; Grady et al., 2008; Reuter-Lorenz, 2008).

Furthermore, it has been proposed that the frontopolar cortex plays a crucial role in the combining of multiple cognitive rules, switching between different subtasks when multitasking and enabling a previously running subtask to be maintained in a pending state for future retrieval and execution upon completion of another ongoing subtask (Koechlin et al., 1999; Koechlin et al., 2003; Ramnani and Owen, 2004). Thus, it is very possible that older individuals, because they tend to operate on information sequentially and delay some executive processes (as previously discussed), need greater frontopolar involvement than younger individuals.

Our study did not show any bilateralization of brain activity in the older group, even though the WWST relies heavily on lexical-retrieval processes. Such an age-related bilateralization could have been excepted since several studies requiring lexical access and retrieval have shown increased recruitment of right hemisphere regions in high skilled old individuals (Wierenga et al., 2008; Person et al. 2004)) in both ‘core’ and ‘supplemental’ language regions defined respectively by Wingfield and Grossman (2006) as regions necessary for the task performance and as regions revealed in healthy adults by neuromimaging studies that are outside the traditional language areas. These findings are consistent with the HAROLD model of Cabeza (2002) which describes age-related hemispheric bilateralization as a compensatory mechanism. A possible reason for why our study failed to illustrate similar results relies most certainly on the fact that our younger individuals showed very important bilateral activity themselves (Simard et al., 2010). Therefore, a comparison between the two groups did not allow detecting any age-related hemispheric asymmetry.

Finally, another of our prediction was that the older group would recruit similar frontal regions for both positive and negative trials as both types of trials should require compensatory mechanism involving frontal areas, while only the negative trials would require important frontal involvement for younger participants. Indeed, when comparing negative vs. positive trials for both receiving and matching events (Tables III and VI), we saw that there were significantly fewer regional activation differences in the older group than in the younger one. This was especially true for the receiving negative feedback vs. receiving positive feedback contrast where the elderly showed almost the same activity for both positive and negative trials except in visual regions, while the younger group showed much greater activity in the PFC and the basal ganglia. Furthermore, even if these similarities during receiving feedback events seemed actually to be the result of decreased recruitment in the older group during negative trials, instead of increased recruitment during positive trials, as a consequence of age-related delayed activation (as discussed above), the same claim cannot be made for matching events. Indeed, during matching events, where recorded brain activity in the older group was at least as important (if not greater) as in the younger one, the elderly still presented fewer differences between negative and positive trials. The younger group showed increased PFC and putamen activity during negative matching compared to positive matching, while in the older group, even if there was still increased prefrontal activity during negative matching, the magnitude and the area extent of the increase was smaller. As well, the older group did not reveal any differences between the two types of trials regarding thalamus and basal ganglia activity. These findings corroborate the ones of Ansado et al. (submitted) who found that older individuals, during the performance of a two level load-condition (low and high) visual letter-matching task, showed important and similar frontal cortex activity in both conditions, an observation they attributed to age-related neural compensation. Our study, though, tends once more to show that these compensatory mechanisms are not limited to fronto-cortical areas, but may include the basal ganglia and the thalamus as well, since all these regions are involved in a cognitive cortico-striatal loop (Alexander et al., 1986; Middleton and Strick, 2002). Interestingly, regarding parietal areas, a different phenomenon occurs. These regions tend to be more and more recruited in older individuals as cognitive demand increases (Corbetta and Shulman, 2002) suggesting that elderly adults tend to call upon the neural reserve when neural compensation becomes insufficient to maintain performance. It should be noted, that the same observation can be made in our study: the elderly showed increased parietal activity in negative trials compared to positive ones (data not shown).

A limitation of the present study is the fairly small sample size of both our groups, especially the older one. Particularly, since differences in cortical activity (such as decreased DLPFC activation) between individuals in their 50s and those in their 70s have been reported (Hampshire et al. 2008). Therefore, bigger groups would have allowed for within group age stratification. In the future, similar studies should aim for greater sample sizes to allow for a more comprehensive data analysis.

In summary, the present study suggests that both the young and the elderly show fronto-striatal loop activity associated with planning and execution of set-shifts. The period events, however, in which these loops are activated differ between the two groups: older individuals show delayed fronto-striatal activity compared to the young. This finding may be a manifestation of the "load-shift" model postulated by Velanova and al. (2007). Moreover, we propose that a somewhat different phenomenon may also occur: older individuals may not engage in costly executive processes until these become absolutely necessary.

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CHAPTER 6

Article 2

CHAPTER 6

Article 2

Authors' contributions

Ruben Martins was the main author of the experimental protocol that led to Article 2. This protocol (detailed in the **Materials and Methods** section of the paper) was inspired by the one elaborated by France Simard (refer to [31] and [32] in the References section). It was also conceived under the guidance of Oury Monchi (main supervisor). Ruben Martins trained 18 individuals aging from 55 to 75 years old (old group) on the WWST and supervised all the fMRI sessions for each these participants (the data from 14 of the 18 participants was used – the data of 10 of those same participants had also been employed in Article 1 [different set of analyses]). France Simard had previously trained and scanned 14 young (from 18 to 35 years old – young group) individuals whose results were used in this study. Ruben Martins performed the data analysis (for the older group as well as the intergroup analysis) with the help of a research assistant (Nagano Atsuko). The results were interpreted by Ruben Martins under the supervision of Oury Monchi. The article was entirely written by Ruben Martins. France Simard and Oury Monchi provided useful feedback and suggestions on the different drafts of the article before the final version was completed and submitted.

6.1. Introduction

The second article was published on June 27 2014 in *PLOS ONE*. It was submitted a first time to the same scientific journal on January 2014; the editor's decision was "Major Revision". All comments from the reviewers were taken into consideration and addressed, after which a revised manuscript was resubmitted and eventually accepted for publication. It should be noted that the article and its references are presented in this Chapter respecting the submission formatting requirements of *PLOS ONE*. This article is based on the same fMRI experiment as for the first article, but employs a different set of analyses focusing on language processes. Once again, we used the WWST to explore differences between younger and older individuals, but this time, regarding the recruitment of the language pathways introduced in Chapter 2, namely a semantic pathway relying on the DLPFC, the VLPFC, the fusiform gyrus, the ventral temporal lobe and the CN, and a phonological pathway relying more on the posterior Broca's area (area 44), the temporal lobe (area 37), the temporoparietal junction (area 40) and motor cortical areas. For that reason, this article addresses the second major objective of this thesis: to investigate how healthy aging affects patterns of neural activity related to language processing (phonology and semantics). As for Article 1, given the high performing nature of the older participants, it informs about some compensatory mechanisms that allow for cognition to be preserved despite aging. Indeed, in this article, the semantic and phonological routes seem to merge in a single pathway in the older participants, but not in the younger ones. In other words, during semantic processing, older individuals use specific semantic pathways (neural reserve) and non-semantic (phonological) language-related regions (neural compensation); while during phonological processing, they use specific phonological pathways (neural reserve) and non-phonological (semantic) language-related regions (neural compensation). On the other hand, younger participants use primarily semantic pathways for semantic processing and phonological pathways for phonological processing. Therefore, older individuals appear to rely extensively on both neural reserve and neural compensation for both semantic and phonological processing during the performance of the WWST.

Title: Differences between patterns of brain activity associated with semantics and those linked with phonological processing diminish with age.

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Short title: Neural activity associated with different language processes in aging.

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Abstract

It is widely believed that language function tends to show little age-related performance decline. Indeed, some older individuals seem to use compensatory mechanisms to maintain a high level of performance when submitted to lexical tasks. However, how these mechanisms affect cortical and subcortical activity during semantic and phonological processing has not been extensively explored. The purpose of this study was to look at the effect of healthy aging on cortico-subcortical routes related to semantic and phonological processing using a lexical analogue of the Wisconsin Cart-Sorting Task. Our results indicate that while young adults tend to show increased activity in the ventrolateral prefrontal cortex, the dorsolateral prefrontal cortex, the fusiform gyrus, the ventral temporal lobe and the caudate nucleus during semantic decisions and in the posterior Broca's area (area 44), the temporal lobe (area 37), the temporoparietal junction (area 40) and the motor cortical regions during phonological decisions, older individuals showed increased activity in the dorsolateral prefrontal cortex and motor cortical regions during both semantic and phonological decisions. Furthermore, when semantic and phonological decisions were contrasted with each other, younger individuals showed significant brain activity differences in several regions while older individuals did not. Therefore, in older individuals, the semantic and phonological routes seem to merge into a single pathway. These findings represent most probably neural reserve/compensation mechanisms, characterized by a decrease in specificity, on which the elderly rely to maintain an adequate level of performance.

Introduction

How does age-related cognitive decline affect language? Surprisingly, not many studies have tried to answer this question. One possible reason is that it is somewhat difficult to separate pure language processes from working memory, which is often required during the execution of language tasks [1] [2] [3] [4] [5]. Nonetheless, most existing studies indicate that language function shows little performance decline with healthy aging [6] [7] [8]even if some older individuals do show impaired execution during language production tasks [9], and that errors accessing phonological word forms tend to occur more often in the elderly [10]. Indeed, most of these findings can be explained by a decline in working memory instead of language per se [7]. Furthermore, some language attributes such as semantic knowledge clearly increase as time passes by [8] [11]. Therefore, normal aging is characterized by language abilities preservation despite important cerebral tissue loss including white matter integrity [12] [13] [14].

Syntactic and narrative discourse processing studies have reported that the elderly tend to show increased bilateral cerebral activity compared to younger individuals [15]. Because such patterns seem to be associated with preserved language function in the elderly [15], they have been postulated to reflect a compensatory mechanism similar to the HAROLD (hemispheric asymmetry reduction in older adults) model conceptualized by Cabeza [16]. Other neuroimaging studies that looked at language function have also reported increased bilateral activity in high performing older persons during verbal generation [17] and naming tasks [18]. More recently, Obler and colleagues [19] have even shown anatomical evidence (using diffusion tensor imaging) that older individuals with high naming skills tend to rely more extensively on right-hemisphere frontal regions (peri-Sylvian and the midfrontal areas). Therefore, language function has been proposed to depend on similar compensatory mechanisms as other cognitive processes to maintain high performance despite age-related atrophy. Those mechanisms are namely the mentioned HAROLD model and intrahemispheric reorganization of activation, mainly from the occipitotemporal to the frontal cortex [20] [21] [22] [23] [24], an observation referred by Dennis and Cabeza [25] as the Posterior-Anterior Shift in Aging (PASA) phenomenon. Indeed, Grossman et al. [26] showed that during the execution of a language comprehension task, older good “performers” showed increased prefrontal cortex (PFC) activity compared to younger participants. On the other hand, some semantic neuroimaging studies showed the opposite: older participants presented increased posterior activation compared to the young [27] [28] [29]. All of these findings, however, represent brain activity reorganization and can therefore be considered neural compensation mechanisms.

The elderly may also rely on pre-existing brain networks that are more efficient and less susceptible to age-induced disruption in order to maintain high levels of performance, a compensatory mechanism known as neural reserve [30]. Grossman et al. [26] have shown that, when both older good and poor "performers" were compared during the execution of a sentence-comprehension task, poor "performers" engaged significantly less activation in some important sentence-processing areas (inferior frontal cortex and posterior-superior temporal cortex) relatively to good "performers". This finding appears to show that old good "performers" are able to rely more extensively on some well-preserved language networks, therefore using neural reserve as a compensatory mechanism.

In the present study, we aimed to explore how healthy aging affects two language functions, namely semantic and phonological processing. To do so we used the Wisconsin Word Sorting Task (WWST), a lexical analog of the Wisconsin Card Sorting Task (WCST) [31]. The principles governing this task are exactly the same as those in the original WCST. However, in the WWST, subjects have to classify words, instead of pictograms, according to one of the three following lexical rules: semantic, syllable onset, or syllable rhyme. In particular, the present study was designed to explore the compensatory mechanisms on which high performing older individuals rely to preserve language abilities and what is the specific effect of those mechanisms on the cortico-subcortical routes related to semantic and phonological processing.

We hypothesized that network specificity would be reduced with aging. Indeed, we thought that the elderly, in order to maintain performance, would rely extensively on neural reserve and compensation for both semantic and phonological processing which would lead to a loss in network specificity between rules [30]. We also expected reaction times to follow the same pattern as cerebral activity and therefore show fewer differences between classification rules in the older compared with the younger group since previous studies have shown that brain activity and reaction times were correlated [1]. Furthermore, given the fact that young healthy candidates have shown important frontal and bilateral activity during the performance of the WWST [32], we wanted to explore what would happen with respect to reduced hemispheric asymmetry (HAROLD model) and intrahemispheric reorganization of activity (PASA phenomenon) in the older group when compared to the younger one.

Materials and Methods

Subjects

Twenty-height French-speaking right-handed subjects (fourteen [younger group] whose mean age was 26 [range ± 5; 8 females, 6 males], and fourteen [older group] whose mean age was 63 [range: ± 8.0; 6 females, 8 males]) with no personal nor familial history of psychiatric or neurological disorder participated in the present study. Handedness was assessed by the Edinburgh Handedness Inventory. Participants gave written informed consent to the protocol, which was been approved by the research ethics committee of the Regroupement Neuroimagerie Québec (CMER-RNQ). This committee follows the guidelines of the civil code of Quebec, the Tri-Council Policy Statement of Canada, the Declaration of Helsinki, and the code of Nuremberg.

Cognitive task.

The Wisconsin Word Sorting Task (WWST) developed by Simard et al. [31] was administered using a stimulus presentation software named Media Control Function (Digivox, Montréal, Canada). This task has been previously used to study executive functions such as planning and set-shifting in both young [31] and older adults [33]. However, it can also be used to explore semantic and phonological processes by analysing accurate word matching according to semantics and to syllable onset/rhyme respectively [32]. The WWST is a lexical analog of the computerized Wisconsin Card Sorting Task (WCST) developed by Monchi et al. [34]; however, instead of using pictogram cards, it uses French words. A strict correspondence regarding the stimuli, the rules, and the number of exemplars was established between the two tasks [31]. Explicitly, the three classification rules of the WCST (i.e. classification according to color, shape, and number of visual stimuli) were replaced by three lexical ones: one semantic and two phonological rules, syllable onset (attack) and syllable rhyme.

Throughout the task, a new test word was shown in the middle of the screen below a reference row composed of four fixed words: bateau (ship), araignée (spider), cadran (clock) and poivron (pepper). During scanning, the computer display was projected onto a mirror in the MRI scanner. On each trial, participants had to match the test word with one of the reference words based on (1) semantic categorization, (2) syllable rhyme or (3) syllable onset. To select a word, subjects had to press the appropriate buttons of a magnetic resonance imaging compatible response box held with their right hand: the left button moved a cursor under the reference card from left to right, while the selection was made by pressing the right button. On each trial, participants had to find the proper classification rule and apply it based on the feedback he/she received following each selection. A change in the screen brightness indicated whether the answer was correct (bright screen) or not (dark screen). After six consecutive correct trials, the classification rule changed without warning and the subject had to discover the new appropriate rule.

Similarly to the original WCST, there were four matching possibilities for each one of the categories in the WWST: 4 semantic: transportation, animals, objects, and vegetables; 4 phonological onset syllables: ‘ba’, ‘a’, ‘ca’, ‘poi’; and 4 phonological rhyme syllables: ‘au’, ‘é’, ‘an’, ‘on’. The words have been all carefully chosen so they could have the same phonological syllabic structure and be considered concrete according respectively to the French lexical database *lexique 3* [35] and the concreteness scale of Bonin et al. [36]. Words were four to nine letters long with either two to three syllables. Firstly, the words that shared the most onset and rhyme syllables were chosen and matched into four categories. Then, from this selection, the words that shared the same semantic category were selected.

The WWST trials contained two sorts of periods: a matching period and a feedback period. The matching started with the presentation of a new test word and continued until reference word selection. The length of this period varied from trial to trial depending on participant’s response time. Matching periods were followed by a feedback period, which lasted 2.3 sec and started as soon as a selection was made. Positive feedbacks were indicated by a bright screen and informed the subject that the current classification rule was the correct one, while negative feedbacks were indicated by a dark screen and informed the participant that the selection was incorrect and therefore a shift was required. These periods ended with the presentation of a new test word on the screen initiating a new trial.

Every subject participated in one fMRI session. Each scanning session contained four functional runs; each of one was made up of four task blocks. All blocks consisted of three experimental (corresponding to each one of the three rules) and one control condition presented in a pseudo-random fashion. Just before the scanning session began, subjects were fully trained on the task using a personal computer. Everyone of them practiced until their performance reached a time response plateau with less than 6% of perseverative (incorrect use of the same classification rule following negative feedback more than twice in a row) and non-perseverative (the participant incorrectly changes the classification rule after having correctly applied it at least three times) errors. Finally, prior to training, participants were also familiarized with the list of test words in order to verify that they knew all of them and could classify each one within one of the four semantic categories. For the present study, we explored exclusively language processing, therefore we focused solely on the successful matching periods following positive feedback (removing the first positive trial after a set-shift or an error). Nine contrasts were generated for statistical analysis by subtracting the control matching period trials from that of the matching following positive feedback periods for each of the three classification rules as well as by subtracting the matching following positive feedback period trials of one rule from the same period of another rule. Explicitly, these contrasts are (1) matching following positive feedback according to semantics minus control matching; (2) matching following positive feedback according syllable onset to minus control matching; (3) matching following positive feedback according to rhyme minus control matching; (4) matching following positive feedback according to semantics minus matching following positive feedback according to syllable onset; (5) matching following positive feedback according to semantics minus matching following positive feedback according to rhyme; (6) matching following positive feedback according to syllable onset minus matching following positive feedback according to semantics; (7) matching following positive feedback according to syllable onset minus matching following positive feedback according to rhyme; (8) matching following positive feedback according to rhyme minus matching following positive feedback according to semantics; (9) matching following positive feedback according to rhyme minus matching following positive feedback according to syllable onset.

fMRI scanning

Every participant was scanned at the Unité de Neuroimagerie Fonctionnelle of the Institut de Gériatrie de Montréal using a 3T Siemens TIM MRI scanner (Siemens AG, Erlangen, Germany). Scanning sessions began with a high-resolution T1-weighted three-dimensional volume acquisition for anatomical localization (voxel size, 1 x 1 x 1 mm^3), followed by echoplanar T2*-weighted images with BOLD contrast (TE, 30 msec; FA, 90°) acquisitions. Functional images were acquired every 2.5 sec in four runs containing 210 volumes, and each volumes contained 36 slices with a matrix size 64 x 64 pixels (voxel size, 3.5 x 3.5 x 3.5 mm^3). Stimuli presentation and scanning were synchronized at the beginning of each run. It should be noted that the whole data linked to this study can be made available on a secured server upon request to the corresponding author.

Data analysis

The fMRI data was analyzed following the same method as in our previous studies [31] [32] [33] [34] [37]. It made use of the fMRIstat software developed by Worsley et al. [38]. For the analysis, the first three frames in each run were discarded. Images from all runs were first realigned to the fourth frame for motion correction and smoothed using a 6 mm full width half-maximum (FWHM) isotropic Gaussian kernel. The statistical analysis of the fMRI data was based on a linear model with correlated errors. The design matrix of the linear model was first convolved with a difference of two gamma hemodynamic response functions timed to coincide with the acquisition of each slice. Furthermore, the correlation structure was modelled as an autoregressive process. At each voxel, after bias correction for correlation induced by the linear model, the autocorrelation parameter was estimated from the least square residuals. The autocorrelation parameter was first regularized by spatial smoothing and was then used to 'whiten' the data and the design matrix. The linear model was re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors. Then, the resulting effects and standard effect files were spatially normalized by non-linear transformation into the MNI 305 standard proportional stereotaxic space, which is based on that of Talairach and Tournoux [39], using the algorithm of Collins and colleagues [40]. Anatomical images were also normalized using the same space and transformation. In a second step, using a mixed effects linear model for the data taken from the previous analysis, runs and subjects were combined. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a Gaussian filter. Inter-group analyses were performed by direct comparisons using the effects and standard deviations files of all individuals from both groups. The amount of smoothing was chosen so that 100 effective degrees of freedom would be achieved [38] [41]. Statistical maps were thresholded at $p < 0.05$ correcting for multiple comparisons using the minimum between a Bonferroni correction as well as random field theory in the single and inter-group analysis. This yields a threshold of $t > 4.70$ for a single voxel or a cluster size >534 mm^3 for a significance assessed on the special extent of contiguous voxel [42]. Peaks within the basal ganglia, thalamus, and PFC that were observed in our previous studies using the WWST in young healthy adults [32] were considered predicted and are reported at a significance of $p < 0.001$ uncorrected [indicated by an asterisk (*) in the tables].

Behavioral data (reaction times) were also collected, and intra and inter-group analyses were performed using SPSS 15.0 for Windows. A comparison between the two groups for each classification rule and between classification rules for each group was performed using T-Tests and ANOVAs. For these analyses, the reaction times for control matching trials were subtracted from those of the classification rules in order to account for age-related motor-speed decline [43] [44].

Results

Behavioral performance

On average, in the younger group, control matching lasted 1285 msec (± 166 msec), matching following positive feedback according to semantics lasted 1785 msec (± 235 msec), matching according to syllable onset lasted 1531 msec (± 198 msec) and matching following according to syllable rhyme lasted 1695 msec (± 181 msec). When removing control matching from the different matching following positive feedback periods, then matching according to semantics only lasted 500 msec (± 144 msec), matching according to syllable onset lasted 246 msec (± 128 msec) and matching according to syllable rhyme lasted 410 msec (± 149 msec).
In the older group, control matching lasted 1795 msec (± 292 msec), matching following positive feedback according to semantics lasted 2357 msec (± 495 msec), matching according to syllable onset lasted 2282 msec (± 534 msec) and matching according to syllable rhyme lasted 2399 msec (± 538 msec). However, by removing control matching from matching following positive feedback, matching according to semantics only lasted 562 msec (± 273

msec), matching according to syllable onset lasted 487 msec (± 278 msec) and matching according to syllable rhyme lasted 604 msec (± 285 msec).

Older individuals proved to be slower than younger ones for all conditions (Control: $p < 0.001$ $t= 5.446$, semantics: $p=0.001$ $t = 3.790$, syllable onset: $p < 0.001$ $t= 4.851$, syllable rhyme: $p < 0.001$ $t= 4.581$). However, only time responses during phonological rules proved to be slower in the older group when control times were subtracted (Semantics: $p = 0.4765$ $t = 0.724$, syllable onset: $p = 0.009$ $t= 2.864$, syllable rhyme: $p = 0.041$ $t= 2.176$).

When we perform comparisons between rules within each group, we find that, for younger individuals, response times tend to be shorter for syllable onset compared both to semantics and to syllable rhyme taking or not control response times into account (ANOVA: $F = 5.477$, $p = 0.008$ [semantics vs syllable onset: $p=0.005$ $t = 3.093$, syllable rhyme vs. syllable onset: $p = 0.031$ $t = 2.287$]; ANOVA - control response times subtracted – $F = 11.743$, $p < 0.001$ [semantics vs syllable onset: $p < 0.001$ $t = 4.933$, syllable rhyme vs. syllable onset: $p= 0.004$, $t= 3.124$]). On the other hand, all these differences disappear for the older group (ANOVA: $F = 0.129$ $p = 0.880$;ANOVA - control response times subtracted – $F = 0.452$, $p = 0.641$).

fMRI results

As predicted, the analysis revealed that differences between semantic and phonological pathways tend to diminish with aging. Indeed, while younger individuals showed increased ventrolateral PFC activity during matching according to semantics compared to matching according to syllable onset or rhyme, older individuals did not. Also, when matching according to one of the phonological rules was compared to matching according to semantics, younger individuals showed increased posterior prefrontal activity (rhyme) and posterior parietal activity (onset), while older individuals, once more, did not show increased activity at all.

All significant activation for the younger adults, the older adults and intergroup comparisons are reported in this section. Tables I to IX contain a complete description of all regions significantly activated for younger and older adults as well as intergroup contrasts. The complete results for the younger group can also be found in the study by Simard et al. [32].

Table I. Matching according to semantics minus control matching in the YOUNG

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
YOUNG				
Frontopolar cortex (area 10)	Left	-42 54 -4	7.22	>10000
Anterior cingulate cortex (area 32)	Left	-8 36 28	3.72	>10000
	Right	10 36 28	5.33	>10000
Ventrolateral prefrontal cortex (area 47/12)	Left	-30 30 4	7.46	>10000
	Right	36 28 0	6.62	3120
Ventrolateral prefrontal cortex (area 45)	Left	-48 28 20	6.95	>10000
Dorsolateral prefrontal cortex (areas 9, 9/46)	Left	-52 28 28	7.22	>10000
Superior frontal cortex (area 6, 8 SMA)	Left	-4 20 50	8.31	>10000
Lateral premotor cortex (area 6)	Left	-48 8 44	5.66	>10000
Posterior cingulate cortex (area 23)	Left	-2 -34 26	4.9	2520
Inferior temporal cortex (area 37)	Left	-46 -62 -6	6.15	>10000
Lateral posterior parietal cortex (area 7)	Left	-26 -62 42	7.5	>10000
	Right	28 -68 52	4.41	>10000
Occipital cortex (area 19)	Left	-30 -70 -10	6.79	>10000
	Right	22-68 8	7.08	>10000
Occipital cortex (area 18)	Left	-38 -80 -8	7.84	>10000
	Right	30 -86 4	7.51	>10000
Occipital cortex (area 17)	Left	-8 -84 4	7.15	>10000
	Right	8 -84 8	8.55	>10000
Thalamus	Left	-6 -14 10	5.32	5272
	Left	-26 -34 6	5.09	>10000
	Right	22 -28 0	5.47	824
	Right	8 -14 10	3.87	5272
Caudate nucleus (head)	Left	-12 -2 16	3.58	5272
	Right	12 8 2	4.05	5272
Cerebellum	Left	-38 -62 -28	4.07	>10000
	Right	34 -74 -18	6.45	>10000
YOUNG VS OLD				
Anterior cingulate cortex (area 32)	Left	-16 28 2	3.78	280
	Right	12 32 22	4.12	520
Ventrolateral prefrontal cortex (area 45)	Left	-48 22 20	5.19	7424
Dorsolateral prefrontal cortex (area 9)	Left	-56 24 28	4.88	7424
Superior frontal cortex (area 6, 8 SMA)	Left	-4 12 54	4.17	2152
Lateral premotor cortex (area 6)	Left	-48 2 40	4.35	736
Posterior cingulate cortex (areas 23, 31)	Left-area 31	-20 -66 8	5.30	>10000
	Left-area 23	-2 -26 30	4.71	1128
	Right-area 31	8 -68 14	6.28	>10000
Lateral posterior parietal cortex (area 7)	Left	-32 -56 58	4.00	>10000
Precuneus (area 7)	Left	-10 -66 50	6.25	>10000
	Right	4 -86 42	5.14	>10000
Occipital cortex (area 19)	Left	-24 -66 38	6.47	>10000
	Right	8 -82 40	4.56	>10000
Occipital cortex (area 18)	Left	-30 -84 12	6.37	>10000
	Right	8 -86 8	6.40	>10000
	Right	34 -86 4	5.49	>10000
Occipital cortex (area 17)	Left	-1 -74 12	6.03	>10000
	Right	8 -88 6	6.45	>10000
Thalamus	Left	-20 -32 0	5.25	1792
	Right	22 -30 0	5.26	1072
Cerebellum	Left	-16 -86 -16	6.04	>10000

(1) Semantics

Younger adults

When semantics was compared with control matching (Table I), significant activations were observed bilaterally in the mid-ventrolateral PFC (area 47/12), the mid-dorsolateral PFC (area 9, 9/46), the anterior cingulate cortex (area 32), the posterior parietal cortex (area 7), the occipital cortex (areas 17, 18 and 19), and the cerebellum. The ventrolatrolateral PFC (area 45), the frontopolar cortex (area 10), the lateral premotor cortex (area 6), the posterior cingulate cortex (area 23), and the inferior temporal cortex (area 37, fusiform gyrus) also showed significant activation in the left hemisphere. Subcortically, significant activity was observed bilaterally in the thalamus and the caudate nucleus.

Older adults

In the older group (Table II), there was significant left hemisphere activity in the anterior cingulate cortex (area 32), the mid-dorsolateral PFC (areas 9 and 46), and the SMA (6/8 junction). The cerebellum showed significant right activity.

Intergroup comparison

Significant bilateral activation was found in the younger participants versus the older ones in the anterior cingulate cortex (area 32), posterior cingulate cortex (areas 23 and 31), the posterior parietal cortex (area 7), the occipital cortex (areas 17, 18 and 19), and the thalamus. There was also significantly increased activity in the left hemisphere in theventrolateral PFC (area 45), the mid-dorsolateral PFC (area 9), the posterior cingulate cortex (area 23), the lateral posterior parietal cortex (area 7), and the cerebellum (Table I).

On the other hand, the elderly showed greater bilateral activation in the in the frontopolar cortex (area 10), the insula (areas 41 and 43), the posterior inferior parietal cortex (area 40), and the middle and superior temporal cortices (areas 22 and 39) compared to the young group. There was also significant increased activity in the left hemisphere in the anterior cingulate cortex (areas 32) and the cerebellum, while the posterior cingulate cortex as well as the occipital cortex (area 19) showed increased activation in the right side of the brain (Table II).

Table II. Matching according to semantics minus control matching in the OLD

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
OLD				
Anterior cingulate cortex (area 32)	Left	-8 30 40	3.98	936
Dorsolateral prefrontal cortex (areas 9, 9/46)	Left	-50 26 30	3.49	336
Superior frontal cortex (area 6, 8 SMA)	Left	-2 10 68	4.11	328
Cerebellum	Right	12 -86 -30	3.63	256
OLD VS YOUNG				
Frontopolar cortex (area 10)	Left	-6 64 0	5.42	7848
	Right	4 60 -4	5.72	7848
Anterior cingulate cortex (area 32)	Left	-6 50 -4	4.51	7848
Insula (areas 41, 43)	Left -area 43	-40 0 2	4.80	3224
	Left -area41	-40 16 4	4.39	3224
	Right -area43	40 0 8	4.28	552
	Right -area 41	36 4 -16	4.22	272
Posterior inferior parietal cortex (area 40)	Left	-60 -30 22	5.33	2472
	Right	58 -30 22	4.69	3848
Middle Temporal Cortex (area 39)	Left	-50 -64 14	4.75	5912
	Right	42 -58 18	4.40	2664
Superior Temporal Cortex (area 22)	Left	-64 -54 16	3.95	5912
	Right	52 -56 16	4.14	2664
Posterior cingulated cortex (area 31)	Right	2 -50 36	4.02	1904
Occipital cortex (area 19)	Right	-44 -78 34	4.22	5912
Cerebellum	Left	-22 -84 -36	4.35	464

(2) Syllable onset

Younger adults

When syllable onset was compared with control matching in the younger individuals (Table III), BOLD signal was significantly greater bilaterally in the anterior cingulate cortex (area 32), the ventrolateral PFC (area 47/12), the posterior parietal cortex (area 7), the occipital cortex (areas 17, 18 and 19) and the cerebellum; and significantly greater in the left hemisphere in the frontopolar cortex (area 10), the ventrolateral PFC (area 45), the dorsolateral PFC (area 9, 9/46), the SMA (area 6,8), the lateral premotor cortex (area 6), the posterior parietal cortex (area 40) and the inferior temporal cortex (area 37). Subcortically, significantly increased activity was observed, bilaterally, in the thalamus and the globuspallidus.

Table III. Matching according to syllable onset minus control matching in the YOUNG

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
YOUNG				
Frontopolar cortex (area 10)	Left	-38 62 8	9.91	5904
Anterior cingulate cortex (area 32)	Left	-2 42 34	3.53	>10000
	Right	8 34 32	3.5	>10000
Ventrolateral prefrontal cortex (area 47/12)	Left	-30 28 2	6.29	2120
	Right	32 28 0	5.1	1464
Ventrolateral prefrontal cortex (area 45)	Left	-48 28 20	5.55	>10000
Dorsolateral prefrontal cortex (areas 9, 9/46)	Left	-52 28 28	5.55	>10000
Superior frontal cortex (area 6, 8 SMA)	Left	-2 22 48	9.1	>10000
Lateral premotor cortex (area 6)	Left	-48 6 42	6.11	>10000
Posterior inferior parietal cortex (area 40)	Left	-34 -46 44	5.26	>10000
Inferior temporal cortex (area 37)	Left	-48 -62 -10	6.22	>10000
Lateral posterior parietal cortex (area 7)	Left	-26 -60 42	7.53	>10000
	Right	30 -64 50	5.26	>10000
Occipital cortex (area 19)	Left	-22 -90 22	4.94	>10000
	Right	22 -90 28	6.8	>10000
Occipital cortex (area 18)	Left	-20 -86 -10	7.77	>10000
	Right	8 -82 4	7.5	>10000
Occipital cortex (area 17)	Left	-16 -90 -6	6.85	>10000
	Right	18 -94 -8	5.68	>10000
Thalamus	Left	-6 -14 10	4.15	664
	Left	-22 -32 4	4.53	704
	Right	20 -30 14	4.02	640
Globus pallidus	Left	-16 0 8	3.58	664
	Right	14 0 4	4.73	984
Cerebellum	Left	-28 -66 -30	5.8	>10000
	Right	34 -74 -18	6.82	>10000
YOUNG VS OLD				
Ventrolateral prefrontal cortex (area 47/12)	Left	-30 28 6	3.80	192
Ventrolateral prefrontal cortex (area 45)	Left	-50 24 20	3.72	440
Dorsolateral prefrontal cortex (area 9)	Left	-52 22 24	3.83	440
Superior frontal cortex (area 6, 8 SMA)	Right	8 16 50	3.85	136
Posterior inferior parietal cortex (area 40)	Left	-22 -62 38	5.21	5624
	Left	-38 -46 46	4.44	984
Inferior temporal cortex (area 37)	Left	-44 -44 -10	3.88	488
Lateral posterior parietal cortex (area 7)	Left	-24 -66 50	5.51	5624
	Right	28 -68 50	3.80	940
Precuneus (area 7)	Left	-4 -78 54	3.50	224
	Right	4 -84 42	4.73	>10000
Posterior cingulate cortex (area 30)	Left	-20 -64 8	4.00	>10000
Occipital cortex (area 19)	Left	-22 -74 32	3.55	>10000
	Right	22 -88 28	4.62	1616
Occipital cortex (area 18)	Left	-16 -88 -12	4.98	>10000
	Left	-38 -80 -10	4.02	664
	Right	10 -72 16	5.31	>10000
Occipital cortex (area 17)	Left	-6 -72 12	4.23	>10000
	Right	6 -80 14	5.18	>10000
Cerebellum	Left	-4 -72 -36	4.06	328

Table IV. Matching according to syllable onset minus control matching in the OLD

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
OLD				
Dorsolateral prefrontal cortex (areas 9, 9/46)	Left	-42 14 34	4.10	2168
Superior frontal cortex (area 6, 8 SMA)	Left	-4 36 40	3.94	792
Posterior inferior parietal cortex (area 40)	Left	-38 -52 38	3.92	1896
Lateral posterior parietal cortex (area 7)	Left	-32 -72 46	3.69	408
Occipital cortex (area 19)	Left	-30 -94 12	3.51	4560
	Right	32 -80 18	3.67	144
Occipital cortex (area 18)	Left	-30 -90 8	3.88	4560
	Right	12 -80 2	3.95	1456
Occipital cortex (area 17)	Left	-30 -94 -2	3.95	4560
	Left	-16 -88 18	3.59	1136
	Right	32 -86 -4	3.80	3040
Cerebellum	Right	-42 14 -20	4.02	3040
	Right	-28 -80 -10	3.95	4560
OLD VS YOUNG				
Frontopolar cortex (area 10)	Left	-4 70 4	4.17	2752
	Right	4 60 -4	4.10	2752
Anterior cingulate cortex (area 32)	Left	-1 22 -6	3.76	1888
Superior frontal cortex (area 6, 8 SMA)	Right	6 -12 70	4.04	160
Lateral premotor cortex (area 6)	Left	-40 -2 16	4.13	936
	Left	-52 -6 4	3.97	544
Insula (areas 41, 43)	Left –area 41	-40 -18 2	4.31	648
	Left –area 43	-54 -8 8	3.98	544
Posterior inferior parietal cortex (area 40)	Left	-58 -28 22	4.88	3480
	Right	60 -30 28	4.61	2952
Inferior temporal cortex (area 38)	Left	-36 4 -14	6.95	376
	Right	36 4 -16	4.15	736
Middle temporal cortex (area 39)	Left	-50 -72 14	4.03	1520
	Right	50 -56 12	3.80	1888
Superior temporal cortex (area 22)	Right	42 -56 20	4.69	1888
Precuneus (area 7)	Left	-8 -32 44	4.04	2168
	Right	2 -34 48	4.09	2168
Posterior cingulate cortex (area 31)	Left	-14 -30 40	4.63	2168
	Right	12 -24 44	4.56	304
Occipital cortex (area 19)	Left	-40 -78 40	4.20	744
Cerebellum	Left	-24 -84 -36	3.81	488

Older adults

The older group (Table IV) showed bilateral significant activation in the occipital cortex (areas 17, 18 and 19) only. There was, however, also left activation in the mid-dorsolateral prefrontal cortex (areas 9 and 46), the SMA (6/8 junction), and the posterior parietal cortex (areas 7 and 40), as well as right activation in the cerebellum. No significant subcortical activation was observed.

Table V. Matching according to syllable rhyme minus control matching in the YOUNG

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
YOUNG				
Frontopolar cortex (area 10)	Left	-26 54 14	4.27	1928
Anterior cingulate cortex (area 32)	Left	-8 30 36	4.48	>10000
	Right	8 36 30	4.54	>10000
Ventrolateral prefrontal cortex (area 47/12)	Left	-30 28 2	5.87	3016
	Right	32 28 0	5.36	1816
Ventrolateral prefrontal cortex (area 45)	Left	-48 28 20	5.71	>10000
Dorsolateral prefrontal cortex (area 9)	Left	-46 24 30	5.07	>10000
Posterior prefrontal cortex (area 44)	Left	-34 12 30	5.14	>10000
Superior frontal cortex (area 6, 8 SMA)	Left	-4 14 56	7.03	>10000
	Right	10 22 44	4.08	>10000
Lateral premotor cortex (area 6)	Left	-50 8 44	5.74	>10000
Posterior inferior parietal cortex (area 40)	Left	-28 -50 42	4.63	>10000
Inferior temporal cortex (area 37)	Left	-42 -62 -12	5.82	>10000
	Right	32 -54 -16	3.86	>10000
Lateral posterior parietal cortex (area 7)	Left	-24 -62 42	7.09	>10000
	Right	28 -66 42	4.4	>10000
Occipital cortex (area 19)	Left	-8 -84 8	6.14	>10000
	Right	18 -88 24	7.23	>10000
Occipital cortex (area 18)	Left	-18 -60 6	6.53	>10000
	Right	10 -72 16	8.96	>10000
Occipital cortex (area 17)	Left	-12 -70 12	6.79	>10000
	Right	12 -86 4	8.31	>10000
Thalamus	Left	-8 -12 10	5.29	2104
	Left	-22 -32 4	4.28	760
	Right	18 -14 14	4.7	4848
	Right	22 -28 0	5.95	4848
Globus pallidus	Right	12 -2 0	5.47	4848
Cerebellum	Left	-4 -66 -22	4.68	>10000
	Right	6 -76 -26	6.68	>10000
YOUNG VS OLD				
Dorsolateral prefrontal cortex (area 46)	Left	-48 24 20	3.86	136
Superior frontal cortex (area 6, 8 SMA)	Left	-50 2 40	3.76	144
Posterior inferior parietal cortex (area 40)	Left	-18 -62 54	4.11	2024
	Left	-24 -66 38	3.91	2024
Precuneus (area 7)	Right	4 -84 40	3.76	256
Occipital cortex (area 19)	Left	-6 -66 2	4.44	>10000
	Right	34 -86 4	5.21	>10000
Occipital cortex (area 18)	Left	-20 -64 8	4.74	>10000
	Right	12 -74 14	6.45	>10000
Occipital cortex (area 17)	Left	-12 -68 10	4.94	>10000
	Right	10 -66 12	6.13	>10000

Intergroup comparison

The younger group did show significantly increased bilateral activity in the posterior parietal cortex (areas 7 and 40), the precuneus (area 7) and the occipital cortex (areas 17, 18, as well as 19 in the left hemisphere) when compared to the older group. There was also unilateral increased activation in the leftventrolateral PFC (areas 45 and 47/12), the right mid-dorsolateral PFC (area 9), the left SMA (areas 6 and 8), the left posterior cingulate cortex (area 30), the left inferior temporal cortex (area 37) and the left cerebellum (Table III).

On the other hand, the elderly showed greater bilateral activation in the frontopolar cortex (area 10), and posterior inferior parietal cortex (area 40), the inferior and middle temporal cortices (areas 38 and 39), the posterior cingulate (area 31) and the precuneus (area 7) compared to the young group. There was also significant increased activity in the left hemisphere in the anterior cingulate cortex (areas 32), the lateral premotor cortex (area 6), the insula (areas 41 and 43), the occipital cortex (area 19) and the cerebellum, while the SMA (areas 6 and 8) and the superior temporal cortex (area 22) showed increased activation in the right side of the brain (Table IV).

(3) Syllable rhyme

Younger adults

When syllable rhyme was compared with control matching (Table V), there was significant bilateral activation in the mid-ventrolateral PFC (area 47/12), the anterior cingulate cortex (area 32), the SMA (area 6, 8), the posterior parietal cortex (area 7), the inferior temporal cortex (area 37, fusiform gyrus), the occipital cortex (areas 17, 18 and 19) and the cerebellum. There was also significant increased activation in the left hemisphere in the frontopolar cortex (area 10), the mid-dorsolateral PFC (area 9), the ventrolateral PFC (area 45), the posterior PFC (area 44), the lateral premotor cortex (area 6), and the posterior parietal cortex (area 40). Finally, significant activation was observed subcortically in the right globuspallidus and bilaterally in the thalamus.

Older adults

In the older group (Table VI), there were bilateral significant activations in the SMA (6/8 junction), and the occipital cortex (areas 17, 18 and 19). There was also left increased activity in the mid-dorsolateral PFC (area 9). On the other hand, the right hemisphere sowed increased activity in the cerebellum.

Intergroup comparison

The younger group had bilateral significantly increased activity in the occipital cortex (areas 17, 18 and 19) compared to the older one. They also had significant activation in the dorsolateral PFC (area 46), the SMA (6/8 junction), and the posterior parietal cortex (area 40), as well as right activity in the precuneus (area 7) (Table V).

The elderly, however, showed significant bilateral activity in the lateral premotor cortex (area 6), the insula (areas 41 and 43), the middle temporal cortex (area 39) and the posterior parietal cortex (area 40), right increased activation in the dorsolateral PFC (area 46) and the superior temporal cortex (area 22), as well as increased left activation in the inferior temporal cortex (area 38), the occipital cortex (area 19) and the cerebellum compared with the younger group (Table VI).

Table VI. Matching according to syllable rhyme minus control matching in the OLD

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
OLD				
Dorsolateral prefrontal cortex (areas 9)	Left	-38 6 34	3.88	952
Superior frontal cortex (area 6, 8 SMA)	Left	-4 18 52	4.10	1128
	Right	6 6 70	3.88	168
Occipital cortex (area 19)	Left	-6 -88 -12	3.63	200
	Right	32 -90 -4	3.62	352
Occipital cortex (area 18)	Right	16 -78 -16	4.10	3088
Occipital cortex (area 17)	Left	-4 -90 -10	3.56	200
	Right	14 -92 2	3.70	952
Cerebellum	Right	30 -66 -20	4.01	3088
OLD VS YOUNG				
Dorsolateral prefrontal cortex (area 46)	Right	44 38 10	4.62	920
Lateral premotor cortex (area 6)	Left	-38 2 12	4.48	6296
	Right	38 2 16	4.60	2144
Insula (areas 41, 43)	Left –area 41	-42 16 0	4.25	264
	Left –area 43	-52 -8 8	4.44	6296
	Right –area 43	40 -12 20	3.86	2144
Posterior inferior parietal cortex (area 40)	Left	-60 -28 22	5.89	6296
	Right	60 -30 26	5.31	7688
Inferior temporal cortex (area 38)	Left	-36 2 -14	4.57	456
Middle temporal cortex (area 39)	Left	-40 -76 34	3.64	352
	Right	50 -72 36	3.94	888
Superior temporal cortex (area 22)	Right	58 -34 20	4.67	7688
Occipital cortex (area 19)	Left	-6 -66 2	4.44	>10000
Cerebellum	Left	-22 -84 -38	3.83	320

(4) Inter-rules comparisons

Younger adults

Comparing BOLD signal during semantics with syllable onset (Table VII, Figure 1) yielded significant activation in the left ventrolateral PFC (areas 45 and 47/12), the left temporal regions (areas 37 and 20) and in right occipital regions (areas 17 and 18). In the reverse comparison (Table VII, Figure 2), syllable onset vs. semantic, there was significant activation in the right frontopolar area (area 10), the right posterior parietal cortex (area 40), and the left inferior temporal cortex (area 37).

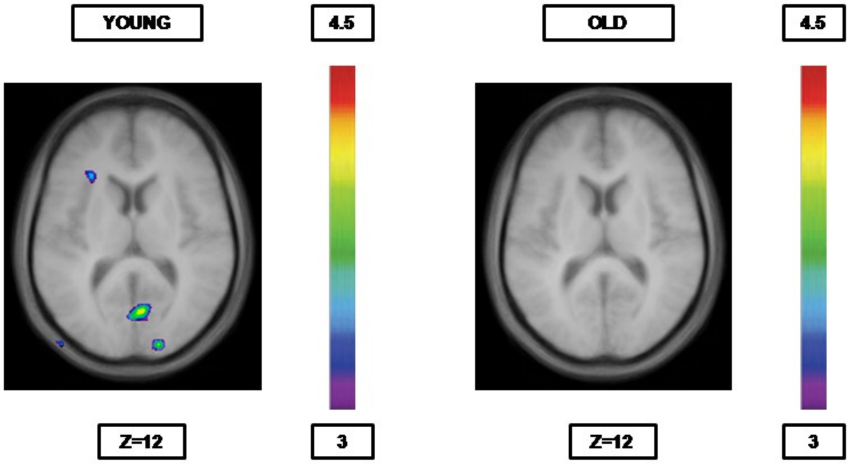

Figure 1.Significant activation when semantics are compared to syllable onset
The younger group (cf. left) shows activation in the left ventrolateral PFC (areas 45 and 47/12), the left temporal regions (areas 37 and 20 - not shown in the figure) and in right occipital regions (areas 17 and 18), while the older group (cf. right) shows no significant peaks of activation at all. The anatomical MRI images are the average of the T1 acquisitions of the 14 younger subjects (cf. left) and the 14 older subjects (cf. right) transformed into stereotaxic space. The color scale represents the T statistic.

When semantics was compared with rhyme (Table VIII), significant activations were recorded in the left hemisphere in the ventrolateral PFC (area 45 and 47/12), the dorsolateral PFC (area 9/46), the hippocampus (area 36), the inferior temporal cortex (area 20), and the occipital cortex (area 17), as well as the right caudate nucleus. In the reverse contrast (syllable rhyme minus semantics), significant activation was observed in the left posterior PFC (area 44), left inferior temporal cortex (area 37) and right occipital cortex (area 17) (Table VIII).

When comparing syllable rhyme and syllable onset matching (Table IX, Figure 3) significant activation was observed bilaterally in regions 17, 18, and 19 of the occipital cortex and in the right anterior cingulate cortex (area 32). In the reverse contrast (Table IX, Figure 4), that is syllable onset minus syllable rhyme, significant activation was observed in the right posterior parietal cortex (area 40) and the left occipital cortex (area 18).

Table VII. Matching according to semantic compared with matching according to syllable onset

Anatomical area	**Hemisphere**	**Stereotaxic coordinates**	**T stat**	**Cluster size**
YOUNG				
Semantics minus syllable onset				
Mid-ventrolateral prefrontal cortex (area 47)	Left	-38 28 4	3.83*	352
Ventrolateral prefrontal cortex (area 45)	Left	-30 24 14	3.93*	344
Inferior temporal cortex (area 37, FG)	Left	-20 -48 -6	3.95*	128
Inferior temporal cortex (area 20)	Left	-42 -30 -20	3.36*	40
Occipital cortex (area 18)	Right	18 -94 14	4.17	936
Occipital cortex (area 17)	Right	4 -72 8	3.92	1448
Syllable onset minus semantics				
Frontopolar cortex (area 10)	Right	6 68 0	3.92*	208
Inferior parietal cortex (area 40)	Left	-60 -32 52	3.34*	80
	Right	44 -36 52	4.35*	360
Inferior temporal cortex (area 37, FG)	Left	-52 -64 -2	3.37*	48
YOUNG VS OLD				
Semantics minus syllable onset				
Occipital cortex (area 17)	Right	18 -92 6	3.90	528
Occipital cortex (area 18)	Right	6 -76 4	3.62	616
Syllable onset minus semantics				
-	-	-	-	-
OLD				
Semantics minus syllable onset				
-	-	-	-	-
Syllable onset minus semantics				
-	-	-	-	-
OLD VS YOUNG				
Semantics minus syllable onset				
-	-	-	-	-
Syllable onset minus semantics				
-	-	-	-	-

Older adults

As expected, the comparisons between rules yielded no significant peaks of activation (Tables VII, VIII and IX, Figures 1, 2, 3 and 4).

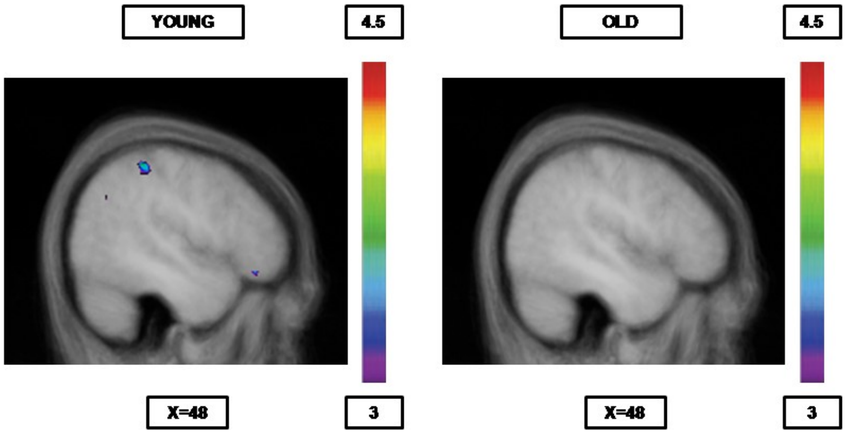

Figure 2.Significant activation when syllable onset is compared to semantics
The younger group (cf. left) shows activation in the right frontopolar area (area 10), the right posterior parietal cortex (area 40), and the left inferior temporal cortex (area 37 – not shown in the figure), while the older group (cf. right) shows no significant peaks of activation at all.The anatomical MRI images are the average of the T1 acquisitions of the 14 younger subjects (cf. left) and the 14 older subjects (cf. right) transformed into stereotaxic space. The color scale represents the T statistic.

Intergroup comparison

The younger group when compared with the older one showed significant greater right activity in the occipital cortex (areas 17 and 18) when matching according to semantics was compared to syllable onset (Table VII). They also showed significantly increased activity in the left ventrolateral PFC (area 47/12), posterior cingulate cortex (area 23), the inferior temporal cortex (area 20), the inferior parietal cortex (area 40), the precuneus (area 7) and the occipital cortex (area 17) when matching according to semantics was compared to syllable rhyme (Table VIII). When syllable onset was compared with syllable rhyme, there was greater right activation in the younger adults compared with the older ones in the mid-dorsolateral PFC (area 9) and the inferior parietal cortex (area 40), as well as left increased activation in the occipital cortex (areas 17 and 18). On the other hand, when syllable rhyme was compared with syllable onset, there was greater right activation in the occipital cortex (areas 17 and 18) (Table IX).

Table VIII. Matching according to semantic compared with matching according to syllable rhyme.

Anatomical area	Hemisphere	Stereotaxic coordinates	T stat	Cluster size
YOUNG				
Semantics minus syllable rhyme				
Mid-ventrolateral prefrontal cortex (area 47)	Left	-56 30 -4	4.38	3656
Ventrolateral prefrontal cortex (area 45)	Left	-58 32 4	3.95	3656
Dorsolateral prefrontal cortex (area 9/46)	Left	-54 34 24	4.44	2016
Hippocampus (area 36)	Left	-30 -38 -12	4.11	392
Inferior temporal cortex (area 20)	Left	-38 -16 -24	3.28*	16
Occipital cortex (area 17)	Left	-14 -94 0	4.28	1560
Caudate nucleus	Right	16 14 2	3.3*	24
Syllable rhyme minus semantics				
Posterior prefrontal cortex (area 44)	Left	-41 3 20	3.43*	32
Inferior temporal cortex (area 20)	Right	48 0 -40	4.09*	208
Inferior temporal cortex (area 37, FG)	Left	-46 -66 -2	3.57*	136
Occipital cortex (area 17)	Right	18 -90 6	3.6*	192
YOUNG VS OLD				
Semantics minus syllable rhyme				
Ventrolateral prefrontal cortex (area 47/12)	Left	-30 26 -2	4.10	504
Posterior cingulate cortex (area 23)	Left	-2 -34 26	4.04	504
Inferior temporal cortex (area 20)	Left	-36 -44 -18	3.88	320
Inferior parietal cortex (area 40)	Left	-34 -70 38	3.56	352
Precuneus (area 7)	Left	-8 -68 50	3.95	464
Occipital cortex (area 17)	Left	-16 -84 -10	4.72	2464
Syllable rhyme minus semantics				
-	-	-	-	-
OLD				
Semantics minus syllable rhyme				
-	-	-	-	-
Syllable rhyme minus semantics				
-	-	-	-	-
OLD VS YOUNG				
Semantics minus syllable rhyme				
-	-	-	-	-
Syllable rhyme minus semantics				
Superior frontal cortex (area 6, 8 SMA)	Left	-4 16 52	3.69	224
Posterior cingulate cortex (area 23)	Left	-2 -32 26	4.05	504
Precuneus (area 7)	Left	-8 -68 50	4.02	312
Occipital cortex (area 17)	Left	-12 -94 2	4.21	3144
Occipital cortex (area 18)	Left	-14 -88 -10	4.82	3144
Occipital cortex (area 19)	Left	-18 -84 -10	4.40	3144
Cerebellum	Left	-28 -74 -14	3.68	264

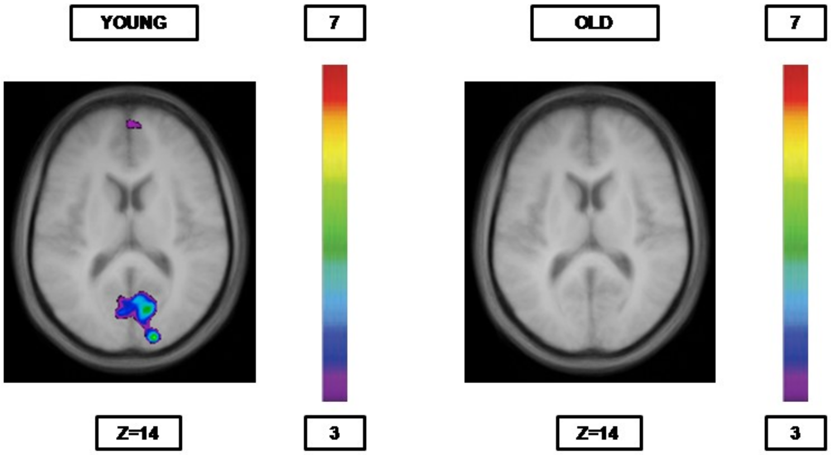

Figure 3.Significant activation when rhyme syllable is compared to syllable onset
The younger group (cf. left) shows significant activation bilaterally in regions 17, 18, and 19 of the occipital cortex and in the right anterior cingulate cortex (area 32), while the older group (cf. right) shows no significant peaks of activation at all.The anatomical MRI images are the average of the T1 acquisitions of the 14 younger subjects (cf. left) and the 14 older subjects (cf. right) transformed into stereotaxic space. The color scale represents the T statistic.

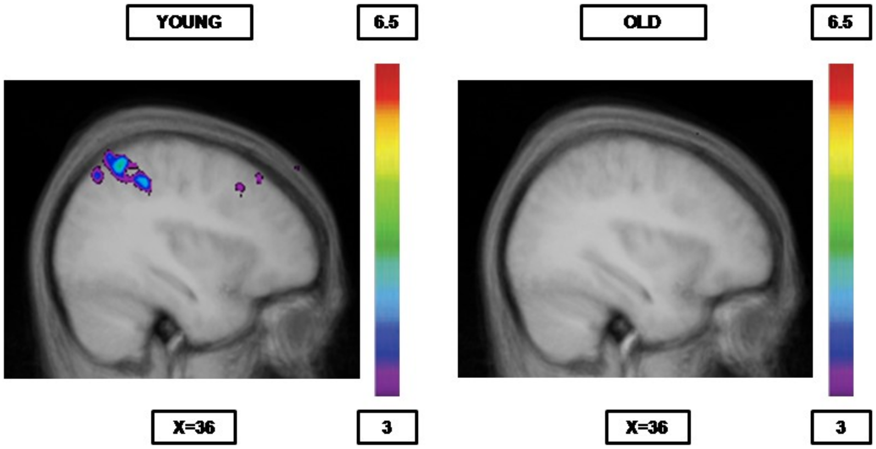

Figure 4.Significant activation when syllable onset is compared to rhyme syllable
The younger group (cf. left) shows significant activation was in the right posterior parietal cortex (area 40) and the left occipital cortex (area 18 - not shown in the figure), while the older group (cf. right) shows no significant peaks of activation at all.The anatomical MRI images are the average of the T1 acquisitions of the 14 younger subjects (cf. left) and the 14 older subjects (cf. right) transformed into stereotaxic space. The color scale represents the T statistic.

The older group when compared with the younger one had significantly greater activity in the left hemisphere, in the SMA (6 and 8 junction), the posterior cingulate cortex (area 23), theprecuneus (area 7), the occipital cortex (areas 17, 18 and 19) and the cerebellum when matching according to syllable rhyme was compared with matching according to semantics (Table VIII). When syllable onset was compared with syllable rhyme, there was greater right activation in the occipital cortex (areas 17 and 18). On the other hand, when syllable rhyme was compared with syllable onset, there was greater activation on the right in the inferior posterior parietal cortex (area 40), and on the left in the occipital cortex (areas 17 and 18) (Table IX).

No significantly greater activity was observed for any other inter-group inter-rule comparison.

Discussion

As predicted, the results indicate that, with aging, differences between semantic and phonological pathways tend to diminish. Indeed, while younger individuals seem to rely on different regions when performing semantic or phonological functions, older individuals seem to depend on similar routes for both language functions. This observation is in agreement with the recruitment of similar pre-existing brain networks (neural reserve) as well as other brain regions (neural compensation) in order to maintain a high level of performance when demanding tasks are required [30].

Younger individuals showed increased activity in regions belonging to the semantic stream proposed by Devlin [45] and other areas involved in semantic processing [46] [47], namely the dorsolateral PFC, the ventrolateral PFC, the fusiform gyrus, the ventral temporal lobe and the caudate nucleus, plus some other regions more often associated with the phonological (non semantic) pathway [45] (the temporoparietal junction and motor cortical areas) when control matching was subtracted from semantic matching (Table I). The older group, on the other hand, showed less significant activation for that contrast (Table II). It is possible that the control condition might have been more difficult for the older group, which led to increased resource recruitment during control matching and therefore less significant activation when the latter was subtracted from matching according to semantics.

Table IX. Matching according to syllable onset compared with matching according to syllable rhyme

Anatomical area	**Hemisphere**	**Stereotaxic coordinates**	**T stat**	**Cluster size**
YOUNG				
Syllable onset minus syllable rhyme				
Inferior parietal cortex (area 40)	Right	34 -40 48	4.61	960
Occipital cortex (area 18)	Left	-16 -88 -6	5.17	1304
Syllable rhyme minus syllable onset				
Anterior cingulate cortex (area 32)	Right	12 38 20	3.84*	240
Occipital cortex (area 17)	Left	-8 -72 18	4.63	>10000
	Right	10 -68 10	5.54	>10000
Occipital cortex (area 18)	Left	-12 -62 6	3.96	>10000
	Right	18 -86 -2	6.54	>10000
Occipital cortex (area 19)	Left	-18 -54 -6	4.56	>10000
YOUNG VS OLD				
Syllable onset minus syllable rhyme				
Mid-dorsolateral prefrontal cortex (area 9)	Right	42 28 42	4.04	408
Inferior parietal cortex (area 40)	Right	32 -40 46	4.10	640
Occipital cortex (area 17)	Left	-14 -90 -8	4.70	1296
Occipital cortex (area 18)	Left	-16 -88 -8	4.70	1296
Syllable rhyme minus syllable onset				
Occipital cortex (area 17)	Right	18 -92 6	4.90	2144
	Right	16 -72 12	4.07	2328
Occipital cortex (area 18)	Right	22 -88 -4	5.03	2144
OLD				
Syllable onset minus syllable rhyme				
-	-	-	-	-
Syllable rhyme minus syllable onset				
-	-	-	-	-
OLD VS YOUNG				
Syllable onset minus syllable rhyme				
Occipital cortex (area 17)	Right	18 -88 -4	5.46	3408
Occipital cortex (area 18)	Right	22 -88 -4	5.46	3408
	Right	10 -68 8	5.24	2632
Syllable rhyme minus syllable onset				
Inferior parietal cortex (area 40)	Right	36 -58 58	4.42	472
Occipital cortex (area 17)	Left	-16 -88 -8	4.09	752
Occipital cortex (area 18)	Left	-16 -84 -10	4.12	752

A similar pattern was noticed when control matching was subtracted from phonological matching. Indeed, in the younger group, significant activations were found in the left posterior and superior PFC (area 44[for syllable rhyme only], and areas 6 and 8), the inferior temporal cortex (area 37 – involved both in semantic and phonology processing) and the supramarginalgyrus of the posterior parietalcortex (area 40) (Tables III and V). These two areas are known to form the “phonological loop” [45] [48] [49], which is involved in storing and rehearsing verbal information, which is required for verbal working memory [50] [51].It should be noted that other regions such as the frontopolar cortex, the anterior cingulate cortex, the ventrolateral PFC, the dorsolateral PFC and the thalamus were also significantly activated when both phonological rules were compared to controls. These regions were most probably recruited because of the executive demand load required during a set-shifting task (even during non-shifting conditions), indeed these results are similar to those obtained in matching period contrasts in our previous studies using the WCST or the WWST [31] [32] [33] [34]. Interestingly, in the younger group, area 40, together with areas 10 and 37, were the only significantly activated regions when syllable onset matching was compared to semantic matching (Table VII), while area 44, with areas 7 and 37, were the only significantly activated regions when syllable rhyme matching was compared to semantic matching (Table VIII), therefore arguing for the importance of areas 37, 40 and 44 in phonological processing. Regarding older individuals, once again, less overall activity was recorded when control matching was subtracted from any of the two phonological rules (Tables IV and VI) probably because the control matching was more cognitively demanding in this age group as previously mentioned. Moreover, area 44 was not even significantly more activated in any of the phonological rules compared to control matching while area 40 was only significantly activated during syllable onset.

When older individuals were compared to the younger ones, they showed significantly increased activation in the insula (areas 41 and 43), the temporal cortex (areas 22, 38 and/or 39) and the lateral parietal cortex (area 40) for the three classification rules (semantic, syllable onset and syllable rhyme) minus control. These results are in agreement with the fact that older individuals seem to rely on similar pathways when performing both semantic and phonological functions. Indeed they showed, independently of the matching rule, significant activation in areas associated with working memory such as the insula [52], semantic processing such as the temporal cortex [29] [53] and phonological processing such as area 40 [48] [49].

Another interesting finding is the fact that when semantic matching was contrasted with either one of the phonological rules, the younger group showed increased activity mainly in regions within the semantic route (the ventrolateral PFC, the dorsolateral PFC, the inferior temporal cortex and the caudate nucleus[when compared to syllable rhyme only]) plus two other regions not primarily associated with semantic processing, that is the hippocampus (when compared to syllable rhyme only) and the occipital cortex, while the elderly didn't show any increased brain activity at all (Tables VII and VIII; Figure 1). Similarly, when the phonological rules were compared to semantics, there was, in younger individuals, increased activity in areas 37 (both phonological rules), 44 (syllable rhyme) or 40 (syllable onset) as previously mentioned, while the elderly, once again, did not show any increased activity (Tables VII and VIII; Figure 2). This pattern of activation is consistent with previous studies using tasks of phonological perception [54] [55] [56] which showed that area 44 plays an important role in the conversion from orthography to phonology which is more importantly required in the rhyme condition than in the syllable onset condition[32]. Indeed, in the WWST, almost all associations according to the syllable onset condition can be performed by simply comparing word spelling (the letters forming the first syllable). Therefore, there is little need to convert from orthography to phonology in that paradigm. On the other hand, associations according to the syllable rhyme condition rely more heavily on the orthography (spelling) to phonology (sound) conversion (and thus solicitating more area 44). Indeed, words rhyming in "o" can actually finish in "au", "aut", "eau", "o" or "ot", words rhyming in "e" can end with "é", "ée" or "er", and finally words rhyming in "ɑ̃" can finish in "an", "eng" or "ent".. Increased activation in the lateral posterior parietal cortex (area 40), on the other hand, was present for both syllable onset and syllable rhyme matching when compared with control matching, this is in agreement with functional imaging studies which noted the activation of area 40 in tasks accessing phonological stores in working memory [57] [58] and requiring phonological processing [59] [60] [61]. Nevertheless, the activation was only recorded in the syllable onset matching when compared to semantics. The reason for this dissimilarity between the two phonological rules remains uncertain, however, it is possible that maintaining in working memory the different word graphologies (which is especially required during the syllable onset condition) may entail more significant involvement of area 40 [32]. It should also be noted that differences in brain activity were found between the two phonological rules for younger individuals, while they were completely absent in the older group (Table IX; Figures 3 and 4). Indeed, the young showed increased activity in the lateral posterior parietal cortex (area 40) when syllable rhyme was subtracted from syllable onset (probably for the same reason mentioned above), and increased occipital and anterior cingulate (area 32) activity in the opposite contrast. It is possible that the syllable rhyme condition requires more attention than the syllable onset condition because of the necessity to convert visual letters forming syllables into sounds in the first condition as previously stated, that would explain why primary and secondary visual regions (occipital cortex) as well as area 32, known to play an important role in focusing attention [62], are significantly more activated during the syllable rhyme matching condition. This being said, the absence of differences between the categorisation rules in the elderly is in agreement with the postulated recruitment of similar global as opposed to specific pathways for semantic or phonological processing in the elderly.Consequently, high-performing old individuals appear to rely on semantic pathways (neural reserve) as well ason other non-semantic language-related regions (neural compensation) during semantic processing, and on phonological pathways (neural reserve) as well as other language (semantic) regions (neural compensation) during phonological processing.

It should be noted that the elderly did show some differences in brain activity in the inter-rule comparisons when they were compared to the young. However, given the nature of intergroup analyses, these results should be interpreted with caution. Therefore, if a region is significantly activated in an intergroup analysis (between groups) for a given contrast, but not in the intragoup analysis for the same contrast (within the group showing the increased activation), the relevance of the significantly increased activity between groups is of limited value. Indeed, it means that for a given contrast (contrast 1), group A likely shows a positive non significant peak of activity in area Z, and that the other group (group B) likely shows a negative peak of activity in the same area Z for the same contrast 1. Thus, when comparing the two groups (A vs B), there is significant activity for contrast 1 in area Z since the negative peak from B, when subtracted from the non significant positive peak from A, gives rise to a more positive (and therefore significant) peak for A minus B. Nevertheless, the difference in activity in area Z between the two conditions forming contrast 1 remains not significant for group A. In the present study, this means that, for the older group, differences between the three conditions are minimal regarding cerebral activation patterns, as previously stated, regardless of the results shown in the intergroup analyses because the latter are largely influenced by negative peaks recorded in the younger group for those same contrasts.

Regarding reaction times, matching periods according to semantics and syllable rhyme were slower than matching periods according to syllable onset in the young. Those results are most probably due to the fact that orthography to phonology conversion was almost not required in the onset syllable condition (as previously stated), but was necessary in the syllable rhyme condition, explaining why matching according to the latter condition took longer than matching according to the first. Matching according to semantics also showed increased response times (compared to syllable onset) because candidates needed to assess semantic categories within the working memory for that condition. Interestingly, in the elderly there were no statistical differences between rule classifications (as it was the case for cerebral activity). The elderly also proved to have slower response times in all classification conditions (except for semantics when control response times were subtracted). This phenomenon is in agreement with an age-related decrease in motor-speed [43] [44].

Finally, we did not observe any age-related intra-hemispheric brain activity reorganization; even if several language studies have shown either increased PFC activity in the elderly[26] or increased posterior activation, especially during semantic processing [27] [28] [29]. On the other hand, the elderly appear to have shown morebilateral activity (HAROLD model) than the young. Indeed, in the intergroup analysis, they presented slightly more bilateral or right activity in the prefrontal, temporal and parietal cortices (Tables I, II, III, IV, V and VI). However, the differences were not very important since younger participants also showed significant bilateral involvement. Therefore, in our experiment and as previously argued, neural compensation seems mainly to take the form of recruiting other language processing regions that are usually used for other language processes (rather than bilateralization or intra-hemispheric reorganization of brain activity).

A limitation of the present study is the fairly small sample size of both our groups. Larger groups would have allowed for within group age stratification in order to explore potential differences between “younger” and “older” elderly, since such differences have been found for executive processing [63].Another limitation comes from the fact that we only have one group of older individuals (high performing persons [33]). A third group composed of "low performing" older individuals would have allowed to confirm if all the differences recorded between the elderly and the young were indeed compensatory in nature (and not due to the inability for the elderly to inhibit some none language relevant areas during language processing). This being said, the fact that the older group is a high performing one is in itself an argument for the compensatory nature of the differences in cerebral activity between the two age groups. Furthermore, we might have missed subtle differences between condition rules regarding reaction times. Indeed, for each trial, response times were influenced by how close the matching card was with the curser. Therefore, the number of times a participant had to press on the button (allowing for the curser to move) in order to select the appropriate matching card changed from one trial to another. This increased the reaction time variance within each trial condition, therefore diminishing the ability to find statistical differences in reaction times between conditions. Finally, based on the results obtained in the younger group, there is evidence to show that the two phonological rules of the WWST rely on both similar and different language processes. Indeed, the syllable onset condition appears to require more orthographic than phonological processing, while it appears to be the reverse for the syllable rhyme condition. These dissimilarities between the two phonological rules prevented us from exploring with more precision the effects of aging on "pure" phonological processing, but they did not undermine the principal finding of the study: age-related reduction in language pathways specificity.

Conclusion

In conclusion, it appears that pathway specificity is reduced with aging. Indeed, in older individuals, the semantic and phonological routes seem to merge into a single one composed of both semantic and phonological pathways. These findings may represent neural reserve/compensation mechanisms in which the elderly, confronted to a demanding lexical task, require to rely more extensively on several brain areas within different language processing routes in order to adequately complete the given task.

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CHAPTER 7

Article 3

CHAPTER 7

Article 3

Authors' contributions

Ruben Martins reviewed the literature on aging, cognition and language processing and chose which scientific articles would be included and evaluated in Article 3 (review). Yves Joanette and Oury Monchi contributed by adding few other significant papers not selected by Ruben Martins. The article was entirely written by Ruben Martins. Yves Joanette and Oury Monchi provided useful feedback and suggestions on the different drafts of the article before the final version was completed and submitted.

7.1. Introduction

The third article was submitted to *Neuropsychologia* (Elsevier), but was rejected. The different reviewers' comments have been taken in consideration and a new version of the article will soon be submitted to *Frontiers in Human Neuroscience*.

This article explores the same compensatory mechanisms that allow for cognition to be preserved despite aging as those reviewed in Chapter 3. Most of the content of the following article is therefore identical to that of the third Chapter; however, this review also takes in consideration the findings of Articles 1 and 2 as well as their contribution to the existing literature. Therefore, it addresses the two major objectives of this thesis: to investigate how aging affects the patterns of neural activity related to executive functions and those related to language processing. More precisely, this article explores the CR model in healthy aging and its two underlying mechanisms: neural reserve and neural compensation. Older individuals seem to rely extensively on those two mechanisms for both semantic and phonological processing during the performance of the WWST as stated in Article 2. Furthermore, this review also details the CRUNCH model. Finally, this article proposes, largely based on the findings of our first article, the existence of another compensatory mechanism characterised by age-related delayed cerebral activation allowing for cognitive performance to be preserved at the expense of speed processing: the Temporal Hypothesis for Compensation (THC).

Based on our experiments (Articles 1 and 2), executive and language processes appear to rely on different age-related compensatory mechanisms in order to maintain performance: THC for executive processing (Article 1) and neural reserve/compensation for language processing (Article 2). However, an exhaustive review of the literature as the one presented in this Article shows that the elderly appear to present evidence of neural compensation, neural reserve and/or delayed brain activation (THC) while performing either executive or language processing tasks. However, the specific functional reorganization of the brain, that is which precise regions of the brain show increased or delayed activation for a given task, may take different shapes depending on the cognitive domain.

7.2. The implications of age-related neurofunctional compensatory mechanisms in executive function and language processing

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Abstract

As the passage of time structurally alters one's brain, cognition does not have to suffer the same faith, at least not to the same extent. Indeed, the existence of age-related compensatory mechanisms allow for some cognitive preservation. This paper attempts to coherently review the existing concepts of neurofunctional compensation when applied to two different cognitive domains, namely executive function and language processing. More precisely, we explore the Cognitive Reserve model in healthy aging as well as its two underlying mechanisms: neural reserve and neural compensation. Furthermore, we review the Compensation-Related Utilization of Neural Circuits Hypothesis. Finally, we propose, based on some functional neuroimaging studies, the existence of another compensatory mechanism characterised by age-related delayed cerebral activation allowing for cognitive performance to be preserved at the expense of speed processing: the Temporal Hypothesis for Compensation.

Keywords: language, execution, cognition, aging, fMRI

1. Introduction

As years pass by, brain modifications occur: the cerebrum loses 1 to 2% of its mass each year as well as white matter structural integrity (Caserta et al., 2009; Fjell et al., 2009; Head et al., 2004; Moseley, 2006; Raz et al., 1997; Sullivan and Pfefferbaum, 2006). Actually, it has been widely found that the cerebrum weight declines at a rate of around 5% per decade after age 40 with the actual rate of decline increasing significantly particularly over age 70 (Scahill et al., 2003). Furthermore, a decrease in dendritic synapses or loss of synaptic plasticity has also been described. (Bames, 2003) Those changes in integrity and volume appear to be particularly important in the prefrontal cortex, the striatum and the hippocampus, regions of primordial significance in executive function and memory. (Raz, 2004). But, do age-related brain changes affect different cognitive domains in the same manner? Do language and executive processes (Table 1) rely on the same compensatory mechanisms to maintain performance as one gets older? Surprisingly, not many studies have tried to answer this question, possibly because it is somewhat difficult to separate pure language processing from executive function which is often required during the execution of language tasks (Humphries et al., 2006; Just et al., 1996; Kemper and Sumner, 2001; Stromswold et al., 1996; Van der Linden et al., 1999). Furthermore, findings tend to be inconsistent. Indeed, while some studies have reported little age-related performance decline (Burke et al., 2000; Burke and Shafto, 2008; Waters and Caplan, 2005) in language abilities, others have shown that older individuals may display impaired execution during language production tasks (Bona, 2014; Ivnik et al., 1996), more errors when accessing phonological word forms (Shafto et al., 2007), decreased speech comprehension (Schneider et al., 2005) and perception not related with hearing loss (Bilodeau-Mercure et al., 2014) as well as more tip-to-the-tongue states (White and Abrams, 2002). However, it appears that at least some of these findings could be explained by a decline in working memory instead of actual language processing per se (Waters and Caplan, 2005).

Enlightened by this last statement, one could then argue that there is less age-related decline in language processing compared to working memory and executive processing. However, even for executive function, it has been shown in some experiments that the age-related decrease in performance would disappear if non-cognitive components (such as motor-speed) were accounted for (Fristoe et al., 1997; Parkin and Java, 1999). Some studies have even suggested that there is no age-related executive decline at all (Boone et al., 1990).

Moreover, other cognitive domains, such as semantic knowledge (Burke and Shafto, 2008; Craik and Jennings, 1992; Laver, 2009; Park et al., 2002; Verhaeghen, 2003) and emotional regulation (Carstensen et al., 2003; 2011), are clearly maintained with age.

Consequently, given the fact that for some healthy old individuals, cognition appears to be largely maintained (semantic knowledge, emotional regulation, etc.) or less impaired than age-related brain atrophy would suggest (language and executive processing), the aim of the present manuscript is to explore the compensatory mechanisms that would allow for this preservation to occur. Furthermore, the present review will explore if these compensatory mechanisms are the same for executive functions (including working memory) and language processing, or if different cognitive domains rely on different mechanisms.

2. Cognitive Domains

Executive function can be summarized as the general cognitive processes that support strategic organization and control other processes that play an important role in complex, goal oriented tasks (Buckner, 2004) (Table 1). Working memory, on the other hand, allows to maintain and to immediately manipulate available information. It relies on brain systems that represent memories in an active, online form (Buckner, 2004) (Table 1). Based on those definitions, one can see how those two concepts, namely executive function (or processing) and working memory, are intimately related, especially when it comes to the manipulation of information in order to achieve a goal. For the purpose of this review, working memory and executive processing will therefore be considered as a single cognitive domain.

Language abilities can be considered as involving multiple cognitive processes allowing for the processing of grammatical rule which interplays with phonology (the speech sound processing system) and semantics (the meaning processing system) (Hauser el al., 2002) (Table 1). Those three systems, themselves composed of several subsystems, enable us to create and understand a potentially infinite number of sentences by using various combinations of words. Even if this review considers language abilities and executive function as different processes, one should be aware that in reality (and that includes during the performance of language processing tasks) those cognitive domains are often intimately linked and hard to separate (since working memory is often needed during the manipulation of language attributes – sounds, works, sentences).

Table 1 Cognitive Domains

Concepts	Definitions
Working memory	Process that allows to maintain and to immediately manipulate available information
Executive processing/function	Cognitive processes that support strategic organization and control other processes that play an important in complex, goal oriented tasks
Language processing/abilities	Multiple cognitive processes allowing for the processing of grammatical rule which interplays with phonology and semantics

3. Cognitive reserve

The cognitive reserve (CR) hypothesis is a ‘functional’ model of reserve conceptualized by Stern (2002) that reflects the inter-individual ability to effectively use cognitive processes and brain networks (Table 2). Regarding elderly individuals, two CR mechanisms have been proposed: neural compensation and neural reserve (Stern, 2009). Neural compensation is the use of new, compensatory brain networks after pathology or normal aging disrupted those typically recruited for a particular task (Table 2). The neural compensation hypothesis was in part based on the fact that several episodic memory, semantic memory, working memory, perception and inhibitory control task studies have reported that high performing older individuals tended to show bilateralization of cerebral activation (Cabeza, 2002; Reuter-Lorenz, 2002; Reuter-Lorenz et al., 2000; Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Park, 2010) as well as intrahemispheric changes in activation patterns, mainly from the occipitotemporal to the frontal cortex (Cabeza, 2004; Cappell et al., 2010; Grady et al., 1994; 2005; Madden et al., 1997; Reuter-Lorenz et al., 2000). These findings led, respectively, to the proposition of the HAROLD (Hemispheric Asymmetry Reduction in OLDer adults) model by Cabeza (2002) and the PASA (posterior-anterior shift in aging) phenomenon by Dennis and Cabeza (2008) (Figure 1). The HAROLD model states that, under similar circumstances, prefrontal activity during cognitive performances tends to be less lateralized in older adults than in younger individuals, it is believed that this "delateralization" has a compensatory function and reflects regional or network mechanisms (Cabeza, 2002). The PASA phenomenon, additionally, has also been shown to reflect the effects of aging (and not differences in task difficulty for example), furthermore age-related increases in frontal activity have been positively correlated with cognitive performance and negatively correlated with the age-related occipital decreases (Davis et al., 2008). Therefore, as previously stated, these patterns of brain activity reorganization may represent a compensatory mechanism based on the recruitment of new brain networks in order to maintain performance. Neural reserve, on the other hand, is another strategy used by healthy individuals when coping with task demands. It emphasizes pre-existing differences in neural efficiency or capacity. It consists in using flexible brain networks or cognitive resources that are less susceptible to disruption (Table 2).

Table 2 Compensatory mechanisms

Concepts	**Definitions**
Cognitive Reserve	Inter-individual ability to effectively use cognitive processes and brain networks
Neural Compensation	The ability to use new, compensatory brain networks after pathology or normal aging disrupted those typically recruited for a particular task
Neural Reserve	The ability to use flexible brain networks or cognitive resources that are less susceptible to disruption

Compensation-Related Utilization of Neural Circuits Hypothesis	Individuals activate more cortical regions as task load increases. Older individuals need to engage more neural resources at lower levels than younger adults
Temporal Hypothesis for Compensation	Age-related delay in brain activity, particularly in the PFC, during cognitive processing. Age-related shift from proactive to reactive cognitive control strategies when cognitive processes imply both anticipation and resolution. These age-related temporally based functional changes in brain activation patterns allow for cognitive performance to be preserved at the expense of speed processing.

3.1. Neural compensation

3.1.1. Executive function

Stern and companions have extensively explored the neural compensation hypothesis in several of their studies. Zarahn et al. (2007), part of the same group, published a functional magnetic resonance imaging (fMRI) study in which young and old participants were compared while performing the letter Sternberg task (a working memory task) using Multivariate Linear Modeling (MLM). Their results showed that load-related activation during the retention phase of the task was characterized by two spatial patterns: one composed of areas often associated with working memory (including the cerebellum, the insula, the inferior and middle frontal gyrus, the hippocampus, the superior frontal gyrus, the inferior and superior parietal lobules and cingulate), and another composed only of the right hippocampal region. While the first pattern was used by both the young and the elderly, the second one was only used by the older subjects. Interestingly, the activation of the second network was linked with a decrease in performance.

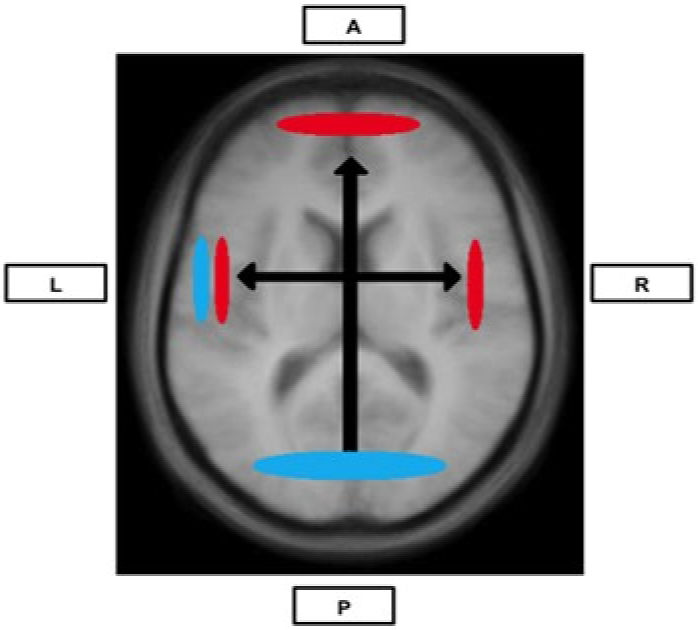

Figure 1. Neural Compensation. Brain image illustrating an age-related hemispheric asymmetry reduction in brain activity (HAROLD) and a posterior-anterior brain activity shift (PASA), two phenomena believed to represent age-related neural compensatory mechanisms. Blue represents activity in younger individuals and red represents activity in older individuals. A: Anterior; P: Posterior; L: Left hemisphere; R: Right hemisphere

There are two possible explanations for this finding. One is that this observation cannot represent a compensatory mechanism since as older individuals increasingly use the alternative network, worse is their performance. However, one could also argue that this alternative network is needed to maintain function as age-related neural changes diminish the efficacy of the first (primary) network. In other words, those individuals using the primary and alternative network would perform even worse if they relied only on their (impaired) primary pathway. If the latter explanation proves to be true, the second network would then be an example of neural compensation.

The same group (Steffener et al., 2009) tried to shed some light on this dilemma. They predicted that, if the second network was compensatory, individuals who express the second pathway should have age-related neural changes that affect the primary network. To explore their hypothesis, they used voxel based morphometry (VBM) to test if atrophy in the primary pathway was related to expression of the secondary network, and they found that a decrease in grey matter density of the left pre-central gyrus was linked with an increase in secondary pathway recruitment. They also found that there was a correlation between gray matter density in the pre-central gyrus and age, but only in the elderly. Based on those findings, they postulated that the elderly increasingly recruit alternate pathways when the primary networks are affected by age-related atrophy. Therefore, this is an example of neural compensation in which older individuals use an alternate network to maintain (at a lower level) task performance.

As previously mentioned, several studies exploring different cognitive modalities have obtained results compatible with neural compensation. Among the results more frequently reported is the tendency for high performing older individuals to show interhemispheric dedifferentiation of cerebral activation (Cabeza, 2002; Reuter-Lorenz, 2002; Reuter-Lorenz et al., 2000; Reuter-Lorenz and Cappell, 2008; Reuter-Lorenz and Lustig, 2005; Reuter-Lorenz and Park, 2010) and intrahemispheric changes in activation patterns, mainly from the occipitotemporal to the frontal cortex (Cabeza, 2004; Cappell et al., 2010; Grady et al., 1994; 1998; 2005; Madden et al., 1997; Reuter-Lorenz et al., 2000): the HAROLD model and the PASA phenomenon (Figure 1).

Recently, Springer et al. (2005) have shown using a working memory task that high performing old individuals tend to rely more extensively on frontal regions and that those regions tend to be bilaterally activated. This observation is in agreement with both the HAROLD and PASA phenomena. However, their complementary analysis did not show any significant correlation within old participants either between frontal activity and performance, or between frontal activity and level of education. Based on those findings, it is difficult to argue for or against the compensatory nature of this increase in frontal recruitment. However, other studies looking at aging and executive processes have shown an increase in frontal activity in older individuals compared to younger persons. Indeed, our group (Martins et al., 2012) has found that high performing older individuals tended to rely more extensively than younger individuals on the frontopolar cortex while performing a lexical version of the Wisconsin Card Sorting Test (WCST - a test often used by neuropsychologists to assess executive function). In this version of the WCST, also known as the Wisconsin Word Sorting

Task – WWST (Simard et al., 2011), participants have to match test words with reference words according to one of the following rules: syllable onset, syllable rhyme or semantics. Participants are unaware of which rule they have to apply and have to find it by trial and error (as for the classical WCST). In that particular experiment, the difference in performance between the younger and older group was minimal. Moreover, it should be noted that, in some studies in which the elderly presented impaired performance, age-related decreased frontal activity has also been reported both in PET (e.g. Reuter-Lorenz and Cappell, 2008) and fMRI studies (e.g. Hampshire et al., 2008) suggesting that increased frontal and bilateral activity are indeed neuronal compensation mechanisms.

3.1.2. Language abilities

Several neuroimaging studies that looked at language processing have also reported increased bilateral activity in high performing older persons compared with younger individuals during verbal generation (Persson et al., 2004) and naming tasks (Wierenga et al., 2008). More recently, Obler et al. (2010) have even shown anatomical evidence (using diffusion tensor imaging) that older individuals with high naming skills tended to rely more extensively on right-hemisphere frontal regions (peri-Sylvian and the midfrontal areas). Therefore, those results seem to indicate that language function also relies on neural compensation.

In 2002, Grossman et al. (2002a) published an article in which brain activity of young, older good and older poor "performers" was compared while the participants were performing a language task. The task consisted in answering a probe question about who performed the action described in a sentence previously presented. The older good performers were as accurate as the younger participants, while the older poor performers showed impaired sentence comprehension compared to the young individuals. The difference between the poor performers and the other two groups of participants became more important as sentences became more syntactically complex.

Regarding brain activity patterns, older good performers showed significant increased activation in two areas compared to their younger peers. Indeed, the dorsal portion of the left inferior frontal cortex, an area known to play a role in working memory including maintaining and rehearsing stored verbal information (Chein and Fiez, 2001; Smith et al., 1998), was more activated in the older group. Moreover, the successful older adults also showed additional activation in the right posterolateral temporal-parietal region (while the left counterpart was more activated in the younger group). Those two findings are in agreement with neural compensation, and they seem to show the co-occurrence of the PASA phenomenon and the HAROLD model.

When the activation pattern of the poor performers was compared to the one of the good performers, it was revealed that the poor performers had increased dorsolateral prefrontal cortex (PFC) activity. The dorsolateral PFC has been reported in several studies implying problem-solving activities, regardless of the nature of the material (e.g. Martins et al., 2012; Monchi et al., 2001; Paulus et al., 2001; Ramnani and Owen, 2004; Simard et al., 2011). That region was not activated in the younger group. Therefore, it seems that the less successful older participants were attempting to understand more grammatically complex sentences by using a problem-solving approach that was not very effective for this particular task. This finding may as well be another example of neural compensation in which poor performers recruit the dorsolateral PFC in an attempt to compensate for age-related insults; unfortunately, contrarily to the good performers, their “strategy” is not sufficient to adequately perform during sentence comprehension.

Tyler et al. (2010) explored syntactic processing in older individuals and found that bilateral recruitment of frontotemporal regions was correlated with improved performance. More recently, Ansado et al. (2013) studied the comprehension of word semantics using a semantic judgment task. During the fMRI experiment, young and old participants had to indicate if a given word presented on a screen identified an animal or not. Behavioral results were similar for both groups, with slightly longer response times for the older one. The fMRI results, on the other hand, showed that older individuals had more parietal and temporal bilateral activations as well as left fusiform activations, while younger subjects had more dorsolateral PFC activations. In the same article, Ansado et al. (2013) also presented data from another preliminary study in which young and older healthy individuals had to perform a verbal fluency (VF) task which involved eight alternating 90-s blocs of four orthographic and four semantic VF conditions as well as a reference condition (repeating the months of the year). The neuroimaging results showed that older individuals had increased bilateral temporal activations during semantic conditions, while similar frontal activations were observed in both groups. However, older participants showed more frontal bilateral activations during orthographic conditions. Both experiments showed that the elderly had a pattern of activation compatible with the HAROLD model (increased bilateral activity in the elderly). However, the apparent posteriorization of some activation in the older group (during semantic judgment and semantic fluency) is in contradiction with the PASA phenomenon.

The authors mention that the discrepancy between their results and what is usually shown in the literature may suggest that during the semantic judgment task, older individuals rely more on their semantic memory and knowledge (processes more associated with posterior regions) while younger individuals rely more on an executive strategy (which imply the involvement of the PFC). They also point out that semantic fluency tends to rely on temporal regions whereas orthographic fluency is more dependent on frontal regions (Henry and Crawford, 2004) which would explain the results of the VF experiment. These observations are actually congruent with other semantic neuroimaging studies (Hazlett et al., 1998; Wingfield and Grossman, 2006) in which older participants presented increased posterior activation. Therefore, Ansado et al. (2013) propose that the nature of a task seems to be a determinant factor for neurofunctional activity reorganization in aging. Even if we agree with this conclusion, we also would like to point out that both age-related anteriorisation and posteriorisation of activation are examples of neural compensation. Consequently, different language domains appear to rely on similar compensatory mechanisms, namely neural compensation (even if the form of the neural compensation may vary).

Our group (Martins et al. 2014) has used the WWST to study how aging affected brain patterns involved in semantic and phonological (syllable onset and rhyme) processing comparing young to high performing old participants. In this particular analysis, only accurate matching trials were considered. Our results indicated that while young adults tended to show increased activity in the ventrolateral PFC, the dorsolateral PFC, the fusiform gyrus, the ventral temporal lobe and the caudate nucleus during semantic decisions (semantic pathway) and in the posterior Broca's area, the temporoparietal junction and the motor cortical regions during phonological decisions (phonological pathway), older individuals showed increased activity in regions of the two pathways during both semantic and phonological decisions. Therefore, in older individuals, the semantic and phonological routes seemed to merge into a single route composed of the semantic and the phonological pathways. This was even more evident when brain activity during one rule was contrasted to the activity during another rule: young individuals showed significant inter-rule activity differences, while the elderly did not (Figure 2). These findings represent, once again, most probably a neural compensation mechanism on which the elderly rely to maintain an adequate level of performance.

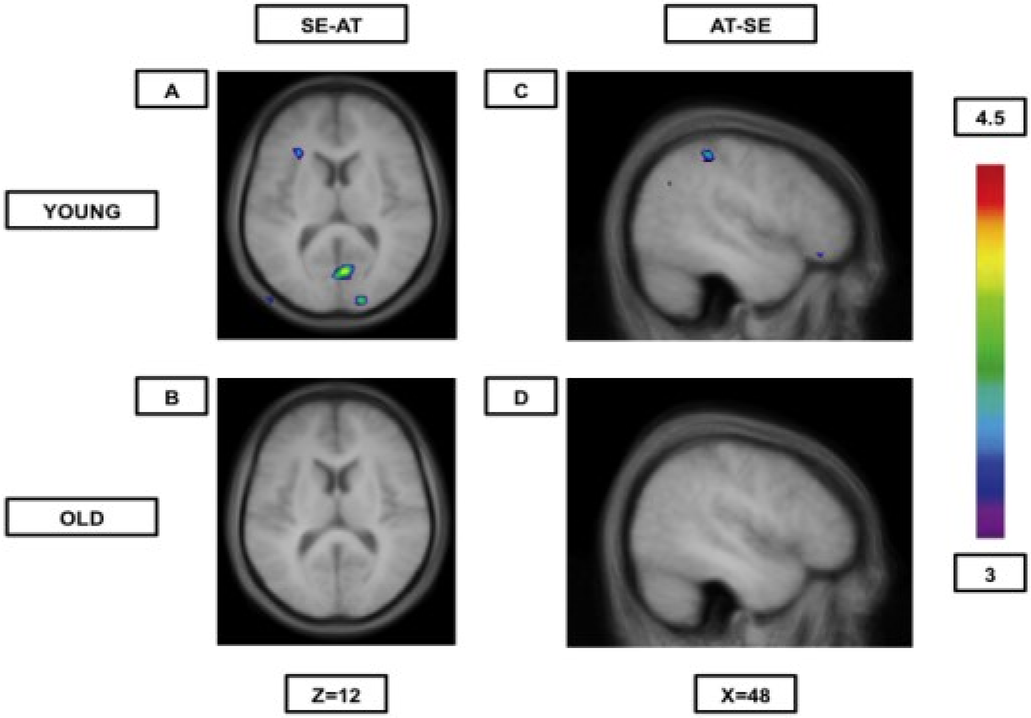

Figure 2. Brain activation contrasts during language processing using the WWST in young and old adults. Old individuals show fewer differences in brain activity between different language processes than young individuals. A: Activation in the left ventrolateral PFC (areas 45 and 47/12) and in right occipital regions (areas 17 and 18) when SE is compared to AT in young adults. B: No significant peaks of activation at all when SE is compared to AT in old adults. C: Activation in the right frontopolar area (area 10) and the right posterior parietal cortex (area 40) when AT is compared to SE in young adults. D: No significant peaks of activation at all when AT is compared to SE in old adults. The anatomical MRI images are the average of the T1 acquisitions of 14 younger subjects and 14 older participants transformed into stereotaxic space. The color scale represents the T statistic. SE: correct matching according to semantics events; AT: correct matching according to syllable onset (attack) events

Similar neural compensatory mechanisms have also been found during speech comprehension tasks. Indeed, age-related hearing loss is accompanied by auditory cortex atrophies (Harris et al., 2009; Peelle et al., 2011; Eckert et al., 2012), explaining why older adults likely have to recruit different neural resources in order to maintain appropriate speech comprehension. That explains why Eckert et al. (2008) observed an age-related upregulation of frontal areas during an easy word recognition task in older individuals, while younger adults recruited these areas merely during difficult listening conditions. Wong et al. (2009) also found that during single word recognition tasks older subjects, when compared to younger ones, showed reduced activation in the auditory cortex but an increase in working memory and attention-related cortical areas (prefrontal regions). Both of these findings are compatible with the PASA phenomenon. More recently, Erb and Obleser (2013) studied neural speech processing in a group of older adults with varying degrees of sensorineural hearing loss and a group of younger individuals with normal hearing. All the subjects had to hear and repeat back degraded sentences. Their results showed that the older adults adapted to degraded speech at the same rate as younger listeners; however, for correct speech comprehension, older individuals relied on the middle frontal gyrus in addition to a core speech comprehension network recruited by the young which is suggestive of a compensatory mechanism.

3.1.3. Are phenomenon such as PASA and HAROLD necessarily compensatory?

Most of the studies presented in this review rely on functional neuroimaging to "measure" brain activity. However, one has to be careful when interpreting fMRI data. While it is appropriate to consider BOLD signals as measures of neural activity of a specific brain region in healthy young adults, the validity of such interpretations is less robust when comparing signals across individuals or states during which significant variations in physiology may prevail. Indeed, increasing evidence suggests that changes in neurovascular coupling (due to medication, disease, age, etc.) have the potential to significantly modify task-related BOLD responses (Carusone et al., 2002; D'Esposito et al., 2003; Iannetti and Wise, 2007; Lindauer et al., 2010; see Liu, 2013 for review). Therefore, the PASA phenomenon, for example, may as well represent age-related changes in patterns of brain activity as changes in vascularity.

Secondly, age-related over-recruitment, particularly bilateralization of cerebral activity, has been interpreted as compensatory both when the correlation between bilateral activity and performance was positive (Obler et al., 2010; Persson et al., 2004; Springer et al., 2005; Wierenga et al., 2008), as well as negative (de Chastelaine et al., 2011; Steffener et al., 2009). Indeed, as previously mentioned, Steffener et al. (2009) postulated that increased recruitment of the right hippocampal region by the elderly (Zarahn et al., 2007) during the performance of a working-memory task was compensatory even if the overall performance was worse in the older group compared to the younger one. de Chasterlaine et al. (2011) also found, during a verbal encoding memory task, that increased right frontal activity in older adults was negatively correlated with memory performance, and they too postulated that this increased right hemisphere recruitment could nonetheless reflect the engagement of processes that compensate only partially for age-related neural degradation, therefore the impaired performance. Cabeza and Dennis (2012) expanded on this idea and hypothesized the existence of three different types of compensation: “attempted”, “unsucessful”, and “successful” compensation. When there is a mismatch between available cognitive resources and task demands, additional neural resources are recruited, reflected in increased brain activity. This over-recruitment is called “attempted compensation”. If the increase in brain activity is associated with better task performance, it then becomes an example of “successful” neural compensation. On the other hand, if it is associated with worse task performance (as for the examples presented above), it is then defined as “unsuccessful” neural compensation.

Another possible explanation for increased brain activity in the elderly is that it does not represent any type of compensation at all, but is actually a manifestation of age-relate brain disruption. Such hypothesis has been favored in some studies in which over-recruitment was associated with impaired cognition (e.g. Duvern et al., 2009). With age, one would lose the ability to inhibit certain regions of the brain, those areas would therefore be more activated in older individuals during the performance of a cognitive task, but they would not contribute to cognition. Differentiating “unsuccessful compensation” from “disrupted over-activation” is almost impossible, especially since both mechanisms can most probably concomitantly occur.

We have mentioned earlier that certain cognitive domains don’t appear to show any performance decline with aging (e.g. emotional regulation) (Carstensen et al., 2003; 2011), some may even show improvement, such as semantic knowledge (Burke and Shafto, 2008; Craik and Jennings, 1992; Laver, 2009; Park et al., 2002; Verhaeghen, 2003). Thus, is it appropriate to talk about “compensation” when performance improves? Therefore, we would like to offer yet one more possible explanation for increased brain activity in the elderly regarding those particular cases, and that is the ability for older individuals to rely on neural over-recruitment, not as means of compensation, but as a “strategy” to increase cognitive performance.

In the present review, the PASA phenomenon, age-related activity dedifferentiation or bilateralization and general neural over-recruitment have been considered manifestations of neural compensation. However, one should keep in mind that this is just one possible interpretation; age-related over-activation could also be a sign, as stated above, of dysfunction (the inability to inhibit certain brain areas) especially when it is correlated with impaired performance; or, on the contrary, improved function when it is associated with better performance.

3.2. Neural reserve

3.2.1. Executive function

Neural reserve has been extensively studied in the context of working memory. Indeed, Zarahn et al. (2007) scanned young and old individuals while performing the letter Sternberg task, a task involving the presentation of a list of letters to memorize (stimulus phase), followed by a period during which the participants must maintain the list in memory (maintenance phase), because afterwards they are asked to respond if new letters presented to them were in the list they had to memorize or not (probe phase). In that study, it was determined that both the younger and the older groups showed similar spatial patterns during the stimulus and probe phases of the task. The authors decided to address the question of whether there were age-related differences in network efficiency between the two groups as they both showed similar pattern activation. Interestingly, they found that as the task got more difficult, the elderly increased network recruitment to a greater extent in the stimulus phase than the younger participants; however they also benefited less from the network recruitment in terms of performance (they made more errors in the probe phase). This result seems to show how age-related neural changes may impair network efficiency even when the network itself remains unchanged. This being said, the fact that the older group was capable of activating the networks to the same degree as the younger one demonstrates that neural reserve is a compensatory mechanism on which older individuals may rely.

In 2009, the same group (Holtzer et al., 2009) conducted a similar analysis on data resulting from young and old subjects performing the shape Sternberg task. This task is similar to the letter Sternberg task, but uses shapes as stimuli rather than familiar letters. This last feature is believed to make the task more challenging than its close relative (Holtzer et al., 2009). However, once again, both the young and the elderly used similar brain pathways during the performance of the stimulus and probe phases. But in this case, they found that the "probe phase" network expression was greater in the younger group compared to the older one. In other words, the younger individuals performed better and showed increased expression of the underlying brain network, which suggests a capacity difference between the two age groups (that is a difference in the ability to recruit the network in question). It is quite probable that the use of the shape Sternberg task, which is more demanding than its letter counterpart, explains why both age groups show differences in capacity in that study (Holtzer et al., 2009), but not in the previous one (Zarham et al., 2007). Indeed, the first study was not challenging enough for either group to reach their capacity potential, while the second one was: the elderly reached their capacity limits before the young. Nonetheless, age-related decline in capacity does not equate with elderly inability to rely on neural reserve as a compensatory mechanism, however, it emphasis the need for the co-occurrence of other compensatory mechanisms if function is to be preserved.

Recently, our group (Martins et al., 2012) have also shown that young and high performing older individuals tend to use the same frontostriatal loops while performing the WWST, namely a cognitive loop including the ventrolateral PFC (area 47/12), the caudate nucleus and the thalamus involved in the planning of a set-shift, and a motor loop important in the execution of a set-shift that includes the posterior PFC and the putamen. Overall, there was no intergroup difference in activation except in the caudate nucleus (significantly more activated in the young) when we looked at all the periods combined (receiving feedback and matching following feedback). Therefore, not only did the elderly rely on cognitive reserve, they also showed little decline in capacity.

3.2.2. Language abilities

Grossman et al. (2002b) have shown that when both older good and poor performers were compared while performing a sentence-comprehension task (which consisted in reading a sentence and answering a question about who performed the action described in the given sentence), poor performers engaged significantly less activation of some important sentence-processing areas in the left inferior frontal cortex and the left posterior-superior temporal cortex relative to good performers. This finding seems to show that old good performers are able to rely more extensively than old poor performers on some language pathways, therefore using neural reserve as a compensatory mechanism.

In the study of Erb and Obleser (2013) (mentioned above) exploring neural speech processing in a group of older adults with varying degrees of sensorineural hearing loss and a group of younger individuals with normal hearing, the authors found that both groups relied on the left anterior insula when presented with degraded more than clear speech. However, anterior insula recruitment in the older group was dependent on hearing acuity. Therefore, older individuals with less impaired hearing were able to rely more extensively on the left anterior insula similarly to the young which represents an example of neural reserve.

Our group (Martins et al., 2014) explored language function and aging using the WWST. As previously mentioned, our results showed that the elderly tended to use similar regions for both semantic and phonological processing. In other words, the elderly showed both cognitive compensation (by relying on regions often associated with phonological processing during semantic processing for example) and cognitive reserve (by relying on the semantic pathway during semantic processing on top of the other regions often associated with phonological processing) for both semantic and phonological decisions (Figure 2). However, another experiment comparing semantic and phonological processing has shown that the first tends to rely more extensively on age-related neural reserve than the latter. Indeed, Diaz et al. (2014), have found that when younger and older adults were asked to make semantic and phonological decisions about pictures, the older group was as accurate and efficient as the younger one in the semantic task, but not during the phonological task. Interestingly, both groups also showed increased activity of similar left-hemisphere language regions during semantic decisions, while they presented more bilateral and widespread activations during the phonological task (especially the older group). Therefore, the older adults were able to recruit more efficiently left-hemisphere language regions (neural reserve) during semantic processing than during phonological processing which was associated with better behavioral results.

4. Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH)

Some of the studies reported so far have shown that compensatory mechanisms (brain over-activation) are not limited to older individuals, but they also occur in younger people when task demands increase (e.g. Braver et al., 2001; Grady et al., 1998; Holtzer et al., 2009; Logan et al., 2002; Rypma and D'Esposito, 2000; Schneider-Garces et al., 2010; Zarahn et al., 2007). Other studies in verbal working memory have also shown that the elderly don't always reveal increased brain activity compared with the young, but under-activation instead, mainly at the level of the dorsolateral PFC (Ansado et al. 2013, Rypma and D'Esposito 2000, Rypma et al., 2001). These observations led Reuter-Lorenz and Cappell (2008) and Reuter-Lorenz and Lustig (2005) to propose a model implying that people will generally activate more cortical regions as task load increases (Compensation-Related Utilization of Neural Circuits Hypothesis; CRUNCH) (Table 2). However, due to age-related decline in neural processing and efficiency, older individuals might need to engage more neural resources at lower levels than younger adults. It should be noted that this hypothesis does not enter in conflict with the concept of CR proposed by Stern (2002); on the contrary, it complements it. Indeed, as age advances and cognitive reserve diminishes, older individuals will need to rely more heavily on task specific pathways (neural reserve) and/or other brain areas (neural compensation) at low task loads. Therefore, it is expected for old individuals to reach their resource limitations (in terms of cortical regions used) at lower levels of cognitive demand compared to younger individuals, leading to a decline in performance as demand increases. At this "crunch" point, brain activity may plateau or even decrease with increasing task loads, explaining why some studies report that the elderly show reduced brain activity compared to the young or higher performing individuals (e.g. Hampshire et al., 2008; Reuter-Lorenz and Cappell, 2008) (Figure 3).

4.1. Working memory

Some studies have been designed to explore the CRUNCH model, especially in the context of working memory. For example, Cappell et al. (2010) scanned (using fMRI) young and old adults while performing a verbal memory task with a load varying between four, five and seven letters. Older adults performed as well as the younger ones when verbal memory loads were of four or five items, but less accurately for memory loads of seven letters.

Interestingly, and with agreement of the predictions of the CRUNCH model, the elderly showed brain over-activation when their performance was similar to the young and under-activation with increased memory load and reduced performance (mainly in the right dorsolateral and ventrolateral PFC). Another study performed by Schneider-Garces et al. (2010) showed similar results. Indeed, in that experiment, young and old subjects were scanned while performing the letter Sternberg's task with memory set sizes varying from two to six letters. The behavioral data indicated that the older group had significantly more difficulty with the task than the younger one, especially when set sizes were larger than four items. On the other hand, the fMRI data showed that several brain regions (including the PFC) had significant bilateral increases of activity as set sizes got larger and thus for both groups. However, while older adults presented a large increase in brain activation between set sizes of two and four letters as well as a negligible further increase at larger set sizes, younger adults showed most of their increase at larger set sizes (five and six letters). Once again, the elderly tended to rely on compensatory mechanisms at lower levels of cognitive demand and reached their resource limitations faster than the young.

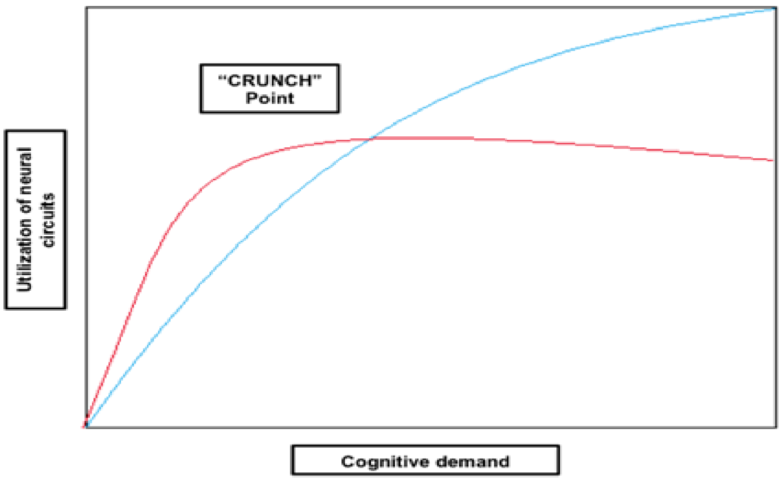

Figure 3. Theoretical illustration of how neural circuit utilization varies with an increase in cognitive demand in old (red) and young (blue) individuals according to the Compensation-Related Utilization of Neural Circuit Hypothesis. This model implies that people will generally activate more cortical regions as task load increases; however old individuals need to engage more neural resources at lower levels of cognitive demand than young adults. Old individuals also reach their resource limitations (shown in the figure as the "CRUNCH point") at lower levels of demand, after which their brain activity may plateau or even decrease as does performance.

4.2. Language abilities

Even if the study of Grosman et al. (2002b) was not designed to explore the CRUNCH model in sentence comprehension, it nonetheless shows quite elegantly how the model may apply to language processing. Indeed, in that study, older poor performers show significantly less activation of some important sentence-processing areas when compared to old good performers, and thus especially when task load increases. In other words, old poor performers have reached their resource limitations while old good performers have not. Meinzer et al. (2012a, b) have also shown, using fMRI and a VF task during which participants had to generate in a limited amount of time as many words as possible under specific category conditions (e.g. animals), that increased bilateral compensatory activity (especially in the inferior gyrus) was mediated by task difficulty more than by age. In other words, as task demands increased, both the young and the elderly showed more bilateral activations which is congruent with the CRUNCH model. Finally, Eckert et al. (2008), in a study presented earlier, observed an increase in activity in frontal regions during an easy word recognition task in older individuals, while younger adults only recruited these areas during difficult listening conditions. Therefore, over-recruitment was not solely due to aging, but to task difficulty as well in accordance with the CRUNCH model.

5. Temporal hypothesis for compensation (THC)

The previous compensatory mechanisms described so far presented anatomically based functional changes in brain activation patterns. However, there is still the possibility of another compensatory mechanism involving not so much WHICH regions of the brain show increased activation, but WHEN are these regions activated.

5.1. Executive function

Velanova et al, (2007) have suggested the existence of an age-related compensatory mechanism that consists of a shift from early to late selection processing during memory retrieval (the load-shift model). In fact, using the concepts of Rugg and Wilding (2000), who divided retrieval into three entities: retrieval orientation (anticipation of retrieval demands), retrieval effort (access of information), and postretrieval monitoring (evaluation of the appropriateness of the recollected information), Velanova et al. (2007) postulated that older participants would most probably rely more on retrieval effort and post-retrieval monitoring and less on retrieval orientation than younger individuals. To explore their hypothesis, they did two fMRI experiments. Thrity-six young and thirty-height old subjects participated in the first one, while twenty-nine young and thirty-seven old subjects were part of the second one. In both studies, participants had to distinguish new words from words that have been previously presented to them (old words), the difference being that in the first study there was only one type of load condition, while in the second experiment there were low (with old words repeatedly studied) and high load conditions (with old words only presented in the incidental deep encoding task, as for experiment 1). Data from both experiments showed that older adults had increased and delayed recruitment of frontal regions compared with the younger ones during demanding retrieval. Based on these results, the authors stated that this strategy shift could explain the retention of high-level cognitive function in some older individuals but at the expense of less flexible and slower performance on demanding cognitive tasks.

Paxton et al. (2008) contrasted the activity dynamics of younger and older adults during the performance of a cognitive control task (the Continuous Performance Test – AX version) relying on some executive processing (mainly discrimination ability and sustained attention). During the test, individuals are instructed to respond with a mouse press whenever the stimulus is an X that was preceded by an A. Their results showed a significant age-related temporal shift in lateral PFC regions: older adults presented both reduced cue-related (letter A) activation and increased probe-related (letter X) activation relative to younger adults. These findings are consistent with previous behavioral studies, in which older adults showed smaller cue-based expectancy effects but larger probe-related interference effects compared to younger individuals (Braver et al., 2001; 2005; Paxton et al., 2006). Based on those results, Braver and colleagues (Braver et al., 2007) developed a theory, named dual mechanisms of control (DMC), which postulates a distinction between proactive and reactive modes of cognitive control. During the proactive control mode, individuals actively maintain in a sustained/anticipatory manner goal-relevant information before the occurrence of cognitively demanding events. On the other hand, in the reactive mode, attentional control is mobilized only when and if needed. Therefore, proactive control relies on the anticipation of interference before it occurs, while reactive control relies on the resolution of interference after its onset.

Jimura and Braver (2010) compared brain activity dynamics in healthy old and young adults during the switch and performance of two semantic classification tasks. During the first task, participants were required to make a decision as to whether a word described an object that is either larger or smaller than a computer monitor. During the second task, subjects had to make a decision as to whether the object was man-made or natural. Before every comparison (for both tasks), a cue appeared and signaled to the participants the semantic classification judgment to be made (LRG-SML or MAN-NAT). There were two block conditions in the study: the mixed-block condition during which the classification task to be performed varied randomly from trial to trial, and the single-task condition during which a single task was performed. Relative to young adults, older individuals presented decreased sustained activity in the anterior PFC during task-switching blocks, but increased transient activity on task-switch trials. Also, younger individuals showed a cue-related response during task-switch trials in the lateral PFC and posterior parietal cortex, whereas older adults presented switch-related activation during the cue period in posterior parietal cortex only. These results are in agreement with the DMC hypothesis and therefore suggest that older individuals shift from a proactive to reactive cognitive control strategy as a means of retaining relatively preserved behavioral performance despite age-related neurocognitive changes. It should be noted that this study is as much an executive function experiment (set-shifting) as it is a language processing experiment (semantic categorization).

Our group (Martins et al., 2012) has shown, as formerly mentioned, that both young and high performing older individuals seem to rely on the same frontostriatal loops while performing the WWST. However, whereas the young showed the involvement of a ‘‘cognitive loop’’ during the period that indicates that a set-shift will be required in the following trial (the receiving negative feedback period) and the involvement of a ‘‘motor loop’’ during the period when the set-shift must be performed (the matching after negative feedback period), the elderly showed significant activation of both loops during the matching after negative feedback period only (Figure 4). Thus, there seems to be an age-related shift in the timing of frontostriatal recruitment (delayed in the elderly). Consequently, those results may indicate, that with aging, individuals tend not to engage in costly executive processes until these become absolutely necessary. These results and this interpretation are also in agreement with the DMC hypothesis.

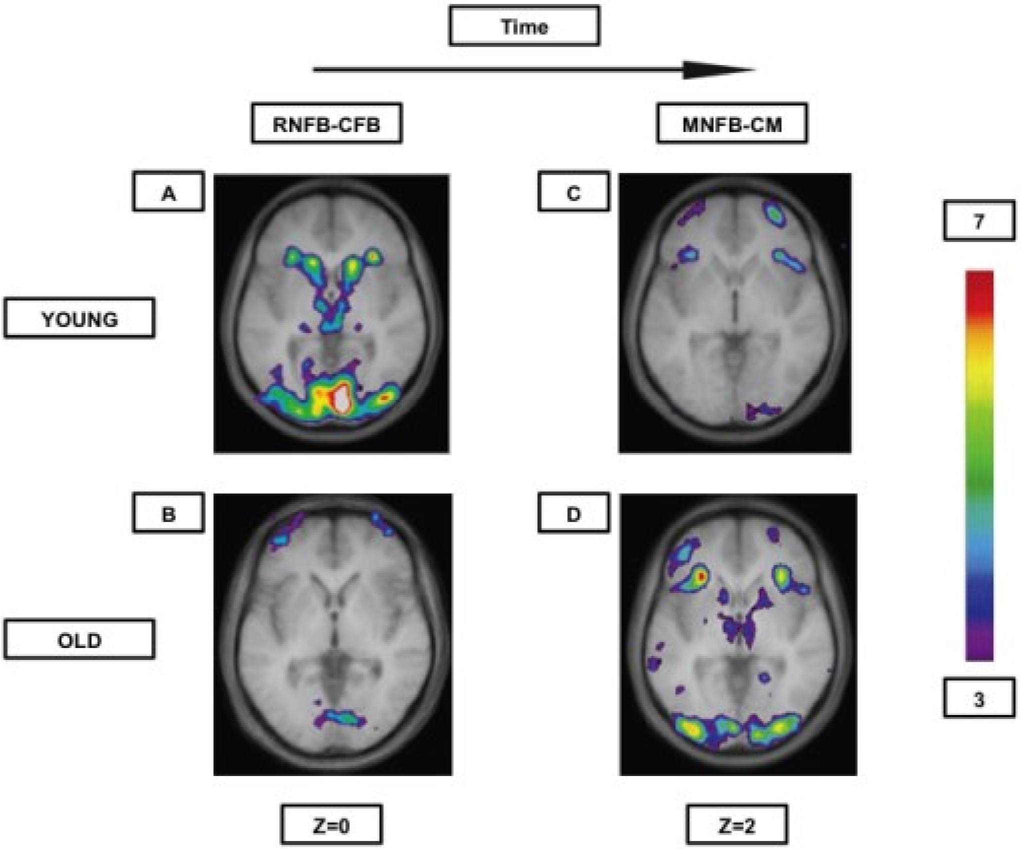

Figure 4. Brain activation contrasts during executive processing using the WWST in young and old adults. Old individuals recruit corticostriatal pathways later than young individuals during the WCST. A: Activation of a corticostriatal loop composed of the midventrolateral PFC (area 47/12), the caudate nucleus, and the thalamus when RNFB is compared to CFB in young adults. B: Activation of the frontopolar cortex (area 10) when RNFB is compared to CFB in old adults. C: Activation of the midventrolateral PFC (area 47/12) and the frontopolar cortex (area 10) when MNFB is compared to CM in old adults. D: Activation in a corticostriatal loop composed of the midventrolateral PFC (area 47/12), the caudate nucleus, and the thalamus, as well as in the putamen (which, with the posterior PFC, makes up another corticostriatal loop) when MNFB is compared to CM in old adults. The anatomical MRI images are the average of the T1 acquisitions of 14 younger subjects and 10 older participants transformed into stereotaxic space. The color scale represents the T statistic. RNFB: receiving negative feedback events; CFB: control feedback events; MNFB: Matching following negative feedback events; CM: Control matching [A and B are reproduced from Figure 2 in Martins et al. (2012), and C and D are reproduced from Figure 3 in Martins et al. (2012)]

5.2. Language abilities

Cook et al. (2006) performed an fMRI study on young adults in which they explored the neuroanatomic substrate and time course (using early and late time windows) associated with processing different grammatical features in a sentence. They used a grammatical test in which the participants had to judge the coherence of sentences that did or did not contain a grammatical violation. There were three possible violations: an inflectional form of the past participle (*ed* was omitted); a noun-verb substitution (rehearsed would be replaced by rehearsal for example); and a transitivity violation (a sentence containing a verb that cannot be expressed in a passive form because the verb is intransitive). These three violations are presented in an ascending order regarding cognitive demand. In early time windows, the participants showed significant left inferior frontal cortex (IFC) recruitment in low-demanding judgments, and bilateral IFC recruitment in more-demanding judgments. In late time windows (BOLD activity levels measured 2 s later than the usual point at which the BOLD signal is monitored), the young participants did not show any activation during low-demanding conditions, but presented left IFC recruitment in the noun-verb substitutions and transitivity violations. Wingfield and Grossman (2006) presented, in their review article, that data with additional results from older individuals who performed that exact same task. The older participants showed a completely different pattern. Indeed, they increasingly activated the ventral portion of left IFC during the late time windows for even the simpler conditions; furthermore they also showed bilateral IFC activation during the more-demanding violations in the late time window (contrarily to unilateral activation for the young). Therefore, not only are those results compatible with the HAROLD model of neural compensation, they also show that the compensatory hypothesis may extend to the temporal domain for language processes.

5.2.3. A new hypothesis

In summary, age-related delayed brain region activation has been reported in several memory, executive, semantic categorisation and syntax processing experiments. Therefore, it does not appear to be a marginal finding, but a possible compensatory mechanism related to several cognitive domains and that may interact with other compensatory mechanisms such as neural compensation and neural reserve. Some of the experiments have shown that older individuals tend to present delayed activity in the frontal regions compared to younger individuals during tasks in which cognitive operations are not preceded by cues, such as in the studies of Velanova et al. (2007) and Wingfield and Grossman (2006). On the other hand, other studies from Braver and colleagues (Jimura and Braver, 2010; Paxton et al., 2008) as well as our group (Martins et al., 2012) have shown that in tasks during which cognitive operations are introduced by cues (anticipation phase) a shift in activity from the cue-phase to the probe-phase has been reported in older individuals. Those findings gave rise to the DMC hypothesis (Braver et al. 2007); with aging, individuals shift from proactive (anticipation) to reactive (resolution) cognitive control strategies. Our group (Martins et al., 2012) proposed that such an age-related shift could be beneficial since it allows for older individuals not to engage in costly cognitive processes until these become absolutely necessary.

In this review, we propose to formalize all the age-related delayed brain region activation reported in the different studies under a single hypothesis, namely the Temporal Hypothesis for Compensation (THC). This hypothesis states the following: 1) there is an age-related delay in brain activity, particularly in the PFC, during cognitive processing (the PFC is singled out due to its primordial role in working memory); 2) there is an age-related shift from proactive to reactive cognitive control strategies when cognitive processes imply both anticipation and resolution; and 3) these age-related temporally based functional changes in brain activation patterns allow for cognitive performance to be preserved at the expense of speed processing (Table 2, Figure 5).

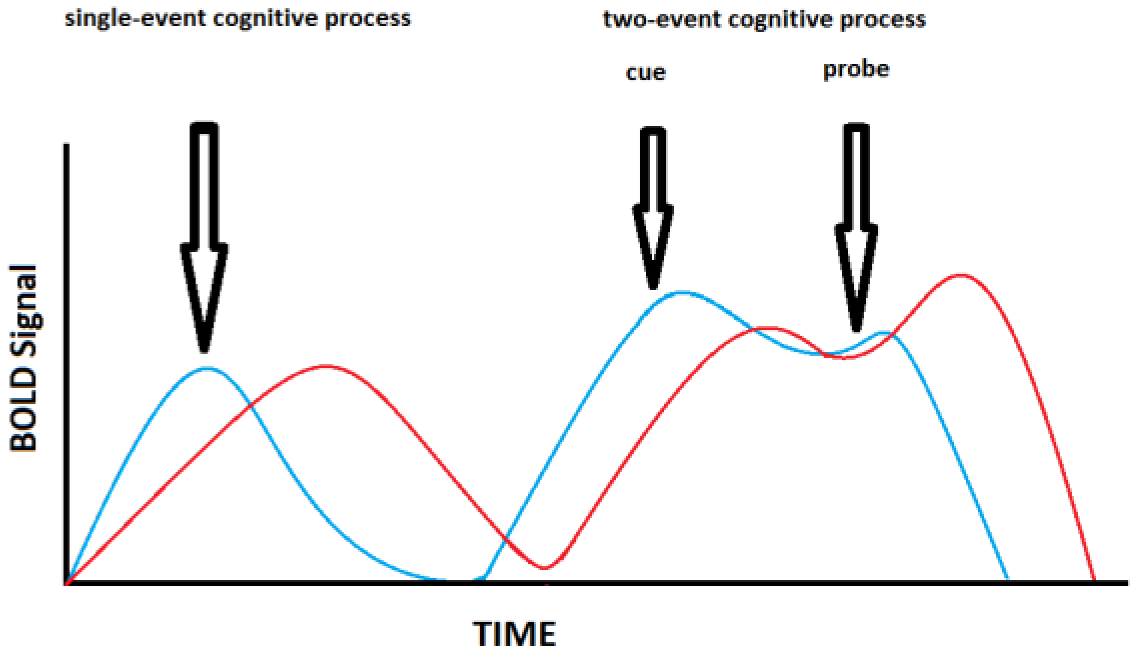

Figure 5. Theoretical illustration of how BOLD signal varies with time in old (red) and young (blue) individuals according to the Temporal Hypothesis for Compensation. This model implies that here is an age-related delay in brain activity during cognitive processing, and that old individuals shift from proactive to reactive cognitive control strategies compared to young individuals when cognitive processes imply both anticipation and resolution.

6. Conclusion

As the passage of time structurally alters one's brain, cognition does not have to suffer the same faith, at least not to the same extent. Indeed, the concept of CR coined by Stern et al. (2002) implies that with age, decline in cognitive performance can be totally or partially compensated. Compensatory mechanisms can take the form of neural compensation and neural reserve. Neural compensation is the use of new, compensatory brain networks different from those pathways typically recruited for particular tasks (e.g. the HAROLD model, the PASA phenomenon). It should be noted that age-related over-activation may not always be compensatory, but may also represent dysfunction (the inability to inhibit certain brain areas) especially when it is correlated with impaired performance. Neural reserve, on the other hand, consists in using primary flexible brain networks or cognitive resources that are less susceptible to disruption.

It has been shown that compensatory mechanisms can also be used by young individuals when cognitive demands become significant. This observation led Reuter-Lorenz and Cappell (2008) and Reuter-Lorenz and Lustig (2005) to propose a model implying that people will generally activate more cortical regions as task load increases (the CRUNCH model). However, since older individuals might need to engage more neural resources at lower levels than younger adults (due to brain atrophy), it is expected for them to reach their resource limitations at lower levels of cognitive demand as well, leading to a decline in performance as demand increases. At this point, brain activity may plateau or even decrease with increasing task loads.

The previous compensatory mechanisms presented anatomically based functional changes in brain activation patterns. However, some studies have also shown delayed brain activation in older individuals compared to the young. Furthermore, those findings are associated with cognitive preservation. Therefore, we postulate that they represent another form of compensatory mechanism and we decided to formalize such a temporally based mechanism under the name of Temporal Hypothesis for Compensation (THC). This new theory builds on previous hypothesis that postulated a shift from proactive to reactive cognitive control strategies in the elderly, namely the dual mechanisms of control (DMC) hypothesis.

In the introduction, we asked if different cognitive domains including language and executive function rely on similar compensatory mechanisms. Based on this review the elderly appear to present evidence of neural compensation, neural reserve and/or delayed brain activation (THC) while performing working memory, executive and/or language processes tasks. Why? First, because cognitive tasks rarely explore solely one cognitive domain at the time. Working memory, for example, not only merges with executive processes, but affects language abilities as well. It is known to constrain sentence comprehension especially regarding sentences with complex syntactic structures (Wingfield and Stine-Morrow, 2000) and plays a role in producing syntactically complex utterances (Kemper, 1992). Second, because there is a limited amount of strategies available: brain activation may be functionally reorganized from an anatomical perspective, from a temporal perspective, or from both perspectives. It makes intuitive sense for all cognitive domains to eventually rely on all these strategies so that performance can be maintained as demand increases.

However, as suggested by Ansado et al. (2013), the specific functional reorganization of the brain, that is which precise regions of the brain show increased or delayed activation for a given task, may take many different forms. For example, in language processing, while several studies looking at orthographic fluency have shown an age-related posterior-anterior shift in brain activation (PASA phenomenon), other studies exploring semantics presented an anterior-posterior shift instead. Both of these findings are examples of cognitive compensation, but the specifics of the compensation differ.

We believe that future research in the field of functional neuroimaging and aging (both normal and pathological) should to try to explore the factors affecting these specific patterns of neurofuntional reorganization. Indeed, the nature of the task, the complexity of the task, the cognitive processes explored and the cognitive strategies used by participants appear to be determinant in the specific shape compensatory mechanisms will take. We also strongly believe that the THC model should be explored in greater depth given the little research there is on temporal neurofuntional reorganization compared to anatomical changes in activation patterns. Finally, there should be more functional connectivity studies whose role is to investigate age-related compensatory mechanisms since some studies suggest already that task-relevant functional connections between specific brain regions can be disrupted with age and that these disruptions have a negative impact on task performance (Bollinger et al., 2011; Madden et al., 2010).

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CHAPTER 8

Conclusion

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Conclusion

"Thus, while the Sun sinks down to rest
Far in the regions of the west,
Though to the vale no parting beam
Be given, not one memorial gleam,
A lingering light he fondly throws
On the dear hills where first he rose."
William Wordsworth, 1786

As you might have been told by a mother, father or teacher: "Finish what you start," and this is what we intend to do. We are now at the end of our journey, time to reflect on the contribution of this thesis to the fields of neuroscience, aging, executive function and language processing. We shall do so by reviewing the main findings of our two experiments exposed in Chapters 5 and 6.

8.1. Aging, compensatory mechanisms and set-shifting

The primary purpose of our first study (Chapter 5) was to investigate how aging affects different fronto-striatal loops involved in set-shifting, namely cognitive loops including the VLPFC (area 47/12), the DLPFC (areas 9 and 46), the CN and the thalamus responsible for the monitoring and the planning of set-shifts, and a motor loop important in the execution of set-shifts that includes the PPFC and the putamen (Monchi et al., 2001).

Simard et al. (2011) showed that significant activation is required in those cognitive and motor cortico-striatal loops for set-shifting in young adults performing the WWST, and we showed the same for a group of older participants. However, the period events during which the cortico-striatal loops were recruited proved to be very different between the young and the old (refer to Chapter 1 for details on the WWST and its period events). In other words, aging influenced the timing of fronto-striatal recruitment. In fact, in younger adults, the analysis showed the involvement of the cognitive loops during the receiving negative feedback period and the involvement of the motor loop during the matching following negative feedback event. In the older participants, however, all loops were only activated during the matching following negative feedback period. Therefore, it seems that during the performance of the WWST, younger individuals, when confronted to a set-shift, plan during the receiving negative feedback period event, and execute the set-shift during the matching event; while older individuals tend to plan and execute the set-shift during the matching following negative feedback period only.

Age-related delayed brain region activation had been reported before in syntax processing and memory experiments. Indeed, Wingfield and Grossman (2006) showed that old individuals presented increased activity in the PFC (compared to young participants) in late time windows during the performance of a grammatical test; furthermore, Velanova et al. (2007) also found that older individuals, during the performance of memory retrieval tasks, showed delayed PFC activation recruitment, suggesting a shift strategy. They postulated that younger individuals may extensively use early-selection processes and thus anticipate memory retrieval demands, while older people tend to rely on late-selection processes to operate on information sequentially.

Paxton et al. (2008) contrasted the activity dynamics of younger and older adults during the performance of a cognitive control task including both a cue and probe phase, and relying on discrimination ability and sustained attention. Their results showed a significant age-related temporal shift in lateral PFC regions: older adults presented both reduced cue-related activation and increased probe-related activation relative to younger adults. These findings are consistent with previous behavioral studies, in which older adults showed smaller cue-based expectancy effects but larger probe-related interference effects compared to younger individuals (Braver et al., 2001; 2005; Paxton et al., 2006). Based on those results, Braver and colleagues (Braver et al., 2007) developed a theory, named dual mechanisms of control (DMC), which postulates a distinction between proactive and reactive modes of cognitive control. During the proactive control mode, individuals actively maintain in a sustained/anticipatory manner goal-relevant information before the occurrence of cognitively demanding events. On the other hand, in the reactive mode, attentional control is mobilized only when and if needed. Therefore, proactive control relies on the anticipation of interference before it occurs, while reactive control relies on the resolution of interference after its onset.

Our study (Chapter 5: Article 1) appears to indicate that age-related delayed brain activation is not limited to memory retrieval, syntax processing or discrimination ability, but applies to executive functions as well (e.g. set-shifting). More interestingly, it also shows that the phenomenon can be recorded in subcortical regions such as the striatum and not just in cortical areas. Furthermore, the fact that our older group performed almost as well as the younger one during the execution of the WWST (the elderly were slower, but did not commit many more mistakes) argues in favour of the phenomenon as a compensatory mechanism. Finally, since the older participants in our study seem to wait until the moment they actually have to execute the task to plan the set-shift, an explanation for delayed recruitment may be postulated: with aging, individuals tend not to engage in costly executive processes until these become absolutely necessary. In our review article (Chapter 7), we decided to formularize this potential time-related compensatory mechanism under the name of Temporal Hypothesis for Compensation (THC). This hypothesis states the following: 1) there is an age-related delay in brain activity, particularly in the PFC, during cognitive processing; 2) there is an age-related shift from proactive to reactive cognitive control strategies when cognitive processes imply both anticipation and resolution (based in our experiments and those of Braver et al., 2007); and 3) these age-related temporally based functional changes in brain activation patterns allow for cognitive performance to be preserved at the expense of speed processing.

The delayed brain activation measured in the elderly is probably the most important finding of our first study (if not of this entire thesis), but it is not our sole result. We also showed, in agreement with the literature (Wang et al., 2009), that the older group presented reduced CN activity compared to the younger one during negative events. Moreover, the study also revealed significant age-related increased activity in the FPC (area 10) during both positive and negative events. This observation is consistent with the neural compensation view of the PASA phenomenon (Dennis and Cabeza, 2008). Indeed, this compensatory model implies that age-related increased prefrontal activity reflects the dynamic reallocation of resources to maintain task performance in response to altered aging brain function (Cabeza, 2004; Grady et al. 2005; Reuter-Lorenz and Cappell, 2008) (refer to Chapters 3 or 7 for more details).

8.2. Aging, compensatory mechanisms and language processing during word reading

Our second study (Chapter 6) was developed to explore how aging affects semantic and phonological processing using the WWST. Simard et al. (2013) had already shown using the same task that young individuals seemed to rely on the DLPFC, the VLPFC, the fusiform gyrus, the ventral temporal lobe and the CN for matching words according to semantics, while they relied more on the posterior Broca's area (area 44), the temporal lobe (area 37), the temporoparietal junction (area 40) and motor cortical areas during matching according to syllable onset or rhyme. Those results were in agreement with those of Duffau et al. (2008) who found similar areas to be involved in semantic and phonological processing in the right hemisphere of some patients undergoing neurosurgery as well as with the "semantic" and "phonological" pathways recruited during reading postulated by Devlin (2008).

Older individuals showed a different picture. Indeed, in our study, older individuals appeared to be using similar regions for both semantic and phonological decisions. That was particularly apparent when we compared the activity between the matching periods according to the different classification rules. Indeed, when semantic matching was contrasted with either one of the phonological rules, the younger group showed increased activity in the VLPFC and the CN (semantic route), while the elderly didn't show any increased brain activity at all. Similarly, when the phonological rules were compared to semantics, there was, in younger individuals, increased activity in the PPFC (syllable rhyme) and the parietal lobe (syllable onset), while the elderly, once again, did not show any increased activity at all.

Therefore, the older group, in our study, appeared to rely on regions belonging to both semantic and phonological pathways for both semantic and phonological processing (instead of specific pathways for specific rules). These findings are in agreement with the concept of cognitive reserve proposed by Stern (2002, 2009) (refer to Chapter 3 or 7 for more details). Indeed, they most probably represent neural reserve/compensation mechanisms on which the elderly, confronted to a demanding lexical task, rely in order to maintain performance. Consequently, a possible interpretation of our results would be that during semantic processing associated with word-reading, high-performing old individuals use both specific semantic pathways (neural reserve) and other non-semantic language-related regions (neural compensation), and the model could apply to phonological processing as well.

8.3. Future directions

The WWST appears to be an adequate tool to study both executive function (set-shifting) and language processing (semantics and phonology). Up until now, the task has been exclusively used in fMRI studies performed on young and high-performing healthy older individuals. However, one could wonder if the WWST could be employed to detect major or minor neurocognitve disorders. Actually, a pilot study during which people suffering from mild cognitive impairment (memory domain) were asked to perform the WWST was started three years ago. Unfortunately, the task proved to be too difficult for most participants and the study was stopped prematurely (results never published). However, that doesn't mean that the WWST could not be useful to detect cognitive impairments in people with other mild or major neurocognitive disorders (such as in Lewy Bodies and Parkinson's disease). Therefore, both behavioural and functional neuroimaging studies using the WWST should be performed in people suffering from pathological aging (other than Alzheimer's disease). The task could also be used in the investigation of other types of psychiatric illness such as schizophrenia since impaired performance in the classical WCST has been reported in individuals suffering from such a disorder (Cannon et al., 2005).

Future fMRI studies using the WCST or the WWST should also focus on functional connectivity. Indeed, this type of analyzes would allow establishing a functional link between all the regions involved in the cognitive and motor fronto-striatal loops postulated in this thesis; those could therefore be regarded as functional networks.

Finally, more age-related compensatory mechanism studies should explicitly explore the THC. Up until now, delayed brain activation in the elderly has only been reported in very few studies, possibly because most experiments so far have not been adequately equipped to detect it. Future fMRI studies should, therefore, use late latency periods, divide cognitive tasks in more events or simply look at the shape of BOLD responses in order to figure out if older individuals tend to show delayed activations, and if so, during which circumstances.

8.4. A conclusion to the Conclusion

In this thesis, we reviewed set-shifting, semantic processing as well as phonological processing in the context of functional imaging. We also looked at how aging affected those same cognitive domains particularly in terms of the compensatory mechanisms involved in cognitive preservation. We showed that both executive function and language processing relied heavily on neural compensation and neural reserve if performance was to be maintained with age. Finally, we also discovered that during set-shifting, older individuals showed delayed activation in some regions which allowed us to formulate another potential compensatory mechanism, namely the Temporal Hypothesis for Compensation (THC). And on those words, we would like to thank you for reading this thesis (especially if you read the entire “thing”, and didn’t jump directly to the end).

Farewell

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